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Original Article

Early health economic analysis of 1.5 T MRI-guided radiotherapy for localized prostate cancer: Decision analytic modelling

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ABSTRACT

Background and purpose: 1.5 Tesla magnetic resonance imaging radiotherapy linear accelerator (MR-Linac) is gaining interest for treatment of localized prostate cancer. Clinical evidence is lacking and it therefore remains uncertain whether MR-Linac is cost-effective. An early health economic analysis was performed to calculate the necessary relative reduction in complications and the maximum price of MR-Linac (5 fractions) to be cost-effective compared to 5, 20 and 39 fractionation schedules of external beam radiotherapy (EBRT) and low-dose-rate (LDR) brachytherapy.

Materials and methods: A state transition model was developed for men with localized prostate cancer. Complication rates such as grade ≥2 urinary, grade ≥2 bowel and sexual complications, and utilities were based on systematic literature searches. Costs were estimated from a Dutch healthcare perspective. Threshold analyses were performed to identify the thresholds of complications and costs for MR-Linac to be cost-effective, while holding other outcomes such as biochemical progression and mortality constant. One-way sensitivity analyses were performed to outline uncertainty outcomes.

Results: At €6460 per patient, no reductions in complications were needed to consider MR-Linac cost-effective compared to EBRT 20 and 39 fractions. Compared to EBRT 5 fractions and LDR brachytherapy, MR-Linac was found to be cost-effective when complications are relatively reduced by 54% and 66% respectively. Results are highly sensitive to the utilities of urinary, bowel and sexual complications and the probability of biochemical progression.

Conclusions: MR-Linac is found to be cost-effective compared to 20 and 39 fractions EBRT at baseline. For MR-Linac to become cost-effective over 5 fractions EBRT and LDR brachytherapy, it has to reduce complications substantially or be offered at lower costs.

Current treatments for prostate cancer (PCa) including external beam radiotherapy (EBRT), brachytherapy, and (robotic) surgery, are associated with substantial adverse effects [1–3]. High-field (1.5 Tesla) magnetic resonance (MR) imaging with a linear accelerator (Linac), MR-Linac [4,5], allows online and real-time, soft-tissue imaging and targeted MRI-guided radiotherapy. During treatment delivery, the prostate can be precisely tracked, which allows the reduction of uncertain dosage margins, exposing less healthy tissue to radiation [6–8]. Theoretical advantages of this approach include reduction of acute and late complications, improved local tumor control and hypo-fractionation (1–5 treatment fractions) [7,9–12]. In a phase 2 study of MRI-guided radiotherapy delivered in 5-fractions for localized PCa, the rates of grade ≥2 early (up to three months) urinary and bowel complications was reported to be 23.8% and 5.0%, respectively [13]. Hence, real-life data of long-term and other treatment outcomes (e.g., sexual complications and biochemical progression) are still lacking, impeding a comprehensive cost-effectiveness analysis.

Despite theoretical benefits, the lack of empirical evidence of clinical effectiveness and the substantial upfront investments create a high implementation burden and uncertainty for users and payers [14]. An early health economic analysis can be conducted when both costs and effects of the innovation are still largely unknown and when technologies are still in development [15,16]. These analyses often rely upon decision analytic models in which costs and effects are combined from different sources. They can provide directions for research and development, by identifying areas where new technologies have the potential to

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be cost-effective, and conditions that need to be met to achieve cost-effective outcomes.

So far one early economic evaluation estimated the potential cost-effectiveness of MRI-guided radiotherapy compared with CT-guided radiotherapy for localized PCa [17]. This study suggested that MRI-guided radiotherapy can be cost-effective through minor reduction in urinary and bowel complications. This study lacked comparisons with other standard radiotherapy regimens such as brachytherapy and 20-fractions EBRT [12,18,19]. Furthermore, the appraisal of adverse effects did not include sexual complications, which is an important outcome following radiotherapy [20–23].

Our objective is to estimate the relative minimally required reduction in grade ≥2 urinary, grade ≥2 bowel and sexual complications in patients with low- and intermediate risk localized PCa, and the maximum price of MR-Linac provided in 5 fractions to be cost-effective, compared to current radiotherapy regimens. Furthermore, we will assess the impact of several treatment-related features on the required reduction of complications of MR-Linac to be found cost-effective.

Material and methods

A state transition model was created to identify the thresholds of complications and costs for MR-Linac to be cost-effective, compared to low-dose-rate (LDR) brachytherapy and EBRT provided in 5, 20 or 39 fractions (common fractionation schedules for localized PCa) [18,24,25]. Our hypothetical cohort consisted of 1000 men with low- and intermediate-risk localized PCa and no other severe comorbidities, treated at age 65 years.

State transition model

Within the constructed model the patient cohort moved hypothetically through different health states over a life-time time horizon. The health states included: "free from complications", "grade ≥2 urinary complications", "grade ≥2 bowel complications", "sexual complications" (moderate-to-severe erectile dysfunction), "biochemical progression" (either local disease progression or metastasis to distant sites) and "death" (either disease-related or other causes) (Fig. 1, Appendix A).

Transition probabilities

The likelihood of moving from one state to another at the end of a three-month cycle was governed by transition probabilities. All events occurring within three months were regarded as acute complications and events taking place thereafter were registered as long-term complications. Overall mortality was based on the annual mortality of the Dutch population from 65 year onwards [26]. Death from cancer can only occur after a patient has been transitioned to biochemical progression.

Since real-life data of costs and effects for MR-Linac treatment were limited, the study the study required several assumptions and estimates. Hence, MR-Linac's baseline is assumed on grade ≥2 acute urinary and bowel complications (23.8% and 5.0% respectively) from a phase 2 MRI-guided radiotherapy study by Bruynzeel et al [13] having other outcomes of equal effectiveness to EBRT 5-fractions. Table 1 provides an overview of all transition probabilities for the comparator strategies. These parameters are based on published literature [41–48].

Quality of life

Effectiveness of PCa treatments was expressed in QALYs that combines the quality and length of life, where one QALY equals a year in perfect health. A utility score indicates quality of life on a zero to one scale, with 0 reflecting death and 1 reflecting full health (Table 2). Since no data of the impact of MR-Linac treatment on quality of life were available, we assumed similar post-treatment (free from complications) utility as conventional EBRT. The discounting of utilities was performed using an annual rate of 1.5% [26]. This means that the value of the effect is adjusted for the point in time they occur. Future benefits and costs are generally valued lower than those of today [27].

Costs

Cost data were derived from published health economic evaluations in radiotherapy, the Dutch guideline for costing research and the Dutch online database for medication costs [25,26,28]. For instance, costs for grade ≥2 urinary and bowel complications (e.g., physician visits, incontinence materials and medicines) were derived from a health economic evaluation for PCa by Peters et al

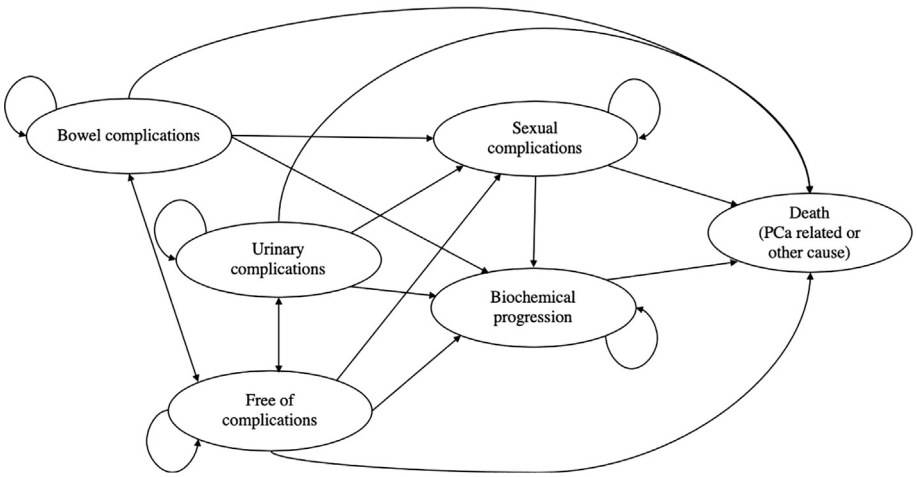

Fig. 1. State transition model of the follow-up of men with localized prostate cancer. The model consists of six health states. The cohort enters the model in the health state "urinary complications", "bowel symptoms" or "free of complications". After the first cycle, patients with urinary and bowel complications can remain in the related state or go to the health state "free from complications", "sexual complications" (moderate-to-severe erectile dysfunction) or "biochemical progression" (either local disease progression or metastasis to distant sites). Patients without acute complications can also remain in this state or go to the health state urinary, bowel or sexual complications, or biochemical progression. "Death" from any cause can occur at any health state transition. Death from cancer can only occur after a patient has been transitioned to biochemical progression.

Table 1
Transition probabilities of health states for MR-Linac and comparator strategies.

Health states	MR-Linac 5 Fx Probability (source)	EBRT 5 Fx Probability (source)	EBRT 20 Fx Probability (source)	EBRT 39 Fx Probability (source)	LDR Brachytherapy Probability (source)
Gr ≥2 acute urinary complications[a]	0.24 [13]	0.30 [41]	0.49 [42]	0.46 [42]	0.22 [43]
Gr ≥2 late urinary complications (gr ≥2)[b]	0.18 [41]	0.18 [41]	0.12 [42]	0.23 [42]	0.16 [43]
Gr ≥2 acute bowel complications[a]	0.05 [13]	0.14 [41]	0.39 [42]	0.25 [42]	0.03 [44]
Gr ≥2 late bowel complications[b]	0.18 [41]	0.13 [41]	0.12 [42]	0.06 [42]	0.02 [45]
Sexual complications[b]	0.35 [41]	0.35 [41]	0.65 [42]	0.67 [42]	0.35 [46]
Biochemical progression	0.07 [41]	0.07 [41]	0.08 [42]	0.06 [47]	0.05 [48]
Disease mortality	0.01 [47]	0.01 [47]	0.01 [47]	0.01 [47]	0.01 [47]

a. Acute complications occur within 3 months.
b. Late and sexual complications occur later than 3 months.
EBRT = external beam radiotherapy; Fx = fractions.

Table 2
Overview of utilities of each health states and cost data used in the decision analytic model in Euros.

Utility parameters	Value (Source)
Post-treatment	0.73 [49]
No complications	0.95 [50]
Urinary complications	0.83 [49]
Bowel complications	0.71 [49]
Sexual complications	0.89 [49]
Biochemical progression	0.73 [49]

Description	Unit costs (Euros)	Travel costs (Euros)	Total cost per patient (Euros)	Source
Treatment costs				
EBRT 5 fractions	1165	470	1635	Details in Appendix B [24,30]
EBRT 20 fractions	4660	1870	6530	Details in Appendix B [24,30]
EBRT 39 fractions	9090	3650	12,740	Details in Appendix B [24,30]
LDR brachytherapy	4490	95	4585	Details in Appendix B [30,51]
MR-Linac	5830	630	6460	Details in Appendix B [17,30]
Medication costs				
Gr ≥2 acute urinary complications			68	[51]
Gr ≥2 late urinary complications			309/year	[29,51]
Gr ≥2 acute bowel complications			108	[51]
Gr ≥2 late bowel complications			902/year	[51]
Sexual complications			160/year	[52]
Biochemical progression			915/year	[29]

[29]. We assumed that patients with biochemical progression received hormonal therapy only.

We calculated the costs per fractionation schedule of EBRT based on the cost-per-fraction (€233/fraction) on the conventional linear accelerator from a cost analysis including upfront capital (e.g., construction, maintenance, equipment) and operating (e.g., staffing, overhead) costs [24]. The cost-per-fraction on the MR-Linac was based on a previously published early economic evaluation of MRI-guided radiotherapy [17].

In the Netherlands, the total travel expenses for cancer treatment are reimbursed in the Netherlands once a personal payment of up to €108 has been made [30]. The Dutch Healthcare Institute identified that 60% of the nearly 60,000 cancer patients compensated their travel expenses by their health insurer in 2017 [30]. We therefore included taxi costs for 60% of the patient cohort. We assumed that the fractionation schedules are provided on separate days, hence the number of fractions equals the number of returned taxi rides. For EBRT and LDR brachytherapy, we assumed taxi costs with the average distance of 46 km to a medical cancer center in the Netherlands (€156/treatment session) [30]. For MR-Linac, we assumed the longest distance to a general medical cancer center, which is 62 km (€210/treatment session), as this treatment is expected to be offered in less hospitals than standard cancer treatment [30]. Appendix B provides an overview of treatment costs.

Table 2 presents all costs per treatment strategy and complication. Costs were calculated in Euros, corrected for inflation to 2019, from the Dutch healthcare perspective. Future costs were discounted using an annual rate of 4% [26].

Model analysis

Main outcomes of the analysis were the necessary relative reductions of urinary, bowel and sexual complications, needed with the maximum price of MR-Linac, to become cost effective over present-day standard radiotherapy treatments. Strategies were considered cost-effective if the incremental cost-effectiveness ratio, indicating the cost per QALY gained by the innovation versus the standard of care, was below a cost-effectiveness threshold of €80,000/QALY. This is the ceiling ratio for a high burden of disease in the Netherlands [26].

Threshold analyses

Threshold analyses were performed to identify the relative minimum reduction required in grade ≥2 urine, grade ≥2 bowel and sexual complications of MR-Linac to be cost-effective at the cost-effectiveness threshold of €80,000/QALY [15]. We also performed threshold analyses to identify the maximum price of MR-Linac at different reductions of complications of alternative strategies at €80,000/QALY. The analyses were performed assuming MR-Linac's grade ≥2 acute urinary and bowel complications from Bruynzeel et al. [13] having other outcomes of equal effective as EBRT 5-fractions.

Sensitivity analyses

One-way deterministic sensitivity analyses were performed to determine the parameters to which the necessary reduction of urinary, bowel and sexual complications of MR-Linac to be cost-effective are most sensitive. The effect of changing the mean input parameters with standard deviation or +/− 20% was shown in a tornado diagram to illustrate the impact of the range of each parameter. The parameters were ranked from the largest to the smallest impact.

Model validation

Validation of the model structure, input parameters, and discussion of major model assumptions was undertaken with methodological and clinical experts. The performance of the model has been appraised by using it similarly by an independent expert. Furthermore, the model was constructed in Microsoft Excel (Microsoft, Redmond, Washington, USA) and has been rebuilt in R Studio 1.1.383 (Boston, MA) which produces exactly the same results. For cross validation, a structured literature search was performed to compare our model structure, assumptions and outcomes of interest with cost-utility models. For instance, reviews of economic evaluations using the (Mesh-)terms 'review', 'prostatic neoplasm' and 'economics', systematic reviews or large trials were used to identify and compare the input parameters.

Results

Threshold analyses were performed assuming MR-Linac's grade ≥2 acute urinary and bowel complications to be 23.8% and 5.0% from the phase 2 MRI-guided radiotherapy study [13] having other outcomes of equal effectiveness to EBRT 5-fractions. If MR-Linac costs €6460 per patient, no additional reductions in grade ≥2 urinary, grade ≥2 bowel and sexual complications were needed for MR-Linac to be found cost-effective compared to EBRT 20 and 39 fractions (Table 3). Compared to 20-fractions, MR-Linac could save €1160 and gain up to 0.23 QALYs. Compared to 39 fractions, MR-Linac could save €9170 while gaining 0.11 QALYs.

MR-Linac appears to be cost-effective compared to 5-fractions EBRT when grade ≥2 urinary, grade ≥2 bowel and sexual complications are reduced by at least 54%. *c*, probability of acute and late urinary complications will need to be reduced from 23.8% to 11% and from 18% to 8% respectively. Acute and late bowel complications need to be reduced from 5% to 2% and from 13% to 6% respectively, and sexual complications from 35% to 16%. In this case, the incremental cost of MR-Linac would be €4948 while gaining up to 0.06 QALYs. MR-Linac may also be cost-effective when only acute and late bowel complications are reduced to at least 1% and 3% (a reduction of 79%), if sexual and acute urinary complications cannot be reduced more than the rates as found by Bruynzeel et al [13]. Total elimination of urinary or sexual complications alone will not make MR-Linac cost-effective compared to EBRT 5-fractions.

Furthermore, MR-Linac should reduce complications by at least 66% to become cost-effective over LDR brachytherapy. Hence, acute and late urinary complications need to be reduced from 24% to 8% and from 18% to 6% respectively. Acute and late bowel complications will have to be reduced from 5% to 2% and from 13% to 4%, and sexual complications from 35% to 12%. The incremental costs and QALYs provided by MR-Linac would be €2020 with an increase of 0.03 QALYs. The individual reduction of urinary, bowel or sexual complications separately will not make MR-Linac cost-effective compared to LDR brachytherapy.

We modelled the maximum price per patient for MR-Linac relative to comparators from conservative to no complications at the cost-effectiveness threshold of €80,000/QALY for being cost-effective (Fig. 2). Relative to EBRT 20-fractions, costs of MR-Linac may range from €26,400 to €86,900 per patient to be cost-effective. Compared to EBRT 39-fractions, costs of MR-Linac may range from €22,100 to €78,000 per patient.

Compared to EBRT 5-fractions, costs of MR-Linac may range from €2050 to €62,500 per patient when reducing complications from conservative to no complications. Relative to LDR brachytherapy, costs of MR-Linac may range from €600 to €51,000 per patient when reducing complications from conservative to no complications.

Fig. 3 shows the results of the one-way deterministic sensitivity analysis of MR-Linac versus EBRT 5-fractions and LDR brachytherapy which are the scenarios in which MR-Linac is unlikely to be cost-effective. Compared to EBRT 5-fractions, the probability of biochemical progression and the utilities of urinary and sexual complications have the highest impact on the necessary reduction in complications of MR-Linac. Relative to LDR brachytherapy, model outcomes are most sensitive to the probability of biochemical progression and the utilities of sexual and bowel complications.

Table 3
Probabilities of necessary reduction in urinary, bowel and sexual complications for MR-Linac versus comparator strategies to be cost-effective at 80,000 Euros per QALY. The incremental costs and QALYs of MR-Linac are also presented in each comparison.

	MR-Linac 5 fractions		
	Relative required reduction in urinary, bowel and sexual complications to be cost-effective	Incremental costs (Euros)	Incremental QALYs
EBRT 5 fractions	54%	+4840	+0.06
EBRT 20 fractions	0	−1160	+0.23
EBRT 39 fractions	0	−9170	+0.11
LDR brachytherapy	66%	+2020	+0.03

Discussion

Our early health economic analysis demonstrated the effect needed for MR-Linac treatment in 5-fractions to be cost-effective compared to conventional and stereotactic EBRT and LDR brachytherapy for low- and intermediate-risk localized PCa. Due to the limited data of MR-Linac, clinical effectiveness, complication rates, the impact on quality of life and costs still need to be determined. Therefore, MR-Linac's baseline in the analyses were considered with: (i) grade ≥2 acute urinary and bowel complications from the phase 2 study [13] (ii) having other outcomes of equal effectiveness to EBRT 5-fractions, and (iii) post-treatment utility equivalent to conventional EBRT.

MR-Linac provided in 5-fractions is found to be cost-effective compared to EBRT 20- and 39-fractions at the cost-effectiveness threshold of €80,000 per QALY. When compared to EBRT 5-fractions and LDR brachytherapy, MR-Linac is found to become cost-effective when large reduction in complications relative to the baseline are achieved (54% and 66% for EBRT and LDR respectively). Alternatively, MR-Linac will have to be offered at lower costs, as can be seen from varying the conservative complications to zero. No complications following treatment is unlikely and hence it remains to be proven whether the substantial reductions in complications needed to make MR-Linac cost-effective are feasible in practice.

It is also doubtful if the costs of MR-Linac can be reduced considerably to improve cost-effectiveness. To illustrate, the implementation of MR-Linac deals with substantial investments and

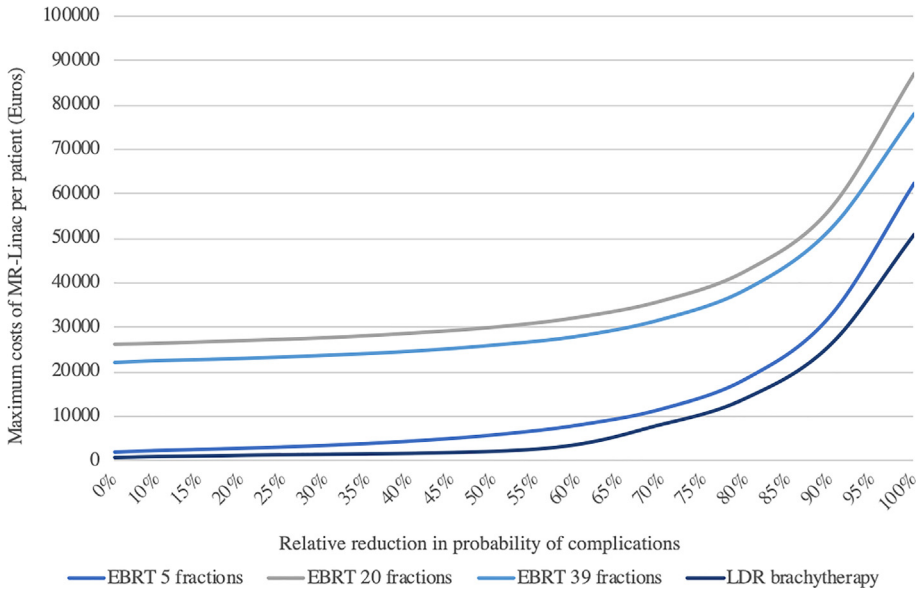

Fig. 2. Acceptable prices of MR-Linac relative to comparator strategies at different reductions of complications at a cost-effectiveness threshold of 80,000 Euros per QALY. At base line of MR-Linac, we assumed its grade ≥2 acute urinary and bowel complications from Bruynzeel et al. [13] having other outcomes of equal effectiveness to EBRT 5 fractions.

its use for PCa requires a considerable number of physician persons-hours with a relatively long duration fraction delivery time of about 45 min [14,23,31,32]. Potential efficiencies will emerge over time as MRI imaging is increasingly being used within radiotherapy [23]. So beyond clinical challenges, also operational and technical aspects presently impede the cost-effectiveness of MR-Linac for localized PCa.

Alongside the aforementioned obstacles, the ongoing technological development of MR-Linac and potential learning curves may improve cost-effective outcomes [14,23,31,33]. MR guidance with the potential of improved adaptive contour propagation and rapid dose reconstruction during radiation may allow smaller uncertainty margins around the prostate. Over the course of the last 15-years urinary and bowel complications after EBRT have decreased substantially as uncertainty margins were reduced due to the introduction of 3D conformal MRI-guided radiotherapy and image-guidance by fiducial marker placement within the prostate [34]. Hence, improved accuracy of treatment delivery and further reduction in uncertainty margins may result in less toxicity as less healthy tissue (e.g., bladder and rectum) is exposed to radiation [12,23].

The potential automation of components in the workflow of MR-Linac may also reduce the workload, treatment time and costs [23,31]. More precise radiotherapy may also allow for PCa treatment in 1 to 2 fractions [35,36]. These technical advancements, together with learning curves, may allow operational efficiencies and positively impact the actual costs [33]. Eventually, this may manifest in reduced side effects and fewer clinic visits [37,38]. This is expected to positively influence the patient's quality of life, and hence would benefit the potential cost-effectiveness of MR-Linac. Further studies can examine the treatment-related utility scores as relatively better patient comfort may be of value and highly valid outcomes are essential.

The results are highly sensitive to the probability of biochemical progression and the utilities of urinary, bowel and sexual complications. A higher level of biochemical progression creates the need for a larger reduction in complications of MR-Linac in order to achieve cost-effective outcomes. Compared to EBRT 5-fractions and LDR brachytherapy, an increase in biochemical progression of 20% requires a reduction in complications of at least 72% and 81% respectively (instead of 54% and 66%). Hence, these variables are a major source of uncertainty; future cost-effectiveness analysis has to anticipate the impact of these parameters.

Some limitations of the present study need to be considered. An inherent limitation of early health economic modelling is the implication of assumptions resulting from the lack of technology data [15]. For instance, we could not assess combined health states and post-treatment utility. And while we focus on the 1.5 Tesla (T) MR-Linac (Elekta Unity), we assumed its acute urinary and bowel complications from the phase 2 study on the 0.35 T MR-Linac (Viewray MRIdian) [13]. Given the different imaging units, further studies are required to demonstrate treatment outcomes with both MRI guidance systems. Future studies can also compare MR-Linac with other potential trends in prostate radiotherapy (e.g., conventional EBRT with spacers [39]).

We used the official cost-effectiveness threshold for a high burden of disease in the Netherlands which is €80,000 per QALY, whereas £20,000–£30,000 per QALY is the cut-off value in United Kingdom and $50,000–$100,000 per QALY in United States [40]. A certain threshold must therefore always be considered when interpreting the results. We also used Dutch cost data to estimate cost-effectiveness, so the exact numbers may not be applicable in other countries. And while our study lacks a comprehensive costing approach of MR-Linac, present costs of technology usage may, however, currently not be a good predictor of final expenses given its ongoing development with potential efficiencies in the long run [23].

Our results can be used in prospective studies for PCa as a preliminary insight into the magnitude of effect needed for MR-Linac to be cost-effective and the impact of individual parameters. Studies on the potential cost-effectiveness of MR-Linac treatment of other tumor sites are also needed to demonstrate its value. Furthermore, the hypothetical cost-effectiveness scenarios of MR-Linac can also guide the ongoing technology development. Decision analytic modelling can thus provide information and directions for technology users and research in MRI-guided radiotherapy. Not all possible outcomes of new technologies such as MR-Linac, however, can be verified in advance using solid evidence.

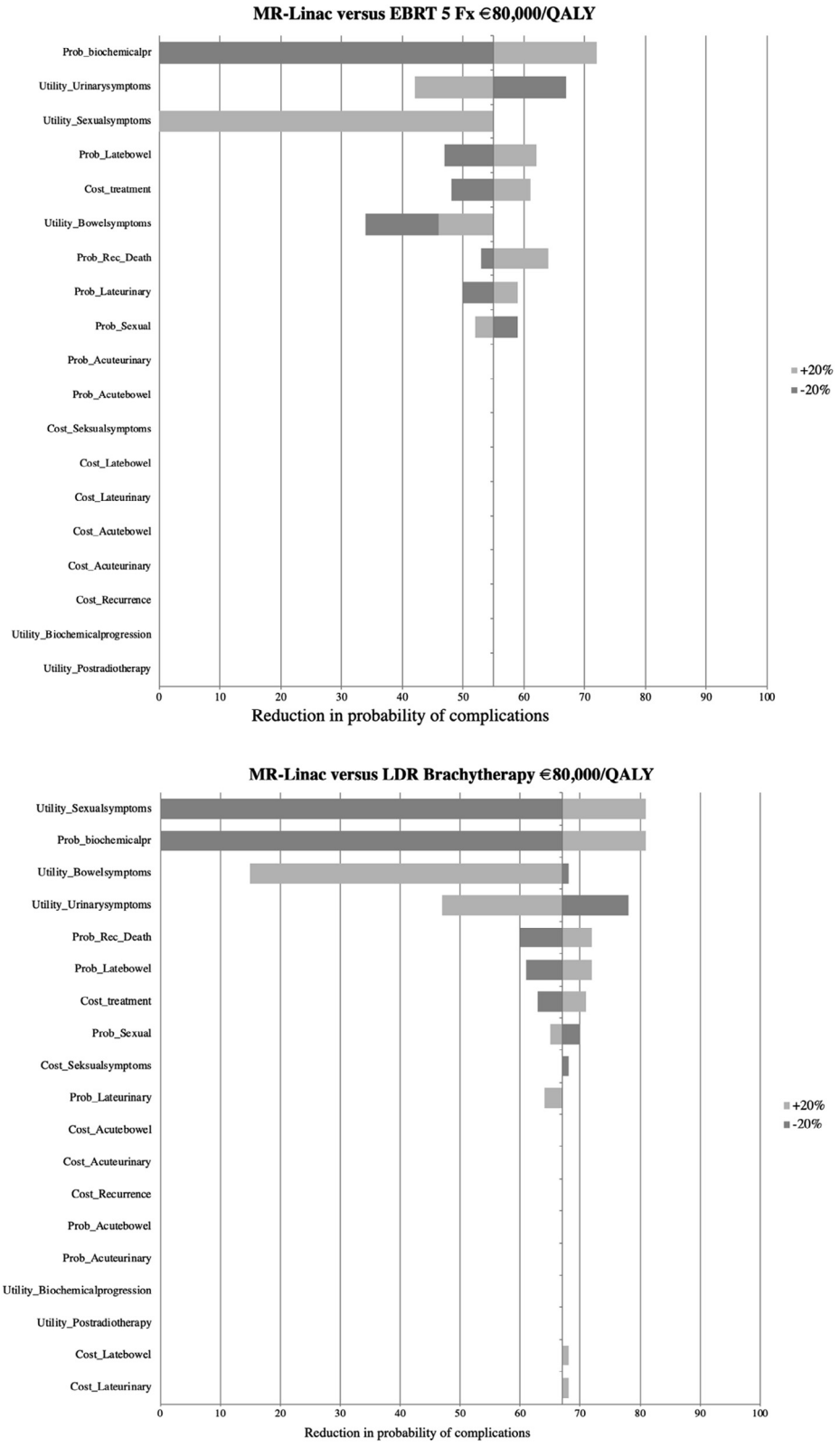

Fig. 3. Results of sensitivity analyses of MR-Linac versus (i) EBRT 5 fractions and (ii) LDR Brachytherapy. The variables are ordered with those with the largest impact on the top. In both comparisons, results are most sensitive to the probability of biochemical progression and the utility of urinary, bowel and sexual complications.

Conclusion

MR-Linac is found to be cost-effective compared to EBRT 20- and 39-fractions, hence no further reduction in complications is needed. More challenging scenarios exist for EBRT 5-fractions and LDR brachytherapy in which rates of complications or costs need to be reduced significantly to come to cost-effective outcomes. Cost-effectiveness outcomes are highly sensitive to biochemical progression and utilities of urinary, bowel and sexual complications. Outcomes should eventually be used as early

insight, investment choices and insight on the most essential parameters in prospective studies. A prospective cost-effectiveness analysis investigating empirical costs and effects is therefore needed to verify these outcomes and to evaluate added-value.

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Authors' contributions

Study design was developed by CH, GFF, JRNVZ and HMV. The literature search was primarily done by CH. Development of state transition model, data collection and analysis were done by CH. Data interpretation was performed by CH, GFF, JRNVZ, JPCG and HMV. CH prepared the first draft of figures and this manuscript. GFF, JRNVZ, BGLV, JPCG, HMV and DEG contributed and commented on the draft. All authors read and approved the final manuscript. CH has final responsibility for the decision to submit for publication.

Declaration of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare no personal conflicts of interest. Several MR-Linac scientific projects at the Division of Imaging and Oncology of University Medical Center Utrecht have been partly funded Elekta AB (Stockholm, Sweden) and Philips Medical Systems (Best, The Netherlands).

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Appendix A. Background of the model structure

Health states

Free of complications: Serves as the initial and continuing state for those who do not experience urinary, bowel and sexual complications as well as treatment-related morbidity, biochemical progression, cancer-specific mortality or overall mortality.

Urinary complications: Serves as the states for patients without biochemical progression, considers grade 2 and 3 side urinary complications.

Bowel complications: Serves as the states for patients without biochemical progression, considers grade 2 and 3 side bowel complications.

Biochemical progression: This state occurs from 5 year onwards. Biochemical progression is defined as increasing prostate specific antigen levels and is an indicator of disease progression (e.g., either local or metastasis to distant sites). We assume that there are no salvage options for patients who experience biochemical progression after primary treatment; these patients will be given continuous hormonal treatment only.

Sexual complications: Serves as the state for patients without biochemical progression, but with moderate-to-severe erectile dysfunction.

Death: General and disease-related mortality. Disease-related mortality serves as a worst-case end result of biochemical progression only. General mortality is based on the annual mortality of the Dutch population from the age of 65 year onwards [26].

Appendix B. Detailed costs of treatment modalities

Cost input	Cost (2019)	Volume	Mean	Source
MR-Linac 5 fractions				
Fraction	€1165	1/fraction	€5825	Schumacher et al. 2020
Travel costs	€126	1/ride	€630	Zorginstituut Nederland cost manual
Total:			€6455	
EBRT 5 fractions				
Fraction	€233	1/fraction	€1165	Peeters et al. 2010
Travel costs	€94	1/ride	€470	Zorginstituut Nederland cost manual
Total:			€1635	
EBRT 20 fractions				
Fraction	€233	1/fraction	€4660	Peeters et al. 2010
Travel costs	€94	1/ride	€1870	Zorginstituut Nederland cost manual
Total:			€6530	
EBRT 39 fractions				
Fraction	€233	1/fraction	€9090	Peeters et al. 2010
Travel costs	€94	1/ride	€3650	Zorginstituut Nederland cost manual
Total:			€12,740	
LDR brachytherapy				
Treatment	€4990	1×	€4490	Helou et al. 2017
Travel costs	€94	1/ride	€95	Zorginstituut Nederland cost manual
Total:			€4585	

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