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Original Article

# Cost-effectiveness analysis of multiple imaging modalities in diagnosis and follow-up of intermediate complex cystic renal lesions

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## Objectives

To compare health-economic aspects of multiple imaging modalities used to monitor renal cysts, the present study evaluates costs and outcomes of patients with Bosniak IIF and III renal cysts detected and followed-up by either contrast-enhanced computed tomography (ceCT), contrast-enhanced magnetic resonance imaging (ceMRI), or contrast-enhanced ultrasonography (CEUS).

## Patients and Methods

A simulation using Markov models was implemented and performed with 10 cycles of 1 year each. Proportionate cohorts were allocated to Markov models by a decision tree processing specific incidences of malignancy and levels of diagnostic performance. Costs of imaging and surgical treatment were investigated using internal data of a European university hospital. Multivariate probabilistic sensitivity analysis was performed to confirm results considering input value uncertainties. Patient outcomes were measured in quality-adjusted life years (QALY), and costs as averages per patient including costs of imaging and surgical treatment.

## Results

Compared to the 'gold standard' of ceCT, ceMRI was more effective but also more expensive, with a resulting incremental cost-effectiveness ratio (ICER) >€70 000 (Euro) per QALY gained. CEUS was dominant compared to ceCT in both Bosniak IIF and III renal cysts in terms of QALYs and costs. Probabilistic sensitivity analysis confirmed these results in the majority of iterations.

## Conclusion

Both ceMRI and CEUS can be used as alternatives to ceCT in the diagnosis and follow-up of intermediately complex cystic renal lesions without compromising effectiveness, while CEUS is clearly cost-effective. The economic results apply to a large university hospital and must be adapted for smaller hospitals.

## Keywords

computed tomography, contrast-enhanced ultrasonography, cost-effectiveness analysis, cystic renal lesion, magnetic resonance imaging, #kcsm, #KidneyCancer, #uroonc

## Introduction

In 1986, M.A. Bosniak [1] presented a classification system of renal cysts based on their appearance in contrast-enhanced CT (ceCT). Evidence that has accumulated over the years indicates that the risk of malignancy of renal cysts increases with the Bosniak category [1,2]. Silverman *et al.* [3] recently proposed an updated classification system criticising overdiagnosis of malignancy with the original Bosniak system, potentially driven by its high inter-reader variability. Based on the updated system, follow-up for at least 5 years instead of surgery is recommended for renal cysts of Bosniak class IIF [3]. For both Bosniak IIF and III lesions, active surveillance has been shown to be more cost-effective than nephron-sparing surgery (NSS) [4].

Over the last decade, contrast-enhanced MRI (ceMRI) and contrast-enhanced ultrasonography (CEUS) have emerged as

the primary modalities for the further evaluation of cystic renal lesions incidentally detected by US. While avoiding the radiation exposure of ceCT, ceMRI has shown similar diagnostic performance in several studies [5,6]. A study of focal liver lesions reports the same cost-effectiveness for CEUS and ceMRI [7]. A recent study of cystic renal lesions based on United States healthcare data indicates that CEUS is comparable to MRI in economic terms [8]. Among these three modalities, ceCT remains the most widely available imaging test, and the American College of Radiology, in a recent review, concludes ceCT to be equivalent to ceMRI and CEUS in the imaging of indeterminate renal masses [9]. Therefore, the present study uses real-world economic data of a European university hospital for analysis and includes both ceCT and Bosniak IIF cysts; hence, giving additional insights compared to Gassert *et al.* [8].

As renal cysts are a very common incidental finding and, depending on age, can be encountered in up to 40% of individuals, effectiveness of imaging follow-up has important implications for society [10,11]. For a comprehensive evaluation of the three imaging modalities used in the diagnostic evaluation of incidental cystic renal lesions, we conducted a study to model economic aspects of follow-up with ceCT, ceMRI, and CEUS using as input the real-world costs of a European university hospital.

## Patients and Methods

This study was approved by the local institutional ethics committee.

### Markov Model and Cost-effectiveness Analysis

Markov models with a time horizon of 10 years and a cycle length of 1 year were implemented, starting at an age of 60 years. A time horizon of 10 years was chosen because the German S3 guideline for RCC requires imaging follow-up for a total of 108 months after surgical resection, and this follow-up period was chosen for malignant renal cysts within this simulation [12]. A start age of 60 years was chosen to ensure comparability with other cost-effectiveness studies [4,8]. Microsoft Excel® software (Microsoft, Redmond, WA, USA) was used for Markov modelling. Age-adjusted death rates were taken from the European Union (EU) Life Table 2018 (Eurostat [13]) and filtered to the entire German population regardless of sex.

The underlying model starts with a decision tree (Fig. 1a) [8,12] depicting the possible imaging findings in each modality depending on frequency of malignancy of Bosniak IIF and III cysts, as well as the diagnostic performance of the respective imaging modality (Table 1) [2,5,6,13,14,19–24]. This decision tree can simulate the proportions of the four possible resulting clinical situations (true negative, false positive, true positive, false negative) of a cohort, for example a population of 1000 patients. The subcohorts then pass through different Markov models, explained in Fig. 1b for benign cysts and in Fig. 1c for malignant cysts.

The following input data were used: cost per imaging modality including contrast agent (Table 2) [32,33], cost of surgical treatment per patient (Table S1), transition probabilities, and quality of life (QoL) in the appropriate states (Table 1). Costs and benefits beyond year 1 were discounted using a 3% discount rate [14].

Thereby, the meta-analysis by Sevcenco *et al.* [2]was used for investigation of the rates of malignancy, instead of other meta-analyses [2,4,8,15] like that of Schoots *et al.* [15], as its results were used in further cost-effectiveness analyses and comparable results were desired.

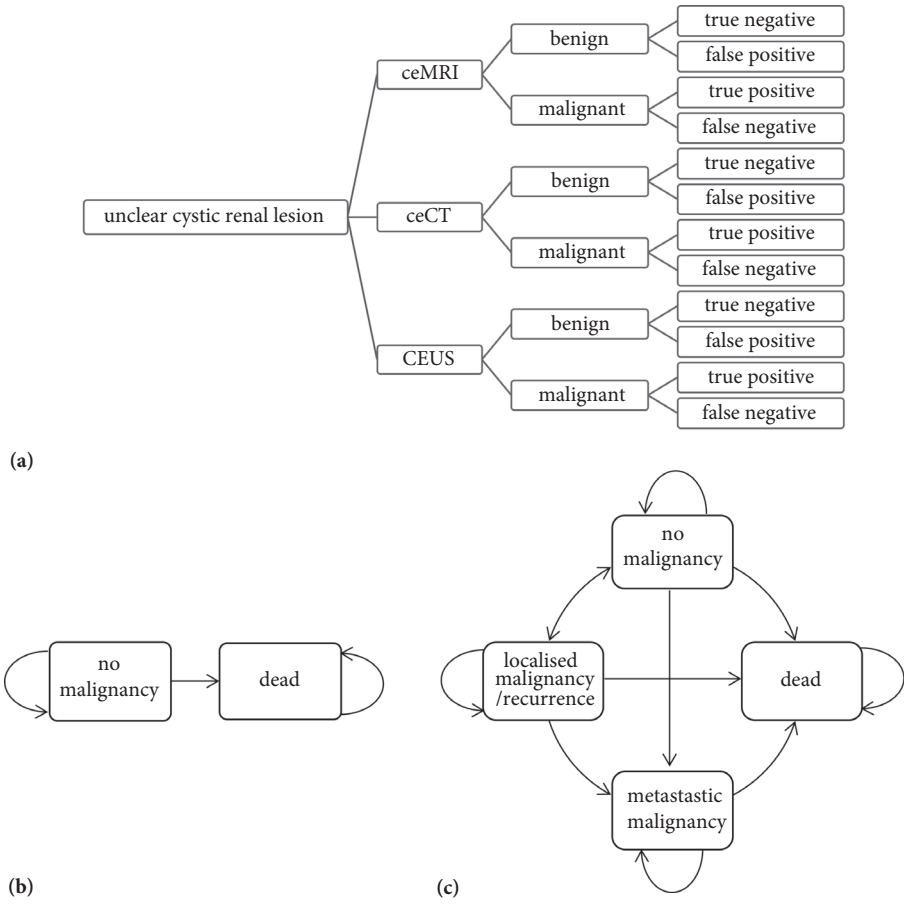
### Imaging Follow-up

As shown in Table 3 imaging follow-up takes place annually after initial imaging until year 5 in the true-negative cohort. The false-positive cohort undergoes surgery after initial imaging and, because of a benign histology result, requires no further imaging follow-up thereafter. In patients with malignant lesions, postoperative imaging follow-up, which may lead to an indication for repeat surgery, is performed at intervals of 1, 3, 5, 7 and 9 years, as recommended by the German S3 guideline for RCC [12] after surgery. Surgery is performed as first-line management in the true-positive cohort, while it is delayed by 1 year in the false-negative cohort, due to initially missed malignancy.

### Cost Breakdown

For cost comparison of different strategies in the management of cystic renal lesions, we used internal data from our hospital's finance department, which reflect the hospital's cost perspective. Therefore, monetary conversion factors of 2018 per cost centre and per cost element group, representing different functional units of service provision, were used. In case of CEUS, the point values of ceCT were used as they realistically map those of CEUS, for which specific point values do not exist. These point values were multiplied with the number of points reflecting the cost of one examination with each modality. This point system ensures that even initially less obvious ancillary costs such as hospital administration or other overheads (staff, electricity, cleaning, and room costs) are included and results in a weighted calculation. The examination

**Fig. 1** Model structure of Markov analysis modified from Gassert *et al.* [8] (**a**) Diagram of the decision tree used in our analysis. Each Bosniak class is associated with a specific incidence of malignancy. Diagnostic performance (sensitivity and specificity) of the respective modality generates a specific proportion of true and false negative, as well as true- and false-positive findings. Depending on the findings in Fig. 1a the cohorts start in their specific proportion in the Markov model. (**b**) Markov model for patients with a benign renal cyst (true-negative and false-positive cohorts) corresponding to freedom from malignancy. The only possible transition, next to continuation in the state 'no malignancy', is age-adjusted death (Table 1). Total costs in true-negative patients include an initial imaging study and one follow-up examination within the first 5 years after initial examination, considering only patients alive. In the false-positive cohort, costs comprise the initial imaging study and surgery. This cohort does not get a follow-up examination due to benign histology findings. (**c**) Markov model for patients with a malignant renal cyst (true-positive and false-negative cohorts): within this Markov model, a fictive cohort walks through different states. The arrows symbolise the possibility of transition between states. The probabilities of transition between these states are provided in Table 1. The model includes the two states, 'no malignancy' and 'death', from the simplified model (Fig 1b) supplemented by two additional states, 'localised malignancy/recurrence' and 'metastatic malignancy'. The state 'localised malignancy/recurrence' includes all patients with recurrence in case of true-positive findings, all patients starting with undetected malignancy in the false-negative cohort and patients with possible recurrence after successful surgery or non-R0-resection. These two cohorts take part in a follow-up programme including imaging 1, 3, 5, 7, and 9 years after surgery [12]. Therefore, the proportional finding of a recurrence at each of these time points is simulated as well. Patients in the state of 'localised malignancy/recurrence' can change to the state of 'no malignancy' with a probability calculated with possibilities of a true malignant finding (depending on the sensitivity of the imaging modality), metastatic spread (these patients switch to the state of 'metastasised malignancy'), the age-adjusted death rate (then these patients go to the state 'death'), and the possibility of a non-R0-resection (persistence in the state of 'localised malignancy/recurrence'). A characteristic event in the first year after initial surgery is the risk of metastatic spread from 'localised malignancy/recurrence' since to that time, it is not a metastatic spread after recurrence, but like during active surveillance, since the transition applies directly after surgery (Table 1).




constellations used in our cost analysis are presented in Table 2.

As general purchase costs for the imaging devices (MRI and CT scanners, and US devices) are difficult to estimate, we only included running costs in our analysis.

## Cost of Contrast Agents

For cost calculation, we considered purchase prices of all commonly used contrast agents in terms of cost per mg of iodine-based agent for CT and cost per mmol of gadolinium-based agent for MRI. For each contrast agent,

**Table 1** Base case estimates for Markov analysis and associated ranges for sensitivity analyses.

| Variable | Value | Range for sensitivity analyses, % | Source |
|---|---|---|---|
| Incidence of malignancy | | | |
| Pre-test probability of malignancy in Bosniak IIF cyst | 6.7% | 5.0–8.4 (95% CI) | Sevcenco *et al.* 2017 [2] |
| Pre-test probability of malignancy in Bosniak III cyst | 55.1% | 45.7–64.5 (95% CI) | Sevcenco *et al.* 2017 [2] |
| Diagnostic performance | | | |
| ceMRI sensitivity | 92% | 88–95 (95% CI) | Zhou *et al.* 2018 [5] |
| ceMRI specificity | 91% | 87–93 (95% CI) | Zhou *et al.* 2018 [5] |
| CEUS sensitivity | 95% | 92–97 (95% CI) | Zhou *et al.* 2018 [5] |
| CEUS specificity | 84% | 79–88 (95% CI) | Zhou *et al.* 2018 [5] |
| ceCT sensitivity | 90% | 85–93 (95% CI) | Lan *et al.* 2016 [6] |
| ceCT specificity | 85% | 80–88 (95% CI) | Lan *et al.* 2016 [6] |
| QoL | | | |
| QoL of patients without tumour | 1 | | |
| QoL of patients with metastatic tumour* | EQ-5D 0.66 | 0.547–0.773 (95% CI) | de Groot *et al.* 2018 [24] |
| QoL of patients with localised tumour* | EQ-5D 0.75 | 0.709–0.791 (95% CI) | de Groot *et al.* 2018 [24] |
| Death | 0 | | |
| Transition probabilities | | | |
| Annual risk of death without malignancy | age-adjusted | – | EU Life Tables 2018 [13] |
| Annual risk of death with localised malignancy | age-adjusted | – | EU Life Tables 2018 [13] |
| Probability of initial non-R0-resection | 5.73% | 2.87–8.60 | Orosco *et al.* 2018 [23] |
| Yearly risk of metastatic spread during active surveillance | 0.62% | 0.31–0.93 | Rosales *et al.* 2010 [19] |
| Yearly probability of recurrence after NSS† | 0.37% | 0.19–0.56 | Manikandan *et al.* 2004 [20] |
| Yearly probability of metastasis after NSS† | 0.18% | 0.09–0.26 | Manikandan *et al.* 2004 [20] |
| Yearly probability of metastasis after local recurrence‡ | 26.22% | 13.11–39.32 | Itano *et al.* 2000 [21] |
| Yearly risk of death in distant metastatic RCC§ | 33.51% | 16.76–50.27 | Howlader *et al.* 2020 [22] |
| Discount rate | | | |
| Discount rate beyond year 1 | 3% | 0–6 | Attema *et al.* 2018 [14] |

*BCE, base case estimation; EQ-5D, EuroQol-five Dimension. *Data refer to patients with RCC with and without metastasis. †Data refer to renal tumours ≤4 cm treated by NSS. ‡Data refer to local recurrence of RCC in the renal fossa after nephrectomy. §Data refer to 5-year relative survival of patients with kidney and renal pelvis cancer and distant metastasis.*

**Table 2** Calculation of absolute costs per examination for each of the three imaging modalities, figures in Euro (€).

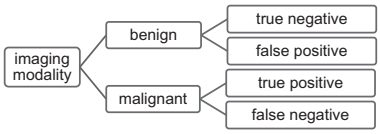
| | ceCT* | ceMRI† | | CEUS‡ |
|---|---|---|---|---|
| Consultation | 2.55 | 4.14 | Consultation | 2.55 |
| First series | 82.85 | 227.73 | US examination of one organ | 6.37 |
| Contrast agent | 88.44 | 98.57 | Extra charge for Doppler examination | 7.97 |
| Automatic injection of contrast agent | 9.56 | 15.53 | Contrast agent | 87.68 |
| Additional phase | 15.93 | 51.76 | Manual injection of contrast agent | 4.14 |
| Computer-aided image processing | – | 41.41 | Extra charge for contrast-enhanced examination | 12.75 |
| Detailed findings report | 4.14 | 6.73 | Detailed findings report | 4.14 |
| Total | 203.47 | 445.86 | | 125.60 |

*An examination with any of the three modalities comprises a consultation and information on the use of contrast agent as well as a written detailed findings report. Different costs can result for the modalities due to different point values resulting from different proportional personnel costs as well as ancillary costs per examination. Additionally, costs of individual subcomponents of each modality have been added. *CT examinations are performed with a biphasic protocol (e.g. unenhanced/nephrographic or arterial/nephrographic phase) [32,33]. The contrast agent is bolus injected into an antecubital vein using a dual-head power injector. The amount is adapted to the patient's body weight (60–80 kg: 80 mL, 80–100 kg: 100 mL, for example Ultravist 370 [Bayer Healthcare, Berlin, Germany], or dose equivalent), followed by a 50 mL saline flush. †MRI is routinely performed at 1.5 T or 3.0 T using phased-array body coils. Imaging is performed with a triphasic protocol [33,34] The amount of contrast agent is adapted to the patient's body weight (1.0 mmol gadolinium/10 kg body weight) and is administered by automatic injection followed by a 40 mL saline flush. Computer-aided image processing is performed for abdominal protocol-specific parameters and image preparation like kinetics of contrast agent, quantification of contrast enhancement, volumetric measurements, subtraction of enhanced and non-enhanced series or comparison with previous imaging series. ‡CEUS examinations are performed using high-end US systems with up-to-date CEUS-specific protocols including B-mode and Doppler US. A bolus of 1.2–1.6 mL of US contrast agent (SonoVue®, Bracco Imaging, Milan, Italy) is used. Nevertheless, a full package size is considered.*

we used the pack size with the largest volume discount. Using this approach, we calculated the lowest price per dose for a model patient (see below) for the different contrast agent compounds. Furthermore, we used general market prices for the least expensive contrast agents for ceCT and ceMRI in terms of dose equivalent. Note though that price differences among contrast agents are negligible.

For CEUS, the cost of contrast agent we used as input was the price of one package containing a 5-mL vial (SonoVue®, Bracco Imaging, Milan, Italy). This was done because the

**Table 3** Calculation of total costs in the Markov simulation.




| Initial imaging | Initial surgery | Imaging follow-up | Surgery for malignant finding during follow-up |
|---|---|---|---|
| X | | X* | |
| X | X | | |
| X | X | X† | X§ |
| X | | X‡ | X§ |

*Overview of total costs per imaging modality. The final costs per modality are the sum of all partial costs. An 'X' symbolises a settlement. False-positive patients do not get an imaging follow-up examination due to a benign histology finding. *In the years 1–5, applies to all patients alive. †In the years 1, 3, 5, 7, 9 as the true-positive cohort is treated without delay starting follow-up directly after surgery; applies to all patients alive. ‡In the years 1 (with initially assumed benign lesion), 2, 4, 6, 8, 10 as this cohort is treated predominantly after the second imaging examination; the beginning of the follow-up process is assumed to start for all patients in this cohort after the first year, as all compared imaging modalities provide a sensitivity of ≥90%; applies to all patients alive. §Only possible in years with follow-up as a result of a possible malignant finding; adjusted to diagnostic performance of the imaging modality; applies only to patients alive in the state of 'localised malignancy/recurrence'.*

vials are for single use even though a smaller dose of 1.0–1.6 mL injected as a single bolus is typically used in a routine clinical CEUS examination [16].

As the contrast agent dose is adapted to the patient's body weight in ceCT and ceMRI, we calculated contrast agent costs for a model patient (180 cm, 80 kg). For this model patient, we estimated an average dose of contrast agent including 37 g iodine for ceCT and 8 mmol gadolinium-based contrast agent for ceMRI.

## Cost of Surgical Treatment

The costs of surgical treatment and inpatient care were determined by our hospital's financial department separately for tumour enucleation and for partial kidney resection/NSS in two representative patients. As the actual surgical technique depends on tumour size and the patient's general condition and comorbidities, we used average costs for these two surgical options for analysis of true-positive, false-negative, and false-positive cases (Table 3) [17]. We used these costs minus the shares for additional imaging examinations, which we estimated as outlined above in order to generate standardised conditions for both surgical techniques (Table 2).

## Transition Probabilities

While robust data from several studies are available for the frequency of malignancy in cystic renal lesions of the different Bosniak classes (Table 1), there is a lack of studies evaluating the risk of metastatic spread in the different classes. We therefore used an alternative approach to ensure consistency:

The decision tree (Fig. 1a) allows a dependable and evidence-based division into benign and malignant lesions. Due to a lack of reliable data for cysts of the different Bosniak classes, we used transition probabilities of small renal neoplasms for malignant cysts. A comparable approach was already used by Smith *et al.* [4] in investigating the cost-effectiveness of active surveillance vs NSS. In this way, it is possible to fill the gap by using as input sufficient data that are available for a similar entity.

As we needed 1-year transition probabilities for our analysis, published probabilities were converted using the following formula established by Briggs *et al.* [18]:

$$\text{yearly transition probability} = 1 - e^{\frac{\ln(1-\text{reported frequency})}{\text{reported mean time horizon[years]}}}$$

A complete overview of data on annual transition rates can be found in Table 1.

## Quality of Life

In patients with no malignancy, values for QoL were set to 1 (100%), disregarding comorbidities and focussing on renal neoplasm alone. For deceased patients, QoL was set to zero. Values for the states of 'localised malignancy/recurrence' and 'metastatic malignancy' were taken from the literature on patients with RCC (Table 1) [24].

## Incremental Cost-effectiveness Ratio

It was planned to compare the cost-effectiveness of ceMRI and CEUS if either of the two turned out to be more effective, but also more expensive compared the 'gold standard' of ceCT. This was done using the incremental cost-effectiveness ratio (ICER) [25] with mean values per patient for cost and quality-adjusted life years (QALY). ICERs are calculated as follows and allow quantification of differences in cost effectiveness:

$$\text{ICER} = \frac{(\text{costs of ceMRI or CEUS} - \text{costs of ceCT})}{(\text{QALY of ceMRI or CEUS} - \text{QALY of ceCT})}$$

The resulting ICER reflects the additional costs per QALY gained.

### Sensitivity Analyses

For sensitivity analyses, the range of input values was assumed to be ±50% of the base case value. For diagnostic accuracy, incidence of malignancy and QoL, the range limits were defined by 95% CIs reported in the pertinent literature, and for imaging and treatment costs, an uncertainty range of ±25% of the base case was assumed, reflecting the relatively precise determination of these input values (Table 1). The discount rate was variated between 0% and 6%. Conversely, no uncertainty was assumed for annual death rates, which we consider to precisely reflect the situation.

To evaluate how single parameters affect the result of the respective analysis, a deterministic sensitivity analysis was performed. Thereby, the single input parameters were varied and the lower and upper limits of their range as presented in Table 1 inserted. The result was given as difference of the ICER compared to ceCT.

A multivariate probabilistic sensitivity analysis was performed to examine the uncertainties related to the variables underlying the present simulation [26,27]. This analysis was performed using Microsoft Excel® software (Microsoft). To this end, random values within predefined limits were generated simultaneously for each model run. A normal distribution of values around the base case estimation was assumed for costs of imaging and surgery, as they can be considered as prices of standardised procedures. For the included probabilities and utilities, a beta-distribution was assumed. In this way, 1000 iterations of the Markov models were performed and the effects (QALY as measured) and costs of CEUS and ceMRI were compared to ceCT (as the 'gold standard') in every iteration.

## Results

### Cost Breakdown

The costs of ceCT, ceMRI, and CEUS including contrast agent are presented in Table 2. With the methods described, we estimated total costs of €203.47 (Euro), €445.86, and €125.60 for a routine clinical ceCT, ceMRI, and CEUS examination, respectively. These diagnostic imaging costs were used in calculating total treatment and imaging costs as presented in Table 3. Costs for surgical treatment and inpatient care were €6589 for tumour enucleation and €4849 for partial kidney resection/NSS (Table S1). Due to neutrality of this work between enucleation and NSS, the average cost of surgical treatment of €5719 including hospitalisation per patient was used in our cost-effectiveness analysis.

### Cost-effectiveness Analysis

The underlying Markov simulation was performed and both QALY and average costs per patient and per imaging modality were determined. In each case, the QALY of the Bosniak IIF cysts was higher than that of Bosniak III cysts due to the lower rate of malignancy (Table 4). However, even for Bosniak III cysts, Markov analysis yielded QALYs of >8.0 for patients with a start age of 60 years. For cysts of both Bosniak classes, CEUS was found to be the most effective modality compared to the two tomographic imaging modalities, and ceMRI showed slightly higher effectiveness than ceCT. In terms of overall costs, CEUS was least expensive per patient in a decennial process for both Bosniak IIF and III cystic renal lesions followed by ceCT and ceMRI. With respect to the relative contributions of imaging and surgery to total average costs per case, the costs for imaging were highest for ceMRI compared to the other two modalities for both Bosniak class IIF and III (Fig. 2).

The ICER combines effectiveness (i.e. QALY) and costs. As shown in Table 4, ceMRI was found to be more effective, but also more expensive compared to the 'gold standard' of ceCT with a resulting ICER of €71 650 for Bosniak class IIF and €186 305 for Bosniak class III. CEUS was dominant compared to the 'gold standard' of ceCT for both Bosniak classes in terms of total costs, as well as effectiveness.

### Sensitivity Analyses

The results of the deterministic sensitivity analysis are presented in Fig. 3. For every imaging modality and the two Bosniak classes considered, diagnostic accuracy and the costs for imaging and surgery were found to have the greatest single impact on the results of the analysis.

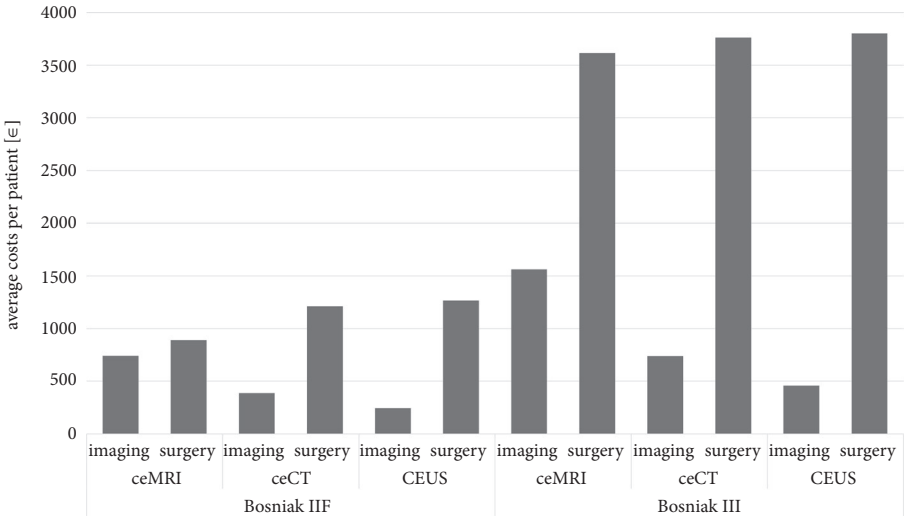
The results of our probabilistic sensitivity analysis are presented in Fig. 4. In this analysis, we compared ceMRI and CEUS with the 'gold standard' of ceCT. In patients with Bosniak IIF cysts, ceMRI was more expensive in 60.0% of cases and more effective in 84.0% of cases. Conversely, CEUS

**Table 4** Result of the cost-effectiveness analysis (comparator ceCT).

| Bosniak classification | Modality | QALY | Average costs per patient, € | ICER to ceCT, €/QALY |
|---|---|---|---|---|
| IIF | ceCT | 8.0868 | 1600 | – |
| | ceMRI | 8.0872 | 1632 | 71 649.72 |
| | CEUS | 8.0878 | 1511 | CEUS dominant |
| III | ceCT | 8.0245 | 4499 | – |
| | ceMRI | 8.0282 | 5174 | 186 304.65 |
| | CEUS | 8.0328 | 4256 | CEUS dominant |

*The table presents average outcome per patient in a decennial follow-up process broken down into efficiency (measured in QALY) and average costs per imaging method and per Bosniak class.*

**Fig. 2** Overview of the distribution of average costs per patient with Bosniak IIF and III cystic lesions with regard to imaging and surgery. Presented are the costs for imaging and surgery as shares of the total average costs per patient, e.g. in a cohort consisting of 1000 patients per modality. When the proportional costs of imaging and surgery are compared as average values per patient in a decennial process, Bosniak III cysts show higher costs for both imaging and surgery. This is an expected result attributable to the higher rate of malignancy in Bosniak III renal cysts. Furthermore, differences in diagnostic performance between the modalities also contribute to different total costs and a different distribution of costs. A higher specificity of ceMRI compared to ceCT and CEUS results in lower surgical costs due to a lower rate of false-positive findings.




was more expensive in only 23.4% of cases and simultaneously more effective in 99.9% of cases.

In Bosniak III cysts, the results were even clearer: ceMRI was more expensive in 99.9% of cases and more effective in 84.0% of cases. CEUS was more expensive in only 0.5% of cases and more effective in 99.9% of cases compared with ceCT. Overall, CEUS was clearly dominant in the probabilistic sensitivity analysis as well.

## Discussion

The main findings of our present analysis can be summarised as follows: (i) ceMRI is more effective in both the base case scenario and in the majority of iterations of the probabilistic sensitivity analysis, but more expensive than ceCT from a hospital's point of view, and (ii) CEUS is both more effective and less expensive in both the base case scenario and in the majority of iterations of the probabilistic sensitivity analysis and therefore dominant to ceCT, again from a hospital's point of view.

Regarding patient outcome measured in QALY, the higher mean QALY in patients with Bosniak IIF cyst compared to Bosniak III cysts can be explained by the lower malignancy of the former, which our model maps precisely. The high effectiveness of CEUS is attributable to its high sensitivity avoiding a number of false-negative cases [5]. Although CEUS has turned out to be the most cost-effective modality, it is limited by requiring an experienced examiner, which reduces its availability significantly and by patient factors such as obesity, atrophic kidney, or bowel gas. On the other hand, CEUS is a suitable alternative in patients who cannot undergo an MRI examination due to claustrophobia or other contraindications. Furthermore, CEUS avoids the radiation exposure of a biphasic ceCT required for kidney imaging [28,29], which is especially important in younger patients, and US contrast agents do not impair renal function, particularly relevant to patients with already impaired renal function. These factors play a role in implementing patient-tailored imaging approaches in addition to cost-effectiveness considerations. If CEUS is not available, our present results show ceMRI to be more effective than ceCT. In this scenario, the surcharge of ceMRI is lower for Bosniak IIF cysts than for Bosniak III cysts, while, for both cyst categories, ceMRI is clearly more effective and likely to result in better overall patient outcome. However, according to internationally accepted threshold values, ceMRI is not cost-effective compared with ceCT, given an ICER of €71 650/QALY and €186 305/QALY for Bosniak IIF and III cysts, respectively (Table 4) [30]. This is above the threshold of £20 000–£30 000 (British Pound) per QALY gained as proposed by the National Institute for Health and Care Excellence (NICE) to define cost-effectiveness in the UK [31]. Nevertheless, ceMRI should be considered as an alternative to ceCT not only if CEUS is not available, but also to avoid radiation exposure in younger patients or in patients with conditions such as hyperthyroidism or who do not tolerate iodinated contrast agents.

**Fig. 3** Results of the deterministic sensitivity analysis. Presented are the results of the deterministic sensitivity analysis in a tornado diagram, performed for ceMRI. (**a, b**) and CEUS (**c, d**), both in comparison to ceCT as 'gold standard'. Furthermore, the charts distinguish between analyses regarding Bosniak IIF (**a, c**) and Bosniak III (**b, d**) renal cysts. The light grey bars represent the results of the lower range values and the dark grey bars represent the results of the upper range values as shown in Table 1. As visible in **a** and **b**, the lower range of ceMRI sensitivity and the upper range of ceCT sensitivity invert the ICER and therefore, both bars are unidirectional.

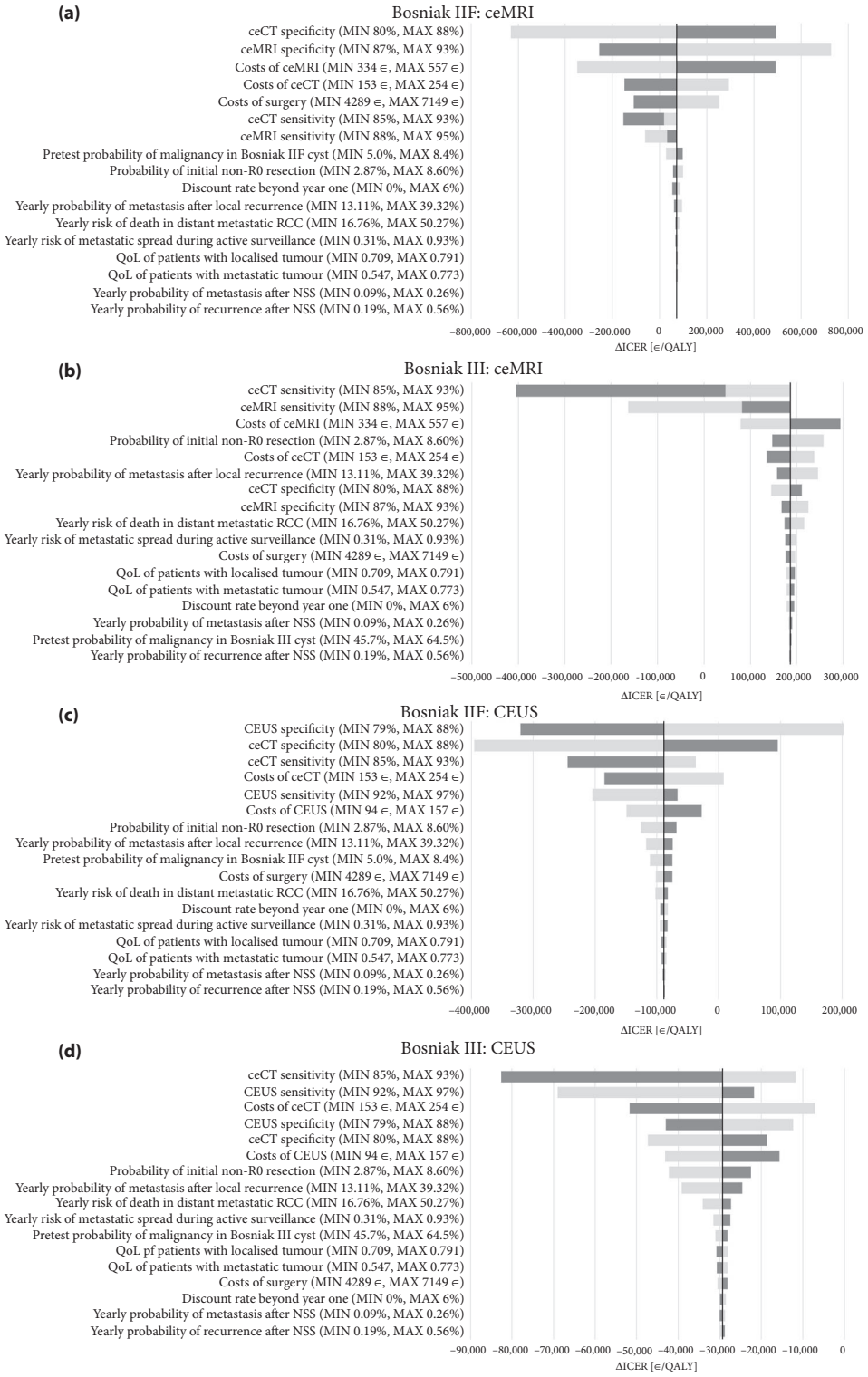
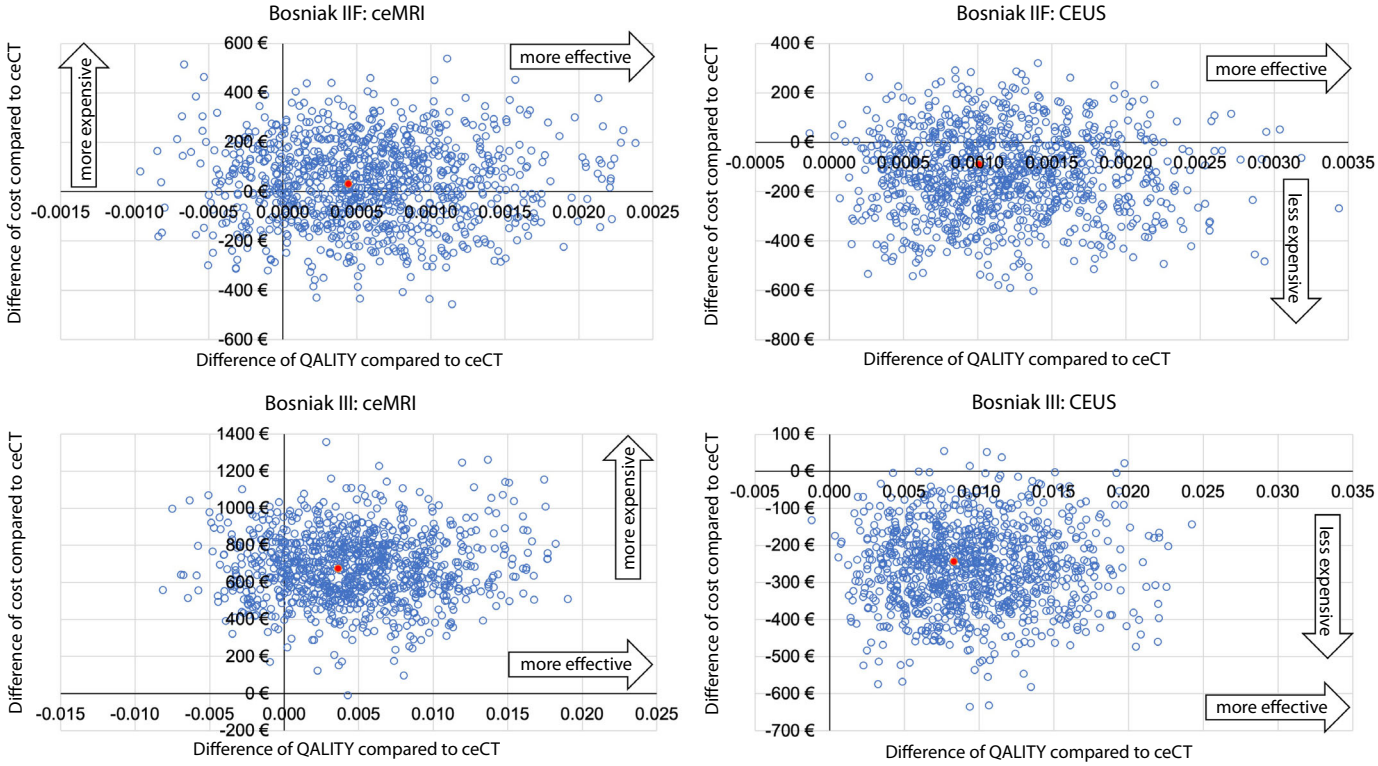


**Fig. 4** Results of the probabilistic sensitivity analysis with 1000 iterations. • base case results; ○ random sample results. The graphs visualise differences in outcome (measured in QALY) and costs of CEUS and ceMRI compared to the 'gold standard' of ceCT. The results of each iteration are represented by blue circles and the result of the base case estimation by a red dot. Overall, the probabilistic sensitivity analysis confirms the results of the base case estimation. The abscissa represents the difference in QALY compared to ceCT and therefore, positive values show an overall higher mean effectiveness of the compared modalities. The ordinate represents the difference in mean costs per patient compared to ceCT with positive values indicating higher costs per patient. (**a**) Probabilistic sensitivity analysis auf ceMRI in Bosniak class IIF cysts compared to ceCT. (**b**) Probabilistic sensitivity analysis auf CEUS in Bosniak class IIF cysts compared to ceCT. (**c**) Probabilistic sensitivity analysis auf ceMRI in Bosniak class III cysts compared to ceCT. (**d**) Probabilistic sensitivity analysis auf CEUS in Bosniak class III cysts compared to ceCT.




Contrary to our present results, Gassert *et al.* [8] found a similar cost-effectiveness of CEUS and ceMRI using Medicare data in a United States healthcare survey; however, without a direct comparison with ceCT as 'gold standard'. We obtained different results using data of a representative university clinic in a EU healthcare system and local death rates in a follow-up perspective. Although both CEUS and ceMRI are established imaging tools for cystic renal lesions, ceCT continues to be the 'gold standard' for the Bosniak classification and should therefore be incorporated in a cost-effectiveness analysis.

Methodically, our present calculation yields a comprehensive cost estimate including ancillary costs as well. In this approach, small inaccuracies might have resulted from the use of an averaged cost allocation and incomplete internal documentation of activities. However, such inaccuracies are expected to be negligible as documentation of radiological examinations is usually adequate. Concerning absolute costs per examination from the hospital's point of view (in the sense of internal costs caused within the hospital), it should be noted that in comparing both tomographic imaging modalities, the first series of the scan, which is the basis of the examination, accounts for the greatest part of the cost difference between ceMRI and ceCT, followed by surcharges for computer-aided image processing and the additional contrast phase scan, accounting for 17.1% and 14.8% of the cost difference, respectively (Table 2).

Overall, our present results indicate that using CEUS in the follow-up of cystic renal lesions can save resources without compromising effectiveness, leaving more MRI slots for other patients. Economically, we recommend the use of the saved resources for additional follow-up examinations of patients with Bosniak III cystic renal lesions put on an active surveillance programme, e.g. 6 months after initial diagnosis as recommended by Silverman *et al.* [3] for Bosniak IIF lesions. This could reduce the proportion of false-negative findings against the background of the general risk of malignancy of Bosniak III renal cysts and a reduced QoL and

life expectancy of patients with a wrong diagnosis. Finally, the three imaging modalities compared in the present study have very good but no perfect diagnostic performance, and an additional follow-up examination can thus help reduce the rate of misdiagnosis. Furthermore, future diagnostic research should address the problem of up- and down-scoring of renal cysts assigned Bosniak classes using different imaging modalities, especially to reduce the rate of false-positive diagnoses in clinical practice [3,32].

### Limitations

Our present input data are derived from a large German university hospital, and cost structures may be different in terms of imaging equipment and staffing in smaller hospitals.

Generally, any modelling approach simplifies reality, whereby uncertainties were considered, and the probabilistic sensitivity analysis confirmed the base case results.

Economically, an identical revenue situation between the three modalities was assumed. The considered costs used in this simulation derive from ideal, exemplary cases, but not from large patient cohorts, so that our present results are valid for patients undergoing complication-free surgery and imaging.

## Conclusion

In conclusion, both CEUS and ceMRI can be used as alternatives to the 'gold standard' of ceCT in the diagnosis and follow-up of Bosniak IIF and III renal cysts without compromising effectiveness, as shown in both the base case scenario and in the majority of iterations of probabilistic sensitivity analysis. CEUS was thus shown to have the same effectiveness at lower cost.

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## Conflict of Interest

None of the authors reports a relationship with industry and other relevant entities, financial or otherwise, that might pose a conflict of interest in connection with the submitted article. The following authors report financial activities outside the submitted work: Paul Spiesecke reports no conflict of interest. Thomas Reinhold reports no conflict of interest. Yano Wehrenberg reports no conflict of interest. Sven Werner reports no conflict of interest. Andreas Maxeiner has received payments as a speaker from Hitachi-Medical-Systems, Canon Medical Systems, Stryker and Janssen-Cilag. Jonas Busch reports no conflict of interest. Thomas Fischer reports having received consultancy honoraria from Bracco and Canon Medical Imaging. Bernd Hamm reports having received consultancy honoraria from Canon Medical Imaging. Markus H. Lerchbaumer reports having received consultancy honoraria from Siemens Healthineers.

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Abbreviations: CEUS, contrast-enhanced ultrasonography; ceCT, contrast-enhanced CT; ceMRI, contrast-enhanced MRI; EU, European Union; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NSS, nephron-sparing surgery; QALY, quality-adjusted life year; QoL, quality of life; US, ultrasonography.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Costs of surgery (partial resection vs enucleation and average) in a representative patient, absolute amounts in Euro (€) with percentages of total.