# Rapid on-site evaluation (ROSE) with EUS-FNA: The ROSE looks beautiful

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## INTRODUCTION

Since EUS-FNA was first reported in 1992, it has become the first-line technique for the acquisition of tissue from gastrointestinal and adjacent organs with high safety and reliability.[1,2] EUS-FNA is a multistep procedure that is affected by various uncertain factors,[3-8] including rapid on-site evaluation (ROSE), whose use has been under debate for many years.

The rationale for using ROSE of EUS-guided tissue acquisition is the real-time evaluation of sample adequacy and diagnostic yield. This technique was expected to decrease the period of diagnosis with fewer needle passes as well as achieve a real-time and accurate diagnosis of digestive diseases.[9] In addition, during the ROSE procedure, cytopathologists can determine whether additional sampling is required for further auxiliary diagnosis.[10-13]

## THE DEBATE LASTED 20 YEARS: RAPID ON-SITE EVALUATION OR NOT?

Early in this century, although experts advocated using ROSE to acquire adequate tissue samples, there are few data supporting this recommendation. Klapman *et al.*[14] compared EUS-guided tissue acquisition results from two medical centers and found that ROSE increased the diagnostic yield of EUS-FNA. In a single-center prospective study reported in 2005,[15] high accuracy in a series of EUS-FNA with ROSE was again demonstrated. Consequently, EUS centers were recommended to be equipped with ROSE.

Eloubeidi *et al.*[16] evaluated a series of EUS-FNA specimens sampled by one endoscopist in 2006. The ROSE outcomes were consistent with the final cytological evaluation (kappa score: 84.0%) in this prospective study.

In subsequent years, observational studies were repeated, and the diagnostic accuracy and tissue adequacy of EUS-FNA were demonstrated to improve significantly with the use of ROSE in gastrointestinal lesions. The greatest improvement was seen in solid pancreatic lesions. One meta-analysis[17] of 34 studies was designed to evaluate whether ROSE affects the diagnostic accuracy of EUS-FNA in solid pancreatic lesions. In that study, the meta-regression model showed that ROSE remained an independent determinant of EUS-FNA accuracy ($P$ = 0.001). Although the

Access this article online
Quick Response Code:
Website: www.eusjournal.com
DOI: 10.4103/eus.eus_65_19



**How to cite this article:** Yang F, Liu E, Sun S. Rapid on-site evaluation (ROSE) with EUS-FNA: The ROSE looks beautiful. Endosc Ultrasound 2019;8:283-7.

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**Received:** 2019-09-10; **Accepted:** 2019-09-22; **Published online:** 2019-10-01

sensitivity was relatively low in many studies which were short of ROSE, only 2 of 14 studies that did not use ROSE had a sensitivity of 95% or higher. The authors concluded that the accuracy of EUS-FNA would be higher with the availability of ROSE.[17]

Another meta-analysis reported in 2014 has also shown that ROSE increases the adequacy rate of EUS-FNA in solid pancreatic lesions by 3.5%.[18]

Less information is available on the adverse events in EUS-FNA associated with ROSE. In 2011, Iglesias-Garcia *et al*.[19] reported a study to evaluate the influence of ROSE on EUS-FNA in the differential diagnosis of solid pancreatic lesions in an unselected series of consecutive patients. The incidence of complications was significantly lower in the ROSE group, a result possibly associated with the lower number of passes required to obtain sufficient samples.[20-22]

If this were the end of the research journey, the method of ROSE would seem highly favorable. However, studies are increasingly showing the contrary.

The effects of EUS-FNA with ROSE have been estimated in two randomized controlled trials involving patients with solid lesions of the pancreas.[23,24] In the two studies, seven passes were performed in randomized patients without ROSE. Therefore, the number of needle passes was significantly smaller in ROSE group than seven. There was no significant difference in other outcomes, including diagnostic yield, sample quality, and adequacy between the two groups.[23] In contrast to findings from a previous study,[19] the lower number of needle passes in the ROSE group did not indicate a lower incidence of complications or a shorter procedural duration.[23] The use of ROSE did not decrease the expense of EUS-guided biopsy and has been suggested to increase it.[23-25]

In a multicentric randomized controlled study[26] evaluating whether ROSE might improve the diagnostic yield rate of EUS-FNA in lymph node lesions, ninety patients were divided into two groups: ROSE+ and ROSE−. The slides' review time was shorter, and postprocedural pain was found less in the ROSE+ group. There was no statistical difference in the procedural times, complication rates, and mean costs between the two groups ($P = 0.06$, $P = 0.99$, and $P = 0.91$, respectively). These findings indicated that the diagnostic yield of EUS-FNA in lymph node lesions had no relationship with the application of ROSE. These results do not support the recommendation to apply ROSE in EUS-FNA for lymph node lesions.

Hewitt *et al*.[27] performed a meta-analysis and found that the pooled sensitivity of EUS-FNA with and without ROSE was 88 (87%–90%) and 80 (78%–82%), respectively, thus suggesting an 8% improvement in the sensitivity of EUS-FNA with ROSE. However, there was no statistical difference in this improvement ($P = 0.077$).

Kong *et al*.[28] reported a systematic review including seven studies with 1299 patients. In that study, EUS-FNA with ROSE did not enhance the diagnostic yield or the diagnostic adequacy. There was no statistically significant difference in the number of needle passes between the ROSE and non-ROSE groups. The pooled sensitivity and specificity of the two groups were comparable.

The results of four meta-analyses,[17,18,27,28] most of which were studies of patients with pancreatic masses, were contradictory. Two of the meta-analyses concluded that there was an improvement in the specimen adequacy and diagnostic yield associated with ROSE.[17,18] However, the other two meta-analyses did not support these advantages.[27,28]

Given that the current evidence is not concordant, the European Society of Gastrointestinal Endoscopy panel recommends EUS-FNA with or without ROSE equally (moderate-quality evidence, strong recommendation).[25]

Therefore, evidence of whether ROSE might improve the results of EUS-FNA remains conflicting. In the debate on whether to use this method, the lack of on-site cytopathologists is always the key problem. According to a study on the practice patterns in EUS-FNA published in 2016, ROSE was available in 48% of European centers, 55% of Asian centers, and almost all centers (98%) from the USA.[29] The obstacles to expanding ROSE include limited cytopathologist staffing, cost-effective performance, longer procedural duration, and a lack of belief in its added value.[29]

Nevertheless, the diagnostic efficiency of EUS-FNA is dependent on the EUS techniques and experience of the endosonographers. Considering that not every

endoscopist works in a big center, ROSE seems to be a helpful tool for making up for the lack of EUS experience and technology in improving the diagnostic yield of EUS-FNA. ROSE, performed by a cytopathologist, provided a highly accurate diagnosis, which was highly consistent with the final results.[16] ROSE may improve the adequacy of FNA specimens by 10%–30%, reduce the number of passes, decrease the duration of diagnosis, and lessen adverse events such as abdominal pain.[30] After analyzing all studies, the clinical benefits of ROSE are obvious, and the ROSE should be applied, especially for the endosonographers, in the learning stage of EUS-FNA and for centers in which specimen adequacy rates are not high enough.[30]

## COULD ENDOSONOGRAPHERS LEARN TO PERFORM RAPID ON-SITE EVALUATION?

Cytopathologist staffing is not possible for all EUS centers, let alone all EUS-FNA procedures. Thus, it may be a possible solution to train endosonographers to evaluate the specimen themselves during the EUS-FNA procedure. Experienced endosonographers are thought to be able to assess the adequacy of the specimen obtained by EUS-FNA. Some researchers have begun to verify this possibility. However, a double-blind prospective controlled trial[31] indicated that even well-trained endosonographers were less accurate than a cytopathologist in evaluating the specimen adequacy ($P = 0.004$) and in the preliminary estimate of malignancy ($P < 0.001$).[31]

In a prospective double-blinded study on gross visual inspection during FNA between cytotechnologists and endoscopic technologists, neither cytotechnologists nor trained endoscopic technologists were able to evaluate the specimen adequacy accurately just by gross visual inspection of the slide.[32]

Hayashi *et al*.[33] retrospectively evaluated patients who underwent EUS-FNA for solid pancreatic lesions. Before the study, two endosonographers were trained for cytological interpretation, especially the four cytological features of pancreatic cancer, namely anisonucleosis, nuclear membrane irregularity, overlapping, and enlargement. The authors concluded that in this case, sample evaluation by trained endosonographers using a simple cytology grading system was very helpful.[30]

## TELECYTOPATHOLOGY

In recent years, advances in digital imaging technology have made it possible to remotely evaluate FNA specimens through telecytology. Khurana *et al*.[34] first evaluated telecytopathology for ROSE of EUS-FNA samples of pancreas in 2012. Real-time images of Diff-Quik™ stained cytology smears were transmitted and evaluated by a cytopathologist. They found that the accuracies of preliminary diagnosis for pancreatic cancer between telecytopathology and conventional microscopy were comparable.

Two years later, Khurana *et al*.[35] performed on-site telecytopathology evaluation on 95 cases. This study indicated that the telecytopathology could reduce the nondiagnostic rate, especially in the characteristics of solid lesions, and may serve as an adequate substitute for ROSE.

The current development of sharing economy model offers us a possibility that the on-site evaluation available in one center could be shared online across multiple centers to improve the efficiency of ROSE, which may alleviate the shortage of cytopathologists.

## ARTIFICIAL INTELLIGENCE AND RAPID ON-SITE EVALUATION

In recent years, because of improvements in deep-learning techniques and increasing computational power, artificial intelligence (AI) has made impressive progress in interpreting complex images. Researchers have begun applying AI to learn and analyze pathology images.[36-38]

Inoue *et al*.[39] reported an automatic visual inspection method based on supervised machine learning for ROSE in EUS-FNA. This approach aims to clarify the relationship between the content of cellular structures, including tumor cells, and the image quality of specimens sampled by FNA. A stationary Gaussian mixture model is used to classify the local statistics of sample images because it can sufficiently estimate the universal mode. The results indicated that the method is helpful for EUS-FNA in aiding on-site visual inspection of cellular tissue, thus indicating areas highly likely to include tumor cells.

## CONCLUSION

EUS-FNA has been developed as an analytical technique to sample digestive system lesions. The

requirement for ROSE remains one of the most controversial topics in the field of EUS-FNA. Based on the consideration that EUS-FNA combined with ROSE must not be inferior to non-ROSE, we still recommend implementing ROSE in the centers with enough staffing of the cytopathologists. The rapid development of electronic communication technology and AI technology has the potential to fundamentally change this issue, in terms of both cytopathologist time and clinical cost, and we look forward to this becoming a reality in future.

### *Conflicts of interest*

There are no conflicts of interest.

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