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Original article

Conventional versus contrast-enhanced harmonic endoscopic ultrasonography-guided fine-needle aspiration for diagnosis of solid pancreatic lesions: A prospective randomized trial

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ABSTRACT

Objectives: Contrast-enhanced harmonic endoscopic ultrasonography (CEH-EUS) has been used to diagnose solid pancreatic lesions (SPLs). The aim of this study was to investigate the efficacy of CEH-EUS-guided fine-needle aspiration (CEH-EUS-FNA) compared with that of conventional EUS-FNA for the diagnosis of SPLs.
Methods: Forty patients with solid pancreatic lesions who visited Fukushima Medical University between September 2013 and June 2014 were recruited for this prospective study. Twenty patients underwent CEH-EUS-FNA, and 20 patients underwent conventional EUS-FNA. The sampling rate, sensitivity, accuracy, and number of needle passes required to obtain sufficient samples were compared between the two groups.
Results: Patient characteristics, sampling rate, accuracy, and sensitivity were not significantly different between the two groups. The final diagnosis of patients who underwent CEH-EUS-FNA was pancreatic cancer in 19 and intraductal papillary mucinous carcinoma in one. Nineteen patients who underwent conventional EUS-FNA were finally diagnosed with pancreatic cancer and one was diagnosed as cancer of the common bile duct. There was a significant difference in the number of needle passes required. A sufficient sample was obtained on one needle pass in 60% (12/20) of CEH-EUS-FNA group compared with 25% (5/20) of the conventional EUS-FNA group.
Conclusions: Fewer needle passes were required to obtain samples from solid pancreatic lesions using CEH-EUS-FNA than those required using conventional EUS-FNA. Therefore, CEH-EUS-FNA may be more efficient and safer than conventional EUS-FNA for the diagnosis of solid pancreatic lesions.

Introduction

It can be difficult to distinguish organs on percutaneous abdominal ultrasonography, particularly if patient has a large amount of subcutaneous fat or intestinal gas. In particular, the pancreas is difficult to visualize because of its location behind the stomach. Endoscopic ultrasonography (EUS) from the lumen of the stomach or duodenum can be used to visualize organs more clearly and completely because of its high spatial resolution. In addition, EUS rarely has blind spots. Because of the high detection capability of EUS, it is preferred over percutaneous ultrasonography or computerized tomography (CT) for the investigation of pancreaticobiliary diseases [1,2].

Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) is used to collect biopsy samples from many organs throughout the digestive tract and is useful in diagnosing solid pancreatic lesions (SPLs) [3–6]. The reported diagnostic accuracy of EUS-FNA for SPLs is 85–89.4%, the sensitivity is 82–94.7%, and the

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specificity is 100% [7–9]. However, in many cases, four or more needle passes are needed to obtain sufficient biopsy samples [10]. There is a potential risk of tumor seeding associated with needle punctures [11–18]. Therefore, it is important to minimize the number of needle passes.

Contrast-enhanced harmonic EUS (CEH-EUS) using SonoVue (Bracco International BV, Amsterdam, the Netherlands) or Sonazoid (Daiichi-Sankyo, Tokyo, Japan) was reported for diagnosing SPLs [19–25]. Using CEH-EUS, the microvasculature of the target lesion and blood flow of the pancreatic parenchyma can be clearly visualized. Pancreatic cancer is observed as hypoenhanced heterogeneous tumors on CEH-EUS [19,22–25], whereas pancreatic neuroendocrine tumor is observed as hyperenhanced tumors [22,24,25]. Unenhanced areas in pancreatic lesions seen on CEH-EUS are thought to represent fibrosis [26] or necrosis. Therefore, it would be difficult to obtain sufficient biopsy samples through unenhanced areas of SPLs.

In the present study, we used CEH-EUS to visualize SPLs and targeted the enhanced areas of lesions during FNA biopsy. We hypothesized that, using CEH-EUS-guided FNA (CEH-EUS-FNA), fibrotic and necrotic areas could be avoided, improving the sampling rate and diagnostic ability, while reducing the number of needle passes required to obtain sufficient biopsy samples. We compared the diagnostic efficacy of CEH-EUS-FNA with that of conventional EUS-FNA.

Material and methods

Study design

This was a prospective randomized study. To investigate the efficacy and safety of CEH-EUS-FNA, we compared patient characteristics, sampling rate, sensitivity, accuracy, and number of needle passes required to obtain biopsy samples between patients who underwent CEH-EUS-FNA (CEH-EUS-FNA group) and patients who underwent conventional EUS-FNA (conventional EUS-FNA group).

In patients who underwent surgery, the final diagnosis was made on the basis of pathological results of surgical specimens. In patients who did not undergo surgery, the diagnosis was made on the basis of pathological results of EUS-FNA biopsy samples. The study was approved by the ethics committee of Fukushima Medical University (authorization no. 1686).

Patients

Forty patients with SPLs identified on abdominal US or CT at Fukushima Medical University between September 2013 and June 2014 were recruited for the study. SPLs were seen as hypoechoic lesions on abdominal US or as low-density lesions on abdominal CT, and these lesions were provisionally diagnosed as pancreatic carcinoma. The patients were randomly and consecutively assigned to undergo CEH-EUS-FNA ($n = 20$) or conventional EUS-FNA ($n = 20$) using permutated blocks. They were finally diagnosed on the basis of surgical specimens. If their SPLs were unresectable, they were finally diagnosed on the basis of EUS-FNA and imaging examinations. Furthermore, we regarded class IV/V cytology as malignant.

EUS-FNA and CEH-EUS-FNA

The endoscopic and ultrasonic equipment used in this study were GF-UCT260 (Olympus Medical Systems, Tokyo, Japan) and ALOKA ProSound α-10 (ALOKA, Tokyo, Japan), respectively, in the CEH-EUS-FNA group and GF-UC240P, GF-UCT240-AL5, or GF-UCT260 (Olympus Medical Systems), and the EU-ME2 (Olympus Medical Systems), respectively, in the conventional EUS-FNA group. The biopsy needles were Expect 22G (Boston Scientific, MA, USA) in the CEH-EUS-FNA group and Expect 22G or 25G (Boston Scientific), EZ shot2 22G (Olympus Medical Systems), or Echotip 25G (Cook Medical Inc., NC, USA) in the conventional EUS-FNA group.

All patients were sedated with midazolam before endoscopy. In the conventional EUS-FNA group, once the SPL was visualized, needle biopsy was performed. In the CEH-EUS-FNA group, the target SPL was observed before contrast enhancement, and the imaging mode was changed to the extended pure harmonic detection (ExPHD) mode. After images were viewed on the monitor of ALOKA ProSound α-10 (ALOKA) in both B mode and ExPHD mode, 0.015 ml/kg of Sonazoid (Daiichi-Sankyo) contrast media was injected. After infusion, it took several minutes until the parenchyma of the pancreas was enhanced and the point of aspiration could be determined. The slice with the widest contrast-enhanced area was identified and then the biopsy was directed toward that area, while avoiding unenhanced areas and not changing the target lesion (Fig. 1). The needle was passed through the gastrointestinal wall into the target lesion under EUS guidance with visualization of the needle in real time. After the needle was guided into the target lesion, the stylet was withdrawn, and the needle was moved back and forth within the lesion 20 times while negative pressure was applied using a 10 ml syringe connected to the end of the needle. Suction was released, and the needle was withdrawn from SPL. Microscope slides were prepared from the biopsy sample and were stained with Cyto-Quick stain. The slides were assessed by Rapid on-site cytological evaluation (ROSE) [27]. If the sample was adequate, the investigation was complete. If the sample was not sufficient, another needle aspiration was performed. The first aspiration was performed by endosonographers with experience of <100 EUS-FNA procedures (M.S. or N.K.) under the guidance of an expert endosonographer (T.T.) with an experience of >300 EUS-FNA procedures. Second and subsequent aspirations were performed by the expert endosonographer (T.T.) as required.

Statistical analysis

Analysis of patient characteristics, age, and tumor size were performed using Student's *t*-test. Analysis of the patient characteristics, sex, location of SPLs, diagnosis, sampling rate sensitivity, accuracy, and number of needle passes was performed using the Chi-square test or Fisher's exact probability test. A P value of <0.05 was regarded as statistically significant. All statistical analysis was performed using Statcel 3 (OMS Inc., Saitama, Japan).

Results

No statistical differences were observed for age, sex, tumor size, or location of SPLs between the CEH-EUS-FNA and conventional EUS-FNA groups (Table 1). Unenhanced areas were observed in all patients who underwent CEH-EUS-FNA. There was no EUS evidence of chronic pancreatitis, which complicates identification of the border between SPLs and pancreatic parenchyma, in either group. The final diagnosis of 19 of 20 patients who underwent CEH-EUS-FNA was pancreatic cancer and that of the remaining case was intraductal papillary mucinous carcinoma. Nineteen of the 20 patients who underwent conventional EUS-FNA were finally diagnosed with pancreatic cancer, and the remaining was diagnosed with cancer of the common bile duct. The sampling rate for both groups was 100%. Sensitivity and accuracy were not significantly different at 90% (18/20) for the CEH-EUS-FNA group and 85% (17/20) for the conventional EUS-FNA group. Eighteen patients who underwent CEH-EUS-FNA were diagnosed with adenocarcinoma. One of two patients who could not be diagnosed by CEH-EUS-FNA was diagnosed as invasive pancreatic adenocarcinoma on