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Contrast Enhanced Ultrasound in focal liver lesions – a cost efficiency study

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Abstract

Contrast enhanced ultrasound (CEUS) has a well established role for the evaluation of focal liver lesions (FLL). **The aim** of our paper was to evaluate if CEUS is a cost-efficient method for the first line evaluation of FLL. **Material and method:** We performed a prospective study that included all the CEUS evaluations performed in our Department during a 6 months period (September 2009-March 2010). CEUS evaluation was performed with a Siemens Acuson S2000TM Ultrasound System following an intravenous bolus injection of 2.4 ml SonoVue® (Bracco). A CEUS examination was considered conclusive if, following contrast, the FLL had a typical enhancement pattern (after EFSUMB Guidelines 2008), allowing its classification as hemangioma, FNH, adenoma, hepatocellular carcinoma, metastasis, fatty-free area, focal fatty infiltration. We compared the costs of a CEUS positive diagnosis, to the cost of contrast CT and/or contrast MRI positive diagnosis. We also included the additional costs of CT and/or MRI, if CEUS was not conclusive. The cost of CEUS was calculated as the cost of 1/2 vial of SonoVue + the cost of abdominal ultrasound (150 + 30 = 180 RON). The costs of contrast CT scan and MRI were 285 and 650 RON respectively (mean costs practiced in Timisoara). **Results:** In our study were included 316 FLL: 163 (51.6 %) in patients without hepatitis and 153 (48.4 %) in patients with chronic hepatopathies (in 133 cases liver cirrhosis and in 20 cases chronic hepatitis). CEUS was conclusive in 250 (79.1%) of the 316 cases, the cost for the evaluation of these patients being 45,000 RON. For the other 66 patients, the diagnosis cost will include the cost of CEUS + the cost of contrast CT: 30,690 RON. If contrast MRI was used for the differential diagnosis, the cost would be 54,780 RON. So the total cost of diagnosing 316 FLL would be 75,690 RON or 99,780 RON. If contrast CT would be used as the first line diagnosis for the 316 FLL, the cost would be 90,060 RON, by CEUS saving 14,370 RON, or 45.5 RON/lesion (using contrast CT for the differential diagnosis). If contrast MRI would be used as the first line diagnosis, the cost would be 205,400 RON, by CEUS saving 105,620 RON, or 334.2 RON/lesion (using contrast MRI for the differential diagnosis). **Conclusion:** CEUS is a cost-efficient method as a first line diagnosis of FLL as compared to first line contrast-CT or first-line MRI.

Keywords: contrast enhanced ultrasonography; contrast enhanced computer tomography; contrast enhanced magnetic resonance imaging; cost-efficiency.

Rezumat

Ecografia cu substanță de contrast (CEUS) are un rol bine stabilit în evaluarea leziunilor focale hepatice (LFH). **Scopul** studiului nostru este de a vedea dacă CEUS este o metodă cost eficientă pentru evaluarea de primă linie a LFH. **Material şi metodă:** Am efectuat un studiu prospectiv care a inclus toate evaluările CEUS efectuate în serviciul nostru într-o perioadă de 6 luni (Septembrie 2009–Martie 2010). Examinarea CEUS s-a făcut cu un ecograf Siemens Acuson S2000TM după administrarea unui bolus de 2,4 ml SonoVue® (Bracco). Examinarea CEUS a fost considerată concluzivă dacă, după contrast, LFH au avut comportament tipic, permițând clasificarea lor ca şi hemangiom, hiperplazie focală nodulară, adenom, hepatocarcinom, metastază, fatty-free area, steatoză parcelară. Am comparat costurile diagnosticului pozitiv prin CEUS, cu cele ale diagnosticului pozitiv prin CT sau RMN cu contrast. Am inclus şi costurile adiționale ale CT şi sau RMN cu contrast dacă CEUS a fost neconcluziv. Costul CEUS a fost calculat ca şi costul a jumătate fiolă de SonoVue + costul unei ecografii abdominale (150 + 30 = 180 RON). Costurile CT şi RMN cu contrast au fost 285, respectiv 650 RON (costurile medii practicate în Timişoara). **Rezultate:** În studiul nostru au fost incluse 316 LFH: 163 (51,6 %) la pacienți fără hepatite şi 153 (48,4 %) la pacienți cu hepatopatie cronică (133 cazuri cu ciroză şi 20 cazuri cu hepatită cronică). CEUS a fost concluziv în 250 (79,1%) din cele 316 cazuri, costul pentru evaluarea acestor pacienți fiind 45.000 RON. Pentru restul de 66 pacienți costurile diagnostice vor include costul CEUS + costul CT cu contrast: 30.690 RON. Dacă pentru diagnosticul diferențial ar fi utilizat RMN cu contrast, costurile ar fi de 54.780 RON. Deci costurile totale de diagnostic al celor 316 LFH ar fi de 75.690 RON, respectiv 99.780 RON. Dacă CT-ul cu contrast ar fi utilizat ca primă linie de diagnostic pentru cele 316 LFH, costurile ar fi de 90.060 RON, prin CEUS economisindu-se 14.370 RON, sau 45,5 RON/leziune (folosind CT cu contrast pentru diagnosticul diferențial). Dacă RMN-ul cu contrast ar fi utilizat ca primă linie de diagnostic, costurile ar fi de 205.400 RON, prin CEUS economisindu-se 105.620 RON, sau 334,2 RON/leziune (folosind CT cu contrast pentru diagnosticul diferențial). **Concluzie:** CEUS este o metodă cost-eficientă ca primă linie de diagnostic a LFH în comparație cu CT sau RMN cu contrast.

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Introduction

The evaluation of Focal Liver Lesions (FLL) is a problem that has to be solved more and more often in daily practice, since FLL are quite frequently discovered, due to the routine use of imaging methods (ultrasound – US, computer tomography – CT or magnetic resonance

imaging – MRI) and due to screening strategies for patients with liver cirrhosis.

Routine evaluation of FLL included until recently only contrast CT or MRI and, sometimes, liver biopsy. In the last years, Contrast Enhanced Ultrasound (CEUS) has become a reliable imaging method for the assessment of FLL. The European Federation of Societies of Ultrasound in Medicine and Biology (EFSUMB) issued the first Guidelines regarding the use of CEUS [1] in 2004, revised in 2008 [2], in which the main indications of this method are presented.

Incidental lesions discovered on standard US must be evaluated by means of different imaging methods, and, sometimes, this can be a stressful event for the patients, during the waiting time for a new method of evaluation (contrast CT or MRI). CEUS can be performed immediately after the standard abdominal ultrasound, so that in approximately 5 minutes (the total duration of this investigation), a confident diagnosis can be obtained.

On the other hand, FLL evaluation by standard methods increases the medical costs in these patients (since both contrast CT and MRI are expensive imaging methods).

The aim of our study was to evaluate if CEUS is a cost-efficient method, for the first line evaluation of FLL.

Material and methods

We performed a prospective study that included all the CEUS liver evaluations performed in our Department during a 6 months period (September 2009-March 2010). Four experienced ultrasonographists, who were aware of the patients' clinical histories, performed US scanning by means of a Siemens Acuson S2000™ Ultrasound System with a 3.5 MHz convex array probe. A baseline ultrasound examination, including a color/power Doppler analysis, was performed. Once set, the US scan parameters – such as focal zone and time gain compensation – were not changed throughout the study. A low frame rate (5 Hz) and a very low mechanical index (MI), < 0.08, were used for real-time imaging. Cadence™ Contrast Pulse Sequencing Technology was used for the contrast study, software versions 1.5A and 1.6B. One focus was positioned below the level of the lesion. Each examination lasted about 5 min after the bolus injection. The US contrast agent used in the present study was SonoVue® (Bracco, Italy), a perfluoro gas containing agent, provided as a sterile, lyophilized powder contained in a septum-sealed vial. A white, milky suspension of sulphur hexafluoride (SF6) microbubbles was obtained by adding 5 ml of physiological saline

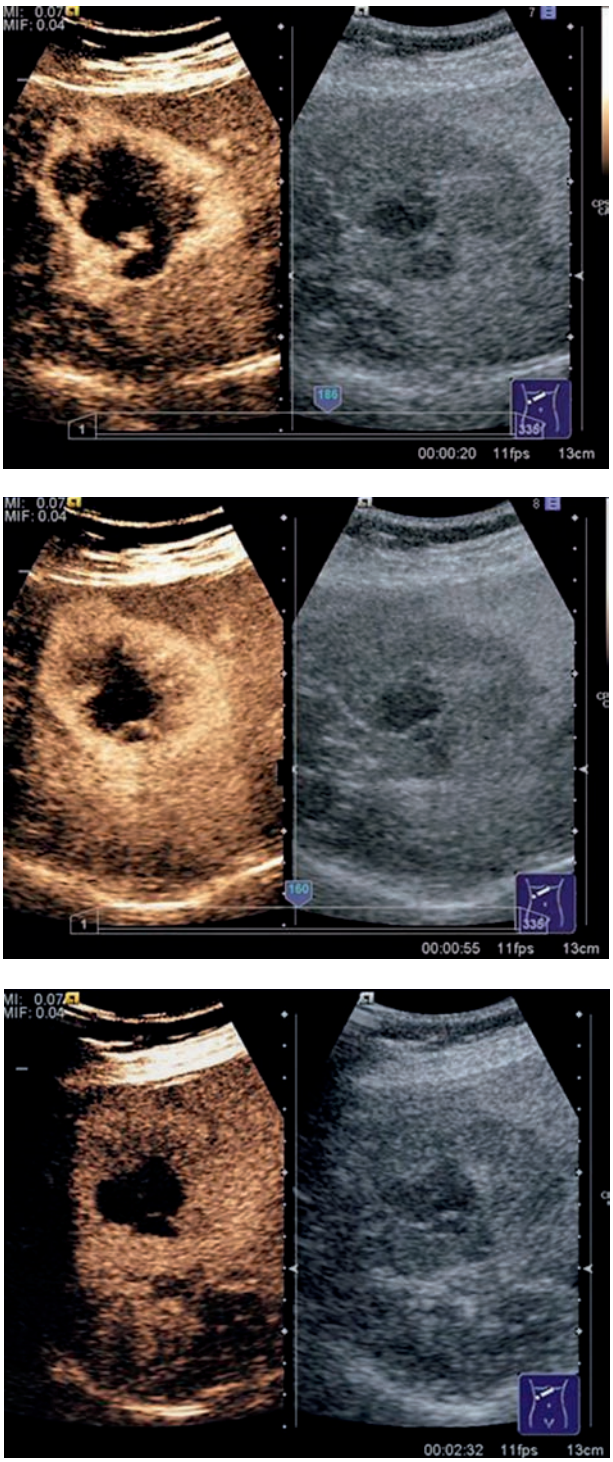


Fig 1. CEUS enhancement pattern of a hemangioma: a) arterial phase - peripheral, nodular enhancement; b) portal phase – peripheral, nodular hyperenhancement with a non-enhanced central area due to necrosis; c) late phase - peripheral, nodular hyperenhancement with a non-enhanced central area due to necrosis

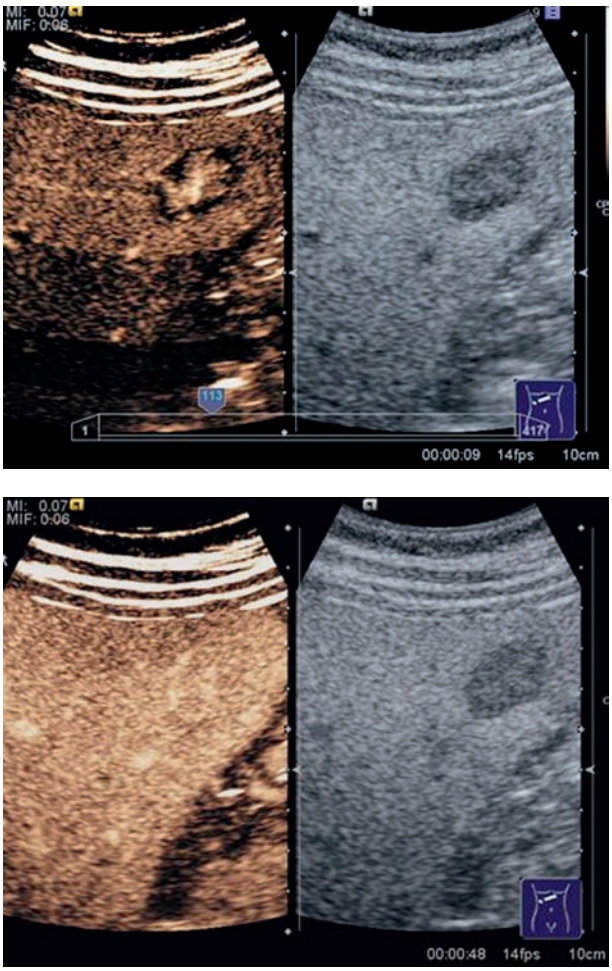


Fig 2. CEUS enhancement pattern of a HNF: a) arterial phase – early, spoke-wheel enhancement; b) portal phase – hyperenhancing

(0.9% sodium chloride) to the powder (25 mg), followed by hand agitation. Each patient received an intravenous bolus injection of SonoVue® for each lesion to be characterized (usually 2.4 ml), via a 20-gauge intravenous catheter, placed in the ante-cubital vein, followed by 10 ml saline flush. To characterize the lesion, the hemodynamic behavior of SonoVue® enhancement during the arterial phase (15-30 seconds), portal venous (30-120 seconds) and late vascular phases (120-300 seconds), was evaluated. All sonographic examinations were digitally recorded.

The location and size of the lesion were assessed on unenhanced and CEUS scans. In addition, the vascularity and pattern of SonoVue® enhancement of the lesion (hypoenhancing, hyperenhancing, isoenhancing), as

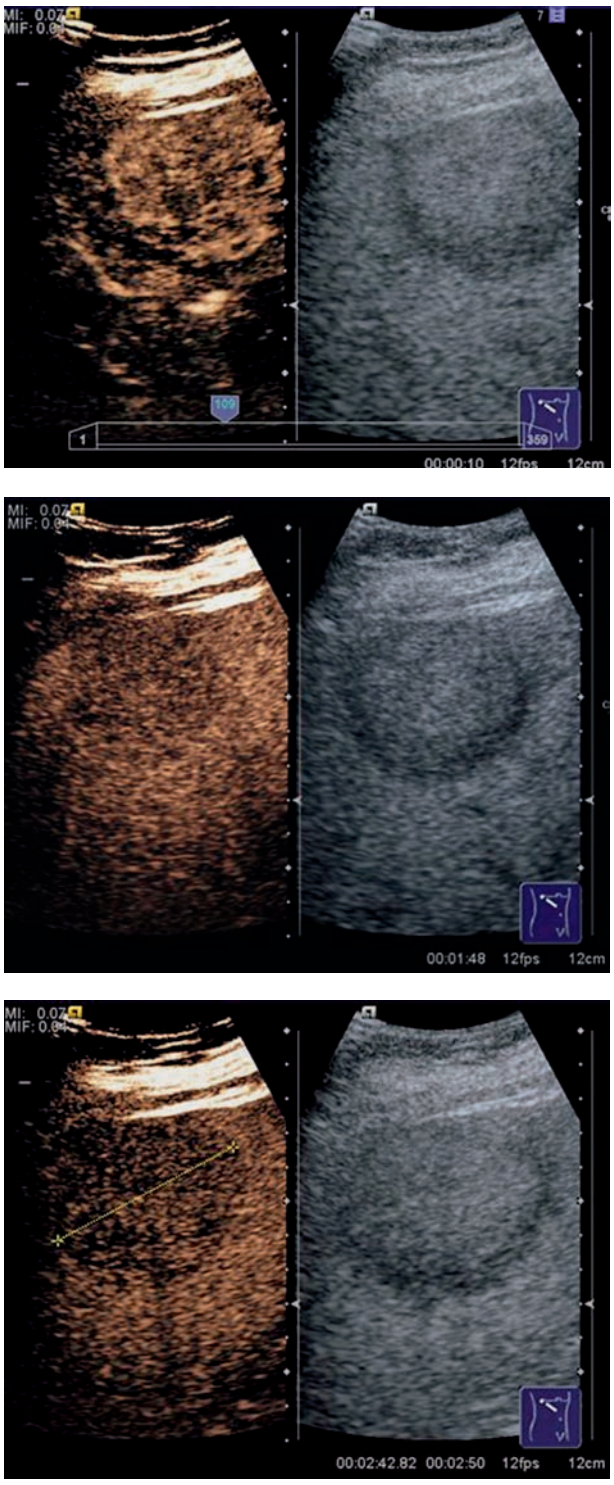


Fig 3. CEUS enhancement pattern in HCC: a) arterial phase – hyperenhancing; b) portal phase – wash-out; c) hypoenhancing in the late phase

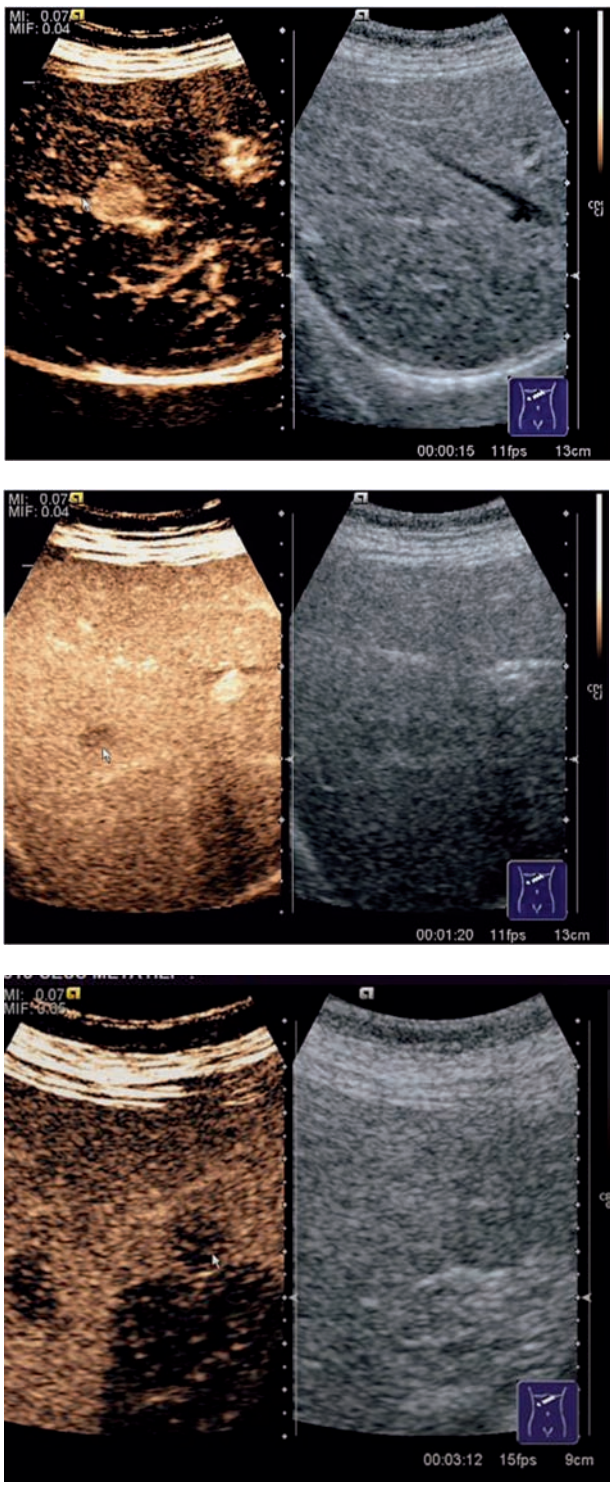


Fig 4. CEUS enhancement pattern of a hypervascular liver metastasis: a) arterial phase – hyperenhancing; b) wash-out in the portal phase; c) hypoenhancing in the late phase, when another lesion is also revealed (arrow).

compared with the adjacent liver parenchyma during the arterial, portal venous and late phases were evaluated. Also, the spatio-temporal pattern of the lesions' filling was assessed in the arterial phase.

A CEUS examination was considered conclusive, if following US contrast, the FLL had a typical enhancement pattern, allowing its classification as hemangioma (Fig.1abc), FNH (Fig.2ab), adenoma, hepatocellular carcinoma (Fig.3abc), metastasis (Fig.4abc), fatty-free area, focal fatty infiltration or others type lesions, according to the EFSUMB guidelines [2].

We compared the costs of a CEUS positive diagnosis, to the cost of contrast CT and/or MRI positive diagnosis. We also included the additional costs of CT and/or MRI if CEUS was not conclusive. The cost of CEUS was calculated as the cost of 1/2 vial of SonoVue + the cost of abdominal ultrasound (150 + 30 = 180 RON). The costs of contrast CT scan and MRI were 285 and 650 RON respectively (mean costs practiced in Timisoara).

The study was approved by the local Ethics Committee.

Results

In our study 316 FLL were included: 163 (51.6 %) in patients without hepatitis and 153 (48.4 %) in patients with chronic hepatopathies (in 133 cases liver cirrhosis and in 20 cases chronic hepatitis).

CEUS was conclusive in 250 (79.1%) of the 316 cases, the cost for the evaluation of these patients being 45,000 RON (180 RON x 250 CEUS examinations). For the other 66 patients the diagnosis cost will include the cost of CEUS + the cost of contrast CT: 30,690 RON (180 RON x 66 CEUS examinations + 285 RON x 66 CT examinations). If contrast MRI would be used for the differential diagnosis, the cost would be 54,780 RON (180 RON x 66 CEUS examinations + 650 RON x 66 MRI examinations). So the total cost of diagnosing the 316 FLL would be 75,690 RON if CT would be used for second line diagnosis or 99,780 RON if MRI would be used for second line diagnosis (Table I).

If contrast CT would be used as the first line diagnosis for the 316 FLL, the cost would be 90,060 RON (285 RON x 316 CT examinations), by CEUS saving 14,370 RON, or 45.5 RON/lesion (using contrast CT for the differential diagnosis) (Table I).

If contrast MRI would be used as the first line diagnosis, the cost would be 205,400 RON (650 RON x 316 MRI examinations) RON, by CEUS saving 105,620 RON, or 334.2 RON/lesion (using contrast MRI for the differential diagnosis) (Table I).

Table I: Comparative costs for the evaluation of the 316 FLL (CEUS conclusive in 250 cases).

	Costs (RON)				Total savings vs. CEUS first line (RON)	Savings/lesion vs. CEUS first line (RON)
	CEUS	CT	MRI	Total		
CEUS first-line + CT second line	45,000	30,690	–	75,690	–	–
CEUS first-line + MRI second line	45,000	–	54,780	99,780	–	–
CT first line	–	90,060	–	90,060	14,370	45.5
MRI first line	–	–	205,400	205,400	105,620	334.2

Discussion

The real value of CEUS for FLL characterization was demonstrated in well known multicentre studies performed in Germany and France, each one including more than 1000 lesions. The German study [3] included 1,349 patients with FLL discovered in standard US that could not be characterized by standard US alone, and in which CEUS was compared with a diagnostic "gold standard": biopsy in more than 75% of the lesions, spiral contrast CT or contrast MRI in the rest of the cases. In this study, the diagnostic accuracy of CEUS was 90.3%. CEUS correctly characterized 723/755 of the malignant lesions and 476/573 of the benign lesions, with 95.8% sensitivity and 83.1% specificity with 95.4% PPV and 95.9% NPV for differentiating benign vs. malignant lesions. Regarding the ability of CEUS in diagnosing different types of lesions, CEUS correctly diagnosed 82.2% of the hemangiomas, 87.1% of the focal nodular hyperplasias (FNHs), 57.9% of the adenomas, 84.9% of the HCCs and 91.4% of the metastases.

In a study [4] on a subgroup of patients from the DEGUM multicentre study, CEUS was compared to standardized spiral-CT (SCT). From the 267 patients, histological findings were available in 158 subjects. In this subgroup assessment of tumor differentiation with CEUS and SCT was concordant in 124 cases and discordant in 30 cases (CEUS/SCT: sensitivity 94.0 / 90.7 %, specificity 83.0 / 81.5 %, PPV 91.6 / 91.5 %, NPV 87.5 / 80.0 %, accuracy 90.3 / 87.8 %). A statistically significant difference could not be established.

In a recently published study [5], also on a subgroup of patients from the DEGUM multicentre study, CEUS was compared to contrast MRI. The study included 262 patients in which the definitive diagnosis in typical liver hemangioma and FNH was based on the MRI as the "diagnostic gold standard", on clinical evidence and additional follow-up (180 patients) or on histology (82 patients). Tumor differentiation was concordant in 56 (68.3 %) and tumor entity in 44 cases (53.7 %). There were no statistically proven differences between CEUS and MRI.

The multicentre French study (STIC) [6] included 1034 FLL. CEUS was compared to contrast spiral CT, contrast MRI or liver biopsy, considered to be the "gold standard". Standard US correctly diagnosed 62.4% of the cases, while CEUS increased the diagnostic performance to 86.1%. The diagnostic concordance between CEUS and the "gold standard" method was 73% (kappa=0.67), better for FLL on non-cirrhotic liver (73.5%, kappa=0.66), than in nodules on cirrhotic liver (71.8%, kappa=0.42).

So, all these studies demonstrated that CEUS is an accurate imaging method for FLL characterization, comparable to contrast-CT and contrast-MRI. But is it cost effective?

In the French multicentre study [7], in which the diagnosis costs of 149 nodules (with liver biopsy as the "gold standard" for diagnosis) were evaluated, the total savings were 128.5 Euros/nodule (considering that the mean CEUS cost is 155.2 Euros – with 1 vial of SonoVue used for each examination, whereas we use only ½ vial; of multislice contrast CT is 191.65 Euros; in contrast MRI is 322.3 Euros).

Also, an Italian multicentre study [8] that included 485 subjects with 575 lesions, compared the costs of a classic patient work-up (which included baseline US followed by contrast CT or MRI with a total cost of 134,576 Euros) to a new scheme in which, following the baseline US, a CEUS examination was performed, in which the total cost was 55,674 Euros. Thus, the total savings were 78,902 Euros or 162 Euros/patient.

A study published by Giesl [9] who conducted a cost-minimization analysis of CEUS as compared to multi-phase computed tomography (M-CT) as the diagnostic standard for diagnosing incidental liver lesions, concluded that CEUS was the more cost-effective method in all scenarios in which CEUS examinations were performed at specialized centers (122.18-186.53 Euros)

as compared to M-CT (223.19 Euros). At an expected 40,000 detected incidental lesions/year in Germany, the total savings would reach 4,000,000 Euros/year. But it must be mentioned that the costs for CEUS would be significantly higher, if it would be performed in non-specialized centers, in which the cost of one CEUS examination could reach 407.87 Euros at an average utilization of the ultrasound machine of 25 % and a CEUS ratio of 5 %.

Also, an Italian study that included 398 patients with 408 lesions analyzed the cost effectiveness of CEUS for the characterization of benign focal liver lesions with indeterminate appearance on ultrasonography, considering whether or not CT was necessary for the diagnosis [10]. This study concluded that during 2002–2005, the introduction of CEUS allowed total savings of 47,055 Euros.

Finally, a recently published Italian study analyzed the costs of different recall diagnostic strategies of small HCC (75 nodules, 10-30 mm in diameter), according to the latest guidelines, which include different strategies for nodules 10-19mm or ≥20mm [11]. This study concluded that the recall strategy starting with CEUS plus CT is the least expensive strategy for patients with at least one nodule 10-19mm in size.

Data from our study also demonstrated that CEUS as the first line of diagnosis for FLL was the most cost-effective, with total savings of 14,370 RON (approximately 4,000 Euros) as compared to contrast-CT and 105,620 RON (approximately 24,900 Euros) as compared to contrast-MRI as first line of diagnosis of the 316 FLL included.

Conclusion

CEUS is a cost-efficient method, as a first line diagnosis method of FLL, compared to first line contrast-CT or first-line MRI.

Conflict of interest: none

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