The Appropriate Allocation of CEUS in the Diagnostic Algorithm of Liver Lesions: A Debated Issue

L. Bolondi

The introduction of a new diagnostic tool into the clinical practice has always been a matter of discussion in the medical literature, both by clinicians and health care managers. There is generally a first phase characterized by enthusiasm and optimism of the authors performing and proposing the new technique, who generally report convincing results that appear significantly better than those achieved by previous techniques in the same field. The counterpart of this optimism is frequently the skepticism of the majority of clinicians not directly involved in the technique. The subsequent phase, often occurring many years later, is characterized by a more balanced evaluation leading, finally, the scientific societies to produce clinical guidelines, in which a quite general agreement about the advantages and limitations of the technique and its diagnostic accuracy has been reached.

This progressive adjustment seems to be particularly complicated and much debated for new advances in ultrasound technology, starting from the introduction of real-time and pulsed and color Doppler and continuing to the recent advent of ultrasound contrast agents (UCAs). It is my opinion that, as far as the ultrasound technology is concerned and, in particular, the use of UCAs, the skepticism and the lack of confidence reported in the literature by nonultrasound-experts, both radiologists and clinicians, has been far greater than for any other technique.

Nevertheless, the use of UCAs and the role of contrast-enhanced ultrasound (CEUS) have nowadays been largely accepted in clinical practice, and the technique has been implemented in most centers for more than a decade. However, CEUS is still waiting for a definite allocation in the diagnostic armamentarium, particularly with respect to computed tomography (CT) scans and magnetic resonance imaging (MRI). Experts in ultrasonography have the feeling that this technique truly represents a great revolution, especially for the diagnosis of liver diseases, allowing in a very quick, simple, and economic way, to provide findings similar to or sometime superior to those obtained by the more sophisticated and expensive CT scans and MRIs, whose availability is and will remain limited. This revolution, however, has not yet been universally understood and acknowledged and, as a consequence, the application of CEUS worldwide is extremely variable.

It is worthwhile remembering that the advantages of CEUS have already been extensively reported in the literature of the past decade. Among them, its cost-effectiveness has to be emphasized, especially now, when economic resources face the increased medical and health bills. An imaging technique (CEUS) with a diagnostic accuracy for the characterization of hepatic tumors of about 90% to 92% [19, 23], comparable to the rates of CT and MRI, that costs less to the national health system, also considering cases of inconclusive diagnoses where another imaging technique is required [10, 16 – 18, 21] is now available for clinicians. Therefore, why to date has its use not been strongly encouraged by all scientific societies and health care providers and accepted by the whole clinical community?

Many reasons underlying the variability of use of CEUS may be searched and analyzed. From the clinical standpoint they include the fact that UCAs were introduced into the clinical practice significantly later than CT and MRI contrast agents, and therefore their contribution has not been immediately appreciated because similar results, with more readable images, could already be obtained by those techniques. Furthermore, most clinicians are resistant to accept changes in their own practice, and they still consider CEUS as something that has been artificially added to CT and MRI, but actually is unable to replace them. Other important points, which have always negatively affected the judgment of any ultrasound technique, are the defect in the standardization, the operator dependence, the variability of results related to the physical characteristics of any individual patient and, last but not least, the difficulty in the interpretation of images by nonexperts, in comparison to CT and MRI. All these points are again a problem for CEUS. These issues play an important role when clinicians without personal experience in ultrasound are included in the panel of experts requested to produce practical guidelines in which recommendations are based on data coming from the literature and expert opinions: for the latter point, personal expertise in ultrasound is more important than it is in any other diagnostic technique.

Added to these issues, there is also the problem of registration for UCAs, which has not yet been achieved in some important countries such as the United States and which is difficult to understand based on a strictly medical evaluation of

Affiliation
Department of Digestive Diseases and Internal Medicine, University of Bologna, Italy

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Correspondence
Luigi Bolondi, M. D.
Department of Digestive Diseases and Internal Medicine, University of Bologna Bologna Italy luigi.bolondi@unibo.it

Guidelines and good clinical practice recommendations for contrast-enhanced ultrasound in the liver: update 2012: A World Federation for Ultrasound in Medicine and Biology (WFUMB)-European Federation of Societies for Ultrasound in Medicine & Biology (EFSUMB) initiative in cooperation with representatives of the Asian Federation of Societies for Ultrasound in Medicine (AFSUMB), the American Institute of Ultrasound in Medicine (AIUM), the American Society of Ultrasound in Medicine (ASUM), and the International Contrast Ultrasound Society (ICUS).
published data. There are many arguments suggesting that the
reasons for the lack of registration may probably be economical
and/or political, or even simply based on industrial strategies.
The latter point may also account for the registration of different
UCAs in Europe and in Japan.

Despite these problems, however, the diffusion of CEUS for the
diagnosis of liver diseases has progressively increased world-
wide, and this poses a question of defining the fields of correct
application and of the position of the technique in the diagnostic
algorithm.

Many practical guidelines have indeed been produced in recent
years regarding the diagnosis of hepatocellular carcinoma (HCC),
which is one of the major fields of possible application of CEUS in
liver diseases, and it is surprising to remark how the role ac-
nounced to CEUS is different in the various guidelines. The
most striking example is provided by the guidelines produced
by hepatologic societies, such as the American Association for
the Study of Liver Diseases (AASLD), the European Association
for the Study of the Liver (EASL), and the European Organisation
for Research and Treatment of Cancer (EORTC), for the diagnosis
of HCC in liver cirrhosis. Although the first EASL document [4]
cluded Doppler ultrasound (US) among the techniques able to
provide the typical vascular pattern of HCC, and subsequently
the first version of AASLD guidelines [2] replaced Doppler US
with CEUS, this technique was unexpectedly deleted in the recent
updated version of both AASLD and EASL guidelines [3, 9]. Rea-
sons for this change have been officially based on the difficulty
of CEUS in distinguishing HCC from intrahepatic colangio
carcinoma and emerged from a single paper produced by 1 of
the authors of the guidelines [24], but to the majority of clinicians
they remain unclear. The lack of registration of CEUS in the Uni-
ted States and, therefore, the problem in recommending a tech-
nique that is not available in clinical practice may contribute to
this position. What is difficult to understand is why EASL has pas-
ively accepted this position despite UCAs (‘SonoVue, Bracco, Mi-
ian Italy) having been registered in all European countries and
their being widely used everywhere. As opposed to the American
and European hepatologic societies, the Asian societies (Asian Pa-
cific Association for the Study of the Liver [APASL]) and the Japan
Society of Hepatology (JSH) produced their own guidelines for
the diagnosis of HCC [13, 15], which include CEUS as a technique
able to display the typical vascular findings in HCC, and it is inclu-
ded in the recommended diagnostic algorithm. It is worth re-
marking how the UCA used in Japan (Sonazoid, Daiichi Pharma-
ceutical/GE Healthcare, Chalfont St. Giles, U.K) is different from
that used in Europe (SonoVue), but this does not explain the dif-
fering positions in the evaluation of the role of CEUS. Looking at
these guidelines, an opposite evaluation of the role of CEUS
seems to exist between Eastern and Western experts.

My interpretation is that all documents providing recommenda-
tions reflect the minds of the authors and their differing clinical
and ultrasound expertise. The situation is different in Eastern
countries and especially in Japan, where hepatologists are per-
sonally performing US. Another point to be underlined is the fol-
lowing: when a panel of experts includes all specialists and clin-
icians coming from both Eastern and Western countries (as occurred
in the first AASLD guidelines; [2]), a more general agreement can be reached concerning the role of CEUS.

This complicated situation has lead the European Federation of
Societies for Ultrasound in Medicine & Biology (EFSUMB), since
2004, to produce guidelines [1, 6] for the clinical use of UCA, and
now the World Federation for Ultrasound in Medicine and Biolo-
gy (WFUMB) and EFSUMB have updated the previous EFSUMB
guidelines, providing the document that is published in this issue
of this journal. The work has been conducted in cooperation with
representatives of the Asian Federation of Societies for Ultra-
sound in Medicine (AFSUMB), the American Institute of Ultra-
sound in Medicine (AIUM), the American Society of Ultrasound
in Medicine (ASUM), and the International Contrast Ultrasound
Society (ICUS) and includes a large panel of experts that is com-
prehensive of all clinical, radiologic, and ultrasound experts, thus
offering the possibility of full understanding and use of the po-
tential of CEUS, avoiding the bias caused by lack of specific clinical
ultrasound expertise present in the updated AASLD [3] and EASL
[9] clinical guidelines. This bias led to the underscoring of many
current advantages of CEUS, such as: (1) the possibility of moni-
toring continuously the perfusion of UCA after administration
by means of real-time imaging and then of appreciating any rapid
hyperenhancement followed by early washout, which are not ap-
preciable with the use of other contrast imaging techniques; (2)
the opportunity to define immediately a diagnosis after detection
of a liver lesion during US surveillance in cirrhosis, with obvious
positive effects in terms of speeding the diagnostic workup and
the clinical and psychologic impacts on patients; (3) the possibil-
ity of immediately monitoring the effects of any ablative treat-
ment and eventually of completing it on site; (4) the absence of
ionizing radiations; (5) the demonstrated cost-effectiveness;
and finally (5) the good diagnostic accuracy, similar in most in-
stances to that of CT.

Taking into account all these positive issues and extensively ana-
lyzing data from the literature, the updated WFUMB-EFSUMB
guidelines now provide a correct allocation of CEUS in each clin-
ical setting in the field of liver diseases, and they represent the
best available contribution to the correct use of this technique in
the clinical practice. The importance and the validity of these
guidelines are further emphasized by the very recent document
by the British National Institute for Health and Clinical Excellence
[18]; NICE diagnostic guidance number 5, issued August 2012,
www.nice.org.uk/dg5), which endorsed CEUS with SonoVue as
the first-line diagnostic assessment in patients with incidentally
detected liver lesions and also in patients with nodules in liver
cirrhosis (different from the AASLD and EASL guidelines) [3, 9].
NICE is generally very strict in selecting contributions from the
literature and in recognizing the validity of any diagnostic tool
or drug, so the EFSUMB should be proud that its name is cited 7
times in the full NICE leaflet, mainly in relation to its guidelines.
There is a final issue that I would like to emphasize: the future
perspectives of this technique. In my opinion, one of the greatest
possibilities of UCAs is the strong potential of developing many
new compounds with differing vascular and tissue diffusion.
Long-lasting liver-phase UCAs, such as BR14 [12] and the above-
mentioned Sonazoid [11], represent 2 of the main recent techni-
cal advances. Furthermore, molecular imaging using targeted
UCAs has been already studied in animal models, with promising
results for the determination of angiogenesis and with potential
translation into clinics, being at last nonimmunogenic [5, 20]. In-
novations in this field also include quantification software, aimed
at overcoming subjectivity in evaluating the intensity of en-
ancement regarding both the characterization of hepatic lesions
and the assessment of response to treatment [7, 14, 22].

All these perspectives have been only preliminarily and very par-
tially explored, but the very rapid development of this field indu-
ces us to believe that the WFUMB-EFSUMB guidelines for the use
of CEUS will need further update in the near future.
References


