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Can Contrast-Enhanced Harmonic Endoscopic Ultrasonography Differentiate Malignancy from Benign Disease?

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See "Clinical Value of Contrast-Enhanced Harmonic Endoscopic Ultrasonography in the Differential Diagnosis of Pancreatic and Gallbladder Masses" by Galam Leem, Moon Jae Chung, Jeong Youp Park, et al., on page 80-88.

Endoscopic ultrasonography (EUS) was developed in the 1980s and is now commonly used for diagnosis and treatment of pancreatobiliary disease. Diagnostic and interventional EUS techniques are diverse and include the detection of small pancreatic or biliary lesions, tumor staging, tumor and cyst ablation, and biliary drainage. However, conventional diagnostic EUS has several limitations. First, the sensitivity and specificity of diagnostic EUS relies on the experience of the endoscopist. Second, EUS cannot be used to assess tumor vascularity and hemodynamics. Third, the use of imaging techniques alone has not proven to be an adequate replacement for pathologic diagnosis. Finally, recent advances in computed tomography (CT) and magnetic resonance imaging (MRI) techniques have allowed for the collection of more objective and comprehensive data than was previously possible. Addressing some of the limitations of EUS, newer techniques have been developed that improve characterization of detected lesions. One of these techniques, EUS-guided fine needle aspiration or biopsy (EUS-FNA/B), represents a major advancement in the diagnosis of pancreatic tumors. To improve the histological yield, novel EUS-FNA needles with core or sharp tips have recently been developed. However, despite EUS-FNA/B having a cytological and histological diagnostic accuracy as high as 95% for pancreatic masses, there is still a need for simpler and less invasive methods.[1-5]

Contrast-enhanced harmonic ultrasonography (CH-EUS) is a new emerging diagnostic technology that can be used to assess blood flow inside tissues. CH-EUS may improve the detectability of tumors, and allow characterization of tumor vascularity. Whereas a Doppler image can detect large vascular lesions, CH-EUS takes advantage of the high image resolution of EUS and identifies smaller vessels by using microbubbles. It is also able to selectively depict microbubble signals from ultrasound contrast agents.[1-4] Thus, CH-EUS may be able to provide real-time information about a tumor, as compared to Doppler, CT, or MRI. Recently developed techniques for EUS system include tissue harmonic echo, elastography, and contrast enhancement.

In a recent issue of *Clinical Endoscopy*, Leem et al.[6] reported the clinical value of CH-EUS in the differential diagnosis of pancreatic and gallbladder masses. While it was not possible to quantitatively measure the degree of enhancement on account of the retrospective study design, the results were sufficient to prove the superiority of CH-EUS over conventional EUS in the differentiation of solid pancreas lesions. The ability of EUS to evaluate both texture and enhancement pattern may improve diagnostic utility, particularly for pancreatic adenocarcinoma. The enhancement pattern alone showed higher sensitivity (82.0%) and specificity (87.9%) for ductal

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adenocarcinoma than echogenic pattern alone (sensitivity and specificity of 49.0% and 93.3%, respectively). When diagnosing neuroendocrine tumors, a combined hyperenhancement and homogeneous pattern on CH-EUS improved sensitivity from 81.1% to 85.3%, and specificity from 90.9% to 91.0%, when compared with a hyperenhancement pattern alone.[6] On the other hand, malignant gallbladder masses did not show a specific enhancement pattern on CH-EUS. For these tumors, the authors used the echogenic and vascular enhancement textures (inhomogeneous or homogeneous) for diagnosis. An inhomogeneous enhancement texture on CH-EUS was the most predictive parameter for diagnosing malignant masses, with a sensitivity of 97.1%.[6]

Recent reports have shown that CH-EUS has a higher diagnostic accuracy for pancreatic cancers than conventional techniques.[7-10] While the benefits of CH-EUS over conventional EUS are readily apparent, a similar level of discrimination is possible with dynamic MRI or CT. Furthermore, CT or MRI is commonly performed prior to EUS and used as a reference. To determine if CH-EUS is superior to conventional methods, more research that directly compares the utility and accuracy of different modalities is required. Currently, EUS is used to supplement conventional imaging, particularly due to the limitations discussed above. While previous studies have reported superior sensitivity and specificity when using EUS, these reports show significant discrepancies among endoscopists, and often do not report objective findings.

Cancer staging, especially depends on the use of imaging techniques such as CT or MRI for objective characterization and differentiation. Recent improvements in conventional techniques have resulted in higher resolution images, which may widen the gap between these modalities and EUS still further. The role of EUS could change in the future as more research is completed, particularly, if EUS is able to alleviate the need for pathologic diagnosis. At present, EUS serves as a useful adjunct to conventional techniques and may provide additional information; the amount of information that it provides could be further increased through the use of CH-EUS.

CH-EUS has a diverse array of uses including assessment of solid tumors and cystic lesions of the pancreas, characterization of submucosal neoplasms, assessment of biliary neoplasms, and assessment of lymph nodes. Some of the additional benefits and limitations of CH-EUS will be discussed subsequently. CH-EUS has limited utility when attempting to differentiate mass-forming pancreatitis, as it cannot distinguish between normal pancreas parenchymal lesions and focal mass forming inflammatory lesions. Regarding additional benefits, first, CH-EUS does have the ability to visualize small blood vessels within a tumor, if used with ultrasonographic contrast agent. This allows for specific targeting of lesions, while avoiding small blood vessels and necrotic tissue, so that CH-EUS-guided FNA/B may require fewer needle passes.[11,12] Second, it is difficult to differentiate between mural nodules and mucus clots using conventional EUS method. Contrast-enhanced dynamic CT or MRI can reveal the vascularity of large mural nodules, however has only limited utility for the assessment of small nodules. An advantage of CH-EUS is its ability to identify and characterize relatively small mural nodules and provide a more accurate differentiation by confirming the presence of vascularity. This is invaluable when differentiating between mural nodules and pancreatic cystic lesions.[13-15] Third, CH-EUS may be applied to cancer staging and post-treatment evaluation. CH-EUS is useful when assessing tumor grade before chemotherapy, and can be used to evaluate the degree of tumor perfusion. The efficacy of successful tumor ablation may be predicted from vascularity changes brought about by chemotherapy, characterized using CH-EUS. The extent of tumor blood flow has been shown to predict chemotherapeutic sensitivity and overall mortality.[16] Matsui et al.[17] showed changes in tumor size and vascularity by using a CH-EUS during chemotherapy in patients who have gastric cancer. Highly vascular tumors may be more chemosensitive due to increased drug penetetration.[18]

In conclusion, CH-EUS is a useful and simple technique for the differentiation of pancreas and solid organ tumors. With further technical improvements, it may adequately substitute conventional imaging techniques and allow diagnostic confirmation prior to the decision to proceed with surgery.

Conflicts of Interest

The author has no financial conflicts of interest.

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