Research Article

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Clinical and economical impact of 2010 AASLD guidelines for the diagnosis of hepatocellular carcinoma

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Background & Aims: Although contrast-enhanced computed tomography (CT), dynamic magnetic resonance (MRI) and fine needle biopsy (FNB) are the standard of care to diagnose hepatocellular carcinoma (HCC), the clinical and economic benefits of the updated AASLD diagnostic algorithm, including the drop of contrast enhanced ultrasound (CEUS), have not been previously evaluated.

Methods: 119 *de novo* liver nodules detected during ultrasound (US) surveillance in 98 cirrhotics, 7 <1 cm, 67 1–2 cm, 45 >2 cm in size, were sequentially examined by CEUS and CT, using MRI as a rescue approach in patients lacking a typical vascular pattern for HCC by one or both contrast techniques in the 1–2 cm nodules and by CT in the >2 cm nodules. A FNB was performed when required to meet both 2005 and 2010 AASLD criteria.

Results: Eighty-four (70%) nodules were HCC: the radiological diagnosis was done in 38 (88%) of those 1–2 cm and in 38 (95%) for those >2 cm HCCs according to 2010 AASLD criteria. CT or MRI detected 13 HCC nodules that were missed by unenhanced US. Despite an absolute specificity, CEUS failed to identify any HCC uncharacterized by CT or MRI. By updated AASLD criteria, 6 (17%) FNB procedures were spared in patients with 1–2 cm nodules ($p = 0.025$), as compared to 2005 criteria. The 2010 *vs.* 2005 AASLD per patient cost was similar in 1–2 cm nodules, 432 € *vs.* 451 € ($p = 0.46$), but lower in >2 cm nodules, 248 € *vs.* 321 € ($p < 0.001$).

Conclusions: A sequential study with either CT or MRI enhances the radiological diagnosis of HCC and reduces costs and liver biopsy need.

Keywords: Hepatocellular carcinoma; Cirrhosis; Surveillance; Clinical guidelines; Imaging techniques.

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Abbreviations: HCC, hepatocellular carcinoma; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; CT, computed tomography; MRI, magnetic resonance imaging; FNB, fine needle biopsy; CEUS, contrast enhanced ultrasounds; ICC, intrahepatic cholangiocarcinoma; APASL, Asian Pacific Association for the Study of the Liver; NICE, British National Institute for Health and Clinical Excellence; US, ultrasounds; IRCCS, Istituto di Ricerca e Cura a Carattere Scientifico; MDCT, multidetector row computed tomography; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; HDV, hepatitis delta virus; NET, n €endocrine tumor; LGDN, low grade dysplastic nodule; MRN, macro regenerative nodule; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio; HGDN, high grade dysplastic nodule; LN, liver nodule; CI, confidence interval; NaN, not a number; n.n., not needed.

Introduction

Surveillance of patients at risk is the only predictive approach to improve treatment and survival of HCC patients [1,2]. This is demonstrated by remarkable differences in the access to and outcome from curative therapies between screened and unscreened patients, even if there are discrepancies in the recommendation policies for HCC screening between geographical areas and substantial limitations in the population access to screening worldwide [2–4]. The updated recommendations of the European (EASL) and American (AASLD) Association for the Study of the Liver have endorsed the sequential application of computed tomography (CT) scan, magnetic resonance imaging (MRI) and echo-guided fine needle biopsy (FNB) to diagnose HCC detected during surveillance of patients with cirrhosis, considering a single imaging technique adequate for the diagnosis of HCC larger than 1 cm in size. Moreover, the new guidelines dropped contrast enhanced ultrasounds (CEUS), since it is considered inaccurate in distinguishing between HCC and intrahepatic cholangiocarcinoma (ICC) [2,3]. This was not the choice of the Asian Pacific Association for the Study of the Liver (APASL), which still endorses CEUS for the diagnosis of *de novo* HCC, and to some extent of the British National Institute for Health and Clinical Excellence (NICE), which recommends CEUS whenever a contrast-enhanced MRI is not clinically appropriate, not accessible or not acceptable to the patient [4,5]. While CEUS could be

perceived as a cost-effective approach in these patients, the evidence supporting this indication was questioned on the assumption that all patients with a radiological diagnosis of HCC would have a subsequent confirmatory scan with CT or MRI performed for purposes of tumor staging and treatment planning [5]. These considerations, along with the low prevalence of ICC in cirrhosis and the limited access of real life patients to MRI with respect to CEUS, led an agency and other international societies to endorse CEUS in the diagnostic algorithm of HCC in cirrhosis [4–6]. Since all these recommendations were largely based on expert opinions rather than on controlled studies while relying on the typical contrast enhanced patterns, a prospective study defining both the diagnostic accuracy and the economic consequences of the AASLD algorithm for the diagnosis of HCC is deemed necessary.

We therefore aimed to prospectively define the number of procedures needed to characterize *de novo* liver nodules detected during surveillance of patients at risk, according to both 2005 and 2010 AASLD guidelines, and corresponding costs. Secondary aim was to assess sensitivity, specificity and diagnostic yield of CEUS in the work package for the characterization of *de novo* liver nodules.

Patients and methods

This is an independent investigator-driven, multicentric prospective study designed to assess the diagnostic performance of the 2010 *vs.* 2005 AASLD recommendations (Supplementary Figs. 1 and 2) for the diagnosis of *de novo* liver nodules detected in cirrhotic patients with compensated cirrhosis under surveillance with ultrasounds (US) [2,7]. Starting in December 2009 to January 2012, all patients with a Child–Pugh A-B cirrhosis and a *de novo* liver nodule detected during US surveillance were consecutively recruited in four referral Italian centers for liver disease (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico – Milan, Ospedale Guglielmo da Saliceto – Piacenza, Policlinico Sant'Orsola-Malpighi – Bologna, Policlinico Agostino Gemelli – Roma). Patients with a pre-existing liver nodule, a previous HCC or ICC diagnosis, and those with poor liver function (Child–Pugh C) were excluded. All the patients were under surveillance by US examinations performed at 6-month intervals by dedicated experienced ultrasound operators. After giving an informed consent in the presence of an independent witness, patients were assessed following the collection of a detailed medical history, a physical examination, complete blood count and biochemical tests, including serum alpha-fetoprotein (AFP), and viral hepatitis and autoimmunity serum markers, and finally enrolled.

The study protocol is conform with the ethical guidelines of the 1975 Declaration of Helsinki and it was approved by the Institutional Review Board of the Department of Internal Medicine.

Study design

In each patient, CEUS and abdominal CT scans were carried out within 1 month from detection of a liver nodule and were sequentially followed by MRI in patients lacking a typical vascular pattern for HCC by one or both contrast techniques in 1–2 cm nodules and by CT in >2 cm nodules. A fine-needle biopsy (FNB) was performed when required to meet both 2005 and 2010 AASLD criteria (Fig. 1A refers to 1–2 cm nodules; Fig. 1B refers to >2 cm nodules). Imaging techniques and FNB were performed also in patients with a <1 cm nodule. The FNB was repeated in all patients with unsolved histological diagnosis.

We arbitrarily introduced CEUS and CT as first imaging techniques due to their wide availability in our country as compared to MRI [8] and the favorable cost of this approach [9].

Diagnosis of the liver nodules

The gold standard for the diagnosis of HCC was the concordance of 2005 and 2010 AASLD radiological criteria [2,7] and histology in the remaining cases. An at least 6 month enhanced follow-up was required to confirm histological non-malignancy. All patients with a nodule lacking histological features of malignancy underwent a repeat US every 3 months and an abdominal CT/MRI every 6 months to assess changes in size and in the vascular pattern of the nodule at imaging. All nodules either enlarging or showing changes in the vascular pattern underwent a further US guided FNB. The clinical and economic impact of the diagnosis of HCC using serum AFP level >200 ng/ml in patients with a *de novo* >2 cm nodule, according to the 2005 AASLD recommendations was evaluated as well.

Vascular pattern of nodules at imaging

Arterial hypervascularity was defined as an increased contrast enhancement of the nodule (i.e., hyperechogenicity on US, hyperdensity on CT and hyperintensity on MRI) taking place during the arterial phase of examination (wash-in), as compared to the surrounding liver parenchyma. Portal/venous contrast wash-out was a hypoenhanced pattern of the nodule (i.e., hypoechogenicity on US, hypodensity on CT and hypointensity on MRI) with respect to the surrounding liver parenchyma taking place during the portal/venous phase. The typical radiological pattern of HCC was a nodule showing arterial wash-in followed by portal/venous contrast wash-out.

CEUS

US studies were performed with a Philips iU22 system (Philips Ultrasound, Bothell, Washington, USA) in Milan, MyLab scanner (Esaote, Genova, Italy) in Bologna and Rome and Technos MPX, CnTI (Esaote, Genova, Italy) in Piacenza. The vascular pattern of focal liver nodules was assessed by CEUS with a second generation US blood pool contrast agent (Sonovue, Bracco, Milano, Italy), using a dedicated US technology as previously reported by each centre [9,10–12]. All examinations were obtained and evaluated in real time and digitally stored and documented by a commercially available system or videotapes. A 3 min minimum video clip was recorded for each patient to evaluate arterial and portal/venous phases.

The reimbursement of a CEUS examination was 78 €, including the cost of contrast.

CT scan

Quadruple-phase CT scan (i.e., unenhanced, hepatic arterial, portal/venous and delayed phases) was performed with a ⩾32-multidetector row CT (MDCT) in all four centers using the following equipments: Definition (Siemens Medical Systems, Erlangen, Germany) in Milan, HiSpeed Multislice (GE Medical Systems, Milwaukee, WI, USA) in Piacenza, Emotion 6 (Siemens Medical Systems, Erlangen, Germany) in Bologna and Light Speed VCT XT (GE Medical System, Milwaukee, WI, USA) in Rome, as previously described by each centre [9,10–12].

The reimbursement of an abdominal contrast-enhanced CT scan examination was 168 €.

MRI

Transverse T1-weighted and T2-weighted MRI and multiphasic contrast-enhanced dynamic 3-dimensional MRI of the whole liver with fat suppression were performed with a 1.5 T system in all the four centers using the following equipments: Avanto (Siemens Medical Systems, Erlangen, Germany) in Milan, Signa (GE Medical Systems, Milwaukee, WI) in Bologna and Rome, Magnetom Vision (Siemens Medical Systems, Erlangen, Germany) in Piacenza. Arterial phase, portal/venous and delayed sequences were acquired as previously described by each center [9,12–14].

The National Health System reimbursement of an abdominal contrast-enhanced MRI examination was 265 €.

Liver histology

The FNB procedure was performed using a 21-gauge cutting needle for microhistology (Biomol, HS Hospital Service, Italy) in Milan and Piacenza, 19-gauge trenchant needle for microhistology (Biomol, HS Hospital Service, Italy) in Bologna and 19-gauge trenchant needle for microhistology (TSK surecut, Hospital Service, Italy) in Rome, to obtain intra- and extra-nodular parenchymal tissue cores, and classified according to the International Working Party criteria [15]. Formalin-fixed paraffin-embedded liver sections were examined by experienced liver pathologists who were unaware of the result of the clinical and radiological examinations.

The hospital reimbursement of a FNB procedure was 236 €, including the histological report and the cost of day-hospital admission.