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ROLE OF ULTRASOUND GUIDANCE IN THE DIAGNOSTIC AND INTERVENTIONAL PROCEDURES OF PANCREATIC LESIONS

Radiodiagnosis

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ABSTRACT

Ultrasound (US) is an important diagnostic tool for the evaluation of the pancreas. It is also a fundamental imaging technique to guide percutaneous interventions for several pancreatic diseases like fluid aspiration and drainage, invasive diagnosis by means fine-needle aspiration and core-needle biopsy, tumour ablation by radiofrequency, microwaves, irreversible electroporation, cryoablation, and high-intensity focused US. Technical improvements, such as contrast media and fusion imaging, have recently increased precision and safety and reduced procedure-related complications. New techniques for the ablation of pancreatic tumours, such as contrast-enhanced US and multimodality fusion imaging, have been recently developed and have elicited a growing interest worldwide. The purpose of this article is to review the most up-to-date role of US in percutaneous procedures for pancreatic diseases, also focusing on new techniques and applications.

KEYWORDS

Core Needle Biopsy, Cryosurgery, Electroporation, Microwaves, Pancreatic Diseases, Radiology (interventional), Ultrasonography

INTRODUCTION

Ultrasound-guided percutaneous core needle biopsy (USPCB) has a major role in the evaluation of pancreatic diseases. Among various modalities such as US, computed tomography (CT), and magnetic resonance (MR) imaging, US has a number of advantages for guiding percutaneous biopsy for pancreatic lesions, including wide availability, cost effective, portability, lack of ionizing radiation, real-time visualization of the biopsy needle and target lesion during the procedure. These advantages make US more effective than CT and MR imaging in obtaining safe access to the target lesions without the need to traverse non-target organs and vessels. The most commonly performed percutaneous US-guided procedures on the pancreas are fluid drainage, especially after surgery or acute pancreatitis, and invasive diagnostic of pancreatic masses. Recently, several percutaneous ablative treatments have been applied to pancreatic malignancies. In this article we analyse the utility of ultrasound guidance in diagnostic and interventional procedures.[1]

US guided Percutaneous pancreatic biopsy (US PCB)

USPCP is a minimally invasive procedure which relies on technical expertise, radiologist's experience, sound knowledge about the procedure and anatomy of abdominal organs.**Prebiopsy preparation** is very important for a successful procedure. Written consent is obtained from the patients for possible risks of the procedure, including bleeding and injury to adjacent organs. Patients are advised to fast without taking solid or semisolid food (water permitted) for at least six hours before the procedure. It is recommended that the route for intravenous access be established before the procedure in patients with high risk of bleed ing or anxiety.

Procedure

Selection of the biopsy needle :

Selecting the appropriate biopsy needle is critical to the success of USPCB. The size of the needle is directly correlated with the amount of target tissue required. Small caliber needles are primarily used to collect cellular samples for cytologic examinations and large-caliber needles provide sufficient tissue for histologic analysis and molecular characterisation.[1,2]

Fine needle aspiration cytology:

For FNA, needles with a 23G to 20G calibre is used. **(Figure1a)** It has an internal stiletto that can be removed so that the material is suctioned by capillarity or aspiration effect. Menghini-modified needles work with an aspiration modality, while Chiba needles collect cells through capillarity. FNA is generally preferred when sampling sites adjacent to major bloods vessel or passing needles through the bowel wall. Fine-needle aspiration of the pancreas is a simple, costeffective, relatively low-risk and high-accuracy diagnostic procedure. Percutaneous image guided FNA has been in use since 1970.

Limitations:

Diagnostic accuracy is limited by the availability of an onsite cytopathologist (Ecka and Sharma 2013; Roy et al. 2016; Song et al. 2010). It is less sensitive in the diagnosis of malignant tumors associated with chronic pancreatitis (Varadarajulu et al. 2005). In addition, tumors such as lymphomas and stromal cell tumors may be difficult to diagnose because of the need for accurate pathologic assessment of tissue structure and morphology.(Levy and Wiersema 2005). When a complete tissue analysis is needed for a correct histological diagnosis and for further pathological analyses, as Ki-67 quantification in neuroendocrine neoplasms, FNA is not adequate, as it only provides a cytological specimen with few histologic structures.

Core Needle biopsy :

For biopsies of the pancreas, needles ranging from 14G to 25G are commonly used. **(Figure1b)** Others include cutting needles, which are manually transferred back and forth within the lesion to obtain histologic samples, and automated "biopsy guns." The 20G needle is found to be highly efficient with more tissue extraction and less complications. (Lee et al. 2000). Eighteengauge needles are slightly less effective in acquiring adequate tissue and are associated with higher complication rates. The size of the needle and the number of passes made may also affect the overall risk of complications. It is recommended that the diagnosis be made with the least number of passes to avoid unnecessary risks. The average incidence of complications of percutaneous core needle biopsy is very low, 2.08%, which is similar to the lower limit of EUS-guided FNAs. Percutaneous image guided core needle biopsy has been in use since 1980.

Figure 1b Core Biopsy needle

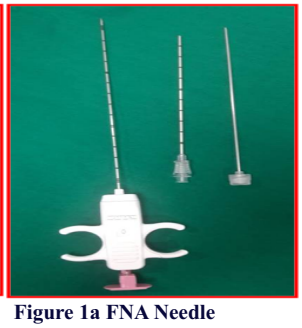

Figure 1a FNA Needle

Complications of biopsy procedure [3,4]

- Intra-abdominal hemorrhage
- Macrohematuria
- Acute pancretitis
- Abscess
- Pancreatic fistula
- Inadvertent biopsy of other organs
- Risk of peritoneal seedling in malignant neoplasms

Selection of Probes

Two types of probes are used for interventional procedures: those with

lateral support and those with discontinuous crystals and central support. The needle supports are fixed laterally or centrally are different in caliber and have different insertion points or positions, which correspond to the angle chosen on the basis of imaging. If the puncture access is not straight or to avoid some important organs during the process of puncture, the curve access is more flexible without guide kits for the freehand technique. Any tracks can be used to reach the target in the safest possible manner.[5]

Planning an optimal approach path:

After the probe is pressed firmly against the abdominal wall, the needle insertion site is determined according to the location of the mass, and the shortest needle insertion route is selected to minimize the risk of injury to adjacent organs. Color Doppler imaging is used to avoid vascular injury. Whenever possible, penetration of abdominal hollow viscera is avoided, and a transperitoneal approach is preferred, but a transhepatic approach is also used in cases of pancreatic head lesions. To avoid damage to important structures, such as the gallbladder and hepatic and gastroduodenal arteries, the ideal insertion point, especially for diagnostic purposes, is the left upper quadrant, left of the midline. Manual compression is often applied to the abdominal wall to avoid needle access into hollow organs. Transgastric passage is commonly used; transcolonic passage should be avoided.

A free-hand technique is generally applied by the radiologist. The operator holds the transducer in one hand while manipulating the biopsy needle with the other. The advantage of this technique is that one can freely fine-tune the needle path during the biopsy. In this technique, appropriate alignment of the needle and the transducer is indispensable for the continuous visualization of the needle tip. Compared with highly flexible smaller needles, large-caliber needles such as 18-gauge provides better visibility on US images. Sometimes, even large caliber needles may not be visualized on US images during biopsy, in such situations, the needle's visibility may be improved by moving its tip to and fro ("pump maneuver") and by using color Doppler US. When approaching the target, the needle should be readjusted to ensure proper inclination and positioning. For larger lesions, acquiring the specimen at the outer portion of the lesion is recommended because the inner portion is often necrotic or cystic, which is not suitable for pathologic diagnosis. In contrast, when a mass has a diameter less than 2 cm, a tissue specimen should be acquired from the center of the target.

Coaxial Technique:

A coaxial technique may be preferable to reduce the number of punctures and the risk of implantation by separating the adjacent tissue from the needle. The coaxial needle is composed of an outer cannula and an inner stylet, which are inserted into the lesion together, after which the inner stylet is removed and the smaller needle is introduced into the larger needle. Thus, the inner biopsy needle is used to acquire the samples needed. The samples are acquired through the cannula after removal of the inner stylet of the biopsy needle. This technique is highly dependent on the experience of the interventional radiologist. [6]

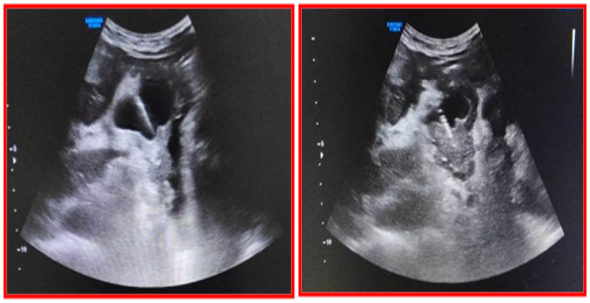

Figure 2a&b Intralesional real time visualisation of echogenic shaft of biopsy needle

Post biopsy:

Immediately after the core tissue is extracted, color Doppler US should be carefully performed to check for any significant post-biopsy bleeding. A linear track of color flow along the biopsy trajectory ("patent tract" sign) strongly suggests the possibility of clinically significant post-biopsy bleeding.

Advantages of US guided Percutaneous pancreatic biopsy (USPCB)[1]

1) On USG real-time imaging and multiplanar monitoring are displayed as the biopsy needle traverse tissues along the path to the lesion.
2) The high spatial resolution of US imaging has led to its ever-increasing use in pancreatic interventional procedures.
3) Compared with endoscopic ultrasound (EUS), percutaneous US scanning can reveal a wider observed area in a single view without gas interference. Similarly, EUS-guided biopsies may not be suitable for lesions in the body, tail or deep regions of the pancreas.
4) Unlike CT, which is time consuming and exposes both patients and radiologists to significantly increased radiation doses, US may be more convenient and its widespread adoption not limited.

Guidelines of the European Federation of Society for Ultrasound in Medicine and Biology (EFSUMB) on diagnostic US-guided interventional procedures [7]

Indications of invasive diagnosis of pancreatic lesions

1) Characterisation of a solid unresectable pancreatic mass
2) Differential diagnosis between neoplasm and focal inflammatory conditions
3) Suspicion of an uncommon entity (i.e. metastases, lymphoma)
4) If resectable tumor which could be treated non-operatively
5) Ki-67 quantification for the prognosis of neuroendocrine neoplasms
6) Cystic lesions those are undefined or suspicious for malignancy after MR imaging evaluation.

Contraindications include

1) Uncooperative patients and non-correctable bleeding disorders.
2) It is contraindicated in patients with a serum platelet count of less than 50 x 109 /L and an international normalized ratio of more than 1.6.

Role of Ultrasound guidance in Diagnostic and Interventional procedures

1)Diagnosis of pancreatic mass: Benign or malignant

An accurate diagnosis is influenced by the lesion size, location, needle gauge, and presence or absence of pancreatitis. The histopathologic result for a solid pancreatic lesions as benign or malignant affects the diagnostic workup and planning. In patients with chronic pancreatitis the difference between pancreatic adenocarcinoma and benign fibrosis from chronic pancreatitis poses diagnostic delimma. In such cases core needle biopsies help a lot to delineate the nature of the lesion. **(Figure 3a and 3b).** It is clear that the diagnostic rate, sensitivity, specificity, negative positive value and accuracy for percutaneous biopsy also depends on the location of the lesion. The lesions in the pancreatic head are higher than the values for biopsy of the pancreatic body and tail. 93%–94% accuracy is reported for lesions in the body and tail of the pancreas, slightly higher than what is resported for pancreatic head lesions 83%– 84%.[8]

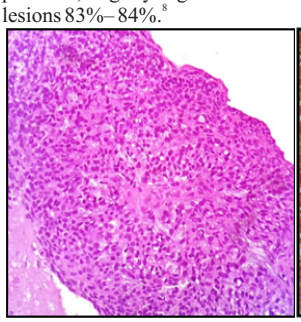

Figure 3a Core biopsy showing a case of neuroendocrine carcinoma of pancreas with neoplastic cells in diffuse sheets (H&E 20x)

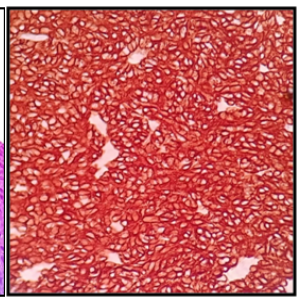

Figure 3b Synaptophysin positivity in the tumor cells (IHCx40x)2) Fluid aspiration and drainage

2) Fluid aspiration and drainage

Aspiration and drainage of peripancreatic fluid collections is frequently performed percutaneously under US guidance. Fluid collections are common after pancreatic surgery. They may represent different pathological entities such as exudate, bile, blood, or infection. Surgical drainage tubes are usually present when fluid collections are seen at post-operative imaging, making easier their characterisation; when drainage tubes are absent, percutaneous US-guided diagnostic

aspiration should be performed to guide further management. Peri- or intrapancreatic fluid collections are typically associated with acute pancreatitis and almost always resolve without any treatment [2]. About 25% pseudocysts associated with interstitial acute pancreatitis become symptomatic or infected and necessitate drainage [4]. Percutaneous US-guided drainage has proved to be an effective alternative to surgery in patients with acute necrotising pancreatitis; nevertheless, the approaches to sterile and infected necrotic collections are different. Necrotic collections without signs of infection at CT should be considered as sterile until otherwise proven, and percutaneous drainage should be avoided, as this procedure has the potential of infection by means of colonisation of the drainage catheter [4]. Nevertheless, patients without radiologic evidence of infection, who do not do well clinically or present clinical instability, may benefit from US-guided aspiration to rule out infected necrosis. When infected necrosis is present, large-sized, or multiple, percutaneous drainage catheters should be placed into the collection as a bridge or as an alternative to surgical debridement.[9,10]

1)Contrast Enhanced Ultra sound in pancreatic Biopsy

There have been some new applications of percutaneous core needle biopsy of the pancreas. As is known, the guidance provided by B-mode US may not be suitable for large tumors with non-liquid necrotic tissue, hypo-echoic severe fibrosis, pancreatic local swelling or poorly visible small lesions. Therefore, the injection of contrast medium to identify the viable portion of a pancreatic tumor is considered useful when performing a diagnostic biopsy used CEUS to depict tumor angiogenesis and neo-angiogenesis, which better visualized pancreatic lesions not clearly observed by gray-scale US. **(Figure 5)** Their results indicated that percutaneous CEUS-guided biopsy of the pancreas is feasible for targeted pancreatic lesions that are not definitively positioned by gray-scale ultrasound. [11,12]

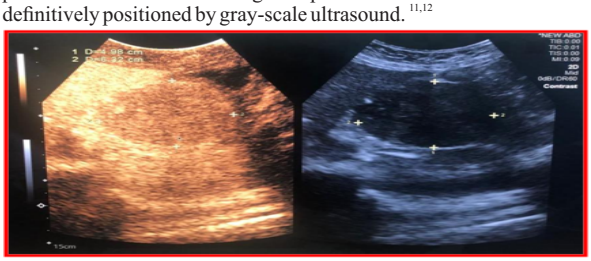

Figure 5 Real time visualisation of the contrast enhanced images of pancreatic lesion

4)Tumor ablation

Tumour ablation was first proposed to debulk tumours that were found to be unresectable during surgery. So many minimally invasive techniques (i.e. laparoscopic, percutaneous, and endoscopic) came into the scenario to avoid unnecessary laparotomies. [13]There are many ablative techniques for pancreatic cancer, which can be divided in three groups

1)Invasive thermal techniques

- Radiofrequency ablation (RFA)
- Microwave ablation (MWA)
- Laser ablation
- Cryoablation

2)Invasive non-thermal techniques

- Ethanol injection
- Irreversible electroporation (IRE)

3) Non-invasive ablative techniques

- high-intensity focused US (HIFU)

Radiofrequency ablation induces coagulative necrosis within the tumour mass through the production of high temperatures, induced by the application of high-frequency alternating current. The necrotic area produced by RFA depends on the type of the needle-electrode. Moreover, technical parameters, as power, influence the temperature and the volume of necrosis. Overall survival is longer in patients treated with RFA instead of classical supportive care. Despite the successful results, there are still few studies regarding percutaneous RFA of pancreatic lesions. However, all authors agreed on the safety and effectiveness of the procedure, not only for ductal adenocarcinoma but also in neuroendocrine tumours and pancreatic metastases.[14]

Microwave ablation is based on tissue heating by mechanical agitation of water molecules induced by microwaves, which ultimately causes coagulative necrosis. Microwaves can spread throughout tissues independently from their electric impedance: this allows to produce faster and larger ablation areas than RFA, thus requiring less applications to obtain complete tumour necrosis. [15]

Irreversible electroporation is the newest and most promising invasive technique for pancreatic cancer ablation. IRE is based on the application of short high-voltage electric pulses, in order to produce multiple micropores on cell membranes causing an irreversible permeabilisation, which leads to disruption of cellular homeostasis, activating apoptotic pathways in tumour cells. The main advantage of IRE compared with other ablative techniques is the ability to preserve the extracellular matrix, thus allowing ablation adjacent to critical structures as nerves, vessels and biliary ducts; IRE is therefore the safest ablative approach for tumours encasing major peripancreatic vessels. Irreversible electroporation has been proposed for palliation of unresectable tumours of the pancreas, as a bridge therapy before surgery, and also as a technique for intraoperative "margin augmentation", in order to reach R0 resection in technically unresectable pancreatic tumours. [16]

Cryoablation is increasingly used for the ablation of unresectable pancreatic cancer. This technique produces a rapid freezing of the lesion down to temperatures between −80° and −160 °C by using a cryoprobe. The biological mechanisms underlying cryoablation are still not fully understood; nevertheless, it is known that this technique leads to the destruction of cell membranes and tissues' ultrastructure, leading to delayed cell necrosis and apoptosis. Ultrasound can be used to guide percutaneous cryoablation, but posterior acoustic shadowing limits visualisation, while at CT the frozen lesion appears as a hypodense "ice ball". [17]

High-intensity focused ultrasound is a non-invasive ablation technique that delivers high-intensity ultrasounds in a definite area in order to produce both thermal and mechanical damage. The target region is heated up to 60–80 °C inducing protein denaturation and tissue necrosis.[18] Both US and MR imaging can be used to guide the procedure; while MR imaging is the most commonly used technique, US has the advantage to identify and displace the bowels in order to improve the effectiveness of the procedure and reduce complications.

One of the most interesting as well as unknown side of ablative techniques is the possible role in immunogenic stimulation. It seems that tumour debris left *in situ* after ablation can induce a systemic immune response against tumour cells, affecting both eventual residual disease and metastases. In particular, non-thermal techniques as well as cavitation phenomenon induced by HIFU, not providing thermal denaturation of tumour antigen, could stimulate strong cytokines production and a T-cell-mediated reaction against tumour cells. [19]Further studies are needed in this field.

CONCLUSION

Ultrasound-guided percutaneous intervention for pancreatic diseases has allowed to develop and refine both diagnostic and therapeutic procedures. Transabdominal US is faster and cheaper than computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic US (EUS). US-guided percutaneous core needle biopsy for pancreatic lesions is promising as it guarantees a real-time imaging that allows to precisely evaluate each step of the procedure. The use of CEUS and fusion imaging allows to increase the accuracy, safety, and feasibility of US-guided percutaneous procedures, reducing time and costs. Ablative techniques are increasingly used and may represent a therapeutic treatment within the multidisciplinary approach to pancreatic cancer.

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