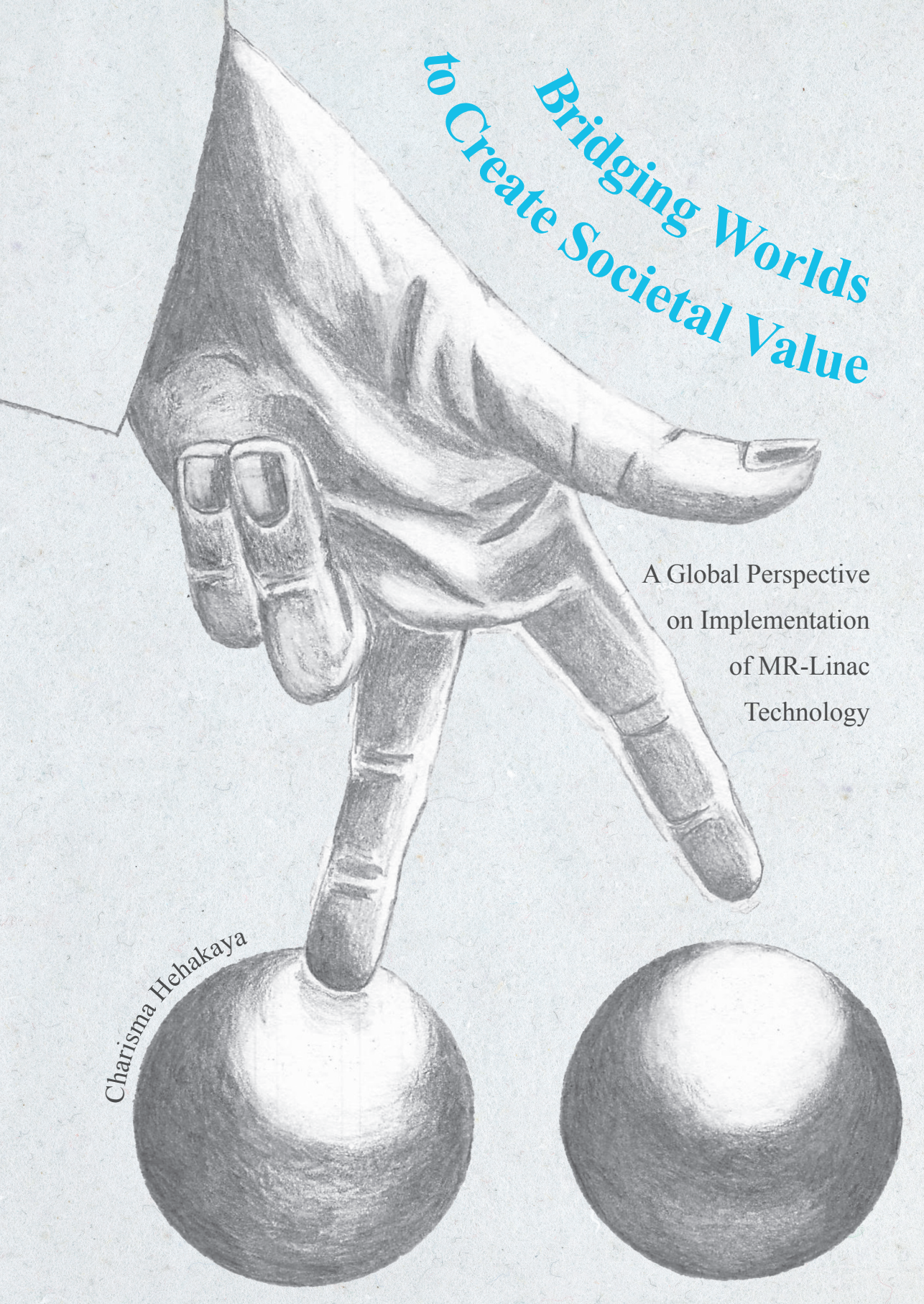
Bridging Worlds to Create Societal Value

A Global Perspective on Implementation of MR-Linac Technology



Charisma Hehakaya

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PhD thesis, Utrecht University, the Netherlands

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Cover: Charisma Hehakaya
Lay-out: Publiss | www.publiss.nl
Print: Ridderprint, Ridderkerk, the Netherlands (www.ridderprint.nl)
ISBN: 978-94-6483-089-7

Publication of this thesis was financially supported by the department of Radiation Oncology of the University Medical Center Utrecht, Chipsoft and Elekta B.V. The research described in this thesis was funded by the Netherlands Organization for Health Research and Development (ZonMw) via Innovative Medical Devices Initiative for Technology for Sustainable Healthcare (project number 104006004), Stichting de Drie Lichten and Nijbakker Morra Stichting.

Bridging worlds to create societal value: A global perspective on implementation of MR-Linac technology

Werelden verbinden om maatschappelijke waarde te creëren:
Een globaal perspectief op de implementatie
van MR-Linac technologie

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 13 juni 2023 des middags te 4.15 uur

door

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geboren op 29 mei 1992
te 's-Hertogenbosch

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TABLE OF CONTENTS

1

GENERAL INTRODUCTION AND THESIS OUTLINE

The increasing need to improve the quality of healthcare worldwide, together with profound scientific developments, leads to the emergence of convergent innovation [1–5]. Convergent innovation can be defined as a new solution-oriented development in which different scientific disciplines, functionalities or devices are combined in one single platform [2,6]. This results in a method with clinical, technical, economic, and social synergies for disease prevention, diagnosis, monitoring or therapy [7]. By doing so, distinct boundaries of medical interventions are integrated which target multiple interacting components, organizational aspects and dimensions of complexity [5,8]. This is why the potential value of implementing convergent innovation is not always straightforward and is not limited to clinical facets alone, but many hurdles – often scientific, technical, financial, social, and regulatory – must be overcome first [3].

Convergence of MRI and radiotherapy

An illustrative example of a convergent innovation is the 1.5 Tesla magnetic resonance (MR) imaging with a linear accelerator (Linac), MR-Linac, developed by the University Medical Center Utrecht (Utrecht, The Netherlands) in collaboration with Elekta AB (Stockholm, Sweden) and Philips (Best, The Netherlands) [9]. The MR-Linac (Unity) takes techniques from two separated clinical methods to create a new medical device that would not have resulted from the work of a single field alone.

A linear accelerator is used to deliver external beam radiotherapy for non-invasive local treatment of cancer. The full dose of radiotherapy is often divided into a number of smaller doses, so-called fractions. This is necessary for the recovery of healthy cells between fractions of treatment. The involvement of MR imaging enables strong magnetic fields and radio waves to produce detailed images of the inside of the body. The convergence of MR imaging with a linear accelerator therefore enables online and real-time, soft-tissue imaging and targeted MRI-guided radiotherapy (MRgRT) [10]. This allows accurate visualization of the tumor and healthy tissues and organs before, during and after treatment [2]. MRgRT thereby offers physicians enhanced control over radiotherapy delivery based on actual anatomical and functional information about the tumor and organs at risk.

MR-Linac promises versus today's reality

MRgRT enables physicians to adapt the treatment plan to the actual anatomy while the patient remains on the treatment table [11,12]. MRgRT also allows margin reduction and

subsequent dose escalation which may lead to a higher delivered radiation dose to the target in fewer sessions. This is called (ultra)hypofractionation, which enables a shorter overall treatment time [3,4]. For instance, five- and two-fractions MRgRT are gaining interest for the treatment of prostate cancer [15]. This can be beneficial since traditional external beam radiotherapy often varies from 20- to 39-fractions [16–18]. Theoretical promises for patients include improved targeting of the tumor, reduced harmful side effects, and improved quality of life [19–23]. MRgRT may also reduce the workload, treatment time and costs [12,24].

While there is little doubt in the minds of many radiation oncologists that the MR-Linac will improve treatment outcomes, technology implementation is accompanied by considerable uncertainty and risks. Theoretical benefits still need to be confirmed in clinical practice and solid proof of (cost-)effectiveness is still lacking [25,26]. Moreover, technology implementation requires high capital investments in equipment, logistics and quality assurance and training [7].

Implementation into routine care

Implementation of medical innovations without evidence of (cost-)effectiveness can increase healthcare costs without improving treatment quality [27,28]. Payers and policymakers are therefore becoming increasingly reluctant to approve and reimburse costly, unproven medical innovations [29]. Incorporating evidence and weighing trade-offs between potential benefits and harms of the new treatment compared to standard care, would support decision-making regarding implementation. For convergent innovations such as the MR-Linac technology, more factors might be important to assess in implementation.

Implementation of innovations in healthcare typically requires a dynamic non-stepwise process, including individual user (e.g., patient, physician), clinical, organizational, socio-cultural, economic, political and regulatory influences [31–33]. For convergent innovation, this process is more dynamic because of the need for integration of traditionally separated knowledge, competences, routines, techniques and potential jurisdictions [5]. For instance, MR-Linac is expected to disrupt some traditional ways of working, within and outside the radiation oncology department [12]. This can bring opportunities, but also challenges. To illustrate, the convergence of diagnostic radiology and radiotherapy may develop new treatment approaches which require updated clinical practice guidelines and new working tasks. Changes in the organization of care because

of technology implementation also call for financial considerations, collective learning and administrative renewal [36,37]. These changes can be hampered by the presence of autonomy and siloed cultures of clinical specialties [32,38].

MR-Linac implementation so far, has mainly been studied from a clinical and technological point of view [20,25,30], whereas a broader view is evidently needed. This thesis intents to broaden the discussion beyond the clinical and technical aspects of MR-Linac implementation among technology users such as radiation oncologists, physicists and radiation technologists. Technology users not only use medical innovations, but also play an important role in evaluating their implementation and assessing their outcomes early on.

Early health technology assessment

Early health technology assessment (early HTA) is useful for assessing organizational impact and identifying cost-effectiveness scenarios of new unproven medical technologies [40–42]. Early HTA can therefore identify worthwhile treatment strategies and facilitate useful insights to avoid setbacks for patients, care givers and payers [39]. This offers valid input for decision-making and reduces the chance of making wrong implementation decisions. A combination of qualitative and quantitative research methods is useful in early HTA.

Implementation of innovation is preferably explored together with all stakeholders at an early stage [43]. Qualitative studies and stakeholder interviews are useful to inventorize interests as well as needs of the field for implementation. For instance, interviews with technology users and healthcare insurers can provide timely insights into important implementation factors such as the required evidence package needed for reimbursement of medical innovations. Moreover, studying implementation transnationally is relevant since local healthcare standards, organizational procedures, professional routines, stakeholders, and legal and regulatory principles vary between different healthcare systems [44–46]. So stakeholder interviews can facilitate country-specific insights into MR-Linac implementation including potential opportunities and challenges.

Second, early health economic evaluations are useful to explore areas where new technologies have the potential to become a cost-effective alternative or addition to standard treatment and determine conditions that need to be met to achieve cost-effectiveness [47]. In these early evaluations, empirical data is lacking for costs and treatment outcomes. It is therefore necessary to make assumptions about costs and clinical effects, using best available sources [48]. In case of MR-Linac, early health

economic evaluations can identify scenarios where the MR-Linac is likely to be too costly or not incrementally effective enough to be cost-effective and guide further technological development towards more worthwhile tumor sites and treatment strategies [42,49]. Early health economic evaluations thus are also relevant since the development of MR-Linac continues and, hence, optimal treatment outcomes and cost-effective treatment strategies are still being explored.

Thesis aim and outline

This thesis focuses on the implementation and the early health economic evaluation of the MR-Linac. We combine qualitative and quantitative methods to explore the opportunities and challenges in implementing the MR-Linac into clinical care and investigate early cost-effectiveness scenarios for the treatment of low- and intermediate-risk localized prostate cancer. These insights can guide decision-making on MR-Linac implementation to a more informed approach.

Prostate cancer is selected as clinical focus in this thesis for several reasons [14,50]. Adaptive MRgRT is most likely to be of benefit for tumors that move between and during treatment, as is the case in prostate cancer [5–7]. Prostate cancer is the most common cancer in men worldwide [51,52] with around 13.500 new cases in the Netherlands every year [53]. Current treatments such as external beam radiotherapy, brachytherapy, and (robotic) surgery, interfere with quality of life and cause adverse effects such as erectile dysfunction and urinary and bowel symptoms [54]. MR-Linac has the potential to reduce treatment toxicity and increase quality of life for prostate cancer patients [22,55].

This thesis explores opportunities and challenges in implementation of MR-Linac in two healthcare systems through in-depth stakeholder interviews. **Chapter 2** focuses on the Netherlands which was the first country where 1.5T MR-Linac was introduced. The study of the Dutch early adopter experience could give insights into initial technology usage and the mandatory technology specifications to deliver MRgRT in routine care [20]. **Chapter 3** focuses on the United States (US), as multiple MR-Linac devices have been installed in the US. Moreover, the US healthcare system is more privatized compared to public healthcare systems such as those found in Europe like the Netherlands [56,57]. The study of these different contexts thus is appropriate to capture diverse implementation experiences in different healthcare systems. **Chapter 4** compares the findings from the previous two chapters and explores how MR-Linac implementation affects the organization of healthcare.

We also explore different early cost-effectiveness scenarios of MRgRT for the treatment of localized prostate cancer in two healthcare systems. **Chapter 5** focuses on five-fractions MRgRT in the Netherlands. **Chapter 6** focuses on two-fractions MRgRT in the United Kingdom. We use decision analytic modelling to identify the relative required reduction in complications in order for MRgRT to become cost-effective compared to standard care, and what the maximum costs of MRgRT are allowed to be.

Chapter 7 provides a summary of the work in this thesis. We end with recommendations for future implementation of complex medical technologies in **Chapter 8**.

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2

INTRODUCING THE MAGNETIC RESONANCE IMAGING LINEAR ACCELERATOR INTO ROUTINE CARE: PROBLEMS AND PROMISES IN THE NETHERLANDS

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Frontiers in Oncology (2020)

ABSTRACT

The new radiotherapy high field, 1.5 Tesla MRI-guided linear accelerator (MR-Linac) is being clinically introduced. Sensing and evaluating opportunities and barriers at an early stage will facilitate its eventual scale-up. This study investigates the opportunities and barriers to the implementation of MR-Linac into prostate cancer care based on 43 semi-structured interviews with Dutch oncology care professionals, hospital and division directors, patients, payers and industry. The analysis was guided by the Non-adoption, Abandonment, Scale-up, Spread and Sustainability framework of new medical technologies and services. Opportunities included: the acquirement of (1) advanced MRI-guided radiotherapy technology with (2) the potential for improved patient outcomes and (3) economic benefits, as well as (4) professional development and (5) a higher hospital quality profile. Barriers included: (1) technical complexities, (2) substantial staffing and structural investments, (3) the current lack of empirical evidence of clinical benefits, (4) professional silos and (5) the presence of patient referral patterns. While our study confirms the expected technical and clinical prospects from the literature, it also unlocks economic, organizational and socio-political challenges.

INTRODUCTION

The implementation of medical technology and services usually involves individual, organizational and environmental factors (1–4). All three are relevant to the introduction of MRI-guided linear accelerator (MR-Linac) systems: the 0.35 Tesla ViewRay MRIdian system and the 1.5 Tesla Elekta Unity system (5,6). Yet, their introduction into routine oncology care has mainly been reported from a technical and clinical perspective (7–10). In this study we will focus on the MR-Linac, recently developed by the University Medical Center Utrecht (Utrecht, The Netherlands) in collaboration with Elekta AB (Stockholm, Sweden) and Philips (Best, The Netherlands). This technology integrates a 1.5 Tesla MR-imaging scanner with a radiotherapy linear accelerator (9,11–15). This enables online adaptive radiotherapy delivery and diagnostic quality imaging simultaneously that allows the visualization of tumor and surrounding organs before, during and after treatment (9,12,16–19), with potentially higher treatment accuracy, the sparing of healthy tissue and the possibility of hypofractionation (providing the total dose in fewer treatment sessions). These features are expected to deliver real health benefits for patients including better tumor control, fewer side effects and a shorter treatment course (17,20–22). Since MR-Linac's CE approval in June 2018 and FDA approval in December 2018, the technology has been installed in institutions worldwide (23,24).

Despite the promising clinical and technological prospects, challenges remain. The use of MR-Linac requires high capital investments in equipment, logistics, quality assurance and complementary training (7), and evidence of superior patient outcomes (8). Implementing technical developments in cancer treatment may disrupt standard treatment practices, which call for financial considerations, collective learning and organizational renewal (25,26). Collective learning and organizational renewal can be hampered by hospital autonomy and by cultures of secrecy within specialties (2,3,27,28). These are potential bottlenecks that are seldom investigated in radiotherapy centers (29). While some attention has been given to potential implementation challenges, these aspects need untangling and a clearer understanding in order to maximize benefits and to avoid setbacks for patients and care givers (8,17,19,25,30).

This study aims to identify the opportunities and barriers for successful implementation of MR-Linac into prostate cancer care. The choice for focusing on prostate cancer is based on the following reasons. First, online adaptive radiotherapy is most likely to be of benefit for tumors that move between and during treatment (13,31), as is the case in prostate cancer (18,32). Prostate cancer, the most common cancer in men worldwide, does have

high survival rates (33,34). However, current treatments may interfere with quality of life: external beam radiotherapy, brachytherapy and even minimally invasive robotic procedures, cause adverse effects such as erectile dysfunction and urinary incontinence (33–35). MR-Linac minimizes uncertainties about the actual tumor's location, shape and the surrounding organs at risk, which may reduce adverse effects and in turn improve a patient's quality of life (9,11). Second, clinical interest in MRI-guided radiotherapy in prostate cancer management has been increasing in recent years (10,17,36), and understanding the dynamics of its implementation is timely.

MATERIALS AND METHODS

Design

We conducted a qualitative study including semi-structured interviews, an approach most appropriated to make sensitive issues and attitudes, opinions and experiences of individuals explicit (37). We used the Non-adoption, Abandonment, Scale-up, Spread and Sustainability (NASSS) framework of new healthcare technologies and services which is designed to explore determinants of success and failure of technology adoption in healthcare organizations. The NASSS framework considers seven domains: the condition or clinical indication, the technology to be implemented, the value proposition, the adopter system (patient, technology user and other staff), the organization, the wider institutional and social context, and organizational resilience and technology development over time (38) (Figure 1).

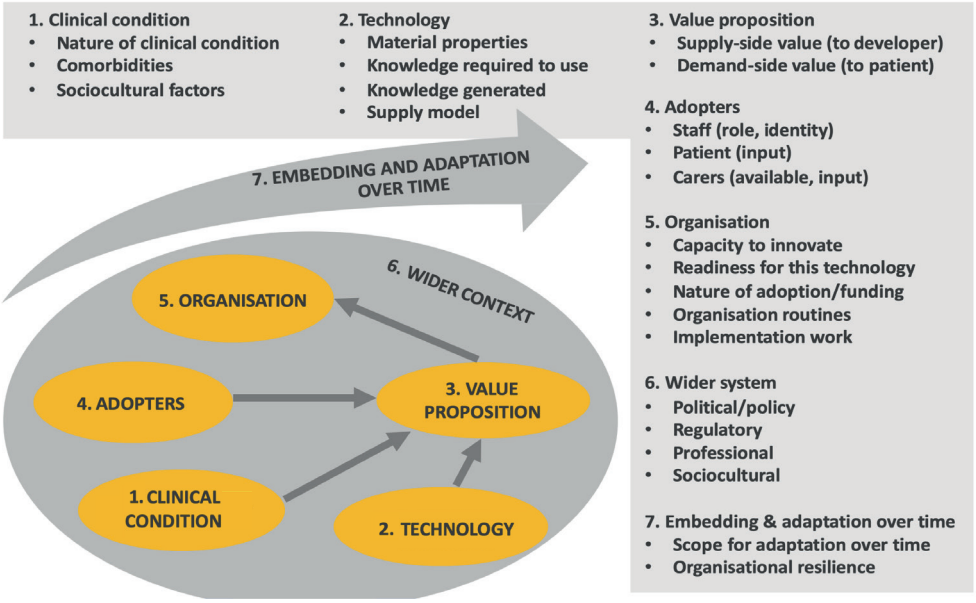


Figure 1. The NASSS framework operates in seven key domains: the clinical condition, technology to be adopted, value proposition, adopter system, organization, wider system and embedding and adaptation over time (Adapted from Greenhalgh et al.).

Recruitment

Respondents were recruited through purposive and snowball sampling using recommendations from initial respondents. We wanted to obtain a convenience sample of compelling roles among the populations of interest. Because implementing medical technologies and services requires a comprehensive multilevel consideration of individual, organizational and environmental influences (1–4), we attempt to select respondents at each of these levels of influence and based on their expertise. Therefore, we adopted a number of selection criteria:

1. Working at a hospital offering MR-Linac treatment; or
2. Providing other prostate cancer treatments (e.g., external beam radiotherapy, low- or high-dose-rate brachytherapy, proton beam therapy, robotic surgery, radiosurgery); or
3. Management experience relevant to the implementation and insurance coverage of new medical technologies or services; or

4. Stakeholders outside the hospital (e.g., patients, care insurers, manufacturing industry).

We included physicists, radiation oncologists, radiotherapy technologists and ICT staff, currently practicing MR-Linac (9). We also interviewed urologists (the referring physician in the Netherlands), radiologists and nuclear medicine physicians. Further, we included hospital directors, division and insurance managers. We included respondents from different hospitals, to limit selection bias. At the time of writing this article, only two hospitals offer Unity MR-Linac treatment in the Netherlands. This country is a suitable context, considering that it has been the first nation in which this technology has been introduced. At the contextual level, we included the perspectives of patients, care insurers and the executives of industries that hold MR-Linac's intellectual property rights. Our respondents, except those in industries, are located in the Netherlands.

Data collection

The research objective was explained in the invitation and at the start of each interview. The questionnaire is based on the interview questions of the NASSS framework and the first interviews (see Supplementary Materials). It included open-ended questions to explore each respondent's experience with and views on MR-Linac for prostate cancer treatment, including implementation opportunities and barriers. All interviews were conducted by one trained researcher and lasted approximately 45 minutes until saturation occurred and no new information appeared in the data. Interviews were conducted in person (N=35), by phone (N=5) or by Skype (N=3). All interviews were audio-recorded with the consent of the respondents and transcribed. Each respondent validated their transcript. Audio recordings and transcript of interviews are confidential and therefore not publicly available.

Table 1. Overview of roles and affiliations of respondents.

Respondent	Position	Seniority	Affiliation	Selection criteria	Additional roles	Method	Duration (min)
R1	Computer scientist	Senior	AMC1	1	Research on MR-Linac	In Person	43
R2	Manager Imaging & Oncology dep.	Senior	AMC1	3		In Person	47
R3	Head of Imaging & Oncology dep.	Full Professor	AMC1	3	Research on functional imaging	In Person	44
R4	Insurance commissioner	Senior	AMC1	3		In Person	25
R5	Insurance commissioner	Senior	AMC1	3		In Person	31
R6	Member Board of Directors	Full Professor	AMC1	3	Research on open Science	In Person	30
R7	Member Board of Directors	Senior	AMC1	3		In Person	44
R8	Member Board of Directors	Full Professor	MC1	3	Radiologist	In Person	45
R9	Nuclear medicine physician	Full Professor	AMC1	2	Board Member National Education Committee Nuclear Medicine	In Person	43
R10	Nuclear medicine physician	Senior	AMC2	2		In Person	41
R11	Radiologist	Senior	AMC1	2		In Person	42
R12	Radiologist	Senior	AMC1	2		In Person	40
R13	Radiation oncologist	Senior	AMC1	1, 2	Research on MR-Linac	In Person	37
R14	Radiation oncologist	Senior	AMC1	1, 2	Research on MR-Linac	In Person	41
R15	Radiation oncologist	Senior	AMC1	1, 2	Research on MR-Linac	In Person	43
R16	Radiation oncologist	Senior	AMC1	1, 2	Research on MR-Linac	In Person	45
R17	Radiation oncologist	Full Professor	AMC2	2, 3	Head of Radiation Oncology department, Research on MR-Linac, Board member European Society Radiotherapy & Oncology	In Person	46
R18	Radiation oncologist	Senior	AMC3	2	Head of Radiation Oncology department	Telephone	39
R19	Radiation oncologist	Senior	AMC4	2		In Person	45
R20	Radiation oncologist	Full Professor	AMC4	2, 3		In Person	48
R21	Radiation oncologist	Senior	MC2	2	Research on MR-Linac	In Person	41
R22	Radiotherapy technologist	Senior	AMC1	1, 2	Research on MR-Linac	In Person	43

Respondent	Position	Seniority	Affiliation	Selection criteria	Additional roles	Method	Duration (min)
R23	Radiotherapy technologist	Senior	AMC1	1, 2	Research on MR-Linac	In Person	39
R24	Radiotherapy technologist	Junior	AMC1	1, 2		In Person	42
R25	Radiotherapy technologist	Senior	MC2	1, 2		Telephone	46
R26	Radiotherapy technologist	Senior	AMC3	2		In Person	44
R27	Physicist	Full Professor	AMC1	1, 2, 3	Research on MR-Linac	In Person	53
R28	Physicist	Senior	AMC1	1, 2	Research on MR-Linac	In Person	41
R29	Physicist	Full Professor	AMC1	1, 2	Research on MR-Linac	In Person	45
R30	Physicist	Senior	AMC1	1, 2	Research on MR-Linac	In Person	44
R31	Physicist	Senior	AMC2	1, 2	Research on MR-Linac	Telephone	38
R32	Physicist	Full Professor	AMC2	2, 3	Manager Radiation Oncology department	In Person	41
R33	Physicist	Full Professor	AMC3	2		Online	39
R34	Physicist	Full Professor	MC2	1, 2	Research on MR-Linac	In Person	43
R35	Physicist	Senior	MC2	1, 2	Research on MR-Linac	In Person	47
R36	Urologist	Senior	AMC1	2		In Person	31
R37	Urologist	Senior	MC3	2		Telephone	29
R38	Urologist	Senior	AMC4	2	Head of Urology department	Telephone	40
R39	Patient representative		National patient organization	4		Telephone	31
R40	Healthcare insurer	Senior	Insurance company 1	4	Radiologist	Telephone	38
R41	Healthcare insurer	Senior	Insurance company 2	4		Telephone	42
R42	Managing Director	Senior	Manufacturing company	4		Online	46
R43	Managing Director	Senior	Manufacturing company	4		Online	33

AMC = Academic medical center, MC = (non-academic) medical center

Data analysis

Interview transcripts were analysed in NVivo software. We first applied open coding based on the research objective. We then applied axial coding, systematically identifying areas of interest based on the NASSS framework. This iterative step involved repetitions aimed at revising primary codes. We triangulated responses across different respondents and subsequently identified the opportunities and barriers. Resulted codes were validated by a second reviewer. We regularly discussed whether the empirical data matched the NASSS framework, ensuring that results were correctly classified within their domain. To include variation in findings and increase construct validity, we interviewed more than one person per profession and also considered perspectives from various hospitals.

RESULTS

We conducted 43 interviews with professionals in MRI-guided radiotherapy as well as other prostate cancer treatments, hospital and department directors, insurance commissioners, and external stakeholders between November 2018 and March 2019 (see Table 1). Hospital respondents work in four academic and three non-academic Dutch hospitals, of which two hospitals installed MR-Linac and one hospital ViewRay MRIdian. Five opportunities and five barriers to the implementation of MR-Linac have been identified (see Figure 2). We first present the opportunities, followed by the barriers according to the frequency stated by the respondents.

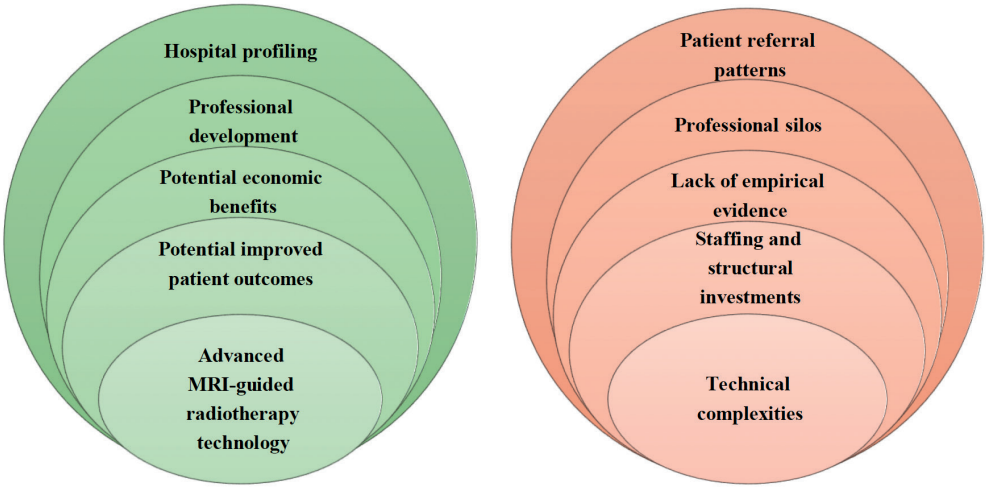


Figure 2. Overview of opportunities and challenges.

OPPORTUNITIES TO MR-LINAC IMPLEMENTATION FOR PROSTATE CANCER

Our respondents revealed five opportunities to MR-Linac implementation for prostate cancer: (1) advanced MRI-guided radiotherapy technology, (2) potential improvement in patient outcomes, (3) potential economic benefits, (4) professional development and (5) hospital profiling. Figure 3 shows the percentages of the interview cohort who discussed the opportunities, by main theme and subtheme. Appendix B provides an overview of the respondents referencing opportunities.

Advanced MRI-guided radiotherapy technology

Given the increasing demand in radiotherapy for advanced image-guidance and adaptive treatments subsequently, the use of MRI during radiotherapy is perceived as an inevitable follow-on advancement in this field. The opportunity of real-time diagnostic-strength 1.5 Tesla MRI-imaging that enables better soft tissue visualization; daily on-table adaptation to anatomical changes; actual adaptive treatment planning; hypofractionation and evaluation of tumor response during the course of radiotherapy. Further, actual anatomical and functional information of the prostate tumor and greater confidence in avoiding organs at risk during treatment is perceived as very promising, allowing more accurate, targeted treatment and avoiding radiation of healthy tissue. According to current technology users, these prospects promise new treatment avenues in radiation oncology as well as in related medical disciplines.

Potential improved patient outcomes

Prostate cancer is a well-characterized disease with effective treatment modalities. However, the potential adverse effects of present treatments are substantial and can interfere with the patient's quality of life; this remains a key target in present treatment development. Radiotherapy practitioners and members of hospital management expect MR-Linac to solve this issue and to yield improved patient outcomes. The majority of respondents mentioned improved patient comfort as main benefit resulting from: (1) possibly fewer adverse effects, (2) possibly improved tumor control, (3) the non-invasive procedure; the implantation of gold fiducial markers within the prostate is no longer necessary for position verification, and (4) hypofractionation allows prostate cancer treatment in fewer hospital visits and may shorten waiting lists. For example, the current standard is to give prostate radiotherapy in 20 fractions and hypofractionation has the potential to perform to allow completion of the entire treatment in only 2-5 times.

Potential economic benefits

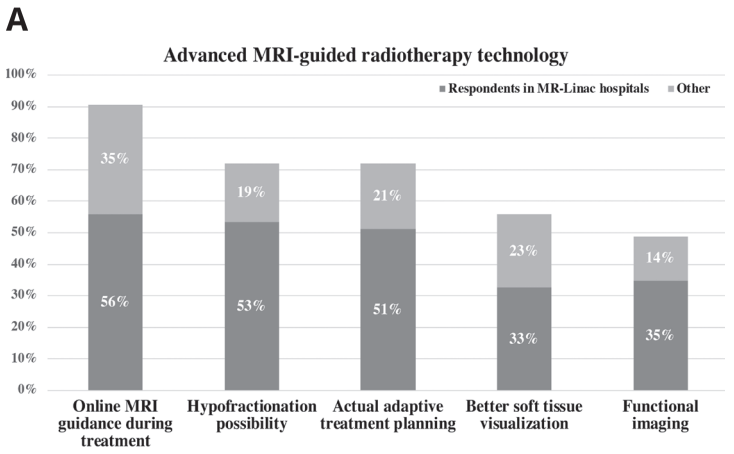
In view of the current, unsustainable growth in medical expenditures, the present-day value of new treatments will require an improvement in both treatment quality and cost reduction. According several radiotherapy professionals MR-Linac may offer quality and efficiency gains. First, both the preparation of the treatment plan as well as the execution takes place on the same device. Second, digital developments, such as deep learning, may allow operational benefits: automation processes during treatment (e.g., automatic contouring of tumor and organs at risk) to reduce staffing needs and waiting times. Ultimately, improved efficiency, together with fewer treatment sessions, fewer hospital visits, potentially fewer adverse effects and lower direct in-hospital costs such as anesthesia provision or indirect care costs (e.g., treatment of adverse effects and transport costs) can reduce overall costs.

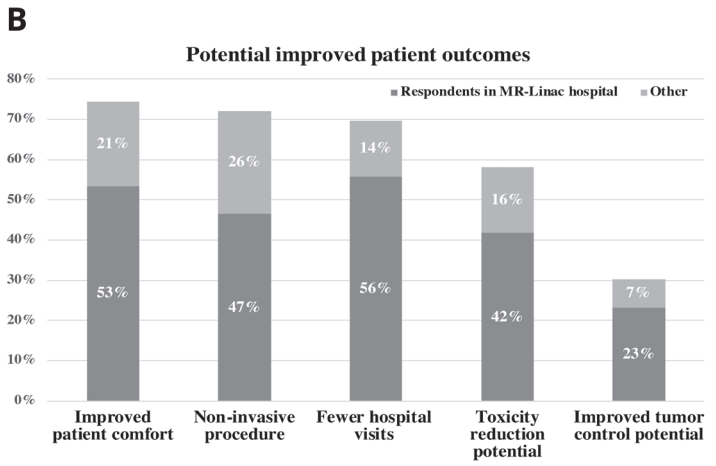
Professional development

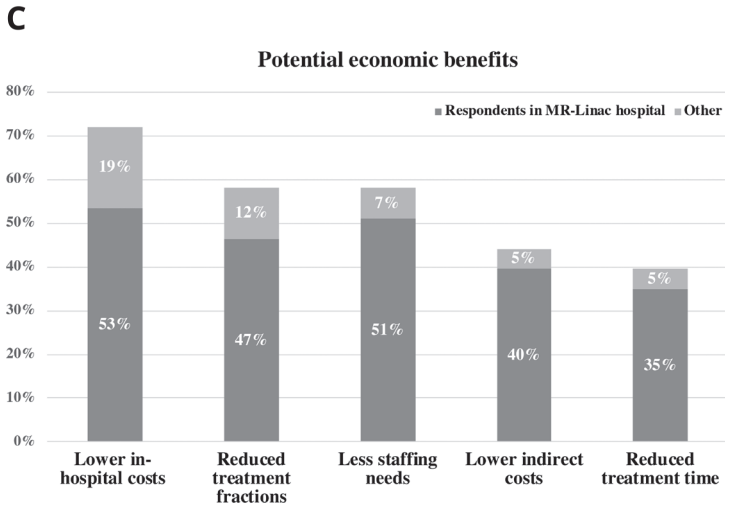
Implementing MR-Linac allows room for professional development and multidisciplinary learning. First, users experience an increased communication and collaboration across radiation oncology and imaging specialties (e.g., for the development of scanning protocols on MR-Linac). In most hospitals diagnostics and treatment are performed by different groups and the interaction between them is therefore limited. Second, the required knowledge of both MR-imaging and radiotherapy integrates different competences and expertise. As consequence, MR-Linac users may be attracted by the development and use of new knowledge and competences and the redevelopment of tasks and responsibilities. Third, radiotherapy technologists als reported their potential increased autonomy and involvement in decisions. They would have more responsibility like the maintenance of MRI protocols and active safeguarding of radiation requirements for target volume and organs at risk. The empowerment of employees fosters a better workplace culture.

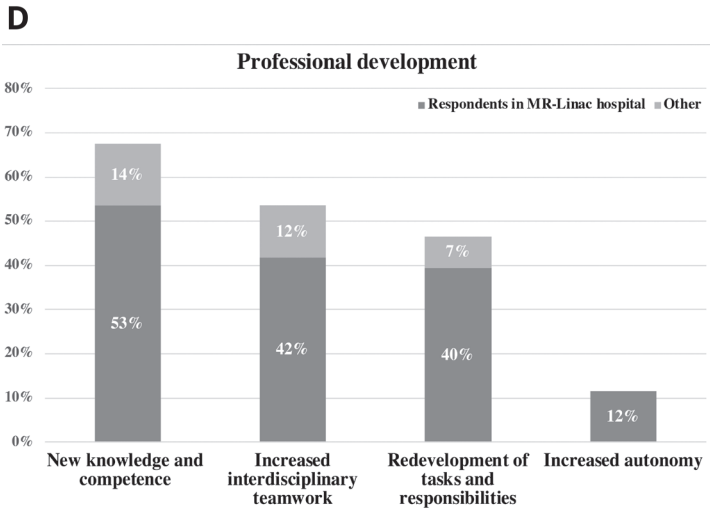
Hospital profiling

The implementation of MR-Linac also offers hospitals a way to profile themselves as innovative; providing potentially high-quality care. They also expect that hospitals implement MR-Linac to keep up with recent developments in radiation oncology and attract patients accordingly. According to the patient representative and several professionals, the target population is generally aware of the treatment modalities and prefers MRI-guided treatment. This could increase patient referral to the radiotherapy department and related medical specialties. Implementing MR-Linac could therefore provide hospitals a competitive advantage.


A
Advanced MRI-guided radiotherapy technology
Respondents in MR-Linac hospitals
Other
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
35%
19%
21%
23%
14%
56%
53%
51%
33%
35%
Online MRI guidance during treatment
Hypofractionation possibility
Actual adaptive treatment planning
Better soft tissue visualization
Functional imaging


B
Potential improved patient outcomes
Respondents in MR-Linac hospital
Other
80%
70%
60%
50%
40%
30%
20%
10%
0%
21%
26%
14%
16%
7%
53%
47%
56%
42%
23%
Improved patient comfort
Non-invasive procedure
Fewer hospital visits
Toxicity reduction potential
Improved tumor control potential


C
Potential economic benefits
Respondents in MR-Linac hospital
Other
80%
70%
60%
50%
40%
30%
20%
10%
0%
19%
12%
7%
5%
5%
53%
47%
51%
40%
35%
Lower in-hospital costs
Reduced treatment fractions
Less staffing needs
Lower indirect costs
Reduced treatment time


D
Professional development
Respondents in MR-Linac hospital
Other
80%
70%
60%
50%
40%
30%
20%
10%
0%
14%
12%
7%
53%
42%
40%
12%
New knowledge and competence
Increased interdisciplinary teamwork
Redevelopment of tasks and responsibilities
Increased autonomy

E

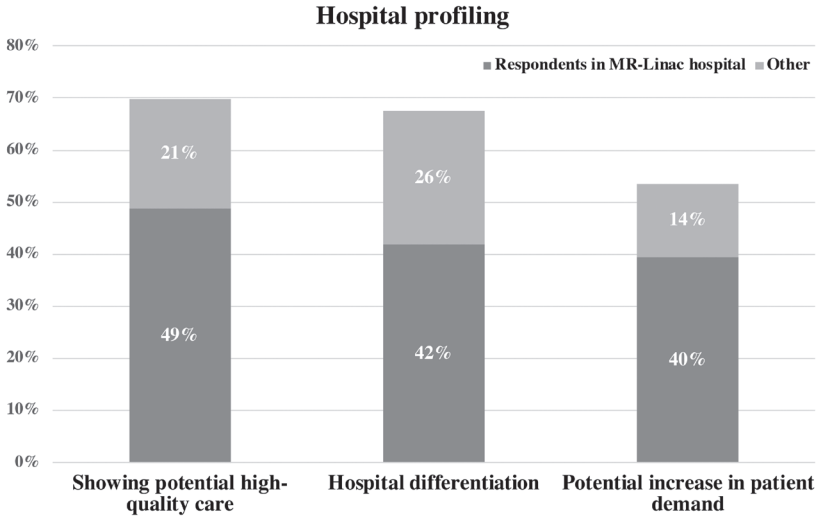


Figure 3. Percentages of the interview cohort who discussed opportunities to the implementation of MR-Linac into prostate cancer care, by main theme and subtheme. (A) Advanced MRI-guided radiotherapy technology, (B) potential improved patient outcomes, (C) potential economic benefits, (D) professional development, and (E) hospital profiling.

BARRIERS TO MR-LINAC IMPLEMENTATION FOR PROSTATE CANCER

Our respondents revealed five main barriers to MR-Linac implementation for prostate cancer: (1) technical complexities, (2) staffing and structural investments, (3) the lack of empirical evidence of clinical benefits, (4) professional silos, and (3) the presence of patient referral patterns. Figure 4 shows the percentages of the interview cohort who discussed the barriers, by main theme and subtheme. Appendix C provides an overview of the respondents referencing barriers.

Technical complexities

The involvement of MRI in radiotherapy is expected to transform current radiation oncology practice in terms of target identification, tumor response assessment, treatment planning and delivery, quality assurance and staffing. MR-Linac's ultimate impact on the current radiation oncology development is not yet known considering its continuous development, which largely depends on software upgrades rather than hardware upgrades. The technology's output is vulnerable to the interpretations of individual practitioners and may associate with inter- and intra-variability in treatment procedure, which in turn could affect clinical outcomes. Hence, the absence of the conventional security of the traditional linear accelerator necessitates the presence of experienced staff. This, together with continuing software developments, requires users to anticipate an ongoing learning curve.

In practice, MR-Linac's value is limited by software challenges in real-time tumor tracking during radiation. One treatment session is relatively also longer compared to conventional external beam radiotherapy, and this longer treatment duration could be a potential barrier for the patient. Each treatment lasts approximately 45 minutes, which is three to four times longer than conventional external beam radiotherapy (22).

Substantial staffing and structural investments

The required MRI competence, knowledge and the need for on-the-spot decision making were at the same time also seen as a challenge. For example, a radiation oncologist reported that brachytherapy practitioners are more used in making decisions on the spot than those involved in conventional external beam radiotherapy only. Adequate training programs are therefore a prerequisite to ensure that MR-Linac is used effectively and that MRI is safe for both patients and users. Further, several respondents also mentioned

the need to expand the responsibilities of radiotherapy technologists to reduce the presence of the radiation oncologist and physicist during treatment and staffing costs subsequently. Although radiation technologists could bear more responsibility, other concerns are their limited availability and that existing Dutch policy does not allow therapists to approve treatment plans.

Another perceived barrier is the substantial structural investments required: today's radiotherapy centers often lack the needed combination of MR-imaging and radiation facilities. To illustrate, a single MR-Linac costs 10 million euros without the requisite infrastructure, such as MRI compatibility, MRI safety, clinical workflow and its accompanying software development, quality assurance and the development of protocols, roles and responsibilities. Early adopters are therefore well financed medical research centers with MR-imaging expertise and facilities.

Lack of empirical evidence of clinical benefits

Despite promising theoretical benefits, clinical value remains undocumented and the patient categories that will most benefit remain unclear. For present prostate radiotherapy, there is some room for improvement in terms of adverse effects and patient comfort. However, some respondents doubted the actual reduction in toxicity and clinical added-value. Also, respondents doubted whether hypofractionation would actually compensate for the increased cost because of more expensive technology, increased treatment time per fraction and organizational investments (e.g. the requirement of more highly trained staff). Further, few respondents questioned the clinical added-value of MR-Linac compared to ViewRay MRIdian as well as other potential emerging techniques in prostate cancer treatment (e.g., CT-based adaptive radiotherapy).

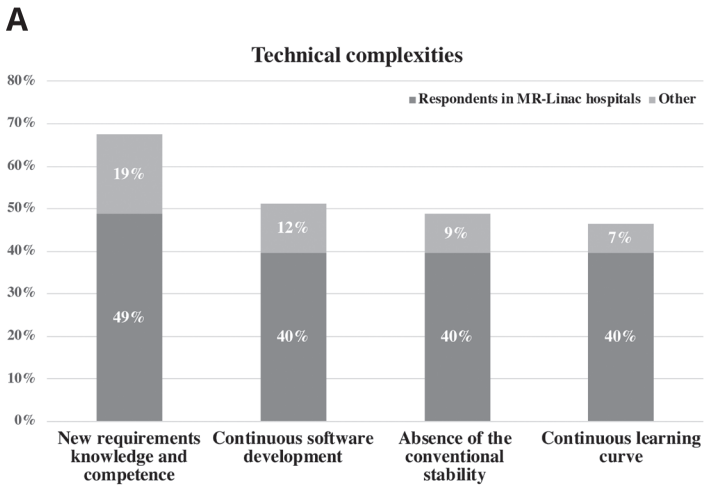
The present lack of empirical evidence also explains MR-Linac's lack of insurance coverage. Consequently, this can hamper real savings for hospitals and care insurers, as the potential reduction in treatment costs cannot be achieved. Further, the provision of treatment with unproven efficacy and safety to the patient may also lead to ethical discussions. High-quality randomized control trials are imperative to compare the value of MR-Linac with alternative treatments: preferably with comparable outcomes across different centers. A multi-center clinical evaluation would also hasten the recruitment of patients needed. Paradoxically, our respondents reported the lack of clinical evidence hindering successful implementation, while also mentioning the need to install the technology in a clinical environment for empirical evaluation.

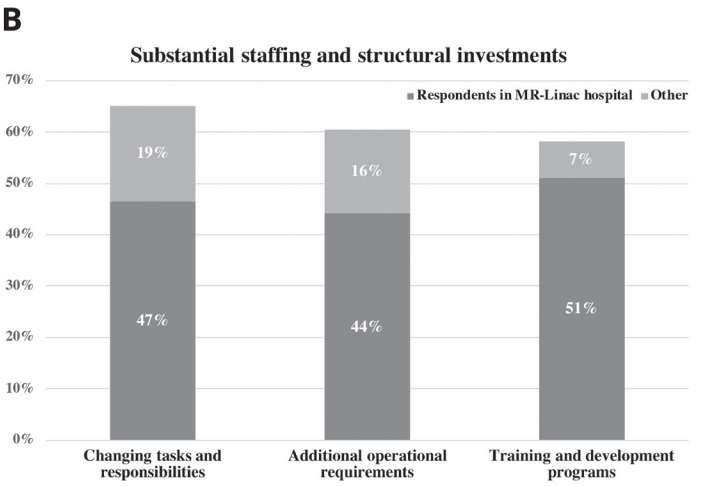
Professional silos

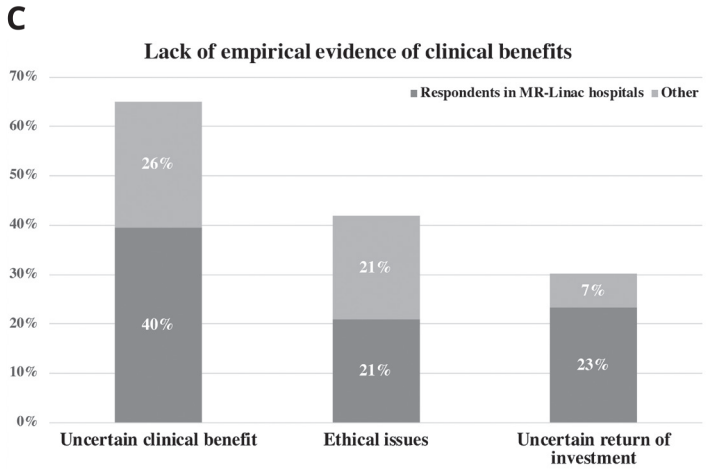
Amongst the redevelopment of tasks and responsibilities, practicing MR-Linac can threaten users' professional identity. Several radiotherapy professionals reported the potential conservative behavior and resistance as response to delegate tasks and change daily practice. Another perceived barrier is the publicity pressure exerted upon medical research centers which may hamper knowledge exchange and open communication about MR-Linac between hospitals. The political climate can hinder effective multicenter collaboration within and across hospitals, and the technology's further development. These challenges relate to the silo mentality and conservative culture that often prevails in hospitals.

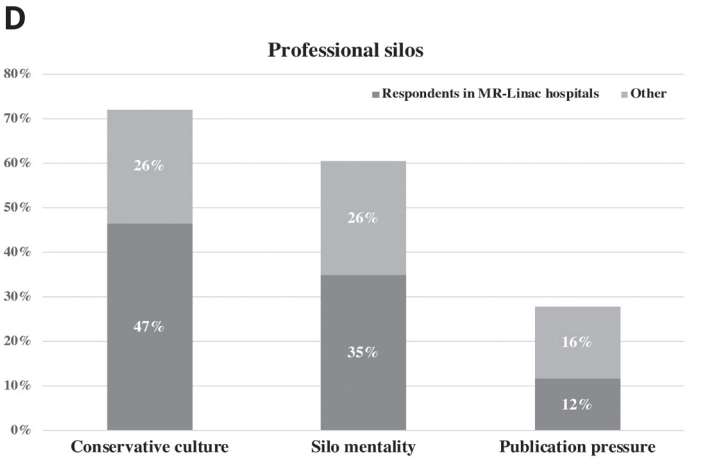
Patient referral patterns

Finally, introducing MR-Linac into routine care could raise patient referral discussions among specialties where patient demand may be compromised. The relationship between radiation oncology and surgery can be complementary, but also be competitive (26). In the Dutch prostate cancer care, urologists play an important role in patient access to MR-Linac as they discuss the treatment modalities with the patient. Likewise, radiotherapy centers offering MR-Linac may also be a perceived threat to hospitals that do not offer this technology, and hence would resist patient referral to this treatment.


A
Technical complexities
Respondents in MR-Linac hospitals
Other
80%
70%
60%
50%
40%
30%
20%
10%
0%
19%
49%
12%
40%
9%
40%
7%
40%
New requirements knowledge and competence
Continuous software development
Absence of the conventional stability
Continuous learning curve


B
Substantial staffing and structural investments
Respondents in MR-Linac hospital
Other
70%
60%
50%
40%
30%
20%
10%
0%
19%
47%
16%
44%
7%
51%
Changing tasks and responsibilities
Additional operational requirements
Training and development programs


C
Lack of empirical evidence of clinical benefits
Respondents in MR-Linac hospitals
Other
70%
60%
50%
40%
30%
20%
10%
0%
26%
40%
21%
21%
7%
23%
Uncertain clinical benefit
Ethical issues
Uncertain return of investment


D
Professional silos
Respondents in MR-Linac hospitals
Other
80%
70%
60%
50%
40%
30%
20%
10%
0%
26%
47%
26%
35%
16%
12%
Conservative culture
Silo mentality
Publication pressure

E

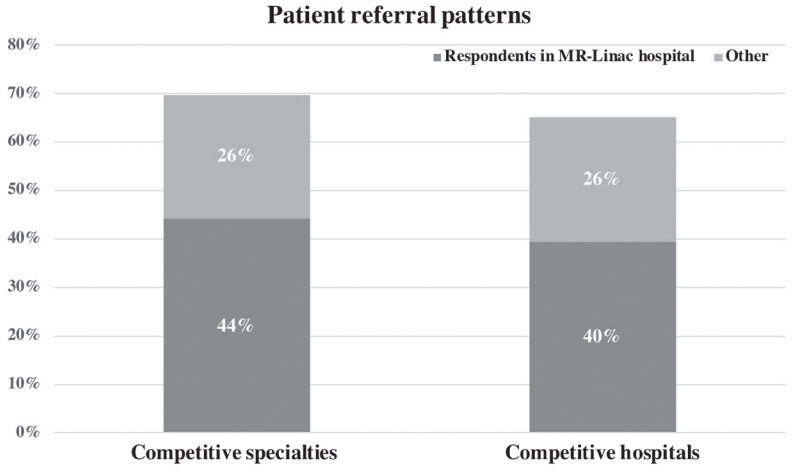


Figure 4. Percentages of the interview cohort who discussed barriers to the implementation of MR-Linac into prostate cancer care, by main theme and subtheme. (A) Technical complexities, (B) substantial staffing and structural investments, (C) Lack of empirical evidence of clinical benefits, (D) professional silos, and (E) patient referral patterns.

DISCUSSION AND IMPLICATIONS FOR PRACTICE AND FUTURE RESEARCH

Our findings help radiation oncology departments determining focus areas in their strategy for successful MR-Linac implementation into prostate cancer care. Consistent with prior research, MR-Linac users expect to benefit from advanced MRI-guided radiation technology with online adaptive treatment and response assessment that may potentially improve patient outcomes and identify new treatment opportunities (7,8,10,19,40). The possibility of prostate hypofractionation promises improved treatment and economic benefits (17,20,41–43). Users boost their hospital profile and professional development, irrespective of radiation oncologists, technologists and physicists (7,8,25,44,45). Our study also confirms the need to generate clinical evidence, while dealing with technical complexities and substantial staffing and structural investments (7). However, simply addressing these barriers is not enough: successful implementation also raises economic, organizational and socio-political concerns embedded in the presence of patient referral patterns and professional silos. These concerns are understudied in the current efforts on MR-Linac implementation into routine prostate cancer care.

Many respondents perceive MR-Linac as a complex innovation with a high implementation burden: its multidisciplinary nature disrupts the traditional barrier between radiation oncology and diagnostic radiology (7,10,26) which practically justifies all barriers. The involvement of MRI in radiation oncology transforms current practices either within and outside the radiation oncology department (7). Users are clearly concerned with substantial structural and staffing investments, established determinants in new technology and service implementation in healthcare (21,53). The substantial investments are also explained by the technical complexities inherent in MR-Linac. Further, our respondents have identified concerns about software deficiencies and the relative longer treatment fractions. Technological development should focus on improving workflow and the automation of both imaging and treatment (12,36,48).

MR-Linac's technical character has a major impact on staffing roles, which can lead to both efficiency improvements and professional identity threats. The ongoing technology development together with the acquirement of new skills (e.g., MRI competence, on-the-spot decision-making) illustrate the need for users to anticipate new learnings and responsibilities. However, the transformation of existing staff roles is not easy and is perceived as more than just learning how to use a new technology. This would require acceptance of changes in professional identity and autonomy as well as increased

communication across disciplinary boundaries. Moreover, current staffing policies in radiation oncology impede the reallocation of responsibilities for radiotherapy technologists. Technology users should therefore invest in workplace training and development with supporting staffing policies. Radiotherapy education will have to change to prepare physicists, radiation oncologists and technologists on the technical developments of MR-Linac. Further impact studies can focus on the professional development of users and the right staff policy to ensure a sustainable use of MR-Linac.

The reallocation of staffing is made more difficult by the presence of professional silos. Interestingly, in prostate cancer and cancer treatment in general, communication and cooperation between different disciplines tangled have already been proposed as prerequisites in effective cancer care (49–52), however, these features are still being raised as potential hindrances in MR-Linac implementation. Professional silos can be expressed by the presence of specialisms and related conservative behavior, a common challenging determinant in changing existing practices in hospitals (27), which also applies here. This also impedes the smooth collaboration and integration of diagnostic imaging and radiotherapy.

Another barrier is patient referral patterns. Safeguarding patients' access to MR-Linac requires participation of radiotherapy professionals as well as referring physicians (the urologist in the context of the Netherlands). Ultimately, successful implementation would therefore require active support and participation from hospital executives, and alignment between departments (radiotherapy and urology. The required communication and collaboration strengthen horizontal connections between different disciplines (e.g., radiation oncology and imaging), but also vertical connections inside (e.g., between radiotherapy technologist and radiation oncologist) and outside the radiotherapy department.

Future efforts should generate clinical evidence to prove expectations and justify return on investment concerns, an indispensable determinant in technology implementation which has been given greater emphasis in the new European Medical Device Regulation since May 2020 (53,54). Evaluation of an evolving technology such as MR-Linac is very difficult (55). Therefore, the international MR-Linac Consortium (9) has set up a prospective registry to include patients treated on MR-Linac in seven large institutions (MOMENTUM registry). Here, patients provide informed consent for the use of their technical (imaging) and clinical data for academic and clinical research as well as response assessment. Costs and quality of life data will be collected as well, to identify cost-effective MR-Linac

treatment strategies compared to alternative treatments. This is particularly useful in the field of prostate cancer, where many treatment modalities with comparable outcomes, but with different costs are available (56). Further MR-Linac impact studies can also provide insights into its effects on prostate cancer treatment allocation and hospital infrastructure.

The lack of clinical evidence also causes gaps in insurance coverage. This, together with the substantial investments, creates a high implementation burden and uncertainty for potential MR-Linac users and payers. Interestingly, this has not prevented radiation oncology departments from implementing the technology. The increasing belief in image-guided technologies without proven results to profile users with state-of-the-art treatments and high quality care also applies to MR-Linac (8,25). Despite the mutual scepticism among fellow professionals and health insurers about the clinical added-value of MR-Linac, collaboration between them facilitates technology users to meet requirements in treatment evaluation for insurance coverage.

Our study provides the first multifaceted assessment of opportunities and barriers in MR-Linac implementation for prostate cancer including perspectives from professionals, hospital and division directors, patients, payers and industry. Interviews with early adopters revealed hitherto unanticipated implementation challenges (29). The value of qualitative research is to explore phenomena in-depth and to question respondents about their relevant knowledge, opinions and experience. Hence, generalizability of our findings to other contexts has to be carefully considered. Future efforts can determine how country-specific therapeutic standards, political and social contexts influence the implementation activities. Whereas this study focuses on prostate cancer, the operational and organizational prospects discussed by respondents are likely to be valid for the implementation of MR-Linac for other tumor indications as well. However, a comprehensive comparison between MR-Linac and other MR-Linac systems (e.g., MRIdian of ViewRay (6)) as well as emerging radiotherapy techniques and present prostate cancer treatments goes beyond the scope of this paper.

CONCLUSION

Given the rapid development of MR-Linac, research into factors that stimulate or hamper its local implementation, is needed, as the first step to understand its long-term impact. Our findings define the main opportunities and barriers for successful MR-Linac implementation into routine care. We raise issues that are known in the field but not

openly discussed in current literature on MR-Linac implementation. The discussion of the topics that emerge from the interviews leads to reflection and learning, but also to new connections in the MR-Linac implementation and the organization of care. Four fundamental conclusions can be given:

- Implementation of MR-Linac not only considers technical and clinical issues, but also economic, organizational and socio-political challenges.
- MR-Linac implementation is expected to affect present prostate cancer care within and outside the radiation oncology department as well as hospital culture and identity of professionals.
- Involvement of the referring physician is crucial in successfully implementing MR-Linac into routine prostate cancer care.
- Clinical evaluation supported by patients, radiation oncology professionals, referring physicians and payers has to justify MR-Linac's perceived potential and substantial investments.

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SUPPLEMENTARY MATERIALS

Appendix A: Questionnaire based on NASSS framework and initial interviews.

	Domains and questions from NASSS framework		Additional questions based on first interviews
	1. Condition		
A.	What is the nature of the condition?	D.	What are recent trends in the treatment regimen?
B.	What are the relevant sociocultural factors?		
C.	What are the relevant comorbidities?		
	2. Technology		
A.	What are the key features of the technology?	D.	What is the current status of the technology development?
B.	What knowledge and skills are required to use the technology?	E.	What are potential condition-specific challenges for the technology?
C.	What is the technology supply model?	F.	Who owns the intellectual property of the technology?
	3. Value proposition		
A.	What is the business case for the technology from the supply side?	C.	What are intrinsic and extrinsic motivations to use this technology?
B.	What are its desirability, efficacy, safety and cost-effectiveness from the demand-side?	D.	What are the requirements to prove the added value of this technology?
		E.	In which areas does the technology may have an adverse effect?
	4. Adopter system		
A.	What changes in staff roles, practices and identities are implied?	D.	Which professions are vital in the introduction of this technology and what are their roles? *[e.g. referring physicians]*
B.	What is expected of the patient, is this achievable and accepted from them?	E.	To what extent do relevant professions interact with each other when it comes to technology implementation?
C.	What is assumed about the extended network of lay carers?	F.	Which ways improve the interactions between relevant professions when it comes to technology adoption?
	5. Organization		
A.	What is the organization's capacity to innovate?	F.	Which intra-organizational discussions will be needed for technology implementation and with whom?
B.	How ready is the organization for this technology-supported change?	G.	Which inter-organizational discussions will be needed for technology implementation and with whom?
C.	How easy will the adoption and funding decision be?		
D.	What changes will be needed in team interactions and routines?		
E.	What work is involved in the implementation and who will do it?		
	6. Wider system		
A.	What is the political, economic, regulatory, professional, sociocultural context for technology rollout?	B.	What is the treatment context for technology rollout?
	7. Organizational resilience and technology development over time		
A.	How much scope is there for adapting and coevolving the technology over time?	C.	Which steps can be taken to improve technology implementation?
B.	How resilient is the organization to handling critical events and adapting to unforeseen eventualities?		

Appendix B: Frequency of respondents who discussed opportunities to the implementation of MR-Linac into prostate cancer care, by main theme and subtheme.

Opportunities	Total	Respondent ID, following Table 1
Advanced MRI-guided radiotherapy technology		
Online MRI guidance during treatment	39	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 33, 34, 35, 36, 37, 39, 42, 43
Hypofractionation possibility	31	1, 2, 3, 6, 7, 8, 9, 11, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 42, 43
Actual adaptive treatment planning	31	1, 2, 3, 4, 8, 9, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 33, 34, 35, 39, 42, 43
Better soft tissue visualization	24	9, 11,12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 34, 35, 36, 39, 42, 43
Functional imaging	21	1, 11, 13, 14, 15, 16, 17, 20, 21, 22, 23, 27, 28, 29, 30, 31, 33, 34, 35, 42, 43
Potential improved patient outcomes		
Improved patient comfort	32	1, 2, 3, 6, 7, 8, 9, 11, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 39, 42, 43
Non-invasive procedure	31	2, 3, 7, 8, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 33, 34, 35, 36, 37, 38, 39, 42, 43
Fewer hospital visits	30	1, 2, 3, 4, 6, 7, 8, 11, 13, 14, 15, 16, 17, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 42, 43
Toxicity reduction potential	25	2, 3, 6, 7, 8, 13, 14, 16, 17, 20, 21, 22, 23, 25, 27, 28, 29, 31, 32, 33, 34, 35, 39, 42, 43
Improved tumor control potential	13	6, 7, 13, 16, 17, 21, 27, 28, 29, 34, 35, 39, 42, 43
Potential economic benefits		
Lower in-hospital costs	31	2, 3, 4, 6, 7, 8, 9, 11, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 42, 43
Reduced treatment fractions	25	1, 2, 3, 4, 6, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 27, 28, 29, 30, 31, 33, 34, 35, 42, 43
Less staffing needs	25	2, 3, 4, 6, 7, 13, 14, 15, 16, 17, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 33, 34, 35, 42, 43
Lower indirect costs	19	2, 3, 6, 13, 14, 15, 16, 17, 21, 22, 23, 27, 28, 29, 30, 31, 34, 42, 43
Reduced treatment time	17	1, 13, 14, 15, 17, 21, 22, 23, 27, 28, 29, 30, 31, 34, 42, 43
Professional development		
New knowledge and competence	29	1, 2, 3, 6, 11, 12, 13, 14, 15, 16, 17, 18, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 42, 43
Redevelopment of tasks and responsibilities	23	13, 14, 15, 16, 17, 18, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 42, 43
Increased interdisciplinary teamwork	20	1, 2, 3, 6, 13, 14, 15, 16, 17, 18, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35
Increased autonomy	5	21, 22, 23, 24, 25
Hospital profiling		
Showing potential high-quality care	30	2, 3, 4, 7, 8, 9, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 27, 28, 29, 30, 31, 33, 34, 35, 36, 38, 40, 41
Hospital differentiation	29	2, 3, 6, 7, 8, 9, 13, 14, 15, 18, 19, 20, 22, 23, 24, 27, 28, 29, 30, 31, 33, 34, 35, 36, 38, 40, 41, 42, 43
Potential increase in patient demand	23	2, 3, 7, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23, 27, 28, 30, 31, 35, 36, 38, 39, 40, 41

Appendix C: Frequency of respondents who discussed barriers to the implementation of MR-Linac into prostate cancer care, by main theme and subtheme.

Barriers	Total	Respondent ID, following Table 1
Technical complexities		
New requirements in knowledge and competence	29	1, 3, 6, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 42, 43
Continuous software development	22	1, 13, 14, 15, 16, 17, 18, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 33, 34, 35, 42, 43
Absence of the conventional stability	21	1, 13, 14, 15, 17, 18, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 33, 34, 35, 42, 43
Continuous learning curve	20	13, 14, 15, 16, 17, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 33, 34, 35, 42, 43
Substantial staffing and structural investments		
Changing tasks and responsibilities	28	2, 3, 6, 7, 8, 9, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23, 24, 27, 28, 29, 30, 31, 32, 33, 34, 35, 42, 43
Additional operational requirements	26	2, 3, 4, 5, 6, 7, 8, 9, 13, 14, 15, 16, 17, 20, 21, 27, 28, 29, 30, 31, 32, 33, 34, 35, 42, 43
Training and development programs	25	2, 3, 6, 7, 13, 14, 15, 16, 17, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 42, 43
Lack of empirical evidence of clinical benefits		
Uncertain clinical benefit	28	2, 3, 5, 6, 7, 9, 12, 13, 14, 15, 18, 19, 20, 21, 22, 27, 28, 30, 31, 32, 33, 35, 36, 40, 41, 42, 43
Ethical issues	18	3, 7, 8, 9, 11,12, 13, 14, 15, 16, 18, 19, 20, 27, 30, 31, 40, 41
Uncertain return of investment	13	7, 15, 18, 20, 22, 23, 24, 25, 28, 30, 32, 33, 35
Professional silos		
Conservative culture	31	2, 3, 4, 6, 7, 8, 9, 11, 13, 14, 15, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 34, 35, 36, 38, 42
Silo mentality	26	2, 3, 6, 7, 9, 14, 15, 18, 19, 20, 22, 23, 24, 27, 28, 29, 31, 34, 35, 36, 38, 39, 40, 41, 42, 43
Publication pressure	12	7, 10, 12, 14, 18, 19, 28, 32, 34, 38, 39, 41
Patient referral patterns		
Competitive specialties	30	2, 3, 6, 7, 8, 13, 14, 15, 16, 17, 18, 19, 20, 21, 27, 28, 29, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 41, 42, 43
Competitive hospitals	28	2, 3, 6, 7, 10, 11, 13, 14, 15, 16, 18, 19, 20, 21, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 40, 41, 42, 43

3

IMPLEMENTATION OF THE MAGNETIC RESONANCE IMAGING LINEAR ACCELERATOR INTO ROUTINE CARE: OPPORTUNITIES AND CHALLENGES IN THE UNITED STATES

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Advances in Radiation Oncology (2022)

ABSTRACT

Background/Objective: MRI-guided radiotherapy with the 1.5T magnetic resonance linear accelerator (MR-Linac) is a rapidly evolving and emerging technology. The MR-Linac literature mainly focused on clinical and technological factors in technology implementation, but it is relatively silent on healthcare system-related factors. Consequently, there is a lack of healthcare system-specific understanding of opportunities and barriers in implementing the MR-Linac. This study addresses this gap with a case study of the United States (US) healthcare system.

Materials and Methods: An exploratory, qualitative research design was used. Data collection consisted of 23 semi-structured interviews ranging from clinical experts at the radiotherapy and radiology department to insurance commissioners in seven US hospitals. Analysis of opportunities and barriers was guided by the Non-adoption, Abandonment, Scale-up, Spread and Sustainability (NASSS) framework for new medical technologies in healthcare organizations.

Results: Opportunities included high-precision MR-guidance during radiotherapy with expected continued technical advances and better patient outcomes. MR-Linac also offers opportunities for research, professional and potential economic development. Barriers included the lack of empirical evidence of clinical effectiveness, technological complexity and large staffing and structural investments. Furthermore, the lack of patients' trust and appropriate regulatory and reimbursement conditions may affect technology implementation.

Discussion/Conclusion: Our study confirms the current literature on the implementation of the MR-Linac, but also reveals additional challenges for the US healthcare system. Alongside the familiar clinical and technical factors, the implementation of the MR-Linac is also affected by sociocultural, reimbursement and regulatory influences. These findings lead to new connections to facilitate technology uptake and provide a richer start to understanding its long-term impact.

INTRODUCTION

Defining the value of new medical technology is important to identifying its potential benefits and obstacles to implementation (1–3). Insight into comparative effectiveness of the medical innovation to current standard of care therapy is critical to ensure patient access to high-quality healthcare at the lowest possible cost levels (4–8). Many new medical technologies, however, lack a comprehensive effectiveness evaluation prior to being implemented in the clinical setting, hence, without proven effectiveess or cost-effectiveness (5,6,9). This is problematic because the implementation of unproven medical technologies may threaten the quality of care and increase healthcare costs (10). Consequently, payers and policymakers are reluctant to approve or reimburse costly medical innovations because of the rising care costs in many healthcare systems.

Despite these concerns, especially with regard to medical technology still in development, it can be difficult to estimate the cost-effectiveness compared to the standard of care, nor its long-term impact on the patient, provider and payer (11). This is particularly relevant for convergent technologies which tent to cross disciplinary boundaries and are becoming dominant in health-related domains (12). For instance, the convergence between biology and informatics knowledge has led to bioinformatics and personalized medicine innovations (13). The involvement of different disciplines means that convergent medical innovation and its impact, cannot be understood and implemented without intertwined institutional practices and unify different medical disciplines and their associated knowledge bases and competences (14,15). Early assessment of crucial factors of the implementation of convergent technologies is therefore of utmost importance for an initial understanding of its long-term impact (16).

A modern example of a new developing and convergent technology in the field of radiation oncology is the MRI-guided linear accelerator (MR-Linac) system, which combines high-precision, real-time MRI exernal beam radiotherapy (MRgRT) (17–19). As a result, the irradiation plan can be adjusted at any time based on these changes. This allows more targeted delivery of radiation to the tumor and avoids the healthy tissue surrounding the tumor compared to most conventional radiotherapy techniques [11-13]. Consequently, the MR-Linac may reduce radiotherapy induced toxicity and improve tumor control outcomes (17,19). The MR-Linac also allows therapy in fewer sessions with a higher dose of radiotherapy, also called hypofractionation, hence, permitting a shorter treatment (20,21). This can be beneficial in a case like prostate cancer, since traditional external beam radiotherapy often varies from 5, 20 to 39 treatment sessions (22).

Alongside technical and clinical opportunities, the MR-Linac may also offer positive professional and economic prospects as identified by a Dutch implementation study (19). For instance, technology adopters may gain a more efficient treatment, a higher hospital quality profile with potential financial benefits, and improve their competence and technical expertise as well as multidisciplinary collaboration. However, technology implementation may also deal with technical complexities, substantial staffing and structural investments, and the presence of patient referral patterns and professional silos. Furthermore, we still know very little about the actual added-value patient benefit of MRgRT due to the current lack of empirical evidence of clinical effectiveness.

The lack of effectiveness evidence has difference implications across healthcare systems since the dynamics of stakeholders, organizational procedures, dominant existing routines, professional identities, and legal and regulatory standards in technology implementation vary between countries (23–26). For instance, developing and acting upon evidence-based practices is perceived to be more challenging in healthcare systems with large private payers such as those in the United States (US), than in publicly funded healthcare systems as in Europe or Canada (5). Furthermore, a fragmented and disjointed public and private healthcare hybrid in the US can result in substantial variations in healthcare delivery (5). This is particularly relevant for MR-Linac systems as several have been installed worldwide, with a considerable number currently operational in US. Hence, it is interesting to study how to facilitate the implementation of new convergent technologies such as the MR-Linac technology in specific healthcare systems.

In the current study, we aim to identify perceived opportunities and barriers to the implementation of the MR-Linac technology in US hospitals.

MATERIALS AND METHODS

We conducted a qualitative study with semi-structured interviews, a method most appropriated to make sensitive issues, attitudes, opinions and experiences of individuals explicit (27).

Data Collection

We used the Non-adoption, Abandonment, Scale-up, Spread and Sustainability (NASSS) framework of new technologies to explore the determinants of success and failure of technology adoption in healthcare organizations (23). The NASSS framework considers seven domains: (1) the targeted clinical indication, (2) the technology to be implemented,

(3) the value proposition for stakeholders, (4) the adopter system (patient, technology user and other staff), (5) the providing organization, (6) the wider institutional, social context and (7) organizational resilience and technology development over time (1).

We conducted 23 semi-structured interviews in 2020 to identify the opportunities and barriers to MR-Linac implementation in seven US hospitals (Table 1). Prior to conducting semi-structured interviews, a questionnaire was designed based on the NASSS framework (see Appendix A in Chapter 2). Interviewees included radiation oncologists, urologists, radiologists, medical physicists, radiation therapists and dosimetrists, as well as non-clinical hospital administrators including strategic and financial department managers as well as insurance councils. We included interviewees from academic and community based hospitals, in order to avoid professional biases. The study was approved by the local medical university research ethics board and all study participants provided verbal consent.

The research objective was explained in the written invitation and at the start of each interview. All interviews were audio-recorded and later transcribed using Sonix© transcription software. Interviews lasted between 45 and 60 min and were carried out face-to-face and via telephone and Skype. Audio recordings and transcript of interviews are anonimised as well as confidential and therefore not publicly available.

Data Analysis

Interview transcripts were analyzed using NVivo software. We applied open coding based on the research objective and ended with axial coding, identifying areas of theoretical interest and common themes. Developed codes were validated by a second reviewer. To include variation in findings and increase construct validity, we triangulated the findings with previously published similar studies.

Table 1. Overview of roles and affiliations of respondents.

Respondent	Position	Seniority	Affiliation	Additional roles	Method	Duration (min)
R1	Head of Imaging & Oncology dep.	Full Professor	AMC1	Research on functional imaging	In Person	44
R2	Radiotherapy technologist	Senior	AMC1	Research on MR-Linac	In Person	43
R3	Insurance commissioner	Senior	AMC1		In Person	46
R4	Head of IT for Oncology	Senior	AMC1	Research on functional imaging	In Person	44
R5	Medical physicist	Senior	AMC1		In Person	41
R6	Nuclear medicine physician	Senior	AMC1		In Person	39
R7	Member Board of Directors	Senior	AMC1		In Person	44
R8	Member Board of Directors	Senior	AMC2		In Person	44
R9	Radiation oncologist	Senior	AMC3		In Person	39
R10	Radiation oncologist	Senior	AMC4		In Person	39
R11	Radiation oncologist	Senior	AMC2	Head of Radiation Oncology department, Research on MR-Linac	In Person	45
R12	Radiation oncologist	Senior	AMC2	Research on MR-Linac	In Person	53
R13	Radiation oncologist	Senior	AMC2	Research on MR-Linac	In Person	39
R14	Radiation oncologist	Senior	AMC5	Research on MR-Linac	Virtual	41
R15	Urologist	Senior	AMC4	Head of Urology department	In Person	40
R16	Urologist	Senior	MC1		In Person	29
R17	Radiotherapy technologist	Senior	AMC1		In Person	41
R18	Radiologist	Professor	AMC1		In Person	35
R19	Radiation oncologist	Senior	AMC4	Head of Radiation Oncology department	Virtual	39
R20	Radiation oncologist	Senior	AMC2	Research on MR-Linac	In Person	45
R21	Radiation oncologist	Full Professor	AMC2		In Person	48
R22	Radiation oncologist	Senior	MC2		In Person	41
R23	Market Access associate	Senior	Manufacturing company		Virtual	46

Abbreviations: AMC = academic medical center; MC = (nonacademic) medical center

RESULTS

We identified four opportunity and five barrier categories for implementation of the MR-Linac technology in US hospitals.

OPPORTUNITIES

We first describe the clinical opportunities before moving on to technological, professional and, economic opportunities. Figure 1 shows the percentages of the interview cohort who discussed the opportunities, by main theme and subtheme.

Clinical opportunities

Interviewees expected a large added-value from MR-Linac implementation in clinical practice as a result of the anticipated technical advancements. Main clinical opportunities included: 1) potential improved tumor control and reduced toxicity due to more precise and targeted radiotherapy, 2) improvement in adaptive treatment planning and prediction in treatment response, and 3) potentially improved patient convenience and quality of life. For the latter, interviewees discussed that superior tumor delineation with real-time imaging and hypofractionation could improve patient comfort and treatment compliance given the potential of less therapy fractions.

Technological opportunities

The MR-Linac technology was perceived by interviewees to be a sophisticated technology with strong MR-guidance with potential technical advances which could allow for both diagnostic and therapeutic opportunities. For instance, one interviewee referred to the potential for adaptive contour propagation and rapid dosimetric reconstruction which would allow for smaller treatment uncertainty margins and avoidance of dose to healthy tissues. This explains the possibility of hypofractionation. There was general agreement amongst interviewees that these opportunities may evolve as software development continues (e.g., application of deep learning, enabling potential technology developments).

The opportunity of real-time MRI-imaging and daily online evaluation of tumor response during the course of radiotherapy could allow for increased data collection including anatomical and functional imaging data sets of both the tumor and surrounding organs. Hence, this data may allow additional understanding to safely deliver a higher dose

the most effective dose to individual tumor biology rather than its stage and location. Furthermore, interviewed perceived these possibilities to bring new treatment avenues in radiation oncology and in related medical disciplines.

Professional opportunities

Implementation of the MR-Linac technology allows different possibilities for professional development. First, using MR-Linac encourages the development of new competencies and welcomed novel responsibilities for staff members because of the technological knowledge required to run both an MRI machine and linear accelerator. For instance, radiation oncologists need to gain understanding of the potential information obtained from different MRI sequences and response evaluation. Furthermore, multidisciplinary relationships could be improved because of increased cooperation between radiology and radiation oncology experts. These opportunities are expected to allow for retention of staff and additional recruitment. As an example, one interviewee stated:

"I think rolling out new technology is always important for your recruitment and retention of the highest-level physicians in the hospital."

Given the ongoing technology development, interviewees felt they could also benefit from research opportunities with increased funding possibilities, which could positively impact their own careers. To elaborate, implementing this technology is also perceived by technology adopters to access prestigious technology which could allow delivery of higher-quality care. Being perceived as a "pioneer" in this area by providing this new technology could also be greatly beneficial for individual and hospital reputation.

Economic opportunities

Most interviewees expected efficiency and operational benefits from MR-Linac in the long run. Factors such as automation of elements in the clinical workflow, such as planning and contouring, were perceived to increase efficiency. To illustrate, the possible absence of pre-treatment planning within an MR-only online workflow could decrease the duration of the total care pathway. Furthermore, the increased potential for hypofractionation could allow operational efficiencies for both the provider and the patient, such as decreased treatment sessions as well as interruptions and hospital admissions.

Operational efficiencies were also expected to evolve over time as technological development continues. Interviewees reported communication efficiencies, for example by the automation of tasks together with more consistent multidisciplinary communication and reporting.

Increased interaction between referring doctors and radiation oncology departments as well as supporting medical specialties such as radiology who would aid in target delineation was expected among interviewees. Interviewees emphasized that the clinical benefit of decreased radiation related side effects and less treatment fractions could result in improved overall efficiency of hospital systems (e.g., lower burden on anesthesia provision).

Furthermore, in the long-term, a possible reduction in the workforce per treatment of technology use is expected. On the one hand, the ongoing software development is expected to enable an automated process with faster quantification of the dose, which may lead to faster treatment delivery with reduced staff time and requirement (e.g., less presence of the radiation oncologist and physicis during actual treatment delivery). On the other hand, professional experience and learning curves can reduce the education time needed to use the technology effectively.

Implementation of MR-Linac was also thought to potentially improve economic outcomes of radiation oncology departments by providing state-of-the-art treatment, particularly in the US healthcare system where health services are privatized and hospitals often compete against one another for patient referrals. Hence, interviewees mentioned that MR-Linac technology could possibly attract more cancer patients to a center. One interviewee stated:

"Especially well insured patients have this belief that that as Americans, we should have the latest and greatest technologies, almost regardless of cost."

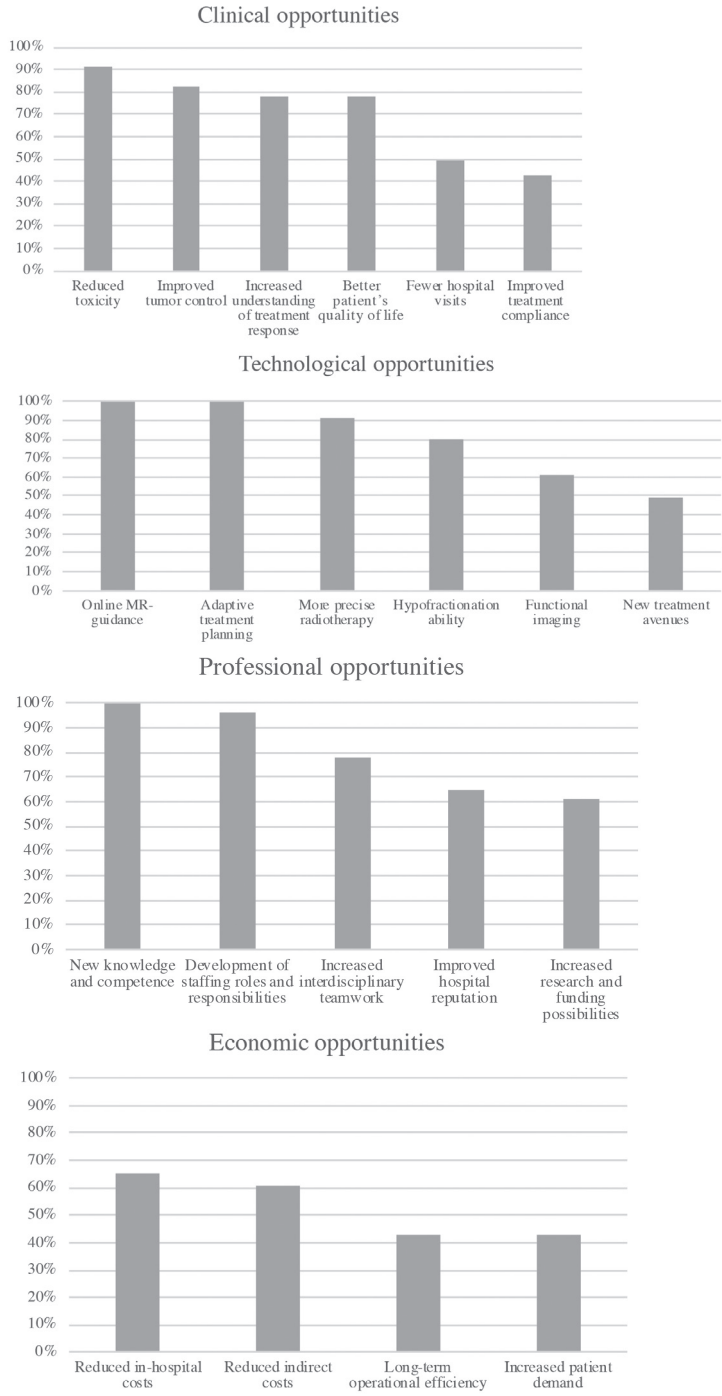


Figure 1. Frequency of interviewees in percentages who discussed opportunities to MR-Linac implementation in US hospi- tals, by main theme and subtheme.

BARRIERS

We identified five barriers for implementation of the MR-Linac technology in US hospitals. These barriers were technology, professional, organizational, market, and regulatory related. Figure 2 shows the percentages of the interview cohort who discussed the barriers, by main theme and subtheme.

Technological barriers

Technology users face substantial investments for the implementation of the MR-Linac in the construction of technical facilities, maintenance, information technology, safety assurance, human resource policy and personnel training. Current radiotherapy centres often have to invest in the required MR imaging facilities. Furthermore, the combined functionality of both the MRI device and the radiation delivery device raises technical complexity. This, together with the ongoing technical development, necessitates the acquirement of new skills and additional understanding of MRI sequences.

Furthermore, the current lack of comparative effectiveness data and the ongoing technical development complicates a clear identification of potential benefits and return of investment. While the MR-Linac was expected to increase the efficiency and precision of existing radiotherapy treatment, interviewees were at the same time critical of the actual clinical impact. The previously mentioned possible advantages, such as online high-resolution imaging during treatment and functional imaging have yet to be proven in clinical studies.

The interviewees also indicated a potential lack of understanding by technology users of the healthcare costs associated with MR-Linac treatment, especially since technology development continues and the true treatment outcomes will evolve. One interviewee stated:

"What would the cost be? What numbers are needed to actually make it a beneficial investment from a capital standpoint while the technological development still continues? I think that's the main discussion."

Professional barriers

Technology adopters may face hurdles from the burden of technology installation in the radiation oncology department to the training of staff as well as the delivery of therapy to patients. As mentioned previously, several interviewees indicated substantial infrastructural investments and strategic decisions on a local level were needed to

implement and provide treatment on the MR-Linac technology. For instance, technology users would need to obtain timely formal training to safely use the technology and to acquire MRI knowledge and skills given the routine use of MRI. Hence, technical advancements would need to be adopted into professional behaviors before the actual use of the technology could flourish. One interviewee asked:

"Do we have appropriate algorithms that are rooted in the science, that are also rooted in the clinical expertise of our medical staff?"

Another concern is the formal approval for the introduction of new treatment workflows into clinical practice due to the lack of empirical evidence of effectiveness. Interviewees illustrated the importance of incorporating findings, as clinical research data become available, into local clinical guidelines for appropriate technology usage in a timely manner. Therefore, interviewees also emphasized the importance of comparative effectiveness evaluation in daily tasks of technology users. Yet, there could be conflicts in prioritizing clinical treatment versus effectiveness research, given limited resources allocation at hospitals, due to the ability to have only one MR-Linac machine and the care burden because of the COVID pandemic. Clinical evaluation of this innovation was therefore not widely accepted as a main research objective among all interviewees.

Organizational barriers

As stated previously, the technology supply model requires substantial structural and organization investments for factors such as workflow, quality assurance and the development of protocols. Alongside these investments, software developments inherent to the MR-Linac's development require technology users to anticipate continuous learning and educational programs. Furthermore, interviewees emphasized that the COVID pandemic was also an important factor leading to changes in resource allocation at the hospital, hence, for more commitment of human resources to direct care provision rather than secondary tasks such as expertise training and clinical evaluation of new technology. One interviewee noted:

"Discussions of decreased reimbursements for radiation delivery are important. A lot of resources are being reallocated to fight the Covid-19 pandemic. So, it is actually a pretty uncertain time economically."

Interviewees perceived the fact that value assessment and clinical trials of the new technology (e.g., demonstrating empirical evidence of (cost)effectiveness) not being integrated into

departmental strategy and culture including vision, goals and key performance indicators, as a significant barrier to identifying the potential value offered by the technology.

Market barriers

Interviewees felt that they may not be appropriately motivated or financially compensated when it came to proving potential values of the MR-Linac technology such as comparative effectiveness. For example, some felt that the external authorities focused more on safety aspects than on demonstrating clinical effectiveness or added-value for the patient. Furthermore, interviewees discussed that decreased financial reimbursement for new radiotherapy delivery techniques may not allow possible financial gains (e.g., a relative reduction in number of treatment fractions and hospital visits as a result of hypofractionation compared to traditional external beam radiotherapy).

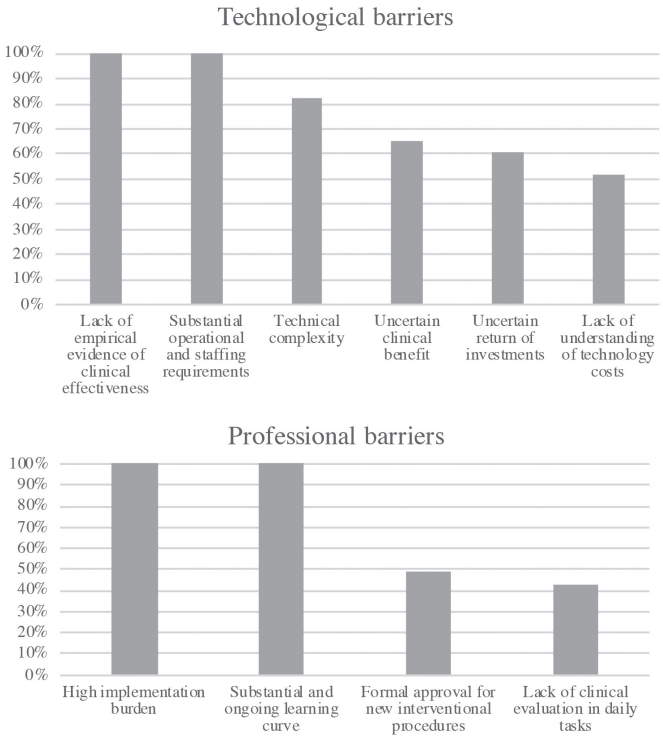
The interviewees also addressed the potential challenge of the presence of patient groups with less beneficial socio-economic background for new, costly therapy. As an example, the main hospital in which this study was conducted was identified as being socio-economically diverse. This location included both wealthy, insured patients which will be beneficial for costly treatment implementation such as the MR-Linac, compared to relatively poor or uninsured patients, which may face hinder to afford costly therapy. Furthermore, while well-insured patients may hold the belief that Americans should have the "latest and greatest" medical therapy options available to them regardless of cost, other more historically marginalized communities (e.g., African-Americans) may be more reluctant to try innovative treatment. These barriers may therefore hinder access to and full realisation of the potential benefits of the MR-Linac.

"There are a lot of undertreated, underdiagnosed cancer patients here in this inner city. So if you're using your resource dollars, you'll get the most benefit from a place like [city]. There is a negative to that. And part of that is patient's reluctance to come in and try new technology given historical health disparities with race and other socioeconomic status. It's both a huge opportunity, but also a challenge, especially here in [city]."

Regulatory barriers

Interviewees identified the lack of appropriate reimbursement arrangements as a barrier to the implementation of this technological innovation. As stated previously, respondents felt more motivated by federal regulators to demonstrate safety than clinical effectiveness for reimbursement of care. Furthermore, interviewees indicated a potential lack

of consensus amongst clinical care providers and reimbursement entities in regards to healthcare cost reimbursement. The definition of insured care costs would be more focused on how much the government or insurers were willing to pay to providers, rather than the costs incurred by providers to deliver treatment. The existence of such gaps between clinical care providers and reimbursement entities was experienced by technology users to discourage the demonstration of value of new technology. To elaborate, as healthcare and reimbursement is structured differently across states and individual hospitals in the US, some interviewees also recognized that this fragmentation could hinder collaboration between MR-Linac providers when implementing the technology and having reproducible results across institutions.



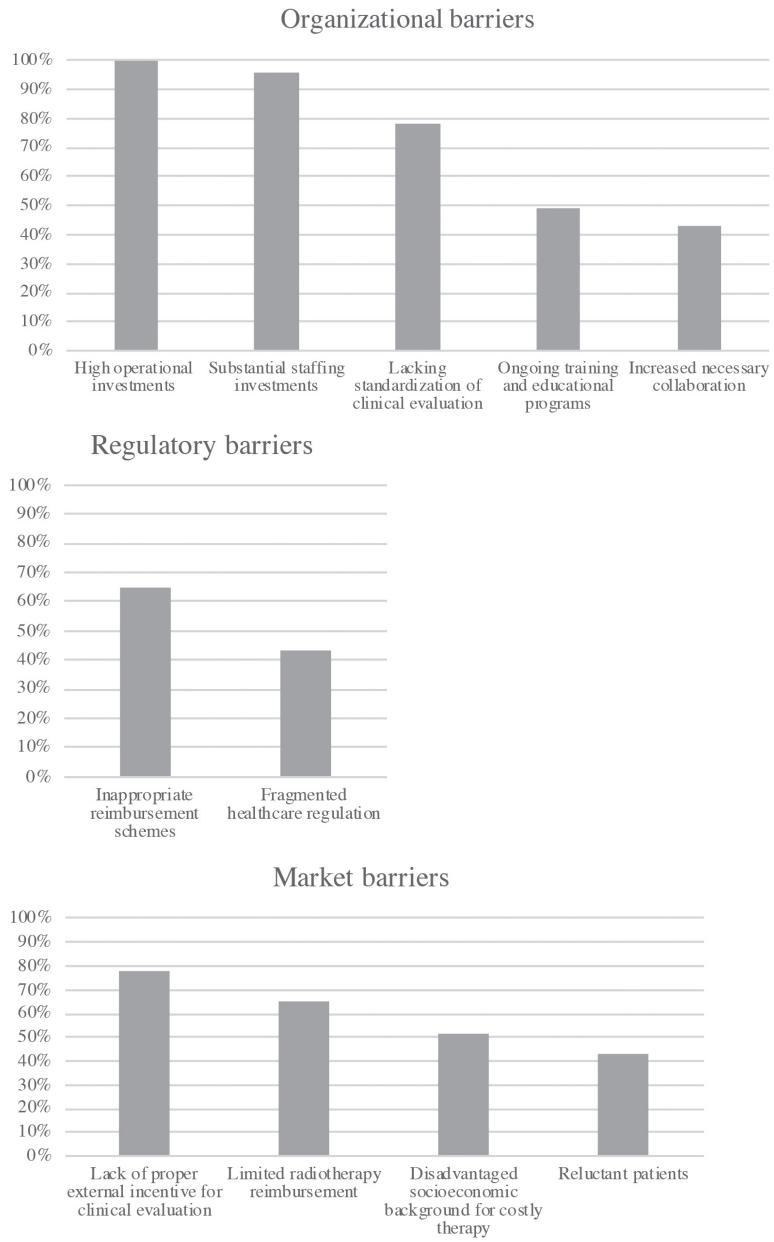


Figure 2. Frequency of interviewees in percentages who discussed barriers to MR-Linac implementation in US hospitals, by main theme and subtheme.

DISCUSSION

Our findings will help US hospitals to identify key points in their strategy when implementing the MR-Linac. MR guidance in radiotherapy has been perceived a technical advancement with potential for therapy improvement and better patient outcomes, as well as scope for research and professional development (17,28,29). Yet, the technological complexity, the substantial operational and staffing investments, and the lack of empirical evidence of the actual added-value raise implementation uncertainties. Furthermore, our findings show that the lack of appropriate reimbursement and regulatory structures may complicate the actual deployment of the potential technology value (17,30). The convergence of diagnostic and therapeutic realms in the MR-Linac technology, also confirms the essential task of solving the common gap between technical innovations in the field of radiation oncology and current national associated treatment guidelines as well as present reimbursement structures (31,32).

The opportunities and barriers identified are fairly similar to those in literature such as the Dutch study on the implementation of MR-Linac (19). Both in US and Dutch cases, findings were consistent about the technology aspects, knowledge and competence needed, and what it expects from radiation oncology departments to use new interventional procedures on the MR-Linac. Hence, the use of new interventional procedures on the MR-Linac with continued software developments require ongoing staffing learning and workflow adaptations, approval from national regulatory authorities before clinical usage and necessary interactions with policy-makers and payers.

There is also consistency in the professional prospects, such as the development of staffing roles and required ongoing learning, and a higher hospital quality profile with potential economic growth. Interviewees in both cases were, however, also critical of the actual clinical added-value of the MR-Linac given the current lack of comparative effectiveness data. Defining the clinical value and operational profits of the MR-Linac at this time would be more of a challenge, given the early stage of the technology and its continued development (21,33–36). Furthermore, the relative cost-effectiveness of the MR-Linac will vary across geographical settings because of specific treatment standards and patient populations in a particular healthcare system.

The inference of the different geographical contexts in the opportunities and barriers to the implementation of MR-Linac shows similarities, but also differences. To illustrate, in the US case, interviewees mentioned potential challenges regarding certain patient groups with a reluctant attitude towards new therapy. In this geographical setting,

interviewees also explicitly stated that they perceive few external stimuli to evaluate clinical effectiveness. The Dutch case, in contrast to the US case, reflected more on the intra- and inter-organizational network required in technology implementation, such as the cooperation with the referring physician and payers to ensure treatment access and reimbursement. Thus, the implementation of the MR-Linac technology may encounter opportunities and challenges that are relevant to one specific healthcare system.

The identified opportunities and barriers to implementing the MR-Linac could relate to each other. Market influences on technology implementation could be caused by regulation while also raising technological barriers (1,37). For instance, governmental decision-making informs reimbursement requirements and may therefore stimulate technology users to evaluate clinical effectiveness as well as to deliver new insured treatment regimes (38). Our findings also showed that technology users may not feel motivated to evaluate the clinical effectiveness by external bodies as well as face hinder in technology implementation due to the lack of appropriate reimbursement structures. Ultimately, securing proper reimbursement structures and regulatory approval for new interventional procedures, are essential for new technologies to prosper.

While market barriers could result from regulatory barriers, cultural barriers may determine these regulatory barriers (39). Our findings confirm that the lack of effectiveness evaluation in the radiation oncology department's strategy hinders to prove the technology's value as well as the steering and development of appropriate treatment guidelines and staffing protocols. Regulation and policy such as financial incentives or cost sharing have an important albeit indirect impact on clinical decision making and staffing allocation (5). Thus, the implementation of the MR-Linac includes factors at clinical and technical level, but also at cultural, market as well as governance level which can strongly influence each other.

Our study provides the first early multifaceted assessment of opportunities and challenges to MR-Linac implementation in US hospitals, which inform local technology adopters to improve and facilitate treatment access (32,40,41). Technology users may face certain influences during implementation that are usually outside their ordinary scope of work. Since these influences are interrelated, the engagement with other healthcare decision-makers such as insurers and policy-makers could be relevant. Future efforts should generate empirical evidence of MR-Linac's effectiveness to prove expectations and justify return on investment concerns. The Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-linac Study (MOMENTUM) study aims to generate empirical evidence of the

MR-Linac's clinical effectiveness and safety, and to identify subgroups of patients who are most likely to benefit from MRgRT (42).

Approaches to assess the potential value of new medical technology, particularly those in early stages of development and implementation are therefore gaining more attention (43–46). Early health economic analyses are useful for identifying areas in which new developing technologies could be cost-effective and conditions that must be met in order to achieve cost-effectiveness (40,47). This analysis is particularly relevant for developing medical technologies such as MR-Linac when both the costs and the effects of the innovation are still largely unknown, thereby guiding research and development and identifying potential meaningful treatment strategies.

The presented findings may be relevant for other convergent medical technology as the MR-Linac represents other technical trends in medicine (e.g., artificial intelligence applications (36)). The converging characteristic and rapidly increasing role of digitization in medical technologies affects the user practices as well as the current organizational and regulatory settings, creating an additional dynamic context (48–50). Therefore, findings could also be relevant to healthcare policy-makers given the interdisciplinary nature of different medical specialties and the role of digitalization in health innovation in general. In-depth knowledge about the functionality and configuration of convergent medical technology, and the redistribution of knowledge, responsibilities and care pathways as well as related regulation and market dynamics are important to further consider in future research for this type of technologies. Moreover, findings can be better interpreted in different healthcare systems when taking into account specific national dynamics, such as healthcare trends, socio-cultural, reimbursement and regulatory structures.

Strengths of the current study include a thorough qualitative study design which allows for maximal stakeholder insight into questions asked. The study was conducted with insights from several US healthcare institutions and different types of stakeholders. Limitations of this study include difficulty contacting private and public insurance regulators, whose insights could have been useful regarding regulatory and policy factors affecting technology implementation. Furthermore, the COVID-19 pandemic during the study timeline limits the number of stakeholders interviewed. Future research could include broader stakeholder perspectives at another time point and across national borders in order to better identify healthcare system-specific opportunities and barriers.

CONCLUSION

Our findings will help US radiotherapy oncology departments to identify main elements in their strategy when implementing the MR-Linac. Our study confirmed the current literature on MR-Linac implementation with technical, clinical and professional prospects, but also reveals additional insights into market, cultural, reimbursement and regulatory challenges. We therefore address implementation factors that are overlooked in the current MR-Linac literature, and which in particular are crucial in the US healthcare system. This leads to new connections to facilitate appropriate introduction of the MR-Linac in US hospitals and is a start to understanding its long-term effects in healthcare systems.

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4

HOW DOES CONVERGENT INNOVATION AFFECT THE ORGANIZATION OF CARE? AN EMPIRICAL STUDY OF THE MAGNETIC RESONANCE IMAGING LINEAR ACCELERATOR IN THE NETHERLANDS AND THE UNITED STATES

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ABSTRACT

Although convergence is a major trend in the development of medical innovations, the implications of the institutionalisation of convergent innovation are understudied. This paper explores how the institutionalisation of convergent innovation affects the organization of health care, by using operational domains and categories of the Non-adoption, Abandonment, Scale-up, Spread and Sustainability (NASSS) and the Institutional Readiness (IR) approach respectively. We use an illustrative comparative case study on the institutionalisation of MRI-guided linear accelerator (MR-Linac) technology in the Netherlands and the United States. Empirically, we conducted 66 interviews with different professionals in the health care system around MR-Linac. The findings show that institutionalisation of convergent innovation affects the organization of health care by: changing the traditional organization of solving a medical problem, thereby transforming and reorganizing work in the health care environment, providing opportunities for individual user development, collective action and cross-sectoral developments, and requiring the additional work of evaluating convergent innovation, including administrative tasks, innovation and research activities.

INTRODUCTION

The increasing convergence of knowledge, competencies and tools from different fields has led to the emergence and diffusion of health care-related innovations worldwide, such as biotechnology, personalised medicine, nanotechnology and information technology (1–3). This so-called convergent innovation has been defined 'as a solution-oriented approach that combines technological and social innovation in a form of "meta-innovation" that integrates human and economic development outcomes through behavioural and ecosystem transformation' (Dubé et al. 2014, p.125). The convergence of knowledge, competences, and tools from different scientific disciplines and domains in a single process or product in health care, then results in a new supporting method for disease prevention, diagnosis, monitoring or therapy (1,5–7).

Digitalisation, an illustrative converging trend in health care (e.g., artificial intelligence, machine learning and deep learning), is often used to support users' decision-making, and frequently requires and provides multidisciplinary knowledge (8,9). This enables disruptive work approaches, regulations and functions for users and organizations, including the potential for cost savings and creativity (2,10–13). Digital convergence may therefore adapt both the delivery and the financial component of health related services, dealing with a wide variety of mechanisms used to fund, commission and deliver the service in question (14).

Beyond the clinical and technical novelties, convergent innovations can create new forms of care, with changes to the organization, delivery and working environment of the entire health care system. Institutionalisation of convergent innovation thus focuses more on the process of innovating through systemic, social and behavioural changes rather than solely on technology development (3,4,15). We define institutionalisation as 'the process to implement an intervention into all subsystems of an organization in its institutional context with all socio-cultural, economic, political and regulatory influences present' (16–18). Convergent innovations are changing the way traditional health care products and services are developed, produced and delivered. These innovations integrate the formerly distinct sectoral boundaries of medical interventions, knowledge and actors, and target multiple interacting components, several dimensions of complexity, and aspects of uncertainty and organization (19,20).

The assimilation of traditionally distinct technical and social features, value networks, and organization aspects in convergent innovation creates additional institutional complexity and uncertainty (18,20,21). Institutionalising convergent innovation may

therefore bring opportunities, but also challenges, since health care systems deal with traditionally separate actors with specific roles, strong routine practices, techniques and strict jurisdictions and regulatory practices (21).

There is no doubt that convergent innovations have an important role in changing and developing health care and beyond. The literature so far has mainly focused on describing convergent innovation rather than explaining its implications for the institutional context (2,20). Institutional effects may play an important role in the dynamics of convergent innovation, but these effects have received little or no attention (22). As such, exploring how the institutionalisation of convergent innovation affects the organization of health care is relevant.

We use the analytical frameworks from the Non-adoption, Abandonment, Scale-up, Spread and Sustainability (NASSS) (Greenhalgh et al., 2017) and Institutional Readiness (IR) (Webster & Gardner, 2019) to explore how the institutionalisation of convergent innovation affects the organization of health care. The NASSS framework focuses on the factors affecting the implementation processes of medical innovations. The IR framework emphasises how technological innovations are diffused in institutional structures within a particular health care context, thereby exploring the necessary work done by involved stakeholders. The NASSS framework describes key elements in the institutionalisation environment, while the IR framework facilitates the understanding of the institutional readiness of implementing convergent innovation. In addition, the IR framework adds a more systemic perspective on the interaction between readiness of organizations and the institutional context.

By using a combination of the NASSS and IR framework, we go beyond the more traditional studies on determinants of adoption focusing mainly on barriers to innovation. We bring in a more dynamic perspective, in which we move away from seeing technological innovation as a stable object or process, but rather as being continual reconfigured by enactment of specific enablers, processes of evaluation, and organizational receptivity. In this way, we integrate and build on recent work from innovation studies and Science and Technology Studies.

We focus on the institutionalisation of the 1.5T MRI-guided linear accelerator (MR-Linac) technology as an illustrative case study of a convergent innovation. The MR-Linac integrates two traditionally separate modalities, diagnostic MRI guidance and radiation therapy, into one device for cancer treatment. Together with digitisation in the MR-Linac technology, it requires different knowledge bases and competences of involved actors.

THEORETICAL FRAMEWORK

Health care related domains are currently transforming and recombining in many novel ways, with convergence of disciplines and sectors, and convergence of ideas and expertise with multiple actors involved. The involvement of multiple actors and disciplines means that convergent innovations in health care cannot be understood without a better understanding of the institutional practices including the redistributed knowledge, responsibilities, agency and power (18,21). To illustrate, traditional health care providers have to redefine their jobs and knowledge, and new health care professions and adapted regulations are needed. In other words, convergent innovations need to be legitimized, aligned and institutionalised in new categories, routines, norms and regulations (4,5,20).

According to Dubé et al. (2014), the essential building blocks of convergent innovation include: (1) a new technology-based invention, (2) developments in the way individuals interact, which opens up new opportunities to individuals as well as the community in which they interact, (3) intra- and interorganizational development that facilitate new activities, (4) advancement in financial instruments and payment systems, and (5) a cross-sector collective action in which institutions are modified or created. Accordingly, convergent innovation manifests through collaborative innovating, including the knowledge available from individuals in terms of rational and less rational motives for engagement and communication (4). The collaborative nature of convergent innovation may encounter difficulties in the siloed health care environment with strict regulations, work routines, values, attitudes, competencies among the individuals and organizations involved, their interactions and the institutional context.

In general, individual, organizational, and contextual elements appear to be important predictors of how hospitals bring new technology into the organization (23). This process may be assumed more complex given the collaborative nature of convergent innovation. Understanding the key elements of institutionalisation of convergent innovation could then help in exploring its impact on the organization of health care.

The Non-adoption, Abandonment, Scale-up, Spread and Sustainability (NASSS) framework (24) describes key elements in implementation of innovation. This framework was applied to several health-related case studies, also including convergent innovations in health care (25–29). Empirical applications ranged from service-oriented innovation to more product-oriented innovations, such as e-health interventions and digital technologies. The analytical framework focuses on implementing and sustaining a new medical innovation over time, according to seven interacting domains (24) (see Figure 1, Chapter 2).

The NASSS framework can also be used to examine the degree of complexity in the domains described above: simple (few components, predictable), complicated (multiple interacting components, still largely predictable) or complex (dynamic and unpredictable). Innovations characterised by multiple complex domains rarely get successfully adopted, scaled up, spread and sustained (24). As such, the NASSS framework could also define degrees of complexity in the environment of the innovation and could forecast the success of an innovation.

We use an additional framework to identify challenges of convergent innovations at the organizational and the systemic level regarding the interaction between readiness of organizations and the institutional context. The Institutional Readiness (IR) framework (30) increases understanding of the institutional readiness of implementing convergent innovation in more depth. Health care contexts are characterized by considerable complexity and heterogeneity including different stakeholders (31). This explains why the inter- and intra-organizational networks around convergent innovations regularly integrate a wide variety of practices, cultures and routines from often traditionally distinct disciplines, institutions and sectors (4,32,33). The IR perspective adds insights into the organizational dynamics and challenges for new technologies at a systemic level, and specifically when and how a particular organization is institutionally ready for a new technology. Its operational categories focus on how new technologies are engaged with and made sense of through the cultural processes and institutional structures within and outside of a specific organization.

In particular the following institutional readiness categories, *(e)valuation processes in place*, *enactment through specific enablers*, and *receptivity,* add complementary insights to the NASSS framework regarding the institutional readiness of convergent innovation:

- The category *(e)valuation processes in place* is relevant in encouraging appropriate (national) protocols and guidelines, and the (shared) assessment of the value of new technologies in specific health care settings. Evaluation guidelines are also relevant to both the context and the guidance function of research, which affects the evaluation processes (21). For instance, the institutionalisation of medical technology is more stringent in the European health care setting compared to the US; e.g. recommending that evaluation processes embed cost-effective innovations into European health care, and to discontinue those interventions that have little or no added value (34–37). This category therefore complements the value proposition domain in order to prosper in the wider institutional and

social context. Evaluation processes can also add insights into important enablers for institutionalising convergent innovation into the hospital environment, such as the needed medical protocols and guidelines.

- *Enactment through specific enablers* stresses how a variety of actors with different roles are represented in the adoption of the convergent technology. This category increases insights into the roles and tasks of specific facilitator stakeholders in the adopter system, the organization and in the wider institutional and social context. Moreover, this category can also provide insights into specific private actors who are perceived as important for the development of convergent innovation (4).

- *Receptivity* considers the changes and structures in an organization in anticipation of unexpected events and challenges when implementing the convergent innovation in the wider institutional and social context. This category offers specific insights of responsiveness to the organization, into, for instance, the external efforts to create legitimacy and to counter potential resistance in the wider institutional and social context. This category enables a better understanding of the actions an institution undertakes to institutionalise convergent innovation (4).

Summarizing, complementing the NASSS framework with the discussed IR categories can provide useful insights into how convergent innovation affects the organization of health care. A detailed analysis of the NASSS' domains provides insights into key elements in the institutionalisation environment for convergent innovation, while the mentioned institutional readiness categories add a further systemic level perspective on the interaction between readiness of organizations and the wider institutional and social context.

MATERIALS AND METHODS

Research design and case setting

We used an exploratory qualitative research method to explore how the institutionalisation of convergent innovation affects the organization of health care. The analytical frameworks act as a starting point for the identification of important elements in institutionalising convergent innovation. We use the institutionalisation of the 1.5T MRI-guided linear accelerator (MR-Linac) technology in the Netherlands and the US as an illustrative comparative case study of convergent innovation.

The MR-Linac is currently being introduced in hospitals worldwide (38–40), and reflects different layers of convergent innovation, integrating different knowledge bases. It

integrates the fields of high-precision cancer diagnosis and non-invasive, real-time radiotherapy in one device, including ongoing software development (41). MR-Linac also includes ongoing software developments to enable automation processes during treatment, and to collect real-time anatomical and functional information about the tumor, and the organs at risk (42,43). The involvement of diagnostic MRI in radiotherapy is also seen to transform ways of working, either within or outside the radiation oncology department (43). MR-Linac enables opportunities for professional development and new knowledge networks between actors, such as between physicians from radiotherapy and radiology as well as information technologists. This may increase innovation processes including the development of new treatment pathways and the regulations, guidelines, norms and new organizational responses involved. It may also affect the traditional capacity for oncology care and create new treatment avenues to meet public needs. Nevertheless, the institutional effects of MR-Linac on the delivery and organization of health care are still understudied (27).

We used interview data from our earlier empirical studies reporting on the opportunities and challenges of introducing MR-Linac in the Dutch and US health care systems (27,44). These studies are published in Frontiers in Oncology, and Advances in Radiation Oncology clinical journals, respectively. In this study, we used these raw interview data for another research purpose to explore how the institutionalisation of convergent technology, MR-Linac, affects the organization of health care in two different geographical health care settings, i.e. in the Netherlands and the US. It is useful to study such different health care settings to identify country specific similarities and differences regarding the involved stakeholders, organizational procedures, dominant existing routines, professional identities, and legal and regulatory standards (24,32,45,46).

The Netherlands was the first country to introduce and implement the 1.5T MR-Linac. The University Medical Centre Utrecht (Utrecht, The Netherlands) developed this convergent innovation in collaboration with its manufacturer, Elekta AB (Stockholm, Sweden) (47,48). Multiple MR-Linac devices have now been installed worldwide, and especially in the US (49). The study of the institutionalisation of MR-Linac in the Netherlands is insightful because of its early adopter experience, its extensive experience with technology institutionalisation, compared to its institutionalisation in the US, which included later adopter experience. Furthermore, the study of the US health care system, a more privatised than the more public-financed health care systems in Europe such as in the Netherlands, is also relevant to study possible differences in implementation processes of convergent innovation (50,51).

Data collection

We conducted interviews with different stakeholders in the two health care settings. Users who directly operate the MR-Linac technology, such as radiation oncologists, (clinical) physicists and radiation technologists were interviewed. Furthermore, we included MR-Linac developers, manufacturer representatives, health insurers, ICT staff, referring physicians, radiologists and nuclear medicine physicians. The interview data was collected from more than one person per professional group, and included perspectives from both academic and non-academic, general hospitals in both health care settings in order to include variation in findings and to increase construct validity.

Forty-three interviews were undertaken in the Netherlands by one researcher between November 2018 and March 2019. This researcher also worked in the MR-Linac department at University Medical Centre Utrecht in the Netherlands. Interviewees were included from five academic and three non-academic Dutch hospitals, of which two hospitals were early MR-Linac adopters. In the US, 23 interviews in five academic and two non-academic hospitals were undertaken by two researchers in 2020. One of these researchers also worked as a radiation oncologist at a hospital providing MR-Linac treatment in the US. Interviewees were mostly identified from a single US hospital involved in the early implementation of MR-Linac. Table 1 in Chapter 2 provides an overview of the Dutch interviewees, and Table 1 in Chapter 3 lists the US interviewees.

Data analysis

We followed an abductive research approach (52). This involved coding transcripts both inductively (starting from empirical data) and deductively (iteratively comparing preliminary results with concepts derived from theory). In order to explore how convergent innovation affects the organization of health care in both the Netherlands and the US, we analysed the interview transcripts for similar and distinct findings about implementing MR-Linac sequentially according to the NASSS domains and the IR categories, using NVivo© software. In a first round, we applied axial coding, systematically identifying areas of interest based on the NASSS domains and IR categories. This involved an iterative process with multiple rounds of coding. The codes developed were validated and discussed in team meetings. We triangulated responses across different respondents to identify consistent results. Finally, we reflected on how the convergent MR-Linac technology affects the organization of health care in two different health care settings.

RESULTS

In order to explore how the institutionalisation of convergent innovation affects the organization of health care, we analysed MR-Linac implementation in the Netherlands and the US. We found similarities and differences when implementing MR-Linac across both countries. We report the main findings according to the NASSS domains and IR categories.

Clinical condition

The first domain addresses the clinical, comorbidities and sociocultural aspects of the condition to be treated. We identified a strong homogeneity in the clinical condition in MR-Linac implementation across the Dutch and US cases. Treatment on MR-Linac potentially reduces toxicity, improves tumor control and implies fewer hospital visits and less hospitalisation for patients. This improves patient convenience and quality of life. However, there is still a lack of evidence regarding clinical effectiveness for specific tumor indications, including knowledge about which patients benefit most from treatment on MR-Linac.

Technology

This domain addresses requirements of the material and technical features of the technology. Similar technology features, knowledge and infrastructure were found when implementing MR-Linac in the Netherlands and the US. Real-time superior MRI guidance during treatment allows more targeted radiotherapy and the collection of anatomical and functional information about the tumor, which leads to additional understanding of individual treatment response and personalised treatment avenues. MR-Linac implementation requires substantial organizational and technical investments, due to the combined functionality of both the diagnostic MRI device and the radiation delivery. To illustrate, a MR-Linac device costs 10 million euros without the necessary infrastructure, such as imaging compatibility, safety, and its accompanying software development, quality assurance and applicable protocols. Furthermore, individual technology users must not only possess knowledge of radiotherapy and MRI, but also must remain informed about the technology's software developments. This requires ongoing learning and active input about operating MR-Linac by technology users, which may result in inter- and intra-variability in treatment procedures.

Value proposition

This domain considers whether the technology is valuable to implement and for whom it generates value. The value proposition of implementing MR-Linac shows similar clinical and technological aspects in both the Dutch and the US case, and also professional, organizational and economic expectations. Technology users would implement (1) a state-of-the-art evolving technology in the field of radiation oncology with opportunities, for (2) improved quality treatment, (3) in-hospital efficiencies, (4) research and funding possibilities, (5) competence enhancement and technical expertise, and (6) hospital profiling with increased demand for care. For instance, the absence of pre-treatment planning within an MR-only online workflow and the combination with diagnostics during the course of radiotherapy decreases reliance on the radiology department, leading to several efficiencies. The automation of tasks within MR-Linac workflow is perceived to allow faster treatment, which reduces treatment times for patients and providers.

Conversely, the final value proposition of MR-Linac is still uncertain, as there is a lack of empirical evidence for short- and long-term treatment outcomes. This also creates scepticism among treatment providers regarding MR-Linac's added-value for tumor indications that already got effective treatments. The clinical added-value of MR-Linac, such as cost-effectiveness, will vary across countries due to national treatment standards, tumor indications and patient populations.

Adopter system

This domain addresses the adoption of the technology by staff, patients and the extended network of lay caregivers. We found both comparable and distinct findings in the adopter system for implementing MR-Linac in the Netherlands and the US respectively. The acquisition of MRI knowledge and competences would change the traditional roles, practices and identities of radiation oncologists, technologists and physicists. Especially the autonomy and involvement in the treatment workflow of radiation technologists would particularly increase. Implementing MR-Linac also requires increased interdisciplinary cooperation between radiation oncologists, radiologists, imaging professionals and ICT experts, due to the need for MRI knowledge and competences during treatment and ongoing software developments. In both the Netherlands and the US, interviewees mentioned a lack of MRI competences among radiation oncologists and technologists.

In the Netherlands, interviewees reported the need for cooperation with the referring physician during implementation of MR-Linac to ensure treatment access, as well as with

health care insurers to ensure development of appropriate reimbursement schemes. The lack of evidence about effectiveness is perceived to result in ethical discussions between physicians and payers about delivering unproven treatment. The limited availability of radiation technologists in the Netherlands is another concern when implementing MR-Linac.

Interviewees in US addressed the existence of patient groups from disadvantaged socioeconomic backgrounds, which could limit the access to new, costly treatment such as MR-Linac. The interviewees also indicated that well-insured patients might believe that high-quality hospitals offer state-of-the-art treatment, while more marginalised communities (e.g., the African-American community) might be more reluctant to accept new therapy.

Organization

This domain relates to the organization's capacity, current routines and work necessary for implementation of the technology. We found both comparable and distinct findings in the organization domain. In both countries, radiotherapy centres often lack the required combination of MR-imaging and radiation facilities. This results in substantial investments for implementing MR-Linac, including technology costs and necessary changes to hospital infrastructures. A long-term structural investment in team work, professional learning and training is also needed in order to use the MR-Linac technology effectively, both now and in the future, given the present ongoing technology development. Changes in the delivery of care and the reallocation of tasks and responsibilities also require adaptations in clinical practice guidelines and personnel policies.

Also differences in MR-Linac implementation appear between the Netherlands and the US. The Dutch interviewees elaborated on the necessary cooperation with competitive physicians outside the radiation oncology department to ensure treatment access. The Dutch interviewees also reported potentially conservative behaviour and resistance among technology users as a response to delegating tasks and changing daily routines. In the US, the interviewees noted that the Covid pandemic was an important factor in that it had led to changes in resource allocation, such as committing more human resources to primary care provision rather than to secondary tasks such as clinical evaluation of implementing MR-Linac.

Wider institutional and social context

This domain addresses the wider institutional and socio-cultural context. Both comparable and distinct findings were found about the implementation of MR-Linac in the Dutch

and US institutional and social context. There is a need to work with policy-makers to adjust clinical guidelines and formal licenses to the redistribution of roles and tasks, such as for radiation technologists. There is also a need for better consensus regarding reimbursement fees among MR-Linac providers and health insurers.

Interviewees in the US case particularly noted that the external authorities for reimbursement focused more on safety issues than on demonstrating clinical effectiveness. In particular, the Dutch interviewees mentioned the pressure of academic publishing which constrains knowledge exchange and open communication about treatment implementation among technology users. This may hinder effective multicentre collaboration and knowledge exchange between hospitals implementing MR-Linac.

The organizational resilience and technological development over time

This domain questions how much scope there is for adapting and coevolving the technology over time. MR-Linac's development is still continuing, without any predefined endpoints. New software features are expected to affect decision-making in treatment delivery, work processes in the radiation oncology department, and outcomes for patients and providers (both individual health care workers and hospitals as a whole). Hence, the scope for adapting and embedding MR-Linac in hospitals is dynamic. These findings suggest that individual and organizational resilience is necessary in managing potential changes and unexpected developments in implementing MR-Linac.

(E)valuation processes in place

This category identifies the necessary assessments of the outcomes of new technologies and how this is shared. It is broadly recognized in both the Netherlands and the US that evaluation processes need to be in place to evaluate treatment safety, outcomes and (cost)effectiveness. MR-Linac is being evaluated by, amongst others, the international MOMENTUM study, which is generating (cost)effectiveness evidence. Four European institutes, two institutes in the US, one in Canada, and the manufacturing industry for the MR-Linac (Elekta AB, Sweden) were involved in founding MOMENTUM (49).

The Netherlands is a forerunner in evaluating MR-Linac. Evaluating clinical effectiveness for new medical technologies is perceived as being more important for care insurers, and in the new European Medical Device Regulation. In the US, interviewees are more motivated by federal regulators to demonstrate safety rather than effectiveness, to ensure reimbursement. This is perceived by all US interviewees, and the reason why clinical evaluation has not been widely integrated into the hospital department.

Enactment through specific enablers

This domain identifies individuals or groups with the formal task to enable adoption of the technology and regulatory standards. It is necessary for specific technology users such as a radiation oncologist, radiation technologist and physicist, to engage with regulators, insurers and policy-makers in both countries. For instance, the implementation of new interventional procedures and personnel guidelines on MR-Linac technology requires endorsement from national regulatory authorities. Only Dutch interviewees indicated it was important for the Professional Association for Radiation Oncology (In Dutch: Nederlandse Vereniging voor Radiotherapie en Oncologie) to be engaged in the creation of appropriate staffing guidelines and referring physicians for treatment access.

In both cases, the manufacturer, Elekta, is important for enabling implementation by solving technical problems and translating research into technical specifications available for technology users (48). The international MR-Linac Consortium, consisting of over 30 centres and the manufacturer, support technology development, knowledge dissemination and best practices at individual and institutional level (48). This large scale academic-industrial partnership with all intellectual property rights and data sharing regulations needs to be recorded in a collaboration agreement.

Receptivity

This domain emphasises the novel institutional structures in anticipation of unexpected events and challenges when implementing the new technology. In both the Netherlands and the US, implementing MR-Linac results in a high level of individual receptivity (e.g., individual workplace training for staff to acquire MRI skills and competences) and organizational receptivity (e.g., new developments in hospital infrastructure, interventional protocols, staffing guidelines and reimbursement fees). The MR-Linac consortium acts as an information and communication platform to expand knowledge on MR-Linac and prepare its implementation at individual and institutional level.

Table 1 summarises the similar and distinct findings regarding the institutionalisation of MR-Linac in the Netherlands and the US respectively. The first column in Table 1 addresses the NASSS domains and IR categories. The second and third columns address the similarities and differences in institutionalisation between the two health care settings respectively. The fourth column addresses illustrative quotes from some of the respondents.

Table 1. Similarities and differences in the institutionalisation of MR-Linac in the Netherlands and the United States.

NASSS domains / IR categories	Similarities in MR-Linac institutionalisation between the Netherlands and the United States	Differences in MR-Linac institutionalisation between the Netherlands and the United States	Illustrative quotes
Clinical condition	• Potential for improved tumor control and reduced treatment toxicity • Scope for treatment new clinical indications • Lack of evidence of (cost) effectiveness		*'The key feature is the ability to see the cancer, to see the target that we want to treat when we're actually treating it to enable us to deliver the radiation dose more precisely. And it also offers the future potential to image the functional attributes of the target, which will further allow us to personalize the treatment by identifying patients that are responding to treatment and those that do not.'* (industry executive, US)
Technology to be adopted	• Superior online image guidance during treatment • Functional imaging of tumor and organs at risks • Scope for new treatment strategies • Substantial infrastructure, staffing and organizational requirements • Continuous software development • Technical complexities		*'The treatment will be finished faster. We will reduce the patient's burden if we reduce the 20 treatment fractions to 5. It can therefore save waiting lists. The present-day waiting list can last for about 6 weeks. Currently, patients are waiting additional hours for the final radiation plan.'* (radiation oncologist, NL) *'I reckon MR-Linac is mainly affordable for large hospitals, due to capital intensive investments and highly skilled staffing. It's an expensive device. It costs about three and a half times more than a conventional device.'* (radiation oncologist, US)
Value proposition	• Advanced technology • Potential for improved treatment quality • Professional development opportunities • In-hospital efficiencies • Research and funding possibilities • Lack of effectiveness evidence • Uncertain return of investment	• Cost-effectiveness potential of treatment can vary across health care systems	*'MR-Linac is a very expensive device that costs millions. However, this can lead to massive savings as a result of low claims on surgical procedures and anesthesia.'* (division manager, NL) *'Hypofractionation allows prostate cancer treatment in one to three times instead of five to twenty times. That saves a lot of time. MR-Linac is an excellent device for this purpose.'* (radiation oncologist, NL)

NASSS domains / IR categories	Similarities in MR-Linac institutionalisation between the Netherlands and the United States	Differences in MR-Linac institutionalisation between the Netherlands and the United States	Illustrative quotes
Adopter system	• New knowledge and competences • Continuous learning curve • Increased professional autonomy • Increased interdisciplinary teamwork • Redevelopment of tasks and responsibilities	• NL: necessary collaboration with referral physician for treatment access • NL: necessary cooperation with payer for reimbursement • US: potential reluctance of patients towards expensive medical innovations	*'I reflect about physics matters and the physicist about clinical matters. There is much more interaction between these two disciplines.'* (radiation oncologist, US) *'It will create a more interesting and challenging job. I really enjoy working on new projects. I cannot think of working in an ordinary radiation therapy department.'* (radiation technologist, NL)
Organization	• Substantial infrastructure and organizational investments • Changing staffing tasks and responsibilities • Ongoing education and development programs • Presence of professional silos	• NL: necessary collaboration with referring departments for treatment access • NL: conservative behaviour among healthcare professionals towards changes in clinical practice • NL: ethical discussions among healthcare professionals to provide unproven treatment • US: limited prioritisation of effectiveness evaluation	*'Traditionally, there is a separation between the preparation and treatment on the conventional radiation system. The preparation includes the creation of a treatment plan based on CT. The next step is the treatment. These two steps are two separated practices. In addition, in most hospitals these are performed by different groups. They are often in other departments and the interaction between them is therefore limited. This separation disappears with MR-Linac. The treatment plan, the diagnostics, is also performed online on this device.'* (physicist, NL) *'The radiotherapy department will require more competences with regard to MRI imaging. And how to interpret MRI images. There is also a need for the people actually at the machine to understand more about the dose symmetry of the treatment plan that's delivered, which hasn't been the case in the past. The doctor will need to increase their skills and the people actually operating the device will increase their skills. The physics group will need to increase their skills in terms of knowing more about MR imaging.'* (industry executive, US)

NASSS domains / IR categories	Similarities in MR-Linac institutionalisation between the Netherlands and the United States	Differences in MR-Linac institutionalisation between the Netherlands and the United States	Illustrative quotes
Wider institutional context	• Necessary changes in traditional reimbursement structures • Necessary changes in traditional staffing policy	• NL: pressing publicity atmosphere between academic technology users to share implementation knowledge	*'I think it's up to the individual organizations to come up with their own protocols and security measures.'* (radiation oncologist, US) *'True innovation is best done outside of the confines of rules that are necessary within a governed society.'* (physicist, US)
Organizational resilience and development over time	• Continuing technology development without clear endpoints • Uncertain clinical, economic, and organizational results over time		*'MR-Linac is a highly complex innovation. Practitioners should have experience to use the device correctly. MR-Linac is not a stable system. You have to be flexible and it's not consistent with the conventional security of ensuring that practices go as planned.'* (physicist, NL) *'The main internal challenge is the number of radiation technologists needed. This is simply a scarce resource. We continuously have a lot of vacancies for radiation technologists. We are not capable of dealing with this challenge.'* (radiation oncologist, US)
(E)valuation processes in place	• Evaluation of technology is necessary to evaluate treatment safety, outcomes and (cost) effectiveness	• US: very limited external incentive perceived to evaluate clinical effectiveness	*'Comprehensive scientific research must have been conducted and reproduced in another hospital.'* (healthcare insurer, NL) *'What would the cost be? What numbers are needed to actually make it a beneficial investment from a capital standpoint while the technological development still continues? I think that's the main discussion.'* (radiation oncologist, US)
Enactment through specific enablers	• Essential engagement between technology providers, policy-makers and insurers to set-up appropriate clinical practice guidelines and reimbursement • The manufacturer is essential to translate research findings into technical specifications available for all hospitals	• NL: preferred engagement with professional association to create appropriate clinical practice guidelines • NL: essential collaboration with referring physicians for treatment access	*'The radiation oncologist is the final decision-maker, but this could be more efficient. Currently, a radiation technologist is not allowed to approve a treatment plan.'* (division manager, NL)

NASSS domains / IR categories	Similarities in MR-Linac institutionalisation between the Netherlands and the United States	Differences in MR-Linac institutionalisation between the Netherlands and the United States	Illustrative quotes
Receptivity	• Necessary workplace trainings to educate technology users • International consortium to facilitate knowledge dissemination and best practices		*'Especially in the early days, structured sessions where we lay out and define what success looks like and we foster an open environment for differing perspectives to be heard.'* (radiation oncologist, US) *'Changing and creating a treatment plan online ad hoc requires a new attitude and mindset among many radiation oncologists. Many radiation oncologists use one day for the final treatment decision, which in this case is not possible when you have to decide right away.'* (radiation oncologist, NL)

NL = the Netherlands, US = the United States

DISCUSSION

While convergence is a major trend in the development of medical innovations, studies of the implications for the organization of health care are still scarce. We contribute by exploring how the institutionalisation of a convergent innovation, the MR-Linac technology, affects the organization of health care. We explored and compared the institutionalisation of MR-Linac in the Netherlands and the US.

The findings show how the institutionalisation of convergent innovation affects the organization of health care at technological (the integration of MRI and a linear accelerator into one device), individual (e.g., individual physicians in diagnostic radiology and oncology working together), organizational (e.g., engaging different departments and hospitals) and institutional levels (e.g., changing the regulatory environment). First, convergent innovation redefines and reorganises traditional working tasks of clinical users by tackling a compelling and complex health care problem. The convergence of diagnostic radiology and radiotherapy provides a real-time, improved understanding of individual treatment response, thereby enabling better-informed medical practice for both radiation oncologists and diagnostic radiologists. MR-Linac thus changes the traditional methods and delivery of radiation treatment and radiology into one common method. The realisation of these potential work changes, however, requires different efforts that enable an appropriate institutionalisation of MR-Linac. This resonates with the need for a high level of receptivity in the institutionalisation environment.

Secondly, convergent innovation empowers the development of new knowledge and competences for individual technology adopters. Technology users, such as radiation oncologists, technologists, and physicists have to learn and integrate fairly new knowledge (on MRI principles) and skills (on the use of advanced software in treatment) into their original knowledge base, i.e. the delivery of radiotherapy without MRI. Radiation oncologists have to acquire more institutional level knowledge (e.g., care insurance structures for new reimbursement schemes) and have be able to process technological and regulatory changes along with socio-cultural changes, such as changing responsibilities, working practices, personnel policies for new medical roles and a more collaboration-oriented hospital culture in general. Individual technology adopters need to further develop their competences in the technological, social, organizational field, and both deepen and broaden their knowledge of the convergent innovation at play.

Thirdly, convergent innovation fuels new means of intra- and interorganizational collaboration and emphasises the process of innovating and shared sense-making. MR-

Linac brings together physicians from radiation oncology, diagnostic radiology and in-house ICT experts. Convergent innovation thus unifies different knowledge flows into new working approaches to treatment, for example, by setting appropriate measurable outcomes for MRI and radiotherapy, and promoting more collaboration between distinct hospital departments. This increases internal hospital working practices, new guidelines, communication and research for individual technology users (50, 54). It also leads to additional administrative requests in the providing organization, such as changes in patient allocation across diagnostic radiology and radiation oncology departments and adaptations in financial and payment structures.

Fourthly, convergent innovation increases interaction and collective action between individual technology users from different backgrounds rather than solely technological development. Convergent innovation integrates intellectually-diverse actors and traditionally separated institutions (e.g., hospitals, the manufacturing industry and health policy-makers), which changes the traditional hospital organization and fosters novel work-related interactions. The actors involved in convergent innovation must find a way to collaborate and understand how their particular knowledge and competences contribute to institutionalisation. For instance, MR-Linac's ongoing software development requires collaboration between individuals with clinical, technical and ICT knowledge (43,55,56). Individual adopters implementing convergent innovation have to engage with actors beyond their daily work routines in the institutional health care setting.

Fifth, evaluation processes are gaining more attention in the institutionalisation of convergent innovation, in terms of the demonstrating treatment outcomes, adapted clinical guidelines and reimbursement opportunities and uncertainties in the wider institutional context. For instance, MR-Linac's treatment outcomes still need to be determined, which creates uncertainties for patients, providers and health care insurers (43,57). Moreover, convergent innovation may be attractive to health care workers to acquire new knowledge and skills, obtain increased autonomy, and further develop their tasks and responsibilities. Evaluation processes are necessary to identify these changes, which need to be included in formal guidelines such as clinical practice and personnel policies.

MR-Linac's ongoing digital development also requires evaluation, which is a continuous activity in response to internal and external decisions or needs of stakeholders. This resonates with the digitisation trend in medical innovation, which fosters personalised medicine and requires case-by-case regulation and policy adaptation (58–61). This also corresponds to the need for knowledge networks, and the development of clinical trials, treatment development and regulatory structures, in the institutionalisation of medical practices (62,63).

Sixth, convergent innovation creates an ecosystem for the organization of health care, including the involvement of a wide variety of institutions. For instance, the evaluation processes of the MR-Linac is also supported by clinical and commercial technology users, and by incentives from regulators in the adopter system. Institutionalising MR-Linac shows the importance of enactment through specific enablers, such as health care insurers, policy-makers, professional associations and the manufacturer industry. This is important to unify different areas of expertise and encourage collaboration among these stakeholders, which would facilitate more evidence-based information on the use of convergent innovation. This corresponds with the needed receptivity and so-called innovation governance efforts, in which diverse public and private actors are involved, steering the stimulation and regulation of novel knowledge creation and innovation processes (64) within the organization, but also in a specific institutional health care setting. Figure 1 summarises how the institutionalisation of MR-Linac affects the organization of health care.

The NASSS framework has proven to be useful for an overall understanding of the institutionalisation of MR-Linac, while the IR framework revealed key how MR-Linac is diffused in institutional structures, such as the role of a professional association, consortium and evaluation trials, for institutional readiness at a systemic level. Our findings also showed how NASSS domains are interdependent and interact in dynamic ways, thereby also providing insights into the complexity of the domains. For example, the value proposition of MR-Linac can be classified as highly complex because of the undefined cost-effectiveness potential and difficulties in formulating a reliable business plan. Hence, the clinical indication and technology domain of a convergent innovation such as MR-Linac can both be characterised as complex domains. The ongoing development of technology is expected to influence the work needed in the hospital and of the adopters, stressing a rather complex organization and adoption system.

The NASSS framework claims that medical innovations with high levels of complexity in domains are rarely successfully adopted and sustained (24). Our empirical work, however, reveals that a high degree of complexity and uncertainty in multiple NASSS domains does not hinder the ongoing large-scale adoption of MR-Linac worldwide (49). Proof of long-term adoption is yet to come, but convergent innovation with a high level of upfront investment and coordination may be difficult to remove from clinical practice. Evaluation processes are therefore necessary to promote and facilitate institutional readiness.

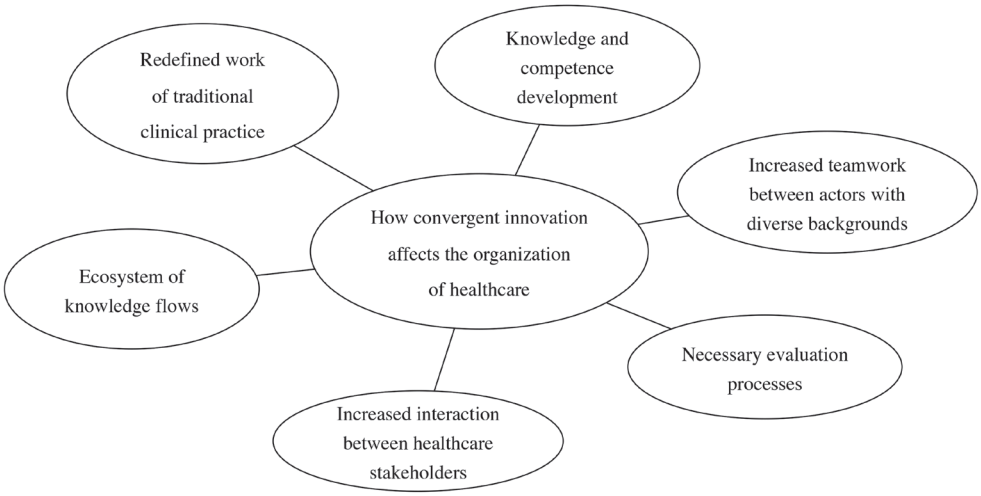

Figure 1. Convergent innovation affects the organization of healthcare by (1) redefining working tasks of traditional clinical practice, (2) developing new knowledge and competences of technology users, (3) fueling intra- and interorganizational teamwork, (4) requiring broad evaluation, (5) fueling collaboration between different healthcare stakeholders and (6) creating an ecosystem of knowledge flows between stakeholders.

Relevance and limitations

Our findings add to a better understanding of the organization of health care in the future, in which convergent innovation and digitisation are expected to play an important role. To obtain an encompassing perspective on MR-Linac institutionalization we included a broad range of stakeholders, including actors from both inside and outside the hospital environment. Applying the NASSS framework (24), complemented with complementary IR categories (30), provided an in-depth understanding of the institutionalisation of convergent innovation on the organization of health care both in the Dutch and the US health care setting. Future studies in other geographical health care settings, and studies of other types of convergent innovations, will add to the empirical evidence base of factors influencing the institutionalisation of convergent innovation (65).

Limitations in the research design include the relatively small number of stakeholders interviewed in the US (23) compared to the Netherlands (43). Interviews in the US were also conducted during the Covid pandemic which may have affected respondent's perspectives on how institutionalization of convergent innovation affects organization of health care. It was difficult to contact private and public insurance regulators in the US, whose insights regarding the regulatory and policy factors influencing institutionalisation

of convergent innovation would have been valuable. Ethnographic research on the institutionalisation of convergent innovation could offer a fine-grained understanding of the behaviour and interactions of individual technology users within a particular health care context. Studying convergence in other clinical conditions to be treated and other technology domains could reveal more specific insights in institutionalisation (66).

CONCLUSIONS

The institutionalisation of convergent innovations does affect the organization of health care. By investigating MR-Linac institutionalisation in two different health care contexts, we presented a study in which convergent innovation changed the traditional professional practice of addressing a medical condition, and the work of individual actors and institutions involved. Convergent innovation transforms the traditional way in which a medical problem is solved, including changes in the work tasks and routines of technology users. Convergent innovation increases individual and collective knowledge and competences development, and innovation and research activities for engaged actors. This is ideally facilitated by the evaluation of convergent innovation on its overall outcomes, which requires collaboration between stakeholders within and across institutions. The insights offered are also relevant for understanding convergence in the medical field, and for rethinking medical innovations in general.

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5

EARLY HEALTH ECONOMIC ANALYSIS OF 1.5T MRI-GUIDED RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER: DECISION ANALYTIC MODELLING IN THE NETHERLANDS

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Radiotherapy & Oncology (2021)

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 €6,460 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.

INTRODUCTION

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 to 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 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.

MATERIALS 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) (Figure 1).

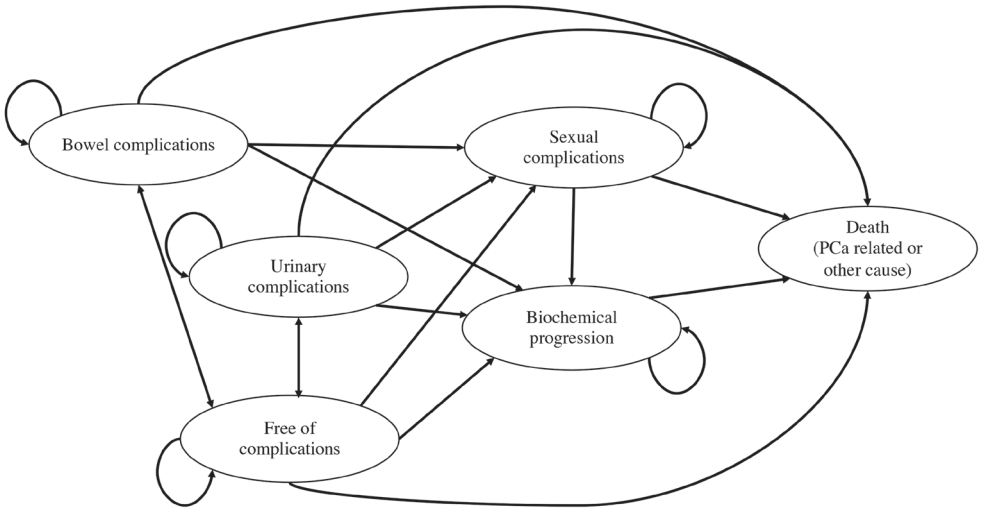

Figure 1. State transition model of the follow-up of men with localized prostate cancer. The model consists of six health states. The cohort enters the model in the health state "urinary complications", "bowel symptoms" or "free of complications". After the first cycle, patients with urinary and bowel 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.

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.

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

	MR-Linac 5 Fx	EBRT 5 Fx	EBRT 20 Fx	EBRT 39 Fx	LDR Brachytherapy
Health states	**Probability (source)**	**Probability (source)**	**Probability (source)**	**Probability (source)**	**Probability (source)**
Gr ≥ 2 acute urinary complications[a]	0.238 (41)	0.30 (13)	0.49 (42)	0.46 (42)	0.22 (43)
Gr ≥ 2 late urinary complications (gr ≥ 2)[b]	0.18 (44)	0.18 (44)	0.12 (42)	0.23 (42)	0.16 (43)
Gr ≥ 2 acute bowel complications[a]	0.05 (41)	0.14 (44)	0.39 (42)	0.25 (42)	0.03 (43,45)
Gr ≥ 2 late bowel complications[b]	0.18 (44)	0.13 (44)	0.12 (42)	0.06 (42)	0.02 (46)
Sexual complications[b]	0.35 (44)	0.35 (44)	0.65 (42)	0.67 (42)	0.35 (47)
Biochemical progression	0.07 (44)	0.07 (44)	0.08 (42)	0.06 (48)	0.05 (49)
Disease mortality	0.01 (48)	0.01 (48)	0.01 (48)	0.01 (48)	0.01 (48)

a. Acute complications occur within 3 months.

b. Late and sexual complications occur later than 3 months.

EBRT = external beam radiotherapy; Fx = fractions

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 (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).

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	1,165	470	1,635	Details in Appendix B (24,30)
EBRT 20 fractions	4,660	1,870	6,530	Details in Appendix B (24,30)
EBRT 39 fractions	9,090	3,650	12,740	Details in Appendix B (24,30)
LDR brachytherapy	4,490	95	4,585	Details in Appendix B (30,51)
MR-Linac	5,830	630	6,460	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	(26,52)
Biochemical progression			915/year	(29)

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 €6,460 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 €1,160 and gain up to 0.23 QALYs. Compared to 39 fractions, MR-Linac could save €9,170 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 €4,948 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 €2,020 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.

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%	+4,840	+0.06
EBRT 20 fractions	0	-1,160	+0.23
EBRT 39 fractions	0	-9,170	+0.11
LDR brachytherapy	66%	+2,020	+0.03

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 (Figure 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.

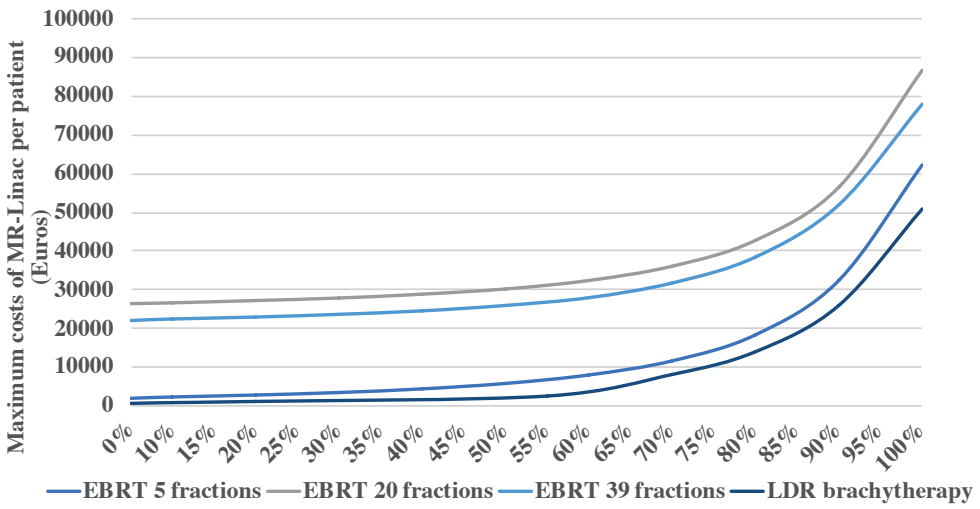

Figure 2. Acceptable prices of MR-Linac relative to comparator strategies at different reductions of complications at a cost-effectiveness threshold of 80,000 Euros per QALY. At base line of MR-Linac, we assumed its grade ≥2 acute urinary and bowel complications from Bruynzeel et al (13) having other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

Compared to EBRT 5-fractions, costs of MR-Linac may range from €2,050 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.

Figure 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.

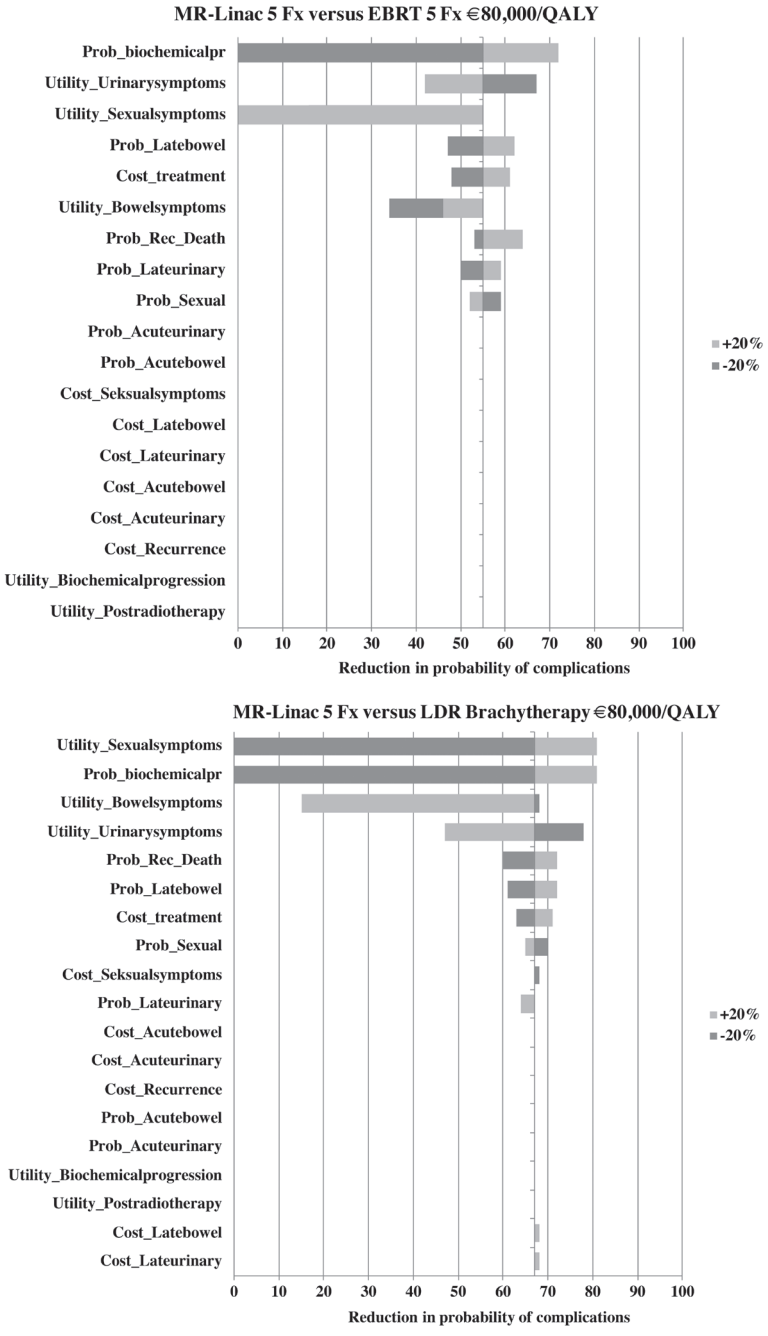

Figure 3. Results of sensitivity analyses of MR-Linac versus (i) EBRT 5 fractions and (ii) LDR Brachytherapy. The variables are ordered with those with the largest impact on the top. In both comparisons, results are most sensitive to the probability of biochemical progression and the utility of urinary,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

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 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 0.35T 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 to £30,000 per QALY is the cut-off value in United Kingdom and $50,000 to $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.

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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SUPPLEMENTARY MATERIALS

Background of 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	€1,165	1/fraction	€5,825	Schumacher et al. 2020
Travel costs	€126	1/ride	€630	Zorginstituut Nederland cost manual
Total:			€6,455	
EBRT 5 fractions				
Fraction	€233	1/fraction	€1,165	Peeters et al. 2010
Travel costs	€94	1/ride	€470	Zorginstituut Nederland cost manual
Total:			€1,635	
EBRT 20 fractions				
Fraction	€233	1/fraction	€4,660	Peeters et al. 2010
Travel costs	€94	1/ride	€1,870	Zorginstituut Nederland cost manual
Total:			€6,530	
EBRT 39 fractions				
Fraction	€233	1/fraction	€9,090	Peeters et al. 2010
Travel costs	€94	1/ride	€3,650	Zorginstituut Nederland cost manual
Total:			€12,740	
LDR brachytherapy				
Treatment	€4,990	1x	€4,490	Helou et al. 2017
Travel costs	€94	1/ride	€95	Zorginstituut Nederland cost manual
Total:			€4,585	

6

EARLY HEALTH ECONOMIC ANALYSIS OF 1.5T MRI-GUIDED RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER: DECISION ANALYTIC MODELLING IN THE UK NATIONAL HEALTH SERVICE

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ABSTRACT

Background and purpose: Ultrahypofractionated MRI-guided radiotherapy (MRgRT) with the 1.5 Tesla magnetic resonance imaging radiotherapy linear accelerator (MR-Linac) is gaining interest for treatment of localized prostate cancer. Theoretical advantages include reduction treatment complications and improved local tumor control. Clinical evidence is lacking and it therefore remains uncertain whether MRgRT is cost-effective. An early health economic analysis was performed to calculate the necessary relative reduction in complications and the maximum price of MRgRT (2-fraction) to be cost-effective compared to 5-fraction stereotactic body radiotherapy (SBRT), 20-fraction external beam radiotherapy (EBRT), and low-dose-rate (LDR) brachytherapy.

Materials and methods: We used a validated state transition model for men with localized prostate cancer. Complication rates and utilities such as grade ≥2 urinary, grade ≥2 bowel and sexual complications were based on PACE randomized controlled trial and systematic literature searches. Costs were collected from the UK National Health Service. The UK decision threshold for a high burden of disease is £30,000 per QALY. Cost scenarios for MRgRT were calculated according to different staff and numbers of fractions on a single MR-Linac device. 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 the highest and lowest price of £6,713 and £4,103 respectively for MRgRT per patient, it was found to be cost-effective when complications were reduced by 68% and 43% compared to SBRT, 72% and 58% compared to EBRT, and 92% and 89% compared to LDR brachytherapy. Results were highly sensitive to the utilities of urinary, bowel and sexual complications and the probability of biochemical progression.

Conclusions: MRgRT was found to be cost-effective over SBRT and EBRT 20-fraction when MRgRT is offered at lower costs or complications are reduced substantially. The cost-effectiveness potential of MRgRT compared to LDR brachytherapy is likely to be the poorest.

INTRODUCTION

The 1.5 Tesla magnetic resonance (MR) imaging with a linear accelerator (Linac), MR-Linac, is being implemented worldwide (1). It allows online and real-time, soft-tissue imaging and targeted MRI-guided radiotherapy (MRgRT) (2). MRgRT allows a higher delivered radiation dose to the target in fewer sessions, also called (ultra)hypofractionation, permitting a shorter overall treatment time (3,4). Two- and five-fraction MRgRT are gaining interest for prostate radiotherapy (5–7). These fractionation schedules can be beneficial as traditional external beam radiotherapy (EBRT) for prostate cancer often varies from 20 to 39 fraction (8–10). The HERMES trial (NCT04595019) is currently studying safety of two-fraction MRgRT for prostate cancer in the United Kingdom (UK).

Theoretical promises of MRgRT include improved targeting of the tumor, higher effectiveness and increased patient convenience (11–15), but solid cost-effectiveness evidence is still missing (1,16). This lack may lead to inappropriate decision-making on treatment implementation and a potential increase in healthcare costs without quality improvement (17,18). MRgRT is a more time- and labour-intensive treatment to deliver, hence, tangible benefits must be demonstrated in order to justify the use of more expensive technology.

Acute and long-term outcomes of MRgRT are still being collected, which hampers a comprehensive cost-benefit analysis at present. Moreover, MRgRT is still in development and, hence, optimal treatment scenarios are still evolving. Early health economic analysis is useful to identify areas where new and developing technologies such as MRgRT are potentially cost-effective and determine conditions for cost-effective outcomes (19,20).

Early health economic analysis often relies on decision analytic modelling, which can be used to explore treatment scenarios by combining costs and clinical effects from different sources when technology data are not yet available (21). By doing so, it can identify worthwhile treatment strategies and guide further research and development choices in MRgRT. This provides valid input into technology decision-making, reducing the chance that wrong decisions will be made early on. Implications of early health economic analysis are often country-specific, as the threshold for cost-effectiveness varies internationally.

The number of published early health economic analyses is limited. One early economic analysis in the USA estimated that MRgRT for prostate cancer may be cost-effective compared to CT-guided radiotherapy through minor reduction in urinary and bowel complications alone (22). In our previous early economic analysis for prostate cancer in

the Netherlands, we found that 5-fraction MRgRT can be cost-effective compared to 20- and 39-fraction EBRT; and that compared to 5-fraction stereotactic body radiotherapy (SBRT) and low-dose-rate (LDR) brachytherapy, MRgRT has to reduce complications by 54% and 66% respectively or be offered at lower costs (22).

This study investigates the cost-effectiveness of 2-fraction MRgRT in patients in the UK with intermediate risk localized prostate cancer, using the transition model from our prior early health economic analysis. Our objective is to estimate the relative minimally required reduction in grade ≥2 urinary, grade ≥2 bowel and sexual complications of MRgRT to be cost-effective compared to current radiotherapy regimens used in the UK. We also calculate the maximum price of MRgRT to be cost-effective, given complication thresholds and assess the impact of treatment-related features on complications of MRgRT to be found cost-effective.

MATERIALS AND METHODS

A state transition model was adapted to country- and scenario-specific parameters. This model was used to identify the thresholds of complications and costs for 2-fraction MRgRT to be cost-effective compared to 5-fraction SBRT, 20-fraction EBRT, and LDR brachytherapy. Our hypothetical cohort consisted of 1000 men with intermediate-risk localized prostate cancer and no other severe comorbidities, treated at age 65 years.

State transition model

Our model was constructed in Microsoft Excel (Microsoft, Redmond, Washington, USA) and has been appraised and rebuilt in R Studio 1.1.383 (Boston, MA) by an independent expert which produced identical results. Within the model the patient cohort moved through different health states over a life-time horizon. 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) (Figure 1, Supplementary Materials).

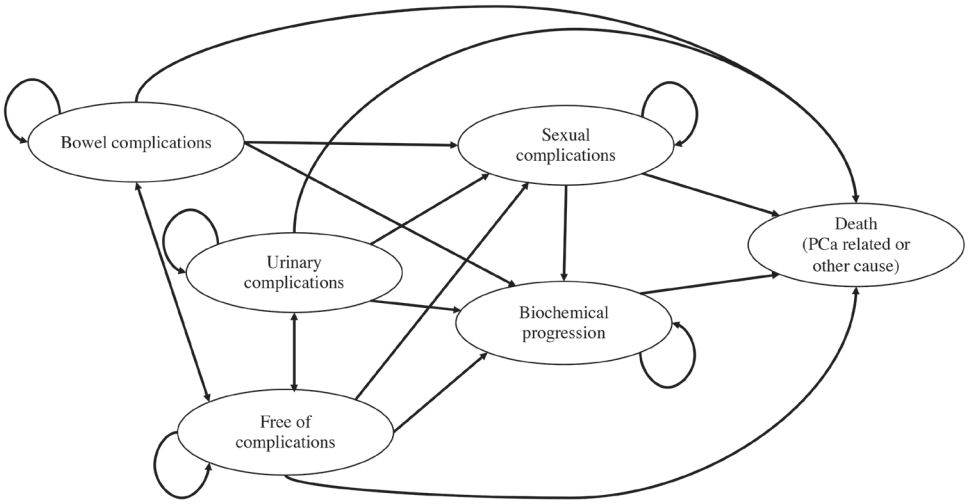

Figure 1. State transition model of the follow-up of men with localized prostate cancer. The model consists of six health states. The cohort enters the model in the health state "urinary complications", "bowel symptoms" or "free of complications". After the first cycle, patients with urinary and bowel 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.

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 British population from 65 year onwards. Death from cancer could only occur after a patient had transitioned to biochemical progression.

Since real-life data of costs and effects for 2-fraction MRgRT were limited, we assumed the baseline of 2-fraction MRgRT's clinical outcomes to be equal effective to SBRT. For SBRT and 20-fraction EBRT, complication rates were based on data from the PACE-B trial (23). PACE-B is a multicentre, phase 3 randomised controlled trial, launched in 2015, to assess whether SBRT offers therapeutic benefit over conventional radiotherapy for prostate cancer. Complication rates for LDR brachytherapy and utilities were based on systematic literature searches (Table 1).

Table 2. Transition probabilities of health states for MRI-guided radiotherapy and comparator strategies.

	MRgRT 2 Fx	SBRT	EBRT 20 Fx	LDR Brachytherapy
Health states	**Probability (estimation)**	**Probability (source)**	**Probability (source)**	**Probability (source)**
Acute GU toxicity gr≥2 3rd month	Assumed equal to SBRT 5 Fx	0.292 (16)	0.223 (16)	0.22 (43)
Late GU toxicity gr≥2 24 months	Assumed equal to SBRT 5 Fx	0.319 (23)	0.195 (23)	0.16 (43)
Acute GI toxicity gr≥2 3rd month	Assumed equal to SBRT 5 Fx	0.149 (16)	0.077 (16)	0.03 (43,44)
Late GI toxicity gr≥2 24 months	Assumed equal to SBRT 5 Fx	0.123 (23)	0.121 (23)	0.02 (45)
Erectile dysfunction	Assumed equal to SBRT 5 Fx	0.193 (23)	0.222 (23)	0.35 (46)
Biochemical progression (from 5 year onwards)	Assumed equal to SBRT 5 Fx	0.094 (47)	0.094 (47)	0.05 (48)
Disease mortality after biochemical progression	Assumed equal to SBRT 5 Fx	0.01 (49)	0.01 (49)	0.01 (49)
Mortality rates; males, age specific (starting from 65 years)	United Kingdom Interim Lifetables			

MRgRT = MRI-guided radiotherapy; SBRT = stereotactic body radiotherapy; EBRT = external beam radiotherapy; LDR brachytherapy = low dose rate brachytherapy; Fx = fraction

Quality of life

Effectiveness of treatments was expressed in QALYs that combine quality and length of life, where one QALY equals one 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 quality of life after MRgRT were available, we assumed similar post-treatment utility as conventional EBRT. The discounting of utilities was performed using an annual rate of 3.5%. Discounting is performed to adjust future costs and outcomes of healthcare interventions to “present” value (24).

Costs

Cost data for treatment and medication for treatment complications were derived from published health economic analyses, from the UK National Health Service (NHS) perspective (25–27). We assumed that patients with biochemical progression received hormonal therapy only.

We calculated the price per fraction for MRgRT based on the costs for technology equipment, construction, maintenance and operating costs. The price was also determined by the annual departmental fraction throughput (total fractions per device

per year) and the staff attendance on a single MR-Linac device. We assumed different price scenarios as the throughput and staffing levels of the MR-Linac can vary and are likely to be streamlined over the coming years.

First, the fraction throughput on one MR-Linac was measured at the Royal Marsden Hospital (London, UK) in 2020 and 2021. Given the context of the Covid pandemic in these two years and a possible different throughput compared in other conditions, three throughput scenarios were created based on the average number of fraction of these years with +/- 20%. The higher the number of fraction throughput, the lower the price for each radiotherapy treatment can be (28).

The presence of staff during the actual treatment delivery on the MR-Linac may differ among hospitals (2). Two staffing scenarios where therefore created: the attendance of (i) one radiation oncologist, one physicist and three therapeutic radiographers, or (ii) the attendance of only three therapeutic radiographers at the device.

Based on throughput and staffing options, six price scenarios for MRgRT were calculated (Appendix B). Table 2 presents all costs per treatment strategy and complication. Costs were calculated in Pounds, corrected for inflation to 2021. Future costs were discounted using an annual rate of 3.5%.

Model analysis

Main outcomes of the analysis were the required relative reductions of urinary, bowel and sexual complications, needed with the maximum price of MRgRT, to become cost-effective over comparison 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 the UK decision threshold for a high burden of disease of £30,000 per QALY (29).

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

Utility parameters		**Value (Source)**
Post-treatment		0.73 (43)
No complications		0.95 (44)
Urinary complications		0.83 (43)
Bowel complications		0.71 (43)
Sexual complications		0.89 (43)
Biochemical progression		0.73 (43)
Treatment costs	**Unit costs (Pound)**	**Source**
SBRT 5 fraction	3.966	UK NHS
EBRT 20 fraction	4.569	UK NHS
LDR brachytherapy	5.961	UK NHS
Medication costs		
Acute urinary complications (gr ≥ 2)	27	UK NHS
Late urinary complications (gr ≥ 2)	376/year	UK NHS
Acute bowel complications (gr ≥ 2)	60	UK NHS
Late bowel complications (gr ≥ 2) flexible sigmoidoscopy once	778/year 411	UK NHS
Sexual complications	20/month	UK NHS
Biochemical progression		UK NHS
PSMA PET (1/3) CT and bone scan (1/3) PSA surveillance (1/3)	1436 320 20	
First 28 days Bicalutamide 150mg/daily (£8.33) afterwards Zoladex every 3 months (£235)	8.33/day 940/year	

MRgRT = MRI-guided radiotherapy; SBRT = stereotactic body radiotherapy; EBRT = external beam radiotherapy; LDR brachytherapy = low dose rate brachytherapy

Threshold analyses

Threshold analyses quantify how much the outcome of interest can change before the recommended input changes. We performed threshold analyses 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 £30,000 per QALY (19). Threshold analyses were also performed to identify the maximum price of MRgRT at different reductions of complications.

Sensitivity analyses

One-way deterministic sensitivity analyses were performed to determine the parameters to which the necessary reduction of complications of MRgRT to be cost-effective were

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 internally validated by building it in another software package by an independent expert. Furthermore, the model was constructed in Microsoft Excel (Microsoft, Redmond, Washington, USA) and was rebuilt in R Studio 1.1.383 (Boston, MA) which produced the exact 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.

RESULTS

The maximal staff scenario included one radiation oncologist, one physicist and three therapeutic radiographers present during treatment delivery on the MR-Linac. The minimal staff scenario included only three therapeutic radiographers. The throughput scenarios included (i) 843, (ii) 1011 and (iii) 674 fraction on the MR-Linac per year. We calculated six prices for MRgRT (Table 3).

MRgRT had to reduce grade ≥2 urinary, grade ≥2 bowel and sexual complications to become cost-effective compared to SBRT, EBRT 20-fraction and LDR brachytherapy (Table 3). When compared to SBRT at the highest price of £6713 per patient, MRgRT was be cost-effective when it reduced complications by at least 68%. At the lowest price of £4103, MRgRT had to reduce complications by at least 43% to become cost-effective compared to SBRT.

For instance, if MRgRT costs £6713, it appears to be cost-effective when complications are reduced by at least 68% compared to SBRT. For instance, a relative reduction of 68% would translate in a reduction in absolute probability of acute and late urinary complications would need to be reduced from 29.2% to 9.3% and from 31.9% to 11.1% respectively. Acute and late bowel complications would need to be reduced from 14.9% to 4.8% and from 12.3% to 3.9% respectively, and sexual complications from 19.3% to 6.2%. In this case, the incremental cost of MR-Linac would be £3,582 while gaining up to 0.12 QALYs.

If MRgRT would cost £6713, it could also be cost-effective compared to SBRT when only acute and late bowel complications were reduced to at least 6.7% and 1.5% (a reduction of 55%), if sexual and acute urinary complications were not reduced more than the rates of SBRT. Total elimination of urinary or sexual complications alone would not make MRgRT cost-effective compared to SBRT.

Compared to EBRT 20-fraction at a cost of £6713, MRgRT appears to be cost-effective when complications were reduced by at least 72%. In absolute terms, acute and late urinary complications would need to be reduced from 22.3% to 6.2% and from 19.5% to 5.5% respectively. For acute and late bowel complications, this represents a decrease from 7.7% to 2.2% and from 12.1% to 3.4% respectively, and sexual complications from 22.2% to 6.2%. The incremental cost of MRgRT would be £3008 while gaining up to 0.11 QALYs. The individual reduction of urinary, bowel or sexual complications separately would not make MRgRT cost-effective compared to EBRT 20-fraction. At the lowest price of £4103 for MRgRT, it has to reduce complications by at least 58% to become cost-effective compared to EBRT.

Compared to LDR brachytherapy, MRgRT at a cost of £6713 had to reduce complications by at least 92% to become cost-effective. In absolute terms, acute and late urinary complications would need to be reduced from 22% to 1.8% and from 16% to 1.3% respectively. Acute and late bowel complications need to be reduced from 3% to 0.24% and from 2% to 0.16% respectively, and sexual complications from 35% to 2.8%. The incremental cost of MR-Linac would be €5917 while gaining up to 0.23 QALYs. The individual reduction of urinary, bowel or sexual complications separately would not make MRgRT cost-effective compared to LDR brachytherapy. At the lowest price of £4103 for MRgRT, it had to reduce complications by at least 89% to become cost-effective over LDR brachytherapy.

Table 3. Thresholds in probabilities of necessary reduction in urinary, bowel and sexual complications for MRgRT versus comparator strategies to be cost-effective in different staffing and throughput scenarios at 30,000 Pound per QALY. The maximum staffing scenario includes one radiation oncologist, one physicist and three therapeutic radiographers and the maximum staffing scenario 2 includes three therapeutic radiographers. The incremental costs and QALYs of MRgRT are also presented in each comparison.

	Maximum staff scenario of MRgRT			**Minimum staff scenario of MRgRT**		
Throughput scenario	-20%	Baseline	+20%	-20%	Baseline	+20%
Costs of MRgRT per patient (£)	6.713	5.367	4.475	6.154	4.920	4.103
			SBRT			
Relative required reduction in complications	68%	60%	50%	65%	56%	43%
Incremental costs (£)	+3.582	+2.248	+1.269	+3.040	+1.776	+802
Incremental QALYs	+0.12	+0.08	+0.04	+0.10	+0.06	+0.03
			20-fraction EBRT			
Relative required reduction in complications	72%	66%	61%	70%	64%	58%
Incremental costs (£)	+3.008	+1.730	+840	+2.481	+1.228	+454
Incremental QALYs	+0.11	+0.06	+0.03	+0.09	+0.05	+0.02
			LDR brachytherapy			
Relative required reduction in complications	92%	91%	90%	91%	90%	89%
Incremental costs (£)	+5.938	+4.865	+4.055	+5.566	+4.500	+4.177
Incremental QALYs	+0.23	+0.18	+0.16	+0.19	+0.16	+0.13

MRgRT = MRI-guided radiotherapy, SBRT = stereotactic beam radiotherapy, EBRT = external beam radiotherapy, LDR brachytherapy = low-dose-rate brachytherapy, QALYs = quality adjusted life years

We also modelled the maximum price per patient for MRgRT relative to SBRT and EBRT 20-fraction from conservative to no complications at the threshold of £30,000 per QALY for being cost-effectivec compared to SBRT and EBRT 20-fraction (Figure 2). Relative to SBRT, costs of MRgRT may range from £3864 to £36,550 per patient to be cost-effective. Compared to EBRT 20-fraction, costs of MRgRT may range from £2873 to £33,156 per patient when reducing complications from conservative to no complications. We did not model the comparison with LDR brachytherapy. A relative reduction in complications of less than 83%, even without a price for MRgRT, leads to less QALYs as well as higher costs compared to brachytherapy, hence, negative incremental cost-effectiveness ratios.

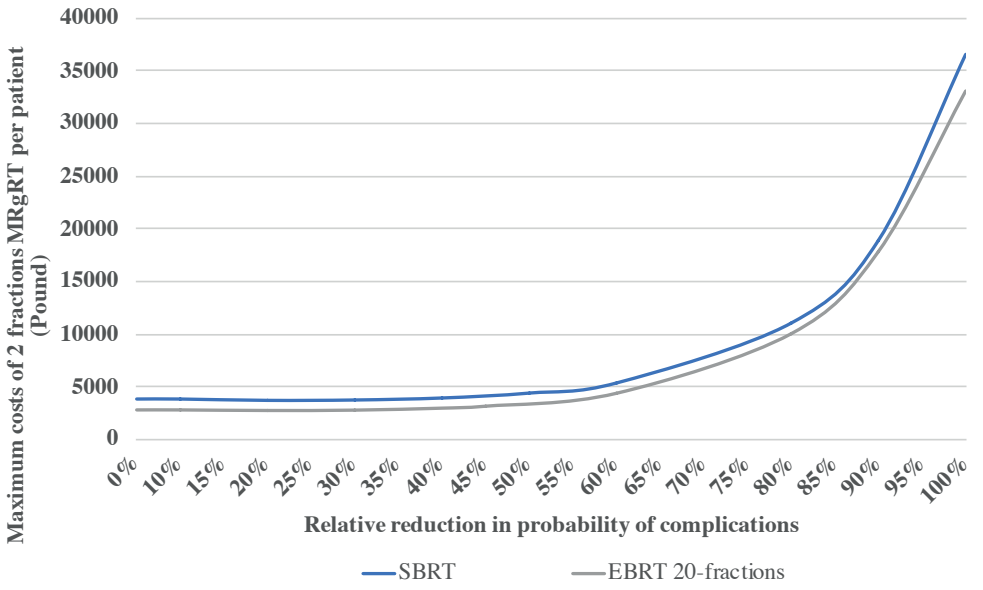

Figure 2. Acceptable prices of MRgRT relative to comparator strategies at different reductions of complications at a cost-effectiveness threshold of 30,000 Pound per QALY. At base line of MRgRT, we assumed its complications to be of equal effectiveness to SBRT.

MRgRT = MRI-guided radiotherapy, SBRT = stereotactic beam radiotherapy, EBRT = external beam radiotherapy

Probability of biochemical progression and the utilities of urinary and sexual complications had the highest impact on the necessary reduction in complications of MRgRT to become cost-effective compared to SBRT (Figure 3). Treatment cost also had considerable impact on the required reduction in complications.

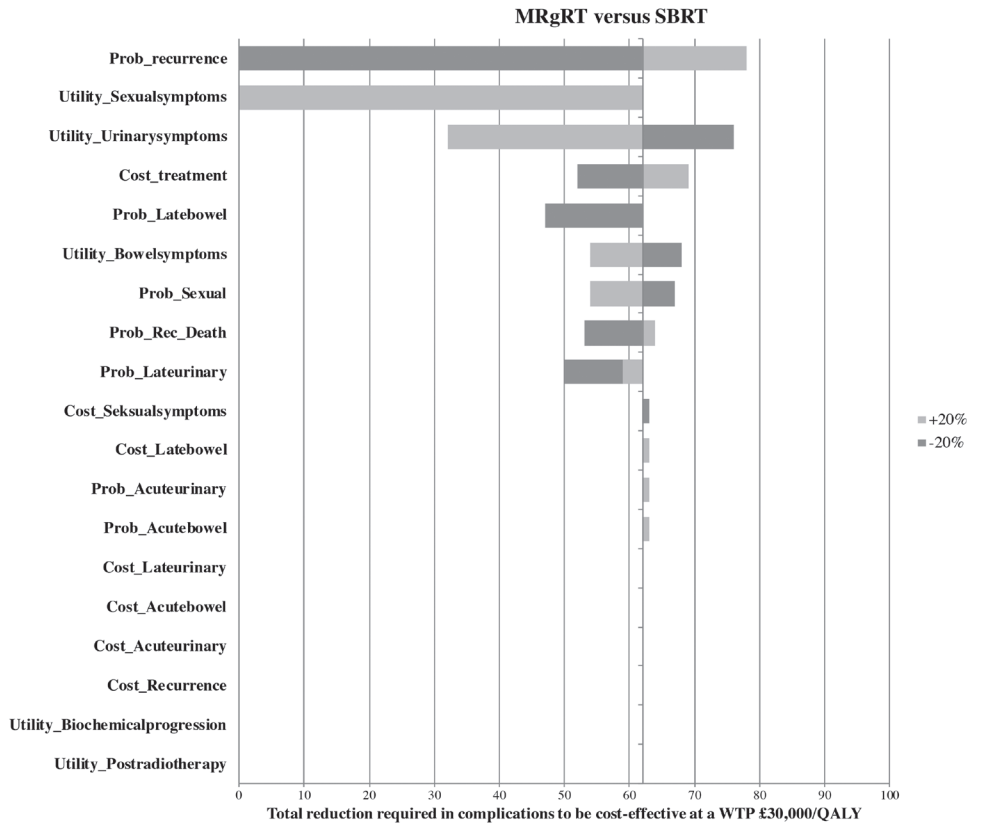

Figure 3. Results of sensitivity analyses of MRgRT versus SBRT. The variables are ordered with those with the largest impact on the top. In both comparisons, results are most sensitive to the probability of biochemical progression and the utility of urinary, bowel and sexual complications.

MRgRT = MRI-guided radiotherapy, SBRT = stereotactic beam radiotherapy, EBRT = external beam radiotherapy, LDR brachytherapy = low-dose-rate brachytherapy, WTP = willingness-to-pay threshold

DISCUSSION

MRgRT in 2-fractions was found to be cost-effective when a large relative reduction in complications compared to the baseline standard treatment was achieved at the cost-effectiveness threshold of £30,000 per QALY (68% and 43% compared to SBRT, 72% and 58% compared to EBRT 20-fraction and 92% and 89% compared to LDR brachytherapy at the highest and lowest price respectively). Alternatively, MRgRT will have to be offered at lower costs, as can be seen from varying the conservative complications to zero.

More challenging cost-effectiveness scenarios exist compared to LDR brachytherapy. MRgRT has to reduce complications by at least 83% to become cost-effective, hence, lower reductions than 83% with even a cost-free treatment leads to non-cost-effective results. Previous studies already claimed that MRgRT may have poor cost-effectiveness potential compared to LDR brachytherapy in intermediate-risk prostate cancer patients (30).

Large reductions in complications for MRgRT may be improbable, given the low rates of complications seen in studies of modern radiotherapy (e.g., Jackson et al. (28)). However, the interim results of the MIRAGE trial have shown a significant reduction in acute grade ≥2 urinary (47% vs 22.4%, p=0.01) and bowel (13.7% vs 0%, p=0.01) toxicity with MR-guided gated, but non-adaptive radiotherapy (32,33). The MRgRT group received radiotherapy with a smaller margin, justified by the use of MR-guidance. Further reduction in uncertainty margins of radiotherapy may result in less complications (15,34).

Our study considers different staff scenarios. For instance, MRgRT's baseline was found to be cost-effective compared to SBRT at a required reduction in complication of 60% with attendance of the radiation oncologist and physicist during treatment delivery on the MR-Linac versus 56% without attendance. Differences in complication thresholds for MRgRT to become cost-effective either with and without attendance of the radiation oncologist and physicist during treatment appeared to be small.

Prostate cancer MRgRT still requires a considerable number of physician person-hours with a relatively long duration fraction delivery time of about 45 min (2,34–36). Personnel expenses may reduce over time since learning curves enable operational efficiencies in MRgRT delivery and positively impact actual treatment costs (37). The ongoing development of MRgRT may also improve its cost-effectiveness potential (34,37,38). MR-guidance may allow faster fraction delivery by unlocking advanced, automated adaptive contour propagation and rapid dose reconstruction during radiation (36).

EBRT provided in 20-fraction remains the standard in the UK for now, but more precise radiotherapy will likely push prostate cancer radiotherapy towards fewer fraction (39,40). Our cost calculations for MRgRT also included the annual throughput of radiotherapy fraction and costs for technology and organizational investments, which are perceived to be key drivers of costs for complex radiotherapy (38). Relatively fewer radiotherapy fractions would also reduce clinic visits and improve patient convenience, waiting times and socioeconomic costs of treatment (6,41).

Results were highly sensitive to the probability of biochemical progression and the utilities of urinary, bowel and sexual complications of MRgRT. If MRgRT were associated with improved oncological outcomes compared to other treatments then a smaller reduction in complications of MRgRT would be required to achieve cost-effective results. For instance, compared to SBRT, an increase of 20% in biochemical progression of MRgRT requires a reduction in complications of at least 63% (instead of 54%). These variables are a major source of uncertainty; future cost-effectiveness analysis has to anticipate the impact of these parameters.

Robust data for the comparison treatment is highly important in early health economic modelling to increase the validity of results (19,42). In this study, no large, multi-centre, randomised data was available to inform the LDR brachytherapy toxicity estimates, so these are less robust results than SBRT and 20-fraction EBRT. Much of the LDR brachytherapy literature is from smaller series and a small number of centres. This is in contrast to SBRT and 20-fraction EBRT, for which the complication rates are derived from the PACE-B study.

To interpret our results we used UK cost data and the formal cost-effectiveness threshold of £30,000 per QALY. This means that the exact numbers may not be applicable in other healthcare systems. A prospective cost-effectiveness analysis investigating empirical costs and effects of MRgRT is needed to reduce uncertainty and evaluate the empirical added-value. Comprehensive micro-costing is useful to determine the cost of MRgRT more precisely, but the ongoing technology development impedes a definitive cost calculation (34).

CONCLUSION

MRgRT was found to be cost-effective compared to SBRT and 20-fraction EBRT only when either rates of complications or costs are reduced substantially. MRgRT had the lowest cost-effectiveness potential compared to LDR brachytherapy. It remains to be seen whether the substantial reductions in complications needed to make MRgRT cost-effective are feasible in practice. Cost-effectiveness outcomes were highly sensitive to biochemical progression and utilities of urinary, bowel and sexual complications. Findings must be used as early insight and guidance in decision-making on MR-Linac implementation and further technological development.

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SUPPLEMENTARY MATERIALS

Background of 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 British population from the age of 65 year onwards.

Costs of MRI-guided radiotherapy

Cost component		**Total cost per year**	
Annual costs 1 MR-Linac		£1.169.170	
Annual maintenance costs		£547.449	
Other components (space, overhead etc)		£165.505	
Staff attendance on one MR-Linac		*Maximum scenario*	*Minimum scenario*
Radiation oncologist (£101.432,00/FTE)		1	0
Therapeutic radiographer (£63.903/FTE)		3	3
Physicist (£87.005/FTE)		1	0
Total costs per year		£2.262.270	£2.073.833
Expected number of fractions MRgRT per year			
Scenario +20%	674		
Baseline scenario	843		
Scenario -20%	1011		
Price for 2-fraction MRgRT according scenario		*Maximum scenario*	*Minimum scenario*
Minimum price scenario +20%		£4.475	£4.103
Baseline price scenario		£5.367	£4.920
Maximum price scenario -20%		£6.713	£6.154

MRgRT = MRI-guided radiotherapy

7

SUMMARY

The 1.5 Tesla magnetic resonance (MR) imaging with a linear accelerator (Linac), MR-Linac, is being implemented worldwide. It enables online and real-time, soft-tissue imaging and targeted MRI-guided radiotherapy (MRgRT). This approach allows a higher delivered radiation dose to the target in fewer sessions, also called (ultra)hypofractionation, permitting a shorter overall treatment time. MRgRT has the potential to provide improved targeting of the tumor, increased effectiveness and better patient convenience. Despite theoretical promises, implementing MR-Linac into oncology care is accompanied by uncertainty and risks given the lack of solid evidence on (cost-)effectiveness and expensive technology investments.

Incorporating evidence and weighing trade-offs between potential benefits and harms of implementing new treatment, would support decision-making regarding technology implementation. MR-Linac implementation so far, has only been studied mainly from a clinical and technological point of view, whereas a broader view is evidently necessary. This thesis combined qualitative and quantitative methods to explore the implementation and early cost-effectiveness scenarios of the MR-Linac for the treatment of prostate cancer.

In **Chapter 2** and **3**, we explored opportunities and challenges in implementation of MR-Linac in the Netherlands and the United States (US). In both countries, opportunities were: the acquirement of (1) advanced MRI-guided radiotherapy technology with (2) the possibility for improved patient outcomes and (3) economic benefits, as well as (4) professional development and (5) a higher hospital quality profile. Barriers in both countries were: (1) technical complexities, (2) large staffing and structural investments, (3) the current missing evidence regarding the clinical benefits, and the presence of (4) professional silos.

There are also differences in MR-Linac implementation between the Netherlands and the US. Dutch interviewees described the necessary cooperation with referring physicians outside the radiation oncology department to ensure treatment access. Dutch interviewees also reported conservative behaviour and resistance among technology users as a response to assigning tasks and changing daily routines. US interviewees mentioned potential challenges regarding certain patient groups with a reluctant attitude towards new therapy. They also explicitly stated the limited external incentive to evaluate clinical effectiveness in implementation. The study of two healthcare settings with different care and compensation procedures (e.g. Dutch public versus US private healthcare funding) validated the relevance of studying implementation across countries and offered a better understanding of country-specific influences.

In **Chapter 4**, we compared the two-country cases and explored how MR-Linac implementation affects the organization of healthcare. Implementation affects the organization of healthcare at the individual (e.g., increased collaboration between individual physicians such as the radiation oncologist and radiologist), organizational (e.g., increased collaboration between different expertise departments such as radiation oncology, radiology and ICT) and institutional levels (e.g., regulatory and policy environment). Findings show that institutionalisation of convergent innovation affects the organisation of health care by: changing the traditional organisation of solving a medical problem, thereby transforming and reorganizing work in the health care environment, providing opportunities for individual user development, collective action and cross-sectoral developments, and requiring the additional work of evaluating convergent innovation, including administrative tasks, innovation and research activities.

Health economic evaluation is important to identify circumstances under which technology implementation could be cost-effective, thereby informing decision-making regarding the use of the new technology. Five- and two-fraction MRgRT are gaining interest for the treatment of prostate cancer. In **Chapter 5** and **6**, we explored different early cost-effectiveness scenarios of MR-Linac for the treatment of low- and intermediate-risk prostate cancer in the Netherlands and the United Kingdom (UK). We identified the necessary decrease in number of complications in order for the MR-Linac to become cost-effective compared to standard care and what the maximum costs may be. When five-fraction MRgRT leads to a big decrease in complications and can be given at low costs in the Netherlands, it is found to be cost-effective over five-fraction external beam radiotherapy (EBRT) and low-dose-rate (LDR) brachytherapy. In the UK, MRgRT provided in 2-fraction was found to be cost-effective over EBRT 5-fraction and 20-fraction when MRgRT is offered at lower costs or complications are reduced substantially. The cost-effectiveness potential of MRgRT compared to LDR brachytherapy is likely to be the poorest.

Traditionally, the main factors driving the value of medical treatments are proven effectiveness and cost-effectiveness. This is different for complex medical technologies such as the MR-Linac technology. These technologies combine scientific disciplines, functions or tools in a single solution-oriented method with clinical, technical, economic, organizational and social synergies for disease management. Patients should be at the center when introducing complex medical technologies, yet, implementation also affects healthcare professionals, providers, researchers, payers, the manufacturing industry, and governmental bodies. Clinical research on effectiveness and cost-effectiveness in implementation is still important, but not enough to realize the potential of complex medical technologies.

GENERAL DISCUSSION

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Submitted

Traditionally, the main factors driving the value of medical treatments are proven effectiveness and cost-effectiveness. This is different for complex medical technologies such as MR-Linac technology that combine scientific disciplines, functions or tools in a single solution-oriented method with clinical, technical, economic, organizational and social synergies for disease prevention, diagnosis, monitoring or therapy. Patients should be at the center when introducing complex medical technologies, yet, implementation also affects healthcare professionals, providers, researchers, payers, the manufacturing industry, and governmental bodies. Implementing complex medical technologies needs to be more than a technical and clinical exercise to achieve their potential; so what can help? Three recommendations can be made.

1. Engage and empower stakeholders before implementation

First, it is important to engage stakeholders before implementing the complex medical technology in clinical practice to promote its relevance, usefulness and effectiveness from multiple perspectives. For instance, employing complex medical technologies requires collaboration between individuals with diverse expertise and backgrounds such as healthcare professionals from different medical specialties, physicists, ICT experts and referring physicians. This may change traditional clinical practice and the working tasks of those involved. It is therefore important to acknowledge that each individual may have different perspectives on characterizing the impact of implementation. This provides opportunities to bridge differences and increase mutual understanding. Early dialogue between individuals is therefore necessary to promote implementation and can tackle organizational barriers such as professional silos, resistance to changing working tasks, ethical deliberations, conflicts of interests, inefficiencies and erosion of trust among physicians. A shift from the traditional medical practice in a soloed culture towards a more open, collaborative culture is crucial. Healthcare professionals need to embrace a team-based attitude in which values and principles are shared and communicated among team members.

Second, it is important to engage stakeholders before implementation to encourage them to take timely and informed implementation steps. Complex medical technologies will transform conventional clinical practice and impact a hospital's administrative processes. Early dialogues between healthcare professionals and external institutions (e.g., payers, manufacturers, governance bodies) is therefore necessary to assure institutional-level knowledge and for processing technological, economic and regulatory changes in time. These could include approved authorizations for new advanced techniques

and appropriate policies for new roles and responsibilities of staff. For instance, early engagement with national and international professional associations is necessary to formulate and update recommendations of clinical practice guidelines as they are major drivers of clinical practice. These associations also play an important role in encouraging healthcare providers to put words into actions. Moreover, engaging health insurers and governing bodies may help to establish the right incentives for encouraging healthcare professionals working together and demonstrating the impact of technology.

During stakeholder engagement, interaction between individuals is crucial to understand their different interests and needs, support and attitude, and influence on technology implementation. These insights need to guide implementation and define metrics to make data-supported decisions. Co-design and participatory approaches (e.g., semi-structured interviews, workshops) can facilitate engagement and provide the necessary formation for further technology design and implementation.

2. Seize the opportunity of professional development and best practices

It is important to explore opportunities for professional development and collaboration. Complex medical technologies may be attractive to healthcare workers such as physicians, technicians and nurses to acquire new knowledge and skills, obtain increased autonomy, and further develop tasks and responsibilities. Moreover, early technology adopters are in a unique position to help later adopters and ease implementation challenges of complex medical technologies, such as the required technical expertise, staff investments, necessary infrastructure changes and financial trade-offs. The early adopter experience provides valuable insights into best practices and may inform the design and dissemination program for future technology implementation. This is especially useful for advanced technologies that are still developing, and thus with changing patterns of use. Best practices would show the best way to deploy the complex medical technology effectively, and have been worked out through trial and error.

Complex medical technologies with digitization may allow remote treatment, treatment planning and supervision. Early adopters could assist later adopters in clinical decision-making, education or training simulations remotely. A digital clinical infrastructure, accelerated developed during the COVID-19 pandemic, can centralize knowledge and clinical decision-making, and enable a virtual community in which physicians execute decisions quickly and in a unified manner. This chain of command reduces the duplication

of responsibilities that may result in additional costs to the later adopter, reducing implementation waste and burden. Moreover, standardized procedures and better supervision in centralized clinical decision-making led by early adopters, can also result in improved quality of work. This would reduce traveling making it more convenient for providers, and improves healthcare access for patients in rural and remote areas.

An interdisciplinary consortium is important to explore clinical, technical, moral, economic, social, political and environmental aspects of implementation in an integrative way. Consortia may act as an information and communication ecosystem, which ideally supports technology development and assessment, early effectiveness studies, (early) health economic analyses, randomized controlled trials, knowledge dissemination, and the exchange of best practices at both the individual and institutional level. This consortium can unify early and later technology adopters, and facilitate dialogues between relevant stakeholders.

3. Demonstrate individual and societal benefits continuously

To effectively use the potential of complex medical technology for relevant stakeholders, it is important to demonstrate the societal effects that implementation has on its environment over the entire period of its life-cycle. Complex medical technologies can transform independent healthcare activities into a single activity organization to generate economies of scale. It is therefore essential to identify which working tasks and clinical practices will be replaced and reduced as a result of implementation. Moreover, it is important to demonstrate and exploit the opportunities of professional development which can increase work satisfaction and a sense of belonging.

Health economic evaluation and modelling early in the development and throughout the evaluation process would be useful, including hybrid designs that seek to jointly test impact on implementation and societal effects. Health economic modelling is a relatively low-cost and quick method to not only estimate cost-effectiveness in later stages, but also examine the potential impact of an innovation. This approach is especially useful for advanced technologies with digital development, where the value proposition is not straightforward and evolves along with digitization. A detailed consideration is necessary including all resource implications, 'hidden' costs related to all implementation activities (e.g., manualizing the technology, costs of developing and delivering education, and train-the-trainer interventions) and broader societal effects. Insights gathered through stakeholder engagement, as recommended earlier, can pave the way for discussing relevant societal effects.

As clear as the need may be for demonstrating the societal effects of complex medical technology, a big challenge is to start assessing these effects, and to realize potential benefits. Working in healthcare is, at its core, caring for patients. Demonstrating societal effects is thus often experienced as "extra work" with additional administrative tasks. However, complex medical technologies have the potential to improve healthcare workers' workload and emotional distress which have been substantially increased since the start of the COVID-19 pandemic. Clinical research on effectiveness and cost-effectiveness in implementation is still important, but not enough to realize the value of complex medical technologies: early stakeholder engagement, professional development and new modes of collaboration are just as relevant.

NEDERLANDSE SAMENVATTING

Nieuwe medische technologieën worden in hoog tempo ontwikkeld. Deze innovaties kunnen de zorg effectiever maken, efficiënter en aanzienlijk veranderen. Het is ook mogelijk dat nieuwe technologieën vooral de zorgkosten verhogen of niet blijken te werken voor patiënten. Nieuwe technologieën worden echter hoofdzakelijk op veiligheid en vroege effectiviteit geëvalueerd wanneer zij op de markt worden gebracht. De effectiviteit ten opzichte van bestaande behandelingen en kosteneffectiviteit hoeven dan niet te worden aangetoond. In ons zorgstelsel, waarin budget en bemensing onder hoge druk staan, introduceren we bij voorkeur alleen innovaties die de zorg echt effectiever en/of betaalbaarder maken.

MRI-gestuurde radiotherapie door MR-Linac technologie bij prostaatkanker

1.5 Tesla (T) 'MR-Linac' technologie combineert een traditioneel bestralingsapparaat (radiotherapie) met een MRI-scanner om tumoren preciezer te bestralen. In 2008 is met een prototype voor het eerst aangetoond dat het mogelijk is om MRI-beelden te maken tijdens de bestraling, en om te bestralen in een magnetisch veld. Het bestralingsapparaat van MR-Linac zorgt voor krachtige röntgenstraling die het DNA van kankercellen kapot maakt. De bestraling komt van buitenaf door de huid heen via uitwendige bestraling. Radiotherapie bij tumoren wordt gebruikt om te genezen. Bestraling kan zorgen dat de tumor verdwijnt door alle kankercellen te doden, en hiervoor zijn vaak meerdere bestralingen noodzakelijk. Omdat de tumor tegen gezonde cellen aan kan liggen, wordt niet vaak in één keer de hoge dosis straling gegeven die nodig is om de kankercellen te behandelen, maar wordt de bestralingsbehandeling opgeknipt in meerdere sessies (dit wordt ook wel een fractie genoemd). Bestraling kan ook bijwerkingen geven, onder andere doordat gezonde cellen mee worden bestraald.

De MRI – afgekort voor Magnetic Resonance Imaging – van MR-Linac maakt met behulp van een krachtig magneet scherpe afbeeldingen van de tumor in de prostaat en de omliggende gezonde organen. Deze MRI-beelden worden voorafgaand en tijdens de bestraling gemaakt om de precieze positie van de tumor en aangrenzende organen te bepalen. Dit is van belang aangezien de positie van deze structuren voorafgaand aan elke bestraling kan variëren en daarnaast kunnen ze ook nog eens bewegen tijdens de behandeling. Beweging van de prostaat kan bijvoorbeeld ontstaan door verandering in blaasvulling en/of door de aan- of afwezigheid van een gas in de endeldarm.

Sinds 2019 wordt MR-Linac wereldwijd al op grote schaal gebruikt voor behandeling van patiënten met kanker, waaronder andere prostaatkanker. Bij ongeveer een op

de negen mannen wordt tijdens het leven de diagnose prostaatkanker gesteld. Vaak is prostaatkanker goed te behandelen door bijvoorbeeld operatie of bestraling. Bij bestraling kunnen patiënten inwendig (brachytherapie) of uitwending behandeld worden. Bij brachytherapie worden radioactieve zaadjes in de prostaat gebracht die de tumor van binnenuit bestralen. Bij uitwendige bestraling wordt de tumor van buitenaf bestraald met een bestralingsapparaat. Deze behandelingen kunnen echter bijwerkingen geven zoals problemen met plassen, ontlasting of erecties.

Met de MRI-beelden kan de arts continu de actuele positie van de tumor controleren en de bestralingsbehandeling beter richten terwijl de patiënt op de tafel ligt. Door aanpassingen van veranderingen van de anatomie kan de prostaat op MR-Linac heel precies worden bestraald ten opzichte van traditionele bestralingen zonder een MRI-scanner. Hierdoor neemt het risico dat er gezond weefsel geraakt wordt af en daarmee de kans op bijwerkingen. Dit is vooral voordelig bij bewegende tumoren zoals in het geval van prostaatkanker. De belofte is dat bij gebruik van MR-Linac deze bijwerkingen minder zullen zijn vanwege de preciezere bestraling en lagere dosis op gezond weefsel. Dit kan ook zorgen voor een betere kwaliteit van leven voor de patiënt. De Mirage studie toont aan dat de bijwerkingen minder zijn op de korte termijn.

Een ander mogelijk voordeel van MR-Linac ten opzichte van een traditioneel bestralingsapparaat zonder beeldvorming is de mogelijkheid tot 'hypofractionering'. Door de nauwkeurige beeldvorming van MR-Linac kan per één bestralingssessie een hogere dosis gegeven worden en zijn er in totaal minder bestralingen nodig: dit heet hypofractionering. MR-Linac maakt het bijvoorbeeld mogelijk om patiënten met een gemiddeld risico prostaatkanker tegenwoordig met slechts vijf bestralingen (dit wordt fracties genoemd) te behandelen in plaats van 20 of meer bestralingen op het traditionele bestralingsapparaat. Bij hypofractioneringsschema hoeven patiënten minder vaak naar het ziekenhuis te komen. Hypofractionering kan ook bijdragen aan een efficiënter gebruik van de bestralingstoestellen.

Parallel aan de klinische introductie, wordt de techniek nog steeds doorontwikkeld. Hierdoor kan de behandeling geautomatiseerd of sneller verlopen.

Doel van dit proefschrift

MR-Linac wordt al in veel ziekenhuizen gebruikt. Er lopen verschillende studies om de meerwaarde voor patiënten en effectiviteit van MR-Linac te onderzoeken. Deze studies moeten inzicht geven in de daadwerkelijke voordelen van de behandeling en deze

afwegen tegen de eventuele nadelen, zoals bijwerkingen, grotere patiënt belasting, en hogere kosten. Bovendien is de technologie nog in ontwikkeling, waardoor de uiteindelijke meerwaarde nog niet vaststaat.

Klinische effectiviteit en kosten spelen een belangrijke rol bij het implementeren van MR-Linac, maar ook andere zaken zoals digitale ontwikkelingen en de manier hoe artsen gewend zijn om radiotherapie te geven. In dit proefschrift exploreren we de mogelijke kansen en barrières bij het implementeren van MR-Linac in de praktijk. Deze inzichten kan de toepassing van MR-Linac gerichter sturen naar effectievere, gunstige en betaalbare behandelstrategieën. De innovatie kan dan beter voldoen aan de behoeften en wensen uit de praktijk, en potentiële negatieve effecten kunnen worden vermeden of beperkt. Dit onderzoek wordt uitgevoerd vanuit een interdisciplinaire lens, waarbij naast klinische en technologische aspecten ook economische, organisatorische, sociale en professionele aspecten van de implementatie van MR-Linac meegenomen worden. We onderzoeken ook wanneer MR-Linac voor de behandeling van prostaatkanker kosteneffectief kan zijn. Dat wil zeggen, we analyseren hoeveel beter de uitkomsten van MR-Linac behandelingen moeten zijn om een kosteneffectief alternatief voor standaardbehandeling te zijn.

Kansen en barrières bij het implementeren van MR-Linac

In **hoofdstuk 2** en **3** hebben we verschillende kansen en barrières van de implementatie van MR-Linac in Nederland en de Verenigde Staten (VS) in kaart gebracht. Hiervoor hebben we betrokkenen geïnterviewd en gevraagd naar hen perspectief, mening en ervaring te bevragen op de implementatie. De geïnterviewde bestonden uit radiotherapeuten, laboranten, fysici, radiologe, ICT-experts, urologen, patiënt(vertegenwoordigers), ziekenhuisbestuurders, zorgverzekeraars en de industrie verantwoordelijk voor de productie van de technologie.

In beide landen werden de volgende factoren geïdentificeerd die in potentie de implementatie van MR-Linac kunnen bevorderen:

- de aanschaf van geavanceerde technologie in radiotherapie met veel potentie voor technische, klinische, organisatorische, professionele en economische kansen – bijvoorbeeld door een nieuwe behandeling die zich bevindt op het snijvlak tussen diagnostiek, minimaal invasieve behandeling en invasieve behandeling; de scherpe beeldvorming; de mogelijkheid tot betere uitkomsten voor de patiënt – bijvoorbeeld door mogelijk minder bijwerkingen, langere overleving en minder vaak naar het ziekenhuis te moeten voor de behandeling; en daarna mogelijk lagere zorgkosten;

- economische voordelen – bijvoorbeeld door potentieel voor minder behandelingen per patiënt ten opzichte van conventionele bestralingsbehandelingen, een mogelijke effectievere en efficiëntere behandeling, potentie voor meer samenwerking op het gebied van MR-Linac besluitvorming tussen ziekenhuizen en patiënten mogelijk beter te behandelen en daardoor in staat stellen meer te werken;
- professionele ontwikkeling voor radiotherapeuten, fysici en laboranten – bijvoorbeeld door het verkrijgen van specialistische kennis en andere verantwoordelijkheden en taken ten opzichte van de traditionele uitwendige bestraling;
- verbetering kwaliteitsimago voor het ziekenhuis – bijvoorbeeld door het beheren van de nieuwste en innovatieve behandeling op het gebied van oncologie.

In beide landen waren de volgende barrières voor de implementatie van MR-Linac gevonden:

- het ontbreken van grondig bewijs in praktijk betreffende de behandeluitkomsten voor patiënten en de werkelijke voordelen van MR-Linac;
- het toepassen van MR-Linac wordt als zeer complex ervaren door het aanleren van een nieuwe techniek en "nieuwe" kennis en vaardigheden die nodig is binnen de radiotherapie;
- forse investeringen in personeel en infrastructuur – bijvoorbeeld de benodigde praktijktraining voor laboranten om te leren werken met MR-Linac, maar ook de technologie investering zelf (€10 miljoen voor MR-Linac zonder kosten voor de bouw versus €5 miljoen voor een traditionele versneller);
- samenwerkingen tussen professionals die van origine niet vaak tot weinig met elkaar interacteren – bijvoorbeeld tussen radiotherapeuten, ICT-experts, beleidsmakers en zorgverzekeraars.

We vonden ook verschillen in de door stakeholders geïdentificeerde kansen en barrières bij het implementeren van MR-Linac tussen de Nederlandse en Amerikaanse. In de VS werd vermeld dat mogelijk patiënten uit traditioneel achtergestelde gemeenschappen zoals Afro-Amerikanen terughoudend zijn ten aanzien van innovatieve behandelingen. Bovendien zouden ziekenhuizen zich beperkt aangemoedigd voelen door beleidsinstanties om de klinische effectiviteit van MR-Linac te evalueren. In Nederland werd, in tegenstelling tot de VS, meer nadruk gelegd op aan noodzakelijke samenwerkingen bij de

implementatie, zoals samenwerking met de verwijzende arts vanwege “concurrerende” behandelingen (zoals operatie en radiotherapie), en zorgverzekeraars om de financiering en toegang tot behandeling en vergoeding te waarborgen.

Hoe MR-Linac de organisatie van zorg beïnvloedt

In **hoofdstuk 4** vergeleken we de Nederlandse en de Amerikaanse cases vergeleken en onderzochten we hoe de implementatie van MR-Linac de organisatie van de gezondheidszorg beïnvloedt. Op basis van beide cases vonden we dat MR-Linac de organisatie van de gezondheidszorg beïnvloedt op individueel (bijvoorbeeld, meer samenwerking tussen individuele artsen zoals de radiotherapeut en de radioloog), organisatorisch (bijvoorbeeld, meer samenwerking tussen verschillende expertiseafdelingen zoals radiotherapie, radiologie en ICT) en institutioneel niveau (bijvoorbeeld, nodige aanpassingen in regelgeving en beleid om MRI-gestuurde radiotherapie te kunnen leveren, en meer samenwerking met beleidsmakers en zorgverzekeraars om geschikte wet- en regelgeving en verzekeringsbudgetten te ontwikkelen).

In **hoofdstuk 4** laten we zien dat MR-Linac de traditionele methode om een medisch probleem aan te pakken verandert en daardoor ook het bijbehorende werk in de zorgomgeving voor de betrokkenen in het ziekenhuis. Bijvoorbeeld, radiotherapeuten dienen voor het gebruik van MR-Linac trainingen te volgen om MRI te begrijpen en meer samen te werken met ICT-experts en radiotherapeuten. Daarmee verandert het traditionele functieprofiel van radiotherapeuten, laboranten en fysici. Kortom, MR-Linac biedt niet alleen technologische en klinische kansen, maar biedt ook mogelijkheden voor professionele ontwikkeling en teamwerk.

De uiteenlopende kansen en barrières van de toepassing van MR-Linac op de praktijk maken een multidisciplinaire evaluatie wenselijk om de nieuwe technologie in de breedste zin beter te begrijpen en te anticiperen op mogelijke uitdagingen. Deze evaluatie wordt idealiter gesteund door alle belanghebbenden bij de implementatie van de nieuwe behandeling. Hierom is het internationale MR-Linac consortium opgericht om gezamenlijk MR-Linac verder te ontwikkelen en de meerwaarde aan te tonen door middel van klinische studies. De interactie in het samenwerkingsverband is belangrijk om een ecosysteem te creëren waarin de verschillende kennisstromen en activiteiten tot hun recht komen voor de implementatie.

MR-Linac's kosteneffectiviteit voor prostaatkanker

De afwezigheid van bewijs van effectiviteit, potentiële organisatorische veranderingen in de zorg alsmede de forse (investerings)kosten vragen om grondig onderzoek naar de kosteneffectiviteit van MR-Linac. Om de kosteneffectiviteit van innovaties te berekenen worden modellen gebruikt waarin een afweging wordt gemaakt tussen de kosten en de effectiviteit van een nieuwe medische technologie (ten opzichte van standaardbehandelingen) om te bepalen of de (extra) kosten opwegen tegen de baten. Deze modellen worden vaak pas gebruikt wanneer een nieuwe technologie al op meerdere plekken is geïmplementeerd en al wordt gebruikt, omdat dan gegevens over de werking, effectiviteit en kosten van de nieuwe medische technologie bekend zijn. Echter, in een laat stadium is het moeilijk om de technologie bij te sturen, danwel uit de praktijk te halen. Om deze reden worden vroege economische evaluaties gebruikt om in een vroeg stadium inzicht te krijgen in de mogelijke randvoorwaarden die een nieuwe behandeling kosteneffectief maken.

Vroege economische evaluaties worden uitgevoerd om vroegtijdig inzicht te generen in potentiële toegevoegde waarde van de innovatie, ruimte voor verbetering zorgpad en mogelijk impact voor de maatschappij. Deze doorrekeningen vinden vaak plaats om de minimale effect maat te schatten om tot een kosteneffectief product te komen, scenario analyses waarin effect maten variëren zijn hierbij dan ook essentieel. Deze informatie kan nuttig zijn om betere, meer integraal afgewogen keuzes te maken en om het innovatieproces bij te sturen om de toegevoegde waarde van de innovatie te optimaliseren.

In **hoofdstuk 5** en **6** hebben we onderzocht of, en hoe MR-Linac kosteneffectief kan zijn voor de behandeling van prostaatkanker. We hebben vroege economische evaluaties uitgevoerd waarin we hebben berekend (1) wat de vereiste afname van plas-, darm- en seksuele bijwerkingen is van MR-Linac om deze behandeling voor prostaatkanker kosteneffectief te maken in verhouding tot standaardbehandelingen en (2) wat de maximale kosten van de MR-Linac mogen zijn. We focussen op patiënten met gemiddeld risico prostaatkanker die tegenwoordig op MR-Linac worden behandeld in vijf fracties en in onderzoeksverband in twee fracties.

In Nederland blijkt vijf fracties op MR-Linac kosteneffectief te kunnen zijn ten opzichte van de traditionele externe bestraling en brachytherapie, wanneer de bijwerkingen fors afnemen (54% en 66%) of wanneer de behandeling tegen lage kosten (van €2050 tot €62,500 per patiënt ten opzichte van traditionele bestraling of van €600 tot €51,000

patiënt ten opzichte van brachytherapie) kan worden gegeven. Ten opzichte van 20 en 39 fracties traditionele externe bestraling blijkt MR-Linac kosteneffectief zijn zonder afname van bijwerkingen of kosten. In het Verenigd Koninkrijk bleek 2 fracties op MR-Linac kosteneffectief te zijn ten opzichte van vijf en ten opzichte van twintig fracties uitwendige bestraling wanneer MR-Linac tegen lagere kosten wordt aangeboden of wanneer de bijwerkingen fors zouden afnemen (68% en 43% ten opzichte van 5 fracties, en 72% en 58% ten opzichte van 20 fracties). In vergelijking met brachytherapie is de kans klein dat MR-Linac kosteneffectief zou kunnen zijn dat wil zeggen dat brachytherapie voor de behandeling van prostaatkanker het meest gunstig zou zijn vanuit een kosten-baten perspectief. Er is meer onderzoek nodig naar de kosteneffectiviteit van MR-Linac op basis van patiënt uitkomsten en kosten uit praktijk.

Lessen voor de implementatie van nieuwe complexe medische technologie

MR-Linac is een complexe medische technologie die bij introductie en klinische uitrol vele technische, organisatorische, professionele en economische afwegingen vereist. Op basis van dit proefschrift kunnen we enkele lessen formuleren voor de implementatie van andere nieuwe complexe technologie. Van oudsher zijn effectiviteit en kosteneffectiviteit de belangrijkste factoren die de toegevoegde waarde van medische innovaties bepalen. Dit zijn echter niet de enige factoren die een succesvolle implementatie faciliteren.

Complexe technologie vragen naast klinisch, technisch en economisch input, ook aandacht voor organisatorische, professionele en sociale aspecten. Hierdoor vraagt de implementatie van deze innovaties meer dan alleen klinische en technische beschouwingen. Bovendien wordt technologie vaak ingezet voor diverse patiëntengroepen, met verschillende doeleinden en verschillende waarden. Een belangrijke vraag is dan hoe een technologie zo waardevol mogelijk kan worden gebruikt. Daarom is het belangrijk dat alle stakeholders vroeg betrokken zijn in het innovatieproces om alle denkbare scenario's in kaart te brengen en om mogelijke nadelige gevolgen te beperken. Economische evaluaties in een vroeg stadium van de technologieontwikkeling en implementatie blijven belangrijk om een nieuwe technologie optimaal in te kunnen zetten.

Digitalisering in technologieën maakt de besluitvorming voor de behandeling op afstand mogelijk. Gebruikers die een innovatie zeer vroeg in gebruik hebben genomen, kunnen gebruikers die later beginnen helpen bij klinische besluitvorming, onderwijs of opleiding. Zo kan technologie ook ruimte bieden voor meer samenwerking en

professionele ontwikkeling (zowel individuele als in een samenwerkingsverband). In deze samenwerkingen kunnen ook “best practices” worden gedeeld onderling om goede manieren aan te geven om complexe medische technologie effectief en op de gewenste manier te gebruiken. Bij voorkeur worden stakeholders vanaf de beginfase van de implementatie betrokken, ook om de implementatie te bevorderen en organisatorische veranderingen tijdig aan te pakken.

In de toekomst worden complexe medische technologieën bij voorkeur niet alleen gebruikt en beoordeeld op hun klinische en technische mogelijkheden, maar ook op hun brede economische, organisatorische en professionele mogelijkheden. Het is belangrijk dat de kansen voor professionele ontwikkeling die de technologie kan bieden, beter worden verkend en benut. Dit kan de arbeidstevredenheid en het werkplezier van het zorgpersoneel verbeteren.

ACADEMIC INSTITUTIONS NEED TO DO MORE FOR FIRST-GENERATION STUDENTS

Charisma Hehakaya

Nature Human Behaviour (2022)

Being the first in her family to graduate university, Charisma Hehakaya discusses how academic institutions can help first-generation students thrive. Heading towards the end of her PhD, she is dedicated to give support to these students.

When I worked as a cleaner in a hospital at the age of 13, I did not expect that one day I would have three master's degrees and pursue a PhD degree. While going to school, I had to work and provide care for my family. I initially failed my secondary school exams. One of my teachers recognised my situation and convinced me to retake the exams in another town. I passed this time, and exactly 10 years ago, I was the first in my family to start university.

Being a first-generation student came with unexpected challenges. Universities have 'unwritten rules' that I was unaware of. It is not only about 'know-what', but also 'know-how': the way of participating in class, reading a lot, the way of speaking or asking questions and having the resources to acquire necessary study materials such as a laptop. Such things were often taken for granted by my fellow students raised in academically educated families. I hardly recognised myself in the students around me and figuring out how the university worked raised many doubts.

I was raised bilingual while being surrounded by partially illiterate parents. Growing up, I spoke Dutch at school and Indonesian at home. I had trouble with the Dutch language and was not used to speaking English, causing me to struggle with the appropriate vocabulary and finding the right words in the right place. I not only faced issues expressing myself, but also understanding what was being said. Therefore, I decided to attend multiple courses: Dutch, English, public speaking, stammering, academic reading, and writing. Repetition brings quality, and good things take time. Advice to take such courses would have been very welcome at the start of study.

When teachers used words to emphasise the gap in language or between the highly educated and the poorly educated, I felt like an outsider at university and uncomfortable to fully express myself. For instance, teachers sometimes condescendingly described the less educated (like my family) as simplistic individuals. Universities have to take care of their language to integrate and access new students with a non-typical background into the academic community.

It was not just the language that was a barrier. Finances were my main concern throughout the first three years of university, as the government's tuition fees and maintenance loans were far from sufficient. Tuition fees, health insurance, a laptop and study books were often paid by fellow students' parents, but I had to pay these myself. My parents used the food bank, so it felt odd spending money on study books instead of helping them. Alongside studying, I worked several side jobs to cover my expenses and living costs. This

affected my focus on study and academic performance. These are invisible challenges for students with financial issues that academic institutions need to be aware of.

At the same time, I also faced challenges at home. No one discouraged me, but my family did not understand how university works or the stress of pursuing an academic degree. The first diploma ceremonies, usually a time for celebrating, felt like a confrontation since my parents were not positive on attending, whereas, for many other students, it was a given that their parents would attend. Today I recognise that it was mainly a lack of knowledge and experience of a world they could not imagine. My lesson is also not to compare myself with others.

There are positives to my experience as well. It taught me to bridge between those with university degrees and those who did not study at university, between the countryside and the city, and between theory and practice. I learned that language is the fuel of cultural capital, to be independent and to ask for help more easily. I feel fortunate to be trusted and supported by many people, friends, and teachers at secondary school and university.

First-generation students have unique talents. They are often good at translating theoretical knowledge into tangible examples, which are valuable skills in science and beyond. They can build bridges between different worlds and people, a critical skill in an increasingly fragmented society. However, the use and recognition of these strengths often come years later because they are hidden, and obstacles must first be overcome.

All universities have open days, but that doesn't mean that all universities are open to everyone. Equality of opportunity is a societal issue that universities are uniquely positioned to help to address. We can do more for students who do not come from academically educated families and do not have the financial means. Universities can offer support both at the application stage and once students have enrolled. My experience is that those who need support in unknown areas do not know where to go, how to access help or whether help exists at all. It is important that all support initiatives are easy to find.

Heading towards the end of my PhD, I decided to give something to other first-generation students. I founded the First Generation Fund at Utrecht University, to encourage first-generation students to make the most of their talents through mentoring and financial support. A mentoring program can be helpful, for instance, experienced students can interact with younger students and learn from each other. Unifying voices is very supportive to recognize experiences and help each other. Providing consultation for financial challenges and financial incentives that support students to stay in university effectively may help. I want to reduce the self-evident at university and increase awareness about the potential challenges and unwritten rules first-generation students face, and provide the necessary resources, to make significant progress toward making them flourish.

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ABOUT THE AUTHOR

Charisma Hehakaya was born on May 29th, 1992 in 's-Hertogenbosch, the Netherlands. Hehakaya grew up in a bilingual household with her parents and two brothers speaking Moluccan and Dutch in Vught. Initially, she was recommended for the theoretical pathway of pre-vocational secondary education, but ended up going to secondary school the Maurick College in Vught. After failing final exams, she got accepted into adult general secondary education and moved to Utrecht, where she passed.

Hehakaya studied Science, Business & Innovation: Life & Health (BSc, MSc) and Business Administration: Strategy & Organization (MSc) at the Vrije Universiteit Amsterdam. During her studies, Hehakaya had different side jobs and was a researcher at MSD Animal Health, Teva Pharmaceuticals and Pfizer. Hehakaya aspired to a career in pharma, but she changed course after meeting Prof. Lenny Verkooijen in early 2018.

Hehakaya worked on her PhD (2018 – 2022) under supervision of a multidisciplinary team: Dr. Jochem van der Voort van Zyp (radiation oncologist), Dr. Geert Frederix (health economist), Prof. Ellen Moors (innovation scientist) and Prof. Lenny Verkooijen and Prof. Diederick Grobbee (clinical epidemiologists). During her PhD, she studied Clinical Epidemiology (MSc) at Utrecht University and Health Economic Modelling at the University of Glasgow, and spent five months at the Institute of Cancer Research and Royal Marsden in London.

Hehakaya is the founder of the First Generation Fund (2021) and the University Pioneers Community (2023). The First Generation Fund offers financial support to first-generation students. The University Pioneers community helps first-generation students find their way in student life and make the most of their talents. Hehakaya has been a member of Young Science in Transition.

Hehakaya will continue her academic career and is motivated to improve environmental impact on health and well-being, interdisciplinary research, sustainable health systems, and stakeholder engagement. She is also passionate about working at the intersection of science and society, and increasing equity in education, health care and science.

A golden retriever a day keeps academic stress away. *Dippy*

The 1.5 Tesla magnetic resonance (MR) imaging with a linear accelerator (Linac), MR-Linac, is being implemented worldwide. It enables online and real-time, soft-tissue imaging and targeted MRI-guided radiotherapy. This PhD thesis combines qualitative and quantitative methods to explore the opportunities and challenges in implementing the MR-Linac into clinical care and investigate early cost-effectiveness scenarios for the treatment of localized prostate cancer. Clinical research on effectiveness and cost-effectiveness in implementation is important, but not enough to realize the value of complex medical technologies.

Charisma Hehakaya worked on her PhD with a multidisciplinary team at UMC Utrecht. Her educational background is in innovation sciences, business administration in strategy and organization, and epidemiology. Hehakaya is the founder of the First Generation Fund and University Pioneers Community. She enjoys interdisciplinary research, working at the intersection of science and society, and increasing equity in education, healthcare and academia.