

International association for the study of lung cancer map, Wang lymph node map and rapid on-site evaluation in transbronchial needle aspiration

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Abstract: The invaluable role of transbronchial needle aspiration (TBNA) in the diagnosis and staging of mediastinal adenopathy and lung cancer has been well established. Different lymph nodes regional nomenclatures and maps had been described over the years. The international association for the study of lung cancer (IASLC) and Wang's maps complement each other benefiting patients with lung cancer. In this article we briefly reviewed the roles of IALSC, Wang's maps and ROSE in TBNA.

Keywords: Lung lymph node map; rapid-on site evaluation; transbronchial needle aspiration (TBNA)

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The transbronchial needle aspiration (TBNA) technique was first described by Eduardo Schieppati in 1949 (1), and optimized for flexible bronchoscopy by Dr. Ko-Pen Wang in 1978 (2). It was principally used for the diagnoses of mediastinal adenopathy and the staging of lung cancer. This technique has been underutilized primarily due to concerns of complications and unpredictable sensitivity, but became more popular after the first puncture site lymph node map published in 1994 (3). Today, a great deal of experience and knowledge about TBNA has been acquired and the role of TBNA in the diagnosis and staging of mediastinal lymphadenopathy (ML) and lung cancer has been well established (3-9). The advantages of safety, low cost, and being minimally invasive make conventional TBNA an impressive tool used widely around the world (4-8). Conventional transbronchial needle aspiration (c-TBNA) yield benefits from utilization of the Wang map and rapid on-site evaluation (ROSE). The international association for the study of lung cancer (IASLC) map is a well-known

pulmonary regional lymph node map that was updated in 2009 (10) and rapidly adopted by the 7th TNM staging system of lung cancer and is considered the standard nomenclature. What's the difference between IASLC map or Wang map and TBNA? And what's the interrelationship between the two maps system? Another often utilized technique during TBNA is ROSE. While previous work by Sindhwani *et al.* indicated ROSE could increase the diagnostic yield of TBNA (11), reduce the number of needle passes (12,13), and ease of utilization (14), some other studies showed different results (12,15). What, then, is the appropriate evaluation for ROSE in TBNA? Therefore, the aim of this paper is to review the role of IASLC map, WANG's map, and ROSE in conventional TBNA (c-TBNA) and to illustrate their complementary value in clinical practice.

IASLC map and WANG lymph node map in TBNA

The IASLC map was conceived to differentiate different

groups of pulmonary regional lymph nodes and thereby facilitate staging of nodal metastases in lung cancer. The latest version provides clear nomenclature and a specific anatomic definition for each station (10,16). In this version, 14 stations including seven zones were illustrated and the lower border definition of 4R/4L or subcarinal lymph node and the demarcation between 4R/4L, as well as, 2R/2L are updated. Consequently, a quite different description of N status in TNM was provided. The intrathoracic lymph nodes in IASLC are defined as follows: N1, there is involvement of the ipsilateral peribronchial and hilar lymph nodes; N2, there is involvement of the ipsilateral mediastinal and/or subcarinal lymph nodes; and N3, there is extension of tumor to the contralateral hilar or mediastinal lymph nodes.

Before talking about the relationship of the IASLC map with TBNA, it is important to mention the relationship of the Wang map with TBNA (3). In Wang's map, pulmonary regional lymph nodes are categorized into 11 stations and 3 groups defined as the middle mediastinal lymph node group (stations 2, 8, 10), left lymph node group (stations 4, 6, 11), and right lymph node group (stations 1, 3, 5, 7, 9) (3,8). In fact, the IASLC map and Wang map are not mutually exclusive for lung cancer diagnosis and staging by TBNA, but rather, have strong interrelations (17).

The Wang endobronchial guide, then, acts as a roadmap tool during c-TBNA. c-TBNA has been adopted as one of the basic biopsy techniques for intrathoracic lymph node sampling greatly influencing lung cancer staging. With the development of modern technology, new bronchoscopic modalities were introduced including endobronchial ultrasound (EBUS). Despite the visualization beyond the airways provided by EBUS, the Wang map is complimentary by finding the appropriate puncture site quickly and aids the bronchoscopist in initial positioning of the EBUS scope according to the endobronchial map.

Several studies suggested the efficiency and adequacy of TBNA when using Wang's map (18-20). Wang *et al.* studied 84 patients with lymphadenopathy who underwent TBNA guided by the Wang lymph node map. About 11 (36.7%) out of 30 lymph nodes of ≤ 0.5 cm and 38 (64.4%) of 59 lymph nodes from 0.6–1 cm in short-axis diameter were obtained and correctly diagnosed. c-TBNA guided by the Wang map has quite a good ability to obtain lymphoid tissue from lymph nodes normal by radiologic criteria, but with very early small mediastinal metastasis. Herth *et al.* (21) also carried out a study to determine the accuracy of EBUS-TBNA in sampling nodes ≤ 1 cm with CT scans of non-

small cell lung carcinoma (NSCLC) patients in diameter. The sensitivity of EBUS-TBNA for detecting malignancy was 92.3%, specificity was 100%, and the negative predictive value was 96.3%. Therefore, as to the very small mediastinal lymph nodes EBUS-TBNA, might have some advantage compared with c-TBNA. The recently published guideline endorsing EBUS-TBNA as the preferred first step in mediastinal staging of lung cancer (grade 1C) is based on the published literature (22). In our opinion it is important to follow the guideline in clinical practice and not deny the role of EBUS-TBNA, which could act as a complimentary technique to c-TBNA. c-TBNA, therefore, has an excellent efficiency and adequacy when using Wang's map in the hand of trained practitioner, and it is not necessary for each bronchoscopy center to obtain EBUS equipment especially in those developing areas with limited resources.

The development of targeted therapy for lung cancer often requires material for the genetic mutations testing. A recent study suggests molecular analysis (i.e., EGFR, KRAS and ALK) can be routinely performed on the majority of cytological samples obtained by c-TBNA. Optimal specimen preparation may vary between institutions depending on the expertise of pathology colleagues which affects the TBNA yield (23).

A recent retrospective study reviewed the accuracy of c-TBNA in the subtyping of lesions located in or around central airways by comparing the histological diagnosis based on TBNA and surgical specimens (24). All c-TBNA was guided by the Wang map. The result suggests c-TBNA with the Wang map is a safe and effective procedure for diagnosing lung cancer. However, the accuracy of TBNA for the histological classification of lung cancer is relatively low, especially for adenocarcinoma.

ROSE in TBNA

ROSE has been used to support c-TBNA for many years and now is widely used, but what's the role of ROSE for c-TBNA or EBUS-TBNA? Does it improve the yield of TBNA? The short answer is that different studies show variable results (12,25-28).

c-TBNA is often compared with EBUS-TBNA with the operator's skill and knowledge of mediastinal anatomy greatly affecting the diagnostic yield of TBNA (3,5,29-32). Sometimes we don't have enough evidence to end TBNA sampling during our procedure without on-site evaluation by cytology. Thus, ROSE has the ability to aid the clinician with immediate feedback that can assist in

guiding the c-TBNA biopsy procedure. Then it is also easy to understand the power of ROSE in the determination of whether we have obtained satisfactory samples from c-TBNA or not. If ROSE yield suggests the prior sample is inadequate, a repeat procedure should be performed. However, the criteria for the adequacy of the sample are not very clear (33).

Another important question is regarding the c-TBNA yield. Some studies suggest ROSE improves the yield of c-TBNA and is helpful in determining specimen adequacy for pathological diagnosis (19,21,22,27,34,35). However, some of the results from randomized trials suggest that ROSE does not increase diagnostic yield. An important result of these studies shows that ROSE possibly prevents additional biopsies (12,28,36). Yarmus *et al.* (12) described that previous reports of increased diagnostic yield with ROSE utilization was likely a selection bias and recommended that ROSE should be used in selected patients.

EBUS-TBNA is a minimally invasive modality for mediastinal lymph node staging in lung cancer patients, as well as, for the diagnosis of mediastinal and hilar lymphadenopathy. In many centers ROSE is used routinely for all EBUS cases, however, the role of ROSE during EBUS-TBNA is still controversial. Compared with c-TBNA, EBUS allows real time visualization of lesions/lymphadenopathy. Is it necessary to use ROSE together with ultrasound to determine whether we have reached the goal for TBNA? A study exploring the utility of ROSE for EBUS-TBNA was reviewed in 294 specimens representing material from 149 patients (37). Their data demonstrate no remarkable difference in diagnostic yield, the number of sites sampled per patient, or clinical decision making between specimens collected via EBUS-TBNA with or without ROSE. Therefore they questioned the value of ROSE for the evaluation of EBUS-TBNA specimens. Another guideline (23) based on a literature review point out ROSE does not increase the yield of EBUS-TBNA or c-TBNA. Similar results have been reported in the other studies (26,38,39). Recently Mallya *et al.* (40) evaluated the utility of ROSE in EBUS-TBNA for the diagnosis of ML. They found ROSE facilitates sample adequacy, aids in rapid clinical decision-making, and equals the gold standard for diagnosis of ML. They thought this approach has an excellent potential in assisting safe and accurate diagnostic interventional bronchoscope.

The diagnosis of more than 70% of patients with lung carcinoma and 10% to 30% of non-small cell lung

carcinoma, not otherwise specified (NSCLC-NOS) in clinical practice largely depend on small biopsies (41,42). Some researchers are evaluating the value of ROSE on the differential diagnosis of lung cancer subtype. Recently, Celik *et al.* (43) investigated 106 cases of NSCLC-NOS. Cytologic, histologic, and immunohistochemistry (IHC) concordance for these diagnosis occurred in 75 cases (70.8%) with discordance in 31 cases (29.2%). Of these 31 cases, 6 cases were classified as NSCLC-NOS histologically and cytologically, 3 were classified as NSCLC-NOS and correctly classified histologically, 2 were classified correctly histologically and cytologically. In the other 15 cases, cytology labeled 1 case NSCLC-NOS, 1 was correctly classified, and 13 misclassified. They conclude that ROSE has a high diagnostic yield for subclassification of NSCLC-NOS and recommend allocating a cytotechnologist for specimen adequacy and a cytopathologist for cytologic diagnosis.

Few researches utilize the nodal diameter in stratifying selection of cases for ROSE or not. A recent study discussed the utility of ROSE in the detection of granulomas in mediastinal lymph nodes (44). They found the overall concordance between ROSE and the final diagnosis obtained by EBUS-TBNA was not impacted by lymph node size and did not improve as the lymph node size increased. However, it is significantly related to the experience of the operator.

What's the impact of ROSE in TBNA on patients and medical care resources? A study by Collins *et al.* (45) examined EBUS fine-needle aspiration (FNA) biopsy procedures with and without ROSE, and investigated the impact of ROSE service on laboratory resource utilization. They found ROSE did not affect the diagnostic accuracy but significantly reduced the number of biopsy sites (33%) and slide preparation (30%) with ROSE. They conclude EBUS FNA biopsy with ROSE service benefits patients by contributing to significantly fewer biopsies and improved patient care and laboratory resource utilization. This result was followed by a comment from da Cunha Santos (46) who thought financial cost should be greatly considered in evaluating the procedure outcome. Griffin *et al.* (37) challenged the notion that ROSE is beneficial for immediately impacting patient care. Their results didn't demonstrate ROSE could save the patients and the health care system resources, additional sampling, or a repeat procedure and that additional health-care dollars spent for on-site services do not result in added clinical benefit. Still more research is needed to investigate what are the financial effects on the patients and the healthcare resources.

The shortage of the specialized cytology experts or resources and reimbursement issues results in the difficulty in the availability of ROSE. Tele-cytopathology and clinicians substituting for a cytopathologist is one of the better alternative options (47-50).

Conclusions

TBNA's invaluable role in the diagnosis and staging of mediastinal adenopathy and lung cancer has been well established with the Wang endobronchial map being a valuable tool to guide the procedure. Its efficacy and accuracy has already been tested and has confirmed its' use to facilitate determination of site selection during TBNA. The IASLC map and Wang's map complement each other benefiting lung cancer staging. ROSE for TBNA is like a frozen section as it does not increase the diagnostic yield. The issue of the benefit ratio and the indication for ROSE application in TBNA should be seriously reviewed. Routine use of ROSE in TBNA is probably not necessary and likely increases procedural cost.

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Footnote

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