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Is diagnostic accuracy of fine needle aspiration on solid pancreatic lesions aspiration-related? A multicentre randomised trial

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ABSTRACT

Background: Endoscopic ultrasound fine needle aspiration has a central role in the diagnostic algorithm of solid pancreatic masses. Data comparing the fine needle aspiration performed with different aspiration volume and without aspiration are lacking. We compared endoscopic ultrasound fine needle aspiration performed with the 22 gauge needle with different aspiration volumes (10, 20 and 0 ml), for adequacy, diagnostic accuracy and complications.
Methods: Prospective clinical study at four referral centres. Endoscopic ultrasound fine needle aspiration was performed with a 22G needle with both volume aspiration (10 and 20 cc) and without syringe, in randomly assigned sequence. The cyto-pathologist was blinded as to which aspiration was used for each specimen.
Results: 100 patients met the inclusion criteria, 88 completed the study. The masses had a mean size of 32.21 ± 11.24 mm. Sample adequacy evaluated on site was 87.5% with 20 ml aspiration vs. 76.1% with 10 ml ($p = 0.051$), and 45.4% without aspiration (20 ml vs. 0 ml $p < 0.001$; 10 ml vs. 0 ml $p < 0.001$). The diagnostic accuracy was significantly better with 20 ml than with 10 ml and 0 ml (86.2% vs. 69.0% vs. 49.4% $p < 0.001$).
Conclusions: A significantly higher adequacy and accuracy were observed with the 20 ml aspiration puncture, therefore performing all passes with this volume aspiration may improve the diagnostic power of fine needle aspiration.

1. Introduction

Endoscopic ultrasound fine needle aspiration (EUS-FNA) plays a central role in the diagnostic algorithm of solid pancreatic masses, with high sensitivity and specificity (75–92% and 82–100%, respectively) [1–3], and carries a low complication rate (1–2%) [4–6]. In the clinical setting of solid pancreatic masses, a histological diagnosis is highly relevant both for differential diagnosis (adenocarcinoma, lymphoma or neuroendocrine tumour) and for optimal therapeutic decision-making. For the cythopathological diagnosis of pancreatic cancer, sensitivity increases with the operator's experience, and reaches 80% after 20–30 EUS-FNA procedures. Furthermore, it has been well demonstrated that on-site cytopathology interpretation during the procedure increases the diagnostic yield of EUS-FNA [7–22]. Expertise and training of the endosonographer,

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and interaction with the cytopathologist, also play a key role [7,13,14,23]. At present, three different sizes of needle are available for collecting cytological material: 25–22 and 19-gauge (G) with an aspiration volume syringe of 10 ml. Most of the studies on EUS-FNA have been done using 22G needles. Data on thinner (25G) or larger (19G) needles are limited, but the diameter of the needle does not appear to affect the diagnostic accuracy of FNA of solid pancreatic lesions [19,20]. Preliminary studies show that using suction during EUS-FNA of solid masses is associated with a significantly higher sensitivity for a diagnosis of cancer (86% vs. 67%; $p = 0.05$) [21]. A pilot trial suggested that applying continuous high pressure suction (using a balloon inflation device) allowed retrieval of tissue samples for histopathological examination in most cases [22].

Until now, no studies have been done to compare the diagnostic yield of FNA on solid pancreatic masses performed with different aspiration volumes (10 and 20 ml) and without aspiration.

The aims of our study were to compare EUS-FNA done with a 22-G needle with an aspiration volume syringe of 10 ml and of 20 ml, and without aspiration in the same solid pancreatic mass, in terms of cellular adequacy, diagnostic accuracy, and complications.

2. Materials and methods

2.1. Patients

This was a prospective randomised clinical study performed at four referral centres for EUS: the Mediterranean Institute for Transplantation and Advanced Specialized Therapies/University of Pittsburgh Medical Centre in Italy (ISMETT/UPMC), Palermo; AUSL Bologna, Bellaria-Maggiore Hospital; Civico-A.R.N.A.S. Hospital, Palermo; and Humanitas IRCCS, Rozzano, Milano. The study protocol conformed to the ethics guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in the a priori approval by the institutions' human research committees. The trial was registered in ClinicalTrials.gov, a service of the National Health Institute [ClinicalTrials.gov Identifier: N NCT01717196]. The procedures were carried out by one or two attending endosonographers for each centre, each of whom had undergone third-tier EUS training, and had performed more than 1000 procedures. One dedicated cytopathologist for each centre was involved in the study. The inclusion criteria for the study were diagnosed or suspected solid pancreatic lesions based on imaging (CT-scan or/and MRI), and no contraindications for FNA (see exclusion criteria). The exclusion criteria were age < 18 years; cystic pancreatic lesions; history of previous gastrectomy; patients hemodynamically unstable or with severe coagulopathy (international normalized ratio [INR] > 1.5 or platelet count<60.000 cells/cubic millimetre [mm^3]); patients unable to suspend anticoagulant therapy; pregnancy; inability to give informed consent; and refusal to participate to the study. Data on comorbidity and chronic treatment were recorded, as were data on possible complications related to the procedure. Patients undergoing anticoagulant therapy for noncritical problems discontinued the treatment at least 5 days before the endoscopic procedure or until INR normalization, and were put on a low dose of heparin. Written informed consent was obtained from all patients for the procedures performed. All procedures were performed under conscious sedation with meperidine ± midazolam or deep sedation with propofol according to each centre's guidelines, and the patient's clinical condition.

2.2. Procedure

Endoscopic ultrasonography was performed with a linear echo-endoscope by five experienced echo-endoscopists. The standard technique for FNA was adopted: the needle was advanced under real-time EUS guidance into the target lesion with a quick, strong thrust of the handle. The stylet was completely withdrawn and a syringe attached to the end of the needle device. Once inside the lesion, and after opening the lock device of the syringe, the needle was moved back and forth 15 times under EUS guidance. The suction syringe was then released, the needle withdrawn into the catheter, and the whole system removed from the echoendoscope.

The needle system was in all cases 22G EUS-FNA (Expect, Boston Scientific, Natick, MA, USA). We performed three punctures with a 22G needle at a volume aspiration of 10 and of 20 cc, and without aspiration for each lesion. The order of the sequences (10 cc, 20 cc, no aspiration) was determined by a pre-printed randomization sequence kept in an opaque sealed envelope that was opened by the EUS technologist after the patient's enrolment. The sequences were generated by a Web-based program. After the three passes of the sequence, if the sample was considered inadequate for interpretation, further FNAs were performed as operator preferences, but not considered for the analysis. Technical success was defined as puncturing the target tissue properly without technical difficulties (e.g., inability of the needle to exit from the channel of the scope) or mechanical rupture, and obtaining some visible tissue specimens or fragments with each puncture. Tissue samples were immediately smeared onto slides after each puncture, fixed and all the prepared slides were viewed by pathologists experienced in rapid on-site evaluation (ROSE). For each pass, after smearing the sample onto two slides, the remaining material was expelled with the stylet and fixed in formalin for cytohistological evaluation. The cytopathologist was always blinded as to which aspiration was used for which specimen. The smeared sample was evaluated as adequate or inadequate for interpretation (see adequacy definition below). For each aspiration two fundamental parameters were evaluated on the slides and the formalin-fixed sample: sample adequacy, intended as overall cellularity (including normal, neoplastic and non-epithelial cells, quantity of blood and inflammatory cells) and diagnostic accuracy. Diagnostic accuracy was defined as the ratio between the sum of true positive and true negative values divided by the total number of masses. The values were acquired by comparing the cytopathological results of EUS-FNA with the final diagnosis, which was defined as the diagnosis obtained from surgical pathology or at least 12 months of clinical observation with necessary studies (CT-MRI).

2.3. Post-procedural follow-up

After EUS-FNA, the patients were monitored for at least six hours in order to immediately detect post-procedural complications, and were followed up with a scheduled protocol during the 30 post-procedure days in order to evaluate clinical status, blood chemistry, and to detect late complications. All patients were followed up for at least 1 month with one visit 15 days and another 30 days after the procedure. All data were recorded electronically on Excel databases, and then entered into a central database at ISMETT for the final analysis. Diagnosis was confirmed through histopathology after surgery or by at least six months of clinical follow-up and repeated spiral CT examinations. Procedure-related complications were defined as follows and noted carefully: pancreatitis, the presence of post-procedure abdominal pain lasting more than 24 h, with a more than threefold increase above the upper limit of normal in serum amylase or lipase; bleeding, the need for blood transfusion or a decrease in haemoglobin level of greater than 2 g/dl; infection, fever over 38.3 °C in the absence of other focus of infection within a 3-day period; and free or retroperitoneal bowel perforation, documented by any imaging studies associated with clinical symptoms.