In this edition of Clinical Quandaries, Ramalingam et al present a 67-year-old man who seeks care for a new, asymptomatic left upper lobe lung mass, which was found incidentally on a routine chest x-ray as part of a preoperative work-up for an elective surgery. Further staging studies included a computed tomography (CT) scan of the chest and a positron-emission tomography (PET) scan followed by a magnetic resonance imaging (MRI) scan of the liver. Pathology from a fine-needle aspiration biopsy of the left lingular lesion was consistent with poorly differentiated adenocarcinoma and immunohistochemical stains consistent with a lung primary. The left lingular lesion and the prevascular lymph node were felt to be the only sites of involvement, making this stage IIIA (T1, N2, M0) lung cancer.

The patient had an excellent functional status with minimal medical comorbidities and was treated with three cycles of neoadjuvant chemotherapy followed by restaging with a PET/CT scan. Since the prevascular lymph node showed near-complete resolution while the lingular lesion continued to be 18F-fluorodeoxyglucose (FDG)-avid, the patient underwent a left upper lobectomy with mediastinal lymph node sampling. Pathology confirmed the primary lesion, and 3 out of 28 lymph nodes were positive, resulting in a pathologic stage of T2, N2. The patient subsequently underwent thoracic radiation and has had no evidence of recurrence during the 1 year of routine follow-up care.

This case presentation brings up many of the complex issues in the management of patients with stage III non–small-cell lung cancer (NSCLC). They include the optimal evaluation of the mediastinum, the heterogeneous nature of this subgroup of NSCLC, the role of surgery with or without induction therapy (and the optimal induction therapy, ie, chemotherapy vs chemoradiation), as well as the role of adjuvant radiation therapy in patients who had undergone surgery for stage III NSCLC.

**Multiple Subgroups**

Patients with stage III NSCLC tend to be a very heterogeneous population with multiple subgroups, ranging from microscopic N2 involvement to bulky multistation node involvement to tumors that directly invade the chest wall. Andre et al reported striking differences in 5-year survival, from 34% for those with microscopic N2 disease to 3% for those with multiple level N2 involvement discernible clinically when treated with primary surgery.[1] Ademuyiwa et al examined prognostic factors in patients with stage III NSCLC considered for definitive chemoradiation.[2] These investigators found that higher pretreatment hemoglobin levels and a forced expiratory volume in 1 second (FEV1) greater than 2 liters were associated with improved overall survival. Although data are sparse, the use of FDG-PET scanning and the intensity of uptake at baseline would identify subgroups with varying outcomes. In the coming years, it is very likely that global genomic expression analysis would help predict survival as well.

**Roles of Surgery and Induction Chemotherapy**

Surgery alone in patients with stage III NSCLC has been previously examined. Historically, patients have had poor outcomes with single-modality therapy such as surgery, leading the way to the investigation of the multimodality approach.[3] Radiation alone in stage III NSCLC has also shown poor results. Adjuvant radiation in patients with resectable NSCLC was associated with worse outcomes compared with surgery alone.[4]
Since the majority of relapses occur at distant sites, induction chemotherapy followed by surgery has received a great deal of attention. Roth et al.[5] and Rosell et al.[6] showed that patients with stage IIIA NSCLC who received induction chemotherapy prior to surgery had significantly improved survival compared to patients who received surgery alone. These studies were terminated early due to these differences, but long-term follow-up of these patients showed that this survival difference was maintained.

These findings of a significant survival advantage to induction chemotherapy were supported by a retrospective review published by Andre et al.[1] In addition, clinical N2 status, involvement of multiple lymph node levels, pathologic T3/4 stage, and no preoperative chemotherapy were found to be negative prognosticators for overall and event-free survival on multivariate analysis. This further supported the likelihood that there are different patient subgroups among those with stage III NSCLC, warranting different management strategies.

Chemoradiation Trials
Another approach combined chemotherapy and concurrent thoracic radiation as induction therapy prior to surgical resection, as reported by Cancer and Leukemia Group B (CALGB) and the Southwest Oncology Group (SWOG). The CALGB studied 41 patients with stage IIIA NSCLC undergoing trimodality treatment and found that this treatment was feasible but associated with significant toxicities. Approximately 66% of the patients achieved a complete response, and there were nine long-term survivors. However, this study also reported 6 (15%) treatment-related deaths.[7] The SWOG study of 126 patients with stage IIIA/IIIB NSCLC undergoing trimodality treatment reported a 26% 3-year survival rate and 13 (10%) treatment-related deaths.[8]

The role of surgery following induction therapy with systemic chemotherapy and thoracic radiation was recently examined in the Radiation Therapy Oncology Group (RTOG) 9309 trial. This study enrolled medically fit patients with T1–3, pathologic N2, M0 NSCLC.[9] These patients received two cycles of cisplatin and etoposide with concurrent thoracic radiation (45 Gy), were reevaluated, and, if there was no evidence of progression, were randomized to surgical resection or continuation of radiation to complete 61 Gy without interruption. All patients then received two more cycles of chemotherapy as consolidation therapy.

The overall survival (primary endpoint of the trial) was not improved by the addition of surgery. However, those assigned to the surgery arm had a significantly decreased risk of local relapse and improved progression-free survival. The investigators noted a trend by year 5 for an absolute survival benefit of 7% in the surgery arm. Improved overall survival was seen with favorable prognostic factors such as minimal weight loss, female gender, and only one positive N2 station lymph node. Patients who achieved pathologic N0 also had a significantly improved overall survival with surgery compared to those who had persistently positive mediastinal lymph glands.

A subset analysis was performed looking at patients undergoing lobectomy vs pneumonectomy, who were then matched to patients who underwent chemoradiation only. Those who underwent pneumonectomy showed a trend toward worse overall survival, but this subset analysis was limited due to small numbers. Patients who underwent lobectomy did show a significantly improved 5-year overall survival compared to patients who received chemoradiation alone (36% vs 18%, P = .002). It is worth remembering that this analysis was retrospective and unplanned. Moreover, decisions regarding pneumonectomy are often (if not always) made at the time of surgery.

Summary and Conclusions
This case illustrates several quandaries clinicians face in the care of patients with stage III NSCLC. As mentioned earlier, they include the role of surgery, the appropriate induction regimen when surgery becomes part of treatment, and the optimal approach to evaluating the mediastinum, to mention a few.

The role of surgery in stage III continues to be a debatable issue. Our own approach is to consider surgery for patients with single-station N2 following induction therapy, provided they have adequate pulmonary reserves and are not “obvious candidates” for pneumonectomy. Following induction therapy (chemotherapy or chemoradiation), patients are evaluated by CT and FDG-PET scan before surgery in order to identify those with distant progression. The optimal induction therapy is another matter of continued debate. The Radiation Therapy Oncology Group (RTOG) attempted to study the question of the optimal induction therapy (chemotherapy or chemoradiation) in patients with stage III NSCLC prior to surgery. However, this study had to be closed prematurely because of poor accrual. One of the ongoing quandaries is how to reassess the mediastinum following concurrent chemoradiation and how to use that information to make decisions regarding the addition of surgery. Repeat mediastinoscopy is fraught with dangers, particularly after induction therapy. Simmering
inflammation following induction chemoradiation limits the utility of FDG-PET scan as a useful tool. A prospective phase II trial conducted by the CALGB demonstrated that it is feasible to use video-assisted thoracoscopic evaluation (VATS) to restage the mediastinum, with a sensitivity of 75%, specificity of 100%, and negative predictive value of 76%. It is likely that diligent use of endoscopic ultrasound or endobronchial ultrasound may be useful in this setting as well. Hopefully, the next generation of trials in this area will clarify the role of surgery and optimal induction therapy.

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