Article published online: 2021-06-03

Endoscopic Ultrasound for Detection of Liver Metastasis: Hope or Hype?

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J Digest Endosc 2022;13:61–64.

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Abstract

Transabdominal ultrasonography, contrast-enhanced computed tomography, and magnetic resonance imaging (MRI) are the common diagnostic tests for the detection of hepatic lesions. Use of enhanced and advanced MRI technique, that is, diffusion weighted MRI and hepatocyte-specific contrast agents, has further improved the accuracy of detection of metastatic liver lesions ≤ 10 mm in diameter. However, even with these advanced imaging modalities sensitivity is low for lesions smaller than 10 mm when compared with standard intraoperative ultrasound. Endoscopic ultrasound (EUS) is an emerging imaging modality with resolution sufficient to detect and sample lesions as small as 5 mm in diameter. In this news and views, we have discussed the role of standard and enhanced EUS for the detection of metastatic liver lesions.

Keywords
- endosonography
- liver
- metastasis

Noninvasive transabdominal ultrasonography (USG) and computed tomography (CT) have long been used to survey the liver structural abnormalities, including benign as well as malignant lesions. Liver is a principal metastatic site for gastrointestinal (GI) malignancies.[1] The most common primary sites for metastatic lesions to the liver are malignancies of the colon, stomach, pancreas, breast, and lung. Multiple liver metastases are common and often vary in size.[2] Transabdominal USG, contrast-enhanced CT (CECT) and magnetic resonance imaging (MRI) are the common diagnostic tests for the detection of hepatic lesions.[3] Other imaging modalities used for the detection of liver metastasis include fluorodeoxyglucose (FDG)-positron emission tomography (PET) and endoscopic ultrasound (EUS).[4]

EUS has increasingly been used for the diagnostic and therapeutic indications for pancreato-biliary lesions. For malignant diseases, EUS is important in the staging of GI and thoracic malignancies.[5–7] EUS provides the information about the depth of invasion (T stage) as well as lymph node involvement (N stage) with additional benefit of EUS guided tissue acquisition in the same setting.[5] EUS has also been used to screen the patients for metastasis at the accessible sites including celiac axis lymph nodes (for tumors arising above the diaphragm), mediastinal lymph nodes (for tumors below the diaphragm), the left adrenal gland, and the liver. Examination of the entire liver requires close attention and frequent "pull-through" views with dynamic transgastric and transduodenal imaging.[8] Despite good visualization of liver on EUS, use of EUS in liver lesions is mainly restricted to obtaining tissue for histopathological evaluation. Emerging role of EUS-guided liver tumor ablation/injection,[9] fiducial placement for stereotactic body radiation therapy,[10] selective portal vein embolization,[11] cyst ablation,[12] and liver abscess drainage[8] has been described. However, the use of EUS for optimizing the screening of the liver for metastasis is unclear and still evolving.

DOI https://doi.org/10.1055/s-0041-1728234.
ISSN 0976-5042.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Among the available noninvasive imaging, sensitivity of transabdominal USG, dynamic CT scan, MRI, and FDG-PET/CT for the detection of metastatic liver lesions are 55%, 72 to 83.6%, 76 to 88.2%, and 90 to 94.1%, respectively.[13–17] The sensitivity further drops to 20% for USG and 48% for dynamic CT when the lesion is $\leq$ 10 mm.[15] The sensitivity of MRI is high when characterization of the lesion deemed to be "too small to characterize" on multidetector CT studies.[18] Use of enhanced and advanced MRI technique, that is, diffusion-weighted MRI and hepatocyte-specific contrast agents, has further improved the accuracy of detection of metastatic liver lesions $\leq$ 10 mm in diameter, peripherally (subcapsular) located lesion, and after neoadjuvant chemotherapy.[19,20] However, even with these advanced imaging modalities sensitivity is low for lesions smaller than 10 mm when compared with standard intraoperative ultrasound. EUS is an emerging imaging modality with resolution sufficient to detect and sample lesions as small as 5 mm in diameter. Diagnosis of these smaller occult lesions can spare the patients from attempted curative resection.

In this news and views, we have discussed the role of standard and enhanced EUS for the detection of metastatic liver lesions. Early studies had used the standard B-mode EUS for the detection of metastatic lesions in the liver and compared with conventional dynamic CT with focus on the left lobe of liver.[21,22] A recent study explored the role of novel Kupffer phase imaging in contrast-harmonic (CH)-EUS for detection of liver metastasis.[23] Though limited studies are available for the usefulness of EUS for detection of liver metastasis, recent study throws some light and gives hope for the detection of small liver metastasis using enhanced EUS.[23]

Studies have shown the added benefit of B-mode EUS in the detection of small occult liver metastasis in 1.9 to 5% of the patients in addition to the conventional imaging, which were either missed or indeterminate on conventional imaging.[22,24,25] However, the additional detection with EUS was mainly restricted for the smaller lesions, that is, $\leq$ 10 mm in diameter. Singh et al in a prospective study found the higher diagnostic accuracy for liver metastasis with EUS/EUS-FNA (98%) compared with CECT (92%) in 132 patients with GI malignancies.[21] The EUS/EUS-FNA detected a significantly higher number of malignant liver lesions in both lobes of the liver compared with CT scan (40 vs.19; p = 0.008). McGrath et al examined the left lobe of liver using EUS in 76 patients of esophageal carcinoma and found occult metastasis in 5% patients that was not evident on noninvasive imaging (dynamic CT scan).[22] 80% of these patients with occult liver metastasis had lesions of size $<$10 mm. Prasad et al[24] and Nguyen et al[25] also reported detection rates of 2.3 and 1.9%, respectively, for occult liver metastases with EUS and suggested the higher accuracy compared with CT scan.

Furthermore, the modifications in EUS techniques, including a validated EUS scoring system,[26] real-time elastography,[8] contrast-enhancement,[27] have improved the diagnostic ability of EUS for focal liver lesions. Recently developed EUS scoring system helped in differentiating the benign and malignant lesion with a positive predictive value of 88%.[26] Among the other techniques, EUS-guided real-time elastography provides semiquantitative measurements of tissue stiffness and helps in determining the nature of the lesions. Contrast-enhanced (CE-EUS) is an emerging technique for characterizing the liver lesions by improving the vasculature image of the lesion and distinguishes vascular-rich and hypovascular areas of a target lesion.[27,28]

In a recent paper, Minaga et al[23] used modified CH-EUS with Kupffer phase imaging in patients with pancreatic cancer. The authors used CH-EUS during the EUS staging, and they compared the sensitivity, specificity, and diagnostic accuracy of CECT, fundamental B-mode EUS (FB-EUS), and CH-EUS for diagnosing the left-lobe liver metastasis. The diagnostic algorithm includes the initial FB-EUS scanning of the left liver lobe, followed by a study of the pancreatic mass, first in FB-EUS and then after the intravenous infusion of contrast agent. After the pancreatic study (for 60 seconds after the injection of contrast agent), EUS-guided biopsy of the pancreatic mass was performed (within 10–15 minutes). Finally, the left liver lobe was studied in the Kupffer phase and an EUS-guided liver biopsy was performed if any evidence of metastasis lesion was detected, to histologically confirm the malignant nature of lesion. Authors found sensitivity of CECT, FB-EUS, and CH-EUS as 69.8, 76.7, and 96.6%, respectively. Liver metastatic lesions, with reduced Kupffer cells, were visualized as a perfusion defect on EUS during the Kupffer phase. This "simple" cell-related mechanism can detect even very small lesions. The sensitivity of CH-EUS for detecting liver metastasis $<$10 mm was higher than that of CECT or FB-EUS ($p < 0.001$). In 2.1% patients, only CH-EUS could detect a single distant metastasis of the left liver lobe that was missed by other imaging modalities including CECT scan, FB-EUS, and even by MRI and FDG-PET in a few cases and saved from unnecessary surgeries. In conclusion, authors demonstrated that the overall diagnostic accuracy of CECT, FB-EUS, and CH-EUS was 90.6, 93.4, and 98.4%, respectively and suggested the use of Kupffer imaging CH-EUS for pretreatment evaluation of patients with pancreatic carcinoma.

Commentary

Liver is the commonest site for the metastasis of GI cancers. The optimal approach to screen liver for metastases is unclear. Conventionally, dynamic CECT is the imaging modality used to detect liver metastasis and extrahepatic lesions. CT provides advantage of easy availability, affordability, and detection of extrahepatic metastasis; however, it suffers from the low sensitivity for detection of liver metastasis particularly for smaller lesions, $\leq$ 10 mm diameter. Among the other available imaging, enhanced MRI imaging has increased the detection accuracy for liver metastasis[19,20] however, MRI suffers from demit of only segmental evaluation with ceiling benefit for detecting small lesions. PET-CT has been proven very sensitive for the diagnosis of liver metastasis with undoubted benefit of whole-body examination for extrahepatic metastasis, which places it ahead of any other imaging for decision making. However, PET-CT is costly, with limited availability and also loses the sensitivity for detection of smaller diameter (≤ 10 mm) lesions.

CE-EUS has come up with a hope for detection of these smaller liver metastases that are often missed on conventional imaging.[23] Recent study by Minaga et al[23] using CH-EUS with Kupffer phase imaging improved the diagnostic accuracy for detection of smaller lesions (≤ 10 mm) even for lesions missed with FB-EUS. CE-EUS also have several benefits over CT and MRI[8]: (1) it provides real-time imaging; (2) contrast used for enhancement is not excreted by kidney and can be performed in patients with renal insufficiency, where CECT or CE-MRI is contraindicated; (3) confinement in the vascular space without extravasation into the interstitial fluid allows a prolonged enhancement of the vascular system and the evaluation in the different vascular phases; (4) it provides higher resolution compared with other imaging modalities and enables the full study of enhancement dynamics of lesions; and (5) EUS-FNA can be performed for liver lesions at the same setting.

Despite potential benefits of EUS, several questions still need answers before EUS can be considered for liver screening for metastatic lesions in routine practice. Which echoendoscope, linear, radial or both, to consider for examination? Whether to consider the standard EUS imaging or enhanced EUS? Whether all lesions detected require histopathological examination? Could complete liver examination be possible with EUS? These issues are unsettled with certain studies providing evidence to solve these concerns. Most studies have used linear echoendoscope that provides additional benefit of tissue acquisition during the same procedure; however, the comparative data for the two types of techniques for metastatic lesion evaluation is not available.[21,23,24] Recent data have supported the use of CE-EUS imaging that increases the diagnostic accuracy for lesion detection.[23] The EUS scoring system also helps in detecting the nature of lesion[26] however, the literature so far favors histopathological examination of any suspicious lesion. For examining the whole liver, studies have used EUS at 5MHz that allow the imaging of the entire depth of the liver including the right lobe, subcapsular location, and abdominal wall. A pertinent question is whether EUS, when done for all the patients with cancer, adds clinically significant information when the patients in most cases have undergone noninvasive imaging, that is, CT scan and MRI. The benefit of added EUS for detection of metastatic lesions is still in early phase and needs more studies to validate its benefit and cost-effectiveness. EUS is an operator-dependent technique with additional cost of procedure and anesthesia compared with conventional imaging. Moreover, recent advances in conventional imaging (e.g., multidetector CT, enhanced MRI, FDG-PET/CT, and FDG-PET/MRI) have also increased the detection accuracy for liver metastasis for smaller lesions (<10 mm in diameter).

In conclusion, EUS with or without enhancement is an emerging newer modality for detection of occult liver metastasis and gives new hopes for detecting smaller lesions, which are missed on conventional imaging. However, the requirement of expertise, limited availability, cost concerns precludes the routine use of EUS for screening of metastatic liver lesions. Further larger studies are required before the EUS can be routinely advocated to screen liver metastasis.

Conflict of Interest
None declared.

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