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# Characterization of focal liver lesions by contrast-enhanced ultrasonography: economic evaluation

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## ABSTRACT

Objectives: Liver imaging techniques aim to correctly characterize focal lesions and influence choices of therapeutic strategies. The objective of this study was to compare diagnostic efficacy and direct medical costs of contrast-enhanced ultrasonography (CEUS) to magnetic resonance imaging (MRI) or computed tomography (CT) in the characterization of focal liver lesions (FLL).

Methods: Prospective study enrolled 170 patients. Two diagnostic algorithms were compared to standard reference: (1) Ultrasonography (US) followed by MRI/CT and, (2) US followed by CEUS. In the economic evaluation, the perspective of the healthcare sector in the Netherlands was used. Clinical outcomes were 'correctly/incorrectly characterized' benign and malignant lesions and life-years (LY). Model inputs were taken from the hospital database, literature and publicly available sources. Univariate and probabilistic sensitivity analyses were performed.

Results: CEUS was able to identify benign and malignant FLLs with a sensitivity of 96.9% and specificity of 92.3%. For correct tumor subgroup characterization, sensitivity and specificity were 86.2% and 85.6%, respectively. Base-case results of the economic evaluation revealed that the CEUS strategy had similar effectiveness compared to the MRI/CT strategy (incremental effects of 0.002 LYs) and resulted in cost-savings of €452 per patient. The cost-savings for diagnostic phase and treatment phase were €160 and €292, respectively. The main drivers of variation were sensitivity, specificity and cost of the diagnostic tests. Results robustness was confirmed by probabilistic sensitivity analysis.

Conclusions: CEUS is a highly accurate and cost-saving alternative compared to the traditional procedures and should be considered as the front-line option in the characterization of FLLs.

## INTRODUCTION

Abdominal ultrasonography (US) is the most common baseline imaging modality for patients with liver disease. However, US findings do not provide sufficient specificity to differentiate benign from malignant focal liver lesions (FLL) and is now regarded as inadequate in their characterization [1-2]. The reported specificity range for unenhanced or baseline US in characterizing FLLs is between 23% and 68% [3].

Contrast-enhanced ultrasonography (CEUS) is increasingly accepted in clinical settings for diagnostic imaging of FLLs [4-8].

Other imaging modalities such as contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are performed to detect and characterize hepatic lesions [9]. But, there are risks associated with both CT and MRI technologies. The contrast agent used in MRI/CT could be harmful in patients with renal failure or for those allergic to iodinated agents. Similarly, there are risks, including cancer, associated with repeated use of both CT and MRI [10-11]. In addition, the use of MRI excludes identification of patients with claustrophobia, leads to disproportionally long waiting times, and high costs.

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) published guidelines and recommendations for the use of contrast-enhanced ultrasonography in the characterization of FLLs [12]. Recent studies showed that CEUS and MRI had comparable diagnostic performance in the characterization of FLLs and numerous multicenter and single center publications reported no significant difference between the diagnostic efficacy of CEUS, MRI and/or CT [13-17]. A meta-analysis also confirmed high pooled sensitivity and specificity of CEUS and reported no significant difference compared with contrast-enhanced CT and contrast-enhanced MRI [14].

In addition to the diagnostic performance, cost-effectiveness considerations of health care interventions are important due to rising costs. Economic evaluations together with clinical analyses provide the foundation for allocation of various resources including new technologies, treatments and procedures. Economic analyses indicated that CEUS was a cost-effective replacement for CT and MRI in various clinical situations [18]. Therefore, the objective to be addressed in this study was to compare diagnostic performance and direct medical costs of CEUS with MRI or CT in the characterization of FLLs in the Netherlands.

## METHODS

### Clinical Evaluation

*I. Patients and Procedure*

Total 199 patients were eligible to participate in this prospective single center study, at the Erasmus MC, Rotterdam, the Netherlands. 29 patients were excluded because of absence of control imaging and/or informed consent. The study population consisted of 170 prospectively enrolled patients (66 men and 104 women), with a mean age of 50.5 yrs (19-86 yrs, SD 15.8) with at least one focal liver lesion detected with baseline ultrasonography. Exclusion criteria were age <18 years, pregnant or lactating women, contraindication to any of the contrast agents, and/or inability to provide informed consent. All subjects underwent CEUS examination, MRI and/or CT for further characterization of their lesions. Patients with benign lesions were followed for at least six months. Patients with malignant lesions received curative treatment or palliative care according to current clinical recommendations. Treatment strategies included in the analysis were related to the primary liver disease only. Clinical and economic outcomes for secondary metastatic sites were excluded. The protocol of the study was approved by the local medical ethical committee. All patients provided written informed consent to participate in the study, which was performed according to the guidelines provided in the Declaration of Helsinki.

*II. Data Collection*

Data collection for the clinical analysis was performed at the single-patient level (bottom up approach) and patients were used as their own control. In addition to the traditional diagnostic protocol for FLL characterization, in which MRI or CT followed unenhanced US, CEUS was performed in all subjects. Two experienced sonographists who were blinded to the results of other techniques performed diagnostic examinations. The sonographists were informed about age and sex of each patient, as it represents obvious patient characteristics during examination.

*III. Imaging Technologies*

Ultrasonography was performed with Hi-Vision Preirus equipment (Hitachi Medical Systems) using contrast agent (SonoVue, Bracco, Italy). Only dominant FLLs were selected for ultrasound image evaluations. Diagnostic criteria for FLLs were followed according to published EFSUMB guidelines [12] [19-20].

Magnetic resonance imaging (MRI) examinations were performed by 1.5 Tesla (Philips Medical Systems, the Netherlands or General Electric, WI, USA), by using a body-array coil, with identical scan protocols. Contrast agent was either non-liver specific gadolinium-chelate (Magnevist, gadopentate-dimeglumine, Schering,

Germany) or liver specific (Multihance, gadobenate-dimeglumine, Bracco, Italy). Computed tomography (CT) examinations were performed with a 64-section scanner (Siemens, Somatom Sensation 64).

The typical appearances of the lesions on MRI and results of histopathology obtained from biopsy or surgical specimens and judgments of clinicians were used as reference standard for diagnosis and characterization. Due to ethical reasons, biopsy samples were not taken without clinical indication. Therefore, it was not feasible to use pathology results from all patients as the reference standard. Biopsy was taken only when deemed absolutely necessary for the diagnosis, and was thus performed according to current guidelines and good clinical practice. CT served as a second reference imaging method when MRI was inconclusive, in patients with claustrophobia or when histology examination was not applicable.

*IV. Diagnostic Performance*

All imaging results were interpreted in a blind manner by two experienced sonographists and consensus was achieved. At the time of analysis, the examiners were unaware of the final diagnosis and the results of other techniques.

Statistical analysis was performed using SPSS software (SPSS Inc, Chicago, IL, USA). Sensitivity of each diagnostic imaging technology was calculated as the percentage of true malignant lesions out of the total number of true malignant and false benign lesions. Specificity was calculated as the percentage of true benign lesions out of the total number of true benign and false malignant lesions.

Diagnostic performance of CEUS, MRI and CT were compared to identify FLLs as benign, malignant and further characterize them into subgroups (i.e. adenoma, FNH, hemangioma, hepatocellular carcinoma (HCC), cholangiocellular carcinoma (CCA), metastasis, other benign and other malignant).

## Economic Evaluation

*I. Decision Analytic Model*

A decision analytic model was developed using TreeAgePro 2009 Software Inc. (Williamstown, MA, USA) to estimate incremental costs and effectiveness of diagnostic imaging technologies from the healthcare perspective in the Netherlands. The results of the clinical evaluation were used as base-case inputs for the economic model. The diagnostic performance of CEUS was compared to MRI/CT. Reference standard comprised imaging (MRI or CT-in case MRI was not applicable), histology and judgments of clinicians. The clinical outcomes were expressed in life-years (LYs). Health related quality of life measures were not available. Figure I. shows the schematic representation of the economic model. The first three branches that originate from the decision node represent the choices between CEUS, MRI/CT and standard

reference. The branches emanating from each chance node represent the probability that a patient is identified correctly or incorrectly with a benign or malignant lesion (with further subgroup characterization). Each subsequent branch emanating from the second chance node reflects the possible outcomes that may occur after diagnosis. Outcomes considered in the model for malignant group were curative treatment after diagnosis or palliative care. Outcomes for benign group were follow-up after diagnosis or no follow-up.

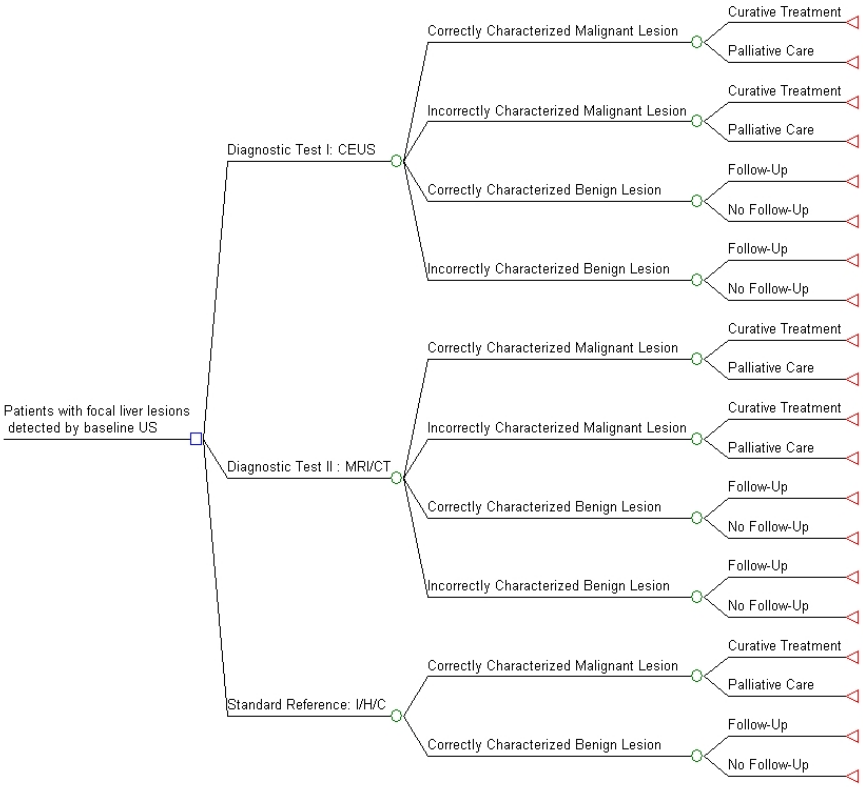


**FIGURE 1: The decision tree.** The decision tree represents the population of patients with focal liver lesions detected by baseline US. Subgroups defined by CEUS diagnostic strategy were then defined as patients with true positive/ false positive (malignant) and true negative/false negative (benign) tumors. Patients in the MRI/CT diagnostic strategy arm were also defined as having true positive/false positive (malignant) and true negative/false negative (benign) tumors. Malignant and benign tumors were characterized further into subgroups (HCC, CCA, Metastasis & Hemangioma, Adenoma, FNH). The branch defined as the Standard Reference: I/H/C strategy represents patients based on typical appearances of their lesions (true positive (malignant) and true negative (benign) after imaging or results of histopathology/FNAB obtained from biopsy or surgical specimens as well as judgments of clinicians. Outcomes were defined as curative treatment after diagnosis or palliative care for malignant lesions. For benign lesions, outcomes were follow-up after diagnosis or no follow-up.

*II. Resource Use and Unit Costs*

Direct medical costs were considered. The following hospital costs were included in the analyses: costs of diagnostic strategies such as MRI, CEUS, CT and 79MBq $TC^{99M}$, liver biopsy, laboratory tests, intensive care days, hospital days, outpatient visits and costs of several treatment strategies such as radiofrequency ablation (RFA), transarterial chemo-embolization (TACE), surgical resection, chemotherapy, palliative care, targeted therapy and screening for liver transplantation. Resource use and unit costs are presented in Table I. For CEUS, the only additional cost compared to the baseline US was the price of the contrast agent. The volume of the cost items was obtained from the Erasmus University Medical Center database and patient files. The costs of the medications were based on the prices listed on the Dutch Health Care Insurance Board (Pharmacotherapeutic Compass – CVZ) [101]. For items with low cost prices (i.e. laboratory tests) Dutch tariffs and the hospital data were used as proxies of the real values. Time horizon was two years. Costs and effects beyond first year were discounted at a rate of 4% and 1.5% respectively, in abidance with the Dutch guidelines (CVZ) for cost-effectiveness analyses [102]. The base year was 2010 (in Euros). All costs were inflated to 2010 values using Statistics Netherlands (CBS) website [103].

*III. Model Assumptions*

Based on available data, the following assumptions were made in the economic analysis: (a) Diagnostic costs were assumed to include the cost of the imaging tests, one outpatient visit and one consultation by phone. (b) Outpatient visits were assumed to be on average three visits per benign and six visits per malignant groups. (c) Average hospital duration in case of complications was assumed to be seven days. (d) Mean laboratory tests were assumed to be €5559 per malignant group and €656 per benign group, based on the patient data. (e) Cost of diagnostic test for CEUS was assumed to be the total of the cost of baseline ultrasonography and the contrast agent SonoVue. (f) Treatments for HCC included in the study were liver resection, RFA, TACE and screening for liver transplantation. Patients with advanced tumor stage and poor liver function were eligible for palliative care. (g) Palliative care was assumed to last for four months. At the end of four months patients were assumed to be deceased. (h) Palliative care was assumed to include general practitioner visits, day-care and medication. Mean costs for palliative care patients were calculated as €12,000. (i) Gemcitabine (1000mg) and cisplatin (250mg) were assumed to be chemotherapy agents for eligible patients. Administration of doublet chemotherapy was on average six cycles. (j) Costs and effectiveness calculations for secondary metastatic sites were excluded. (k) Patients eligible for targeted therapies were assumed to receive sorafenib (400mg, Nexavar, Bayer). Based on the results

**Table 1: Resource Use and Unit Costs.**
Direct medical costs from the hospital perspective were considered and were obtained from the hospital database and patient files. The base year was 2010. The costs of the medications and laboratory tests were based on the prices listed on the Dutch Pharmacotherapeutic Manual (Pharmacotherapeutic Compass – CVZ), Dutch tariffs and Erasmus Medical Center (EMC) data. Time horizon was two-years. Costs and effects beyond first year were discounted at a rate of 4% and 1.5% respectively, in abidance with the Dutch guidelines (CVZ) for cost-effectiveness analyses.

| Resource Use | Unit Cost* | Source |
|---|---|---|
| **Diagnostic Imaging** | | |
| MRI abdomen with contrast† | € 250 | NZA |
| CT abdomen with contrast† | € 216 | NZA |
| US abdomen without contrast† | € 77 | NZA |
| US abdomen with contrast (CEUS) | € 154 | NZA/EMC data‡ |
| 79 MBq TC-99M (Bridatec) | € 313 | NZA |
| **Procedures & Treatments** | | |
| Liver Biopsy† | € 186 | NZA |
| Surgical Resection | € 9,637 | NZA |
| RFA- US guided ¶ | € 950 | EMC data‡ |
| RFA- CT guided § | € 1,655 | EMC data‡ |
| TACE ¢ | € 1,355 | EMC data‡ |
| Chemotherapy (Gem 1000mg-Cis 25mg) | € 372 | F. Kompas (CVZ) |
| Targeted Therapy (Sorafenib 200mg) | € 305 | F. Kompas (CVZ) |
| Screening for Liver Transplantation | € 31,362 | NZA |
| **Palliative Care** | | |
| Mean GP visits/4 months | € 751 | CVZ |
| Mean Care Day /4months | € 11,005 | CVZ |
| Mean Medications/4 months | € 34 | F. Kompas (CVZ) |
| Furosemid (80mg) | € 1 | F. Kompas (CVZ) |
| Spironolactone (300mg) | € 4 | F. Kompas (CVZ) |
| Propanolol (80mg) | € 3 | F. Kompas (CVZ) |
| **Laboratory Tests & Other Resource Use** | | |
| Mean Lab Tests for malignant group | € 5,559 | EMC data‡ |
| Mean Lab Tests for benign group | € 656 | EMC data‡ |
| Inpatient Hospital Day | € 669 | van Gils et. al 2010¥ |
| Outpatient Visit | € 127 | van Gils et. al 2010¥ |
| Intensive Care Day | € 2,120 | van Gils et. al 2010¥ |
| Consultations by telephone | € 14 | Handleiding voor Kostenonderzoek (CVZ) |

* All values were reported in Euros (2010). Decimal digits were rounded to the nearest whole number.
† Including specialist fees
¥ Pilot outcomes research: Effects and costs of oxalipatin stage III colon and metastatic colorectal cancer. (July 2010)
‡ Erasmus University Medical Center
¶ Radio Frequency Ablation -Ultrasound Guided
§ Radio Frequency Ablation -Computed Tomography Guided
¢ Transarterial chemoembolization

of recent trials, sorafenib is currently recommended by the U.S. Food and Drug Administration (FDA) for the management of advanced HCC patients. In the model, administration of sorafenib was assumed to be for four months. (l) Time horizon was assumed to be two-years. (m) Life expectancy of benign group was assumed to remain unchanged in the model. (n) Twenty percent of HCC patients were assumed to be deceased at the end of two-years. (o) Metastasis, cholangiocarcinoma and other malignant groups were assumed to survive for twelve months. (p) Screening for liver transplantation was included in the analysis. Two-year time horizon did not capture patients undergoing liver transplantation. (r) Costs and probabilities for treatment, follow-up and no follow-up phases were assumed based on the reference standard.

*IV. Uncertainty Assessment*

The uncertainty and robustness of the model were evaluated by univariate sensitivity analysis. In addition, probabilistic sensitivity analysis was performed using Monte Carlo Simulation (30). In this method, the chosen parameter estimates in the model were randomly drawn from probability distributions based on many simulations. Triangular distributions for costs, beta distributions for diagnostic accuracy inputs and Dirichlet distributions for probabilities were applied. The results of these simulations were then used to generate probabilities. The cost-effectiveness plot indicates the confidence limits that can be placed around the base case.

## RESULTS

### Clinical Evaluation

*I. Baseline Patient Characteristics*

The study included 170 patients (19-86 yrs) with average age of 50.5 yrs (SD 15.8) and a male: female ratio of 66:104 (38.8%:61.2%). Average age for patients with benign lesions was 44.4 yrs (SD 13.3) and for malignant lesions 60.1 yrs (SD 14.6).

Mean lesion diameter was 54.3 mm (8-180 mm, SD 33.8, median 46.0 mm). Benign lesions were present in 104 (61.2%) and malignant in 65 (38.2%) patients. No tumor was finally detected in one patient (false positive findings). Liver cirrhosis was present in 41 patients (24.1%). In cirrhotic patients the diagnosis of lesion was predominantly malignant (35/41 cirrhotic subjects, 85.4%) whereas, in non-cirrhotic patients the diagnosis was mainly benign (98/129 non-cirrhotic subjects, 75.9%).

CEUS was performed in all patients (100%) in repeated 2 ml boluses. No adverse reactions were observed. At least one MRI examination was performed in 114 patients (67.1%), and CT examination in 111 patients (65.3%). In 55 patients both MRI and CT were performed. The total number of MRI and CT examinations performed

in all patients was 242 (mean: 1.42 exam/patient). In one subject, a $^{99m}$Tc scan was also performed.

*II. Diagnostic Performance*

CEUS was able to identify benign and malignant FLLs with a sensitivity of 96.9 % and specificity of 92.3%. The overall diagnostic accuracy was 94.1%. MRI/CT combined strategy was able to identify benign and malignant FLLs with a sensitivity of 95.4% and specificity of 90.4%. The overall diagnostic accuracy was 92.3%.

In the clinical analysis, focal lesions characterized as benign were further divided into four subgroups, which were defined as hemangioma, adenoma, focal nodular hyperplasia (FNH) and other. Similarly, FLLs characterized as malignant were further divided into four subgroups, which were defined as hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), metastasis and other.

For correct subgroup characterization, the results were somehow lower: the sensitivity, specificity and diagnostic accuracy of CEUS were 86.2%, 85.6% and 85.8%, respectively. MRI/CT combined strategy was able to characterize subgroups with the sensitivity, specificity and diagnostic accuracy of 86.2%, 86.6% and 86.4%, respectively. The results were similar when detailed subgroup characterization was performed.

Table II. shows incorrectly characterized focal lesions including subgroups by CEUS and MRI/CT strategies. Category I represents correctly identified lesions (majority) by both technologies. Category II indicates incorrectly characterized focal lesions by MRI/CT strategy only. (i.e. a patient with HCC was incorrectly characterized as having adenoma by MRI/CT). Patients in this category were correctly identified by CEUS according to the reference standard. Category III shows incorrectly characterized focal lesions by the CEUS strategy only. (i.e. a patient with HCC was incorrectly characterized as having CCA by CEUS). Patients in category III were correctly identified by MRI/CT strategy according to the reference standard. Category IV shows incorrectly characterized lesions by both CEUS and MRI/CT strategies (the overlap of mistakes resulted by both CEUS and MRI/CT). (i.e. a patient with FNH was characterized as having HCC by MRI/CT and characterized as having adenoma by CEUS.) Histology examinations (except for one benign case) and judgments of clinicians were referred to establish the reference standard.

## Economic Evaluation

*I. Base Case Results*

Base case results of the economic evaluation revealed that total discounted per patient costs associated with CEUS and MRI/CT strategies were estimated by the model to be €8,309 and €8,761, respectively. The costs of diagnosis and treatment

**Table II: Incorrectly characterized focal liver lesions by CEUS and MRI/CT.**

| | | **MRI/CT** | **MRI/CT** |
|---|---|---|---|
| | | Correctly Identified FLL | Incorrectly Identified FLL |
| **CEUS** | Correctly Identified FLL | Category I: AGREEMENT | Category II: Incorrect by MRI/CT |
| **CEUS** | Incorrectly Identified FLL | Category III: Incorrect by CEUS | Category IV: OVERLAP |

| **Category II** | **CEUS** | **MRI/CT** | **Gold Standard** | **Remarks** |
|---|---|---|---|---|
| 4 Patients (malignant) | HCC | Adenoma | HCC | Surgery |
| | CCA | Metastasis | CCA | Biopsy |
| | Metastasis | Other Benign | Metastasis | Clinical Judgement |
| | Metastasis | Other Benign | Metastasis | Biopsy |
| 6 Patients (benign) | Hemangioma | Other Benign | Hemangioma | Clinical Judgement |
| | Hemangioma | CCA | Hemangioma | Surgery |
| | Adenoma | Other Malignant | Adenoma | Clinical Judgement |
| | Other Benign | HCC | Other Benign | Clinical Judgement |
| | Other Benign | Metastasis | Other Benign | Clinical Judgement |
| | Other Benign | FNH | Other Benign | Clinical Judgement |

| **Category III** | **CEUS** | **MRI/CT** | **Gold Standard** | **Remarks** |
|---|---|---|---|---|
| 4 Patients (malignant) | CCA | HCC | HCC | Clinical Judgement |
| | Other Malignant | CCA | CCA | Biopsy |
| | Other Benign | Metastasis | Metastasis | Clinical Judgement |
| | Other Benign | Metastasis | Metastasis | Clinical Judgement |
| 7 patients (benign) | Other Malignant | Hemangioma | Hemangioma | Clinical Judgement |
| | Other Malignant | Adenoma | Adenoma | Clinical Judgement |
| | Adenoma | FNH | FNH | Clinical Judgement |
| | Adenoma | FNH | FNH | Clinical Judgement |
| | Adenoma | FNH | FNH | Clinical Judgement |
| | HCC | Other Benign | Other Benign | Clinical Judgement |
| | No tumor found | Other Benign | Other Benign | Clinical Judgement |

| **Category IV** | **CEUS** | **MRI/CT** | **Gold Standard** | **Remarks** |
|---|---|---|---|---|
| 5 Patients (malignant) | Meta/HCC | HCC/Meta | HCC/CCA | Biopsy |
| | Other Malignant | Other Benign | Metastasis | Biopsy |
| | Other Malignant | CCA | Other Malignant | Biopsy |
| | CCA | CCA | Other Malignant | Surgery |
| | Other Malignant | HCC | Other Malignant | Biopsy |
| 6 Patients (benign) | Other Malignant | Other Malignant | Hemangioma | Biopsy |
| | Other Malignant | CCA | Hemangioma | Surgery |
| | Adenoma | HCC | FNH | Biopsy |
| | Other Benign | CCA | Other Benign | Clinical Judgement |
| | Metastasis | Metastasis | Other Benign | Biopsy |
| | Other Malignant | Nonspecific Tumor | Other Benign | Biopsy |

Table shows incorrectly characterized lesion in subgroups. Category I represents correctly identified lesions (majority) by both imaging modalities and is not show in the table. Category II indicates incorrectly characterized FLL's by MRI/CT strategy only. Patients in this category were correctly by CEUS. Category III shows incorrectly identified lesions by CEUS strategy only and these patients were correctly diagnosed by MRI/CT strategy. Category IV shows incorrectly characterized by both imaging methods. Histology examinations (except for one benign case) were used as reference golden standard.

per branch were estimated by multiplying the resource use of each patient with the estimated average unit prices of diagnostic tests and therapeutic interventions. The incremental cost advantage of -€452 per patient was predicted for CEUS strategy. It was further estimated that -€160 was a cost advantage for diagnostic phase and -€292 was a cost advantage for treatment phase.

Life expectancy in the form of years saved or gained was the effectiveness endpoint of the study. Total discounted per patient life years (LYs) were 1.538 for CEUS

**Table III: Parameters and distributions used for the sensitivity analysis:**

| | Model Input | Lower Limit -30% | Upper Limit 30% | Distribution |
|---|---|---|---|---|
| **Cost of Diagnsotic imaging** | | | | |
| CEUS | € 295 | € 207 | € 384 | Triangular |
| MRI/CT combined | € 455 | € 319 | € 592 | Triangular |

| | Model Input | Lower Limit -30% | Upper Limit 30% | Distribution |
|---|---|---|---|---|
| **Assumption Costs Per Subgroup** | | | | |
| HCC | € 10,377 | € 7,264 | € 13,490 | Triangular |
| CCA | € 5,611 | € 3,928 | € 7,294 | Triangular |
| Metastasis | € 2,735 | € 1,915 | € 3,556 | Triangular |
| Other Malignant | € 6,236 | € 4,365 | € 8,107 | Triangular |
| Hemangioma | € 679 | € 475 | € 883 | Triangular |
| Adenoma | € 889 | € 622 | € 1,156 | Triangular |
| FNH | € 789 | € 552 | € 1,026 | Triangular |
| Other Benign | € 837 | € 586 | € 1,088 | Triangular |
| Costs of Palliative Care | € 12,000 | € 8,400 | € 15,600 | Triangular |

| | Model Input | Lower Limit -30% | Upper Limit 30% | Distribution |
|---|---|---|---|---|
| **Treatment Costs Per Subgroup** | | | | |
| HCC Treatment | € 11,673 | € 8,171 | € 15,175 | Triangular |
| CCA treatment | € 12,423 | € 8,696 | € 16,150 | Triangular |
| Metastasis Treatment | € 5,562 | € 3,893 | € 7,231 | Triangular |
| Other Malignant Treatment | € 11,483 | € 8,038 | € 14,928 | Triangular |

| | Model Input | Lower Limit -30% | Upper Limit 30% | Distribution |
|---|---|---|---|---|
| **Follow Up Costs Per Subgroup** | | | | |
| Hemangioma | € 3,900 | € 2,730 | € 5,070 | Triangular |
| Adenoma | € 2,269 | € 1,588 | € 2,950 | Triangular |
| FNH | € 305 | € 214 | € 397 | Triangular |
| Other Benign | € 270 | € 189 | € 351 | Triangular |

| | Model Input | Lower Limit of 95% CI | Upper Limit of 95% CI | Distribution |
|---|---|---|---|---|
| **Diagnostic Performance** | | | | |
| Sen CEUS | 0.862 | 0.757 | 0.925 | Beta |
| Spec CEUS | 0.856 | 0.776 | 0.911 | Beta |
| Sen MRI/CT | 0.862 | 0.757 | 0.925 | Beta |
| Spec MRI/CT | 0.865 | 0.787 | 0.918 | Beta |

| | Model Input | Lower Limit of 95% CI | Upper Limit of 95% CI | Distribution |
|---|---|---|---|---|
| **Probabilities** | | | | |
| pHCC | 0.68 | 0.556 | 0.778 | Drichlet |
| pCCA | 0.09 | 0.043 | 0.187 | Drichlet |
| pMetastasis | 0.17 | 0.097 | 0.278 | Drichlet |
| pOther Malignant | 0.06 | 0.024 | 0.148 | Drichlet |
| pHemangioma | 0.17 | 0.112 | 0.257 | Drichlet |
| pAdenoma | 0.36 | 0.27 | 0.451 | Drichlet |
| pFNH | 0.28 | 0.202 | 0.371 | Drichlet |
| pOther Benign | 0.19 | 0.213 | 0.279 | Drichlet |

Table shows input parameters for deterministic sensitivity analyses with lower and upper limits In order to identify model drivers and examine key areas of uncertainty, one-way deterministic sensitivity analyses were performed. For the efficacy parameters, 95% confidence intervals were used. Resource use and unit costs data were tested by varying the costs by +30% and -30% from the mean.

and 1.536 for MRI/CT, representing similar effectiveness results (incremental effects of 0.002 LYs) for both strategies. The incremental cost of -€452, for an incremental advantage of 0.002 LYs provided a favorable cost-effectiveness ratio (ICER) for CEUS, showing that CEUS strategy achieved slightly higher LYs for lower total per patient costs.

*II. Univariate Sensitivity Analysis*

In order to identify model drivers and examine key areas of uncertainty, univariate sensitivity analyses were performed. Ranges for effectiveness inputs and probabilities were based on 95% confidence intervals. Costs were varied between plus and minus thirty percent. Table III. shows input parameters for univariate sensitivity analyses with lower and upper limits.

The results of the sensitivity analyses indicated that the primary drivers of variation were the sensitivity and diagnostic cost of CEUS, specificity of MRI/CT and CEUS, treatment costs of HCC, diagnostic cost of MRI/CT and treatment costs of CCA (Figure II.). The most influential variable was the sensitivity of CEUS.

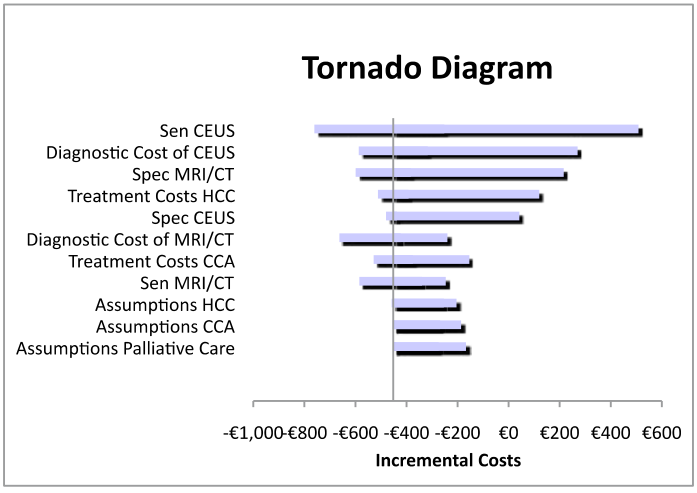


**Figure 2: Tornado Diagram showing the primary drivers of variation.** Tornado diagram represents the incremental costs of one-way sensitivity analysis of CEUS versus MRI/CT testing strategies. The horizontal line indicates the incremental costs under base case conditions. The results of the deterministic sensitivity analyses indicated that the most influential variable was the sensitivity of CEUS.

*II. Probabilistic Sensitivity Analysis*

Probabilistic sensitivity analysis (PSA) was performed using Monte Carlo Simulation [21]. The input parameters and corresponding distributions are presented in Table III. PSA results showed that, in the majority of the scenarios (90% of simulations),

the CEUS strategy was below the €20,000 acceptability threshold. Incremental costs per LYs were grouped below the origin suggesting cost-savings for the CEUS strategy (89.99% of simulations). Given the relatively small differences in estimated incremental LYs and costs for two strategies, the observed level of uncertainty around the incremental cost-effectiveness ratio was expected. Figure III. depicts cost-effectiveness scatter plot based on 100,000 simulations.

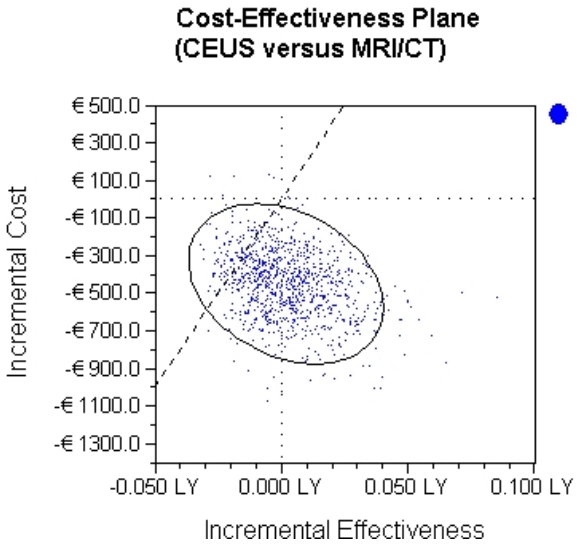


**Figure 3: Incremental cost-effectiveness scatter plot of CEUS versus MRI/CT testing strategies.** Probabilistic sensitivity analysis was performed by using Monte Carlo
Simulation and is based on 100,000 simulations. The incremental costs per LYs were grouped below the origin suggesting cost-savings for the CEUS strategy. Given the relatively small differences in estimated incremental LYs and costs for two strategies, the observed level of uncertainty around the incremental cost-effectiveness ratio was expected.

## DISCUSSION

Base case results for CEUS and MRI/CT diagnostic strategies showed that CEUS was a valuable diagnostic tool in the management of focal liver lesions (FLLs) and it was cost-saving alternative compared to the current front-line diagnostic imaging work-up in the Netherlands. The cost-savings for diagnostic phase were comparable to other already published studies [22-28]. In one study, CEUS determined a change in the diagnostic workup [29]. But the main advantage of our study consists of adding a treatment phase. CEUS economic impact of diagnostic and treatment phase combined was to be found much higher and reached 452 €.

The proportion of correctly diagnosed benign or malignant lesion and characterization of different diagnostic subgroups was accurate and were similar to MRI/CT results.

It is believed that replacing MRI or CT for preoperative assessment of patients with liver tumors is unlikely. MRI and CT offer a more comprehensive assessment

of the liver parenchyma and the abdomen, which is mandatory to properly plan and stage any kind of surgical or interventional procedure. Furthermore, the panoramic pictures obtained by CT or MRI are considered necessary for correct staging and detection of lesions at sites other than liver. This CEUS drawback can be reduced by up-to-date abdominal ultrasound technologies, better operator training and by improvement in accompanying CEUS software and protocols.

In this study, one may argue that a single diagnostic imaging method should have been performed after baseline US. However, it would not be ethical to do a fully randomized study in which a treatment choice is based solely on one of the diagnostic methods to which patients are randomly allocated [30]. Instead, patients should be diagnosed with all necessary methods for correct tumor characterization. For each diagnostic method, the results will then be allocated anonymously to external experts for clinical evaluation [31]. We also used Sonovue as a contrast agent, instead Sonazoid could be another option [32].

In the clinical design of this study, the actual treatment of choice was based on all necessary methods; namely the standard reference (gold standard) results. In the economic evaluation, a treatment decision was based on the characterization of lesions according to each method. Thus, in the decision analytic model a patient was considered for a follow-up according to CEUS, who had in reality received surgical treatment according to the reference standard. The penalty of incorrect characterization of lesions was calculated based on reference standard results.

Characterization and treatment of malignant liver lesions in the economic evaluation model were based only on the primary liver site. Costs and effectiveness calculations did not capture secondary metastatic sites. Different patient characteristics with regard to other metastatic sites (lung, colorectal, brain and others) will likely yield more uncertainty in the outcomes.

Liver transplantation as a first-line treatment in eligible patients is shown to improve survival and is potentially cost-effective in selected groups when compared to other therapies [33-35]. In practice, some of medically eligible patients (with early stage small HCCs) never receive a transplant because the number of potential recipients continues to outnumber the number of donor organs or patients will continue to another treatment option [36]. In this study, a two-year time horizon is not long enough to capture the implications of the liver transplantation.

Guidelines for economic evaluations recommend use of a time horizon that allows inclusion of all relevant costs and effects [102]. In this study, we restricted the time horizon to two years, mainly because of the uncertainty in determining the long-term costs and life expectancy of cancer patients whose primary tumor sites were not liver. On the other hand, inclusion of a longer time horizon would not affect the overall conclusions presented in this study. The main objective of the performed

economic evaluation was to assess the incremental differences between different diagnostic imaging strategies. Hence, marginal differences in costs and effects based on correct diagnosis are more important than the absolute values in each strategy.

Last but not least, one may argue that there was a selection bias in this study. The presence of an FLL detected by US examination was one of the inclusion criteria. Therefore, our study may exclude some patients whose lesions were missed by baseline US. Nevertheless, this bias does not affect the conclusions of the present study but reflects the limitations of unenhanced US in general.

## CONCLUSIONS

CEUS is a highly accurate and cost-saving alternative compared to the traditional diagnostic procedures and should be considered as one of the first line options in the characterization of FLLs. Further research should explore diagnostic performance and cost consequences that would result with the application of CEUS in other clinical settings.

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