Staging lymph node metastases from lung cancer in the mediastinum

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ABSTRACT

Background: The presence of tumor metastases in the mediastinum is one of the most important elements in determining the optimal treatment strategy in patients with non-small cell lung cancer. This review is aimed at examining the current strategies for investigating lymph node metastases corresponding to an “N2” classification delineated by The International Staging Committee of the International Association for the Study of Lung Cancer (IASLC).

Methods: Extensive review of the existing scientific literature related to the investigation of mediastinal lymph node metastases was undertaken in order to summarize and report current best practices.

Conclusions: N2 disease is very heterogeneous requiring multiple modalities for thorough investigation. New research is now focusing on better identifying, defining, and classifying lymph node metastases in the mediastinum. Molecular staging and sub-classifying mediastinal lymph node metastases are being actively researched in order to provide better prognostic value and to optimize treatment strategies. Non-invasive imaging, such as PET/CT and minimally invasive techniques such as endobronchial and endoscopic ultrasound guided biopsy, are now the lead investigative methods in evaluating the mediastinum for metastatic presence.

KEYWORDS

Lung cancer; N2 disease; mediastinal metastasis; lymph node staging

Background

Lung cancer has remained one of the most devastating and deadliest cancers worldwide accounting for 18% of all cancer deaths (1). Imparting some of this lethality is lung cancer’s aggressive heterogeneous nature, often presenting in advanced stage where the five-year survival is less than 5% (2). This heterogeneity has also conveyed difficulties in properly staging lung cancer.

Now in its 7th edition, lung cancer staging has gone through several revisions collectively overseen by The International Staging Committee of the International Association for the Study of Lung Cancer (IASLC) and based on the “TNM” classification system. The newest edition has called for revisions of the “T” and “M” components, and after extensive review, found that tumor size had prognostic relevance and that a better differentiation of tumors produced patients with different prognoses (3). However, these evidence-based sub-classifications made no changes to the “N” component, which has remained relatively unchanged through several lung cancer staging revisions.

N2 nodal disease

Current classification of the “N” component sub-divides it into four divisions, no lymph node metastasis (N0), local peribronchial and/or ipsilateral hilar lymph node metastasis (N1), ipsilateral mediastinal and/or subcarinal lymph node metastasis (N2), and contralateral mediastinal and/or supraclavicular lymph node metastasis (N3). However, the N2 classification can be considered the most expansive as it corresponds with lymph node stations of the superior mediastinum (2R, 2L, 3A, 3P, 4R, and 4L) extending to the lower mediastinum [7, 8, and 9] and including those lymph nodes of the aortopulmonary window and para-aorta (5 and 6, respectively). Due to the broad region and number of lymph nodes that N2 disease comprises, it can lead to a heterogeneous mix of lung cancers that can have different survival rates (4,5).
Although several changes have been proposed for re-classifying the “N” component, the diversity of “N” disease based on global geography and tumor biology, has made it difficult to obtain a consensus validation (3).

Amongst the proposed changes for N2 disease, IASLC has suggested the concept of nodal zones. This classification system arranges 14 lymph node stations into seven lymph node zones (3). Studies supporting this have shown that under this proposed system, patients with single N2 zone positivity have a significantly higher survival rate than patients with multiple N2 zones and have a prognosis similar to patients with multiple positive N1 lymph nodes (3). Other studies have proposed other “N” classification methods based on the number of positive metastatic lymph nodes (6,7), the ratio of metastatic lymph node number to the number of total lymph nodes resected (7-9), and to the combination of both number as well as rate of metastatic lymph nodes (10). Regardless of the kind of reclassification of N2 disease undertaken, any future revision will carry major clinical implications as mediastinal lymph node metastasis is one of the most important factors in determining lung cancer treatment. This is especially true for N2 disease, where metastatic status at time of lung cancer diagnosis can be seen as a “watershed” area between which modality or combination of modalities will be undertaken for treatment.

Moving towards molecular staging

The TNM staging system was established in 1958, and in lung cancer, it is based almost exclusively on determining the anatomic extent of the cancer based on disease burden and spread. Although the American Joint Commission on Cancer (AJCC) was largely responsible for its widespread adoption, the TNM system has now become the gold standard for international reporting of lung cancer staging as shown by its recent refinement in the 2010 IASLC classification/staging reports (11). Since patient survival has long been associated with the anatomical extent of disease from the primary tumor, the TNM staging system has always proved strongly to correlate with lung cancer long-term survival rates (12). Moreover, not only has the clinical outcome of lung cancer been predicted based on this TNM staging, but also the treatment plans of individual patients have been prescribed by physicians based on anatomical extent of disease. It is generally accepted, for example, that local treatment modalities such as surgery and radiation therapy are inappropriate to administer for curative intent once the disease has spread beyond the surgical margins of resection or the confines of the radiation field, respectively. But, since the TNM staging system is anatomically based with visual inspection of tissue being critical, these management decisions about options of patient therapy and insights into prognostics have been until recently reliant on the skill of the pathologist and the optical power of a microscope.

In lung cancer staging through the years, histological type, differentiation, and clinical characteristics of patients such as age or race have not been fully incorporated into the TNM staging system. Recently, however, a worldwide effort, led by William Travis of Memorial Sloan Kettering, has re-examined the previous motley classification of adenocarcinoma histology to reveal distinct histological subtypes that do confer prognostic value (13). As others have suspected, this perhaps speaks to a strong correlation between histology and molecular determinants of lung cancer as exemplified in molecular features such as gene-expression profiles (14,15). In fact, the dawn of polymerase chain reaction (PCR) technology and the burgeoning field of molecular diagnostics are proving to be powerful technologies for determining the extent of cancer spread in pathological specimens. It is anticipated that they may fundamentally change the TNM staging system if accumulated evidence persuades their incorporation into the TNM staging system by the AJCC and/or the IASLC.

At present, most molecular prognostic markers in lung cancer have principally used only the T component of the staging system to estimate survival, such as recent published examples (Table 1). This concept is based on the hypothesis that the genes or proteins being identified in the primary tumor alone molecularly confer a certain clinical outcome due to their presence and function inherently, and that this is necessary and sufficient to determine tumor behavior. The problem with this approach is that it ignores the time tested benefits of all components of the TNM staging system. Instead of the intense focus on defining molecular signatures solely based on the tumor, strategies should also define molecular characterization of N2 lymph nodes and metastatic disease (serum). Eventually, this may enable more value to be added to the current anatomical TNM system.

Some of the reasons for this shift away from examining molecular determinants of lymph node metastases are that early attempts to correlate molecular markers in mediastinal lymph nodes with clinical survival of lung cancer patients were largely unsuccessful (20,21). One of the largest efforts to date to incorporate a molecular evaluation of the N2 lymph nodes for occult, micrometastatic tumor cells was performed in 2002 by the Cancer and Leukemia Group B Cooperative Cancer Group in the U.S.A. which failed to show any clinic benefit of molecular upstaging to patients (22).

Brock et al. recently advanced a step in the direction
of molecular staging by proposing a set of four genes epigenetically modified that could be used to detect tumor DNA in N1 and N2 lymph nodes without evidence of visually discernible cancer cells, and which could be correlated with disease-free survival (23). Detecting tumor DNA rather than intact cells has an innate advantage because intact cells are needed to be visible in the mediastinal lymph nodes to ascertain the presence of cancer whereas tumor DNA may be present without microscopically observing tumor cells. Intact cancer cells are vulnerable to phagocytosis, especially if immune-inhibitory transmembrane receptors such as CD47 are not overexpressed, they can be fractured or fragmented by stress or trauma, and they can undergo apoptosis or necrosis for failure to implant into the nodal tissue. From any dead or dying cell, tumor DNA would be a residual product in the microenvironment fully available to be identified by PCR and detected for diagnostic purposes. Although molecular staging of the TNM system has not yet reached clinical relevance, the concept behind this approach is still powerful and appealing. Future studies and more potent molecular marker technology may be needed to derive the full benefits of molecular staging of primary tumor and N2 lymph nodes.

PET imaging, especially in combination with CT imaging, plays a prominent role in the evaluation of patients with lung cancer and is recommended preoperatively for most patients suspected of having lung cancer (26). Multiple investigations have assessed the validity of PET in identifying and evaluating mediastinal metastases (26-28). In comparison to CT imaging, PET has shown to have significantly better sensitivities and specificities, 77% and 86% respectively, when evaluating for mediastinal metastasis.

However, PET imaging, even when combined with CT, is not without its disadvantages. In areas of endemic granulomatous disease, such as sarcoidosis, HIV infection, and fungal disease, such as histoplasmosis, PET has been shown to increase the rates of false positive malignancy in mediastinal lymph nodes due to the increased metabolic activity these diseases engender in N2 lymph nodes (28-31). False mediastinal lymph node positivity on a PET scan will incorrectly upstage disease, which can erroneously direct patients from curative surgery (26,32). Hence, clinicians must be aware that PET imaging is not a definitive test and tissue confirmation is often needed to confirm PET scan findings. Despite its major positive impact on the stage classification of patients at a higher risk of having distant metastases outside the thorax, when used alone without tissue confirmation, PET imaging has the potential to be harmful if used in less structured settings.

### Imaging modalities for evaluating N2 disease

Recent advancements in imaging modalities, such as computed tomography (CT) and positron emission tomography (PET), have drastically improved the detection and evaluation of lung cancer (24,25). CT imaging is now the most widely available and most commonly used imaging technique to assess intra- and extra-thoracic metastases (26). However, CT imaging has been shown to have limited abilities when evaluating the mediastinum for metastases when used as the sole modality. Investigations have shown that the sensitivity and specificity of CT imaging in identifying mediastinal metastases are 55% and 81%, respectively (26).

### Invasive techniques for evaluating N2 disease

#### Mediastinoscopy

Confirming mediastinal involvement is crucial in the treatment and prognosis of lung cancer. Non-invasive methods for establishing mediastinal involvement, such as PET/CT, are excellent in detecting disease, but do not provide definitive disease confirmation. A plethora of invasive techniques are now
available to obtain tissue as the next step to confirm mediastinal metastases.

Mediastinoscopy has long been viewed as the “gold standard” for diagnostic evaluation of the lymph nodes of the mediastinum. Performed in an operative suite under general anesthesia, the procedure involves an incision just above the suprasternal notch, with insertion of a mediastinal scope alongside the trachea, allowing for biopsies of the mediastinal lymph nodes. Using this approach, lymph nodes stations 1, 2R, 2L, 3, 4R, 4L, and anterior station 7 lymph nodes can be sampled. The use of a video mediastinoscope may allow for greater sampling, such as access to the posterior lymph nodes of station 7, and possible performance of a lymph node dissection (26).

Mediastinoscopy may also be modified to sample the aortopulmonary lymph nodes of stations 5 and 6, such as in an extended cervical mediastinoscopy. In this procedure, using the same cervical incision as a traditional Mediastinoscopy, the mediastinal scope is directed laterally toward the aortic arch (34). However, due to the grave complications of this technique, extended cervical mediastinoscopies are delegated to the few institutions that routinely preform them (35-37).

**Endobronchial and endoscopic ultrasound guided biopsies**

Despite its low rates of morbidity and mortality, 2% and 0.08% respectively (38), the role of mediastinoscopy is changing in favor of less invasive techniques, such as endobronchial ultrasound (EBUS) guided biopsy and esophageal endoscopic ultrasound guided (EUS) biopsy. EBUS has been increasingly used in the staging of lung cancer due to its excellent diagnostic performance (26,39-41). EBUS biopsy was found to be significantly more sensitive for detecting malignant lymph nodes than transbronchial needle aspiration, 69% vs. 36% respectively (39). Overall, in patients who had clinical indications for an invasive investigation of the mediastinum, EBUS was shown to have a sensitivity of 89% with a negative predictive value of 91% (26).

Once considered a complimentary procedure of the mediastinoscopy, EUS biopsy has emerged as a viable alternative (39,42-44). Performed with minimal risks of complications, EUS has been shown to be particularly helpful in evaluating the lymph nodes of station 5 and the lymph nodes of the inferior mediastinum. EUS biopsy is also capable of obtaining tissue from outside the thorax to evaluate distant metastases, such as in the liver, celiac lymph nodes, and areas of the sub-diaphragm (44,45). When used for the detection of metastases to the mediastinum, EUS has been shown to have sensitivities and specificities as high as 89% and 100%, respectively (26).

Currently, and with the support of multiple investigations, EBUS and EUS are now being routinely combined to allow for near complete evaluation of the mediastinum (26,39,46,47). In a meta-analysis of seven studies comprising 811 patients with a lung cancer prevalence of 33%, EBUS plus EUS was able to produce 91% sensitivity and 100% specificity (26). However, despite their high appeal as alternatives to mediastinoscopy as a first line status in evaluating the mediastinum, they both require high levels of expertise to be performed effectively. Additionally, few clinicians are sufficiently trained to do both procedures well, so that two separate qualified clinicians are needed to carry out both procedures.

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In the thoracic surgery literature, there has been a long running debate concerning the correct surgical technique of harvesting hilar and mediastinal lymph nodes from lung cancer patients during surgical resection. At the heart of the debate, is whether a small sampling of relevant lymph nodes is adequate or whether a complete dissection of all visible lymph nodes is needed.

Ludwig et al. added fuel to the fire with a population-based Surveillance, Epidemiology and End Results (SEER) study from 1990 to 2000 based on 16,800 patients with stage 1 NSCLC treated with surgical resection with curative intent which suggested that patient survival was associated with the number of lymph nodes evaluated pathologically for disease (48). Specifically, those patients with 13-16 lymph nodes examined by a pathologist had the best survival as compared to those with only 1-4 lymph nodes harvested (HR 0.78; 95% CI, 0.68-0.90). Surgical procurement of more than 16 lymph nodes did not seem to confer additional benefit. The authors concluded that this was most likely due to “a reduction-of-staging error”, in other words, that as more lymph nodes are sampled, there is a decreased tendency of a pathologist to miss any positive lymph nodes present.

Others have validated these findings for stage 1a lung cancers surgically resected in California, and in those states recorded in the SEER national registry (49,50). Additionally, complete mediastinal lymphadenectomy has been shown to be the most accurate mode of detecting multilevel N2 disease and skipped metastases (Pathologically positive N2 lymph nodes are present, but there is no evidence of histologically involvement of N1 lymph nodes) (51-55). Moreover, there has been concern that only 57% of patients undergoing major pulmonary resection for lung cancer have mediastinal lymph nodes harvested by their surgeon (56).

Darling et al. have largely settled this debate, at least for the
time being, in a large randomized cooperative group trial that showed no difference between the survival of patients whose lymph nodes were procured by either of the two techniques (57). Interestingly, in both the right and left sides of the chest, a median of 18 lymph nodes were harvested per patient (12 N2 nodes and 6 N1 nodes). Based on this study, the cooperative group recommended that a surgeon procure, in addition to the tumor specimen and any N1 lymph nodes associated with it, at least 12 mediastinal lymph nodes during a mediastinal lymphadenectomy from stations 2R, 4R, 7, 8, 9, and 10R in the right chest, and stations 4L, 5, 6, 7, 8, 9, and 10L in the left chest. Finally, as more minimally invasive video assisted thoracic surgery (VATS), (especially VATS lobectomies) are being performed, the cooperative group study suggests a note of caution in that VATS lobectomies in their study were associated with fewer lymph nodes harvested per patient with a median of 15 versus 18/19 lymph nodes from an open thoracotomy (57).

Sentinel lymph node staging

Due to the morbidity of mediastinal lymph node dissection, over the last two decades, there has been an interest in developing a less invasive, more regional mode of determining pathological mediastinal lymph node status by examining a few sentinel lymph nodes. Importantly, this technique has been successful in other solid tumors (58). Sentinel node mapping is very much reliant on lymphatic flow drainage patterns, and the level at which lymph nodes are first impacted by drainage from the primary tumor bed. Recently, a systemic review of the literature on the efficacy of sentinel lymph node staging found that in relation to the proximity from the primary tumor the more distal N2 lymph nodes rather than the closer N1 nodes were the first sites of lymphatic drainage in a wide range of patient distributions ranging from 5% to 95% (59). This exemplifies the difficulty in the sentinel lymph node technique as the current technology of radiotracers and/or dyes shows a large variability in lymphatic drainage among patients as clinically observed with the phenomenon of “skipped metastases”.

Conclusions

Despite the current inadequacies in assessing N2 nodal disease in lung cancer, recent improvements on multiple fronts are allowing better prognostic and predictive information for treating patients. Studies aimed at reclassifying the anatomy, incorporating molecular determinants, improving the technology for imaging and of procuring the nodes, and finally advancing the pathologically assessment of N2 nodes will continue to push the envelope of science forward. Collectively, these multidisciplinary, cooperative efforts will enable patients to be treated more effectively, and hopefully lead to fewer deaths from this terrible disease.

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