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**Cost-effectiveness of preoperative magnetic resonance imaging to optimize  
surgery in ductal carcinoma in situ of the breast**

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## **ABSTRACT**

### **PURPOSE**

Complete surgical excision is the main factor for successful breast-conserving surgery in patients with ductal carcinoma in situ (DCIS) of the breast. Preoperative magnetic resonance imaging (MRI) may allow surgery optimization in this indication. From an economic standpoint, systematic preoperative MRI is associated with an extra cost, which may be offset by a decrease in the number of re-interventions. We performed an economic evaluation alongside IRCIS randomised controlled trial (NCT01112254) to determine whether systematic preoperative MRI in DCIS is a cost-effective strategy.

### **METHODS**

360 patients were included in IRCIS trial. Costs were assessed from the French national health insurance perspective. Resource use was prospectively collected during a 6-month period after randomisation. We estimated the mean cost per averted re-intervention.

### **RESULTS**

Despite extra costs due to MRI and additional biopsies, difference in total costs between arms was not statistically significant (mean cost of €9,980 in MRI arm and €9,682 in no MRI arm, cost difference: €298 [CI<sub>95%</sub> : -470; 1,063]). There was a non-significant decrease in the rate of re-hospitalisations for positive or close margins (20% in MRI arm versus 27% in No MRI arm, difference -7% [CI<sub>95%</sub> : -17; 3]). At a willingness to pay of €500 to avert a re-intervention, the probability that MRI strategy is cost-effective was 93%.

## **CONCLUSION**

Systematic preoperative MRI in patients with DCIS of the breast may be a cost-effective strategy. However, the modest clinical benefit associated with such a strategy limits the interest for this procedure in routine practice given the current MRI techniques.

**Keywords:** Magnetic resonance imaging, Ductal carcinoma in situ of the breast, Cost-effectiveness, Re-intervention

## INTRODUCTION

Ductal carcinoma in situ (DCIS) of the breast represents approximately 15 % of newly diagnosed breast cancer cases in France<sup>1</sup>. Non-extensive DCIS are treated by breast-conserving surgery followed by radiotherapy. A complete removal of the tumor is the main factor of success for this conservative surgical treatment. However, complete surgical excision is not always possible at the outset due to suboptimal preoperative and per-operative evaluation of the extent of the lesions by standard imaging (mammography, ultrasound). As a consequence, re-intervention for positive or close margins is often required in DCIS, with re-intervention rates ranging from 17 to 58%<sup>2</sup>.

Three randomised controlled trials (RCTs)<sup>3,4,5</sup> assessed the impact of preoperative magnetic resonance imaging (MRI) of the breast on short-term surgical outcomes. In the COMICE trial (n=1,623 breast cancer patients) conducted in the United Kingdom, the rate of re-intervention for positive or close margins was not significantly lower in the MRI arm (153/816 (19%) versus 156/807 (19%), p=0.77)<sup>3</sup>. The MONET trial conducted in the Netherlands assessed the rate of additional surgical procedures (re-excisions and conversion to mastectomy) in patients with a non-palpable breast cancer. Paradoxically, the rate of re-intervention for positive or close margins was higher in the MRI arm (18/53 (34%) versus 6/50 (12%), p=0.008). The POMB trial enrolled 440 patients with breast cancer younger than 56 years in three Swedish hospitals. The vast majority of the patients in the POMB study had invasive breast cancer. The breast re-intervention rate was lower in the MRI arm (11/220 (5%) versus 33/220 (15%), p<0.001)<sup>5</sup>. These three RCTs included only a low proportion of DCIS patients (6% in the COMICE trial and 18% in the MONET trial), in whom the benefit of preoperative MRI in DCIS is likely to be higher. The proportion of patients

with DCIS in the POMB study was not reported but was likely to be very low as this study was not selected in a meta-analysis examining the impact of preoperative MRI on the surgical outcomes in patients with DCIS<sup>6</sup>.

The multicentric IRCIS trial focused on patients with DCIS. It aimed to determine whether the addition of MRI to standard radiological evaluation may improve the assessment of tumor extension and reduce the re-intervention rate for positive or close margins in patients with DCIS undergoing breast-conserving surgery. The results of the IRCIS trial have been published elsewhere<sup>7</sup>. In brief, the re-intervention rate for close or positive margins was 20% in MRI arm and 27% in control arm, i.e. a relative reduction of 26% (stratified OR 0.68, [CI<sub>95%</sub> : 0.41, 1.1], p=0.13 in the intention to treat analysis and stratified OR 0.59, [CI<sub>95%</sub> : 0.35, 1], p=0.05 in the per protocol analysis).

From an economic standpoint, systematic preoperative MRI in DCIS patients is associated with an extra cost. However, a potential decrease in re-interventions for positive or close margins and related costs may offset this extra cost. No economic evidence is currently available in DCIS patients and it was a secondary objective of the IRCIS trial to tackle this issue. Our objective was to perform an economic evaluation alongside the IRCIS trial, using patient level data, to determine whether preoperative MRI in DCIS patients is a cost-effective strategy.

## **MATERIALS AND METHODS**

### ***IRCIS trial design***

The IRCIS study<sup>7</sup> (NCT01112254) is a randomised, multicenter phase III trial comparing the use of preoperative MRI (MRI arm) versus standard radiologic evaluation without MRI (No MRI arm) in DCIS accessible to breast-conserving surgery. Ten centers participated in the trial including 8 cancer centers and 2 teaching hospitals. The primary outcome measure was the rate of intervention for positive or close margins in the 6 months following the randomisation. The decision of re-intervention was made according to the histological analysis of the resection margins. Re-intervention (resumption of the tumor bed or mastectomy) was suggested if there were lateral positive or close margins of less than 2 mm<sup>8</sup>, except for anatomical limits (skin or muscle).

### ***Resource use and costs***

The economic evaluation was conducted from the perspective of the French National Health Insurance. Healthcare resource use was prospectively collected during a 6-month period after the randomisation and included all breast cancer-related hospitalisations, visits to the specialists, all imaging procedures and biopsies, radiotherapy, transportations and sick leaves. Transportation for surgery and sick leave costs were collected from the patients using a self-administered questionnaire.

The unit cost data are provided in Table 1. The tariffs per diagnosis-related groups (DRG) were used to cost each hospital stay and radiotherapy. Reimbursement tariffs from the French national health insurance were used for all procedures (including MRIs and biopsies) and visits to the specialists. No reimbursement tariff was available for MRI-guided macrobiopsy. A micro-costing study was carried out to assess the cost of this procedure from the hospital point of view. The cost of a sick

leave was computed using its length and the mean daily compensation paid by the National Health Insurance<sup>9</sup>. As regards transportation costs, we calculated the distance between the patient's home (zip code of residence) and the hospital. Distances for trips back and forth were valued using the tariffs from the National Health Insurance per type of transportation. We used descriptive statistics for both resource use and costs and computed 95% confidence intervals of mean cost difference between arms. All costs are expressed in Euros 2017. Costs were not discounted as the time horizon was 6 months<sup>10</sup>.

### ***Cost-effectiveness analysis***

Economic analyses where costs and outcomes are considered separately ignoring their joint distribution lead to incorrect inference regarding cost-effectiveness<sup>11</sup>. Cost-effectiveness analysis (CEA) represents joint uncertainty associated with costs and outcomes. Results of CEAs are expressed as the difference in costs divided by the differences in health outcomes between two strategies: the incremental cost-effectiveness ratio (ICER). In our study, the ICER was expressed as the incremental cost per averted re-intervention. It was calculated as the cost difference between arms divided by the difference in the re-intervention rates. To address uncertainty surrounding costs and effectiveness, ninety-five percent confidence intervals for difference in costs, difference in effectiveness and a cost-effectiveness acceptability curve were computed using 10,000 non-parametric bootstrap replications (percentile method). The bootstrap method is a resampling technique used to estimate statistics on a population by sampling a dataset with replacement. A cost-effectiveness acceptability curve (which was estimated from the bootstrap replicates) represents the probability that preoperative MRI is cost-effective compared to standard imaging for various willingness-to-pay thresholds to avert a re-intervention. Missing data for



sick leaves (patients under 65 years of age) and transportation costs were imputed with the mean. To test the robustness of our results, we performed a sensitivity analysis (Data Supplement). First, we performed a one-way sensitivity analysis varying the unit cost of MRI, as the unit cost of MRI reimbursed by the French national health insurance is dependent on the equipment characteristics (date of acquisition and volume of activity). Second, we removed sick leaves and transportation costs because of important missing data for these resources. Finally, a sensitivity analysis excluding the cost of re-intervention was performed. The checklist items from the Consolidated Health Economic Evaluation Reporting Standards were used to report this cost-effectiveness study<sup>12, 13</sup>. Statistical analysis was performed with SAS software (version 9.4; SAS Institute, Cary, North Carolina) version 9.4.

## RESULTS

### *Patient population*

Three hundred and sixty patients were randomised in the IRCIS trial. Eight patients were excluded for major protocol deviation, 1 patient died from another cause than breast cancer before the assessment of the primary endpoint, 2 patients withdrew their consent, and information for primary endpoint and resource use was missing for 4 patients. In total, 15 out of 360 patients were excluded from the economic evaluation (6%). Our study population consisted of 345 patients (173 patients randomised in the MRI arm and 172 patients in the No MRI arm (Figure S1)).

### *Cost analysis*

The healthcare resource use for breast cancer treatment over the 6-month period after randomisation is presented in Table 2. The number of re-hospitalisations related to breast cancer was 48 in the MRI arm and 59 in the No MRI arm, with an average of re-hospitalisations per patient of 0.28 in the MRI arm and 0.34 in the No MRI arm. In the MRI arm, patients had fewer re-interventions for positive or close margins than in the No MRI arm: 20% in the MRI arm (35/173) and 27% in the control arm (47/172), although the difference was statistically non-significant (difference of -7% [CI<sub>95%</sub> : -17% to 3%]) in the intention to treat analysis (Table 3).

Overall, mean cost of DCIS management during the 6 months after randomisation amounted to €9,682 in the No MRI arm and to €9,980 in the MRI arm (Table 4). The cost difference was €298 [CI<sub>95%</sub> : -470; 1,063]). The imaging procedures were the only cost component where difference was statistically significant: the cost of procedures was higher in the MRI arm (€545 versus €247, cost difference €298 [CI<sub>95%</sub> : 237; 358]) because patients had an additional MRI in this arm compared to the No MRI arm. There was no statistical difference for the other cost components,

as all confidence intervals of cost differences contained 0 (Table 4). Although not significant, there was a decrease in the cost of re-hospitalisations for positive or close margins (€666 versus €931, difference €-265 [CI<sub>95%</sub> : -633; 100]). Major cost drivers were radiotherapy (€3,258 versus €3,271, cost difference €13 [CI<sub>95%</sub> : -399; 427]), sick leaves (€2,554 versus €2,647, cost difference €93 [CI<sub>95%</sub> : -525; 683]) and hospitalisation for initial surgery (€2,396 versus €2,458, cost difference €62 [CI<sub>95%</sub> : -79; 195]).

### ***Cost-effectiveness analysis***

The cost-effectiveness plane is shown on Figure 1. It shows that in 92% of the cases (bootstrap replicates), the MRI strategy was more effective (less re-interventions in the MRI arm) but is also more costly in 78% of the cases. The cost-effectiveness acceptability curve (Figure 2) represents the probability that preoperative MRI is cost-effective compared to standard imaging for various willingness-to-pay thresholds to avert a re-intervention (up to €2,500 per averted re-intervention). For a willingness to pay of €500 to avert a re-intervention, the probability that the MRI strategy is cost-effective was 93% (Figure 2). Results were similar in the sensitivity analysis (Data supplement). The cost analysis excluding sick leaves and transportations, and the cost analysis in which we varied ( $\pm 10\%$ ) the cost of MRI equipment led to similar results in terms of cost-effectiveness (Data Supplement).

## DISCUSSION

The IRCIS study aimed to assess the clinical impact of systematic preoperative MRI in terms of averted re-intervention for close or positive margins in DCIS patients. The study found a non-significant decrease of re-intervention rate in the MRI arm, which was deemed insufficient to be clinically relevant<sup>7</sup>. Our economic evaluation suggested that MRI strategy may however be a cost-effective strategy in the French context. Cost-effectiveness analyses are decision-support tools that provide information on the uncertainty surrounding both the clinical results and the costs. In the IRCIS trial, clinical results were not statistically significant but in favor of the MRI strategy. In the ITT analysis, patients who did not comply with the allocated strategy (with or without preoperative MRI) were kept in their allocated arm for the analysis whereas they were excluded in the per-protocol analysis. The relative reduction of the re-intervention rate was 26% ( $p=0.13$ ) in the ITT analysis and 33% ( $p=0.05$ ) in the per-protocol analysis. These results suggest that the IRCIS trial may have been underpowered to show a clinically relevant benefit of a systematic preoperative MRI in DCIS patients.

Regarding the difference in cost between strategies, there was an extra cost corresponding to the cost of systematic MRI which was not offset by a decrease in hospital costs which was rather modest due to a limited number of re-interventions for positive or close margins (35 hospitalisations in the MRI arm versus 47 in the no MRI arm). There have been only few cost-effectiveness studies in the field of breast cancer MRI and none in the surgical management of DCIS. This may be explained by the fact that the outcome of imaging procedures does not necessarily translate into different therapeutic pathways. In breast cancer, most of the studies assessed the value of MRI in the diagnosis for women at high risk of developing breast cancer<sup>14-17</sup>.

One study investigated the impact of MRI in the surveillance of women who had previously breast cancer treated with surgery<sup>18</sup>. Three RCTs assessed the addition of preoperative MRI in all types of breast cancer<sup>19, 20, 5</sup>, but only one study included a cost-effectiveness analysis. The COMICE<sup>19</sup> trial, an RCT conducted in the United Kingdom, aimed to determine whether the addition of a preoperative MRI decreases the rate of re-intervention in patients with localized or invasive breast cancer. This trial included 1,623 patients recruited in 45 centers. Our cost results were consistent with this trial. Indeed, in the COMICE trial, mean costs per patient were not different between the arms (€6,249 versus €5,914). Overall costs were lower than in our study because the cost of sick leaves and transportations were not included in the COMICE study. Excluding these cost components in our study led to similar cost estimates to those in the COMICE trial (Data Supplement).

Our study has limitations which have to be mentioned. First, the rate of missing data for sick leaves and transportation questionnaires was high. However, cost-effectiveness results were similar when removing this cost component from the analysis (Data Supplement). Second, we chose to conduct a cost-effectiveness analysis rather than a cost-utility analysis. In the COMICE trial, the quality of life of patients was assessed<sup>19</sup>. The EQ-5D score, at 12 months post initial surgery, was respectively 0.810 in the MRI arm and 0.811 in the No MRI arm. These results suggested that there was no difference in terms of quality of life between the two strategies. In the IRCIS trial, only one-third of the women were re-operated in the No MRI arm and MRI reduced the risk (absolute reduction) of re-intervention by 7%, resulting in 12 re-interventions being averted. Therefore, it is likely that our study would have been underpowered to demonstrate a significant gain in QALYs. The IRCIS trial focused on DCIS, a cancer of good prognosis, in which the aim is to

improve the quality of care optimizing breast surgery. In such a case, no survival gain is expected and it is likely that the impact on QALYs would be very limited. Third, there is a debate on whether or not one should include the cost of averted events in the computation of the cost of a strategy in a cost-effectiveness analysis. Mullins et al<sup>21</sup> underlined that double counting may occur when the benefit of a treatment or a strategy is included in both the estimation of cost difference (numerator) and the estimation of effectiveness (denominator). However, a consensus on this issue has not yet been reached, and, in the literature, cost-effectiveness studies consider the cost of avoided events in the computation of the cost-effectiveness ratio<sup>17,18</sup>. In this article, the main analysis considered the cost of avoided re-interventions. However, cost-effectiveness results were very similar when excluding the cost of re-interventions for positive or close margins (Data Supplement). Finally, costs assessed in this study do not include all costs incurred from DCIS suspicion as well as long-term follow-up costs. In the IRCIS trial, patients were enrolled when a surgical procedure had been decided. Costs included preoperative imaging and biopsies procedures, hospital costs for surgery (including sentinel lymph node biopsies and re-interventions) and follow-up costs during a 6-month time horizon. However, surgery and adjuvant radiation therapy are expected to be the major cost drivers in the management of patients with DCIS.

In conclusion, the addition of preoperative MRI in DCIS may be a cost-effective strategy in France and our results are likely to be transferable to European countries with a similar healthcare system. However, with current imaging techniques, the modest clinical benefit associated with such a strategy limits the interest this procedure in routine practice.

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## TABLES

**Table 1. Unit cost data**

Resource	Unit cost (€)
<b>Most frequent DRGs for breast cancer-related hospital stays:</b>	
Breast-conserving surgery (DRG 09C05J and 09C051)	2,262
Mastectomy without reconstruction (DRG 09C041)	3,913
Mastectomy with reconstruction (DRG 09C111)	8,093
Sentinel lymph node biopsy (DRG 09C101)	1,180
<b>MRI (including contrast agent)</b>	<b>302</b>
<b>MRI-guided macrobiopsy</b>	<b>857</b>
<b>Radiotherapy:</b>	
3-dimensional planning	991
3-dimensional radiation session	170
2-dimensional planning	347
2-dimensional radiation session	83
<b>Outpatient visits</b>	<b>23</b>
<b>Daily sick leave compensation</b>	<b>30</b>
<b>Cost per km per type of transportation</b>	<b>From 0.3 to 2.19</b>

DRG: diagnosis-related group; MRI: magnetic resonance imaging

**Table 2. Healthcare resource use for DCIS treatment over the 6-month period after randomisation**

	Number of patients	
	MRI N=173	No MRI N=172
<b>Hospitalisations related to breast cancer:</b>		
<b>Hospitalisation for initial surgery</b>	173 (100%)	172 (100%)
<b>Re-hospitalisation</b>	48 (28%)	59 (34%)
<b>Re-hospitalisation for positive or close margins</b>	35 (20%)	47 (27%)
<b>Type of initial breast surgery received:</b>		
- <b>Tumorectomy</b>	160	166
- <b>Mastectomy</b>	16	7
<b>Radiotherapy</b>	132 (76%)	130 (76%)

MRI: magnetic resonance imaging; DCIS: ductal carcinoma in situ

**Table 3. Cost-effectiveness analysis results: MRI versus No MRI**

	<b>MRI</b>	<b>No MRI</b>	<b>Difference [95%CI]</b>
	<b>n=173</b>	<b>n=172</b>	<b>(MRI versus No MRI)</b>
			<b>Bootstrap n=10,000</b>
<b>Mean cost per patient (€)</b>	9,980	9,682	298 [-470; 1,063]
<b>Effectiveness:</b>			
<b>Number of re-interventions for positive or close margins</b>	35	47	-12 [-32; 4]
<b>Rate of re-intervention</b>	20%	27%	-7% [-17; 3]

MRI: magnetic resonance imaging

**Table 4. Costs per patient over the 6-month period after randomisation**

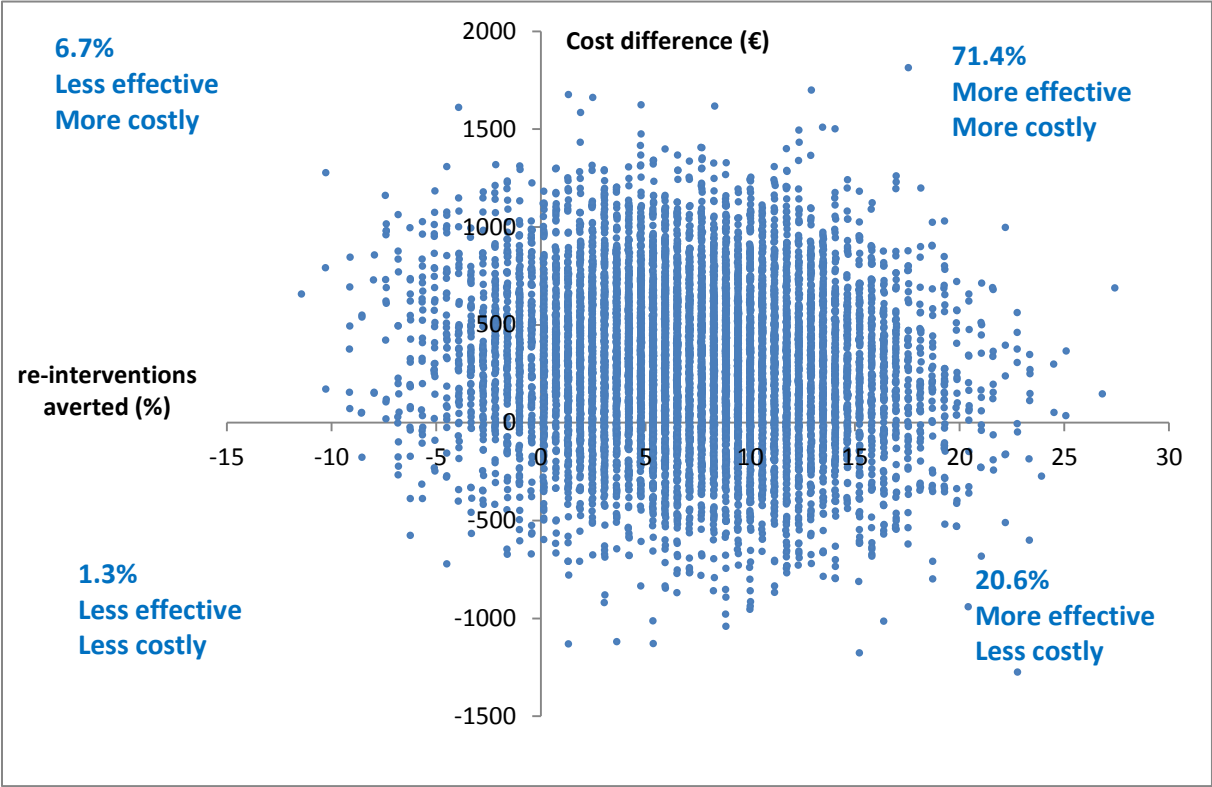
Resource	MRI	No MRI	Mean cost
	Mean $\pm$ SD n=173	Mean $\pm$ SD n=172	difference [95% CI] Bootstrap n=10,000
<b>Procedures (including MRI and biopsies)</b>	545 $\pm$ 325	247 $\pm$ 241	298 [237; 358]
<b>Hospitalisation for initial surgery</b>	2,458 $\pm$ 587	2,396 $\pm$ 717	62 [-79; 195]
<b>All Re-Hospitalisations</b>	922 $\pm$ 1944	1,092 $\pm$ 1,873	-170 [-572; 81]
<b>Among which:</b>			
<i>Re-Hospitalisations for positive or close margins<sup>1</sup></i>	666 $\pm$ 1,927	931 $\pm$ 1,847	-265 [-633; 100]
<b>Radiotherapy</b>	3,271 $\pm$ 1,940	3,258 $\pm$ 1,941	13 [-399; 427]
<b>Sick leaves</b>	2,647 $\pm$ 2,654	2,554 $\pm$ 3,020	93 [-525; 683]
<b>Transportations</b>	49 $\pm$ 33	51 $\pm$ 29	-2 [-8; 5]
<b>Outpatient visits</b>	88 $\pm$ 68	84 $\pm$ 50	4 [-7; 18]
<b>Total cost</b>	9,980 $\pm$ 3,562	9,682 $\pm$ 3,800	298 [-470; 1,063]

MRI: magnetic resonance imaging; SD: standard deviation; CI: confidence interval

<sup>1</sup> Cost is weighted by frequency

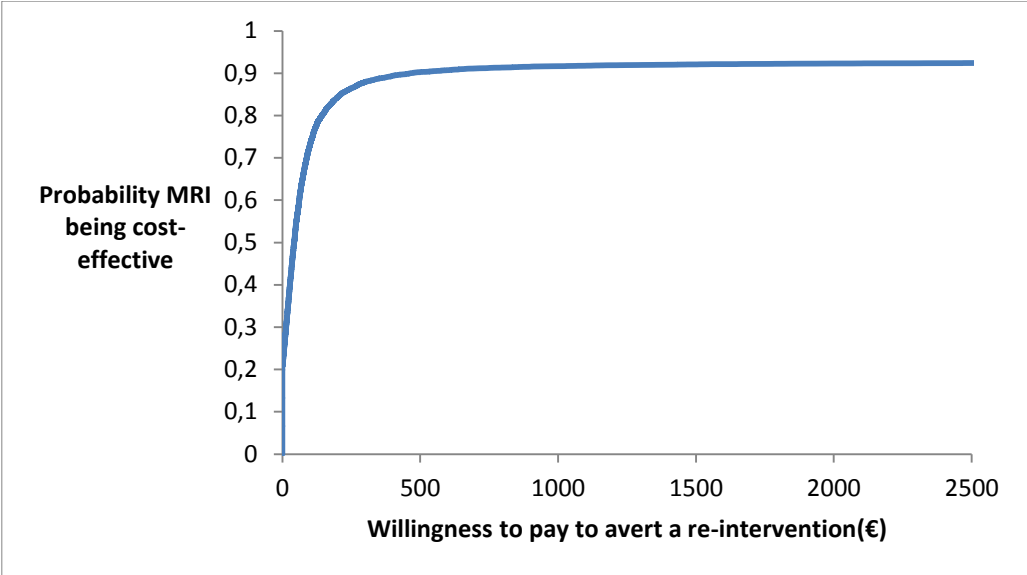
Figures

Figure 1. Cost-effectiveness plane showing the cost difference and difference in effectiveness of MRI versus No MRI; 10,000 bootstrap replications





**Figure 2. Cost-effectiveness acceptability curve (CEAC) for MRI versus No MRI (10,000 bootstrap replications). The CEAC represents the probability that preoperative MRI is cost-effective compared to standard imaging for various willingness-to-pay thresholds to avert a re-intervention**



MRI: magnetic resonance imaging