

EDITORIAL

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Rapid on-site evaluation (ROSE) in pancreatic cancer diagnosis: Doing more with less

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Most of pancreatic masses are represented by neoplastic processes, primarily ductal adenocarcinoma and less frequently neuroendocrine tumor, lymphoma and metastasis. On the contrary, non-neoplastic lesions are represented by chronic, autoimmune pancreatitis and cysts [1, 2]. Pancreatic cancer is the fourth and fifth most common cancer in men and women, respectively [3]. Due to local invasion or distant metastasis, only 15–20% of patients are surgical candidates at presentation. Among them, the five-year survival rate is only 10–15% [4]. About 70% of pancreatic cancers develop in the head while 10–20% in the body and tail [5]. In many cases, pancreatic cancer is diagnosed in the advanced stage of the disease and at this point the tumor cannot be surgically excised. In fact, at the moment of diagnosis, 52% patients show distant disease and 26% have regional spread [6]. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a rapid, safe, cost-effective and accurate technique to evaluate and stage pancreatic tumors [7]. In addition, this technique has proved a very useful in discriminating between suspicious lesions, inflammation and cancer, especially adenocarcinomas. The EUS-FNA demonstrates a low percentage of major complications and a low risk of disseminating neoplastic cells when compared to the percutaneous approach. Cytological evaluation may have some disadvantages such as a limited

amount of material to make a diagnoses especially when differentiation between different tumor types is requested. Authors reported that EUS-FNA may be inconclusive or doubtful in up to 20% cases [8–13]. Explanations could be: (a) an inexperienced endosonographer, (b) small tumors in which it is often difficult to perform a biopsy and cytopathology performances are lower, (c) the absence of a cytopathologist to make on site sampling evaluation, (d) the presence of blood in the sample, (e) the diagnosis may be difficult in cases of well-differentiated adenocarcinoma and reactive atypia, (f) gastric and duodenum cell contamination. Today there are technical improvements, like new generations of needles and ultrasound machines, immunodetection and molecular biology which offer the possibility of diagnostic accuracy.

One of the most important effects of teamwork is to facilitate a rapid diagnosis for the patient. In this case, the synergy between the cytopathologist and experienced ultrasonographer, demonstrates that it is possible to increase the accuracy of diagnosis. In our experience, the advantage of the rapid on-site evaluation (ROSE) during pancreatic EUS-FNA has been the following:

- (a) real time confirmation of neoplastic cell specimens
- (b) adequacy of the sample material for the purpose of molecular or immunocytochemistry analysis
- (c) contribution to the preoperative staging in the case of multifocal/multicentric tumors, lymph node involvement or distant metastasis
- (d) interdisciplinarity, evaluation and integration between clinical, radiological, laboratory and pathological data
- (e) contribution to the trainees for a faster learning curve
- (f) contribution to evolution of interventional maneuvers, for example the choice of trajectory, type and degrees of suction in the mass

In a previous study, we observed that one important factor impacting on transbronchial needle aspiration (TBNA) sensitivity, during fiberoptic bronchoscopy or mediastinoscopy, is the rapid on-site cytological examination (ROSE) [14]. The combination of EUS-FNA and ROSE not only increases the percentage of

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positive diagnoses, but also allows a significant reduction in expenses and time. This is an important factor because hospital managers have to respond not only for the efficacy, but also for the cost of their work. The technological progress has provided a great number of increasingly sophisticated and expensive tools. The task of the modern physician is to use equipment suitable for the patient's needs, based on a careful evaluation of costs, benefits and risk-benefit ratio. Our experience with on-site cytology evaluation and EUS-FNA in pancreatic cancer, shows there are some weak points: a limitation of the available resources of personnel, and an increase in the waiting-time in cases that are difficult to diagnose. To achieve adequate performance, EUS-FNA must be carried out in highly-experienced centers, with the appropriate equipment and possibly with the aid of an on-site cytopathologist. However, on-site cytopathology interpretation may not be available in many centers.

Chang et al. reported that in the presence of an on-site cytopathology assistant, during EUS-FNA, adequate specimens were obtained in 100% patients. On the contrary, the same study observed that absence of an on-site cytologist resulted in 29% of patients requiring a second procedure to obtain an adequate specimen [15]. Erickson et al observed, that when a cytopathologist was not on-site, in addition to prolonging procedure time and potentially increasing the procedural risk using multiple needle passes, the diagnostic yield of EUS-FNA dropped by 10–15% [16]. Tournoy et al. demonstrated that EUS-FNA with on-site cytopathology in mediastinal lymphadenopathy interpretation reported a diagnostic accuracy of 92% [17]. Bruno et al. observed that without and with on-site cytological examination, the application of TBNA in mediastinal lymphadenopathies determined a sensitivity of 65% and 80%, respectively. The same authors conclude that ROSE significantly improved the sensitivity of TBNA because the bronchoscopist can change the needle insertion point [14]. In our experience using EUS-FNA with ROSE in pancreatic suspected masses, it was possible to obtain a definitive diagnosis or an indication to continue with additional samples. Overall sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of cytology samples from EUS-FNA were 80.8%, 100%, 100%, 72.2% and 87.2%, respectively (data not shown). The sensitivity and accuracy of combined histology and cytology was higher than histology or cytology alone. Histologic analysis revealed malignant cells that were not diagnosed by cytology, especially when there were excess of blood clots. In these cases, the blood material was fixed in formalin directly.

The literature reports the risk of a false negative cytology during EUS-FNA in patients with chronic pancreatitis [18, 19], although this is not the only cause. Cell contamination during needle passages and the presence of excess blood covering the slide during on-site evaluation, represent other possible causes of false negative. The former, depends on the cytopathologist's

experience. During the passages, the needle can sample single or groups of cells from stomach or duodenum, which are sometimes in layers, and it is difficult to distinguish them from the pancreatic tissues. The second problem can be excessive blood on the slide which covers the cells. The amount of blood may depend on the type of needle used. In this case, to prevent blood coagulation, the speed with which the material from the needle is smeared on the slide is very important. Differential diagnosis can be difficult because cells remain trapped in the fibrin. Even in experienced hands, these events may be encountered during EUS-FNA. Standardized terminology and nomenclature for pancreatic cytology provides guidance for the diagnosis of pancreatic lesions. Correlation between morphology, biological features and management recommendations is crucial in the presence of pancreatic masses and cysts. About that, an useful terminology scheme has been recently proposed [20]. This scheme allows the pathologist to classify lesions with a low grade of differentiation and slight atypias as compared to ductal pancreatic lesions frequently associated with marked cytological alterations. Following ROSE, there can be cases of specimens classified as inconclusive, indeterminate, or negative. For these cases, ancillary procedures including immunocytochemistry, fluorescence in situ hybridization, genetic analysis for neoplasia-specific mutations, and sequential mutational analysis are potentially useful in cytological interpretation.

In conclusion, EUS-FNA offers great possibilities for future technological development like increasingly defined imaging and more flexible needles to take samples from areas difficult to access. The ROSE is a method that, in its technical simplicity, has many advantages in terms of adequacy of cell material and preoperative cytologic diagnosis. In some cases, with very few cells it is possible to carry out a number of diagnostic procedures for an accurate diagnosis. However, the pathologist must have experience in this specific field and work within a team where it is possible to have clinical and imaging information about the patient. After a careful morphological assessment, if the cytology alone is not conclusive, it may be better to apply ancillary tests, especially if biopsy material is not available and the cytological material is the only choice for diagnosis and therapy decision making.

Keywords: Cancer, Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), Pancreas, Rapid on-site evaluation (ROSE)

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Conflict of Interest

Authors declare no conflict of interest.

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