Italian guidelines for noninvasive imaging assessment of focal liver lesions: development and conclusions

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Objectives To develop guidelines for the noninvasive imaging assessment of focal liver lesions comparing different imaging modalities focused on (i) evaluating the imaging techniques in terms of (a) diagnostic accuracy; (b) role in the management of oncologic patients; (c) follow-up of benign lesions; and (ii) developing standard procedure for their use in patients with focal liver lesions that require targeted diagnostic characterization.

Methods An explicit search strategy was used to conduct a systematic review of the literature in the English language from January 2000 to October 2007; the search covered PubMed, Embase, Pascal, SciSearch, and Cochrane Library databases. A panel of experts evaluated the selected studies and conveyed their view.

Results The online search yielded 4960 titles and abstracts from which 176 studies were considered suitable for the final adherence-to-guidelines topic evaluation. An evidence grading system was not used as the guideline topic and the heterogeneity of the collected data did not fit with the currently used hierarchy of evidence. A panel of experts formulated several recommendations with grade and level which were expressed narratively and nonschematically.

Conclusion The recommendations reported in the study are based on an extensive literature evaluation and were developed by considering the appropriateness of the choice of the imaging techniques while noninvasively detecting and characterizing focal liver lesions. Eur J Gastroenterol Hepatol 23:343–353 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: diagnostic imaging techniques, focal liver lesions, guidelines, liver

Introduction Advances in imaging technology have greatly improved the noninvasive detection and characterization of focal liver lesions (FLLs). Owing to the high prevalence of benign FLLs, lesion characterization at imaging is of utmost importance. In contrast, liver malignancies, including primary liver cancers and metastases, are among the most common tumors in the world [1].

Several diagnostic imaging techniques can be used to detect and characterize FLLs, that is, ultrasound, ultrasound color Doppler, contrast-enhanced ultrasound (CEUS), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET). More invasive imaging techniques, for example, angiography, are seldom used. The availability of newer contrast media materials and of new and more sophisticated diagnostic imaging equipments has enhanced the diagnostic capability of these techniques.

The choice of the most appropriate diagnostic imaging technique for detecting FLLs, determining their benign or malignant nature, and categorizing them is a complex procedure. In everyday clinical practice the choice of the imaging modality best suited for studying FLLs is still difficult because of uncertainty about the diagnostic accuracy of a given imaging modality in each clinical scenario.

In a limited healthcare resources era, procedure-related costs should be taken into account. Choices imposed by unavoidable scarcity of resources from one side, and increasing healthcare demand in quantitative and qualitative terms on the other side, have made it necessary to introduce economic criteria in the decision-making processes.

Therefore, given the need to identify clear intervention strategies in an area that is increasingly found at the forefront of research and clinical innovation, the Italian National Institute of Health’s Sistema Nazionale Linee Guida (SNLG; Italian National Guidelines System) has recently developed ‘Diagnostic imaging of focal liver lesions’ guidelines aimed at verifying the usefulness and...
effectiveness of the noninvasive diagnostic imaging techniques currently available, namely ultrasound, CEUS, CT, MRI, and PET, to detect and characterize FLLs.

The guidelines focused on (i) evaluating the imaging techniques ultrasound, CEUS, CT, MRI, and PET in the assessment of FLLs in terms of (a) diagnostic accuracy; (b) role in the management of oncologic patients; (c) follow-up of benign lesions; and (ii) developing standard procedure for using these imaging techniques in managing patients with FLLs that require targeted diagnostic characterization.

The recommendations reported in the study are based on an extensive literature evaluation and were developed by considering the appropriateness of the choice of the imaging techniques while noninvasively detecting and characterizing FLLs. To our knowledge, these are the first guidelines dealing with this topic promoted by a Governmental Organization.

Materials and methods
Multidisciplinary guidelines development group
The Multidisciplinary Guidelines Development Group (MGDG) included representatives of key stakeholders and professionals from related disciplines, for example, colorectal surgery, endoscopic surgery and gastroenterology, epidemiology, gastroenterology, general practice, hepatology, infectious diseases, internal medicine, oncologic surgery, oncology, radiology, oncologic radiology, and ultrasound experts, as well as experts in guideline development. Each member signed a form to declare a lack of conflict of interest and agreed on the proposed guideline development strategy.

The MGDG met in July 2007 and in June 2008 to discuss and define important methodological issues, identify search strategy keywords, define inclusion/exclusion criteria, and to agree on the final version of the guidelines. Many of the consultations necessary for monitoring the guideline development process and working on the guideline draft took place through e-mail, telephone contact, and especially during the final phase through the website set up to that purpose on the Italian National Guidelines System (SNLG) website (www.snlg.iss.it/og).

The collected evidences were then summarized in accordance with SNLG methodology [2].

Clinical questions
The panel members put forward five key questions concerning the detection and the characterization of FLLs as follows:

(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) Locoregional staging of primary liver cancer, that is, number of lesions, size, site, relations with anatomofunctional structures and lymph nodes involvement.
(4) Assessment of complications and immediate and long-term (follow-up) treatment response in patients undergoing oncologic treatments, for example, chemotherapy, radiofrequency thermal ablation (RFTA), percutaneous ethanol injection, laser, microwave, transcatheter arterial chemoembolization, transcatheter arterial embolization, cryotherapy, surgery.
(5) Follow-up of patients with FLLs characterized as benign.

Literature search
An explicit search strategy was used to conduct a systematic review of the literature in the English language from January 2000 to October 2007 (Table 1); the search covered PubMed, Embase, Pascal, SciSearch, and Cochrane Library databases.

The search terms were then combined with others to specifically answer each key question; different search strategies were then performed, one for each key question.

Inclusion criteria
Systematic reviews, randomized controlled trials, and prospective/retrospective studies assessing the role of diagnostic imaging techniques were included. The selected studies evaluated validity and reproducibility of the imaging techniques ultrasound, CEUS, CT, MRI, and PET in detecting, characterizing, staging FLLs, evaluating both immediate and long-term responses to oncologic treatments, and follow-up of benign FLLs.

Exclusion criteria
Studies were excluded if they did not focus on diagnostic imaging techniques or did not use a standard reference, and if they were case series, editorials, letters, and narrative reviews.

Table 1 Literature search strategy main filter

| #1 | ‘Echography’ |
| #2 | ‘Tomography’, ‘emission-computed’ or ‘diagnostic imaging’ or ‘magnetic resonance imaging’ or ‘MRI’ or ‘PET’ or ‘positron emission tomography’ or ‘positron emission computed’ or ‘tomography emission computed’ or ‘computer-assisted emission tomography’ or ‘positron emission tomography’ |
| #3 | ‘Contrast-enhanced’ and ‘ultrasonography’ |
| #4 | ‘Contrast-enhanced’ and ‘ultrasound sonography’ |
| #5 | ‘US’ and ‘sonography’ |
| #6 | ‘CEUS’ |
| #7 | ‘Computed tomography’ |
| #8 | ‘Ultrasound sonography’ or ‘ultrasound sonography’ or ‘contrast-enhanced ultrasound sonography’ or ‘contrast-enhanced ultrasound sonography’ or ‘contrast-enhanced ultrasound sonography’ |
| #9 | ‘CT’ and ‘tomography’ |
| #10 | #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 |

CEUS, contrast-enhanced ultrasound; CT, computed tomography; US, ultrasound.
Selection criteria and instruments for methodological evaluation
Trained personnel used the Scottish Intercollegiate Guidelines Network’s methodological checklists [3] adapted by the Italian National Institute of Health’s-SNLG group to critically evaluate the literature collected through this broad-based search.

Evidence tables were used to summarize the findings and to develop recommendations.

The draft guideline was then reviewed by an independent expert group consisting of a surgeon, an internal medicine specialist, and a hepatologist expert on sonography.

Results
Literature
The online search yielded 4960 titles and abstracts, 922 of which were considered to be suitable. These titles were subjected to further selection, and only 213 studies were actually used for data rating. Only 176 studies were chosen for the final adherence-to-guidelines topic evaluation [4–180].

In the final discussion phase, on presentation of the guidelines draft, several MGDG members proposed bibliographical material of interest not yielded by the literature search. Although not conforming to the established inclusion criteria, some studies were judged suitable by the panel and were included in the bibliography [181–184].

Grading system
The MGDG decided not to use an evidence grading system as the guideline topic and the heterogeneity of the collected did not fit with the currently used hierarchy of evidence. Hence, after evaluating and discussing the evidence, wherever possible, the group of experts formulated several recommendations, each preceded by a brief account of the studies collected, a plenary discussion, and considerations on the clinical application of each of the diagnostic techniques examined.

Attrition of the level and grade of evidence therefore took study design into account, but grade and level were expressed narratively and not schematically.

Question no. 1
Table 2 reports the final recommendations based on suitable studies obtained by the literature search [4–101].

In oncologic patients, three meta-analyses comparing PET results with CT or MRI results were retrieved [4–6]. Wiering et al. [4] pooled data of 1843 patients from 32 studies and found that the sensitivity and specificity of PET results were 88 and 96.1%, respectively, whereas for CT the pooled sensitivity and specificity results were 82.7 and 84.1%, respectively. In the meta-analysis of Bipat et al. [5], which included 3187 patients in 61 studies, PET showed significantly higher sensitivity on a per patient basis, compared with that of the other modalities, but not on a per lesion basis. Sensitivity estimates on a per patient basis for nonhelical CT, helical CT, 1.5-T MRI, and PET were 60.2, 64.7, 75.8, and 94.6%, respectively; PET was the most accurate modality. On a per lesion basis, sensitivity estimates for nonhelical CT, helical CT, 1.0-T MRI, 1.5-T MRI, and PET were 52.3, 63.8, 66.1, 64.4, and 75.9%, respectively. Sensitivity estimates for MRI with contrast agent were significantly superior to those for helical CT. The meta-analysis of Kinkel et al. [6] included 3080 patients in whom ultrasound, CT, MRI, and PET in the detection of hepatic metastases from colorectal, gastric, and esophageal cancers were compared. The mean weighted sensitivity was 55% for ultrasound, 72% for CT, 76% for MRI, and 90% for PET. In several other studies, sensitivity and specificity of PET in the assessment of liver metastasis showed different results depending on the primary cancer site [7–20]. Sensitivity and specificity were 70–77 and 94–100%, respectively, in patients with pancreatic cancer [7,8], 67 and 81.3%, respectively, in patients with gastrointestinal cancer [9], and 54–100 and 58–100%, respectively, in patients with colorectal cancer [10–18]. In all studies the results were better on a per patient basis rather than on a per lesion basis.

![Table 2: Key questions, selected studies, and recommendations for oncologic patients and patients with chronic liver disease](guide.medlive.cn)
The heterogeneity in MRI results was mainly due to the contrast agents that were administered. The lowest variability was observed when hepatospecific contrast agents were used. MRI showed a sensitivity of 82–94% when extracellular contrast agents were used [21,22], of 66–93.5% when superparamagnetic iron oxide was used [23–26,29–31], and sensitivity of 67–98% with a specificity of 81–93% in case of hepatospecific contrast agents [32–39].

In the detection of FLLs a high sensitivity and specificity of CEUS, 80–98 and 66–98%, respectively; has been reported [43–52,100]. Compared with CECT there were no statistical significant differences between the two imaging techniques. Intraoperative CEUS has shown sensitivity greater than 95%, higher than that obtained with CT or MRI [58,59].

In patients with chronic liver diseases, three systematic reviews of diagnostic studies pointed out that a large number of studies were methodologically incorrect [71–73]. The results of these reviews showed a large variability both in sensitivity (30–100%) and specificity (73–100%) for ultrasound and CT. Two studies proved that sensitivity and specificity of MRI was good (81 and 85% respectively). No studies tested the role of PET. No adequate proofs supported the use of CEUS in this setting.

**Multidisciplinary guidelines development group opinion**

In oncologic patients, CEUS performs better than ultrasound in detecting FLLs. PET, CT, and MRI should be favored in patients presenting the diagnostic difficulties due to obesity or limitations such as heart diseases, and in children.

In patients with chronic liver diseases, CECT and CEMRI are not only the most effective techniques, but also the most expensive and therefore unsuitable for large scale monitoring. Ultrasound is the optimal screening examination, although CECT and CEMRI might be preferable in patients with higher oncologic risk, such as HIV–HCV coinfected patients or in patients with physical characteristics, such as obesity, unsuitable for ultrasound. CECT and CEMRI are preferable for further diagnostic investigation in patients with high α-fetoprotein levels or when hepatocellular carcinoma (HCC) is strongly suspected and ultrasound is negative.

**Question no. 2**

Table 3 reports the final recommendations based on suitable studies obtained by the literature search [14,21,52,69,86,87,95,100,102–137] and on studies proposed by MGDG members [181–183]. Sensitivity and specificity of ultrasound in the characterization of FLLs has been shown to be low. CEUS has a high sensitivity and specificity (> 80 and 90%, respectively) in differentiating benign and malignant FLLs [108–112]. Only in the case of colangiocellular carcinoma is the sensitivity low (< 60%) [108]. Accuracy of CEUS in the characterization of incidental FLLs is 96% [116].

CEUS shows sensitivity and specificity similar to that of 16-row multislice CT and performs better than 4-row multislice CT [121].

In a per lesion analysis, MRI is better than CT, whereas in a per patient analysis there were no statistically significant differences between the two imaging techniques [87].

Unenhanced MRI performed better than CT both in differentiating benign from malignant lesions (sensitivity, 83.3 vs. 81.2%; specificity, 97.5 vs. 77.3%), and in detecting small metastasis (sensitivity, 97 vs. 93%; specificity 97 vs. 82%).

With respect to unenhanced MRI, enhanced MRI increased the detection of FLLs both in cirrhotic and noncirrhotic patients.

There are few published studies that report data of PET in the characterization of FLLs.

**Multidisciplinary guidelines development group opinion**

The available evidences are rather heterogeneous in terms of study population, interventions, and comparisons. In fact, the validity of the diagnostic imaging techniques was studied in terms of characterization and confirmation of malignant/benign and primary/metastatic lesions. Therefore, it is difficult to define the role of each imaging technique in the differential diagnosis of FLLs in patients with and without liver disease. A recently published practice guideline of the American Association for the Study of the Liver Diseases guidelines, which provides a data-supported approach to the diagnosis, staging and treatment of patients diagnosed with HCC, has

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**Table 3  Key questions, selected studies, and recommendations for patients with unknown pathology, chronic liver diseases, or oncologic diseases**

<table>
<thead>
<tr>
<th>Key questions</th>
<th>Studies</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role of US, CEUS, CT, MRI, and PET in the characterization of FLLs in patients</td>
<td>913 identified</td>
<td>The use of CEUS is recommended for the characterization of FLLs and for the diagnostic confirmation of FLLs detected with other imaging modality.</td>
</tr>
<tr>
<td>with unknown pathology, chronic liver diseases, or oncologic diseases.</td>
<td>252 selected</td>
<td>In cases in which CEUS does not yield adequate and definitive results, the use of CEMRI with a hepatospecific contrast agent. CECT is recommended in patients unsuitable for CEUS or CEMRI.</td>
</tr>
<tr>
<td></td>
<td>110 rated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>44 included</td>
<td></td>
</tr>
</tbody>
</table>
pointed out the importance of the washout phase of the nodule, even in the absence of hypervascularization in the arterial phase [181]. This guidelines and another study [182] were included in the final analysis, even though they had not been yielded by the search strategy due to the high degree of specificity with which it had been developed. Moreover, the panel chose to include another study [183], although its publication date did not fall within the literature search time limits, because it defines the optimal use of diagnostic imaging techniques for lesion size. The MGDG agreed with the American Association for the Study of the Liver Diseases guidelines that indicate the concurrent use of two different diagnostic imaging techniques to accurately diagnose HCC between 1 and 2 cm in size [181]. Several experts underscored that in any event, imaging-guided biopsy should represent the optimal standard for obtaining a definite diagnosis. It was therefore concluded that the high sensitivity and specificity of CEUS make it possible to recommend the technique as the optimal examination for differentiating malignant/benign and primary/metastatic FLLs. Nonetheless, being CEUS an ultrasound imaging technique, it is limited by the patient’s body habitus. In this setting, CEMRI with a hepatospecific contrast medium represents the optimal imaging technique.

Questions nos. 3-5
Table 4 reports the final recommendations to these questions based on suitable studies obtained by the literature search [40,88,138–180] and on a study proposed by MGDG members [84].

Compared with intraoperative ultrasound and MRI, in all studies CT showed a lower accuracy in the locoregional staging of primary liver cancer.

In a study conducted on 404 patients to assess the efficacy of CEMRI for detecting and characterizing, or excluding FFLs, the results were compared with those obtained with CECT. CEMRI provided additional diagnostic information in 48% of the patients, modifying patient management in 6% of the cases [40].

In a study conducted on 41 patients to assess response to PEI or RFTA of HCC immediately and 1 month after treatment, CEUS was compared with CECT and showed high sensitivity, specificity, and accuracy (90.9, 96.6, and 95%, respectively), whereas both techniques were slightly useful to evaluate immediate therapeutic efficacy [149]. In three observational studies, CEUS showed a low sensitivity (53.8–83.3%) but a high specificity (90.9–100%) in evaluating both immediate and 1-month efficacy [150–152]. Other studies report specificity of 99–100% in the immediate evaluation of percutaneous treatment efficacy [153,154].

Studies using CEMRI in this setting are few and, due to the outcome used, their results are not reproducible [170–172]. Most of the studies evaluating the diagnostic accuracy of CECT were published before 2000, that is, earlier respect to the period of time used for the literature search strategy.

PET has been used in few patients and the results are inconclusive [173–178].

Recommendation to question no. 5 was based only on experts’ opinion because only one study was included [180].

Multidisciplinary guidelines development group opinion
With respect to staging of lesions, the need of multiphasic techniques to examine the vascularization of lesions, vascular structure and their involvement, the surrounding

Table 4  Key questions, selected studies, and recommendations for patients undergoing oncologic treatments

<table>
<thead>
<tr>
<th>Key questions</th>
<th>Studies</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role of US, CEUS, CT, MRI, and PET in:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) locoregional staging of primary liver cancer</td>
<td>(i) 219 identified</td>
<td>(i) Although the currently available evidence is insufficient to provide a clear, evidence-based recommendation regarding the role of imaging techniques US, CEUS, CT, MRI, and PET in the locoregional staging of primary liver cancer, the panel of experts agree in suggesting the use of CT and MRI in the locoregional staging. Invasive techniques should be performed only in patients undergoing surgery</td>
</tr>
<tr>
<td>(ii) assessment of complications and immediate and long-term (follow-up) treatment response in patients undergoing oncologic treatments</td>
<td>(ii) 1266 identified</td>
<td>(ii) Current knowledge does not allow us to recommend a particular reference imaging technique to assess follow-up, intended as complications and immediate and long-term treatment response in patients undergoing oncologic therapies. Further investigation is therefore advised</td>
</tr>
<tr>
<td>(iii) follow-up of patients with FLLs characterized as benign</td>
<td>(iii) 56 identified</td>
<td>(iii) Current knowledge does not allow for recommendation of a specific diagnostic imaging technique to follow-up patients with FLLs characterized as benign</td>
</tr>
</tbody>
</table>

CEUS, contrast-enhanced ultrasound; CT, computed tomography; FLL, focal liver lesion; PEI, percutaneous ethanol injection; RFTA, radiofrequency thermal ablation; SRT, stereotactic radiofrequency thermocoagulation; TACE, transcatheter arterial chemoembolization; TAE, transcatheter arterial embolization; US, ultrasound.
parenchyma and the lymph nodes was stressed. Although CECT is a routine procedure, to date its use as a standard diagnostic imaging technique has not been validated. Moreover, CEMRI, when compared with CECT, has shown to be the most accurate and adequate imaging technique to detect FLLs in patients requiring a surgical or ablative treatment. In contrast, ultrasound laparoscopy, intraoperative ultrasound, and intraoperative CEUS show sensitivity and specificity higher than CEMRI and their reliability is higher because they produce fewer false-positive results.

With regard to question no. 4, there was general agreement that most of the examined studies were not methodologically sound, because of inadequate sample size or unclear methodology. The diagnostic technique choice is highly dependent on treatment used, and evidence from clinical practice confirms this assumption. The yielded studies did not adequately investigate the possibility of defining follow-up in terms of assessment of complications; nearly all the researches conducted to date have focused on the role of diagnostic imaging in assessing treatment efficacy, overlooking complications. The panel therefore referenced a multicenter study that examined RFTA complication, although the study had not been originally yielded by the search strategy, because it defines the role of CT in this setting [184].

An adequate body of evidence for metastasis assessment is still unavailable. CEUS shows different degrees of sensitivity but a good specificity value in the assessment of immediate and long-term treatment response in patients undergoing oncologic therapies. As it is not a whole body diagnostic technique, compared with CECT and CEMRI it shows a similar efficacy in a per lesion analysis but loses validity in a per patient basis. Nonetheless, CEUS is easily repeatable and less invasive. Although most Italian centers currently use CEUS to assess treatment efficacy, to date the literature has not yet produced a standard of reference. Specific evidence is lacking, especially for immediate assessment of treatment outcome. The experts agreed on recommending CEUS at 30–40 days after treatment and follow-up with CECT or CEMRI at 3 months.

Experts agreed that the lesions already characterized as benign should not be followed up. Diagnostic imaging is recommended only to follow-up patients with confirmed hepatic adenoma, because it has a potential, even though rare, risk for degeneration into HCC. In contrast, ultrasound seems to be the most effective technique for follow-up deemed necessary in the clinical practice to monitor growth in a FLL already characterized as benign.

Discussion
This study was carried out within a national program of guidelines development (SNLG) managed by the health authorities of the Italian government. The need raised from the appraisal of a widespread heterogeneity in choosing the imaging modality to perform in each clinical setting. In this field, the use of diagnostic imaging techniques in the assessment of FLLs was a crucial issue. Indeed, because of remarkable technological advances, imaging plays a pivotal role for the diagnosis, staging treatment planning, and follow-up of FLLs. In the majority of cases, a correct diagnosis can be based on imaging modalities alone.

The literature search did not yield any randomized controlled trial allowing the evaluation of a particular diagnostic strategy related to clinical relevant outcomes, for example, case-specific mortality. Instead, information on the diagnostic accuracy of each imaging technique was achieved. The reported values of sensitivity and specificity often are referred to definite populations, that is, patients with cirrhosis, hence the predictive significance of an imaging modality is related to definite circumstances.

The time interval adopted for the literature search might have introduced a bias in selecting more recent studies in which more advanced diagnostic imaging techniques were evaluated. In contrast, the opinion of the MGDG should have partially corrected the bias.

To give value to the debate that always precedes the sharing of a recommendation, the document was drawn up by including the report of the debate to allow the readers to fully comprehend the process of the drafting. For the same reason, it was decided not to adopt a grading system but to prefer the narrative form in drawing up the recommendations. This process is intended to give all the information available to the readers, avoiding reductive summaries that, although more effective from the point of view of the communication, involve an inevitable loss of depth of the treated issue.

A key element emerging from the panel discussion was the need to formulate recommendations complying with the clinical practice as closely as possible. As major developments in the rapidly evolving field of diagnostic imaging can occur only in a few years, it was also agreed that the recommendations formulated should be given because of consideration to the current state-of-art in imaging techniques and their use nationwide throughout Italy.

The MGDG agreed that valid evidence today would likely become obsolete or questionable over a rather brief period of time. This is particularly true for the new advancements in diagnostic imaging that have not yet produced clear and solid experimental evidence. Updating of the guidelines is therefore planned for September 2011. In the meantime, the following multiple document-circulation and active-implementation methods will be adopted: (i) dissemination of the initiative through the media and press articles; (ii) postal mailings to regional and provincial healthcare departments, local health authorities, hospitals, medical specialists, general practitioners, and opinion leaders; (iii) publication on Internet sites; (iv) scientific publications; (v) in-service training courses; (vi) promotion of formal guideline adoption in
Italian hospitals; (vii) national and international conference presentations; (viii) support to integrated health authority level clinical pathways to care in local settings, aimed at overcoming any barrier in implementation of the guidelines. Implementation outcomes greatly depend on local availability of diagnostic imaging technologies.

Acknowledgements
The Multidisciplinary Guidelines Development Group comprised Mario Angelico, Società Italiana di Gastroenterologia ed Endoscopia Digestiva, SIGE; Vincenzo Arioni, Società Italiana di Medicina Interna, SIMI; Carlo Bartolozzi, Società Italiana di Radiologia Medica, SIRM; Luigi Bolondi, Esperto in Epatologia ed Ecografia, Dipartimento di Malattie Apparato Digerente e Medicina Interna, Policlinico S. Orsola Malpighi-Università di Bologna; Elisabetta Buscarini, Associazione Italiana Gastroenterologia ed Endoscopisti Ospedalieri, AIGO; Roberto Buzzoni, Associazione Italiana di Oncologia Medica, AION; Fabrizio Calliada, Istituto di Radiologia, Università di Pavia; Vito Cantisansi, Dipartimento di Scienze Radiologiche, Università La Sapienza, Roma; Lorenzo Capussotti, Associazione Chirurghi Ospedalieri Italiani, ACOI; Antonella Giabattoni, Associazione Italiana di Radioterapia Oncologica, AIRO; Salvatore De Masì, Dipartimento di Prevenzione, ASL 6 Livorno; Carlo Filice, Società Italiana di Malattie Infettive e Tropicali, SIMIT; Alfredo Garofalo, Società Italiana di Chirurgia Oncologica, SICO; Luigi Grazioli, Esperto in Imaging Epatico, Dipartimento di Radiologia, Spedali Civili di Brescia; Pasquale Ialongo, Società Italiana di Chirurgia, SIC; Luigi Lupo, Società Italiana di Chirurgia Colorettale, SICCR; Maria Franca Meloni, Società Italiana di Ultrasonologia in Medicina e Biologia, SIUMB; Alessandro Maria Paganini, Società Italiana di Chirurgia Endoscopica e Nuove Tecnologie, SICE; Gian Ludovico Rapaccini, Associazione Italiana per lo Studio del Fegato, AISF; Paolo Ricci, Dipartimento di Scienze Radiologiche, Università La Sapienza, Roma; Letizia Sampao, Istituto Superiore di Sanità; Angelo Sangiovanni, Esperto in Gestione Clinica delle lesioni focali epatiche, Unità Operativa Gastroenterologia 1, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli-Regina Elena, Milano.

No funding was received for this study.

Conflicts of interest: none declared.

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