REVIEW

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A Review of the Appropriateness of the Current Italian Guidelines for Noninvasive Imaging Assessment of Focal Liver Lesions

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ABSTRACT

In 2007 the Italian National Institute of Health issued Guidelines for the use of diagnostic imaging techniques in the detection and the characterization of focal liver lesions. Since the publication of these guidelines in 2008, several studies relating to this topic have been published. Thus, we felt the need to assess whether interval research and new advancements in diagnostic imaging have yielded new evidence that should modify the recommendations that were previously issued. The literature search confirmed the appropriateness of the current guidelines. Although most modalities did not show substantial changes, interval introduction of DW-MRI is a valuable technique with a high diagnostic accuracy in the detection and characterization of FLLs, and its sensitivity is higher when combined with MRI.

Key words: diagnostic imaging techniques – focal liver lesions – guidelines – liver – contrast-enhanced ultrasound – computed tomography – magnetic resonance imaging – positron emission tomography – ultrasound – ablation therapy.

Abbreviations: AASLD: American Association for the Study of Liver Disease; CE-IOUS: contrast-enhanced intraoperative US; CEUS: contrast-enhanced ultrasound; CRLM: colorectal liver metastasis; DW-MRI: diffusion weighted MRI; EOB-MRI: gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid MRI; FLLs: focal liver lesions; HCC: hepatocellular carcinoma; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NPV: negative predictive value; PET: positron emission tomography; PPV: positive predictive value; RF: radiofrequency; TACE: transarterial chemoembolization

INTRODUCTION

As several imaging modalities for detection and characterization of focal liver lesions (FLLs) are available, the challenge is to choose the optimal modality for each particular clinical setting. In asymptomatic patients without risk factors, FLLs incidentally detected on imaging are usually benign; thus, it is of the outmost importance to arrive at a definitive diagnosis without unnecessary risks and costs [1, 2]. On the other hand, primary liver cancer (HCC) is the second common cause of death from cancer worldwide, with an estimated 746,000 deaths in 2012 [3]. The prognosis for liver cancer is very poor, with an overall ratio of mortality to incidence of 0.95, and as such the geographical patterns in incidence and mortality are similar [3, 4]. Imaging of HCC is an integral component of a multi-modality approach and frequently requires the most sophisticated techniques, which are often repeated throughout the course of the disease. Further, early detection and characterization of primary and metastatic liver cancers may allow more effective treatments, thus improving the patients' survival.

For all these reasons, in 2007 the Guidelines System of the Italian National Institute of Health produced guidelines for the use of the noninvasive diagnostic imaging techniques in the detection and the characterization of FLLs [5, 6]. They were based on a systematic review of the literature in the English language. Since the publication of these guidelines, several other studies have been published motivating us to assess whether interval research and new advancements in diagnostic imaging have yielded new evidence that would justify modification of the recommendations that were previously issued.

We used the same key questions as used to develop the original guidelines, except for question no.5, regarding the follow-up of patients with FLLs characterized as benign, as we felt that there is no additional current knowledge on this topic since the original publication of the guidelines.

METHOD

Clinical questions

What is the role of ultrasonography (US), contrast-enhanced ultrasonography (CEUS), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) in:

(1) Detection of FLLs in (i) oncologic patients; (ii) patients with chronic liver disease;

(2) Characterization of FLLs in patients with (i) unknown pathology; (ii) chronic liver diseases; (iii) oncologic diseases;

(3) Loco-regional staging of primary liver cancer; that is, number of lesions, size, site, relations with anatomo-functional structures and lymph node involvement;

(4) Assessment of complications and immediate and long-term (follow-up) treatment response in patients undergoing oncologic treatments, for example, chemotherapy, radiofrequency (RF) ablation, percutaneous ethanol injection, laser, microwave, trans-catheter arterial chemoembolization, trans-catheter arterial embolization, cryotherapy, and surgery.

Literature search, inclusion and exclusion criteria

An electronic search of all published articles in English was completed on PubMed, Pascal, Embase, Cochrane Library and SciSearch using the following search terms alone or in combination: echography, ultrasonography, ultrasound, sonography, contrast-enhanced, US, CEUS, contrast-enhanced ultrasound, contrast-enhanced sonography, contrast-enhanced ultrasonography, CT, computed tomography, tomography, emission computed, diagnostic imaging, tomography emission computed, computer-assisted emission tomography, positron emission tomography, magnetic resonance imaging, MRI, PET, positron emission computed, positron emission tomography.

We used the same inclusion and exclusion criteria as before except for studies dealing with the comparison between US and CEUS, which were excluded because today in our belief the superiority of CEUS over US for characterization of FLLs is accepted as a fact.

All articles published between January 2008 and December 2013 were included: systematic reviews, meta-analyses, clinical trials and diagnostic studies, prospective and retrospective, on the use of imaging techniques for the study of FLLs.

Studies that did not have as their primary objective the evaluation of FLLs using imaging techniques and that did not have a reference standard were excluded. Case reports, letters to the editors and narrative reviews were also excluded.

The online search yielded 4,376 titles and abstracts, 1,511 of which were considered to be suitable. These titles were subjected to further selection; 650 studies were selected and 317 actually used for data rating. One hundred and seventeen studies were chosen for the final adherence-to-guidelines topic evaluation.

In reporting the data of the included studies it was understood that CT, MRI, or PET/CT were performed using also a contrast agent unless otherwise specified.

RESULTS

Question no. 1

What is the role of US, CEUS, CT, MRI, and PET in the detection of FLLs in oncologic patients and patients with chronic liver disease?

Oncologic patients

The performance of CT, MRI and PET in the diagnosis of liver metastases from colorectal cancer (CRLM) was analysed in two meta-analyses [7, 8]. On a per-patient basis, sensitivity was 74.8- 83.6% for CT, 81.1-88.2% for MRI and 93.8-94.1% for PET. On a per-lesion basis, sensitivity was 74.4-82.6% for CT, 80.3-86.3% for MRI and 81.4-86.0% for PET. In a per-lesion analysis, the performance of MRI was higher than that of CT when liver-specific contrast agents were administered.

With respect to PET, CT showed a lower sensitivity in the per-patient analysis ($P = 0.025$). For lesions smaller than 10mm, the sensitivity of MRI was higher than that of CT. No difference was found for lesions ≥ 10mm.

In a meta-analysis that included 13 studies with a total of 1,900 lesions the accuracy of MRI with liver-specific contrast agent for the detection of liver metastases was determined [9]. The pooled weighted sensitivity and specificity were 0.93 (95% CI, 0.90-0.95) and 0.95 (95% CI, 0.91-0.97), respectively, and the positive (LR+) and negative likelihood ratio (LR-) were 18.07 (95% CI, 10.52 -31.04) and 0.07 (95% CI, 0.05-0.10). The area under the receiver operator characteristic (AUROC) curve was 0.98 (95% CI, 0.96-0.99).

For the detection of CRLM, the diagnostic accuracy of MRI on a 3 Tesla system and of PET/CT were compared [10]. EOB-MRI showed better performance than PET/CT for lesions ≤ 1cm (mean area under the Az 0.92 vs. 0.60, $P < 0.001$). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) on a patient basis were 100%, 71%, 97%, and 100% for MRI and 93%, 71%, 97%, and 57% for PET/CT.

A systematic review investigated the diagnostic accuracy of PET/CT for CRLM [11]. PET/CT had higher sensitivity and specificity than CT (PET/CT: 91–100% and 75–100%, respectively; CT: 78–94% and 25–98%, respectively). For local recurrence PET/CT demonstrated better accuracy than CT (sensitivity, 93-100%; specificity, 97-98% for PET/CT vs. 0–100% and 97–98% for CT).

The studies that compared the accuracy of CEUS to that of CT found that these methods have similar sensitivity and specificity in the detection of liver metastases [12-14]. It was reported that contrast-enhanced intraoperative US (CE-IOUS) could provide additional information to that obtained using either preoperative imaging or conventional intra-operative examinations [15].

Patients with chronic liver disease

A meta-analysis demonstrated a statistically significant higher sensitivity for early HCC detection with US every 6 months than with annual surveillance [16]. The sensitivity of US surveillance for the detection of HCC ranged from 36.4% to 94% [17, 18].

For several years, DW-MRI has been available. Two meta-analyses investigated the diagnostic performance of MRI and diffusion weighted (DW)-MRI for the detection of HCC [19, 20]. DW-MRI allows tissue characterisation by probing tissue micro-structural changes, quantified as the apparent diffusion coefficient. These meta-analyses showed that, among patients with low pre-test probabilities, MRI enabled exclusion of HCC. In studies in which both DW-MRI and conventional MRI were performed, the comparison of DW-MRI performance with that of conventional MRI suggested that there were no major differences between these two methods. DW-MRI combined with MRI had higher pooled sensitivity than DW-MRI alone (93% vs. 73%; $P < 0.05$).

The diagnostic performance of MRI is reported to be higher than that of CT; however, these differences did not reach statistical significance [21, 22].

In conclusion, the literature review confirmed the robustness of the previous recommendations; i.e. MRI is the preferred first-line imaging modality for evaluating CRLM in patients who have not previously undergone therapy. PET can be used as the second-line modality. CEUS could be used as a screening examination for the detection of FLLs in oncologic patients. In cases of negative CEUS results, a diagnostic confirmation with CT or MRI using a hepato-specific contrast agent is necessary. US surveillance should be performed at 6-month intervals in patients with cirrhosis. CT or MRI using a hepato-specific contrast agent should be used only when the results are doubtful (new nodules > 1cm or nodules that enlarge over a time interval), or when the patient has a lesion which is highly suspected for HCC.

Question no. 2

What is the role of US, CEUS, CT, MRI, and PET in the characterization and in the diagnostic confirmation of FLLs in patients without known pathologies, in oncologic patients and in subjects with chronic liver disease (cirrhosis or not)?

Patients without known pathologies

In a meta-analysis that included 21 studies, the diagnostic value of CEUS with SonoVue® was compared to that of CT and MRI [23]. Sensitivity and specificity, respectively, were 88% (95% CI, 87–90) and 81% (95% CI, 79–84) for CEUS; 90% (95% CI, 88–92) and 77% (95% CI, 71–82) for CT; 86% (95% CI, 83–88) and 81% (95% CI, 76–85) for MRI. The diagnostic accuracy of CEUS was not significantly different compared to CT or MRI.

Some studies analysed the characterization of benign and malignant lesions comparing CT and MRI [24-26]. Sensitivities were 71.1-92.9% for CT, and 93.4-97.6% for MRI.

Two meta-analyses [27, 28] and two studies [29, 30] evaluated the ability of DW-MRI in differentiating malignant hepatic tumours from benign lesions: the rate of correctly characterized FLLs using DW-MRI was 73.2-89.1% for all lesions, 64-83% for benign lesions and 84.5-92.3% for malignant lesions.

Patients with chronic liver disease

The diagnostic accuracy of CEUS and MRI in the assessment of arterial hypervascularity of HCC and dysplastic nodule, using CT during hepatic arteriography as the reference standard, was compared [31]. The average AUROC curve was significantly higher with CEUS (0.94; 95% CI, 0.88-1.00) than with MRI (0.84; 95% CI, 0.74-0.93) ($P = 0.0014$). Compared to dynamic MRI, CEUS showed a slightly lower diagnostic performance for the characterization of nodules ≤ 20 mm detected during US surveillance [32]. Sensitivity, specificity, PPV and NPV were 61.7%, 96.6%, 97.4%, 54.9%, for MRI, and 51.7%, 93.1%, 93.9%, 50.9%, for CEUS.

The diagnostic performance of unenhanced US, CT and MRI in cirrhotic patients who were candidates for liver transplantation were compared [33]. The accuracy for detection of HCC ≤ 1 cm was 0.58 (95% CI, 0.40-0.74) for unenhanced US, 0.57 (95% CI, 0.39-0.70) for CT, 0.56 (95% CI, 0.38-0.70) for MRI and 0.62 (95% CI, 0.45-0.73) for MRI (pre + dynamic + hepatobiliary phase).

Sensitivity and specificity of DW-MRI and MRI for the characterization of small HCC (≤2 cm) were 52-74.3% and 60%- 94.7% for DW-MRI, 37.1%-84% and 57.9%- 65% for MRI, respectively. The combined use of DW-MRI/MRI had a sensitivity ranging from 71.4% to 97.5% [34-37].

Oncologic patients

The usefulness of CEUS with Sonazoid for the diagnosis of hepatic malignancies in comparison with CT findings was evaluated [38]. Sensitivity, diagnostic accuracy and PPV were higher for CEUS than CT: 95.4%, 94.7%, 99% for CEUS vs. 85.2%, 82.3%, 95.8% for CT, respectively. For the evaluation of CRLM, the sensitivities of CEUS and CT were 69% for CEUS and 59% for CT for all lesions; 37% for CEUS and 20% for CT for lesions < 1cm [39].

As for the performance of PET/CT and CT in the detection and characterization of hepatic metastases, the sensitivity and specificity of CT were 87.9% and 16.7%, whereas that of PET/CT were 97 and 75%, respectively [40].

A meta-analysis assessed the diagnostic performance of DW-MRI in patients with hepatic metastases [41]. Across 11 studies including 537 patients, DW-MRI showed 87% (95% CI, 80-91) sensitivity and 90% (95% CI, 86-93) specificity. In studies in which both DW-MRI and MRI were performed, the comparison of DW-MRI performance with that of MRI suggested that there were no major differences between the two methods ($P > 0.05$). DW-MR imaging combined with MRI had higher sensitivity and specificity, respectively, than DW-MRI alone (97% vs. 86% and 91% vs. 90%) ($P < 0.05$).

Sensitivity, specificity, and accuracy for characterization of liver lesions detected on non-enhanced PET/CT were 67%, 60% and 66%, respectively; those on CE-PET/CT were 85%, 100%, and 86%, and those on MRI were 98%, 100%, and 98%, respectively [42].

In conclusion, the literature search confirmed that CEUS is a good imaging tool for the characterization and the diagnostic confirmation of lesions detected by other imaging technique, in particular in the assessment of arterial hypervascularity of HCC and the dysplastic nodule. If CEUS is not available or does not give a definitive result, the use of MRI with a hepato-specific contrast agent is recommended. CT should be used only when CEUS and MRI are not available. The combined use of DW-MRI/MRI has a better sensitivity than DW-MRI

or MRI alone for the characterization of small HCC (≤2 cm) and liver metastases.

Question no. 3

What is the role of US, CEUS, CT, MRI, and PET in the locoregional staging of primary liver cancer, that is, number of lesions, size, site, relations with anatomo-functional structures and lymph nodes involvement?

The role of CEUS in the assessment of tumour vascularity was analyzed only in two articles and they concluded that CEUS is a useful tool for assessing the vascularity of HCC and for evaluating microvascular morphology and angiogenesis [43] and it is as accurate as dynamic CT; however, the detectability of HCC vascularity is affected by location [44].

Three CT studies have concluded that the presence of minute hepatic venous invasion in HCC is difficult to determine even on combined CT hepatic arteriography and CT arterioportography [45-47].

In a study of 66 patients, the preoperative MRI findings, that reflect histopathological microvessel invasion in HCC were identified [48]. In the multivariate analysis, irregular circumferential peritumoral enhancement showed statistical significance (odds ratio 13.0), suggesting a high probability of microvessel invasion of HCC.

The literature search confirmed that CT and MRI are recommended in the loco-regional staging of primary liver cancer.

Question no. 4

What is the role of US, CEUS, CT, MRI and PET in the assessment of complications and immediate and long-term (follow-up) treatment response in patients undergoing oncologic treatments (chemotherapy, RF ablation, percutaneous ethanol injection, laser, microwave, trans-catheter arterial chemoembolization, trans-catheter arterial embolization, cryotherapy, surgery)?

Several articles evaluated the role of imaging in the early assessment of response to treatments (24 h) [49-53]. CEUS was compared with CT as reference standard in several studies [49-52]. One study concluded that the diagnostic accuracy of CEUS performed at the end of the thermal ablation session is comparable to both CEUS and CT performed at 24 h [51]. Post-procedural CEUS can be used to detect and retreat residual viable tissue in the same ablation session [49, 50].

CEUS performed one day after TACE is more sensitive than CT performed at one month for detecting residual viable HCC [52].

The role of DW-MRI in evaluating therapeutic efficacy after TACE in HCC was analysed [54, 55]. Apparent diffusion coefficient from DWI can evaluate the efficacy of TACE for HCC as effectively as CT and may help in deciding whether to repeat TACE.

The role of PET for detecting local tumour recurrence of ablated CRLM was assessed in a meta-analysis [56]. Sensitivity and specificity were 73% (95% CI, 50–88) and 85% (95% CI, 72–93), respectively. PET/CT was superior to CT in detecting recurrence after RF ablation in 25% of patients with CRLM [57].

Another meta-analysis assessed the diagnostic performance of MRI, CT, PET, and PET/CT for preoperative detection of CRLM in patients treated with neo-adjuvant chemotherapy [58]. Pooled sensitivity estimates of MRI, CT, PET, and PET/CT were 85.7% (95% CI, 69.7–94.0), 69.9% (95% CI, 65.6–73.9), 54.5% (95% CI, 46.7–62.1), and 51.7% (95% CI, 37.8–65.4), respectively.

The literature review confirmed that for the assessment of complications and immediate and long-term treatment response in patients undergoing oncologic treatments, the most suitable diagnostic imaging technique is highly dependent on the type of treatment used.

CEUS is a good diagnostic tool for the early evaluation and for the follow-up at 1 month of treated HCCs, In fact, it shows efficacy similar to CT and MRI. To evaluate treatment efficacy it is advisable to perform CEUS immediately after RF ablation of HCC.

Perfusion CT at 1 month has the ability to evaluate the perfusion changes in HCC after TACE, which can be used to monitor the response of HCC to TACE.

For the evaluation at 3-6 months, MRI has higher sensitivity and specificity and may be a preferable imaging tool for patients who have undergone TACE.

MRI is the first choice in oncologic patients with CRLM treated with neo-adjuvant chemotherapy.

COMMENTS

Due to its wide availability, noninvasiveness, absence of ionizing radiation, repeatability, and low cost, US imaging modality is increasingly utilized for diagnostic purpose and this has, in turn, led to an increased rate of incidentally discovered FLLs in asymptomatic patients. On the other hand, several imaging technologies for the detection and characterization of focal liver lesions are available and the challenge is to choose the most appropriate in each clinical scenario. The aim of this review is to suggest the best diagnostic approach for the detection and characterization of focal liver lesions. The literature search confirms the appropriateness of the guidelines issued by the National Guidelines System of the Italian National Institute of Health in 2008 [6].

CEUS could be used as a screening examination for the detection of FLLs in oncologic patients. However, MRI is the preferred first-line imaging modality for evaluating CRLM in patients who have not previously undergone therapy.

In patients with chronic liver disease, CEUS is a good imaging tool for the characterization and the diagnostic confirmation of lesions detected by other imaging techniques, in particular in the assessment of arterial hypervascularity of HCC and the dysplastic nodule. CEUS is a real-time dynamic imaging technique that can be used when MRI or CT are inconclusive or contraindicated. In fact, the high temporal resolution combined with the real-time imaging capability of CEUS may allow detection of the transient enhancement of a lesion that could be missed by other imaging modalities.

Recently, the American College of Gastroenterology has issued a practice guideline regarding the suggested diagnostic approaches and management of FLLs [59]. CEUS has not been included in this guideline, a decision which could reflect the

current status of microbubble contrast agents in the USA as they are not approved for liver imaging by Food and Drug Administration. Thus, CEUS is seldom used for liver imaging in the USA, and then, only off-label. Moreover, CEUS has been removed from the diagnostic algorithm for nodules in cirrhosis in the updated version of the guidelines for the management of HCC produced by the American Association for the Study of Liver Disease (AASLD) [60]. This is attributed to one publication claiming CEUS may give a false positive HCC diagnosis in patients with cholangiocarcinoma. The study on which this decision was based, included a relatively small number of patients recruited over a long time interval, thus a bias could have occurred [61]. Conversely, in the updated diagnostic algorithm for HCC proposed by the Liver Cancer Study Group of Japan in 2014, Sonazoid CEUS is considered a very important diagnostic modality [62].

CONCLUSIONS

Credited to their panoramic view of the entire body, CT and MRI are recommended in the loco-regional staging of primary liver cancer.

For the assessment of complications and immediate and long-term treatment response in patients undergoing oncologic treatments, MRI is the first choice in oncologic patients with CRLM treated with neo-adjuvant chemotherapy. The diagnostic imaging technique is highly dependent on the type of treatment used. CEUS is a good diagnostic tool for the early evaluation and for the follow-up at 1 month of treated HCCs.

DW-MRI seems a valuable technique that shows a high diagnostic accuracy in the detection and characterization of FLLs, and its sensitivity is higher when combined with MRI.

Conflicts of interest: No conflict to declare.

Authors' contribution: F.G. and F.C. designed the research; F.G. and D.C. performed the literature search, selected the articles and wrote the manuscript; F.G., D.C., M.M.F., C.F. and F.C. reviewed the articles and approved the final version of the manuscript.

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