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Cost analysis of recall strategies for non-invasive diagnosis of small hepatocellular carcinoma

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ABSTRACT

Background: Which is the least expensive recall policy for nodules in the cirrhotic liver remains unclear.
Aim: Aim of the study was to analyze the costs of different recall diagnostic strategies of hepatocellular carcinoma (HCC) on cirrhosis on a real series of patients.
Methods: 75 consecutive small liver nodules (10–30 mm) detected at conventional ultrasonography in 60 patients with cirrhosis were submitted to contrast-enhanced ultrasound, computed tomography and gadolinium-magnetic resonance imaging with a final diagnosis established according to the latest guidelines which include different strategies for nodules 10–19 mm or ≥20 mm. The actual costs required to fully characterise any nodule and staging HCC in every patient, if one or the other imaging modality had been used as the first diagnostic step, were calculated. The theoretical hypothesis that each nodule was present in each patient was also investigated from an economical point of view.
Results: The recall strategy starting with contrast-enhanced ultrasound plus computed tomography is the least expensive strategy for patients with at least one nodule 10–19 mm in size, in nearly all combinations (single or double nodules). In patients with single 20–30 mm nodules the least expensive strategy is to start with computed tomography and to use contrast-enhanced ultrasound as a second step technique.
Conclusions: wider use of contrast-enhanced ultrasound has the potential to save healthcare costs after first ultrasound detection of a single small nodule in cirrhosis.

1. Introduction

Hepatocellular carcinoma (HCC) is the leading cause of death in patients with cirrhosis in the United States and Europe [1]. The burden of cirrhotic and hepatocellular malignant disease is increasing in Western Countries due to the cohort effect of HCV infection epidemics in the 60s and 70s and to the rising number of patients with dysmetabolic cirrhosis [2,3]. Practice guidelines for the management of HCC published in recent years have stressed the importance of diagnosing hepatic lesions in the cirrhotic liver when they are still small. Early detection of malignant liver nodules is critical to select patients with limited disease, potentially candidates for curative treatments such as liver transplantation [4], resection [5,6], alcohol injection or thermal ablation [1,7–9].

Ultrasound surveillance of cirrhotic patients is recommended at 6–12 month intervals [1]. However, the appearance of a nodule does not always signify malignancy, since non-neoplastic lesions may also develop [10]. Therefore practice guidelines issued a recall strategy based on imaging techniques able to establish a diagnosis of malignancy by contrast-enhanced modalities in up of 70–80% of nodules. Diagnosis may be reached by computed tomography (CT) [11] and/or magnetic resonance imaging (MRI) [12] and/or dynamic ultrasound [13–15].

Given the expected burden of disease we investigated whether any specific recall strategy for the diagnosis of HCC would be significantly less expensive than other strategies.

2. Materials and methods

The present retrospective study is based on a case series collected in a prospective study conducted to assess the efficacy of imaging techniques in the diagnosis of HCC in small nodules, according to international guidelines [16]. That study investigated contrast-enhanced CT, contrast-enhanced ultrasound (CEUS) and MRI performed with vascular (gadolinium chelates) and non-vascular (super paramagnetic oxide, SPIO) contrast agents in the diagnosis of HCC and details, including the technical aspects on how imaging techniques were performed, are reported in a sep-

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arate paper [16]. CEUS was performed with SonoVue according to accepted recommendations [17] and lasted 3–5 min (arterial phase range 10–40 s after injection and late phase takes place after 2 min).

The present manuscript reports on the cost estimates of imaging techniques performed with vascular contrast agents, corresponding to those accepted by the most updated international guidelines [1].

Inclusion criteria were as follows: patients had to be discovered having (1) focal liver lesions between 10 and 30 mm in diameter; (2) number of lesions between 1 and 3; (3) visibility of nodules at conventional ultrasonography; (4) detection of nodules during surveillance; (5) age of patients >18 years; (5) absence of contraindications to imaging techniques (allergy to contrast agents; claustrophobia; magnetic devices, metallic plaques or splinters in the body not compatible with MRI); (6) having underlying cirrhosis; (7) absence of neoplastic portal thrombosis or extrahepatic metastases.

The study complied with the principles of the latest update of the Helsinki Declaration and was approved by the Institutional Review Board of the Department; written consent was obtained for the original study before performing imaging techniques and liver biopsies, but was not required by the Review Board for this study, given its retrospective nature.

Patients. The present study analyzes 60 consecutive patients in whom 75 liver nodules were detected by conventional US. Patient characteristics are summarized in Table 1. Two patients were not enrolled in the study since reporting contraindication to iodinized contrast agent (history of allergic reaction) and claustrophobia.

Study design. The study design adopted was based on the retrospective assessment of the minimum imaging techniques required to achieve a diagnosis of HCC according to the AASLD guidelines [1] in each prospectively enrolled individual, if one or the other technique had been used as first, second or third step. Each of these imaging techniques were interpreted blindly to the others, but operators were aware of the size and location of the nodule detected at ultrasound.

2.1. Imaging diagnosis of very early HCC (10–19 mm in diameter)

A non-invasive diagnosis of HCC is established when a coincidental typical pattern for HCC (hypervascularity in the arterial phase and washout in the early or delayed venous phase) is detected by at least two contrast-enhanced imaging techniques [1]. When one or both techniques are inconclusive a third technique is recommended. When the three imaging techniques are negative or only one imaging technique shows a typical pattern, US guided biopsy is to be performed.

US guided biopsy of nodules was performed using 19-gauge modified Menghini needles (Biomol; HS Laboratories, Pomezia, Italy). Specimens were routinely processed and stained with hematoxylin and eosin and by the Masson trichrome method. Diagnosis of HCC was made according to the International Working Party criteria [10].

Table 1
Patient characteristics.

Number of patients	60
Age range (mean)	40–83 (65) years
Sex M/F	52/8
Cirrhosis aetiology	
- HCV+	33
- HBV+	18
- HCV+ HBV+	1
- Cryptogenic	2
- Alcoholic	6
Total number of nodules	75
Nodule per-patient	
- single	43
- double	13
- triple	1

2.2. Imaging diagnosis of early HCC (≥20 mm)

Diagnosis of HCC is established in nodules ≥2 cm in diameter by the presence of one non-invasive dynamic imaging technique with vascular contrast agent, demonstrating the typical vascular pattern of HCC. Biopsy is limited to nodules ≥2 cm, with all imaging techniques inconclusive.

When liver biopsies were not technically feasible or were refused by patients, lesions were submitted to 3-month interval follow-up. Cases with stability in size over time (at least 6 months) were considered benign, whereas cases increasing in size were resubmitted to diagnostic investigations and the last emerging diagnosis was accepted.

No side effects of any contrast agent were observed during the present study.

2.3. Cost analysis study

The current investigation focused on estimating the standard direct costs of different possible diagnostic recall strategies following the AASLD criteria for characterizing liver nodules in cirrhosis.

In Italy costs for CT, MRI and biopsy were based on the fees reimbursed by the National Health Ministry in 2008. Costs in the U.K. for CT and MRI were derived from those reported in a recent article on an analysis of costs for surveillance of cirrhosis [18], whereas the U.S.A. costs were derived from an average of common medical reimbursements according to personal communication of colleagues working in the U.S.A. (Table 2). It is known that fees reimbursed by different agencies and in different locations may vary considerably. By reporting fees from different Countries and the exact prices utilized herein, we leave to the reader the possibility of adjusting the results of our study to his/her own setting, in case that consistent variations in fees apply in that situation.

A single fee for CEUS has not yet been established nationwide in Italy and was therefore approximated to the fee reimbursed for an upper abdominal ultrasound scan plus 50%, as overhead for vein cannulation and nurse assistance, plus the cost of one vial of Sonovue at the price sold to hospitals. This cost matches that currently reimbursed in our hospital, while awaiting a definitive national agreement. A similar approach was utilized also for U.K. and U.S.A., since not even the use of US contrast agents for liver investigation is registered in U.S.A. and thus reimbursements costs are not available. This estimate lead to prices for liver CEUS of $178 (=€121) in Italy, $185 (=£90) in UK and $164 in USA (Table 2).

The cost analysis was carried out in a step-by-step fashion, considering how many techniques had been required to achieve a final diagnosis for each patient and for each nodule.

For the purpose of the present analysis all patients were considered as technically feasible to undergo biopsy, whenever required. In fact a cost analysis including long-term follow-up in patients in whom biopsy could not be performed would be extremely complicated and inaccurate.

Table 2
Computed fees of different imaging techniques in various Countries, expressed in US dollars (1$ = 0.6804 Euros = 0.4867 Sterling). For Italian costs the same fees in Euro are also reported within brackets.

Technique	Cost in Italy $	Cost in U.K. $	Cost in U.S.A. $
CT	341 (€232)	226	392
RM	456 (€310)	411	906
CEUS	178 (€121)	185	164
US guided biopsy	188 (€128)	247	348

Table 3
Characteristics of the study population according to number and size of liver nodules in order to match diagnostic classes reported according to AASLD guidelines for HCC.

Number of nodules	Dimension	Number of pts
Single	Nodule 10–19 mm	27
Single	Nodule 20–30 mm	19
Double	Both nodules between 10 mm and 19 mm	2
Double	One nodule between 10 mm and 19 mm and one nodule between 20 mm and 30 mm	7
Double	Both nodules between 20 mm and 30 mm	3
Triple	One nodule between 10 mm and 19 mm and two nodules between 20 mm and 30 mm	1

Diagnostic approach considered for very small nodules (10–19 mm) was:

(1) Two imaging techniques (CT + CEUS or MR + CEUS or MR + CT) were considered for all patients,
(2) A third technique was considered only for patients with positive findings at only one of the two previous techniques, and
(3) US guided biopsy was calculated for nodules negative at both techniques after first step (since a third imaging technique would be unable to achieve a final diagnosis, even in case of typical pattern) and for those that did not reach concordance of imaging techniques even after the third modality (corresponding to only one conclusive technique).

Diagnostic approach considered for small nodules (≥20 mm) was:

(1) One imaging technique (CT or MR or CEUS) as initial approach,
(2) One of the two remaining imaging techniques for nodules (=patients) with inconclusive pattern at the first step,
(3) The technique remaining from the combination used in the previous two steps was considered for nodules for which diagnostic features of HCC were absent even after the second step, and
(4) US guided biopsy was then calculated for the remaining nodules negative at all non-invasive techniques.

Moreover, since using CEUS as a first diagnostic step does not meet the requirements for HCC staging (which requires a more panoramic and "heavy" radiological technique, such as CT or MR), we also considered an additional approach starting with two techniques including CEUS also in all patients with nodules greater than 20 mm, even though CEUS alone could be enough for the characterization of such nodules.

For the purpose of the present study, we calculated the costs theoretically needed for each patient to reach a definite diagnosis in every nodule, considering the real findings obtained in our previous study [16]. This includes categorization of patients into different diagnostic strategies depending on numbers and size of nodules, as reported in Table 3. Regarding cost calculation, it is worth noting that CEUS is usually performed with only 2.4 mL of Sonovue [13,19], despite vials are made in 4.8 mL amounts. Therefore, up to two nodules in one single patient can be adequately characterized at the cost of one single CEUS examination reported herein. In the single patient with three nodules we calculated the cost of a double CEUS examination.

Since cost analysis on a per-patient basis is strictly linked to the specific findings in this limited patient population, which could produce results difficult to generalize, we also calculated costs on a nodule-by-nodule basis, assuming that each nodule matches one patient.

3. Results

A pattern considered diagnostic for HCC according to the AASLD guidelines was displayed by 39 of 75 nodules at CEUS, by 36 nodules at CT and by 42 nodules at MRI. A more detailed description of how many nodules were diagnostic at each technique and concurrently positive/negative at the other two techniques is made elsewhere [16].

A final diagnosis of HCC was reached in 57 of 75 (76%) nodular lesions.

Taking into account fulfilment of diagnostic criteria by 1 technique in nodules ≥20 mm and by 2 techniques in nodules ≥20 mm [1], a non-invasive diagnosis of HCC would be established in 47 out of 75 (61%) nodules, similarly to data reported by previous studies [19,20]. A total of 20 of 75 nodules (of which 14 of 10–19 mm and 6 of 20–30 mm) showed instead a coincident negative vascular pattern at all 3 imaging techniques according to AASLD criteria. A final diagnosis of HCC was finally made in 4 (all of 20–30 mm) of these 20 nodules, making these cases false negatives at imaging techniques based on vascular contrast agents. The remaining 8 of 75 nodules had only one typical diagnostic technique and were all nodules 10–19 mm in size, not achieving therefore a diagnosis of HCC. A total of 6 of these 8 nodules were finally diagnosed as HCC, while the other 2 resulted negative for malignancy at biopsy and were considered false positive respectively to CEUS and MRI.

Table 4
Overall (and mean) costs of different recall strategies of population with single nodule.

1st step exam	2nd step exam	3rd step exam	4th step exam	Total costs in Italy	Total costs in the U.K.	Total costs in the U.S.A.
Total and mean cost analysis in single 20–30 mm nodule population (19 pts)						
CT	MR	CEUS	Biopsy	$12.493 ($658)	$10.070 ($530)	$18.372 ($967)
CT	CEUS	MR	Biopsy	$11.103 ($584)	$8.940 ($471)	$14.662 ($772)
MR	CT	CEUS	Biopsy	$12.505 ($658)	$11.057 ($582)	$21.822 ($1.149)
MR	CEUS	CT	Biopsy	$11.838 ($623)	$10.749 ($566)	$20.974 ($1.104)
CEUS	CT	MR	Biopsy	$8.613 ($453)	$7.893 ($415)	$11.434 ($602)
CEUS	MR	CT	Biopsy	$8.502 ($447)	$8.037 ($423)	$12.070 ($635)
CEUS + CT	MR	Biopsy	–	$12.705 ($669)	$10.605 ($558)	$16.138 ($849)
CEUS + MR	CT	Biopsy	–	$14.315 ($753)	$13.195 ($694)	$23.334 ($1.228)
Total and mean cost analysis in single 10–19 mm nodule population (27 pts)						
CT + CEUS	MR	Biopsy	–	$21.205 ($785)	$18.665 ($691)	$28.944 ($1.072)
MR + CEUS	CT	Biopsy	–	$23.501 ($870)	$22.036 ($816)	$38.074 ($1.410)
MR + CT	CEUS	Biopsy	–	$25.209 ($934)	$21.705 ($804)	$40.718 ($1.508)

Costs are expressed in US Dollars. According to the step-by-step analysis and to the per nodules analysis in first column are summarized the techniques to be performed in all patients and in second and third lines techniques to be performed only in patients not achieving a final characterization of the nodule at the previous step(s).

Table 5
Overall (and mean per-patient) costs of different recall strategies of population with multiple nodules.

1st step approach	2nd step approach	3rd step approach	3rd step approach	Total costs in Italy	Total costs in the U.K.	Total costs in the U.S.A.
Total and mean cost analysis in patients with 2 nodules, both 10–19 mm (4 pts)						
CT + CEUS (0 pts)	MR (1 pts)	2 Biopsies (2pts)	1 Biopsy (1 pts)	$4.384 ($1.096)	$4.112 ($1.028)	$6.682 ($1.671)
MR + CEUS (0 pts)	CT (1 pts)	2 Biopsies (2pts)	1 Biopsy (1 pts)	$4.840 ($1.210)	$4.523 ($1.131)	$7.588 ($1.892)
MR + CT (1 pts)	CEUS (0 pts)	2 Biopsies (2pts)	1 Biopsy (1 pts)	$4.662 ($1.166)	$4.338 ($1.085)	$7.424 ($1.856)
Total and mean cost analysis in patients with 2 nodules: one 10–19 and one 20–30 mm (7 pts)						
CT + CEUS (1 pts)	MR (3 pts)	2 Biopsies (2pts)	1 Biopsy (1 pts)	$7.309 ($1.044)	$6.578 ($940)	$11.068 ($1.581)
MR + CEUS (4 pts)	CT (0 pts)	2 Biopsies (2pts)	1 Biopsy (1 pts)	$6.401 ($914)	$6.085 ($869)	$10.406 ($1.487)
MR + CT (1 pts)	CEUS (3 pts)	2 Biopsies (2pts)	1 Biopsy (1 pts)	$7.587 ($1.084)	$6.738 ($963)	$11.810 ($1.687)
Total and mean cost analysis in patients with 2 nodules, both 20–30 mm (2 pts[a])						
CEUS (1 pts)	CT + MR+ 2 Biopsies (1 pts)			$1.529 ($765)	$1.501 ($751)	$2.232 ($1.161)
CT (1 pts)	CEUS + MR + 2 Biopsies (1 pts)			$1.692 ($846)	$1.542 ($771)	$2.550 ($1.275)
MR (1 pts)	CT + CEUS + 2 Biopsies (1 pts)			$1.807 ($904)	$1.727 ($864)	$3.064 ($1.532)
Total cost analysis in the patient with 3 nodules (2 nodules 20–30 mm and 1 nodule 10–19 mm)						
CT + (CEUSx2)				$697	$596	$720
MR + (CEUSx2)				$812	$781	$1.234
MR + CT				$797	$637	$1.298

The initial comprehensive imaging approach is reported in column 1, whereas the added technique(s) required to achieve the final diagnosis are reported from the second to the fourth column according to the step-by-step analysis. The number of patients (pts) achieving a final diagnosis at each step, thus not requiring further investigations is reported within brackets. Costs are expressed in US Dollars.

[a] One patient showed typical HCC pattern in both nodules at all imaging techniques, whereas the second patient, affected by HBV cirrhosis, showed two nodules, which resulted negative for malignancy and finally characterized as large regenerative nodules.

Table 6
Cost of different recall strategies for the diagnosis of HCC of 10–19 mm in diameter (AASLD 2005 Guidelines).

1st step approach	2nd step exam	3rd step exam	Total costs in Italy	Total costs in the U.K.	Total costs in the U.S.A.
CT + CEUS	MR	Biopsy	$33.749 ($785)	$29.683 ($690)	$46.060 ($1.071)
MR + CEUS	CT	Biopsy	$36.854 ($857)	$34.678 ($806)	$59.938 ($1.394)
MR + CT	CEUS	Biopsy	$40.543 ($943)	$35.045 ($815)	$65.438 ($1.522)

Costs are expressed in US Dollars. Each strategy includes in first step techniques to be performed in all patients and in second and third lines techniques to be performed only in patients not achieving a final characterization of the nodule at the previous step(s).

3.1. Costs per-patient of different recall strategies.

Patients with single nodules are reported in Table 4 (separated as below or above 2 cm in diameter) and patients with multiple nodules in Table 5. The costs in the tables are all expressed in one single currency (US dollars) to allow an easier comparison between different Countries and different strategies.

In patients with single nodules below 2 cm, the cheapest strategy in Italy would be to include CT and CEUS in the first step, with a mean of $785 for patient (compared to $934 if starting with CT plus MRI, +19%). In patients with single nodules ≥20 mm, in which one single technique could be enough for diagnosis, the cheapest strategy would be start with CEUS. However, in every patient a radiological technique (CT or MRI) would be required anyway, either to stage the disease for nodules with HCC features at CEUS or to proceed in the diagnostic pathway in nodules negative at CEUS. Therefore overall the least expensive strategy would be to start with CT, followed by CEUS if no malignant features are present at CT. Such an approach would cost a mean of $584 per-patient. If CEUS had been the first technique in all patients, the mean cost per-patient would rise to $669 (+14.6% in comparison to the least expensive), since also CT (or MRI) would be required anyway in all patients (Table 4). The most expensive approach (MRI as first step and CT as second) would cost 12.3% more than the least expensive.

In all instances of multiple nodules, of which at least one <2 cm, CEUS was part of the least expensive strategy (Table 5).

3.2. Costs per nodule of different recall strategies.

The cost per-patient of the present study may be difficult to generalize, especially when derived from patients with multiple nodules, since subgroups were rather small. In such small subgroups, an atypical behavior in one or two patients may significantly affect the final results. We decided therefore to calculate also the costs of different diagnostic recall strategies considering one nodule present in one patient. Such calculations are summarized in Table 6 for very early HCC and in Table 7 for early HCC.

Table 7
Cost of different recall strategies for the diagnosis of HCC of 20–30 mm in diameter (AASLD 2005 Guidelines).

Combination	1st step exam	2nd step exam	3rd step exam	4th step exam	Total costs in Italy	Total costs in the U.K.	Total costs in the U.S.A.
I	CT	MR	CEUS	Biopsy	$20.482 ($640)	$16.544 ($517)	$29.698 ($928)
II	CT	CEUS	MR	Biopsy	$18.358 ($574)	$14.777 ($462)	$24.340 ($761)
I	MR	CT	CEUS	Biopsy	$21.073 ($659)	$18.785 ($587)	$36.868 ($1.152)
II	MR	CEUS	CT	Biopsy	$20.065 ($627)	$18.251 ($570)	$35.628 ($1.113)
I	CEUS	CT	MR	Biopsy	$13.882 ($434)	$12.950 ($405)	$18.504 ($578)
II	CEUS	MR	CT	Biopsy	$13.771 ($430)	$13.094 ($409)	$19.140 ($598)
I	CEUS + CT	MR	Biopsy	–	$21.384 ($668)	$17.922 ($560)	$27.128 ($848)
II	CEUS + MR	CT	Biopsy	–	$23.803 ($744)	$22.136 ($692)	$39.072 ($1.221)

Costs are expressed in US Dollars. Each strategy includes in first step techniques to be performed in all patients and in second and third lines techniques to be performed only in patients not achieving a final characterization of the nodule at the previous step(s).

Starting the recall strategy with CEUS and CT after detection of a nodule 10–19 mm in diameter at US, would hypothetically produce the lowest cost to establish the final diagnosis (Table 6), whereas starting with CT and MR is the most expensive strategy. CEUS plus MRI as first step would cost 9.2%, 16.8% or 30.2% more in Italy, U.K. and U.S.A. respectively, than starting with CEUS plus CT, whereas using CT plus MRI as a first step would cost respectively 20.1%, 18.1% and 42.1% respectively more than with CEUS plus CT.

Regarding nodules 20–30 mm in size, the least expensive approach would be to start with CEUS alone. However, in cases in which CEUS would be enough to establish a diagnosis of HCC, a "heavy" radiologic technique, such as CT or MRI should be performed in any case to stage the disease, as discussed previously. Therefore, an additional strategy, as reported in Table 7, was devised to take this problem into account. In nodules 20–30 mm in size the least expensive strategy would be to start with CT, followed by CEUS in inconclusive cases, whereas starting with MRI followed by CT would cost 9.2% more in Italy, 23.4% in the U.K. and 46.3% in the U.S.A. than starting with CT followed by CEUS.

Lastly, we produced mathematical formulas, based on the number of diagnostic and non-diagnostic examinations to take into consideration that the costs of the procedures may change over time or may differ in various Countries. Using these formulas, reported in Appendices A and B, the costs of the various strategies, as emerging from our series of patients considering one nodule for one single patient, can be calculated by simply inserting the costs of various procedures and can be adapted to any currency or update upon revision of the costs of the procedures.

4. Discussion

The present study attempted to quantify the costs of different diagnostic recall strategies for the diagnosis of HCC based on a cohort of real patients and adhering to current guidelines. Results showed that CEUS is nearly always included in the least expensive first step approach and that the extent of differences between the least and most expensive strategy is in the range of 6–20% in Italy.

The ideal pre-requisite for the present analyses would be for a patient to have similarly easy access to any of the three imaging modalities (CEUS, CT or MRI), each performed by operators experienced in liver imaging. If these pre-requisites are met, the physician in charge of a patient with a liver nodule detected by ultrasound could choose the least expensive approach.

Conversely if any of the techniques is difficult to access and would delay the final diagnosis, or is not performed by operators experienced in liver imaging, then the decision should be made on a local basis considering local resources.

Our findings are in agreement with very recent ones [21], wich also showed that the least expensive diagnostic strategy in nodules 10–19 mm in size is to start with CT plus CEUS.

This similarity emerged despite our estimated fees were higher than those in Milan, and especially for CEUS, a condition which could have hindered this technique (MRI in our study was 1.17 times the cost in Milan, CT 1.38 and CEUS 1.55). CT plus CEUS satisfies both the needs to characterize a nodule and stage the neoplastic disease according to current guidelines [1]. Using CT in addition to MR in place of CEUS would imply an additional cost of 18–42% compared to CEUS + CT. As a consequence, CEUS can be validly offered immediately after detection of a very small nodule at ultrasound, when surveillance is performed in (secondary or) tertiary centers, whose US scanners not only perform B-mode conventional US, but also CEUS. This approach would significantly reduce the time to diagnosis and hence to treatment in case of HCC and possibly also further cut the cost of CEUS, since a single US session would be required. Furthermore, patients usually appreciate to achieve the final diagnosis as soon as possible, since uncertainty generates anxiety in the oncological setting

For small nodules (20–30 mm in diameter), CEUS alone as a first step despite being the least expensive approach should not be considered acceptable to adequately assess a patient. The least expensive acceptable combination strategy, would therefore be to start the recall strategy with CT and to leave CEUS as a second step. Starting with the combination of CEUS and CT in all cases would not increase greatly the costs per-patient (Tables 3 and 4) and could be considered in all cases, at least in tertiary centers, since also the technical feasibility of percutaneous ablation can be immediately considered or ruled out.

We acknowledge some limitations in our economic approach, which are currently difficult to solve. Firstly, if more than two nodules are present it becomes more relevant to have a panoramic overview of the liver (also because the likelihood of multifocal HCC increases) and hence CT or MR are to be favoured regardless of costs. Similar considerations should probably also appear valid in patients investigated for recurrent liver nodule(s) after a previously treated HCC. In this case the probability of multifocal disease becomes higher and thus a panoramic exploration of the liver with radiological techniques is recommended. Secondly, ongoing technological advancements may enhance the accuracy of MRI and CT. This means that the present calculations could be reassessed on the basis of technologies made available after 2006, but a completely new series of patients would be needed.

One further critical point, which could modify the cost assessment reported herein, is the rate of additional nodules seen by CT but not by MRI or vice versa. In fact, if one of the two techniques was able to see significantly more nodules than the other, then the economic approach could change. However, according to the current literature the difference in sensitivity between CT and MRI with vascular contrast agents, despite slightly favouring MRI, appears small. Moreover, in the setting of first detection of a small nodule in cirrhosis the a priori probability of other HCCs is low, so that even a very sensitive technique has little to improve in comparison to the other. Finally, considering that in any of the proposed strategies, either CT or MRI is already included, it appears that the current economical analysis maintains its validity.

In conclusion, this economic assessment helps to support choices in allocating health resources to reach a first diagnosis of HCC according to international guidelines. In keeping with other very recent data [21] a greater use of CEUS has the potential to save health care costs, especially in very early (10–19 mm) nodules.

Conflicts of Interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.dld.2010.03.003.

References

[1] Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42(5 (November)):1208–36.
[2] El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. Gastroenterology 2004;127(5 Suppl. 1 (November)):S27–34.
[3] Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology 2002 Jul;123(1):134–40.
[4] Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996 Mar 14;334(11):693–9.
[5] Sala M, Fuster J, Llovet JM, et al. High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. Liver Transpl 2004 Oct;10(10):1294–300.

[6] Cucchetti A, Ercolani G, Vivarelli M, et al. Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. Liver Transpl 2006 Jun;12(6):966–71.
[7] Tateishi R, Shiina S, Teratani T, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. Cancer 2005;103(6 (March 15)):1201–9.
[8] Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology 2008 Jan 1;47(1):82–9.
[9] Livraghi T, Bolondi L, Lazzaroni S, et al. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. A study on 207 patients. Cancer 1992;69(4 (February 15)):925–9.
[10] Terminology of nodular hepatocellular lesions. International Working Party. Hepatology 1995 Sep;22(3):983–93.
[11] Tomemori T, Yamakado K, Nakatsuka A, et al. Fast 3D dynamic MR imaging of the liver with MR SmartPrep: comparison with helical CT in detecting hypervascular hepatocellular carcinoma. Clin Imaging Sep-Oct 2001;25(5): 355–61.
[12] Ward J, Guthrie JA, Scott DJ, et al. Hepatocellular carcinoma in the cirrhotic liver: double-contrast MR imaging for diagnosis. Radiology 2000 Jul;216(1): 154–62.
[13] Gaiani S, Celli N, Piscaglia F, et al. Usefulness of contrast-enhanced perfusional sonography in the assessment of hepatocellular carcinoma hypervascular at spiral computed tomography. J Hepatol 2004 Sep;41(3):421–6.
[14] Quaia E, Calliada F, Bertolotto M, et al. Characterization of focal liver lesions with contrast-specific US modes and a sulfur hexafluoride-filled microbubble contrast agent: diagnostic performance and confidence. Radiology 2004 Aug;232(2):420–30.
[15] Nicolau C, Catala V, Vilana R, et al. Evaluation of hepatocellular carcinoma using SonoVue, a second generation ultrasound contrast agent: correlation with cellular differentiation. Eur Radiol 2004 Jun;14(6):1092–9.
[16] Leoni S, Piscaglia F, Golfieri R, et al. The Impact of Vascular and Nonvascular Findings on the Noninvasive Diagnosis of Small Hepatocellular Carcinoma Based on the EASL and AASLD Criteria. Am J Gastroenterol 2009;(November 24).
[17] Albrecht T, Blomley M, Bolondi L, et al. Guidelines for the use of contrast agents in ultrasound. January 2004. Ultraschall Med 2004;25(4 (August)):249–56.
[18] Thompson Coon J, Rogers G, Hewson P, et al. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. Health Technol Assess 2007 Sep;11(34):1–206.
[19] Forner A, Vilana R, Ayuso C, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology 2008 Jan;47(1):97–104.
[20] Bolondi L, Gaiani S, Celli N, et al. Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. Hepatology 2005 Jul;42(1):27–34.
[21] Sangiovanni A, Manini MA, Iavarone M, et al. The diagnostic and economic impact of contrast imaging technique in the diagnosis of small hepatocellular carcinoma in cirrhosis. Gut 2009;(December 1).