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Review Article

Endoscopic ultrasound-guided needle-based confocal laser endomicroscopy for diagnosis of solid pancreatic lesions

Rapat Pittayanon, Pradermchai Kongkam,* Rungsun Rerknimitr

ABSTRACT

An accurate diagnosis of solid pancreatic lesions (SPLs) is important because pancreatic cancer cannot be ignored if curative treatment is possible. Prompt and reliable diagnostic procedures are greatly needed for patients presenting with SPLs, particularly where resection is possible for a malignant mass. Several endoscopic ultrasound (EUS)-related technologies including a novel EUS-guided needle-based confocal laser endomicroscopy (EUS-nCLE) can provide real-time images at the cellular level (1,000-fold magnification). A 19-gauge EUS-guided fine needle aspiration (EUS-FNA) needle is recommended because its channel is large enough for the 0.85-mm diameter nCLE miniprobe. The procedure is performed by standard EUS-FNA techniques with either pre- or post-loading technique. Ten percent fluorescein sodium (2.5–5 mL) is used as an enhancing agent and is intravenously injected immediately before puncturing the lesion. Only a few studies have used the technique and reported results. A recent study from 19 malignant and 3 benign SPLs classified EUS-nCLE findings according to 4 signs: dark clumps, and dilated vessels (predominantly seen in malignant SPLs) and fine white fibrous bands and normal acini (predominantly seen in benign SPLs). Using these criteria, researchers correctly diagnosed 18 of the malignant SPLs (94.7%). Another study described 2 lesions as having “dark cells aggregates with pseudo-glandular aspects, and straight hyperdense elements more or less thick corresponding to tumoral fibrosis” in 17 of 18 malignant SPLs. Thus far, no large and systematic study has been performed to evaluate the potential clinical use of EUS-nCLE for diagnosing SPLs. However, based on available information from a few studies and the current limitations of EUS-FNA, EUS-nCLE can potentially provide a complementary role in diagnosing such lesions. Nevertheless, more studies are certainly needed.

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Keywords: Confocal; Endoscopic ultrasound-guided fine needle aspiration; Endoscopic ultrasound-guided needle based confocal laser endomicroscopy; Pancreatic mass; Solid pancreatic lesion

Introduction

An accurate diagnosis of solid pancreatic lesions (SPLs) is important because pancreatic cancer cannot be ignored if curative treatment is possible. On the other hand, unnecessary operations for benign SPLs should be avoided because there is a high rate of major complications after pancreatic surgery. Pancreatic adenocarcinoma is one of the worst cancers, prognostically. The only curative treatment is complete surgical resection, which unfortunately, is possible only if the cancer is small and in an early stage. Hence, prompt and reliable diagnostic procedures are greatly needed for patients presenting with SPLs, particularly where resection is possible for a malignant mass. Currently, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the most

commonly used preoperative pathological diagnostic method because it provides a low complication rate, relatively high diagnostic yield, and it can avoid needle tract seeding in potentially resectable pancreatic cancer at the head of the pancreas. The recent meta-analysis reported sensitivity and specificity rates at 85%–91% and 94%–98%, respectively.¹ These values seem to be high; nevertheless, given the poor prognosis of pancreatic cancer, they are not adequate, particularly for confirming benign results of EUS-FNA.² Moreover, in chronic pancreatitis, the sensitivity of EUS-FNA is only 54%–73% because of difficulties in getting adequate samples of fibrotic masses.^{3,4} Several EUS-related technologies, such as elastography, contrast enhancement, and real time histopathology, have been developed to decrease the rate of false negatives when using EUS-FNA for diagnosing SPLs.⁵ Real-time

Gastrointestinal Endoscopy Excellent Center, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand

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* Corresponding author. Gastrointestinal Endoscopy Excellent Center, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, 1873, Rama 4 Road, Patumwan, Bangkok 10330, Thailand.
E-mail address: kongkam@hotmail.com (P. Kongkam).

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histology of SPLs is thus far possible by EUS-guided needle-based confocal laser endomicroscopy (EUS-nCLE). This review will focus on the practical points of EUS-nCLE for diagnosing SPLs.

Equipment

Confocal laser endomicroscopy (CLE) uses a novel endoscopy probe that can provide real-time images at the cellular level (1,000-fold magnification). It was originally used for examination of luminal gastrointestinal mucosal lesions. Clinical uses have been demonstrated in a variety of diseases, including Barrett's esophagus, gastric metaplasia, and colonic lesions.⁶⁻¹⁰

The probe has since been developed into a needle type with a 0.85-mm diameter.^{11,12} This probe is used in nCLE and can be inserted through a 19-gauge EUS-FNA needle.¹³ Consequently, EUS-nCLE has then been used for diagnosing pancreatic lesions.

Technique

Lesions are examined and identified using EUS, after which, the EUS-nCLE is prepared. A 19-gauge EUS-FNA needle is recommended because its channel is large enough for the nCLE miniprobe. The stylet of the EUS-FNA needle is removed and replaced with the nCLE miniprobe. The tip of the nCLE is placed 3 to 10 mm outside the tip of the needle and fixed with a locking device to keep an appropriate distance between the nCLE probe and the sheath of the EUS-FNA needle (Fig. 1). The locking device is released, and the nCLE miniprobe is pulled back 2 to 5 cm from the tip of the EUS-FNA needle so that the EUS-FNA needle can be sharpened for puncturing. A standard EUS-FNA is subsequently performed. This is called the pre-loading technique. In the other hands, if the endosonographer performs a standard EUS-FNA technique with the stylet in place, the stylet is pulled back and replaced with an nCLE miniprobe. This is so called the post-loading technique.¹⁴

To produce cellular images of target pancreatic lesions by EUS-nCLE, 10% fluorescein sodium (2.5–5 mL) is used as an enhancing agent and is intravenously injected immediately before puncturing the lesion. Endosonographers then look for the most optimal place that may provide the highest yield of cytopathology

similar to standard EUS-FNA technique. It should be noted here that first pass of EUS-nCLE is the most important one as following pass will face with post puncture bleeding which may interfere images of EUS-nCLE. After the tip of the EUS-FNA needle is in the target area, the nCLE miniprobe is pushed through the distal end of the EUS-FNA needle. Standard movements are made with the EUS-FNA needle to obtain satisfactory real-time cellular nCLE images. The endosonographer can move or adjust the length and depth of the nCLE miniprobe to gain optimal images according to his/her clinical judgment. Even slight movements in the EUS-FNA needle significantly changes confocal images, so slow and ultra-short adjustments are suggested for exploring the target lesions.

Fig. 2. An endoscopic ultrasound-guided needle-based confocal laser endomicroscopy reveals heterogeneous, irregularly-shaped structures with unclear margins ranging 40 to 200 microns in size atop a heterogeneous, cloudy pancreatic background. This image is obtained from a patient with pancreatic adenocarcinoma.

Fig. 1. Locking device to fix the length of the miniprobe beyond the tip of the endoscopic ultrasound-guided fine needle aspiration needle.

Fig. 3. An endoscopic ultrasound-guided needle-based confocal laser endomicroscopy reveals multiple linear regular straight whitish bands equally interspersed over a heterogeneous grey pancreatic background. This image is obtained from a patient with mass-forming chronic pancreatitis.

Nevertheless, if the nCLE miniprobe is in an undesirable position, moving the EUS-FNA needle using a fanning technique (moving the nCLE miniprobe back and forth, up and down, or left and right inside the mass) can aid in adjusting it to the most appropri-

ate position. However, if these techniques do not yield satisfactory images, the endosonographer can withdraw all needles and repuncture the lesions. It has been my experience that EUS-nCLE should be performed before standard EUS-FNA for cytopathology to avoid artifacts from post EUS-FNA bleeding.

Image Interpretation and Clinical Use

Only a few studies thus far have used EUS-nCLE for diagnosing SPLs. From 19 malignant and 3 benign SPLs, Kongkam et al¹⁵ classified EUS-nCLE findings according to 4 signs: dark clumps, dilated vessels (predominantly seen in malignant SPLs), fine white fibrous bands, and normal acini (predominantly seen in benign SPLs) (Fig. 2–4). Using these criteria, researchers correctly diagnosed 18 of the malignant SPLs (94.7%) (Table 1). A false positive diagnosis was made in one case where an inflammatory mass resulted from recent acute pancreatitis. In another instance, a patient presented with an inflammatory mass in the head of the pancreas and an obstruction of the main pancreatic duct causing a large pseudocyst; EUS-FNA and EUS-nCLE diagnosed a lesion in head of the pancreas as a benign mass. This result was a false negative—the mass later enlarged, and subsequent pathology showed pancreatic neuroendocrine tumors.

Giovannini et al¹⁶ studied SPLs using EUS-nCLE and described 2 lesions as having “dark cells aggregates with pseudo-glandular aspects, and straight hyperdense elements more or less thick corresponding to tumoral fibrosis” in 17 of 18 malignant SPLs. The authors presented these findings in an abstract form. They also described that “both signs were absent in the tumors with acini

Fig. 4. A confocal laser endoscopic image of normal acini of the pancreas. It reveals a homogeneous dark, regular-border surrounding round structures and measuring about 60 to 80 microns, equally distributed in the pancreatic parenchyma.

Table 1 EUS-nCLE Diagnosis, Clinical Diagnosis and Findings of EUS-nCLE

Case No.	Age (yr)	Sex	nCLE findings	nCLE diagnosis	Final diagnosis
1	46	M	Fine white fibrous band, small black cell movement	Benign	Benign
2	59	M	Small black cell movement, dark clump	Malignant	Malignant
3	66	M	Small black cell movement, dark clump	Malignant	Malignant
4	85	M	Dark clump, dilated vessel	Malignant	Malignant
5	66	M	Dark clump	Malignant	Malignant
6	49	F	Small black cell movement, dark clump	Malignant	Malignant
7	64	F	Dark clump, dilated vessel	Malignant	Malignant
8	50	M	Small black cell movement, dark clump, dilated vessel	Malignant	Malignant
9	56	M	Dark clump	Malignant	Benign
10	36	M	Fine white fibrous band, normal acinar cell	Benign	Benign
11	65	M	Small black cell movement, dark clump	Malignant	Malignant
12	85	F	Dark clump	Malignant	Malignant
13	81	M	Small black cell movement, dark clump	Malignant	Malignant
14	66	M	Dark clump, dilated vessel	Malignant	Malignant
15	44	F	Small black cell movement, dark clump	Malignant	Malignant
16	59	F	Small black cell movement, dark clump	Malignant	Malignant
17	75	M	Small black cell movement, dark clump	Malignant	Malignant
18	72	F	Small black cell movement, dark clump, dilated vessel	Malignant	Malignant
19	43	M	Fine white fibrous band, small black cell movement, normal acinar cell	Benign	Malignant
20	72	F	Small black cell movement, dark clump	Malignant	Malignant
21	75	M	Dark clump	Malignant	Malignant
22	66	F	Dark clump	Malignant	Malignant

EUS-nCLE, endoscopic ultrasound-guided needle-based confocal laser endomicroscopy; M, male; F, female.

cells and endocrine tumor” and “normal pancreas shows an aspect of coffee beans corresponding to acinis.” These findings were obtained by 4 investigators and one pathologist.

Conclusions

Thus far, no large and systematic study has been performed to evaluate the potential clinical use of EUS-nCLE for diagnosing SPLs. However, based on available information from a few studies and the current limitations of EUS-FNA, EUS-nCLE can potentially provide a complementary role in diagnosing such lesions. Nevertheless, more studies are certainly needed.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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