

REVIEW

## Onsite evaluation of endoscopic ultrasound fine needle aspiration: the endosonographer, the cytotechnologist and the cytopathologist

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### ABSTRACT

Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) has become an essential tool in the management of multiple diseases. Its accuracy is related to different aspects of the technique, one of the most important being the experience and interaction of the endosonographer and pathologist. Certain studies over the past years have highlighted the importance of having rapid on-site evaluation (ROSE) of samples obtained at the time of EUS-FNA. We have reviewed the role of ROSE, performed by the same endosonographer, a cytotechnologist and an expert cytopathologist. The available data suggest that ROSE (either by the endosonographer, the cytotechnologist, or the cytopathologist) improves sample adequacy and diagnostic yield, with the best option to have ROSE performed by an expert cytopathologist. However, if non-ROSE accuracy is already very high, any improvement is harder to achieve.

**Key words:** Rapid on-site evaluation. EUS guided tissue acquisition. Cytology. Histology.

### INTRODUCTION

Endoscopic ultrasound with fine needle aspiration (EUS-FNA) has become a mainstream means of tissue acquisition in otherwise difficult to access anatomic locations within the abdomen, retroperitoneum, mediastinum, and peri-rectal space. However, despite the worldwide acceptance of EUS-FNA, the availability of onsite analysis of any type is far from uniform. In this paper, we will review the evidence supporting the utility of onsite cytological assessment of EUS-FNA samples performed by three individuals: a) the endosonographer; b) the cytotechnologist; and c) the cytopathologist. Rapid onsite-specimen evaluation (ROSE) is believed to have three major purposes:

a) ensuring that the target organ has been sampled; b) allowing an immediate course of action for further samples (flow cytometry, microbiology, need for core biopsy); and c) allowing for preliminary diagnosis (1).

A systematic review and meta-analysis not specific to EUS examined the adequacy rates of ROSE (pathology) vs non-ROSE across studies of different designs and different organs (for example, breast and thyroid) (2). The studies showed considerable heterogeneity in the non-ROSE adequacy rates. After adjustment, ROSE improved case adequacy rates by 12%; however, diagnostic yield was not examined. In our recent review on celiac plexus neurolysis (CPN), having a cytopathologist onsite confirming pancreatic adenocarcinoma allowed CPN to be performed for unresectable tumors at the time of diagnosis with ultimate benefits to the patient (3). The utility of confirming a diagnosis in real-time on-site in the endoscopy suite cannot be underestimated as other potential EUS therapies evolve.

### THE ENDOSONOGRAPHER

Since frequently there is no availability of on-site cytopathologist nor cytotechnologist, there has been increased interest in having endosonographers perform ROSE themselves.

### Endosonographers vs cytotechnologists

A prospective double-blind controlled study compared endosonographers and cytotechnologists to determine whether an on-site FNA specimen is an adequate sample and/or label the specimen as suspicious or malignant (4). Three endosonographers received training by the cytopathologist. One hundred and seventeen specimens were

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included (59 were lymph nodes, 49 were pancreatic nodes, and nine were liver nodes). The accuracy of endosonographers with regard to specimen adequacy was 68-76%, significantly lower or with a lower tendency than cytotechnologists, at 82% (95% CI for cytotechnologist was better than each of the three endosonographers 7% [-1-15%], 6% [-3-16%], 15% [6-24%]). However, even the cytotechnologist presented a low sensitivity for adequacy, hardly reaching 60%. Not surprisingly, the greatest difference was detected in pancreatic cytology. For suspicious/malignant specimens, cytotechnologists were superior to the three endosonographers, with an accuracy of 89% vs 69-72% ( $p < 0.001$ ). Endosonographers were found to be unreliable in their assessment of the adequacy and identification of malignancy. However, the low sensitivity of the cytotechnologist for the evaluation of the specimen adequacy would have led to premature termination in 40% of the cases that were labeled adequate when they were not. This study was also performed remotely from the actual EUS and it was not clear if the endosonographers themselves prepared the slides. Certainly, slide preparation and interpretation during EUS-FNA affect assessment and may have been over-estimated here. The study also highlights two important concepts that have applicability throughout this review. Firstly, there is no standard on how to define adequacy of a sample. Also, extracting cells from a malignant lymph node is often easier than from a solid pancreatic mass. Probably, adequacy cannot be defined equivalently across different organs and systems, and even more contentious, there is a need to define how many cells are required to label a slide positive for malignancy.

### Endosonographers vs cytopathologists

A retrospective study by Hikichi et al. evaluated the diagnostic accuracy of EUS-FNA with ROSE by endosonographers compared to cytopathologists (5). Solid pancreatic masses with a known final diagnosis were included. Of 73 cases, endosonographers performed ROSE on 38 and cytopathologists, on 35. Only sample adequacy was assessed.

There was no statistical significant difference between mean number of passes ( $4.0 \pm 1.6$  and  $3.4 \pm 1.5$ ), or specimen adequacy (97.4% and 97.1%) between the endosonographer and the cytopathologist, respectively ( $p = 0.51$ ). Endosonographers were found to have a final (not-on-site) diagnostic accuracy of 94.7% (36/38), which was not statistically different to that obtained by cytopathologists, which was of 94.3% (33/35). The conclusions of this study are in striking contrast to the study by Savoy et al. (4). However, the studies are not entirely comparable. As Hikichi et al. pointed out, the number of passes was not provided by Savoy et al., a factor which clearly influences final specimen quality. Diagnostic accuracy was not based on on-site interpretation, but on final pathologist interpreta-

tion. Also, endosonographers had been performing ROSE for two years before the study, so presumably had far greater experience based on a previous training strategy.

### Training endosonographers

Two studies assessed the training process for endosonographers (6,7). In the first study, two endosonographers underwent a pathologist-guided training program, which focused on four of the ten cytological features of pancreatic ductal carcinoma, in addition to being taught about normal pancreatic parenchymal cells. They compared pre and post-training performance on solid pancreatic lesions. Training reduced the median number of passes from three to two ( $p = 0.004$ ), decreased the rate of inconclusive diagnoses from 26.4% to 8.2%, and increased diagnostic accuracy from 69.2% to 91.8% ( $p < 0.001$ ). Similar to Hikichi et al., endosonographers had previous experience with ROSE, and similar to Savoy et al., they assessed not only adequacy but also malignancy.

Harada et al. studied the impact of a two-hour interactive training program on the endosonographers' ability to judge the sample adequacy and diagnose malignancy. Twenty endosonographers and 14 cytologists (13 cytotechnologists, one cytopathologist) participated. All evaluated 28 cytological pictures of pancreatic specimens (adenocarcinoma, autoimmune pancreatitis, and benign tissue) before and after the training.

Training significantly improved the ability of the endosonographers in the evaluation of the specimen's adequacy, from 75% to 98% ( $p < 0.001$ ), and in their diagnostic accuracy from 61% to 82% ( $p < 0.001$ ). The cytologists (almost only technologists) improved their ability to detect malignancy from 70% to 91% ( $p < 0.001$ ). Limitations included the fact that this was not a real time study, all slides were adequate, and had been prepared by non-endosonographers.

We can conclude at this point that ROSE by endosonographers is a valuable endeavor that can allow real-time assessment of adequacy and maybe even provide a preliminary diagnosis. With a paucity of studies, it appears that training endosonographers with previous experience in ROSE is the most effective, but the type of teaching and true number of cases for competency in those new to the technique remains to be determined.

### ONSITE CYTOTECHNOLOGIST

Cytotechnologists are trained to process cytological specimens and assess adequacy. Many of them are also capable of assessing malignancy, given their extensive training and exposure to cytology. We assume that, unlike experienced endosonographers or specialized cytopathologists, the training for cytotechnologists both between

countries and between provinces/states within a country had a high degree of variability, making generalization of studies in this section even more difficult.

A prospective, double blind, controlled study of 37 patients undergoing EUS-FNA for solid pancreatic mass examined EUS technologists and cytotechnologists (8). The study did not define either profession. More importantly, this study assessed gross slide appearance for adequacy (not microscopic evaluation). Slides were then sent to the cytopathologist. Nine percent of specimens were deemed as inadequate by the EUS technologist and 8% by cytotechnologists. The cytopathologist agreed with inadequacy in 71% and 78%, respectively. However, 27% of slides deemed to be adequate were finally considered as inadequate by the cytopathologist. Gross examination was not able to accurately assess pancreatic mass specimens.

The first study to examine the cytotechnologist's microscopic assessment of ROSE was a single center retrospective study (9). In group I, the endoscopic nurse prepared the cytology slides but these were not examined in the endoscopy suite, while in group II a cytotechnologist on site prepared and evaluated slides for adequacy only. Organ site varied between pancreatic, mediastinal lymph nodes and abdominal lymph nodes or masses. Surprisingly, there was no difference in the mean number of FNA needle passes between groups (2.14 vs 2.63), with the authors pointing out that 2.14 passes is very low and hard to improve upon. However, cytopathologists reached a definite diagnosis in 53% in group I, compared to 77% in group II ( $p = 0.01$ ; 95% CI 0.04-0.30). Inconclusive cases decreased from 47% in group I to 23% in group II ( $p = 0.001$ ; 95% CI -0.48-0.13). Although the overall inconclusive rate seems high in both groups (perhaps due to the low number of passes), there was a clear improvement. Also, all slides in group I were made by the endoscopy nurse with undefined training. If specimens had been placed in fixative for cell block, the adequacy and definite diagnosis rate might have increased, thereby diluting the observed effect.

More recently, Nayar et al. retrospectively investigated the influence of cytotechnologists on the diagnostic accuracy of EUS-FNA samples for pancreatico-biliary lesions (10). They defined diagnostic accuracy as the number of cases that were correctly classified as benign or malignant. Cytology specimens were prepared by the endosonographer (group I) or cytotechnologist (group II). The diagnostic accuracy was similar in both groups (group I 89.0%, group II 91.8%, n.s.). In addition, the sensitivity, specificity, positive and negative predictive values were not significantly different.

The findings reported by Nayar et al. seem to contradict those reported by Alsohaibani et al. Although the exact reason for the conflicting results would be difficult to identify, one common reason for "failure" of ROSE across all studies is the non-ROSE accuracy rates. When high, a benefit of any type of ROSE will be marginal at best. This appears to be very institution-dependent, since the endo-

sonographer experience, competency and volume, as well as the difficulty level of cases themselves can all influence non-ROSE rates. A recent meta-analysis suggested ROSE benefit should be assessed on a site-by-site basis (2).

## ONSITE CYTOPATHOLOGIST

In an ideal world, an onsite cytopathologist communicating in real time with the endosonographer should provide the highest quality and most definitive interpretation of on-site EUS-FNA samples. Interpretation of EUS-FNA slides depends on physical slide preparation skill, and must be interpreted in the context of the needle having traversed the gastrointestinal mucosa, which can contaminate or complicate assessment. Some have even suggested courses for cytopathologists with no previous EUS-FNA experience (11). Furthermore, the concern with formal onsite diagnosis of malignancy is the inherent risk of false positives, along with their clinical and medico-legal implications. Although it is generally accepted that the presence of ROSE by a cytopathologist improves both specimen adequacy (since the slides are prepared with better skill, less crush artifact and less blood, and they make high quality slides out of the material given) and diagnostic accuracy, few studies have examined this issue.

## Studies with EUS-FNA at varied anatomic sites

A retrospective study at two university centers investigated the influence of ROSE by a cytopathologist on diagnostic yield of solid masses (12). Center 1 used a cytopathologist ( $n = 108$ ) and center 2 did not ( $n = 87$ ). The endoscopist was the same for both centers, and in center 2 specimen adequacy was assessed based only on gross visual inspection. In center 1, the cytopathologist assessed adequacy and provided a preliminary diagnosis. More cases at center 1 were lymph nodes (50% vs 21%), while center 2 had more pancreatic masses (58% vs 35%). The mean number of passes was similar. The presence of a cytopathologist appeared to lower the inadequate specimen rate from 20% to 9% ( $p = 0.035$ ). Inadequacy rates for pancreatic masses were similar between sites; therefore, the authors felt specimen site did not influence inadequacy rates. This study demonstrated a benefit for lymph nodes in addition to pancreatic masses; therefore ROSE still appeared beneficial for potentially easier sites. The odds were three times greater after multivariate analysis for final cytologic diagnosis being confirmed positive or negative for malignancy in center 1.

Similarly, a single center retrospective study (13) compared non-ROSE (with slide preparation by an endoscopy nurse [ $n = 375$ ]) to ROSE by a cytopathologist ( $n = 271$ ). Again, one endosonographer performed all EUS-FNA and assessed sample adequacy by gross appearance only. For

both groups, mediastinal and abdominal lymph nodes were the most common lesions. Needle passes did not differ between groups (3.12 vs 3.24,  $p = 0.30$ ). A definite diagnosis (positive or negative for malignancy) improved with cytopathologist interpretation from 64.8% to 97.7% ( $p = 0.001$ ). In the first group, a diagnosis could not be given in 25.3% of cases due to the absence of diagnostic material and in 2.93%, because of crush artifact. Absence of diagnostic material was reported only in 1.5% with the cytopathologist present, with a 0% crush artifact. On-site cytopathologist presence was associated with better sample adequacy and increased diagnostic yield. Once again, if slides had not been made onsite by the endoscopy nurse but rather left for the cytology department, some slide degradation and crush artifact might have been avoided. As referred to in previous studies, the accuracy between onsite diagnosis and final diagnosis was not explored.

### Studies of pancreatic masses

A single hospital center retrospectively examined only pancreatic masses including 182 patients, 95 of which had ROSE by a cytopathologist (14). Cytopathologists were only present on certain days depending on availability. For malignancies, 96.2% were positive with the cytopathologist and 78.2% without ( $p = 0.002$ ). ROSE was associated with a lower number of needle passes (2.0 vs 3.5;  $p < 0.001$ ), higher adequacy rates (98.9% vs 87.4%;  $p = 0.002$ ), and higher diagnostic accuracy (96.8% vs 86.2%;  $p = 0.013$ ). This study supports the presence of an on-site cytopathologist and was one of few studies demonstrating benefit in reducing number of needle passes from ROSE.

A risk-benefit analysis with simulation model was used to study if needle pass reduction by ROSE is beneficial (15). If one stopped after observing the first adequate sample, a fixed number of four passes would be required to achieve a per-case accuracy of 97%, which ROSE would provide with 2.2 passes. If two adequate samples are required before stopping with ROSE, more than six passes in a fixed sampling system without ROSE would be required. As suggested above, the advantage of ROSE decreases when the per-pass adequacy rate is high and therefore lesions that are difficult to sample (or inexperienced/low volume centers) may benefit the most. This was also demonstrated in two studies (16,17), where per case adequacy rate was high and final diagnostic yield was not improved with ROSE.

A cost benefit analysis of 5,688 cases over five years (18) was performed in an institution with an extremely low non-diagnostic rate of ~1% with ROSE compared to the literature, with a reported 20% without ROSE. If all non-diagnostic procedures were repeated, savings of greater than two million dollars over five years was predicted with ROSE.

Another meta-analysis (19) examining only EUS-FNA for pancreatic adenocarcinoma showed that, on multivar-

iate analysis, the relative diagnostic odds ratio remained significant for on-site cytopathology (5.95, 95% CI 2.15-16.45); however, it does not distinguish between a diagnosis made in real-time in the endoscopy room or a diagnosis made after all staining and analysis were performed.

### ROSE compared to final cytologic diagnosis

This important analysis comparing ROSE diagnosis by a cytopathologist to final cytologic evaluation reported that, of 300 cases diagnosed as malignant by ROSE, 294 remained malignant after final diagnosis (98%) (20). Four were downgraded to suspicious, one to atypical and one to benign. Overall agreement with ROSE to final results was excellent ( $\kappa = 84\%$ ); however, only the malignant diagnoses at the time of ROSE are relevant if additional intra-procedural therapies are to be applied.

Jhala et al. published another retrospective study, analyzing ROSE *versus* final diagnosis (21). Pancreas was the most frequent organ where on-site diagnosis was deferred or not provided (64.8%), compared to all other sites (35%). ROSE diagnosis of malignancy had the highest concordance with final cytologic diagnosis 196/198 = 98.9%, compared to 200/205 = 67.2% for non-malignant cases ( $p < 0.001$ ). Furthermore, the two pancreatic cases downgraded to suspicious were confirmed malignant on repeat EUS-FNA, making the positive predictive value 100%.

### CONCLUSION

When examining the benefit of ROSE for EUS-FNA, there appear to be two key issues to be considered: a) the skill level of the endosonographer, cytotechnician or cytopathologist to improve the final diagnostic yield after evaluation by the cytopathologist after the procedure (this relies on quality of physical slide preparation and interpretation to guide the need for additional passes); and b) ideally, ROSE could provide a definitive in-room diagnosis (with no need for further confirmation).

The available data suggest that ROSE (by the endosonographer, cytotechnologist, or cytologist) improves sample adequacy and diagnostic yield. However, if non-ROSE accuracy is already very high, any improvement is much harder to achieve.

When a cytologist is available for ROSE, the correlation between the in-room and final diagnosis is extremely high. As EUS evolves, intraprocedural techniques, which could be performed immediately following a definitive, in-room diagnosis of malignancy, could be expanded to include not only early celiac plexus neurolysis, but possibly fiducial marker placement, injection of anti-tumoral chemotherapeutic agents, or ablative therapy (e.g., by ethanol injection, radiofrequency, photodynamic therapy, laser, cryotherapy, brachytherapy, etc. [22-27]), and also,

the placement of stents (metal *versus* plastic) and immediate surgical evaluation. Further work is needed to determine for which clinical situations and applications ROSE is beneficial.

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