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Research Progress on the Diagnosis and Treatment of Pancreatic Space-Occupying Lesions Using Endoscopic Ultrasonography

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Abstract

The pancreas is a retroperitoneal organ, and the accuracy of traditional imaging in the diagnosis of pancreatic diseases is not high. When a malignant tumor is found, it is often in an advanced stage and the patient loses the opportunity for surgery. Endoscopic ultrasound guided fine needle biopsy has high diagnostic value for pancreatic diseases and is widely used in the diagnosis of pancreatic diseases. Some emerging ultrasound endoscopic imaging techniques, such as elastography and confocal laser endoscopy, have also become important diagnostic tools. Endoscopic drainage under ultrasound guidance is the preferred method for intrapancreatic drainage. Ultrasound-guided radiofrequency ablation, as a new therapeutic approach, is also beginning to play an important role in neoadjuvant and palliative care for pancreatic cancer. The development and popularization of endoscopic ultrasound will provide a new way for the diagnosis and treatment of solid pancreatic diseases.

Keywords

Endoscopic Ultrasonography, Pancreatic Diseases, Diagnosis, Treatment

1. Introduction

Endoscopic ultrasound (EUS) is a technique that combines endoscopy with ultrasound. With the assistance of the endoscopic system, an ultrasound probe is placed in the gastrointestinal cavity for close examination of the digestive tract and adjacent organs. EUS examination is not affected by gas, fat or bone, and can provide real-time high-resolution ultrasound images. EUS is widely used in the diagnosis of pancreatic diseases. With the continuous development of endoscopic

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technology, EUS has gradually developed from the initial diagnostic means to a therapeutic tool. This article introduces the diagnosis and treatment of pancreatic space occupying lesions by EUS.

2. Application of EUS in the Diagnosis of Pancreatic Diseases

2.1. EUS-Guided Fine-Needle Aspiration/Biopsy (EUS-FNA/B)

Endoscopic fine needle aspiration biopsy is a technique for obtaining pathological specimens by fine needle aspiration under endoscopic guidance, which was first reported by Vilmann P [1] in 1992. In the past 30 years, with the continuous evolution and development of endoscopic ultrasound technology, EUS-FNA/B has been widely used in the diagnosis of pancreatic diseases [1]. EUS-FNA technique has good diagnostic value for pancreatic space occupying lesions, and different researchers have different conclusions on the detection rate of its diagnosis. Guo Meng [2] *et al.* showed that the detection rate of EUS-FNA in the diagnosis of pancreatic space occupying diseases was 94.12%, the sensitivity was 92.86%, and the specificity was 100%. Other literature [3] reports detection rates of 70% - 90% for EUS-FNA in pancreatic space-occupying diseases. Sugiyama T [4] *et al.* obtained 97 pancreatic puncture samples from 96 patients with pancreatic space occupying by EUS-FNA, among which 35 were small masses (≤24 mm) and 62 were large masses (>24 mm). The study showed that the size of the masses did not affect the accuracy of EUS-FNA diagnosis. The study showed that tumor size did not affect the accuracy of EUS-FNA diagnosis. One study indicated that rapid on-site evaluation (ROSE) could improve the detection rate, accuracy, and sensitivity for pancreatic malignant tumors [5]. For special pancreatic cystic space-occupying diseases, EUS-FNA/B technology still has important diagnostic significance. A retrospective study [6] found that using direct observation under EUS combined with EUS-FNA could increase the diagnostic rate of neuroendocrine tumors. Current literature shows differences in diagnostic effectiveness between EUS-FNA and EUS-FNB. A meta-analysis of 12 studies showed that compared to EUS-FNB, EUS-FNA had lower diagnostic accuracy and specimen adequacy rates, and required more needle passes, but overall complications and technical failure rates were similar between EUS-FNB and EUS-FNA, suggesting that EUS-FNB seems to be a better choice for diagnosing suspected pancreatic lesions [7]. Another study found that the EUS-FNB group had better diagnostic rates, average number of punctures, and total operation time than the EUS-FNA group, but there was no significant difference in adverse event rates between the two [8].

2.2. Endoscopic Ultrasound Elastography (EUS-EG)

Elasticity refers to the physical property of reversible deformation of an object's surface under external pressure. Objects with different elasticity values deform to different degrees under external pressure. For example, the harder or more solid a tissue is, the less elasticity it has, and thus the less it deforms. Based on this physical phenomenon. Ophir [9] *et al.* described the principle of ultrasound elasto-

graphy (US-EG) in 1991, which quantitatively measures tissue elasticity through imaging to assess tissue hardness. It is generally believed that the hardness of cancerous tissue is higher than that of corresponding healthy tissue, so elastography can be used to determine the benign or malignant nature of tissues. Surface ultrasound is limited by the influence of gas, adipose tissue, and bones, making it difficult to measure the elasticity of the digestive tract and its adjacent organs. However, EUS-EG can overcome these interferences, clearly identify the nature of pancreatic space-occupying lesions, and determine lymph node metastasis. EUS-EG is divided into qualitative elastography and quantitative elastography. A meta-analysis [10] indicated that the sensitivity and specificity of qualitative EUS-EG for diagnosing pancreatic malignant tumors were 98% and 63%, respectively, while those of quantitative EUS-EG were 95% and 61%, respectively. Both qualitative and quantitative EUS-EG have high diagnostic value for pancreatic malignant tumors. Since EUS-EG cannot directly obtain tissue specimens, it cannot directly replace EUS-FNA/B, but can only serve as a supplement when EUS-FNA/B cannot determine the benign or malignant nature of tissues, and guide the optimal area for puncture.

2.3. Contrast-Enhanced Endoscopic Ultrasonography (CE-EUS)

CE-EUS is a relatively new imaging method that uses contrast agents to observe vascular distribution and perfusion in lesions. Based on the different principles and modes of action of contrast agents, CE-EUS is divided into contrast-enhanced color and power Doppler endoscopic ultrasound (CD-EUS) and contrast-enhanced harmonic endoscopic ultrasound (CH-EUS). CH-EUS uses microbubble contrast agents to produce harmonic signals in blood vessels to determine blood flow conditions and differentiate between benign and malignant lesions. CD-EUS uses the Doppler effect principle to display blood flow direction, velocity, and distribution by detecting the reflection of ultrasound waves by moving red blood cells in blood vessels within lesions. CE-EUS can selectively detect vascular lesions and has certain advantages in the diagnosis of pancreatic space occupying diseases. A meta-analysis [11] found that CH-EUS had a sensitivity of 84%, specificity of 78%, positive likelihood ratio of 3.80, and negative likelihood ratio of 0.13 for diagnosing pancreatic solid space-occupying lesions. Another study [12] involving 78 patients with pancreatic solid space-occupying lesions showed that CE-EUS had higher diagnostic rates, sensitivity, and specificity than enhanced CT. Therefore, CE-EUS has good diagnostic value for pancreatic space-occupying diseases.

2.4. Confocal Laser Endomicroscopy (CLE)

CLE uses confocal laser principles to perform high-resolution imaging of tissues during endoscopic examination, simulating real-time "optical tissue biopsy". There are two types of CLE systems: endoscope-based CLE (eCLE) and probe-based CLE (pCLE) that is placed through the endoscope's biopsy channel. eCLE has poor endoscopic operability and is rarely used now, while pCLE can adapt to the diagnosis

of different diseases by selecting different probes. Among them, needle-based CLE (nCLE) is more commonly used in the diagnosis of pancreatic cystic and solid space-occupying lesions. A meta-analysis showed that CLE had a diagnostic accuracy of 88.6% for pancreatic cystic space-occupying lesions, with a combined overall sensitivity and specificity of 82.4% and 96.6%, respectively. Compared to EUS-FNA, nCLE had higher diagnostic rates (91.4%) and sensitivity (94.9%) for patients with pancreatic mucinous cysts, and nCLE was significantly superior to EUS-FNA in terms of diagnostic accuracy for pancreatic cystic space-occupying lesions [13]. Giovannin M first reported that nCLE has high specificity for pancreatic solid space-occupying lesions, with an accuracy of 78%, suggesting that in the absence of ROSE, nCLE can help make judgments based on the cellular morphology of suspected lesions. However, further large-scale studies are needed to confirm the characteristics of mass-forming pancreatitis and other benign lesions [14]. Another study showed that nCLE treatment for focal pancreatic space-occupying lesions is safe and feasible, but its value as an auxiliary diagnosis to EUS-FNA is limited [15]. To improve the accuracy of nCLE in diagnosing focal pancreatic space-occupying lesions, the industry needs to work together to develop new diagnostic standards.

3. Application of EUS in the Treatment of Pancreatic Diseases

3.1. Endoscopic Drainage under Ultrasound Guidance (EUS-GD)

For pancreatic pseudocysts caused by pancreatitis, a meta-analysis including 14 studies showed that compared to percutaneous catheter drainage, EUS-GD could significantly reduce the postoperative recurrence rate and re-intervention rate of pancreatic pseudocysts, with advantages in drainage success rate, clinical cure rate, and postoperative complication rate [16]. Stents commonly used for endoscopic ultrasound-guided pancreatic internal drainage include plastic stents and metal stents, with metal stents further divided into fully covered self-expandable metal stents, partially covered self-expandable metal stents, and uncovered self-expandable metal stents. One study [17] showed that both plastic stents and lumen-apposing metal stents had a 100% success rate in treating pancreatic pseudocysts, with a total adverse event rate of 7.7%, suggesting that lumen-apposing metal stents have advantages in preventing complications and reducing re-interventions. Another study [18] showed no significant differences in success rates and adverse event rates between metal stent and plastic stent groups in treating pancreatic pseudocysts. Currently, using metal stents to treat pancreatic cysts seems to be a better choice, but more research is needed to confirm this.

3.2. Endoscopic Ultrasound-Guided Fine-Needle Injection (EUS-FNI)

EUS-FNI is a technique that precisely injects chemotherapy drugs into unresectable tumor tissues under endoscopic ultrasound guidance to treat advanced pancreatic cancer. Currently, the types of injected drugs include immunotherapy drugs, chemotherapy drugs, oncolytic viruses, and other biological therapies.

Chang K J [19] first used EUS-FNI technology for local injection treatment of pancreatic cancer. This experiment used allogeneic mixed lymphocyte cultures to produce mixed lymphocyte reactions, leading to cytokine release and immune effector cell activation, thereby killing cancer cells. The study included 8 patients with a median survival time of 13.2 months. EUS-guided ethanol ablation (EUS-EA) is currently mainly used for the treatment of pancreatic cystic tumors and pancreatic neuroendocrine tumors. Bang, J.Y *et al.* considered EUS-EA to be a safe procedure with an extremely low rate of serious adverse reactions [20]. Currently, further research is needed on the selection of drugs for injection in pancreatic cancer patients using EUS-FNI technology.

3.3. Endoscopic Ultrasound-Guided Radiofrequency Ablation (EUS-RFA)

Radiofrequency ablation (RFA) is a common surgical method that has been effectively used to treat solid tumors, such as hepatocellular carcinoma [21]. RFA delivers thermal energy to tumors through electrodes, causing tumor cell reduction through different mechanisms such as coagulative necrosis, protein denaturation, and activation of the tumor microenvironment immune system [22]. Due to potential adverse reactions such as acute pancreatitis and thermal damage to adjacent organs, the application of EUS-RFA in pancreatic tumors is not yet widespread [23]. EUS-RFA can be considered an effective, safe, and minimally invasive option for treating pancreatic cystic space-occupying lesions. Khoury T [24] *et al.* evaluated 11 studies and found that the technical success rate of EUS-RFA for treating pancreatic cystic space-occupying lesions was 99.2%, with a total adverse reaction rate of 20.0% and a very low rate of serious adverse reactions at only 0.9%. A case-control study [25] showed that the average tumor diameter significantly increased after treatment in the group receiving systemic chemotherapy alone for pancreatic cancer, while the tumor necrosis rate was significantly higher and the anesthesia requirement was significantly reduced in the group receiving EUS-RFA combined with systemic chemotherapy. However, further multi-center, large-sample studies are needed to confirm the effectiveness of EUS-RFA in treating pancreatic cancer.

3.4. EUS-Guided Photodynamic Therapy (EUS-PDT)

Photodynamic therapy (PDT) is a local ablation technique that uses photosensitizer administration to induce cell death through the production of free radicals after light activation [26]. The effect of PDT in treating solid gastrointestinal malignancies stems from its relative selectivity for malignant cells, minimal impact on connective tissue, and maintenance of intestinal integrity [27]. The application of PDT in the treatment of pancreatic cancer is still in the experimental stage. A study that included 12 patients with pancreatic cancer showed that all patients who received EUS-PDT combined with paclitaxel or gemcitabine experienced an increase in tumor necrosis volume and an overall survival of 2.6 months. Adverse reactions occurred in 8 patients, but none were related to EUS-PDT. One patient

underwent surgery and pathology showed a complete response [28]. In one study [29], 8 patients received EUS-PDT treatment using verteporfin as a photosensitizer. Five patients showed tumor volume reduction, and no adverse events were observed in all patients during surgery or the 3-day postoperative observation period. As a palliative treatment for advanced pancreatic cancer, EUS-PDT requires large-sample, multi-center studies for confirmation, and the selection of photosensitizers also needs further validation.

Overall, the development of endoscopic ultrasound (EUS) has led to significant advances in the diagnosis and treatment of pancreatic space-occupying diseases. In the past few decades, various technologies related to endoscopy have been updated and changed continuously, and the integration of various treatment methods has promoted the progress of technology. The dynamic interaction between these and various treatment methods restored the vitality of the ultrasound endoscope and formed the development trajectory of the treatment of pancreatic diseases. This treatment is developed in the direction of simplification and minimization, aiming to improve the quality of life and survival rate of patients. In the future, ultrasound endoscopy will require the endoscopist to reach a more proficient level. At present, there is limited long-term evidence or prognostic data for some endoscopic ultrasound techniques, but their progress is expected to lead to wider recognition of their use in pancreatic diseases and a deeper collection of various assistive technologies, promoting integration and dissemination, and ultimately bringing more benefits to patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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