

# Evaluation of lymph node metastasis in lung cancer: who is the chief justice?

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**Abstract:** Accurate determination of the diagnosis and the stage of lung cancer play a critical role to ensure that patients are provided the optimal treatment. However, the process is usually beyond complex. Early studies have suggested lymph nodes (LNs) >1.0 cm in size on computed tomography (CT) are considered as metastatic nodes, while the sensitivity of this criterion is not satisfied. Subsequently, positron emission tomography-computed tomography (PET-CT) was shown to be superior to CT alone on assessment of nodal involvement and was widely used to estimate suitability for resection with curative intent, but the dependability also remains controversial. Furthermore, transbronchial needle aspiration (TBNA) with and without endobronchial ultrasound (EBUS), as a well-accepted minimally invasive approach for LN biopsy, has been documented as an efficient tool in evaluation of CT and PET-CT negative LNs. Additionally, radiographic features including ground-glass/solid nodules ratio, referring as imaging biomarker, were indicated to be correlated with metastasis. Hence, we highlight the importance of comprehensive estimation of mediastinal and hilar LNs, and we suggested the judgment of LNs by radiographic tools alone might not be reliable and TBNA is indispensable in certain circumstances.

**Keywords:** Lymph node (LN) metastasis; lung cancer; computed tomography (CT); positron emission tomography-computed tomography (PET-CT); transbronchial needle aspiration (TBNA)

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## Introduction

Lung cancer is the leading cause of cancer related morbidity and mortality among men and women worldwide. Although a good number of progress has been achieved in lung cancer management, including diagnostic approaches, biomarkers and treatments, lung cancer is still hard to be diagnosed until advanced stages, leading to a 17% 5-year overall survival rate according to the latest cancer statistics (1). But even worse, the enormous burden constituted by lung cancer has shifted to less developed countries, which are

currently responsible for about 58% of cases and 61% of lung cancer deaths (2).

The prognosis of lung cancer is directly related to its stage at the time of diagnosis. Even within stage, metastatic spread of cancer to distant organs is the cause for most cancer deaths, which is estimated via N and M descriptor in TNM staging system. However, up to 75% of patients with lung cancer present with symptoms due to locally advanced or metastatic disease, who are not amenable to cure (3). Hence, early detection and accurate staging is no doubt significant and closely related to

disease outcome. Mediastinal and hilar lymph node (LN) involvement determines N, which could be assessed by noninvasive approaches, such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) scan, and by invasive meanings, including mediastinoscopy, transbronchial needle aspiration (TBNA) and trans-esophageal fine needle aspiration (TENA). Traditionally, the size of targeted LN is the major implication for metastasis involvement and LNs smaller than 1.0 cm short-axis diameter are considered as normal. This conclusion is based on the assumption that malignant nodes will be larger than benign. However, the sensitivity of CT scan on these normal LNs is only 57%, indicating the malignant nature of non-enlarged nodes (4). Meanwhile, emerging studies on normal LNs in concert interpreted relatively high malignant frequency (5-10), suggesting differentiation of malignant mediastinal nodes from benign by size alone is not reliable. Here, we will discuss the relations of LN size with the prevalence of metastatic involvement.

### How to define “normal” LN?

Over the years, many studies concerning LN metastasis have been performed in which LN size was used as a determinant criterion for the prediction of LN involvement. Among diverse non-invasive technologies used for determining resectability and for assessing intra- and extra-thoracic spread of lung cancer, CT, although the dependability remains controversial (11), is the most commonly employed. Compelling studies demonstrated CT was recommended in the preoperative staging of lung cancer (12-14). One initial study evaluated the mediastinum preoperatively in 49 patients with non-small cell lung cancer (NSCLC), who had a thorough surgical pathologic determination of mediastinal node status. The authors stated that the optimal size criterion for diagnosing malignant mediastinal adenopathy was 1.0-1.5 cm in short axis and negative CT could make mediastinoscopy unnecessary (15). Subsequent evident from Glazer and colleagues confirmed the threshold of 1.0 cm as the upper limit of normal LNs (16). Besides, they pointed out that the short-axis of LN was superior to long-axis when used as the criteria, since long-axis was often affected by spatial orientation of the nodes, the variation was apparent.

It has been decades since the threshold of normal LNs was proposed, 1.0 cm is still being used as the cut-off point nowadays. However, data from up-coming findings provided

further information about the size of normal LN with the major concern on the false-positive value when the diameter was set as 1.0 cm. In light of American Thoracic Society (ATS) LN map, a Japanese group devised a more specific standard for maximum normal short-axis in each region: 12 mm for nodes in region 7; 10 mm for nodes in regions 4 and 10R; and 8 mm for nodes in other regions (17). More recently, autopsy data derived from 62 samples who did not die from chest malignancies, extra-thoracic malignancies or any kind of infections exhibited the definition of normal LNs at the stations 4R and 7 may be extended to 1.5 cm and 2.0 cm, respectively (18). It has to be mentioned that no size threshold will prove totally reliable, since microscopic metastases can occur in normal-sized nodes and enlarged nodes may be tumor free.

### Enlarged LN and lung cancer metastasis

The N descriptor, which specifies the presence and location of nodal metastatic disease, presented a significant influence on therapeutic decisions. In this regard, identification of the metastatic LN is extremely critical. Early studies used to applying CT for nodal staging, which relies on a threshold of greater than 1.0 cm as discussed above. By this means, LNs larger than 1.0 cm were called enlarged LNs. However, the results of these studies are very disparate with the pooled sensitivities of 57%, specificity of 82%, positive predictive value (PPV) of 56%, whereas negative predictive value (NPV) of 83% (4). Interestingly, the malignant frequency of LNs was not increased with elevated LN size. In contrast, the probability of metastasis in LNs measuring 10 to 15 mm on CT was 29%, which was two-fold higher than the larger ones (19).

PET imaging has been proven to be superior than CT alone in distinguishing benign from malignant lung lesions, as well as mediastinal LNs (20), especially for the differentiation of N0 or N1 from N2 disease in patients with NSCLC (21). Meanwhile, PET showed identical efficacy in evaluation of small (<1 cm) and larger LN lesions (22). Actually, 18F-fludeoxyglucose-positron emission tomography/computed tomography (FDG PET-CT) imaging has been taken advantage of detecting mediastinal LNs involvement in patients with lung cancer. Evidence from several groups in concert revealed that PET-CT was insufficient to replace mediastinoscopy for mediastinal staging in patients with lung cancer (21,23), while the debate remains open (24). Hence, two meta-analyses were carried out to evaluate the test performance of FDG PET-CT

for nodal staging in NSCLC and the most recent studies were included (25,26). In the mediastinal LN-based data analysis, the pooled sensitivity was 68% with the specificity around 90%. Integrated PET-CT presented a high specificity, but low sensitivity for detecting LN metastasis in patients with NSCLC. Concomitantly, a Germany group compared the diagnostic accuracy of low dose non-enhanced CT and standard dose contrast-enhanced CT in combination of PET and they elucidated that contrast enhanced PET-CT protocols were indispensable owing to their superiority in precise staging (27). Noteworthy, extended cervical mediastinoscopy was shown to be an effective technique used in the determination of aorta-pulmonary artery window (equivalent to region 4, 5 & 6) LN metastasis and PET-CT does not reduce the need for the invasive procedures at this region (28). The role of other radiographic techniques, such as MRI, PET-MRI, was sporadically investigated and less recommended. Until recently, the initial experience on PET-MRI using a three-segment model attenuation correction algorithm appears to be competitive of PET-CT, while the dependability requires further investigations (29).

Besides above formulated non-invasive approaches, TBNA, a remarkably invaluable and minimally invasive procedure, is wildly used for the assessment of intrathoracic LNs and the lesions adjacent to the tracheobronchial tree (30). Conventional TBNA (cTBNA) was firstly described in the 1980s by Dr. Ko-Pen Wang. Later on, during over 3 decades' clinical application, cTBNA has contributed significantly to the success of definitive diagnoses and staging of lung cancer, which requires low cost, ease of performance and training, while the diagnostic yield is extremely varied, spanning a wide range of 39% to 86% (31). On the other hand, recent emerging endobronchial ultrasound (EBUS) TBNA has revolutionized the estimation and management of both benign and malignant diseases with higher diagnostic yield compared to cTBNA (32,33). A retrospective analysis by Dhooria and colleagues illustrated a significant correlation between CT and EBUS for measuring the LNs size, but the limits of agreement were fairly wide (34). Interestingly, it has been reported that the diagnostic yield of EBUS-TBNA was higher than that of PET when postoperative LN recurrence is suspected (35). In addition, TENA is another candidate for mediastinal staging of lung cancer. Merging evidence of comparing EBUS TBNA and TENA failed to show comparative conclusions (36,37). Indeed, EBUS-TBNA and TENA are complementary methods owing to different accessibility to the mediastinum. A wealth of data

has been accumulated to support the notion that combination of TENA in conjunction with TBNA could provide better diagnostic accuracy than either one alone and totally replace the use of mediastinoscopy as well as avoid unnecessary thoracotomies (38-42). Although the combined procedure has been recommended in the latest guideline in Europe (43), it is noteworthy that only a small increase in sensitivity within these trials has not resulted from identification of malignant disease from stations 8 and 9 (accessible by TENA, rather than EBUS-TBNA), but from sampling of stations accessible by both techniques (44). Taking patient's compliance and cost into consideration, TENA should only be carried out when the LN stations are difficult or not available by TBNA (45). Nevertheless, no matter TBNA or TENA, both the largest and the second largest node at each station should be sampled, especially in adenocarcinoma (46).

### Is non-enlarged LN really safe?

Intrathoracic nodal status is a major determinant of treatment offered to patients with lung cancer. It has been well-documented that enlarged LNs were correlated with a higher incidence of metastasis and supposed to be examined with caution, while these radiographic non-enlarged ones are usually acquiesced in normal without evaluation. In this case, the accurate staging, to a certain extent, is more dependent on the accuracy of the assumption. To date, an arsenal of different complementary tests is being utilized to rule out the lymphatic micrometastasis. Early evidence showed 64% patients with N2 LNs were misdiagnosed by CT due to the non-enlarged size (5). Data from an independent group also raised the concern on these "normal" LNs and they demonstrated 14 out of 19 patients with non-enlarged LNs were missed by CT scan (8). Furthermore, a study analyzed 2,891 LNs from 256 patients and found that among 127 patients with metastasis involvements, 12% had metastatic LNs in normal size (7). Collectively, these data suggest that metastases in normal sized nodes seen on the CT scan would be a major problem in staging.

PET-CT, with the non-invasive nature, is primarily used in triaging patients by identifying patients with no spread to the mediastinum, who may thus be candidates for resection. Moreover, PET-CT exhibited identical competency for detecting malignancy in small LNs compared to larger ones (22). However, the role of PET-CT in the accurate staging pathway of lung cancer is still debated. A false negative rate that is consistently above 20% would cause

clinicians to question the utility of the test, especially in a given circumstance of normal size mediastinal nodes. In regards, a Cochrane review just released very recently examined the efficiency of PET-CT in distinguishing N0 and N1 from N2 and N3 disease (47). The data revealed the sensitivity and specificity of FDG PET-CT imaging ranged from 0.77 to 0.81 and 0.79 to 0.90, respectively, and was related to the brand of scanner, NSCLC subtype, FDG dose, and country of study origin. The authors concluded the sensitivities and specificities derived from recruited studies were unlikely to warrant reliance on FDG PET-CT scanning alone to make therapeutic decision for patients with potentially resectable NSCLC.

In light of the high false negative rate of PET-CT on normal size LNs detection, we have to figure out the means to improve the sensitivity and specificity of PET-CT. The most definitive test is surgical staging with systematic nodal dissection. However, the excessive invasion of surgical procedure dramatically restricts the utility in clinical practice in patients who are potentially suitable for resection with curative intent. TBNA is an alternative with way lower invasion in LNs biopsy. A prospective study aimed to probe the efficiency of EBUS-TBNA and mediastinoscopy, and the data indicated two approaches achieved similar results for the mediastinal staging, suggesting EBUS-TBNA might replace mediastinoscopy in patients with potentially resectable NSCLC (48). Notably, Yasufuku and colleagues evaluated the yield of EBUS-TBNA for mediastinal staging of NSCLC in patients with N0 or N1 stage assessed by CT or PET-CT. In N0 patients, EBUS upstaged in 7 out of 94 (7.4%), N1 in 1, N2 in 6). In 69 N1 patients, EBUS downstaged 47 LNs (28.8%), and upstaged 3 LNs (1.8%) (49), suggesting EBUS-TBNA was accurate and feasible for preoperative mediastinal nodal staging. Similarly, Shingyoji *et al.* reported the overall rate evaluated by EBUS-TBNA of N2 disease was 17.7% (20 of 113) on radiographic negative patients with lung cancer (50). These findings are consistent with the previous findings by Herth and Kuo supporting the concept that radiologically normal mediastinum does not mean healthy LNs and cancer presents the skipping metastases nature (51-53).

Our group tried to determine the role of cTBNA in the diagnosis of non-enlarged and PET negative mediastinal and hilar LNs. Some unpublished preliminary data showed the successful biopsy rate on non-enlarged LNs with cTBNA reached 75%, and relatively high diagnostic yield mainly relied on the full understanding of LN anatomy by the utilization of IASLC's and Wang's nodal maps to (54),

indicating even cTBNA without EBUS is still a potent tool for staging "normal" LNs. The micro metastasizes were detected in 25% patients with NSCLC and in 13.8% with small cell lung cancer, confirming the potential risk of metastasis in radiographic negative LNs. To well-describe the staging, some researchers proposed the standardized TBNA protocol, which requires first evaluating the N3 level nodal stations, followed by those of the N2 level, and finally the N1 level. Each nodal station should be considered for possible needle aspiration, regardless of PET avidity. However, the systematic survey of mediastinal and hilar LNs is obviously profoundly invasive, time-consuming and costly. Logically, it is reasonable to look for the hints via non-invasive methods to select the subgroup of patients who really need the systemic evaluation with priority.

Evidence has been accumulated to result in an evolution in our understanding: many of lung adenocarcinoma and related lesions appear as ground-glass opacities (GGOs) on chest high-resolution computed tomography (HRCT) (55). Matsuguma and colleagues analyzed the chest CT features from 90 tumors and elucidated that GGO area no smaller than 50% was correlated with high (87%) incidence of lung cancer (56), while others set this predicting value of GGO proportion at 60% (57). Also, lymphatic and vascular invasions, nodal involvement and recurrences were found only in patients with a smaller proportion of GGO (<50%) (56). Additionally, excessive GGO size (>3 cm), elevated serum carcino embryonic antigen (CEA) (>5 ng/mL) or presence of retraction sign was suggested to be predictors of node metastasis-positive and prognosis (58,59). Hence, systematic LN dissection or TBNA biopsy should be carried out on the patients with pure solid tumors or part-solid in GGO (>50%), especially on the one with increased serum CEA or symptoms at presentation.

## Summary

Conventionally, the enlarged LNs on CT were suspected as metastasis. With the development and popularization of PET in the recent decade, the lesions with greater maximum standardized uptake values (SUVmax) were considered as malignancy. However, the sensitivity is still far from optional. On the other hand, CT or PET/CT negative LNs, which were traditionally thought to be normal, have been shown to present a high false-negative value indeed. Notably, TBNA with and without EBUS both exhibited satisfactory efficiency in estimation of these non-enlarged mediastinal and hilar LNs. In lung cancer patients with the



radiographic features including lower GGO proportion over part-solid nodule, excessive GGO size, elevated serum CEA and presence of retraction sign, requires systematic TBNA evaluation or LN dissection in regardless of PET avidity. In the future, technological advances may lead to rapid changes in clinical practice to avoid overestimation of the enlarged LNs or underestimation of the non-enlarged ones. The association of LNs and lung cancer has been an old story, but never ends.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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