Intraoperative challenges after induction therapy for non–small cell lung cancer: Effect of nodal disease on technical complexity

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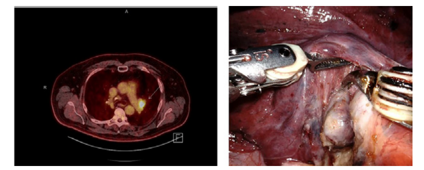
ABSTRACT

Objectives: Neoadjuvant therapy has been theorized to increase complexity of non–small cell lung cancer resections; however, specific factors that contribute to intraoperative challenges after induction therapy have not been well described. We aimed to characterize the effect 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 + non–small cell lung cancer between 2010 and 2020. Patients were categorized according to clinical N1 versus N2 disease. To evaluate the effect of nodal response to therapy, thoracic radiologists measured clinically suspected and pathologically involved lymph nodes before and after induction therapy. Operative reports were reviewed to identify technical challenges specifically related to nodal disease. Categorical outcomes were compared using Fisher exact test.

Results: One hundred twenty-four patients met inclusion criteria, among whom 107 (86.3%) were treated with neoadjuvant chemotherapy, whereas 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, whereas this was necessary in only 2/88 (2.3%) of N2 cases ($P = .001$). Likewise, sleeve resection and arterioplasty were needed more frequently during resection of N1 disease (7/38, 18.4%) versus N2 disease (0/88, $P < .001$). Increased nodal response to therapy was associated with greater likelihood of requiring change in vascular approach ($P = .011$).

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. (JTCVS Open 2022;12:372-84)



Imaging (*left*) and intraoperative findings (*right*) reveal lymph node adherence to pulmonary artery.

CENTRAL MESSAGE

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

Neoadjuvant therapy before 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.

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Non–small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths in men and women in the United States and worldwide.[1] In recent years, substantial developments have been made in the realm of

Abbreviations and Acronyms

CT	= computed tomography
EBL	= estimated blood loss
IQR	= interquartile range
NSCLC	= non–small cell lung cancer
PA	= pulmonary artery
PET	= positron emission tomography

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 after 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 might have historically been offered systemic therapy only.

Surgical indications for NSCLC patients pretreated with systemic therapy are expanding throughout all stages of the disease spectrum. As such, previous investigators have evaluated pathologic end points, 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 effect 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 might 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 might 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 might be likely to be correlated with more complex operative cases, nor is there even clear consensus in terms of defining those elements that might 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 previous 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.[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[18]—although data associating these findings with intraoperative events are lacking.

In this study, we aimed to evaluate the effect 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.

METHODS

Study Population

Before retrieval of data, a waiver of informed consent was obtained from our institutional review board (2020-0929; approved October 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 and May 2020. To be included in the study, patients were required to have cross-sectional chest imaging (computed tomography [CT] and/or positron emission tomography [PET]/CT) available for review from 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 before the initiation of neoadjuvant therapy and also after completion of neoadjuvant treatment. Targeted lymph nodes to be measured were selected on the basis of Response Evaluation Criteria in Solid Tumors 1.1 criteria,[19] and short axis diameter was measured on pre- and post-treatment imaging studies. Additionally, all nodes proven to be positive for malignancy on the basis of pathologic assessment were identified and measured. Lymph nodes were defined as pathologically positive on the basis of pretreatment 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 pretreatment lymph node station was evaluated for nodal reduction. Imaging studies were reviewed by 2 experienced dedicated thoracic diagnostic radiologists (C.S. and M.G.).

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 because of nodal adherence, change in extent of resection because of lymph nodal adherence to structures, and pulmonary arterioplasty or sleeve resection related to nodal adherence. Cases in which PA reconstruction was required because of 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 because of encountering difficulty related to nodal adherence. These criteria were selected in advance of chart review on the basis of 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 are presented as median and interquartile range (IQR) and categorical variables are expressed as frequency and percentage. Differences between groups were analyzed using the Mann–Whitney *U* test for continuous data and Pearson χ^2 or Fisher exact test for categorical data as appropriate. On the basis of 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. All analyses were performed using R, version 4.0.2 (R Foundation for Statistical Computing).

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 most presented with clinical stage IIIA disease (75, 60%), adenocarcinoma (79, 64%), and a history of current or previous cigarette smoking (102, 82%; Table1). 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 video-assisted thoracoscopic surgery with 2 converted nonemergently to open and 8 were begun and completed via robotic-assisted thoracoscopic surgery. 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% (interquartile range [IQR], 9.3%-40%), and thus a cutoff value of 30% was chosen for subsequent analyses of nodal reduction by rounding to the nearest 10th.

Effect 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 to 3 disease. Importantly, we found that patients with cN1 disease were reliably more likely to require a change in approach to the vascular dissection because of adherent lymph nodes (21.1% vs 7.0%; P = .035), with more cases necessitating proximal PA control (21.1% vs 2.3%; P = .001) and even intrapericardial PA control (P = .03) to safely perform the vascular dissection. Furthermore, all cases necessitating arterioplasty or arterial sleeve because of adherent lymph nodes occurred in cases performed for patients with cN1 disease (Table 2). A subgroup analysis in which we compared complexity of cases performed in patients with N1 and N2 nodal stations involved versus those with skip N2 disease is shown in Table E1.

Effect 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 after neoadjuvant therapy, on the frequency of challenging intraoperative nodal findings requiring advanced maneuvers. We found that >30% short axis nodal reduction was associated with the node that could not be removed from the PA (15.8% vs 3.0%; P = .023) as well as an increased likelihood of requiring a change in approach to the vasculature (19.9% vs 4.5%; P = .011; Table 3).

Hilar Nodal Reduction and Surgical Complexity

Forty (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

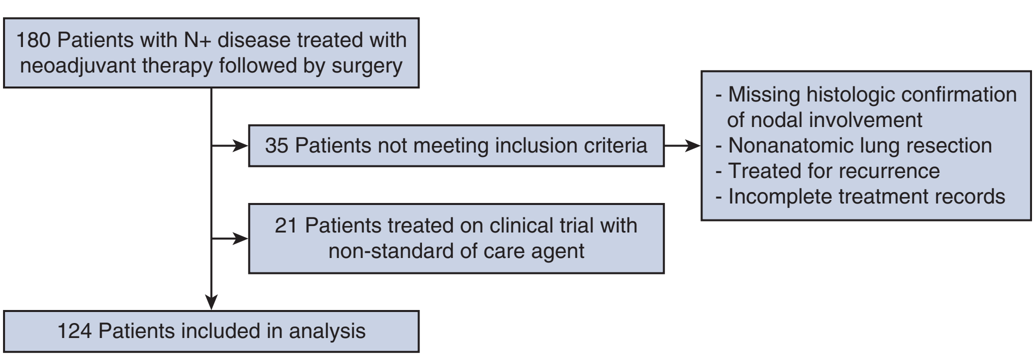


FIGURE 1. Patient flow diagram.

TABLE 1. Patient demographic and clinical features (N = 124)

Feature	Value
Age, y	62 (56-67)
Female sex	63 (51)
Clinical stage	
IIA	8 (6.5)
IIB	25 (20)
IIIA	75 (60)
IIIB	8 (6.5)
IV	8 (6.5)
Histology	
Adenocarcinoma	79 (64)
Squamous	35 (28)
Adenosquamous	2 (1.6)
Neuroendocrine	2 (1.6)
Carcinoid	1 (0.8)
Large cell	2 (1.6)
Mixed	1 (0.8)
NSCLC NOS	2 (1.6)
Smoking history	
Never	22 (18)
Former	86 (69)
Current	16 (13)
Neoadjuvant therapy	
Chemotherapy	107 (86.3)
Chemoradiation	8 (6.4)
Targeted therapy*	9 (7.3)

Values represented as n (%) or median (interquartile range). *NSCLC NOS*, Non–small cell lung cancer not otherwise specified. *Targeted therapies include bevacizumab (3), erlotinib (3), afatinib (1), alectinib (1) and osimertinib (1).

therapy (6 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 >30% required a change in approach to vasculature whereas 2 of 16 (12.5%) with lesser response required a change in approach (Table 4). Although this trend might indicate a signal that merits further investigation, the *P* value was greater than .05 here. 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. Five of 13 (38.5%) required arterioplasty because of lymph node adherence to the PA, 5/13 (38.5%) required proximal PA control, and in 5/13 (38.5%) the nodal adherence necessitated a change in response to the vasculature.

Use of Novel Therapeutic Agents

For the purpose of our primary analyses described previously, we excluded patients who received therapeutic agents outside of currently approved, standard of care therapy. However, because of 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 >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 because of 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 (Table E2). Although these findings were not found to have a *P* value less than .05, likely because of 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

TABLE 2. Clinical nodal status and intraoperative challenges

	cN1 (n = 38), n (%)	cN2-3 (n = 86), n (%)	*P* value
Node could not be removed from PA	6 (15.8)	5 (5.8)	.095
Node stuck to PA causing tear	1 (2.6)	0	.307
Node forces change in approach to vasculature	8 (21.0)	6 (7.0)	.035
Intrapericardial PA control because of node	4 (10.5)	1 (1.2)	.03
Proximal PA control because of lymph node	8 (21.0)	2 (2.3)	.001
Extent of surgery changed because of node	2 (5.2)	2 (2.3)	.586
Arterioplasty/sleeve because of lymph node	7 (18.4)	0	<.001

PA, Pulmonary artery.

TABLE 3. Clinical nodal reduction and intraoperative challenges

	Node reduction <30% (n = 67), n (%)	Node reduction ≥30% (n = 57), n (%)	*P* value
Node could not be removed from PA	2 (3.0)	9 (15.8)	.023
Node stuck to PA causing tear	1 (1.5)	0	.46
Node forces change in approach to vasculature	3 (4.5)	11 (19.9)	.011
Intrapericardial PA control because of node	1 (1.5)	4 (7.0)	.179
Proximal PA control because of lymph node	4 (6.0)	6 (10.5)	.51
Extent of surgery changed because of node	3 (4.5)	1 (1.8)	.624
Arterioplasty/sleeve because of lymph node	2 (3.0)	5 (8.8)	.25

PA, Pulmonary artery.

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 >30% was predictive of increased EBL (Table E3) or length of procedure (Table E4). However, when analyzing cN2 to 3 versus cN1 independently, we found that the association was negatively correlated with EBL (estimate, −112; SE, 56.5; $P = .050$), indicating that patients with cN1 disease are more likely to have increased EBL.

Comparison With the Cohort That Underwent Upfront Resection

The database query identified 41 patients with cN1 pN1 disease managed with upfront surgery. Compared with 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%; $P = .043$), intrapericardial PA control (0 vs 10.5%; $P = .049$), or arterioplasty/sleeve because of adherent lymph node (0 vs 18.4%; $P = .004$; Table E5).

DISCUSSION

In this study, we found that 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 previous studies that relied on subjective assessments to evaluate operative difficulty,[20] and serve as a foundation for future studies that might use surgical complexity as an end point 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 procedure and might allow for anticipation of difficulties while enabling adequate planning to ensure safe outcomes (Video 1).

In recent work published by Takeda and colleagues,[18] the authors reported that lymph node size >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 Wang[21] reported that interference by lymph nodes was the most common reason for conversion from minimally invasive lung resection 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 nodal response to therapy and location of involved nodal stations are important predictors of intraoperative challenges. Unlike previous studies, we did not find that this nodal adherence was associated with increased conversion to open thoracotomy, although it is important to note that most of the postinduction cases in this series were initiated via open approaches. The current study focused on the hypothesis of nodal reduction in size, because we were aimed to characterize the specific effect 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 fluorodeoxyglucose avidity on PET

VIDEO 1. Presentation of data and discussion of clinical importance. Video available at: https://www.jtcvs.org/article/S2666-2736(22)00370-9/fulltext.

TABLE 4. Extent of hilar nodal reduction among pathologically involved, radiographically measurable hilar nodes and intraoperative challenges

	Reduction <30% (n = 16), n (%)	Reduction ≥30% (n = 18), n (%)
Node could not be removed from PA	3 (18.8)	4 (22.2)
Node stuck to PA causing tear	0	1 (5.6)
Node forces change in approach to vasculature	2 (12.5)	6 (33.3)
Intrapericardial PA control because of node	1 (6.3)	1 (5.6)
Proximal PA control because of lymph node	3 (18.8)	4 (22.2)
Extent of surgery changed because of node	3 (18.8)	1 (5.6)
Arterioplasty/sleeve because of lymph node	2 (12.5)	3 (16.7)

PA, Pulmonary artery.

imaging, Response Evaluation Criteria in Solid Tumors criteria, or others. Although those other measures might be of interest in predicting pathologic response, they were not related to our central hypothesis of nodal sclerosis affecting 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 previous investigations that have described potential intraoperative features of challenging cases,[22,23] this study has produced a comprehensive list of intraoperative findings for measuring complexity of dissection. These features might be used in future evaluations of surgical complexity, particularly in the growing body of clinical trials aimed to assess pathologic end points after neoadjuvant therapy.

TABLE 5. Perioperative outcomes

	Median or n (N = 124)	IQR or %
Procedure duration, min	194	149-236
Length of stay, d	5	3-6
EBL, mL	200	150-302.5
Clavien–Dindo ≥3	15	12.1
Death before discharge	2	1.6
Admission to ICU	4	3.2
Pulmonary	–	–
Prolonged air leak	8	6.5
Chylothorax	2	1.6
Atelectasis requiring bronchoscopy	1	0.8
Effusion requiring drainage	1	0.8
Reintubation	1	0.8
Respiratory failure and tracheostomy	1	0.8
DC with chest tube	10	8.0
DC with home o_2	11	8.9
Cardiovascular	–	–
Atrial fibrillation	15	12.1
Pericarditis	1	0.8
Hematologic	–	–
Transfusion	5	4.0

IQR, Interquartile range; *EBL*, estimated blood loss; *ICU*, intensive care unit; *DC*, discharged.

There is a shifting paradigm in the management of NSCLC, in that treatments previously shown 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 surgery might play a role in multimodal therapy. As a result of these changes, the patients 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.[23-25] Similarly, operating on patients with advanced and oligometastatic disease poses unique challenges.[22] However, it is important to note that in this study as well as the previous studies out of our institution, these procedures can be performed safely.

Because these cases were all completed safely and with reasonable morbidity, the question might 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 1500 cases being performed by general surgeons over a recent 4-year period.[26] Surgical outcomes have been shown to be better among patients treated by thoracic surgeons and at high-volume centers,[26-28] 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. Although the complication rate in our cohort is appropriate for the procedures performed,[29] it

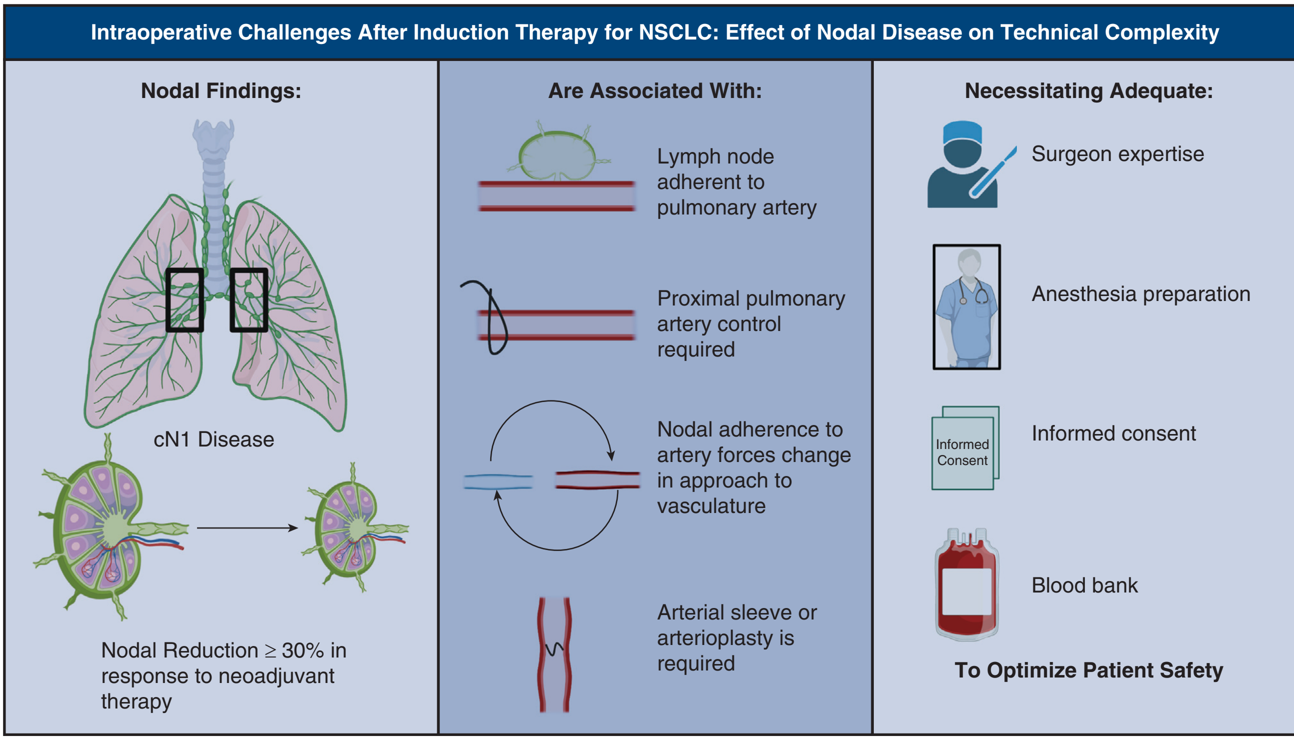


FIGURE 2. Visual abstract. *NSCLC*, Non–small cell lung cancer.

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 because of 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 after 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 might 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 might 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 might 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.[30,31]

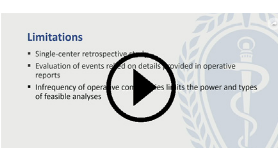
Although to our knowledge, this is the first report to show that clinical nodal staging and response to therapy may be correlated with increased risk of operative complexity, there are some inherent limitations. First, this was a retrospective analysis that relied on review of operative reports, and, 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 to show a meaningful relationship between clinical findings and operative complexity. Furthermore, a comparison was made between patients who underwent upfront resection versus those who received neoadjuvant therapy and there are likely variables not accounted for in the analysis that might contribute to different operative findings in these 2 populations. Because in this study we used data collected from a single quaternary academic center where, in our practice, we undertake advanced procedures in sometimes very aggressive disease, there might 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.

CONCLUSIONS

In this study, we have shown that cN1 disease and nodal reduction in short axis diameter of $\geq$30% are associated with increased complexity of anatomic lung resection because of 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).

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/1414.



Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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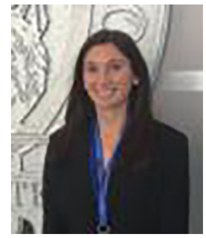
Key Words: non–small cell lung cancer, neoadjuvant therapy, surgery, pulmonary artery, nodal disease

Discussion

Presenter: Dr Hope Feldman

Unidentified speaker 1. Discussion will be opened by Lana Schumacher from the Mass General Hospital.

Dr Lana Schumacher *(Boston, Mass)*. 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 affect you? So, my first question is how do you think your group is going to use these 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, Tex)*. 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 Van Haren's 2018 paper that noted a minimal difference in outcomes in patients who undergo open versus Video-assisted thoracoscopic surgery 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 are 9 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. 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 Antonoff is definitely continuing this work in the setting of targeted therapies.

Dr Schumacher. Great. Excellent job.

Dr Feldman. Thank you.

Dr Schumacher. Thank you.

Dr Robert Cerfolio. 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 less than 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 Fio_2 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 completing two years of research [crosstalk]. [applause]

Dr Feldman. So, I'll use that as a learning opportunity. Thank you.

Unidentified speaker 1. Wait. Robert, if you still have the node invading the artery, you've got to do the sleeve.

Dr Cerfolio. [inaudible].

Dr Mara Antonoff. 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.

Dr Schumacher. Excellent job. [applause]

TABLE E1. Complexity of resections performed on isolated N2 disease compared with resections for patients with N1 and N2 disease

	N2 involvement only (n = 51), n (%)	N1 and N2 (n = 33), n (%)
Node could not be removed from PA	2 (3.9)	3 (9.1)
Node stuck to PA causing tear	0	0
Node forces change in approach to vasculature	3 (5.8)	3 (9.1)
Intrapericardial PA control because of node	0	1 (3.0)
Proximal PA control because of lymph node	1 (1.9)	1 (3.0)
Extent of surgery changed because of node	0	2 (6.1)
Arterioplasty/sleeve because of lymph node	0	0

PA, Pulmonary artery.

TABLE E2. Clinical nodal status and reduction and operative complexity among patients receiving novel therapeutic agents on trial

	Reduction ≥30% or cN1 (n = 14), n (%)	Risk factors absent (n = 7), n (%)
Node could not be removed from PA	7 (50)	2 (28.6)
Node stuck to PA causing tear	1 (7.1)	0
Node forces change in approach to vasculature	6 (42.9)	2 (28.6)
Intrapericardial PA control because of node	1 (7.1)	0
Proximal PA control because of lymph node	2 (14.3)	1 (14.3)
Extent of surgery changed because of node	1 (7.1)	0
Arterioplasty/sleeve because of lymph node	2 (14.3)	0

PA, Pulmonary artery.

TABLE E3. Multivariable model to evaluate predictors of increased EBL

Predictor	Estimate	SE	95% CI Lower	95% CI Upper	*t*	*P* value
Intercept	244.5	86.2	73.8	415.2	2.836	.005
Ever vs never smoker	114.5	72.1	-28.2	257.2	1.588	.115
cN2 or 3 vs cN1	−101.8	56.6	−213.9	10.2	−1.799	.74
LN reduction ≥30% vs <30%	20	52.3	−73.5	133.5	0.574	.567
Neoadjuvant chemo vs other	115	82.2	−47.7	277.7	1.400	.164

SE, standard error; *CI*, confidence interval; *LN*, lymph node; *chemo*, chemotherapy.

TABLE E4. Multivariable model to evaluate predictors of increased operative duration

Predictor	Estimate	SE	95% CI Lower	95% CI Upper	*t*	*P* value
Intercept	186.62	24.8	73.8	137.61	236.0	<.001
Ever vs never smoker	32.56	20.8	−8.67	73.8	1.564	.120
cN2 or 3 vs cN1	−8.49	16.3	−40.7	23.7	−0.522	.603
LN reduction ≥30% vs <30%	−14.84	15.0	−44.56	14.9	−0.989	.325
Neoadjuvant chemo vs other	24.14	24.4	−24.22	72.5	0.989	.325

SE, standard error; *CI*, confidence interval; *LN*, lymph node; *chemo*, chemotherapy.

TABLE E5. Neoadjuvant effect on cN1 operative challenges

	Neoadjuvant treatment (n = 38), n (%)	Upfront surgical resection (n = 41), n (%)	*P* value
Node could not be removed from PA	6 (15.8)	2 (4.8)	.145
Node stuck to PA causing tear	1 (2.6)	1 (2.4)	1.000
Node forces change in approach to vasculature	8 (21.0)	3 (7.3)	.107
Intrapericardial PA control because of node	4 (10.5)	0	.049
Proximal PA control because of lymph node	8 (21.0)	2 (4.9)	.043
Extent of surgery changed because of node	2 (5.2)	2 (4.9)	1.000
Arterioplasty/sleeve because of lymph node	7 (18.4)	0	.004

PA, Pulmonary artery.