Management of Stage IIIA (N2) Non–Small Cell Lung Cancer

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KEYWORDS

• Stage IIIA • Non–small cell lung cancer • PORT • Adjuvant • Neoadjuvant • Surgery • N2

KEY POINTS

- There is no consensus as to the optimal management of IIIA (N2) non–small cell lung cancer, nor for the role of surgery in treating this disease stage.
- Clinical trial evidence struggles to keep up with technology advancement and the evolution of expert opinion.
- Despite advances in chemotherapeutic regimens, methods of delivery for radiation, and less invasive surgical techniques, survival for patients with stage IIIA (N2) malignancies remains poor.
- Further developments in both will stimulate and maintain controversy in the field for years to come.

BACKGROUND

Approximately 15% of patients with non–small cell lung cancer (NSCLC) will present with stage IIIA (N2) disease.[1] The optimal management of patients with stage IIIA (N2) NSCLC disease remains widely debated among surgeons, pulmonologists, and oncologists. Many trials have set out to determine the optimal combination and timing of multimodality treatment. Such trials have historically been challenged by accrual issues and relevance to modern practice by the time of publication. Unfortunately, this leaves many aspects of patient care for IIIA (N2) disease unclear.

Despite advances in chemotherapeutic regimens, methods of delivery for radiation, and less invasive surgical techniques, survival for patients with stage IIIA (N2) malignancies remains poor. Here, the current literature evaluating neoadjuvant and adjuvant therapies, surgical indications, and new immunomodulators in the context of their relevance to the treatment of IIIA (N2) disease is reviewed.

STAGING CONSIDERATIONS

Stage IIIA (N2) NSCLC is a varied mix of tumor sizes and nodal involvement. Tumors vary dramatically from subcentimeter to being greater than 7 cm or invading surrounding structures such as the chest wall. Nodal involvement, although defined as N2 or ipsilateral mediastinal, also varies significantly. Survival outcome and treatment considerations for single-station, microscopic disease are very different from multistation, bulky nodal disease (**Table 1**).

Accurate Determination of IIIA (N2) Non–Small Cell Lung Cancer

Appropriate staging of lung cancer is essential, because treatment recommendations and prognosis vary significantly by stage. Even with a thorough preoperative workup, there will still be a percentage of patients who will have occult mediastinal disease at the time of surgery that will become clear only on final pathology.

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Thorac Surg Clin 26 (2016) 271–285
http://dx.doi.org/10.1016/j.thorsurg.2016.04.001
1547-4127/16/$ – see front matter

Table 1
Seventh edition lung cancer staging: stage IIIA

Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0

Initial Staging

Computed tomography (CT) scanning, a standard part of the workup for lung cancer, is the least sensitive and specific modality for the identification of lymph node involvement. The utility of PET scanning has evolved and now holds an important role for extrathoracic staging in ruling out distant metastasis, which would render a patient unresectable. However, confirmation of PET scan abnormalities with tissue diagnosis remains important because the study also carries a significant rate of false positive upstaging.[2]

Endobronchial ultrasound (EBUS) with transbronchial needle aspiration has increasingly been used as a favored method for diagnosis of suspicious mediastinal nodes. Review of available publications reveals a median sensitivity of 89%, although values range in the literature from 46% to 97%.[2]

Mediastinoscopy was considered the gold-standard diagnostic technique for the assessment of mediastinal lymph nodes for decades. Although replaced in many centers by EBUS as the first line for mediastinal assessment, mediastinoscopy remains an important tool, with a sensitivity of 89% and specificity of 100%.[2]

How Do Endobronchial Ultrasound and Mediastinoscopy Compare?

Yasafuku and colleagues[3] presented their findings at the American Association for Thoracic Surgery in 2011. The study enrolled 153 patients who underwent EBUS followed directly by mediastinoscopy, with an average of 3 to 4 nodal stations sampled by EBUS per patient. They found no significant difference between EBUS-TBNA and mediastinoscopy in determining the pathologic N stage. There were no complications from EBUS-TBNA, while mediastinoscopy had minor complications in 2.6% of patients. They concluded EBUS-TBNA could safely replace mediastinoscopy for mediastinal staging in potentially resectable patients.

How transferable these results are to routine practice remains unknown. Procedural proficiency is certainly a confounding factor for both EBUS and mediastinoscopy, and it will be important to confirm these and other results in a broader setting. Furthermore, it will be important to sort out where endoscopic staging works best and which cases best benefit from mediastinoscopy, such as the dilemma of how best to restage a patient after receiving neoadjuvant therapy.[4]

Unfortunately, even guidelines for mediastinal assessment are debated, with some physicians favoring routine sampling of all lymph node stations, whereas others favor sampling of only those nodes that are suspicious on imaging. Thorough sampling is most important in central tumors with radiographically normal-appearing nodes. When nodes are grossly abnormal, these can be sampled initially and are much more likely to yield a positive diagnosis, in some cases obviating sampling additional areas.[5] The authors remain committed at their institution to an approach of routine sampling of all lymph node stations to accomplish thorough preoperative staging.

Occult N2 Disease

Even with negative imaging, negative surgical biopsy, and a small (T1) cancer, there will still be a subset of patients found to have occult N2 disease on frozen section at the time of lung resection or discovered later on final pathology.

The rate of occult N2 disease with T1 primary tumors and negative imaging is in the range of 4% to 6%, and 9% to 10% for T2 tumors. In clinical stage I patients, higher risk features for N2 disease include central tumors, larger T size, and positive N1 disease.[6,7] Prediction models to try to determine the risk of N2 disease have been developed and tested, although are not widely accepted and adopted.[8,9]

Is Restaging Necessary After Neoadjuvant Therapy?

"Restaging" has different definitions depending on the investigator's perspective and the medical or surgical subspecialty involved. To some, restaging represents an imaging-based evaluation to rule out distant metastases that would render surgery a futile exercise for improving survival. For many, this involves a more comprehensive workup, including pathologic reassessment of the mediastinum to determine if there is persistent disease, given the known improvement in survival for resected patients, wherein mediastinal sterilization has been achieved.