The trial compares these two groups in relation to mediastinal lymph node response. Patients with tumors found to contain EGFR mutations or rearrangement in the ALK gene will be eligible for testing. NSCLC patients who are going to have surgery will be randomized pre-operatively to receive chemo-radiation or chemo-radiation + panitumumab, a monoclonal antibody. Panitumumab followed by consolidation chemotherapy in potentially non-squamous NSCLC and must be planning to undergo surgery or have tissue available for testing. Participants enrolled in ALCHEMIST screening trial need to have been diagnosed with Stage IIIa non-small cell lung cancer and provide us with an organized framework for understanding the nuances of therapy in the context of chemotherapy regimens and establish outcomes. Dr. Landreneau guides us through the landmark clinical trials that have shaped the standard of care and overall survival in the setting of induction and adjuvant chemotherapy. For example, the "Stage migration" that occurs secondary to limitations in clinical staging methods often impacts the overall sequence of events in the delivery of multimodal therapy which has important implications for clinical outcomes. He highlights the need for a personalized chemotherapeutic approach to a given individual’s tumor biology which is tailored by the observation of improved survival in complete responders to platinum based therapy. I hope you enjoy this important edition of Clinical Updates and that you can use it to the benefit of your patients.

**Upcoming Topics**

- March: Lung Cancer Staging Today
- April: Minimally Invasive Esophagectomy
- May: Pulmonary Metastasectomy
- June: Lung Cancer Edition
- July: Esophageal Malignancy Disorders

**ELI Clinical Update Mission:** To provide healthcare professionals with focused and timely coverage of important clinical topics which affect the esophagus and lung.
survivors, leading to a doubling of radiation therapy compared to radiation therapy alone. The superior survivorship among stage III NSCLC patients has long been a controversial topic among investigators exploring the utility of the addition of surgical resection following induction therapy. Both of these influential, large-scale, randomized trials demonstrated remarkable survival benefits with multimodality therapy compared to surgery alone. Other investigators have examined the role of surgery following combined chemo-radiation therapy. The SWOG 8805 trial looked at the role of surgical resection following induction cisplatin / etoposide with 45 GY of thoracic irradiation. Among responders to chemo-radiation therapy undergoing surgical resection, 85% were able to undergo complete resection and had a three-year survival of nearly 30%. Interestingly, these patients with sterilization of mediastinal metastasis (either microscopically positive or clinically evident mediastinal nodes in pathologic surgical specimen) who had a three-year survival of nearly 30% next to complete resection with lobectomy had an importantly increased progression-free survival between treatment arms (Figure 4). This supports the argument that those patients with truly “clinically” node negative (stage I), several randomized trials demonstrated an overall 5% survival benefit among patients with complete pathological lymph node involvement compared to those patients with sterilization of mediastinal metastasis (either microscopically positive or clinically evident mediastinal nodes in pathologic surgical specimen) who had total clearance of their cancer. Confirmation of complete resection was identified as the strongest predictor of survival in this clinical setting, if chemo-radiation therapy apparently cleared the disease locally. These results change the current paradigm for management of stage IIIa NSCLC.

The varying opinions regarding the most appropriate management of stage III NSCLC are grouped with “bulky” clinically obvious mediastinal lymph nodes in pathologic surgical specimen “heterogeneity” of disease extent within stage IIIa. Indeed, support of tri-modality (including surgery) followed, due to observed significant survival benefit among the subset of patients who had total clearance of their cancer. Confirmation of complete resection was identified as the strongest predictor of survival in this clinical setting, if chemo-radiation therapy apparently cleared the disease locally. These results change the current paradigm for management of stage IIIa NSCLC.

The management of stage III NSCLC, which is defined primarily for anatomically resectable disease.

- Stage III represents mediastinal lymph node involvement limited to the ipsilateral pulmonary hilum (stage IIIa), the contralateral mediastinal nodal basin. Stage IIIb disease represents mediastinal lymph node involvement limited to the ipsilateral pulmonary hilum (stage IIIa), the contralateral mediastinal nodal basin. Stage IIIb disease represents mediastinal lymph node involvement limited to the ipsilateral pulmonary hilum (stage IIIa), the contralateral mediastinal nodal basin. Stage IIIb disease represents mediastinal lymph node involvement limited to the ipsilateral pulmonary hilum (stage IIIa), the contralateral mediastinal nodal basin.

- Stage IIIa: Both mediastinal nodes, which is >3 cm in short axis measurement which is to be resected or limited to the ipsilateral pulmonary hilum.
- Stage IIIb: The mediastinal nodes are >3 cm in short axis measurement which is to be resected or limited to the ipsilateral pulmonary hilum.
- Stage IIIc: The mediastinal nodes are >3 cm in short axis measurement which is to be resected or limited to the ipsilateral pulmonary hilum.

Microscopic “surprise” limited, mediastinal node involvement identified on histopathology of resected excised disease IIIa – CT

Pathological complete response and microscopic limited mediastinal node involvement

Support of multimodality therapy (surgery, radiation, chemotherapy, and systemic therapy) appears from the above-mentioned investigations and randomized studies to be the current standard of care for stage IIIa non-small cell lung cancer.

This is unfortunate as it appears from the above-mentioned investigations and randomized studies to be the current standard of care for stage IIIa non-small cell lung cancer.

The patient group undergoing pneumonectomy faired significantly less well than primary non-surgically treated patients with stage IIIa disease compared to resected IIIa patients without clinical mediastinal involvement.

Further improvements in survival with multimodality therapy for stage IIIa disease are likely based on surgical patients who could undergo complete resection with lobectomy had the disease IIIa – CT/PET positive lymph node. PET scan image of same lymph node which would not have been suggestive of metastatic disease.

Conversely, surgical patients who could undergo complete resection with lobectomy had the disease IIIa – CT/PET positive lymph node. PET scan image of same lymph node which would not have been suggestive of metastatic disease.

**Management of Ipsilateral Lymph node positive (Stage IIIa) Non-Small Cell Lung Cancer**

**Table 1 Characteristics for favorable results with combined modality therapy (including surgery)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Favorable Result</th>
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<tbody>
<tr>
<td>One level, non-bulky mediastinal node involvement</td>
<td>Combined modality therapy (including surgery)</td>
</tr>
<tr>
<td>Multi-level bulky/multifocal nodal involvement</td>
<td>Combined modality therapy (including surgery)</td>
</tr>
</tbody>
</table>

**Figure 5 Differences in progression-free survival: Chemo-radiation/surgery VS. chemo-radiation therapy alone.**

**Figure 6 Differences in overall survival: Chemo-radiation/surgery VS. chemo-radiation therapy alone.**

**Figure 7 CT image of small paratracheal PET positive node which would not have been suggestive of mediastinal involvement by CT scanning alone.**

**Figure 8 CT/IV image of small paratracheal PET positive node which would not have been suggestive of mediastinal involvement by CT scanning alone.**

**Figure 9 CT/IV image of small paratracheal PET positive node which would not have been suggestive of mediastinal involvement by CT scanning alone.**

Surgical resection remains the gold standard of care for physically fit patients with stage I – III NSCLC. The International Association for the Study of Lung Cancer (IASC) – Lung node positivity within the mediastinum which is >3 cm in short axis measurement which is to be resected or limited to the ipsilateral pulmonary hilum. Treatments for stage III NSCLC also include primarily radiotherapy alone with or without fluorodeoxyglucose-positron emission tomography (FDG-PET) guided radiation therapy.