World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i28.9451

World J Gastroenterol 2014 July 28; 20(28): 9451-9457
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Rapid on-site evaluation of endoscopic-ultrasound-guided fine-needle aspiration diagnosis of pancreatic masses

Julio Iglesias-Garcia, Jose Lariño-Noia, Ihab Abdulkader, J Enrique Domínguez-Muñoz

Julio Iglesias-Garcia, Jose Lariño-Noia, J Enrique Domínguez-Muñoz, Department of Gastroenterology and Hepatology, Foundation for Research in Digestive Diseases, University Hospital of Santiago de Compostela, 15706 Santiago de Compostela, Spain
Ihab Abdulkader, Department of Pathology, University Hospital of Santiago de Compostela, 15706 Santiago de Compostela, Spain
Author contributions: Iglesias-Garcia J made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content; Lariño-Noia J and Abdulkader I drafted the article and revised it critically for important intellectual content; Domínguez-Muñoz JE gave final approval of the version to be published.
Correspondence to: Julio Iglesias-Garcia, MD, PhD, Department of Gastroenterology and Hepatology, Foundation for Research in Digestive Diseases, University Hospital of Santiago de Compostela, 15706 Santiago de Compostela, Spain. julio.iglesias.garcia@sergas.es
Telephone: +34-981-951364 Fax: +34-981-955100
Received: October 31, 2013 Revised: April 24, 2014
Accepted: May 19, 2014
Published online: July 28, 2014

Abstract

Endoscopic ultrasound (EUS) has become an essential tool for the study of pancreatic diseases. Specifically, EUS plays a pivotal role evaluating patients with a known or suspected pancreatic mass. In this setting, differential diagnosis remains a clinical challenge. EUS-guided fine-needle aspiration (FNA) and fine-needle biopsy (FNB) have been proven to be safe and useful tools in this setting. EUS-guided FNA and FNB, by obtaining cytological and/or histological samples, are able to diagnose pancreatic lesions with high sensitivity and specificity. In this context, several methodological features, trying to increase the diagnostic yield of EUS-guided FNA and FNB, have been evaluated. In this review, we focus on the role of rapid on-site evaluation (ROSE). From data reported in the literature, ROSE may increase diagnostic yield of EUS-FNA specimens by 10%-30%, and thus, diagnostic accuracy. However, we should point out that many recent studies have reported adequacy rates of > 90% without ROSE, indicating that, perhaps, at high-volume centers, ROSE may not be indispensable to achieve excellent results. The use of ROSE can be considered important during the learning curve of EUS-FNA, and also in hospital with diagnostic accuracy rates < 90%.

Key words: Endoscopic-ultrasound-guided fine-needle aspiration; Rapid on-site evaluation; Solid pancreatic tumors; Diagnostic accuracy

Core tip: Endoscopic ultrasound (EUS) has become a crucial tool for the evaluation of solid pancreatic masses. EUS-guided fine-needle aspiration (FNA) and fine-needle biopsy (FNB) have been proven to be safe and useful tools in this setting, and can diagnose pancreatic lesions with high sensitivity and specificity. The use of rapid on-site evaluation can increase adequacy rates and diagnostic yield of EUS-guided FNA or FNB by 10%-30%.

Iglesias-Garcia J, Lariño-Noia J, Abdulkader I, Domínguez-Muñoz JE. Rapid on-site evaluation of endoscopic-ultrasound-guided fine-needle aspiration diagnosis of pancreatic masses. *World J Gastroenterol* 2014; 20(28): 9451-9457 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i28/9451.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i28.9451

INTRODUCTION

Endoscopic ultrasound (EUS) has become a crucial tool in the study of pancreatic diseases. Specifically, EUS plays a pivotal role when evaluating patients with pancreatic

solid tumors[1,2]. Distinguishing different types of pancreatic solid tumors is an important clinical challenge. Therapeutic strategy in this context is based on the ability to determine the presence of a malignant lesion. Although ductal adenocarcinoma is considered as the main cause of pancreatic mass, many other neoplasms (*e.g.*, lymphoma, cystic tumors, and metastasis) and benign conditions (*e.g.*, chronic pancreatitis) with different prognoses and treatment options can be detected in the pancreas. Taking this into account, a cytopathological confirmation is highly relevant for establishing the best treatment.

EUS-guided fine-needle aspiration (FNA) and fine-needle biopsy (FNB) are considered safe and accurate methods for tissue sampling of intramural and extramural gastrointestinal lesions, including the pancreas. In fact EUS-guided FNA and FNB, by obtaining cytological and/or histological samples, are able to diagnose pancreatic lesions with high sensitivity and specificity[3]. Several studies have evaluated the accuracy of cytology and/or histology after EUS-guided FNA or FNB for the diagnostic evaluation of pancreatic masses.

There are several methodological features, including trying to increase the diagnostic yield of EUS-guided FNA and FNB by rapid on-site evaluation (ROSE). Although experts recommend an on-site evaluation of samples obtained in order to optimize the diagnostic yield of EUS-guided FNA, its effect on diagnostic accuracy has not been properly defined. Reports on the need for ROSE during the procedure are scarce. In this review, we first analyze the role of EUS-guided FNA and FNB for the diagnosis of solid pancreatic masses. Finally, we present the most relevant data published, analyzing the role of EUS-guided FNA and FNB with ROSE in this setting.

USEFULNESS OF EUS-GUIDED FNA AND FNB IN THE DIFFERENTIAL DIAGNOSIS OF SOLID PANCREATIC TUMORS

The role of EUS-guided FNA in the diagnosis of solid pancreatic tumors has been evaluated in many well-designed studies. Reported sensitivity and accuracy for malignancy ranges from 75% to 92% and from 79% to 92%, respectively[4-14]. Two large reviews have been published evaluating the accuracy of EUS-guided FNA in pancreatic masses. One of them included 28 studies (4225 patients). The authors evaluated the usefulness of EUS-FNA to differentiate between benign and malignant lesions. Sensitivity, specificity and diagnostic accuracy were 83% (54%-95%), 100% (71%-100%) and 88% (65%-96%), respectively[15]. The second one, a more recent meta-analysis, published by Hewitt *et al*[16], included 33 studies, with a total of 4984 patients. The authors showed that sensitivity for malignant cytology was 85% (95%CI: 84%-86%), and specificity was 98% (95%CI: 97%-99%). When including atypical and suspicious cytology as true positive, sensitivity increased to 91% (95%CI: 90%-92%); however, the specificity decreased to 94% (95%CI: 93%-96%). EUS-guided FNA also showed a good positive predictive value (99%) and a good negative predictive value (64%). However, it is important to point out that in cases with findings related to chronic pancreatitis, the sensitivity of EUS-guided FNA for the detection of malignancy is clearly decreased[17,18].

In order to optimize tissue retrieval, with the aim of obtaining core specimens, various EUS-guided techniques have been explored. One approach is the use of the Tru-Cut needle (Quick-Core), with variable success and complication rates[19-21]. This Tru-Cut needle has demonstrated that histological samples can be obtained safely[21,22]. However, there are certain limitations with the Quick-Core needle that preclude its routine clinical use. Most importantly, its diagnostic yield is limited for lesions located in the pancreatic head, related to the mechanical friction of the needle-firing mechanism associated with the bent position of the scope[23-25]. In this setting, a novel needle has been designed (Procore) to overcome the limitations of the Tru-Cut needle (mainly in the second portion of the duodenum). A study published with the 19-gauge caliber needle allowed a histological evaluation with an overall accuracy of 85.9% (89.4% in pancreatic solid lesions)[26], with a high inter-observer agreement between pathologists when evaluating the quality of the samples obtained[27]. A new study has been recently published using the 22-gauge Procore needle in pancreatic masses, which was able to obtain a sample suitable for histological evaluation in 88.5% of the cases[28].

However, certain drawbacks of EUS-guided FNA need to be emphasized. In certain cases, the procedure is difficult to perform, because of vessel interposition, duodenal stenosis and/or tumor hardness, particularly in chronic pancreatitis, which hampers the overall accuracy of the procedure. In other occasions, EUS-guided FNA samples cannot be interpreted due to bleeding or noncellular samples. A systematic review of 53 studies estimated a negative predictive value of EUS-guided FNA in the diagnosis of pancreatic adenocarcinoma of 60%-70%[15]. In patients with indeterminate or negative findings at the first EUS-guided FNA, presenting a high suspicion of malignancy, repeating the procedure is highly recommended. Several studies have demonstrated that performing a second EUS-guided FNA was useful for determining the correct and true situation in a high percentage of cases with inconclusive findings at initial EUS-guided FNA; in fact, by repeating EUS-guided FNA up to three times, sensitivity can increase up to 90%[29-31]. Hence, a new puncture seems necessary to exclude malignancy in cases where the first EUS-guided FNA was negative for malignancy. When combining all the information available on the high accuracy in the evaluation of pancreatic tumors, Eloubeidi *et al*[32] recommended performing EUS-guided FNA in all patients with solid pancreatic masses.

ROLE OF ROSE AFTER EUS-GUIDED FNA

The idea of including ROSE is based on the fact that up to 30% of FNA interpretation may be nondiagnostic, because of multiple factors, including scant cellularity and/or crush artifacts from poor slide preparation. In this setting, ROSE of FNA specimens may be beneficial for rapid clinical diagnosis, probably decreasing the number of nondiagnostic procedures. However, data on the role of ROSE are limited, with scant data available over the past few years. In the recently published guidelines from the European Society of Gastrointestinal Endoscopy, the role of ROSE and its relevance in EUS-guided sampling in gastroenterology has been described[33]. We try to analyze different aspects of ROSE evaluation after EUS-guided FNA, and its clinical usefulness in the diagnosis of solid pancreatic masses.

Visual inspection of the samples obtained

It is not clear whether the evaluation of the samples obtained after puncture is useful in order to increase the accuracy of EUS-guided FNA. Neither trained technologists nor cytotechnologists, in a prospective double-blinded study, could properly establish the obtention of an adequate sample by gross visual inspection. The κ score for the agreement between visual evaluation and final microscopic assessment was only 0.2, which is considered poor. False-positive assessments occurred in 30% of the slides[34].

ROSE performed by cytopathologists and cytotechnicians

The role of ROSE has been mainly studied in percutaneous FNA. In this setting, ROSE is accepted as useful, by diminishing the number of inadequate diagnoses. In addition, ROSE may have an impact on costs by decreasing the number of repeat procedures[35-37]. However, data on ROSE in EUS-guided FNA are scarce. Published data suggest that the presence of a cytopathologist during EUS-FNA is cost-effective and useful. We summarize the most important and relevant data reported in the literature.

Chang *et al*[38] reported a 100% rate of adequate specimens with the on-site evaluation of a cytopathologist during EUS-guided FNA. However, the absence of an on-site cytological evaluation resulted in 29% of patients requiring a second procedure to obtain an adequate specimen. Erickson *et al*[39] also published a lower diagnostic accuracy of EUS-FNA (decreasing by 10%-15%) without the presence of an on-site cytopathologist. The only concerns were the prolonged procedure time and the potentially increased risk of complications from the need for multiple needle passes. Klapman *et al*[40] demonstrated that an on-site cytopathologist evaluating the samples improved the diagnostic accuracy of EUS-FNA. In their study, they analyzed the EUS-guided FNA results from two university hospitals. At Center Ⅰ, 108 patients underwent EUS-guided FNA in the presence of an on-site cytopathologist. At Center Ⅱ, 87 patients underwent EUS-guided FNA in the absence of cytopathologist. All procedures at both hospitals were performed by the same endosonographer. At Center Ⅰ, a definite diagnosis of positive or negative for malignancy was reported in 78% compared with 52% for Center Ⅱ (OR = 2.94; $P = 0.001$); the rate of patients with an unsatisfactory sample was 9% compared with 20% in Center Ⅱ (OR = 0.36; $P = 0.035$). Iglesias-Garcia *et al*[14] published their experience in a study including a total of 182 patients. An on-site cytopathologist was available in 95 cases (52.2%). A significantly higher number of needle passes was performed when ROSE was not available (3.5 ± 1.0 *vs* 2.0 ± 0.7; $P < 0.001$). The presence of an on-site cytopathologist was associated with a significantly lower number of inadequate samples (1.0% *vs* 12.6%, $P = 0.002$), and significantly higher diagnostic sensitivity (96.2% *vs* 78.2%; $P = 0.002$) and overall accuracy (96.8% *vs* 86.2%; $P = 0.013$) for malignancy. In a prospective study evaluating 540 patients who underwent EUS-guided FNA procedures of 656 lesions (mostly of pancreatic masses and lymph nodes), which ROSE was available for 607 lesions. From all lesions evaluated on-site by a cytologist, 5/243 considered initially benign (2.1%) finally turned to be malignant. In contrast, among 300 lesions considered malignant after ROSE, 294 (98%) were still malignant at the final report. Agreement was excellent between ROSE and final cytological evaluation (κ = 84.0%, 95%CI: 80.2-87.7). Compared with the true final status, accuracy for final interpretation was slightly higher for ROSE (95.8% *vs* 93.9%). Most of the discrepancies were related the characteristics of the lesions, either because of the presence of scanty cells, strange morphology, or because of the need for different types of immunostaining for final diagnosis[41]. Collins *et al*[42], over a consecutive 3-year period, analyzed 379 patients that underwent ROSE and 377 patients that did not. The percentage of repeat procedures on the non-ROSE group was 5.8%, which was slightly higher than in the ROSE group (2.9%). The use of ROSE decreased the number of repeated procedures by approximately 50% ($P = 0.024$). In patients requiring an additional procedure, the use of ROSE provided a higher number of definitive diagnoses. However, the presence of a cytopathologist is not always possible in many centers, mainly because of the availability according to the organization of the pathology department, which is directly associated with costs. Trying to overcome this common situation, Alsohaibani *et al*[43], in a retrospective study suggested that on-site cytotechnologist interpretation of adequacy of tissue samples might also be useful for improving the diagnostic yield of EUS-guided FNA. The patients were divided into two groups. In Group Ⅰ, samples were prepared by an endoscopy nurse ($n = 47$) and in Group Ⅱ by an on-site cytotechnologist ($n = 55$). Pancreatic masses were the main target site. The final diagnosis was higher in the group with on-site cytotechnologists preparing the slides (77% *vs* 53%), suggesting that if an on-site cytopathologist cannot be provided, a trained cytopathology technician should be present to provide an assessment of

Table 1 Diagnostic performance of rapid on-site evaluation by a cytopathologist/cytotechnician in the evaluation of solid pancreatic masses

Ref.	Year	No. of cases		Accuracy		
		With ROSE	Without ROSE	With ROSE	Without ROSE	*P* value
Klapman *et al*[40]	2003	108	87	78%	52%	0.001
Alsohaibani *et al*[43]	2009	47	60	77%	53%	0.001
Iglesias-Garcia *et al*[14]	2011	95	987	96.80%	86.20%	0.013
Collins *et al*[42]	2013	379	377	97.10%	94.10%	N.S.

ROSE: Rapid on-site evaluation.

sample adequacy.

However, ROSE was not found to be better than the standard approach in all studies. In a prospective multicenter study with 409 patients, two centers used ROSE and two did not[8]. Results were similar in both groups, and merely differed in a higher negative predictive value in the subgroup of patients with extraintestinal mass lesions in the group with ROSE. In another study (analyzing 247 pancreatic solid lesions and 276 lymph nodes), a retrospective analysis of risk factors for inadequate EUS-guided FNA specimens was performed. Cytopathological adequacy was higher for lymph nodes (96% *vs* 84%, $P = 0.008$) but not for pancreatic solid lesions (99% *vs* 100%; $P = 1$) if ROSE was available[44].

Finally, a recent meta-analysis aimed to determine whether ROSE, together with the variability of the reference standard and other sources of heterogeneity may affect the diagnostic yield of EUS-guided FNA when evaluating solid pancreatic masses[45]. Hebert-Magee *et al*[45] included 34 studies. The pooled sensitivity and specificity was 88.6% (95%CI: 87.2%-89.9%) and 99.3% (95%CI: 98.7%-99.7%), respectively. The LR+ and LR- were 33.46 (95%CI: 20.76-53.91) and 0.11 (95%CI: 0.08-0.16), respectively. In this study, the main factor determining the accuracy of EUS-guided FNA was the presence of ROSE ($P = 0.001$). Thus, EUS-guided FNA was considered an effective modality in the diagnosis of pancreatic cancer when evaluating solid pancreatic lesions, which was higher with the availability of ROSE.

Another important point is the potential application of ROSE with the use of new histological needles. A recent study from Krishnan *et al*[46] aimed to investigate the utility of ROSE in achieving a final diagnosis for EUS-guided FNB core specimens. The authors evaluated 60 consecutive patients referred for EUS-guided FNA of lesions inside or adjacent to the gastrointestinal tract. All patients underwent EUS-guided FNB to evaluate the additive value of ROSE to the diagnostic accuracy of specimens obtained using a core biopsy needle. EUS-guided FNB was feasible in all 60 cases. On-site specimen adequacy and final diagnostic accuracy was 58% (95%CI: 45.1%-71.2%) and 83% (95%CI: 71.9%-91.5%), respectively. Results were better than those obtained for standard EUS-guided FNA.

Table 1 summarizes the diagnostic accuracy from the most relevant papers comparing EUS-guided FNA or FNB with and without ROSE.

However, little is known about the impact of ROSE on EUS-guided FNA procedural time, and it remains unclear whether using ROSE prolongs the procedure or makes it less time-consuming by reducing the number of needle passes. According to some published data, it is assumed that an average time for obtaining the specimen and performing on-site examination is 15 min per sample[47]. Average time used by the cytopathologist for ROSE in computed-tomography-guided and ultrasound-guided FNA specimens is relatively high (48.7 and 44.4 min, respectively)[48].

Regarding complications, scarce information is available from the different studies. In the study from Iglesias-Garcia *et al*[14], complication rate in the group of cases without ROSE was significantly higher, probably related to the higher number of passes needed to obtain the final diagnosis. However, all complications reported were considered as mild, and no mortality was associated with the procedures.

ROSE performed by an endosonographer

As previously commented, the presence of cytopathologist is not possible in all centers, for all EUS-guided FNA or FNB procedures. In this context, there is a trend to train endosonographers for ROSE during EUS-guided FNA, in order to reduce costs. Some studies have attempted to resolve this question.

A prospective double-blind study showed that even experienced endosonographers, trained in the management of samples obtained by FNA, were less accurate than a cytotechnician in assessing specimen adequacy (68%-76% *vs* 82%; $P = 0.004$) and in the determination of malignancy (69%-72% *vs* 89%; $P < 0.001$)[49]. A second study, including 73 procedures, could not find any difference when analyzing sample adequacy, number of needle passes, or EUS-guided FNA performance characteristics in two different 2-year periods. In one of them, ROSE was performed by endosonographers and in the other, this evaluation was performed by cytopathologists[50]. Hayashi *et al*[51] retrospectively evaluated patients from two different periods who underwent EUS-guided FNA for the study of solid pancreatic masses. Before initiating ROSE at the start of the second period, two endosonographers underwent training for cytological interpretation, focused on four cytological features of pancreatic ductal

carcinoma: anisonucleosis, nuclear membrane irregularity, overlapping, and enlargement. During EUS-guided FNA in Period 2, endosonographers classified the Diff-Quik smears under three atypical grades and evaluated the adequacy. One made all diagnoses. The rate of inconclusive diagnoses, interpreted as suspicious, atypical, and inadequate for diagnosis was reduced from 26.4% to 8.2% ($P = 0.004$). Moreover, diagnostic accuracy increased from 69.2% to 91.8% ($P < 0.001$). Authors concluded that samples evaluated by trained endosonographers, with a simple cytological grading system, could be considered useful in this context.

CONCLUSION

EUS-guided FNA and FNB are effective modalities for the diagnosis of solid pancreatic masses, with high diagnostic accuracy. It is well known that diagnostic performance is clearly associated with the presence of a skilled team, including both endosonographers and cytopathologists. In this context, ROSE appears to be a useful tool for optimizing the yield of this procedure. Although gross visual inspection cannot assess the adequacy of EUS-guided FNA or FNB specimens for cytopathological examination, ROSE performed by cytopathologists provides a highly accurate diagnosis with an excellent agreement with the final cytopathological diagnosis. ROSE may increase adequacy rates of EUS-guided FNA or FNB specimens by 10%-30%. However, we should point out that many recent studies have reported adequacy rates > 90% without the use of ROSE, indicating that, in high-volume centers, ROSE may not be indispensable to achieve excellent results. Finally, data on cost-effectiveness are limited. After analyzing all data available, implementation of ROSE should be considered, mainly for the learning curve of the technique and at centers in which specimen adequacy rates are < 90%.

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P- Reviewer: Hudacko R, Teschke R, Tian YT, Wu H
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