Review Article

Detailed procedure and clinical application overview of rapid on-site evaluation in diagnostic interventional pulmonology

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Diagnostic interventional pulmonology is widely accepted as a minimally invasive, highly accurate procedure for diagnosing lung cancer, more drug-resistant pathogen infections of lower respiratory tract, and critical respiratory diseases. The efficiency of interventional diagnostics 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, and underlying disease. Specifically, the application of rapid on-site evaluation (ROSE) may avoid additional sampling without compromising diagnostic yield with a preliminary evaluation for adequate diagnostic material and thus reduce the complication rate. In this review article we aimed at elaborate the technical details, clinical roles, and technological progress of ROSE in diagnostic interventional pulmonology, highlighting the importance of ROSE in diagnostic interventional pulmonology. We finally pointed out that it will be a tendency for a pulmonologist, to undergo a short yet intensive training and perform ROSE in diagnostic interventional pulmonology.

Key words: Diagnose, interventional pulmonology, rapid on-site evaluation, sampling

How to cite this article: Li C, Xie W, Cao J, Feng J. Detailed procedure and clinical application overview of rapid on-site evaluation in diagnostic interventional pulmonology. J Res Med Sci 2020;25:35.

INTRODUCTION

In recent years, the use of diagnostic interventional pulmonology has been booming due to the increased prevalence of lung cancer, more drug-resistant pathogen infections of lower respiratory tract, and urgent request for diagnosis of baffling and critical respiratory diseases. The efficiency of interventional diagnostics depends on quite a few factors including size and the anatomic location of lymph nodes, number of biopsy sites and complications rate, underlying disease, which promote the clinical application of numerous advanced technologies and facilities. As a "real-time accompany technique" for diagnostic interventional pulmonology, rapid on-site evaluation (ROSE) has also been paid an unprecedented attention and develops promptly.[1,2]

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_21_18

DEFINITION AND WORK CONTENT OF DIAGNOSTIC INTERVENTIONAL PULMONOLOGY RAPID ON-SITE EVALUATION

The diagnostic interventional pulmonology ROSE is a real-time cytological examination technique which accompanies sequential sampling.[1] The process of ROSE is as follows: A small part of every tissue specimen sampled from target lesion is smeared on a slide without losing tissue material significantly. Then the cytological slide is stained as soon as possible. Finally, the stained slide is interpreted immediately under specialized microscope integrating with all the available clinical information. The cytological content to be interpreted includes: cellular morphology, differential cell counts, constituent ratio, cellular array, mutual relation, cytological background, and analysis of exotic substance.

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Submitted: 18-Mar-2018; **Revised:** 27-Nov-2019; **Accepted:** 07-Jan-2020; **Published:** 13-Apr-2020

As a carrier of cells, ROSE slide plays the following roles: evaluation of adequate sampling, real-time guidance for interventional methods and modalities, approaching a preliminary diagnosis or narrowing differential diagnosis spectrum, optimizing processing scheme for target lesion specimen, analyzing patients' disease status and prognosis in combination with all available clinical and cytological information. It is still controversial about whether ROSE can increase the rate of successful diagnosis in diagnostic interventional pulmonology.

HISTORIC EVOLUTION AND PROSPECT FORECAST FOR CLINICAL PRACTICE OF DIAGNOSTIC INTERVENTIONAL PULMONOLOGY RAPID ON-SITE EVALUATION

"Modern" ROSE was first applied in interventional pulmonology in 1981[1] and went through the process of interventional operation with flexible bronchoscopy for transbronchial aspirates[2] and "minimally invasive internal medicine" techniques including transbronchial needle aspiration (TBNA), began to spread widely. These techniques were not only applied to the diagnosis of lung/mediastinal malignancies, but also benign diseases such as sarcoidosis, tuberculosis etc., If operators are satisfied with the specimen got through these procedures, it is not necessary to perform more invasive surgeries such as mediastinoscopy, video-assisted thoracoscopic surgery, and open lung biopsy.

Meanwhile, interventional pulmonologists have to answer questions regarding: Whether the target specimen is obtained and sufficient? How to deal with target specimen appropriately? Can a preliminary diagnosis be achieved or a wide differential diagnosis spectrum be narrowed? Can patients' disease status and prognosis be analyzed comprehensively in combination with all available clinical and cytological information?

Obviously, this "real-time feedback" ROSE information is invaluable.

During interventional procedures, if target specimen is satisfactory, the procedure stops where it should stop, which can not only save time and medical resources but also reduce pain, trauma, and complications. On the contrary, the procedure should be continued and interventional methods and modalities may have to be changed appropriately.

If a preliminary diagnosis is made, differential diagnosis spectrum is narrowed, or disease status is integrated, an important reference may be provided for clinicians to establish a thorough diagnostic protocol and treatment regimen. And it can also help to select processing scheme for target lesion specimen including oncological examinations such as immunohistochemistry, polymerase chain reaction (PCR), chromosome fluorescence *in situ* hybridization (FISH), electron microscopy, and microbiological examinations such as special staining, grinded tissue culture, etc.

And it can also assist in the selection of further means of procedures. In a case for which ROSE in TBNA has provided a relatively definite diagnosis of malignant tumor and obtained satisfactory specimens for follow-up oncology-related examination, the transbronchial lung biopsy (TBLB) with higher risks of complications is then not necessary.[3] The entire interventional diagnostic operation is thus considered optimized. Therefore, ROSE has been widely accepted and utilized during this period[4] and is matured in about 2010.[5,6]

Since 2010, high-tech equipment represented by virtual bronchoscopy, ultrathin bronchoscopy, endobronchial ultrasound (EBUS), electromagnetic navigation (EMN) bronchoscopy etc., was widely used in interventional pulmonary diagnosis and treatment.[7,8] Due to the high cost of such technical equipment, relatively complicated manipulating process, and expensive consumable items, an extremely high success rate of intervention diagnosis is required; with the addition of the urgent needs of microbial etiology in critical respiratory disease, ROSE has almost become a "standard configuration" in interventional lung disease diagnosis and treatment center.

In 1997, the birth of clone sheep shocked the world, and it showed that single somatic cell could contain almost all the life information. Recently, rapid development and extensive application of molecular diagnostics has brought cytological technology to rejuvenate. At present, the ability to diagnose of cytology is almost comparable to that of histology[9] and is distinctly advantageous in many aspects.[10,11] ROSE glass slide, as a cell carrier, can not only be used to make cytological interpretation, but also can be a "treasure trove" for preserving and studying cells. All cell-based molecular biology and gene technology can be carried out using the ROSE glass slides, including PCR, FISH, immunocytochemistry, second-generation gene sequencing, etc.[11,12] The development of biotechnology is at a tremendous pace; especially the progress of molecular biology and genetic technology is beyond imagination. In this scenario, the future of ROSE is anticipated.

BASIC WORKING CONDITIONS AND EQUIPMENT REQUIREMENTS OF DIAGNOSTIC INTERVENTIONAL PULMONOLOGY RAPID ON-SITE EVALUATION

Rapid on-site evaluation cytological microscope

The main equipment of ROSE is a dedicated cytological microscope, and the ocular lens are usually × 10 (10 times),

while the wide-field objective lens are × 10 (10 times) and × 40 (40 times). "Oil-free" ×100 objective lens (100 times) are recommended, which is not only necessary for observing characteristics of microorganisms but also an easy access to get high-quality graphic information.

Graphic imaging, photographic system

It should be equipped with high-resolution graphic imaging and photographic system for report making, data summary, case review, academic exchange and clinical education etc., A high-resolution camera with autofocus function is recommended to integrate on a microscope as its graphic system.

Rapid on-site evaluation for infectious diseases

In principle, the preparing of infection-related ROSE slides should be carried out in Class II biosafety cabinet. The slides and staining liquor should be specially treated after interpretation. After all, the operators must get biosafety-related training and have the required qualifications.

Location requirements

ROSE must be positioned at the procedure room, providing primary cytological interpretation and exchanging real-time impression. The advanced interventional pulmonary center may be equipped with a professional ROSE room, which should connect to the procedure site or can show microscope graphic information directly to operators in real time through electronic systems.

Preparation for rapid on-site evaluation

Sterile cytological slides with cell adhesion, absorbent paper, powder-free latex gloves, disposable 2.5 ml/5 ml syringe needles should be prepared before procedure and a full set of Diff Quik (DQ) staining liquor can be poured into sealed glass dying cylinders for convenience.

Conservation of stained slides

Stained slides and dyeing liquor for infectious diseases should be treated after use following Class II biosafety protocols.

It is recommended to place stained cytological slides in a cool and dry place directly for long-term preservation and not to use neutral gum for slide sealing to avoid missing cytological information.

THE DETAILED WORK PROCESS FOR RAPID ON-SITE EVALUATION

ROSE is to proceed with the three steps of preparing, staining and interpreting continuously.

As ROSE needs to "guide interventional pulmonary procedures" real-time, in clinical practice, preparing, staining and interpreting of ROSE slides should be accomplished in succession promptly.

The preparation of cytological slides for rapid on-site evaluation

Imprinting (rolling)

It is the most commonly used method, suitable for TBLB, conventional TBNA with tissue incising needles (such as Wang's MW-319 needle), mucosa biopsy under direct bronchoscopic vision, medical thoracoscopy biopsy under direct scopic vision, and percutaneous tissue incising needle lung biopsy.

After target site sampled, the tissue pellets are picked up with a disposable 2.5 ml/5 ml syringe needle from biopsy forceps cup or percutaneous tissue incising needle groove, or are pushed out from tissue incising needle (such as Wang's MW-319 needle). Then the specimens are smeared roundly on the one-third dyeing side of cytological slide, which should have a strong cell adhesion, with a diameter of about 1 cm and a proper thickness without losing materials for histopathological exam as its premise.

After that, the tissue pellets are processed conventionally step by step including pathologic or microbiologic exams, and the target specimen flow direction is optimized according to the results of ROSE interpretation, thus adjusting further process means.

Brushing

It is applicable to specimens brushed with ordinary cell brush, pollution-saved cell brush or ultra-fine cell brush, as well as semi-liquid specimens including sputum, viscous body fluid etc. After target site is drawn, the brush tip is pushed out, and the specimens are smeared on the one-third dyeing side of cytological slide, which should have a strong cell adhesion, forming a rectangle of about 1 cm × 2 cm. Slides in other processes such as regular slides sent to pathology department and microbiology laboratory should be still prepared according to the conventional methods.

Spraying

It is applicable for fine needle aspiration and conventional TBNA with cytological needle such as SW-121, 122, 521, 522 type of Wang's needle and so on. After target site sampled, the needle tip is press against the one-third dyeing side of cytological slide, which should have a strong cell adhesion. As air pressurizing at needle tail, the specimens are smeared roundly with a diameter of about 1 cm and a proper thickness without losing materials for histopathological exam as its premise. Slides in other processes such as regular slides sent to pathology

department and microbiology laboratory should be still prepared according to conventional methods.

Leaving

It is appropriate to EBUS-induced TBNA, so called EBUS-TBNA. After target site sampled, the needle tip is press against the one-third dyeing side of cytological slide, which should have a strong cell adhesion, and the tissue paste is pushed out with the inner needle. After most of the tissue specimens are taken away with filter paper hold by pointed tweezers, the cytological material will be left on the slide to become a ROSE film. Then the tissue paste sent to pathology department and microbiology laboratory should be still prepared according to conventional methods. Or, ROSE cytological slides in EBUS-TBNA can also be prepared using the aforementioned "Spraying" method.

Rapid staining of rapid on-site evaluation cytological slides (staining)

World Health Organization recommends the use of DQ staining liquor to rapidly stain ROSE cytological slides. DQ staining has been modified from Romanowsky Stain technology, which has the similar interpreting results to Wright's staining. DQ staining liquor contains acid dye (eosin) and alkaline dye (methylene blue). DQ staining's rationale is the constituents to be dyed have different affinities to staining liquor and show different colors for identifying the morphological characteristics. It consumes very short time (only about 30 ~ 70 s) for cytological slides to be stained after the target site is sampled. Thus the interpreting process of ROSE forms a "real-time" feedback to interventional procedure because of time-saving preparing and staining.

It is recommended to use "dip" staining rather than "drop" staining to improve quality and efficiency. DQ A solution, DQ B solution, phosphate buffer (PBS) and water are poured respectively in glass vials with lids. Individual ROSE slide is dipped in DQ A solution for 10–30 s and transferred to PBS vial washing DQ A solution. Then the slide is soaked in DQ B solution for 20–40 s and washed in water tank. Finally, residual liquid is removed from slide with bibulous paper. Glass vials holding DQ A solution, DQ B solution, and PBS should be sealed after use because of these solutions are volatilizable.

To interpret rapid on-site evaluation cytological slides promptly and comprehensively

The stained ROSE slide should be delivered immediately to the assistant and interpreted real-timely with specialized cytological microscope. Cytological interpreting impression is indispensable part of the information needed for analyzing disease status comprehensively. In practice, ROSE interpretation should be based on all the available knowledge and clinical information, which should include: (1) multidisciplinary knowledge about respiratory diseases, interventional pulmonology, pathology, clinical microbiology, infectious diseases, oncology, and etc.; (2) detailed medical history and physical examination; (3) all the diagnosis and treatment process and development of the disease; (4) imaging manifestations, especially comparison of imaging data before and after treatment; (5) laboratory tests, comparison of laboratory data before and after treatment; (6) manifestations of endoscopic vision and physical properties of the specimens obtained during the interventional procedure; and (7) "Real-time" ROSE impression of the cytological interpretation after target site is confirmed and sampled precisely.

EFFECT ON DIAGNOSIS OF DISEASE/DISEASE STATUS AND INTERVENTIONAL PROCEDURES OF DIAGNOSTIC INTERVENTIONAL PULMONOLOGY RAPID ON-SITE EVALUATION

Rapid on-site evaluation is significative and putative in the diagnosis and differential diagnosis of lung disease/disease status as listed below

1. Most common types of solid malignancies and histological typing of tumor
2. Tuberculosis and its different development stages
3. Sarcoidosis
4. Mycoplasma pneumonia
5. Viral pneumonia
6. Some kinds of mycotic pneumonia (such as aspergillus, cryptococcus, or candida)
7. Organizing pneumonia or organizing status (i.e., organization) or fibrosis
8. Pyogenic infection
9. Necrotic infection or necrotic changes (necrosis)
10. Some kinds of allergic diseases or allergic changes
11. Some kinds of rheumatic diseases, immune diseases (such as certain types of vasculitis) or immune changes
12. Others, such as postchemotherapy immune reconstitution or related changes of lung transplantation.

Applying rapid on-site evaluation may benefit more to the following interventional procedures

1. Procedures applying "high-tech equipment" such as EMN and R-EBUS
2. Target lesions difficult to sample, such as lesions cannot directly viewed through endoscope, very small target lesions, or lesions difficult to access
3. Procedures with high risk of complications, to minimize the sampled material and stop where it should stop
4. Short of sampled material, may optimize the use of specimens with the help of ROSE preliminary impression
5. Diagnosis and treatment that should be completed at the

same time, such as EMN positioning thermal ablation for pulmonary peripheral nodules
6. Urgent target lesion assessment for critical respiratory diseases, require timely differential diagnosis and treatment plan
7. To narrow the spectrum of differential diagnosis or analyze patients' disease status and prognosis in combination with all available clinical and cytological information
8. "Exact diagnosis" or "immediate diagnosis" must be made in a single procedure or the obvious existence of psychological and objective pressure
9. Operation demo, academic exchange, technical training or clinical teaching.

CONSENSUS AND CONTROVERSY IN CLINICAL PRACTICE OF RAPID ON-SITE EVALUATION

Rapid on-site evaluation and histopathology/laboratory medicine are mutual complementation, rather than mutual repulsion

ROSE is a carrier of cytological information, and it is independent and interrelated among cytology, histopathology, and ecsomatics. ROSE will not compromise the status of histopathology or ecsomatics in clinical diagnosis. On the contrary, high quality specimens can be obtained and delivered to the department of pathology and laboratory with the help of ROSE. Thus the target specimen quality can be controlled and the use of specimens can be optimized, when it will provide focus of attention to the auxiliary departments without delay. Similarly, the evaluation of ROSE cytological significance should not depend absolutely on whether the histopathology/laboratory examination has "positive results" or not. Cytological interpretation of ROSE is based on its own analysis index. ROSE impressions should be considered as a key component of diagnosis basis and integrated with all the available clinical information. It is not appropriate to excessively limit the flow of specimens according to ROSE impressions unless ROSE diagnosis is definite or the specimen amount is insufficient and further sampling is impossible. It is recommended to add nonstandard specimen inspection process not designed originally, such as special pathogen staining on tissue sections, according to ROSE results, thereby increasing the diagnostic efficiency.

Obtaining target lesion is the basis of rapid on-site evaluation interpretation

The interpreting and comprehensive analyzing of ROSE should not be carried out until the specimen is obtained precisely from target lesions. Otherwise, the ROSE interpretation is worthless or even misleading clinical decision. If target lesion is not obtained, interventional modes and modalities should be modified to attempt repeatedly with the help of ROSE.

Rapid on-site evaluation is not exactly "observe the pathogenic microorganism itself"

In some kinds of mycotic pneumonia (such as aspergillus, cryptococcus, or candida), ROSE can interpret the pathogen directly according to microbial morphology. In case of other infectious diseases like tuberculosis, interpreting ROSE should be based more on cytological background integrated with available clinical information. ROSE is not only a "real-time" state analysis of illnesses but also an auxiliary beforehand anticipation for progression of disease.

It is still controversial whether rapid on-site evaluation can increase the yield rate of diagnostic interventional pulmonology

In the 1980s, emergence of ROSE was aimed at improving the yield rate of diagnostic interventional pulmonology.[1,2] As a carrier of cytological information, ROSE clinical value is continuously explored, and it is utilized further with the development of biotechnology. In recent years, there have been researches to question ROSE's "original intention" in improving diagnostic yield rate. The controversy is mainly reflected in TBNA for lymph nodes, regardless of conventional lymph node TBNA or EBUS-lymph node TBNA. In cases of conventional lymph node TBNA, some researchers argue that ROSE can improve the positive rate.[13,14] While others thought that it cannot.[5] Similar arguments have been put forward for EBUS-lymph node TBNA. Some argue ROSE's positive value,[15-17] especially for lymph node malignancy genotyping[18] or benign diseases,[19] when others deem there's no difference.[20-22] However, from the perspective of reducing complications and improving the "exact diagnosis" efficiency, using ROSE is not only recommended in conventional-lymph node TBNA,[5] but also suggested in EBUS-lymph node TBNA,[3] which was demonstrated by a large multi-center study. In other diagnostic interventional procedures in applications of "high-tech equipment" except of lymph node TBNA, such as pulmonary peripheral lesion TBNA,[23] positioning biopsy with peripheral lung radial EBUS (R-EBUS),[24,25] peripheral lung precise bronchoscopic brushings,[26] and positioning biopsy with peripheral pulmonary EMN,[27-29] ROSE is proven to increase the positive rate of diagnostic interventional procedures in majority of current studies. More prospective randomized controlled studies are warranted for further conclusions.

Who will interpret rapid on-site evaluation slides?

ROSE should be completed under the predominance of a clinical (interventional) physician, and so is a comprehensive evaluating process rather than just a histopathology/laboratory process. Staffs involved in ROSE interpretation

should be cytopathologists, cytopathological technicians, laboratorians and trained clinical/interventional physicians, nurses, common technicians, interns, etc.[30] If ROSE report is needed for medical records or charges, it can be issued by a qualified cytopathology physician or laboratorian.

CONCLUSION

The diagnostic interventional pulmonology ROSE is a real-time cytological examination technique which accompanies detailed sampling process including preparation, rapid staining and interpret of cytological slides. ROSE is significative and putative in the diagnosis and differential diagnosis of lung disease/disease status, including lung cancer, more drug-resistant pathogen and specifically infectious disease, noninfectious pulmonary disease and critical respiratory diseases. We finally pointed out that it will be a tendency for a pulmonologist, to undergo a short yet intensive training and perform ROSE in diagnostic interventional pulmonology.

Financial support and sponsorship

This study was funded by the National Natural Science Foundation of China (81270144, 30800507, 81170071 and 81400063).

Conflicts of interest

There are no conflicts of interest.

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