



# SNLG18

Diagnostic imaging of focal hepatic lesions

GUIDELINES

**Publication date: September 2008**

**Next update: September 2011**

## **NOTICE:**

The following is a partial translation of the Italian *SNLG-ISS* Guidelines: *Diagnostic Imaging of Focal Hepatic Lesions*. Full translation of the document is underway and the final, complete English text will be available at [www.snlg-iss.it](http://www.snlg-iss.it) by early 2009

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## ABBREVIATIONS

**AASLD** American Association for the Study of the Liver Diseases  
**ADI** Agent Detection Imaging  
**ADC** Apparent Diffusion Coefficient  
**AFP** AlfaFetoProteina  
**BH-FSE** BreathHold Fast Spin Echo  
**CECT** Contrast Enhanced Computed Tomography  
**CE-IOUS** Contrast Enhanced Intraoperative Ultrasonography  
**CEPD** Contrast Enhanced Power Doppler  
**CEUS** Contrast Enhanced UltraSonography  
**CTAP** Computed Tomography during Arterial Portography  
**CTHA** Computed Tomography during Hepatic Arteriography  
**EASL** European Association for the Study of the Liver  
**EMRI** Enhanced Magnetic Resonance Imaging  
**FDG-PET** Fluor-18-Deoxyglucose-Positron Emission Tomography  
**Gd-BOPTA** Gadobenate dimeglumine (gadolinium-BenzylOxyPropionic TetraAcetate)  
**Gd-DTPA** Gadopentetate dimeglumine (Gadolinium-DiethyleneTriamine Penta-acetic Acid)  
**Gd-EOB-DTPA** Gadolinium-EthOxyBenzyl-DiethyleneTriamine Penta-acetic Acid  
**GRASE** GRAdient and Spin Echo  
**HCC** HepatoCellular Carcinoma  
**HCT** Helical Computed Tomography  
**HU** Unità Hounsfield  
**IODA** Iodized-Oil Defect Area  
**IOUS** Intraoperative Ultrasonography  
**LFE** Lesione Focale Epatica  
**mdc** mezzo di contrasto  
**MDCT** Multirow Detector Computed Tomography  
**Mn-DPDP** Manganese DiPyridoxal DiPhosphate (Mangafodipir trisodium)  
**MR** Magnetic Resonance  
**MRI** Magnetic Resonance Imaging  
**PEI** Percutaneous Ethanol Injection  
**PET** Positron Emission Tomography  
**PIH** Pulse-Inversione Harmonic  
**PMAT** Percutaneous Microwave Ablation Therapy  
**RCT** Randomized Controlled Trial  
**RFTA** RadioFrequency Thermal Ablation  
**RM** Risonanza Magnetica  
**RMN** Risonanza Magnetica Nucleare  
**RT-FSE** Respiratory Triggered Fast Spin Echo  
**SPECT** Tomografia Computerizzata a Emissione di Fotoni Singoli  
**SPIO** Super Paramagnetic Iron Oxide  
**SRT** Terapia di Riduzione del Substrato  
**T** Tesla  
**TACE** Transcatheter Arterial ChemoEmbolization  
**TAE** Transcatheter Arterial Embolization  
**THI** Tissue Harmonic Imaging  
**TC** Tomografia Computerizzata  
**UMRI** Unenhanced Magnetic Resonance Imaging  
**US** Ultrasonografia (Ecografia)



# INTRODUCTION

As the body's bloodstream filter, the liver can be the site of many types of benign and malignant tumoural lesions. The main goal of modern diagnostic imaging is the early and reliable detection of malignant lesions, allowing for swift and targeted treatment for patients thereby. Although most hepatic lesions (FHLs) are benign, distinguishing among different types of lesions is not a simple task. The choice of the most appropriate diagnostic technique for detecting lesions, determining their benign or malignant nature, and categorizing them is a complex procedure that is frequently conducted randomly or determined by the local availability of one or more of the several diagnostic imaging methods science currently offers. The aim of the present guidelines is to identify the most appropriate diagnostic imaging technique(s) for a given patient's clinical scenario.

Various diagnostic imaging techniques can be used to detect and characterise focal hepatic lesions, e.g., ultrasound and Echo-colour-Doppler, spiral Computerised Tomography (CT), Nuclear Magnetic Resonance (NMR), Positron Emission Tomography (PET), and--when necessary--percutaneous biopsy. Angiographic techniques are used only in certain situations. The introduction of numerous contrast media agents ("dyes") and of new and ever-more-sophisticated diagnostic equipment into clinical practice has enhanced the diagnostic capacity of these techniques, which are now routinely used in the management of patients with focal hepatic lesions.

Yet, this consequent and rapid growth in knowledge has led to a high degree of clinical practice variability, due to general uncertainty about the diagnostic potential of these various techniques, as well as to disparities in the local availability of equipment and therefore, in the nationwide utilisation of diagnostic imaging. It has therefore been necessary to formulate evidence-based guidelines for use as a rationalisation instrument in a streamlined and unambiguous diagnostic process.

Hence, the present guidelines analyse the validity of various imaging techniques in the detection and characterisation of focal hepatic lesions in hepatopathic and non-hepatopathic patients, based on a systematic analysis of the literature.

## Methods

### **Establishment of Guidelines Development Group (GDG), identification of aims, and of key questions**

The multidisciplinary Guidelines Development Group (GDG) developing these guidelines included clinicians representing the main disciplines involved in the diagnostic imaging of focal hepatic lesions, as well as experts in EBM (evidence-based medicine) and guideline-developing methodology.

The GDG (the “Panel”) was made up of at least one specialist in the following disciplines: Colon-Rectal Surgery, Endoscopic Surgery, Oncological Surgery, Information Science, Ultrasound Technology, Oncological Ultrasound Technology, Hepatology, Epidemiology Endoscopic Gastroenterology Infectivology, General Practice, Oncology, Radiology, Oncological Radiology, and Internal Medicine.

The panel met in July 2007 and in June 2008, and many of the consultations necessary for monitoring the guideline development process and working on the guideline draft took place via email, telephone contact, and (especially during the final phase) via the web community set up to that purpose on the Italian National Guidelines System (SNLG) website ([www.snlg-iss.it/og](http://www.snlg-iss.it/og)). The web community made it possible for GDG members to interactively share the activities and emerging evidence, and to present and discuss the preliminary draft in the final phase of the work.

The participating national scientific societies involved were contacted during the start-up phase, and each sent an expert to participate in the GDG. All Panel members signed a form declaring lack of conflict of interest and agreement on the proposed guideline development methodology<sup>1</sup>. The intermediate work documents--i.e., methodology checklists and evidence tables, can be viewed at the SNLG website,

[www.snlg-iss.it/lgn\\_diagnostica\\_lesions\\_focali\\_epatiche](http://www.snlg-iss.it/lgn_diagnostica_lesions_focali_epatiche).

The GDG first defined the guideline aims; relevant key questions; and coherently with these, the study inclusion and exclusion criteria. It also identified the information sources and biomedical databases that were to be consulted, as well as search words for constructing the search strategy.

## **Main aims**

1. To evaluate the diagnostic accuracy of the imaging techniques of US, CEUS, CT, NMR, and PET in characterising hepatic lesions detected via other means.
2. To define monitoring strategies employing the diagnostic imaging techniques of US, CEUS, CT, NMR, and PET in patients with chronic (cirrhotic and non-cirrhotic) hepatopathology.
3. To evaluate the efficacy of the diagnostic imaging techniques of US, CEUS, CT, NMR, and PET in the conduction of oncological treatment and in patient follow-up.
4. To define monitoring strategies employing the diagnostic imaging techniques of US, CEUS, CT, NMR, and PET in patients with benign focal hepatic lesions.
5. To develop standard procedures for employing the diagnostic imaging techniques of US, CEUS, CT, NMR, and PET in managing patients with focal liver lesions, which require targeted diagnostic characterisation.

## **Questions**

At the first GDG meeting, the guideline aims and topics were established, and the following questions were then defined:

### **Question 1**

What is the role of the imaging techniques of US, CEUS, CT, NMR, and PET in the detection of focal hepatic lesions in:

- A. oncological patients
- B. patients with chronic (cirrhotic and non-cirrhotic) hepatopathy

### **Question 2**

What is the role of the imaging techniques of US, CEUS, CT, NMR, and PET in differential diagnosis, i.e., in the characterisation of focal liver lesions and in the diagnostic confirmation (second-tier diagnosis) of focal liver lesions detected via other means in:

- A. patients with unknown pathology
- B. patients with chronic (cirrhotic and non-cirrhotic) hepatopathy
- C. oncological patients

### **Question 3**

What is the role of the imaging techniques of US, CEUS, CT, NMR, and PET in the locoregional staging of primitive hepatic cancer (in terms of number of lesions, size, site, relations with anatomofunctional structures, and lymph nodes)?

### **Question 4**

What is the role of the imaging techniques of US, CEUS, CT, NMR, and PET in assessing complications and immediate and long-term (follow-up) treatment responses in patients undergoing oncological therapies (chemotherapies, RFTA and PEI, laser, microwave, TACE, SRT, TAE, cryotherapy, surgery)?

### **Question 5**

What is the role of the imaging techniques of US, CEUS, CT, NMR, and PET in following up patients with lesions characterised as benign?

The experts also decided to exclude all topics that referred to focal hepatic lesions but did not specifically examine imaging techniques.

## **Study inclusion and exclusion criteria**

The GDG established eligibility and exclusion criteria for selecting studies yielded by the bibliographic searches conducted, keeping in mind, however, the possibility that these criteria could be reconsidered if the number of the studies found for each question did not suffice.

Clinical studies (systematic reviews, metanalyses, clinical trials, and diagnostic studies) with the following characteristics were considered eligible:

### **1) study topic:**

- the validity and replicability of diagnostic imaging techniques in diagnosing focal hepatic lesions;
- the role of diagnostic imaging techniques in characterising, staging, and evaluating the immediate and long-term responses to oncological therapies;
- the role of diagnostic imaging techniques in following up benign lesions.

### **2) primary outcomes:**

- cause-specific and all-cause mortality;

- global and illness-free survival;
- recurrence of tumour treated as local recurring- or new lesions;
- complication rates;
- the replicability and validity of diagnostic imaging techniques.

### 3) surrogate outcomes

(e.g., radicality of treatment as a survival proxy) in the absence of studies with primary outcomes;

4) **publication date:** January 2000 - October 2007

5) **language:** English

## Literature searches

A main research filter restricting the search to studies examining diagnostic imaging techniques was developed to gather the evidence required for evaluation. The filter was then combined with other terms specific to each key question; the search was then repeated on each originally established database, each with its own consulting language and interface. The complete search strategy can be viewed online at

[www.snlg-iss.it/lgn\\_diagnostica\\_lesions\\_focali\\_epatiche](http://www.snlg-iss.it/lgn_diagnostica_lesions_focali_epatiche).

The following bibliographic data bases were the online information sources consulted:

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PubMed	Embase
Pascal	SciSearch
Cochrane Library	

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The main search filter comprised the following search words:

**#1** *echography*

**#2** *tomography, emission-computed OR diagnostic imaging OR magnetic resonance imaging OR MRI OR tomography 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 *ultrasonography OR «ultrasound sonography» OR «contrast enhanced ultrasound sonography» OR «contrast enhanced ultrasonography»*
- #11 *CT AND tomography*
- #12 *#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #11*

## **Systematic reviews and primary documents**

Diversified research strategies were launched for each Panel-established question at the beginning of October 2007. The search outcome yielded a large quantity of material, especially for some questions -- a situation that frequently created difficulty in study selection. Yet, upon closer examination, most of the literature available turned out to be unsuitable, as it was too heterogeneous for method comparison; was based on inadequate sample sizes; or, in any event, referred to studies conducted with unclear methodology. Systematic reviews, meta-analyses, clinical trials, and diagnostic studies considered to be pertinent and methodologically valid, and illustrating the validity and replicability of diagnostic imaging techniques in diagnosing focal hepatic lesion, were analysed and summarised in charts.

## **Other studies**

In the final discussion phase, upon presentation of the guideline draft, several GDG members also proposed bibliographical material of interest not yielded by the bibliographic search. Although not conforming to the originally established inclusion criteria, some studies judged favourably and accepted by the Panel were included in the bibliography. The titles included under this criterion appear in the Discussion boxes pertaining to the key questions for which this situation occurred.

## **Selection criteria and instruments for methodological evaluation**

The on-line search yielded 4,960 titles and abstracts, 922 of which were considered to be pertinent; their complete texts were therefore requested. These titles were then subjected to further selection, and only 213 studies were actually used for data rating. Only 192 documents were chosen for the final methodological and adherence-to-guideline topic evaluation.

Evaluation and data-rating for each study were conducted by using the Scottish Intercollegiate Guidelines Network methodological checklists, SIGN<sup>2</sup>, which had been translated, and specifically adapted by the SNLG-ISS. The intermediate work documents--i.e., methodology checklists and evidence tables, can be viewed on the SNLG-ISS website:

[www.snlg-iss.it/lgn\\_diagnostica\\_lesions\\_focali\\_epatiche](http://www.snlg-iss.it/lgn_diagnostica_lesions_focali_epatiche).

## **Data rating, evidence synthesis, and recommendation formulation**

Study selection, methodological evaluation, and data-rating were conducted by personnel specifically trained personnel. The evidence yielded by each study was summarised in evidence tables specific to each question and each type of study. The adopted tables were either those developed by the National Institute for Clinical Excellence, NICE<sup>3</sup>, or were developed by the Panel--when appropriate charts were unavailable.

## **Grading system**

These guidelines did not use an evidence grading system. In fact, the guideline topic and the heterogeneity of the collected data rendered conformity with the currently used hierarchy of evidence quite difficult. Moreover, current international guideline-production trends suggest that, even when the intent of a recommendation is made schematic and clear, its adoption without comprehension of the

complex evaluation process involved in its formulation and of the difficulties frequently encountered by other colleagues in clinical practice, diminishes its potential and flexibility of use, by imparting a univocal and definitive character to it. Hence, an indirect advantage of the Panel's approach was doubtlessly that of a return to, and recovery of the original role of scientific research and its reinstatement into daily clinical practice thereby.

Hence, after evaluating and discussing the evidence, wherever possible, the group of experts formulated several recommendations, each preceded by a Discussion--i.e., a brief account of the studies collected, the plenary discussion, and considerations on the clinical application of each of the diagnostic techniques examined.

Attribution of the level and grade of evidence therefore took study design into account, but grade and level were expressed narratively and non-schematically, as can be inferred from the Discussion box appearing at the end of each key question and from the Recommendations that follow it.

## **Referee review**

The GDG-defined document was sent to external experts (referees) with specific instructions to evaluate the document's legibility and clarity as well as its clinical significance and the applicability of the recommendations contained therein. This review group was composed of one surgeon, one internist, and ultrasound hepatologist.

## Updating, implementation, monitoring, and evaluation

The Guidelines Development Group agreed that apparently valid and proposable evidence today will likely become obsolete or questionable over a rather brief period of time. This view is particularly true for the most recent diagnostic techniques, the utilisation of which has not yet produced sufficient data, but which are nonetheless harbingers of new evidence. Guideline updating is therefore planned as early as September 2011.

In the meantime, the following multiple document-circulation and active-implementation methods will be adopted:

- diffusion of the initiative through the media and popular press articles;
- postal mailings to Autonomous Regional and Provincial healthcare departments, Local Health Authorities (*ASL*'s), hospitals, medical specialists, general practitioners, and opinion leaders;
- publications on internet sites (*SNLG-ISS*, *ASP* [public health agencies], scientific societies, healthcare agencies, etc...);
- scientific publications;
- continuing Education-in-Medicine (*ECM*) in-service training courses;
- promotion of formal guideline adoption in Italian hospitals;
- national and international conference presentations;
- adaptation of guidelines to local contexts, by promoting integrated health authority-level clinical pathways to care, with particular focus aimed on surmounting any barriers to guideline implementation.

The guideline topic is of a notably technical nature, and implementation outcomes for the recommendations contained in the guidelines will be difficult to monitor, as they depend greatly on the local availability of the diagnostic technologies examined herein. These premises made it impossible to define several universal audit indicators that might be useful for monitoring adoption of the guidelines in health care agency and hospital-care fields. It is therefore suggested that an appropriate set of indicators be prepared locally during the reception- and implementation phases of the recommendations reported in these guidelines. Moreover, data gathered nationwide in the unique and characteristic experience of various future programmes, whether underway or concluded at the time of reporting, will be documented on the *SNLG* website.

## **Complete text availability**

The complete text of the guidelines and related documents are available at:

[www.snlq-iss.it/lqn\\_diagnostica\\_lesions\\_focali\\_epatiche](http://www.snlq-iss.it/lqn_diagnostica_lesions_focali_epatiche).



**Questions concerning  
the diagnostic imaging  
of focal hepatic lesions**



## **Question 1**

**What is the role of the imaging techniques of US, CEUS, CT, NMR, and PET in the detection of focal hepatic lesions in:**

**A. oncological patients**

**B. patients with chronic (cirrhotic and non-cirrhotic) hepatopathy**

**Raised titles: 2.407**

**Selected titles: 460**

**Rated titles: 110**

**Included titles:**

**3 Metanalyses**

**3 Systematic reviews**

**92 Observation studies**

## **Question 1A:**

**What is the role of the imaging techniques US, CEUS, CT, NMR, and PET in the detection of focal hepatic lesions in oncological patients?**

## **Discussion**

A key element emerging from the Panel discussion was the need to formulate recommendations that adhere to clinical practice as closely as possible. Given that major developments in the rapidly evolving field of diagnostic imaging can occur in only a few years, it was also agreed that the recommendations formulated should give due consideration to the current state of the art in imaging techniques and their use nationwide throughout Italy. The 3 metanalyses and the large quantity of diagnostic studies showed the superior efficacy of CEUS over ultrasound in detecting focal hepatic lesions in oncological patients. The Panel members also agreed, however, that other, more panoramic diagnostic exams, such as PET, PET/CT, and NMR should be favoured over CEUS in patients presenting the diagnostic difficulties that are inherent in obesity or cardiopathy, and in children.

## **Recommendation**

Currently available knowledge on the detection of focal hepatic lesions in oncological patients suggests **recommendation** of CEUS use as a screening exam. Moreover, the evidence yielded by the reviewed metaanalyses--especially concerning the detection of colo-rectal cancer metastatic liver lesions, in instances of negative CEUS results, and in patients requiring surgical or ablative procedures--allow for **recommendation** of PET as a diagnostic confirmation exam, in association, when deemed necessary, with CT and NMR using a hepatospecific contrast media agent.

## **Question 1B:**

**What is the role of the imaging techniques of US, CEUS, CT, NMR, and PET in the detection of focal hepatic lesions in patients with chronic (cirrhotic and non-cirrhotic) hepatopathy?**

## **Discussion**

The Panel found that the literature reports a huge amount of data pertaining to the use of rather dated techniques and that sufficient evidence on new diagnostic techniques has not yet been published. The few findings that are available, however, can be considered harbingers of new evidence. The Panel agreed that evidence emerging from the literature review indicated CT and NMR as being the most effective techniques, but also the costliest and most invasive, and therefore unsuitable for large-scale monitoring.

As one of the least costly techniques, ultrasound, was found to be an optimal screening exam, although it was noted that, a different diagnostic technique (CT or NMR) might be preferable in patients with higher oncogenic risk, such as co-infected patients (HCV and HIV). Similar considerations should also be made for cases in which ultrasound is ineffective due to a patient's physical characteristics (e.g., obesity). The Panel agreed that NMR or CT are preferable for further diagnostic investigation when these patients present high alpha-fetoprotein levels, or a strongly suspected illness (HCC). The experts moreover established that, regardless of the diagnostic potential of Italian health care facilities in general, the recommendations must explicitly indicate the most appropriate diagnostic choice and should become each facility's code of reference.

## **Recommendation**

US is **recommended** for chronic hepatopathic patients who are at risk of developing hepatocarcinoma. In instances, however, of positive or dubious test results, or in patients with highly suspected illness, the exam must be followed by CT or NMR using a hepatospecific contrast media agent.

## Question 2

What is the role of the imaging techniques of US, CEUS, CT, NMR, and PET in differential diagnosis, i.e., in the characterisation of focal liver lesions and in the diagnostic confirmation (second-tier diagnosis) of focal liver lesions detected via other means in:

- A. patients with unknown pathology
- B. patients with chronic (cirrhotic and non-cirrhotic) hepatopathy
- C. oncological patients

**Raised titles: 913**

**Selected titles: 252**

**Rated titles: 110**

**Included titles:**

- 1 Systematic review**
- 1 Randomised controlled trial**
- 47 Observation studies**

## **Discussion**

The Panel found the evidence available for this question to be rather heterogeneous in terms of study populations, interventions, and comparisons. The validity of the diagnostic imaging techniques examined herein was in fact studied in reference to the characterisation and confirmation of both malignant/benign and primitive/metastatic lesions. The GDG therefore found it quite difficult to define the role of the imaging techniques of US, CEUS, CT, NMR, and PET in the differential diagnosis of focal liver lesions in hepatopathic and non-hepatopathic patients.

Several key points, however, emerged during the discussion. Concerning HCC, one of the experts underscored that a recently conducted revision of the American Association for the Study of the Liver Guidelines<sup>a</sup>, examined the monitoring of patients at risk of HCC and evaluated the importance of the

“wash-out” phase, also in the absence of a hypervascularisation in arterial phase. The experts considered the cited practice guideline to be of great importance, although it had not been yielded by the search strategy and, as a consequence, had not been included in the selected titles, due to the high degree of specificity with which it had been developed. The Panel therefore decided to include it in the evidence, together with the work of Bolondi, a study serving as a reference point for the drafting of the present guidelines<sup>b</sup>. Moreover, for the same reasons, the Panel chose to reference a study by Forner (although its publication date did not fall within the literature search time limits: January 2000 – October 2007), as it attempted to define the optimal utilisation of diagnostic techniques in function not only of a patient’s contrastographic behaviour, but also of lesion size<sup>c</sup>. A third consideration concerned the proper characterisation of focal hepatic lesions in patients at risk of HCC—i.e., the expert group once more considered it essential to cite the above-mentioned AASLD guidelines, which provided indications on the necessary concurrent use of two different techniques in accurately diagnosing HCC. Several Panel members underscored that, in any event, imaging-guided biopsy represents the optimal standard for obtaining certain diagnosis.

The Panel therefore concluded that the very high sensitivity and specificity of CEUS make it possible to recommend it as the optimal exam for differentiating malignant/benign and primitive/metastatic lesions of the liver. Yet, they noted the importance of keeping in mind that CEUS, being an ultrasound method, is inevitably constrained by the limitations imposed by certain types of patients. In instances in which CEUS is found to be insufficient or inadequate, NMR conducted with a hepatospecific contrast media agent represents the optimal second tier exam.

<sup>a</sup> Bruix J et al. *Hepatology* 2005; 42: 1208-36.

<sup>b</sup> Bolondi L et al. *Hepatology* 2005; 42: 27-34.

<sup>c</sup> Forner A et al. *Hepatology* 2008; 47: 97-104.

## Recommendations

- The use of CEUS is **recommended** for the characterisation of focal liver lesions and for the diagnostic, i.e., second- tier, confirmation of focal liver lesions detected via other means.
- The use of NMR with a hepatospecific contrast media agent is **recommended** in instances in which CEUS does not yield adequate and definitive results. Spiral-CT scan is **recommended** for patients in particular situations that do not allow for the use of either CEUS or NMR.

### Question 3

**What is the role of the imaging techniques of US, CEUS, CT, NMR and PET in the locoregional staging of primitive hepatic cancer (in terms of number of lesions, size, site, anatomo-functional structure relations, and lymph nodes)?**

**Raised titles: 219**

**Selected titles: 118**

**Rated titles: 13**

**Included titles: 13 Observation studies**

## **Discussion**

In light of the literature yielded by the bibliographical search, the Panel carefully considered the advisability itself of including this question in the guidelines.

Concerning the staging of lesions, some experts underscored the need for multiphasic techniques that make it possible to examine (in function of the post-contrast media injection time phase) vascular structures and their involvement, the vascularisation of cancer lesions, and then, the surrounding parenchyma and the lymph nodes.

Although spiral-CT is a routine procedure, no studies to date have validated its use as a standard diagnostic imaging technique. Moreover, Spiral-CT comparisons with NMR have shown the latter to be the most accurate and adequate technique for detecting lesions in patients requiring a surgical or ablative operation.

In terms of the sensitivity and specificity of NMR, comparisons with invasive techniques, such as ultrasound laparoscopy, IOUS, and CE-IOUS have found that these latter two techniques produce fewer false positives and, consequently, an optimal degree of reliability.

## **Recommendation**

Although the currently available evidence does not allow for formulation of actual recommendations concerning the role of the various imaging techniques of US, CEUS, CT, NMR, and PET in the locoregional staging of primitive hepatic cancer, the Panel members agree in suggesting that CT and NMR be used in locoregional staging, and that invasive techniques should be limited exclusively to be used as support for patients undergoing surgery .

#### Question 4

What is the role of the imaging techniques of US, CEUS, CT, NMR, and PET in assessing complications and immediate and long-term (follow-up) treatment responses in patients undergoing oncologic therapies (chemotherapies, RFTA AND PEI, laser, microwave, TACE, SRT, TAE, cryotherapy, surgery)?

**Raised titles: 1.266**

**Selected titles: 58**

**Rated titles: 31**

**Included titles: 31 Observation studies**

#### **Discussion**

The Panel members unanimously agreed that most of the studies examined were not very methodologically sound, as they referred to inadequate sample sizes and had frequently been conducted with unclear methodology

Furthermore, it was considered that the dearth of studies with negative outcomes could risk biasing the Panel's final evaluation.

The literature review and Panel discussion indicated that diagnostic technique choices are highly dependent on the type of treatment utilized, and evidence from clinical practice confirms this assumption. Indeed, given the current panorama of available evidence, even attempts to categorise the various techniques in terms of treatment type would not lead to definition of a standard technique (which would then, of course, require further investigation). It was therefore possible to formulate only the following considerations: The yielded studies did not adequately investigate the possibility of defining follow up in terms of an assessment of complications; nearly all the research conducted to date has focussed on defining the role of diagnostic imaging in assessing treatment efficacy and has overlooked its potential for assessing complications. The Panel therefore referenced Livraghi's

multicentric study, as it examined RFTA complications (although the paper had not been originally yielded by the search strategy), because it defines the role of CT in this regard<sup>a</sup>.

Hence, considering that the selected studies mostly concerned HCC treatment, and given that sufficient evidence for metastasis assessment is still unavailable, CEUS shows strongly dishomogenous and occasionally contrasting sensitivity values, but good specificity in the assessment of immediate and long-term (follow up) treatment responses in patients undergoing oncologic therapies. Moreover, the technique takes on varying sensitivity and specificity value, in function of treatment type. Given that it is not a whole-body diagnostic technique, in comparisons with CT and NMR, it loses validity in *per patient* analysis, but shows similar efficacy in a *per lesion* analysis. Lastly, CEUS is easily repeatable and less invasive. Although most Italian centres currently use CEUS to assess treatment efficacy, the literature to date has not produced a standard of reference. Specific evidence is lacking, especially concerning the “immediate” (i.e., 24 hours’ post-treatment) assessment of treatment outcomes.

Conversely, the experts agreed on recommending follow up with CT or NMR at three months’ post-treatment, because both are whole-body techniques and can serve adequately in illness restaging.

The Panel therefore unanimously agreed to recommend CEUS at 30-40 days and CT at three months for follow up and restaging.

The literature conversely reports no evidence concerning the diagnostic imaging assessment of surgical treatment.

<sup>a</sup> Livraghi T et al. Radiology 2003; 226: 441-51.

## Recommendations

- Current knowledge does not allow for recommendation of a diagnostic imaging technique of reference for assessing follow up, intended as complications and immediate-/long-term treatment responses in patients undergoing oncological therapies; further investigation is therefore advised.
- Moreover, current findings do not provide sufficient evidence for the treatment efficacy of diagnostic imaging at 24 hours' post-treatment in patients undergoing oncologic therapies. CEUS shows uncertain sensitivity and a low degree of specificity--although the technique's sensitivity and specificity varies in function of type of treatment. Its use is therefore only **moderately recommended**.
- In 30-40 days' post treatment follow up in patients undergoing oncologic therapies, CEUS shows slightly lower efficacy than CT does, but good specificity, although, once again, the technique's sensitivity and specificity varies in relation to type of treatment. Hence, considering the lower biological risk of CEUS, as compared to CT, its use is **recommended** for this follow-up phase.
- CT or NMR follow up at three months' post oncological therapy is **recommended**, especially for RFTA and PEI. NMR use is conversely **recommended** for TACE

### Question 5

What is the role of the imaging techniques of US, CEUS, CT, NMR, and PET in following up patients with lesions characterised as benign?•

**Raised titles: 56**

**Selected titles: 35**

**Rated titles: 3**

**Included titles: 1 Prospective diagnostic study**

### **Discussion**

The experts found a dearth of evidence (only one valid and relevant study was yielded on the advisability of using imaging techniques to follow up patients with benign FHLs. Moreover, the Panel underscored the fundamental pointlessness of following up patients with lesions already characterised as benign (see question 2, p. 19).

Diagnostic imaging is recommended only for following up patients with confirmed hepatic adenoma, which has been found to present a potential (although rare) risk for degeneration into hepatocellular carcinoma.

Ultrasound also appears to be the most effective technique for any form of follow-up deemed necessary in clinical practice, when the main aim is to monitor for growth in a FHL already characterised as benign.

### **Recommendation**

Current knowledge does not allow for recommendation of a specific diagnostic imaging technique to follow up patients with lesions characterised as benign. Hence, further studies investigating and evaluating the role and advisability of use of all available diagnostic techniques monitoring the progress of this type of lesions are recommended, when required.