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Review Article

Utilization of rapid on-site evaluation (ROSE) in transbronchial needle aspiration (TBNA), it is not a simple statistical issue

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Abstract: Transbronchial needle aspiration (TBNA) is widely accepted as a relatively minimally invasive, highly accurate and reliable procedure for a variety of malignant, infectious or granulomatous mediastinal and lung lesions. Rapid on-site evaluation (ROSE) guided TBNA is primarily used for staging pulmonary malignant lesions and for the diagnosis of unexplained mediastinal lymphadenopathy. The overall success rate of TBNA depends on quite a few factors, including size and the anatomic location of lymph nodes, number of biopsy sites and complications rate, characteristics of the lesion, skill of the aspirator, needle type used, underlying disease, prevalence of the disease being ascertained and the use of ancillary imaging techniques, etc. Specifically, the application of ROSE by cytopathologists may avoid additional sampling without compromising diagnostic yield with a preliminary evaluation for adequate diagnostic material and thus reduce the complication rate of TBNA procedure. In this review article we aimed at elaborate the technical details, clinical roles, cost performance, patient preference, and technological progress of ROSE in TBNA, highlighting the importance of ROSE with TBNA to gain the optimal sensitivity in obtaining histological diagnosis. We finally pointed out that it will be a tendency for a pulmonologist, to undergo a short yet intensive training, and perform ROSE guided TBNA with a high agreement with histopathological results, which may increase patient preference finally.

Keywords: Transbronchial needle aspiration (TBNA), rapid on-site evaluation (ROSE), cytopathology, histopathology, endobronchial ultrasound (EBUS), staging of lung cancer

TBNA profile today

Transbronchial needle aspiration (TBNA) via flexible bronchoscopy (FB) is a sampling technique that involves passing a catheter containing a needle through the tracheal or bronchial wall into lymph nodes or masses to obtain samples for pathologic assessment [1]. TBNA is widely accepted as a relatively minimally invasive, highly accurate and reliable alternative to mediastinoscopy for a variety of malignant, infectious or granulomatous lung and node lesions, which is a complex multistep process [1]. TBNA can establish a diagnosis and permit cancer staging in a single procedure [2], can be superior to almost all the other sampling modalities in peribronchial and submucosal lesions, which has been shown to decrease the need for diagnostic thoracic surgery in lots of cases [3]. Even for endobronchial lesions, TBNA may attain an average diagnostic yield on par with bronchoscopic forcep biopsy [4]. However, TBNA is still underutilized [5], which can be ascribed to lack of formal training, difficulties with needle handling, safety and insufficient success rates. In the process of TBNA's historical development, there are conventional transbronchial needle aspiration (C-TBNA) and endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) coming to the force. EBUS-TBNA, through simultaneous convex probe endobronchial ultrasound and optical imaging of surrounding vessels and nodal size and nature, has the ability to perform real-time

TBNA under direct visualization of the needle. And it has been known as a revolution in the field of pulmonology and gradually accepted by pulmonologist as a safe and efficient technique for mediastinal and hilar lymphadenopathy sampling and staging [6, 7]. C-TBNA refers to TBNA without EBUS, which is also deemed as a blind technique for its dependence on extremely thorough understanding of anatomy. The diagnostic yield of TBNA varies widely in reported series, ranging from 20 to 90% [8-11]. Endobronchial ultrasound (EBUS) [12] and fluoroscopy with computed tomography (CT) [13] for needle guidance have shown potential to increase the yield of TBNA, but their impact has been limited. Besides the use of rapid on-site evaluation (ROSE) by cytopathologists, the overall success rate of TBNA depends on a variety of factors, such as size and the anatomic location of lymph nodes, number of biopsy sites and complications rate, characteristics of the lesion (size and texture), skill of the aspirator, needle type used, underlying disease, prevalence of the disease being ascertained (lung cancer, metastases from other neoplasms, sarcoidosis, tuberculosis, etc.) and the use of ancillary imaging techniques [14, 15]. Besides a study comparing EBUS-guided TBNA with conventional TBNA for mediastinal adenopathy interestingly showed an equally high yield with both methods [16], EBUS is still costly, requires more considerable technical skill than conventional TBNA, and is unlikely to become popular outside specialized centers in the near future.

What is ROSE?

Experienced bronchoscopists harvest TBNA samples in a quick succession by repetitively aspirating multiple targeting sites, as requires a really "rapid" ROSE procedure keeping up with the pace of continuous sampling. ROSE staining methods should therefore find a compromise between speed, ease of preparation and staining quality [21]. Cytologic fast stains commonly used in clinical conventional ROSE are modified versions of standard laboratory-based staining methods, such as Wright-Giemsa, Papanicolaou and Diff-Quik. Wright-Giemsa-based rapid stains are water-based and provide mainly cytoplasmic definition on air-dried slides, when alcohol-based modified Papanicolaou stains on alcohol-fixed slides can provide superior demonstration of nuclear features [17].

Diff Quik (DQ), which is superior for demonstrating lymphocytes, is an alcoholic, quick staining method for cytology. This kind of fast staining is the most common ROSE method utilized in TBNA suite recently. Generally speaking, the cytologic specimens obtained with TBNA are processed with the smear technique for ROSE, when liquid-based preparations or cell blocks are prepared simultaneously for permanent out-site slides, histologic examination or for other post-TBNA procedures, such as immunohistochemistry or immunocytochemistry, molecular analysis, mutation analysis, flow cytometry etc, which is especially of great help to delineate differentiated tumors. In detail, once the needle is removed, the material is collected and smeared on clean glass slides. For each pair of slides smeared, one is air-dried and the other was fixed in 95% ethanol solution. Permanent slides are routinely stained with the May-Grunwald Giemsa and Papanicolaou methods. Special stains and/or immunocytochemistry are performed as appropriate.

Sampling is a process with uncertain outcomes, and categorization of ROSE results is performed on-site as adequate, inadequate, or positive. The presence of material consistent with the architecture of lymph nodes or the presence of a preponderance of lymphocytes defines the adequacy of the specimen. Thus, the cytopathologist present in the bronchoscopy theatre can declare and feed back to the pulmonologist that diagnostic material has been harvested in sufficient quantity and quality for a preliminary diagnosis and for all later laboratory requirements, which helps the pulmonologist decide to waive further sampling taking the anatomical and clinical situation into account. Inadequate samples contain a preponderance of bronchial cells, a minority or no lymphocytes, and no findings specific to a diagnosis, when positive means an on-site diagnosis decision can be made through ROSE or a specific finding can be found and the wide differential diagnosis of targeted lesions can be considerably narrowed.

ROSE of cytologic material obtained with TBNA is generally used to assist the bronchoscopists in the diagnosis of lesions that are not directly visible through the eyepiece or the monitor connected to bronchoscopy camera, such as those lesions located in the hilar and mediastinal regions or in the pulmonary parenchyma [18]

regardless of the subject of controversy [19]. And after recently International Association for the Study of Lung Cancer, American Thoracic Society and the European Respiratory Society has provided a standardized classification for lung cancer diagnosis considering small biopsies and cytology, ROSE is especially of great importance [20] and emerges as an important adjunct for cytological diagnosis.

A formal off-site review involving routine and ancillary staining methods, e.g. for microorganisms and immunocytochemistry is obligatory to confirm provisional ROSE results. ROSE is particularly useful when an infectious disease is suspected since ROSE will obtain the cell components, which may suggest or even sometimes identify the presence of infectious agents on the basis of cytological features. Meanwhile, morphological diagnosis from direct smears and special stains on ROSE slides allows the detection of specific microorganisms, such as fungi, parasites, mycobacteria and viruses.

Roles of the ROSE in TBNA

Providing an ideal cellularity adequacy

Cellularity adequacy of the acquired sample is the most important component of TBNA performance and is the key quality of service. ROSE of transbronchial aspirates by a cytopathologist present in the bronchoscopy theatre reduces the incidence of inadequate specimens [22].

ROSE, a simple and cost-effective technique, has proven advantageous in reducing the sampling error and thus increasing the sample adequacy pre-analytically in the cytological diagnosis [23]. It may also yield preliminary diagnosis especially in distinguishing between nonneoplastic and neoplastic, if not the precise categorization, for samples from submucosal, exophytic and peripheral lung lesions, which are known to have a good yield with TBNA [24]. There are several plausible reasons why ROSE can improve the yield of TBNA. One reason is that negative or uncertain findings on ROSE can be addressed immediately with repeated aspirations of the same site with a slightly modified technique, which leads to a variable number of aspirates and is indisputably better than sampling an arbitrary number of aspirates of uncertain quality [25]. Another often overlooked but important reason is that without ROSE the often minute TBNA samples will not handled and processed in the best possible way. Furthermore, there will form a virtuous cycle that the availability of ROSE leads to a more frequent use of TBNA and hence practical expertise, which in return is likely to improve the performance of both the bronchoscopists and cytopathologists [26]. In addition to without loss in diagnostic yield, another important benefit of the use of ROSE is associated with a significant reduction of the complication rate of bronchoscopy. Patients with multiple targets available for biopsy (e.g., lung nodule and lymphadenopathy), in fact, are more likely to terminate bronchoscopy after the initial hilar/mediastinal TBNA, therefore avoiding the sampling of concomitant lung parenchymal lesion. And ROSE reduces the risk of major complications several-fold in particular transbronchial lung biopsy.

However, there are still controversial about the yield of TBNA with ROSE. The key problem of the observational trials is the extremely high risk of selection bias. In fact, none such studies set a priori parameter for the allocation of the patients in the ROSE or no-ROSE arms, a practice which makes it impossible to rule out those more complex cases affected by confounding factors allocated to the ROSE arm or vice versa (a larger proportion of patients with non-neoplastic diseases in which the yield of TBNA is lower). Furthermore, the study population of some trials often include patients undergoing bronchoscopy for lymphadenopathy alone, peripheral lung lesions alone, or both, which is extremely heterogeneous [27-30]. In the meantime, important limitations are observed during ROSE [31]. For example, aggregates of plump spindle cells or columnar cells are often misinterpreted as epithelioid cells or inversely occasional sparse granulomas comprising of few epithelioid cells are sometimes missed thus limiting the accuracy of cytology for diagnosis of granulomatous inflammation.

Generally speaking, increasing the number of needle passes or puncturing more target lesion sites are directly associated with an increased diagnostic yield and therefore greater diagnostic accuracy with regard to TBNA, but continuous increasing the number of needle passes arbitrarily may show diminishing returns. Only small improvements in effectiveness are ob-

tained if the number of aspirations is increased to more than four. Meanwhile, the benefits of an adequate sample must be balanced with the risk of adverse events accompanied with the increasing number of needle passes [32]. ROSE in TBNA performance provides the bronchoscopist with real-time guidance by addressing negative or uncertain findings, modifying in real-time the sampling plan or technique basing on the results of on-site review, and allows for termination of sampling when the diagnostic objective has been met [33, 34]. Continuous ROSE-feedback allows for prompt sampling of the diagnostic portion of the lesion [35] and this feedback-guided strategy of ROSE may lead to a variable number of needle passes and is indisputably better than sampling continuously with uncertain quality. It allows avoiding additional sampling from the same or multiple lesion sites without loss in diagnostic yield so as to reduce the complication rate of the procedure [36].

There are now several studies in the literature (albeit mainly retrospective or observational) that have compared EBUS-TBNA with ROSE or without ROSE in both lung cancer and granulomatous disease (see **Table 1**). Nakajima et al. [37] demonstrates that there is a low rate of non-diagnostic sampling of ROSE during EBUS-TBNA for material adequacy and a high agreement between the on-site and final pathologic evaluation in nodal staging of lung cancer patients. They argues that ROSE is an important part of the EBUS-TBNA procedure for tissue diagnosis and staging of lung cancer. Griffin et al. [38] suggest that there is no remarkable difference with respect to the acquisition of robust samples between specimens collected via EBUS-TBNA with or without ROSE, especially in the setting of suspected sarcoidosis, where the on-site evaluation of diagnostic specimens in cell block material is unlikely to result in a preliminary diagnosis of granulomatous inflammation as virtually. They explain that the employment of ultrasound during EBUS-TBNA procedures results in accurate and better sampling of the targeted lesion, and the overall acquisition of diagnostic specimens partly is attributed to the high skill of their experienced EBUS operators and may not be applicable to other institutions. Conversely, Yasushi Murakami et al. [39] have reported that ROSE dose not have any impact on diagnostic yield of EBUS-TBNA for SCLC, but the use of ROSE is associated with fewer lesions or aspirates per-procedure. In another study [40], they found that ROSE is not associated shorter bronchoscopy times, though there is lower number of examined lesions or aspirates without loss in diagnostic yield.

As the saying states “While waiting to buy a Ferrari, do not leave your current car in the garage!”, it is reasonable to encourage the utility of cTBNA when appropriate. Considering large size and location of lymph nodes (LNs) are crucial predictive factors of a successful aspirate [41], cTBNA should be the first and high yield diagnostic step in the case of large LNs (>1.5) in favourable locations (#4R and/or #7). The use of ROSE may be another one predictive factor. Otherwise, since the first use of ROSE, there is controversial about the potential impact of ROSE on TBNA diagnostic yield in several previous reports (see **Table 2**). Andreas et al. [42] performed an observational, yet small trial of ROSE for diagnosis of lesions accessible for conventional TBNA on computed tomography. ROSE was shown to limit the need for further specimen collection, with a reduction in the need for forceps biopsy. They showed that ROSE is a highly useful, accurate time-effective and cost-effective addition to routine diagnostic bronchoscopy. Diette et al. [43] published a prospective study involving 204 cases with TBNA, in which a total of 81 of 204 cases (40%) used ROSE. The investigators show that the diagnostic yield is higher in ROSE group than that in the no-ROSE group and point out that the study is limited by the nature of observational trial and uncontrollability of the use of ROSE. Baram et al. [44] demonstrated that, for the first time, ROSE failed to increase the diagnostic yield or the specimen’s adequacy, yet allowed to avoid additional sampling without losing diagnostic yield. And the results prompted a critical re-evaluation of the clinical research with respect to ROSE, and led to the identification of several problems limiting the reliability of the previous results, including the extremely high risk of selection bias and the extremely heterogeneity of study population in these trials.

Avoiding risk of major complications and encouraging utilization of TBNA

During bronchoscopy, there are often multiple biopsy targets and multiple sampling modali-

Table 1. Studies of EBUS-TBNA with ROSE in lung cancer

Study	Type	Number	Inclusion criteria	Outcome	Conclusion
Nakajima et al. 2013 [5]	Retrospective	438	Suspected or diagnosed lung cancer, EBUS-TBNA	No false-positive results on ROSE; (5.7%) were falsely evaluated as negative on ROSE; The concordance rate for staging between ROSE and final pathologic diagnosis was 94.3%.	ROSE is an important part of the EBUS-TBNA procedure for tissue diagnosis and staging of lung cancer.
Griffin et al. 2011 [8]	Unknown	294	All EBUS-TBNA cases,	Favoured EBUS-TBNA with ROSE (Diagnostic specimens 94% vs. 90% for EBUS-TBNA without ROSE, cell block obtained 92% vs. 88% for EBUS-TBNA without ROSE).	No remarkable difference in diagnostic yield, the number of sampling sites, or clinical decision making between EBUS-TBNA with or without ROSE.
Murakami et al. 2014 [3]	Retrospenctive	780	EBUS-TBNA	Favoured EBUS-TBNA with ROSE (diagnostic yield 99% vs. 90% without ROSE, P=0.1, lesions (mean 1.1 vs. 1.6 without ROSE, P<0.01) or aspirates (mean 2.3 vs. 4.0 without ROSE, P<0.01).	ROSE dose not have any impact on diagnostic yield of EBUS-TBNA for SCLC, but is associated with fewer lesions or aspirates.
Oki et al. 2013 [6]	Randomized trail	120	Suspected of having lung cancer, EBUS-TBNA	Mean puncture number (2.2 vs. 3.1 punctures for non-ROSE, P<0.01), mean bronchoscopy time (22.3 vs. 22.1 min, P=0.95), sensitivity and accuracy (88 and 89% vs. 86 and 89%).	ROSE during EBUS-TBNA is associated with a significantly lower need for additional bronchoscopic procedures and puncture number.

EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; ROSE, rapid on-site evaluation.

Table 2. Comparative studies or cTBNA with ROSE vs. cTBNA without ROSE in lung cancer

Study	Type	Number	Inclusion criteria	Outcome	conclusion
Diacon et al. 2005 [2]	Retrospective	90	Patients with lesions accessible for TBNA on CT	Sensitivity and specificity of ROSE with positive TBNA (both 96.7%), Negative and positive predictive values (93.5 and 98.3%), a reduction for forceps biopsy from 65 to 18% with ROSE, savings of 24.8 Rand by ROSE.	ROSE increases the value of TBNA as a diagnostic modality.
Diette et al. 2000 [4]	Observational	204	TBNA for lung nodules or masses or mediastinal lymphadenopathy	Favoured TBNA with ROSE (diagnostic yield 81% vs. 50% for no-ROSE), higher dose of narcotic, shorter procedure time.	Increasing the use of on-site cytopathology assessment may improve the quality of TBNA services.
Baram et al. 2005 [2]	Retrospective	44	Bronchoscopies with TBNA	Fewer biopsies with ROSE; Diagnostic yield, TBNA sensitivity and accuracy, and procedural time were similar between these two groups.	ROSE during TBNA allows for deferring additional biopsy without loss in diagnostic yield, likely lowers procedural risk, and is cost-effective.

cTBNA, conventional transbronchial needle aspiration; ROSE, rapid on-site evaluation.

ties available. Obtaining samples from multiple targets with multiple sampling modalities increases the diagnostic yield of bronchoscopy, which, meanwhile, adds to the cost, length, and risk of bronchoscopy [45]. For a patient with multiple targets available for biopsy, such as endobronchial lesions, parenchymal lesions/consolidations, peripheral lung nodule, and hilar/mediastinal lymphadenopathy, with the help of ROSE, most bronchoscopy procedures can be terminated after the initial hilar/mediastinal TBNA, therefore avoiding the sampling of concomitant available lesions. This aspect related to the use of ROSE is very important during bronchoscopy procedure, as forceps biopsy, and in particular transbronchial lung biopsy, raises the risk of major complications [46]. In study series, transbronchial biopsy raises the risk of major complication 10-fold to 22-fold. Pneumothorax rates vary from 1 to 4% and depend on the use of fluoroscopy, the need for mechanical ventilation, and immunocompromised status. Significant hemorrhage occurs in approximately 1% of patients undergoing transbronchial biopsy [47]. TBNA is relatively safe, with only case-reportable complications, such as pneumomediastinum, pneumothorax, purulent pericarditis, and hemomediastinum [48].

Furthermore, during clinical practice, ROSE can encourage the utilization of TBNA not only for cancer staging but also for aspiration in submucosal, exophytic and peripheral lesions, which may expand the application field of TBNA [49].

Selecting appropriate additional post-TBNA sampling modalities and appropriate post-TBNA processing mode of specimens

When TBNA is certainly not a new modality, parallel developments in advanced imaging techniques, molecular testing, and targeted therapies have coincided with a rapid increase in the number of TBNA performance. With ROSE, the cytologist in the bronchoscopy theatre can declare if diagnostic material has been harvested in sufficient quantity and quality for a provisional diagnosis, or if additional post-TBNA sampling modalities should be selected and if later laboratory demands can be met after TBNA procedure. A proper specimen preservation of procured tissue for appropriate ancillary testing should be also based on the informal preliminary diagnoses.

Coming into an immediately provisional diagnosis is important in the bronchoscopy suite. Consequently, the pulmonologist can choose whether or not to waive further sampling with additional post-TBNA sampling modalities taking the anatomical and clinical situation into account. Given an acceptable accuracy, ROSE may simplify and abbreviate bronchoscopic sampling.

Of course, the concordance of TBNA and forceps biopsies is the best outcome. There is no a single sampling method that is always better than others. It is widely accepted that combining multiple sampling methods (bronchial washing, brushing and endobronchial biopsy) with TBNA together will increase the yield of bronchoscopy examination. Meanwhile, ROSE may make the often minute TBNA samples to be handled and processed in the best suitable way, which is an often overlooked but important factor of TBNA [49]. Furthermore, the wide differential diagnosis can be considerably narrowed by ROSE, which will provide real-time guidance as to whether sampling can be terminated (when bronchogenic carcinoma cells are harvested) or should continue for confirmation of lymphoma (additional TBNA for flow cytometry, large bore TBNA for histology), sarcoidosis-type granulomatous inflammation (transbronchial and mucosal biopsies, bronchoalveolar lavage) or granulomatous inflammation with necrosis as seen in tuberculosis (specimens for mycobacterial culture), in detail as the following:

1. When carcinoma cells are harvested enough, the wide differential diagnosis of targeted lesions can be considerably narrowed or an on-site diagnosis decision can be made. For further management in lung cancer, the accurate distinction of small cell lung cancer (SCLC) from non-small cell lung cancer (NSCLC), in which ROSE can be competent well, is of utmost importance. After on-site diagnosis and immediate classification of NSCLC from SCLC (see **Figure 1**), sampling procedure can be terminated or more TBNA are needed for proper type of immunohistochemistry or immunocytochemistry. In clinical management, a full mutation analysis (EGFR, K-ras or ALK) that allows to single out the therapeutic target of the new drugs currently available and of those being presently developed is needed for NSCLC. Under these circumstances, ROSE can be an efficient quality control method because suffi-

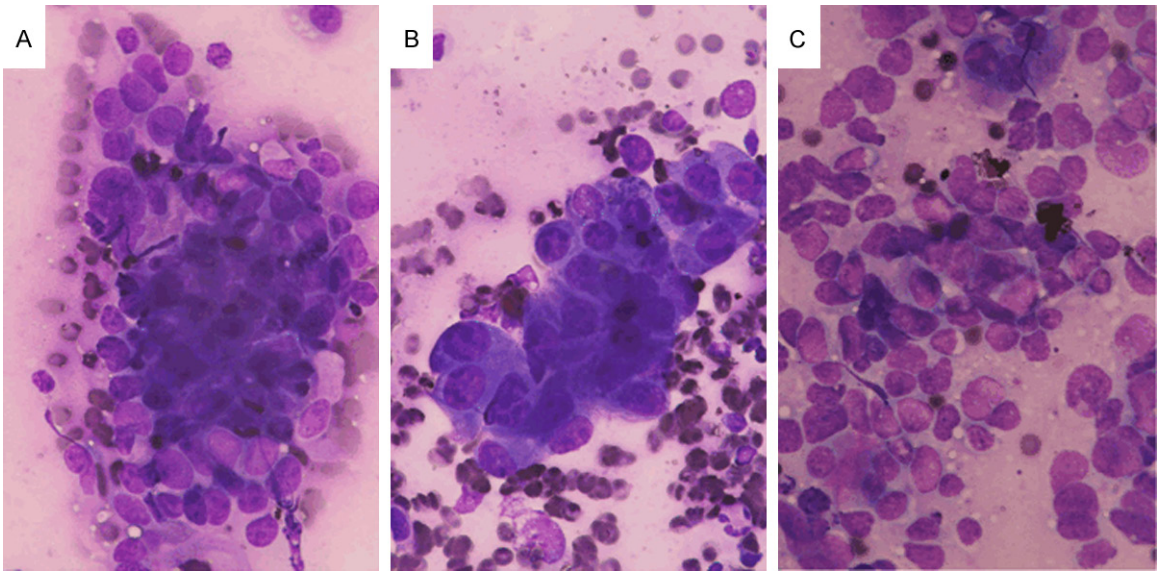

Figure 1. Cytology specimens on ROSE obtained via transbronchial needle aspiration (TBNA) stained with Diff Quik staining (A: Squamous cell carcinoma, ×1000; B: Adenocarcinoma, ×1000; C: Small cell lung cancer (SCLC), ×1000).

cient cellularity is very important for both pathologic diagnosis and full mutation analysis with the "first bronchoscopy". If not, the diagnostic procedure would be just a preliminary diagnostic, and a repeat bronchoscopy would still be required to get more specimens for establishing molecular diagnosis and typing in this era of individual oncological therapy.

2. ROSE could help to establish in real time the correct site for obtaining diagnostic material, allowing the bronchoscopist to return to that specific site during the same examination to try to harvest the amount of tissue sufficient for the determination of the biomarkers necessary for accurate treatment planning [50]. In staging of suspected bronchogenic carcinoma, stepwise TBNA of nodal stations is performed from the highest-rated potentially involved regions down to the primary tumor. The positive aspiration results of N2 or N3 lymph nodes may terminate further TBNA exploration with the associated adverse complications and increasing cost [51, 52].

3. When the diagnosis of lymphoma can be confirmed, special type of immunohistochemistry or immunocytochemistry may be performed, additional TBNA may be needed for flow cytometry, and large bore of TBNA may be requested for histology.

4. When aggregates of epithelioid histiocytes consistent with noncaseating granulomatous inflammation is found and a clinical and radiological assessment, especially that based on highresolution computed tomography is suspected of sarcoidosis, transbronchial mucosal or parenchymal forceps biopsy may be recommended, and in most cases, bronchoalveolar lavage should be done. Conventional TBNA is reported to allow to diagnose stage I (hilar adenopathies only) or II (hilar lymph nodes and parenchymal infiltrations) sarcoidosis (**Figure 2**) during initial bronchoscopic assessment as transbronchial lung biopsy (TBLB) being not used as a standard mediastinal node sampling technique with the high risk of pneumothorax and hemoptysis, although the method relies on "blind" needle puncture guided only by computed tomography and is highly operatordependent [53]. And EBUS-TBNA seems to show higher yield and sensitivity in the diagnosis of sarcodosis than conventional TBNA, by which mediastinal and hilar lymph nodes can be aspirated under realtime ultrasound control from either the esophagus or large airways [54].

5. When aggregates of epithelioid histiocytes consistent with granulomatous inflammation with necrosis is found and tuberculosis is suspected, bronchoalveolar washing and transbronchial mucosal/parenchymal brushing should be done for acid-fast staining, and these specimens should also be treated for mycobacterial culture. Transbronchial mucosal or parenchymal forceps biopsy may be needed in most

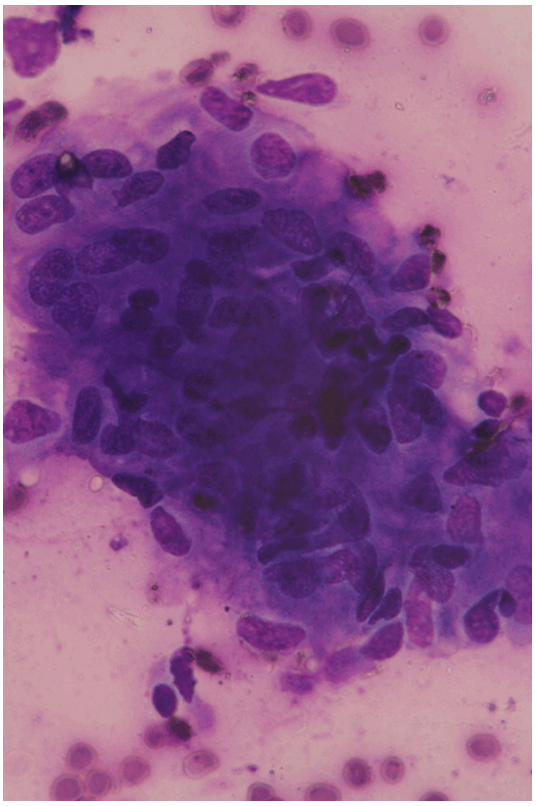

Figure 2. Papillaroid fragment of sarcoidosis on rapid on site evaluation on (ROSE) obtained via TBNA (Diff Quik, ×1000).

cases for histologic confirmation of tuberculosis. Tuberculosis was confirmed with either a positive stain for acid-fast bacilli or a positive culture of Mycobacterium tuberculosis on a respiratory specimen. Multiple previous reports have confirmed that EBUS-TBNA is capable of diagnosing mediastinal mycobacterial infection whose samples are mycobacterial culture positive or supportive histological changes [55-57] though few have examined diagnostic accuracy, particularly the ability to obtain microbiologic confirmation of TB infection. Geake et al. [58] conclude that when culture and histological results are combined with high clinical suspicion, EBUS-TBNA demonstrates excellent diagnostic accuracy (98%) and negative predictive value (98%) for the diagnosis of mediastinal TB lymphadenitis. And they suggest EBUS-TBNA should be considered the procedure of choice for patients in whom TB is suspected.

Fail to diagnose- a heavy price

The cost of a non-diagnostic procedure is inestimable. At least a repeated bronchoscopy with or without TBNA should be counted in, which, in most cases, may be avoided through quality control circles for cellularity adequacy provided by ROSE. In addition to being less invasive, a successful TBNA is also more cost-effective compared with its invasive surgical alternatives.

However, it is not only a trivial expense involved a failed TBNA or even a failed first bronchoscopy. Obtaining a diagnosis in the first bronchoscopy can reduce future risks, costs, morbidity, mortality and anxiety of patients, as well as avoid the zigzag and roundabout ways to final diagnosis and appropriate treatments [59].

Potential risk of combined ROSE

The major risk of ROSE is prematurely ending a TBNA procedure before diagnostic tissue, not merely cytologic specimen, is obtained. Data suggested that, with proper planning and experience, this kind of risk was quite low [62].

Other relevant matters

Cost

ROSE leads to shorter procedure duration, fewer biopsy tools used, fewer cytology and histology specimens prepared and submitted, less paperwork and saved administrative cost. On the other hand, the cytopathologist on average spends more time per patient with ROSE than for a standard laboratory-based analysis, but the reduced hardware and salary costs compensate for the time and cost of the on-site cytopathology service. Furthermore, Bonifazi et al. [60] demonstrated that training pulmonologists to have a basic knowledge of cytopathology could obviate most difficulties related to the involvement of cytopathologists in routine diagnostic activities and may reduce the costs of the procedure. They also showed a pulmonologist, after a short yet intensive training period, can perform ROSE of conventional TBNA from lymphadenopathy with an 81% inter-observer agreement with the pathologist taken as gold standard [61].

In addition, we believe that the cost of ROSE is generally overestimated. The superior access to clinical and radiological information in theatre is an advantage that may compensate the cytopathologist for the inconvenience of displacement. Certainly, most analysis about the

cost of ROSE in TBNA is arbitrary and not universally generalizable and factors such as hospital geography, local healthy care system and available expertise must be accounted for elsewhere.

Patient preference

Combined with ROSE, the TBNA procedure is extremely safe with only case-reportable complications, and it increases patient comfort for shortened procedure time especially in cases with multiple targets available for biopsy, when a positive ROSE result may spare the patient a transbronchial lung biopsy or other biopsy modalities [62]. Safety, high efficiency, comfort, saved expenses and saved time and energy, all these, are the synonym of patient preference.

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Disclosure of conflict of interest

None.

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