Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Application Number: 2024-001

Magnetic resonance-guided radiotherapy (MRgRT)

Evidence synthesis to support a generic justification decision

Date of decision: 30 May 2025

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About the Health Information and Quality Authority

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- **Regulating health services** — Regulating medical exposure to ionising radiation**.**
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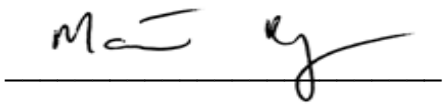
Foreword

The European Union Basic Safety Standards for the Protection Against Dangers from Medical Exposure to Ionising Radiation (Euratom) were initially transposed into Irish law under SI 256 in January 2019.[1] These Regulations named HIQA as the competent authority for medical exposure to ionising radiation. One requirement under the Regulations is that new practices involving medical exposures must be justified by HIQA before they are generally adopted – this is known as generic justification.

This report sets out a systematic review which provides the evidence base to inform HIQA's generic justification decision. The report also includes the consideration of this evidence by HIQA's multidisciplinary Medical Exposure to Ionising Radiation Expert Advisory Group which is formally reported using an evidence-to-decision framework. The review considers the net benefit for this patient population in the context of the medical exposure to ionising radiation; the potential for occupational and public exposure is also considered.

This review was undertaken by the Ionising Radiation Evidence Review Team from the HTA Directorate in HIQA and was supported by HIQA's Medical Exposure to Ionising Radiation Expert Advisory Group who advised on the preparation of this report and participated in the evidence-to-decision exercise. HIQA would like to thank the Evidence Review Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.



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Acknowledgements

HIQA would like to thank all the individuals and organisations who provided their time, advice and information in support of this report. Particular thanks are due to the members of the Medical Exposures to Ionising Radiation (MEIR) Expert Advisory Group (EAG).

The findings of the evidence review prepared by HIQA informed the deliberations of the MEIR EAG in completing the evidence to decision framework. The output of the framework was reached through consensus.

The membership of the EAG is as follows:

Prof Daniel Cagney*	Consultant Radiation Oncologist, Mater Private Hospital
Prof Mary Coffey, Chairperson	Independent Chairperson
Dr Jennie Cooke	Principal Physicist, Children's Health Ireland, Irish Association of Physicists in Medicine, (Diagnostic Radiology)
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Gerard White	Patient/Patient advocate, National Cancer Control Programme

Key: *Not a member of the standing Expert Advisory Group, but attended as an ad hoc member for the meeting where this practice was discussed.

The following members of the HTA Directorate contributed to the management, technical writing or dissemination of this report:

Andrew Dullea*, Maeve McGarry*, Marie Carrigan, Elaine Foley, Fearghal Foley**, Patricia Harrington, Louise Larkin, Dane Moriarty, Kirsty O'Brien, Michelle O'Shea, Lydia O'Sullivan, Máirín Ryan, Debra Spillane, Kieran Walsh.

*Joint project leads; Maeve McGarry left the HTA Directorate in November 2024.

**Fearghal Foley contributed to this report as part of a summer research internship in the HTA Directorate over the summer of 2024.

Conflicts of interest

Cynthia Eccles reported that, as an employee of the Christie NHS Foundation Trust, she is a member of the Elekta Unity MR Linac consortium and is part of the clinical steering committee for this consortium. She has no financial interests in, nor does she receive funding from Elekta.

Sara Hackett reported receipt of funding from the Dutch Research Council which receives contributions in kind from Elekta.

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Plain language summary

Radiotherapy (or radiation therapy) is a cancer treatment that uses high doses of radiation to kill tumours or reduce their size. About two out of every three people who develop cancer have radiotherapy at some point during their treatment journey.

It is important to carefully target the treatment area, to ensure that the radiation dose is delivered to the right place, while also avoiding healthy tissue. Pre-treatment planning therefore includes medical imaging, so that the treatment area and healthy tissues can be seen. While computed tomography (CT) scans are often used as part of this pre-treatment imaging, magnetic resonance imaging (MRI) scans can also be used and may help to target the treatment area more precisely. MRI is particularly helpful for visualising soft tissues — for example, if radiotherapy is being delivered to the pancreas or liver. Radiotherapy is commonly delivered using precise machines called linear accelerators. More recently, manufacturers have developed delivery systems that combine an MRI scanner (to carefully target the treatment area) with a linear accelerator (to deliver radiotherapy). Treatment delivered using these delivery systems is known as magnetic resonance–guided radiotherapy, or 'MRgRT', for short.

Under Irish law, new practices that involve the exposure of patients to ionising radiation must be justified by the Health Information and Quality Authority (HIQA). Justification means making sure that the benefits of the practice outweigh the risks involved for the kind of patients undergoing this treatment. To decide if this practice is justified, HIQA has reviewed the available evidence in the medical literature, and sought input from a group of experts, including patient representatives. HIQA has also considered the occupational and public radiation safety issues in this review.

The evidence review carried out by HIQA found a large number of studies which explored the use of MRgRT. However, we have very low confidence in the results of these studies — this is mainly due to how the studies were designed and carried out. While there are still gaps in the evidence supporting MRgRT, no safety concerns were found in the literature. Moreover, unlike other imaging practices currently being used to guide radiotherapy treatments, MRgRT does not involve the use of ionising radiation. After reviewing the risks and benefits of the practice, and considering the recommendation from its Medical Exposure to Ionising Radiation Expert Advisory Group, HIQA decided to justify this practice of MRgRT for patients with cancer requiring external beam radiotherapy.

Key Points

Application

- This review was conducted in response to an application submitted by Elekta Limited for the generic justification of magnetic resonance-guided radiotherapy (MRgRT) using an MR linear accelerator (MR-linac) for patients with cancer requiring external beam radiotherapy.
- An MR-linac combines a linear accelerator used for treatment delivery with a magnetic resonance imaging (MRI) scanner for image guidance into one therapeutic delivery system.

Summary of evidence synthesis process

- In accordance with HIQA's Methods for generic justification of new practices in ionising radiation, a systematic review to establish the evidence base for this new type of practice was conducted.
- In total, 136 primary studies, 58 ongoing trial registrations, five international practice guidelines and reports, and one systematic review were identified.
- An evidence and gap map was created that categorised the included MRgRT data based on study sample size, patient-relevant outcomes, and treatment sites in order to highlight the research gaps. Out of the 136 primary studies, six studies included a relevant comparator; these included:
    - one randomised control trial (RCT) (prostate cancer)
    - two prospective cohort studies (prostate cancer)
    - three retrospective cohort studies (pancreatic, lung and liver cancers).
- These six comparative studies were assessed for risk of bias using the Cochrane's RoB-2 or the Risk of Bias in Non-randomised Studies (ROBINS-I) tools, as appropriate.
- The findings of the six comparative studies were synthesised narratively and used to inform the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tables.

Clinical effectiveness evidence

- Clinical effectiveness outcomes included overall survival (OS), progression free survival (PFS), local control (LC) and quality of life (QoL).

- Two studies (pancreas, lung) reported on OS and PFS with two studies (liver, lung) reporting on LC. No statistically significant difference between MRgRT and conventional image-guided radiotherapy (IGRT) was observed for any of these outcomes in any of the studies.
- Two of the three prostate cancer studies reported on symptoms and QoL, providing evidence that MRgRT may be associated with less deterioration in some QoL and symptom domains compared with conventional IGRT at one, three and 24 months. These studies defined 'clinically relevant deterioration' of QoL scores differently based on different literature.
    - The MIRAGE RCT found that a significantly higher proportion of patients in the computed tomography-guided radiotherapy (CTgRT) arm had a clinically relevant rise in International Prostate Symptom Score (IPSS) (≥15 points) at one month (19.4% vs. 6.8%; p=0.01), but not at three months (1.4% vs. 4.1%; p=0.30).
    - The MIRAGE RCT found that a lower proportion of patients in the MRgRT arm reported a clinically relevant deterioration in the EPIC-26 urinary irritation domain score (≥14 points) at any point between six and 24 months (19.2% vs. 35.3%, p=0.03). The SCIMITAR study found no statistically significant difference at one, three or six months post-stereotactic body radiotherapy (SBRT) for this domain score.
    - At 24 months, the MIRAGE RCT reported that MRgRT was associated with significantly lower odds of a clinically relevant deterioration in bowel function (OR 0.44 95% CI 0.21–0.94). This was supported by the SCIMITAR study which found CTgRT was associated with a significantly higher odds of a clinically relevant decline in EPIC-26 bowel domain score upon multivariable analysis (OR 3.02, 95% CI, 1.12-8.17, p=0.03).
    - At 24 months, considering clinical relevant scores, the MIRAGE RCT reported MRgRT was associated with better Sexual Health Inventory for Men (SHIM) scores (OR 0.37, 95% CI 0.15–0.91) but not EPIC-26 sexual domain scores (OR 0.68, 95% CI 0.27-1.69). The SCIMITAR study found no clinically relevant differences in EPIC-26 sexual domain scores at one, three or six months post-SBRT.
- Assessment of these outcomes across the studies were often limited by the short follow-up time, a range of possible confounders and the high risk of bias across the studies, which at times favoured the MRgRT intervention.

Adverse events and safety evidence

- All six comparative studies assessed toxicity outcomes, however only the three prostate studies found a statistically significant difference in favour of the MRgRT intervention.
- In the MIRAGE RCT (prostate cancer), compared with CTgRT, MRgRT was associated with:
  - Significantly lower rates of acute Grade ≥2 genitourinary (GU) toxicity (24.4% vs. 43.4%; p=0.01) and acute Grade ≥2 gastrointestinal (GI) toxicity (0.0% vs. 10.5%; p=0.003).
  - Significantly lower cumulative late Grade ≥2 GU (27.0% vs. 51.0%; p=0.004) and GI toxicity (1.4% vs. 9.5%; p=0.02) at two years, and with less deterioration in urinary irritation and bowel function (p=0.03 and p=0.05, respectively).
- Data from three studies (liver, pancreatic and lung cancer) showed non-statistically significant differences in the incidence of Grade 1-2 acute toxicities in favour of MRgRT.
- None of the six studies reported safety concerns or unexpected toxicities.

Certainty of the evidence

- The certainty of the evidence was assessed as very low for all clinical effectiveness and safety outcomes found in this systematic review. The certainty of the evidence was downgraded predominantly due to the high risk of bias, wide confidence intervals (where reported), low number of events predominately due to the availability of only one estimate from a single small study for some outcomes.

Clinical significance of reported change in ionising radiation dose

- Compared with conventional IGRT, the imaging associated with MRgRT involves no ionising radiation.
- Accurate estimation of the clinical significance of dose reduction is challenging as there are many risk factors for cancer, and the dose from medical imaging only forms part of a person's long-term risk of developing cancer. However, it is accepted that there is a clinical benefit in keeping dose, even for low-dose medical exposures, as low as reasonably achievable.

Medical Exposure to Ionising Radiation Expert Advisory Group (MEIR EAG)

- Informed by the review of the above evidence, the MEIR EAG completed judgements under a modified GRADE evidence-to-decision framework to arrive at a recommendation to HIQA on the generic justification of MRgRT in patients with cancer who require external beam radiotherapy.
- The MEIR EAG considered that the evidence of benefits with MRgRT primarily relate to reductions in toxicity relative to conventional IGRT. This is likely due to improved visualisation, particularly of challenging anatomical regions supporting more precise targeting of the tumour site. It is unclear if MRgRT will lead to improvements in clinical effectiveness. Risk of harm may however be lower, even if this is limited to reduced radiation exposure to healthy tissue due to removal of the CT imaging component. The benefits were therefore judged to be small.
- The MEIR EAG also discussed potential challenges associated with MRgRT such as claustrophobia, increased time on the treatment bed, and contraindications associated with implantable medical devices. While recognising that these issues may affect some patients more than others, the overall harms were judged to be trivial.
- The MEIR EAG highlighted that additional resources are required to implement MRgRT, with significant upfront capital investment. System-level impacts— such as increased linac downtime for maintenance — may influence the perceived value of MRgRT. Despite these factors, they agreed that there is probably no important uncertainty or variability in how patients value the main outcomes.
- When considering the balance between the desirable and undesirable effects, the MEIR EAG agreed that the balance probably favours the use of MRgRT.
- The MEIR EAG recommended that MRgRT should be generically justified for patients with cancer who require external beam radiotherapy.

Decision-making

- Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified.
- The practice of MRgRT for patients with cancer who require external beam radiotherapy is generically justified under SI 256/2018.

- The generic justification of this practice is effective from 30 May 2025.

List of abbreviations used in this report

AAPM	American Association of Physicists in Medicine
ACR	American College of Radiology
ADT	androgen deprivation therapy
ART	Adaptive Radiotherapy
ASN	Autorité de Sûreté Nucléaire (France)
ASTRO	American Society for Radiation Oncology
CADTH	Canadian Agency for Drugs and Technologies in Health
CBCT	cone beam computed tomography
CE	Conformité Européenne
CI	confidence interval
CTgRT	computed tomography-guided radiotherapy
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
EAG	expert advisory group
EBRT	xternal beam radiotherapy
EtD	evidence to decision
EPA	Environmental Protection Agency
EPIC-26	Expanded Prostate cancer Index Composite-26
ESR	European Society for Radiology
ESTRO	European Society for Radiotherapy and Oncology
FDA	Food and Drug Administration (US)
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GTV	gross tumour volume

HAS	Haute Autorité de Santé (France)
HIQA	Heath Information and Quality Authority
HSE	Health Service Executive
HPRA	Health Products Regulatory Authority (Ireland)
HTA	health technology assessment
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
IGRT	image-guided radiotherapy
INESSS	Institut national d'excellence en santé et en services sociaux
IPSS	International Prostate Symptom Score
IQR	interquartile range
IRR19	Ionising Radiation Regulations of 2019
kV	kilovoltage
NCCN	National Comprehensive Cancer Network (US)
NCCP	National Cancer Control Programme
MEIR	medical exposure to ionising radiation
MR	magnetic resonance
MRgRT	magnetic resonance-guided radiotherapy
MRI	magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and care Research
OARs	organs at risk
PICOS	Population, Intervention, Comparison, Outcomes and Study (PICOS) design

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCR	Royal College of Radiologists
RCT	randomised controlled trial
ROB-2	risk of bias-2
RT	radiotherapy
RQ	research question
SBRT	stereotactic body radiotherapy
SHIM	Sexual Health Inventory for Men
SI	statutory instrument
SWiM	synthesis without meta-analysis
TWiC	trial within a cohort

1 Introduction

1.1 Background to application

Internationally, magnetic resonance-guided radiotherapy (MRgRT) delivery systems have been developed for use in clinical practice to support the treatment of a range of cancers for which radiotherapy is indicated.[2] MRgRT delivery systems typically combine a linear accelerator used for radiotherapy treatment delivery with a magnetic resonance imaging (MRI) scanner for image guidance into one therapeutic delivery system, known as an MR-linac.[3]

In March 2024, HIQA received an application from Elekta Limited for the generic justification of external beam MRgRT using Elekta's Unity MR-linac. In accordance with the regulations and HIQA's methods for generic justification, HIQA must justify new *classes* or *types* of practice before they are generally adopted.[1, 4] Therefore, the scope of this evidence review and generic justification decision applies to all MRgRT solutions provided by any manufacturer.

The linear accelerator-based Unity system produced by Elekta was CE marked in 2018 and gained Food and Drug Administration (FDA) 510(k) clearance in 2023.[5] According to Elekta, there are 90 Unity systems in clinical use globally including 27 clinical systems in Europe. Other CE-marked MRgRT delivery systems currently in clinical use in Europe that were identified include those produced by ViewRay: a cobalt-60-based MRgRT solution and a later linear accelerator-based model known as the MRIdian linac. These technologies were CE marked in 2014 and 2016 for the European market and underwent the FDA's 510(k) notification process for the US market in 2012 and 2017, respectively.[6, 7] In 2023, ViewRay ceased operations; while these devices are now no longer in production, some systems may still be in clinical use.[8, 9] More recently in June 2024, the MagnetTx Aurora-RT® system was CE marked for the European market, having previously received 510(k) clearance from the FDA in 2022.[10, 11] Another system is also in development by an Australian-based group.[12, 13]

There are currently no MRgRT delivery systems installed in Ireland. Radiotherapy service planning by the Health Service Executive (HSE) has included the construction of radiotherapy bunkers in a number of public hospital sites, which could also be used to house MRgRT delivery systems. On receipt of the application from Elekta, HIQA liaised with relevant members of the Medical Exposure to Ionising Radiation (MEIR) Expert Advisory Group (EAG) and determined that the practice of MRgRT represents a new practice in Ireland, and therefore requires generic justification before it can be generally adopted.

Topic exploration performed by HIQA in advance of developing this report indicated that the most recent high-quality systematic review related to this practice was contained within a health technology assessment (HTA) published by Canada's Drug Agency (CDA, formerly known as the Canadian Agency for Drugs and Technologies in Health - CADTH) in 2019.[14] The CADTH assessment reported one relevant study and concluded that overall, given the limited availability and low quality of evidence, the effectiveness and utility of MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy was uncertain. However, both topic exploration and documentation provided by Elekta indicated that a number of research studies have been published since the date of the search carried out by CADTH as part of their assessment. Due to the high radiological risk associated with this practice and the lack of an up-to-date, high-quality systematic review, in accordance with HIQA's Methods for generic justification of new practices in ionising radiation,[15] a full evidence review (a systematic review) was carried out.

1.2 Overall approach

A standing multidisciplinary MEIR EAG has been convened by HIQA comprising representation from key stakeholders. A full list of the membership of the EAG is available in the acknowledgements section of this report. The terms of reference for the EAG are published on the HIQA website.

This report was prepared to provide an evidence base to inform the discussions of the MEIR EAG and their recommendation-making process as well as the subsequent decision-making by HIQA. The following summarises the steps taken to date and those planned:

- A systematic review was performed to provide the evidence base for a generic justification decision.
- This review systematically identified relevant evidence which related to the safety and efficacy (including health-related quality of life) of MRgRT in patients with cancer requiring radiotherapy.
- A draft report summarising the benefits and harms associated with this practice was produced and circulated to the EAG for review.
- Following a meeting of the MEIR EAG, a draft of the report was amended as appropriate and is being circulated to the MEIR EAG for review.
- The final report was sent to the Director of HTA, along with a recommendation from the MEIR EAG regarding the generic justification of the practice.

- Following HIQA's decision, the final report and generic justification decision was published on the HIQA website.

2 Description of technology

2.1 Introduction

External beam radiotherapy, which involves the delivery of high doses of X-rays, is the most common treatment modality used in radiation oncology.[16] Machines known as linear accelerators (linacs) are typically used to deliver external beam radiotherapy. Modern external beam radiotherapy is underpinned by image guidance, which allows localisation and tracking of the tumour and surrounding organs. This is commonly referred to as image-guided radiotherapy (IGRT). IGRT can facilitate the accurate delivery of a therapeutic dose of radiation to the treatment site while reducing the risk of radiation-induced complications and side effects.[17] Typically, linear accelerators used for treatment delivery have on-board computed tomography (CT) imaging and or static kilovoltage (kV) imaging for guidance and verification purposes.[3, 18] IGRT may be performed using a variety of methods including CT-guided radiotherapy (CTgRT), two dimensional megavoltage (MV) portal images, kV planar radiographs or ultrasound.[19] While CTgRT options include MV CT and kV or MV cone-beam CT (CBCT), kV CBCT is typically considered the standard care.[3, 19-23] CBCT provides three-dimensional (volumetric) information about the tumour and surrounding organs using a relatively low radiation dose.

MRI is increasingly being used as a novel IGRT modality as it provides superior soft tissue visualisation and does not use ionising radiation.[18, 24] Where available, MRgRT is being used for a broad range of anatomical sites as an alternative to conventional CTgRT. A 2021 publication based on data from the MOMENTUM registry — a prospective registry developed through an international academic partnership with Elekta[25] — indicated that MRgRT had been used for 39 different tumour sites, most commonly tumours of the prostate, pancreas, lung, brain and rectum, in addition to oligometastatic disease (typically defined as when a primary tumour has metastasised to five or fewer anatomical sites).[25, 26]

2.2 Overview of currently available MRgRT technologies

As outlined in the introduction above, a number of MRgRT delivery systems have been identified that are either currently in clinical use or in development. While each delivery system has unique features, they all aim to combine the superior soft tissue imaging capability (compared to conventional IGRT) of MRI, with external beam radiotherapy delivery.[27] These systems are briefly described below with the key characteristics and differences among the devices outlined in Table 1.

The ViewRay MRI-cobalt based system (ViewRay Inc., Ohio, US), which was cleared by the FDA in May 2012, was the first MRgRT delivery system to be developed, with

the first patient treated in 2014. This system combines a 0.35 Tesla (T) MRI scanner with an external beam radiotherapy (EBRT) system comprising three cobalt (^{60}Co) sources, located at intervals of 120° in a ring-type bore, producing a total of 600 centigray (cGy) per minute at the isocentre. Each ^{60}Co source is equipped with double-focused multileaf collimators and can deliver static intensity-modulated radiotherapy (IMRT). For treatment planning and localisation, three-dimensional volumetric MRI could be acquired, and during treatment sagittal planar MR images could be acquired in real time.[28] ViewRay subsequently developed the first MR-linac, known as the MRIdian® MR-linac. MR-linac systems combine a linear accelerator used for radiotherapy treatment delivery with a MRI scanner into one therapeutic delivery system.[3] The MRIdian® MR-linac maintains the nominal dose rate of 600 cGy/min and 0.35T MRI capability, but with a 6 MV in-line linear accelerator. The magnet was designed using a vertically-gapped superconducting solenoid pair separated by a 28cm gap to allow for placement of the radiation delivery gantry. The linac aims the beam through the superconducting coil gap and is therefore perpendicular to the main magnetic field. The linac is collimated by a dual-layer MLC delivering IMRT.[6] Both ViewRay systems use a magnetic field strength of 0.35T. A magnetic field strength of between 0.2 to 1.0T is considered low-field MRI, while a field strength greater than 1T is considered high-field MRI; higher magnetic field strengths are associated with improved image quality.[2]

The Elekta Unity MR-linac was developed as the first high-field MRgRT system with a magnetic field strength of 1.5T; as such, it is capable of diagnostic quality MR imaging.[29] In 2018, it was CE marked for the European market and received 510(k) clearance from the FDA for the US market. In September 2024, Elekta indicated that there were now 90 of these MR-linac systems installed internationally. Per the manufacturer's instructions for use submitted under the CE marking process, the system is broadly indicated for radiotherapy and stereotactic radiation treatment for malignant and benign disease anywhere in the body.[30] It consists of a high field 1.5T MRI scanner combined with a 7MV flattening filter free linac. It is a bore type machine where the linear accelerator rotates around the MRI system. The radiation beam passes through a specially designed cryostat, enabling a low attenuating, homogenous region between the gradient coils while maximising the magnetic field (B-field) homogeneity to enable diagnostic quality MR images. The radiation beam is collimated via a non-rotational 160 MLC in-plane direction, parallel to the bore of the magnet. The maximum field size is 22cm x 57cm at the isocentre.[31] Treatment is delivered using step-and-shoot IMRT.[32] The system allows for motion management with real-time tracking with MR imaging and automatic gating, which is where treatment is enabled when the target is in the appropriate position.[19]

More recently in June 2024, the MagnetTx Aurora-RT® system was CE marked for the European market; it previously received 510(k) clearance from the FDA in

2022.[11] This system has a 0.5T open biplanar rotating MR system and 6MV linac.[10] This low-field system can be used with the magnetic field either perpendicular or parallel to the radiation beam. The parallel configuration is the version that is currently available commercially and is advantageous in terms of reducing dose perturbations from the magnetic field.[33-35] Furthermore, as the magnetic field in the system flows between posterior to anterior direction, radiofrequency "belt-style" receiver coils are outside the radiation field which avoids interactions with radiation. A number of factors means that the Aurora-RT® system can be used in line with a conventional linac workflow. These include a wide bore of 110 x 60 cm which may also reduce patient claustrophobia; the ability to make large couch movements of ±23cm in the vertical and lateral directions, meaning that online re-planning is not required for all patients; and the ability to house the machine within a standard linac vault.[11] Tumour auto contouring and auto tracking on the Aurora-RT® system is enabled by artificial intelligence.[34]

The above companies were invited to complete a factual accuracy check of this information. In the case of the ViewRay systems, this check was provided by ViewRay Systems, Inc., which was established in 2024 acquiring the ViewRay assets following the company's bankruptcy.[36-39] There is at least one further MRgRT treatment delivery system currently in development. This system, which has been developed by an Australian research group, is described as a 1T open-bore MRI/6-MV linac system.[13]

In terms of the software underpinning MRgRT systems, many of the advanced functions such as adaptive radiotherapy (ART) and an MRI-only workflow are enabled by deep learning methods.[40-43] Specifically, deep learning techniques are used in segmentation, creation of synthetic CTs, radiomics and real-time/4D MRI.[43] Segmentation tools allow automatic delineation of tumours, organs at risk (OARs) and other structures, but the accuracy of auto-segmentation varies across anatomical regions.[43] Radiomics includes classification of structures on MRI and also tools for prognosis of treatment side effects and tumour response. Deep learning is also being used to synthesise MR images, to reduce acquisition time, and to improve image quality and to enable auto-replanning.[42]

Table 1: Overview of MRgRT delivery systems currently in clinical use or under development

System name	MRIdian system	MRIdian® Linac	Unity	Aurora-RT®	Currently referred to as Australian MR-linac
Manufacturer	ViewRay Technologies Inc. (Oakwood, Ohio, USA)	ViewRay Technologies Inc. (Oakwood, Ohio, USA)	Elekta AB (Stockholm, Sweden)	MagnetTx Oncology Solutions (Edmonton, Alberta, Canada)	Australian MRI-linac program (Ingham Institute, Liverpool, New South Wales, Australia)
Technology	Tri-Cobalt-60 MR system	MR-linac	MR-linac	MR-linac	MR-linac
MRI field strength (Tesla)	0.35	0.35	1.5	0.5	1
Beam strength	^{60}Co source	6 MV	7 MV	6 MV	6 MV
Bore Diameter (cm)	70	70	70	60	82
Orientation of photon beam to magnetic field	Vertical	Vertical	Vertical	Parallel/perpendicular	Parallel/perpendicular
Special features	Delivery with 3 ^{60}Co sources to increase dose rate, each with their own identical MLC systems.	Gating clinically possible; receiver coil not integrated in table; double stack MLC.	No laser, table cannot be moved laterally; MLC leaves are in longitudinal direction; automatic gating and tumour tracking is clinically possible.	Large bore 110 x 60 cm; 0.5 T open biplanar magnet; parallel configuration can limit electron return and streaming effect.	Capable of delivering radiation inline and perpendicular to the orientation of the magnetic field.
Current status	No longer in production	No longer in production	In production	In production	In development
CE marking status	2014	2016	2018	2024	N/A
FDA clearance	2012	2017	2018	2022	N/A

Key: ^{60}Co – cobalt 60; linac – linear accelerator; FDA – Food and Drug Administration; MLC – multi-leaf collimator; MR – magnetic resonance; MV – mega voltage; N/A – not applicable.

2.2 Potential benefits of MRgRT

There are several potential advantages of MRgRT which are hypothesised to improve the therapeutic index, increasing the probability of local tumour control with the same or lower probability of normal tissue complications.[2, 18, 44] These include improved soft tissue visualisation, motion management, use of adaptive RT, and the integration of biologic image guidance.[27] While used for the treatment of a wide range of anatomical sites, the potential for MRgRT to improve the therapeutic index will most likely apply to sites where tumours and OARs are difficult to visualise with conventional (CT-based) IGRT. In the upper abdomen, for instance, CT-based IGRT is challenging due to organ motion and the proximity of tumours to normal dose-limiting structures of similar electron densities.[23] For these anatomical sites in particular, MRgRT has the potential to improve accuracy in target delineation and visualisation during treatment, thereby allowing for reduced expansions of the gross tumour volume (GTV) and minimisation of the overlap of target volumes with OARs.

Internal organ motion occurs due to respiration and cardiac motion as well as motion from within luminal organs (those with a cavity inside a tubular structure, such as the intestines).[19] Conventional IGRT typically compensates for this motion as well as for anatomical variation and patient positioning by using geometric expansions of the target volumes or by using four-dimensional (4D) CBCT scans acquired over time.[23] This 4D imaging can be used to track motion and can allow for gating, which is where treatment is enabled when the target is in the appropriate position.[19] Conventional methods of gating typically rely on either internal or external surrogates of anatomical motion using external cameras or internal markers which do not always correlate to internal anatomy.[19, 23] In contrast, the MR-linac can produce real-time cross-sectional beam-on imaging which allows real-time monitoring without the need for fiducials (small markers placed within or on a patient's body to assist with localisation or verification of the treatment area).[2] MRgRT aims to address both intra-fraction and inter-fraction motion and also supports gated treatment delivery to compensate for respiration and tumour motion.[18, 24] Furthermore, the MR-linac also facilitates geometric online adaptive radiotherapy which allows real-time adaptation of the planned radiotherapy dose distribution based on the current position and shape of the tumour and surrounding organs at risk.[45] While CBCT can be used for adaptive radiotherapy, it often results in image distortion due to artefacts caused by organ motion and has inferior soft tissue contrast compared with MR-based imaging.[27] MRgRT delivery systems have integrated systems and workflows to allow daily or on-demand geometric adaptive radiotherapy to be performed.[46]

MRgRT also has the potential to provide adaptive radiotherapy beyond geometric parameters via biologic IGRT based on cancer biology. While it is reported that most

MRgRT protocols in the current clinical setting are based on morphological (structural) MR sequences,[22] the functional imaging capabilities of MRI have the potential to provide information on organ and tumour function, which could be used to predict specific treatment response and facilitate selective treatment tailoring.[24, 46]

2.3 Limitations of MRgRT

While there are many potential advantages of MRI over CT, the move from CTgRT to MRI-based delivery systems presents some challenges.[24] Firstly, MRgRT requires additional healthcare resources — for example, financial, staffing expertise and physical infrastructure.[47, 48] Radiotherapy bunkers must meet radiation protection requirements irrespective of whether they are housing a conventional linac or an MRgRT system. However, existing bunkers may not support the installation of MR linacs given the requirement to also house MRI infrastructure such as radiofrequency cages and quench pipe installations.[46]

A key challenge in MRgRT systems is the influence of the magnetic field on the radiation dose distribution which causes the electron return effect. This is where secondary electrons from the radiation beam interact with the magnetic field, particularly at the beam exit point and in the presence of air cavities causing hot and cold spots in the dose distribution.[49] While MRgRT systems have been designed to minimise the impact of the magnetic field on the dose distribution, the electron return effect must be considered in the calibration, choice of dosimeters, quality assurance, plan optimisation and plan adaption.[50] The concordance between the MRI origin and the radiation isocentre should be considered and also susceptibility of MRI to geometric distortion, which are dependent on the MR protocols used and patient characteristics.[24]

The MRgRT systems developed to-date are limited to a single photon energy and cannot deliver electron treatment.[46] Also, the delivery technique is currently limited to static field IMRT, using only coplanar beams, which might be sub-optimal, compared with volumetric modulated arc therapy (VMAT) treatments, in terms of target coverage and organs at risk avoidance.[51] However, VMAT-based treatment delivery using a MR linac might be possible in future as the proof of concept has been explored.[52] Table movements are either absent or limited in currently available MR-linac systems, resulting in a non-conventional workflow to compensate for patient positioning errors.[24]

The MRgRT workflow is sometimes dependent upon deformable image registration and delineation accuracy, both of which are potential sources of uncertainty. Consideration of such potential sources of uncertainty is important particularly when margins are being reduced.[24]

2.4 Cost and capacity

MRgRT is associated with substantial upfront costs.[24] UK data indicate that the cost of an MR-linac is approximately three times that of a conventional linac.[53] In addition, facility renovation may be required to prepare for the MR-linac installation. There are also increased operating costs associated with MRgRT, including increased maintenance and personnel costs.[54] The increased personnel cost is primarily due to the potential requirement for additional team members and upskilling of staff. In some situations, there may be a cost implication to physicians and or physicists as they may have to be present for adaptive MRgRT treatments.[55, 56] However, as utilisation and learning increases this will be mitigated by growing radiation therapist expertise and the emergence of radiation therapist-led workflows.[57] While the cost of delivering a course of MRgRT is estimated to be more expensive than delivering a course of stereotactic body radiotherapy (SBRT) or conventionally fractionated RT, there may be potential for cost offsets due to a reduction in the number of fractions delivered or reductions in treatment-related toxicity.[55]

From a service perspective, MRgRT is associated with considerably longer treatment times and decreased workflow efficiency compared with CTgRT.[54, 58-60] This is typically due to more complex patient positioning including coil placement, MR safety considerations, re-contouring, re-planning, lower dose rates and increased staff requirements at treatment delivery.[22, 24] However, it is anticipated that workflow efficiency can improve as institutional experience grows and due to improvements in software support. Increased MRgRT costs can be mitigated by forgoing CT simulation, avoiding the placement of fiducial markers where relevant, and reducing the number of treatments delivered.[60] Patient burden may also be reduced with MRgRT given fewer hospital visits and therefore reduced travel costs.[55]

3 Description of clinical indications

3.1 Who gets radiotherapy in Ireland?

During the period 2019-2021, almost one in four (24%) cancers diagnosed in Ireland were non-melanoma skin cancers. Excluding such skin cancers, the most commonly diagnosed cancers in men were prostate, colorectal cancer, lung cancer, melanoma of skin and non-Hodgkin lymphoma. In women, the most commonly diagnosed cancers were breast, lung, colorectal, melanoma of skin, and uterine cancer.[61] The National Cancer Registry Ireland (NCRI) indicates a projected increase in invasive cancers by 84% for females and 107% for males between 2010 and 2040, based only on changes in population size and age distribution.[62]

Radiotherapy can potentially benefit 50% of cancer patients as part of their care.[63-66] It can be used on its own as a treatment modality or in combination with chemotherapy and or surgery. In England, in December 2023, the most common tumour groups treated with radiotherapy were breast, followed by prostate, lung, head and neck, rectal, skin and lymphoma.[67] In Ireland, data provided via personal communication from the National Cancer Control Programme (NCCP) reported that in 2017, almost 7,500 patients were treated with radiotherapy in public and private facilities in Ireland.[68] Projections by the GLOBOCAN European cancer database suggested that cancer cases with an evidence-based indication for external beam radiotherapy would increase by approximately 36% in Ireland between 2012 and 2025.[63]

3.2 What is MRgRT intended to replace?

Topic exploration indicated that internationally, MRgRT is replacing CT or X-ray imaging guidance for shorter courses of radiotherapy such as ultra-hypofractionation and SBRT, which are delivered in one to five hospital visits. MRgRT is particularly being used for SBRT, which is a treatment modality in radiotherapy that delivers a very high dose of radiation to the tumour target with high precision using single or a small number of fractions.[69] Tumour sites where SBRT has a role include lung cancer, spinal tumours, liver tumours, prostate cancer, pancreatic cancer, head and neck cancer, renal cancer and oligometastatic bone disease.[70] Currently in Ireland, SBRT using CT or X-ray imaging guidance is provided in a number of public and private radiotherapy facilities.

Patterns of care from the MOMEMTUM registry indicated that MRgRT is primarily being used to deliver SBRT with a median of five fractions to treat prostate, lymph nodes, rectum, liver and pancreas sites.[71] For example, for prostate cancer, targets were treated with a median dose of 36Gy in five fractions.[71] Similarly, US-based

data from 2014 to 2020 indicate that Viewray MRgRT systems were most commonly used to treat pancreas, liver, prostate, breast and lung sites.[72] Short courses of radiotherapy were predominantly used, with over 70% of courses using one to five fractions and approximately 20% of fractions were adapted.[72] The data indicated that by 2020, the use of short courses (one to five fractions) had increased to over 80% and adaptive RT was applied in over 50% of treatment courses.[72]

3.3 Who is likely to benefit from MRgRT

The benefits of MRgRT are dependent upon the treatment site.[2] MRgRT can benefit clinical management through enhanced soft tissue visualisation, motion management and access to adaptive RT. Table 2 provides an overview of the proposed rationale for MRgRT, broken down by anatomical site. Topic exploration and information provided by Elekta indicated that key sites where MRgRT is being used currently are prostate, liver, pancreas and treatment of oligometastatic disease, primarily for SBRT.

Table 2: Rationale for MRgRT by disease site

Disease site	Enhanced soft tissue visualisation	Motion management	Inter-fraction adaptive re-planning	Margin reduction	Facilitate dose escalation
Prostate[58]	✓			✓	
Pancreas[73]	✓	✓	✓		✓
Liver[74, 75]	✓	✓	✓		✓
Breast[76, 77]	✓	✓		✓	
Lung[78, 79]		✓	✓		
Oligometastases[80]	✓	✓	✓	✓	✓
Cardiac ablation[81]	✓	✓			

Reproduced from *Clinical Applications of Magnetic Resonance-Guided Radiotherapy: A Narrative Review* by Ladbury et al, 2023; Creative Commons license (CC BY) 4.0[72]

Prostate cancer is a key treatment site for MRgRT, as the addition of MRI significantly improves visualisation of the prostate and adjacent soft tissues including the urethra.[54] MRgRT is proposed to reduce genitourinary (GU) and gastrointestinal (GI) toxicity in prostate cancer by margin reduction enabled by improved visualisation and avoidance of soft tissue OARs, coupled with daily adaption.[2] MRI guidance can be used to potentially control for motion of the prostate during treatment due to rectal gas, bladder filling, patient movement and respiration, improving treatment accuracy and potentially reducing toxicity.[54]

The NCRI cancer projections indicate that the rate of cancers of the upper GI tract which include oesophagus, pancreas and hepatobiliary tract are expected to increase by over 100% by 2040 in Ireland.[62] In the pancreas, radiotherapy has previously

had a limited role due to the radioresistance of tumours which benefit from higher doses. Poor soft tissue contrast between target volumes and adjacent OARs such as duodenum and small bowel on CBCT has limited the confidence to treat pancreatic tumours with sufficiently therapeutic doses.[82] Poor visualisation necessitates larger volumetric expansions to account for uncertainty, which ultimately increases OAR dose. High doses to the OARs can cause bowel or gastric ulcers, biliary stricture or renal dysfunction.[23] Pancreas is one of the treatment sites proposed to benefit from online adaptive techniques and motion management strategies due to close proximity to the diaphragm.[2, 82] These strategies can help to optimise the target volume and avoid OARs, thereby reducing toxicity.

In liver, as per pancreas, radiotherapy is challenged by proximity of OARs, diaphragm movement and changing organ volumes between treatments. CTgRT has been limited by the similarity of tissue electron densities making visualisation and adaption difficult.[23] The On-Target UK IGRT guidance published in 2021 references MRI as a promising technique for on–treatment image guidance, gating and motion monitoring of liver tumours due to the low soft-tissue contrast of liver tumours.[19]

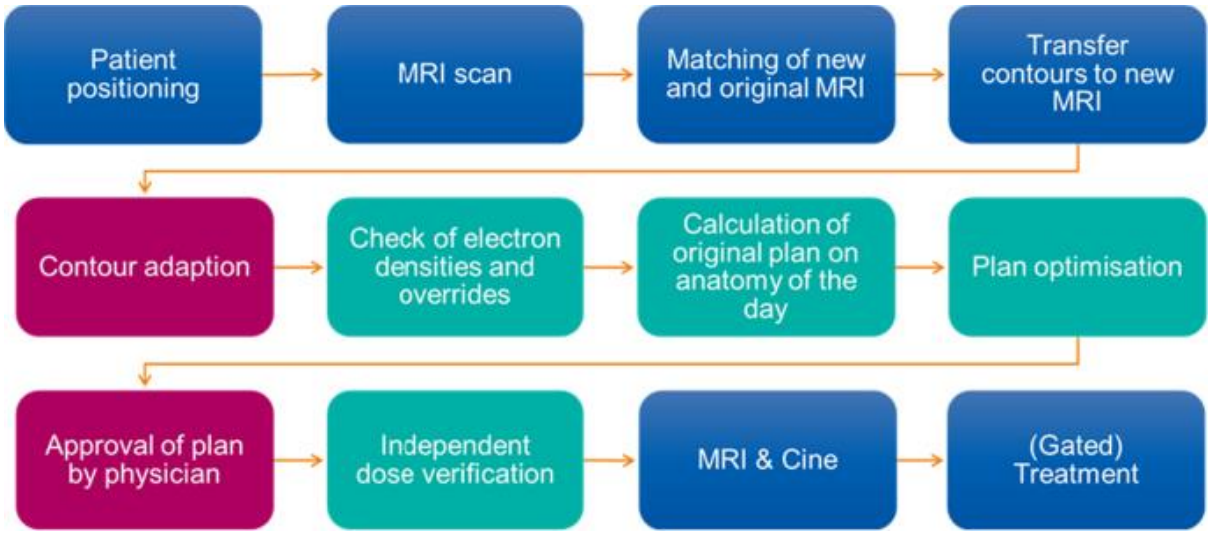
In the treatment of oligometastatic disease, CT-guided SBRT has been associated with improvements in overall survival.[83] Depending on the location of the metastatic treatment site, patients may benefit from MRI-guided SBRT to ensure that ablative doses can be delivered, which can in turn improve local control.[2] As per other indications, oligometastatic tumour sites close to critical structures, prone to motion or lacking visualisation on CT, can potentially benefit from MRgRT.[84]

3.4 Implementation of MRgRT

The European Society for Radiotherapy and Oncology (ESTRO) and the Advisory Committee for Radiation Oncology Practice (ACROP) have developed a consensus guideline on commissioning and quality assurance of online MRgRT systems.[85] This guideline noted that MRgRT systems are an emerging technology and that the evidence available on quality assurance procedures and frequencies is limited.[85] ESTRO-ACROP also published clinical implementation recommendations for MRgRT systems, highlighting how unlike other radiotherapy techniques, MRgRT adds the MR environment to daily RT practice.[84] Considerations prior to the implementation of an MR-linac system included staff training on MRI safety, image acquisition, image registration, contouring/delineation, treatment planning and delivery. The recommendations also highlighted the importance of patient selection and indications for the MR-linac in terms of patient physical compatibility, performance status due to the required degree of compliance and suitable treatment sites based on current evidence. Potential suboptimal patient selection has been highlighted as a risk to the successful implementation of MRgRT, with the warning also that where

new workflows provide improved geometric accuracy, overconfidence in the accuracy of the treatment chain can lead to local recurrences.[24] Therefore, clinical implementation of any new RT workflow should be considerate of all potential sources of error or inaccuracy. Figure 1 outlines a sample MRgRT workflow.

Figure 1: Adaptive workflow for a treatment at the MR-LINAC



Tasks performed by radiation therapists are blue, by physicians depicted in red and by physicists or dosimetrists/RTTs in turquoise.

Reproduced from Operating procedures, risk management and challenges during implementation of adaptive and non-adaptive MR-guided radiotherapy: 1-year single-center experience by Schüler et al, 2021 Creative Commons license (CC BY) 4.0.[86]

4 Methods

A protocol detailing the methods undertaken in this systematic review has been published previously and also registered on PROSPERO (CRD42024551825). The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria — see Table A.1 in Appendix A for the PRISMA checklist.[87]

The generic justification process is informed by two research questions (RQs). RQ1 considers clinical effectiveness and RQ2 considers harms, toxicities and adverse events. In Ireland, public and occupational exposure is primarily the responsibility of the Environmental Protection Agency. However, the regulations require HIQA to consider public and occupational exposure as part of the justification of medical exposures.[88] The approach taken to this issue and the two RQs is outlined in the following sections.

4.1 Research questions

This evidence review to inform decision-making on generic justification comprised two distinct RQs:

RQ 1 In patients with cancer requiring radiotherapy, does the choice of image-guided modality (MRgRT versus other image-guided radiotherapy systems) result in a difference in clinical effectiveness?

RQ 2 In patients with cancer requiring radiotherapy, does the choice of image-guided modality (MRgRT versus other image-guided radiotherapy systems) result in a difference in potential harms?

Table 3 outlines the Population, Intervention, Comparison, Outcomes, Setting (PICOS), as well as details of the eligible records and languages.

Table 3: PICOS

PICOS	Description
Patient/Problem:	Patients who require external beam radiotherapy for cancer treatment.
Intervention:	External beam radiotherapy delivered using magnetic resonance-guided radiotherapy (MRgRT) delivery systems such as MR-linac — that is, MRI combined with a radiotherapy linear accelerator, such as Elekta Unity, ViewRay MRIdian, ViewRay MRIdian linac or any other MRgRT hybrid delivery system.
Comparison:	▪ External beam radiotherapy delivered with other image-guided radiotherapy systems (for example, CT or X-ray or other image-guided modality) ▪ Studies without a comparator will be included, such as before-and-after treatment comparisons
Outcomes:	RQ1: any measure of clinical effectiveness ▪ Overall survival, progression-free survival ▪ Quality of life or symptom control measured using a validated instrument ▪ Mortality ▪ Treatment duration RQ2: Harms: ▪ Frequency and severity of radiotherapy-related adverse events and toxicities ▪ MRI-related harms: adverse events resulting from contraindications to MRI (for example, pacemakers, neurostimulators, or from metallic objects acting as projectiles in the magnetic field)
Study Design:	Included: ▪ High-quality systematic reviews*, RCTs and non-randomised controlled trials, cohort studies, case-control studies, self-controlled case series. ▪ Only studies relating to external beam radiotherapy. Excluded: ▪ Case reports, cross-sectional studies, case studies, non-systematic literature reviews, narrative reviews ▪ Case series and studies with <10 participants ▪ *In silico* studies and studies only reporting dosimetric data ▪ Animal studies ▪ Studies relating to brachytherapy ▪ Studies relating to MRI used only for radiotherapy simulation and planning

Languages:	Only articles for which an adequate English translation can be obtained will be included.
Search period	01/01/2018 to current*

Key: CT – computed tomography; MRI – magnetic resonance imaging; MRgRT – magnetic resonance-guided radiotherapy; RCT – randomised controlled trial; RQ – research question

Notes: *For the purpose of this evidence review, a high-quality systematic review is considered to comprise reviews reporting on at least one outcome of interest with all of the following characteristics:

- A clearly stated set of objectives with an explicit, reproducible methodology.
- A systematic search of at least two databases, carried out since January 2018, which attempts to identify all studies that would meet the eligibility criteria.
- A systematic presentation and synthesis of the characteristics and findings of the included studies.
- A critical appraisal of the available evidence.

Ideally, the systematic review will have evaluated the certainty of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[89]

**Search period selected because the search from a relevant assessment by the Canadian Agency for Drugs and Technologies in Health (CADTH) was conducted up until this time point[14]

4.2 Protocol deviations

A large number of completed non-randomised studies were identified from the search carried out for this systematic review, many of which had relatively small sample sizes and did not include comparators, thereby limiting insight into the effectiveness of MRgRT over current practices. Given the availability of larger (non-randomised) studies which directly relate to the research questions, a number of deviations from the published protocol were made. These deviations and the rationale for them are listed below:

- Only studies which included ≥10 participants were included at full text screening.
- Studies which only reported patient experience or radiotherapy treatment times were excluded at full text screening.
- *In silico* studies and studies which only reported dosimetric data were excluded at full text screening.
- Limited data extraction was initially completed for all studies which met the inclusion/exclusion criteria (see Table 3). An evidence and gap map was then prepared to give an overview of the current evidence landscape in MRgRT with a focus on the study designs, anatomic site and sample size of the available studies. Having considered the available evidence, only comparative studies underwent the predefined full data extraction process.
- While patient anxiety during imaging and treatment on a MR linac was not included as an outcome in the PICOS for this systematic review, a high-level

summary of the findings of three studies that used validated questionnaires was included.

Rationale: Given the availability of larger studies which directly relate to our research questions, small case series with fewer than 10 participants were excluded as they are unlikely to be powered to estimate absolute effects or determine significant differences between groups. Also excluded were studies that only reported surrogate dosimetric endpoints; studies that only reported patient experience (for example, patient satisfaction), but did use a validated questionnaire; and those reporting treatment times only, as these were deemed to be less informative.

Findings from this systematic review indicated that patient claustrophobia and other discomforts such as noise may be an important consideration for patients undergoing treatment on a MR linac. For this reason, a high-level summary of the relevant findings related to these issues are presented.

4.3 Search strategy

Electronic searches were last conducted on 9 December 2024 in MEDLINE (EBSCOhost), Embase (Ovid) and CINAHL (EBSCOhost). Several clinical trial registries were also searched: Clinicaltrials.gov (https://clinicaltrials.gov/ct2/home), World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP) (https://trialsearch.who.int/) and Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library to identify ongoing trials.

The search strategy for the MEDLINE (EBSCOhost) search is outlined in Table A.2 of Appendix A. A targeted search of the grey literature was also carried out — details of this search are outlined in Table A.3 of Appendix A. This included a search of regulatory websites for any safety alerts or updates.

Reference lists from the included systematic review was searched for potentially relevant citations. Forward citation searching of included studies was undertaken using Citation Chaser https://estech.shinyapps.io/citationchaser/. No language or date restrictions were applied to the eligibility criteria or the search strategy. Complete documentation of all search strategies for this project can be found on the Zenodo open repository: https://zenodo.org/records/11244102.

4.4 Record selection

Returned citations from the collective search were added to Endnote for reference management. Following the removal of duplicates, the records were transferred to Covidence for screening. Title and abstract screening was performed by two reviewers independently, against the eligibility criteria (Table 3). At the end of title and abstract screening, the protocol deviations were discussed and agreed upon by

the review team. The full text of potentially eligible articles was retrieved and assessed for eligibility by two reviewers according to the eligibility criteria (Table 3). Any disagreements were resolved through discussion or by consulting with a third reviewer. Reasons for exclusion following full-text review were documented and summarised in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart (Figure 2).[87] DeepL Pro Translate professional software was used to obtain translations of non-English language documents.[90] The references and tables of any systematic reviews meeting our PICO were searched to ensure all relevant primary studies were included. As primary studies were the unit of inclusion in this review, the systematic reviews identified were not further assessed, but are referred to in the discussion.[91]

4.5 Data extraction and synthesis

As noted previously, a large volume of completed primary studies was identified by this systematic review, spanning a range of anatomical sites. Core variables were extracted from all included primary studies, in line with the revised PICOS. From this full list of studies, studies that were most likely to inform a generic justification decision (that is, those that included a comparator) were selected for full data extraction and risk of bias assessment. An evidence and gap map was produced to demonstrate the availability (or lack thereof) of published evidence and the type of studies that have been conducted using MRgRT for each anatomical site. A modified version of the 'Evimapper' package was used to produce the map using bubbleplots in R using R Studio version 4.3.2.[92]

All data extraction was performed by one reviewer using a pre-piloted standardised data extraction template in Microsoft Word and checked by a second reviewer. The results of this review are reported per treatment site, focusing on studies with a relevant comparator. The term 'multiple sites' was used to categorise studies which reported outcomes across various indications for MRgRT. Meta-analyses were not performed as there were too few studies and data per anatomic treatment site. The findings from the included comparative studies are narratively synthesised and reported following Synthesis Without Meta-analysis (SWiM) guidelines – see the SWIM checklist in Table A.4 of Appendix A.[93] A high-level narrative summary of ongoing research studies identified from the search of the trial registries was also generated.

4.6 Risk of bias assessment

Two reviewers independently assessed the risk of bias of the included comparative studies which had a comparator. The Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) and the Risk of Bias tool for randomised trials-2 (RoB-2)

were used to assess cohort studies and randomised controlled trials (RCTs), respectively. Any disagreements were resolved through discussion or by consulting with a third reviewer.

4.7 Grading of Recommendations Assessment, Development and Evaluation (GRADE)

The completed primary studies that included a relevant comparator were used to help populate the modified evidence-to-decision table for generic justification, as outlined in HIQA's methods for generic justification document.[4] As per GRADE guidelines,[89] evidence was graded as high, moderate, low or very low certainty, the definitions of which are outlined in Table 4 below.

Table 4: GRADE working group definitions of the evidence grades

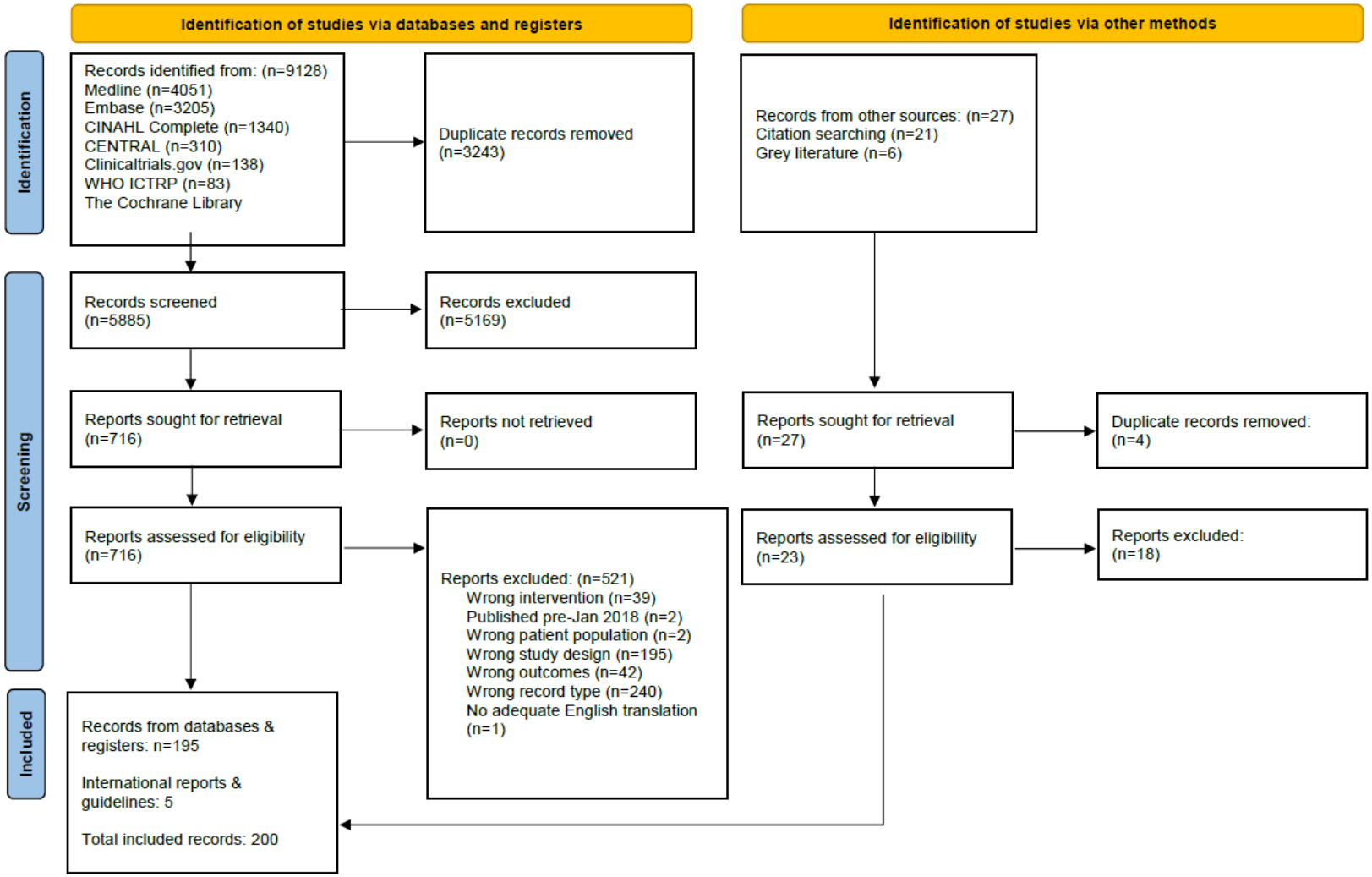
Certainty rating	Definition
High	'We are very confident that the true effect lies close to the estimate of the effect.'
Moderate	'We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.'
Low	'Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.'
Very low	'We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.'

Results

5.1 Search results

After removal of duplicates, 5,888 title and abstracts were assessed for eligibility; 719 articles required full text review, with 200 records requiring data extraction. An overview of the article selection process is presented in the PRISMA flowchart (Figure 2). After application of the inclusion and exclusion criteria, 136 completed primary studies (studies which had published at least one set of findings) and one systematic review were identified for inclusion in this report. The included systematic review, Westerhoff et al.,[94] reported 11 observational studies and one RCT describing patient reported outcomes following MRgRT in patients with prostate cancer; all 12 of these studies were identified during our systematic database search. Fifty-eight ongoing research studies were identified from the search of the trial registries and five international practice reports and guidelines were identified from the grey literature search.

Figure 2: PRISMA Flow Diagram



5.2 Summary of included records

Only six completed studies reported comparative data; these included one RCT (which was recently updated by a brief report),[58, 95] two prospective phase II cohort studies[51, 59] and three retrospective cohort studies.[51, 96, 97] These studies included patients with prostate cancer, lung cancer, liver cancer (including metastatic spread to the liver), and pancreatic cancer (including metastatic spread to the pancreas). Of the six studies, five employed a 0.35T MRgRT system, while one employed a 1.5T MRgRT system. Characteristics of these six comparative studies are detailed in Table 5. Results of these six comparative studies are described below and in Table B.1 of Appendix B.

In addition, 130 non-comparative studies were found, of which 72 and 58 were prospective and retrospective in design, respectively. One study contained pooled data from two independent prospective and retrospective cohorts; for simplicity this was coded as a prospective study. These 130 non-comparative studies investigated some aspect of MRgRT outcomes in the following tumour or anatomical sites: prostate (n=32), pancreas (n=22), liver (n=19), oligometastatic cancers (n=13), lung (n=12), multiple radiotherapy treatment sites (n=12), adrenal (n=6), rectum (n=4), breast (n=3), gynaecological cancers (n=2), renal (n=2), head and neck (n=1), bladder (n=1), and high grade gliomas (n=1).

Sample size varied greatly across the 136 comparative and non-comparative studies, ranging from fewer than 10 participants to 1,772.[71] The median study size was 35 participants, and 24 studies had a sample size >100. Of these 24 larger studies, three were comparative studies,[58, 59, 98] while the others were single-arm studies, including four reports from the prospective MOMENTUM registry,[25, 71, 99, 100] one report on baseline data from an ongoing a trial within a cohort (TWiC) study,[101] 11 prospective cohort studies,[102-112] and five retrospective studies.[113-117]

An evidence and gap map is presented in Figure 3 — this gives a visual representation of the evidence according to study design and anatomical site. Each record included in our systematic review contributes one 'bubble' per included outcome (overall survival, disease control, QoL and toxicity), provided it contains data on those outcomes. Summary of characteristics tables for these studies will be available from our Zenodo repository: https://zenodo.org/records/15518924

Table 5: Summary of characteristics of included studies comparing MRgRT with other image-guided radiotherapy systems

Author and Year Country	Study Design	Number of patients Age (range*)	Primary Tumour	Intervention Comparator	Treatment Dose Margins	Follow-up	Outcome(s) Reported**	Conflicts of Interest
Prostate (n= 256)								
Kishan 2023[58] United States MIRAGE	Non-blinded single centre phase III RCT	n=156 CTgRT =77 (49.4%) MRgRT = 79 (50.1%) Median age: Not reported CTgRT 71 years (IQR 67-77 years) MRgRT 71 years (IQR 68-75)	Intermediate, high, or very high risk prostate cancer	MRgRT (0.35TMR-linac; SBRT; gated; non-adaptive) CTgRT (CBCT; SBRT; fiducial markers; non-adaptive)	40Gy in 5 fractions 42Gy in 5 fractions SIB to dominant intra-prostatic lesion 35Gy in 5 fractions SIB to a pelvic node identified on functional imaging MRgRT PTV = 2mm isotropic expansion of CTV CTgRT PTV = 4mm isotropic expansion of CTV	All patients had three months or more of follow-up	Acute & late toxicity (CTCAE, IPSS) QoL (EPIC-26) Erectile dysfunction (SHIM scores)	No industry funding, sponsorship or financial relationship declared for this study. Some authors reported financial relationships with ViewRay.

Ma 2023[98] United States SCIMITAR	Phase II, dual-center, open-label, single-arm trial, non-randomised	n=100 CTgRT = 69 (69.0%) MRgRT = 31 (31.0%) Median age: 69 years (range 50-82) CTgRT arm 69 (range 52-79) MRgRT arm 68 (range 50-82)	Prostate cancer (post-prostatectomy)	MRgRT (0.35T MR-linac; SBRT; gated; predominantly non-adaptive [~97.5%]) CTgRT (CBCT; SBRT; gated; use of fiducial markers not reported; use of adaptive not reported)	Median dose 32Gy (30 to 34 Gy) in 5 fractions MRgRT PTV = 3mm isotrophic expansion of CTV CTgRT PTV = 5mm isotropic expansion of CTV	Median follow up: 29.50 months	Biochemical recurrence free survival QoL (EPIC-26 & IPSS) Acute & late toxicity (CTCAE)	The trial was partially funded by ViewRay. Some authors reported financial relationships with ViewRay.
Nicosia 2023[59] Italy	Prospective Phase II single-centre cohort study	n=135 MRgRT= 72 (53.3%) CTgRT= 63 (46.7%) Median age: Not reported MRgRT 72 years (54-84) CTgRT 74 years (57-83)	Low or favourable intermediate risk prostate cancer	MRgRT (1.5T MR-linac; SBRT; gated; adaptive) CTgRT (CBCT; SBRT; fiducial markers; non-adaptive)	35Gy in 5 fractions PTV = CTV +5mm in each direction, except 3mm posteriorly	Patients included if they had at least six months follow up	Toxicity (CTCAE, IPSS) Pre- & post-treatment PSA	One author reported financial relationships with Elekta. No industry funding, sponsorship or financial relationship declared for this study.

Liver (n=59)								
Tallet 2023[51] France	Retrospective study	n=59 MRgRT = 18 (30.5%) CTgRT = 41 (69.5%) Median age: Not reported MRgRT 70 years (range 38-89) CTgRT 69 years (range 30-83)	Primary or secondary liver tumours (colorectal, breast, other)	MRgRT (0.35T MR-linac; SABR; gated; adaptive [~20.0% of fractions]) CTgRT (CBCT; SABR; fiducial markers; non-adaptive; no gating; abdominal compression)	Median dose 40Gy (35–50) in 5 fractions (3–10). MRgRT PTV = GTV + 5mm (poorly distinguishable tumours) or GTV+3mm (accurately distinguishable from the liver parenchyma), CTgRT PTV = ITV + 5mm laterally & anterior/posterior & 7mm cranio-caudally	Median follow up: 16.7 months (1.18-73.02)	Toxicity (CTCAE) Local response (RECIST)	Department and some authors report financial support from ViewRay
Pancreas (n=50)								
Lee 2022[96] South Korea	Retrospective study	n=50 CTgRT= 24 (48.0%) MRgRT = 26 (52.0%)	Pancreatic adenocarcinoma & oligometastases not otherwise specified	MRgRT (0.35T system; SBRT; adaptive; real-time gated; abdominal compression)	Median dose was 50.0 Gy (range, 40–50 Gy) in 5 fractions. PTV = CTV + 6mm margin	Median follow up: 18.8 months (4.10–61.00)	Toxicity (CTCAE) 1- & 3-year OS Local response (RECIST)	No industry funding, sponsorship or financial relationship declared. No conflict

		Median age: 62 years (range, 39–78 years)		CTgRT (CBCT; SBRT; Non-adaptive; Not gated; Six hour fasted; Abdominal compression)			One- and three-year LPFS	of interest declared.
Lung (n=81)								
Kang 2022[97] South Korea	Retrospective study	n=81 MRgRT = 41 (50.6%) CTgRT = 40 (49.4%) Median age: Not reported MRgRT 75 years (range 46-87) CTgRT 75 years (range 45-88)	Lung cancers (adenocarcinoma, squamous cell cancer, NSCLC, not otherwise specified).	MRgRT (0.35T MR-linac; SABR; gated; non-adaptive) CTgRT (CBCT or MVCT; SABR; non-adaptive; abdominal compression)	48 to 60Gy in 3–5 fractions Gy. MRgRT PTV = GTV + 5-7mm CTgRT PTV = ITV + 5mm	Median follow up: 19 months (3-105).	Toxicity (CTCAE,) Local response (RECIST,) 1-year PFS 1-year OS	No industry funding, sponsorship or financial relationship declared. No conflict of interest declared.

Key: CTCAE – Common Terminology Criteria for Adverse Events; CTgRT – Cone Beam Computer Tomography Guided Radiotherapy; CTV – Clinical Target Volume; EPIC-26 – The Expanded Prostate Cancer Index Composite; GTV – Gross Tumour Volume; Gy – Gray; IPSS – International Prostate Symptom Score; ITV – Internal Target Volume; LPFS – Local Progression Free Survival; MRgRT – Magnetic Resonance Guided Radiotherapy; MVCT – Mega Voltage Computer Tomography; NSCLC – non-small cell lung cancer; OS – Overall Survival; PFS – Progression Free Survival; PSA - Prostate Specific Antigen; PTV – Planning Target Volume; RECIST- Response Evaluation Criteria In Solid Tumours; SABR – Stereotactic Body Radiotherapy; SHIM - Sexual Health Inventory for Men

Note: *Unless otherwise specified; **Only outcomes consistent with the PICOS in Table 3 are reported.

Figure 3: MRgRT evidence and gap map

Note: Each record contributes one 'bubble' per outcome included in their published paper. Gaps in the map indicate that no records identified in this systematic review had any data on that outcome for that radiotherapy treatment site. The size of each 'bubble' is proportionate to the number of participants included in the published paper.

*Disease control includes measures of local control, local failure, disease-free survival, time to recurrence, biochemical free survival, and local, regional or distant progression free survival.

5.3 Risk of bias assessment

Risk of bias was assessed using the ROB-2 tool for the RCT and ROBINS-I for the five cohort studies.[118, 119] The risk of bias in the cohort studies was assessed for both RQ1 (clinical effectiveness) and RQ2 (safety) outcomes. However, there were no differences in the risk of bias judgements for either set of outcomes in any of the studies. The overall risk of bias assessment for each study is presented in Table 6 below.

In the prostate RCT conducted by Kishan et al., the overall risk of bias was high due to concerns around deviations from intended interventions and how these deviations were considered in the analysis.[58] The risk of bias assessment also reflected the lack of blinding as outcome assessors, participants, carers and people delivering the interventions were aware of intervention groups during the trial. However, it is acknowledged that blinding of physicians or those assessing outcomes is often not practical nor feasible in radiation oncology studies as factors such as the treatment techniques are difficult to conceal from patients and must be known by the physician prescribing and overseeing the patients' radiotherapy.[95]

In the five cohort studies, bias due to baseline confounding was a consistent area of concern.[51, 59, 96-98] In particular, there was either concern or a lack of information surrounding how pre-intervention prognostic factors might have determined whether participants were assigned to the MRgRT or conventional IGRT interventions. These prognostic factors included breathing difficulties, pre-radiotherapy interventions and MRI contraindications. In particular, Lee et al. 2022 (pancreatic cancer cohort study) was found to be at critical risk of bias as baseline characteristics including pre-radiotherapy interventions, performance status and metastatic status were not reported per treatment arm nor did they appear to be controlled for.[96]

Risk of bias was also identified in how these studies selected participants. Nicosia et al. selected patients from two different prospective studies, which had differing inclusion criteria leading to concerns about baseline confounding.[59] In the cohort study conducted by Kang et al. (lung cancer), patient selection was largely based on whether they had treatment before or after the institution introduced MRgRT and it was unclear how patient characteristics impacted assignment, particularly when both technologies were concurrently available.[97] Similarly, in the study conducted by Lee et al., patients were assigned to the conventional arm if they had breathing difficulties or could not tolerate longer treatment times in the MRgRT arm.[96]

Concerns regarding bias were also found in how these studies measured their outcomes. Assessors of outcomes were not blinded and were aware of the intervention in all of the included studies. This bias could have impacted assessment of toxicity, disease progression and local control, thereby effecting both RQ1 and

RQ2 outcomes, most likely in favour of the intervention. However, it is again acknowledged that blinding was likely not feasible.[95]

For all five cohort studies, bias due to deviations from intended interventions were unclear or not reported.[51, 58, 59, 96-98] Studies were assumed to be carried out in line with usual practice acknowledging that some practices differed across treatment arms. For example, adaptive strategies were sometimes applied in the MRgRT arm only and abdominal compression used in the control arm only, but this was largely in line with usual clinical practice for the individual technologies.

Finally, there was a lack of reporting on missing data in three of these cohort studies.[51, 96, 98] Where information was provided on missingness in the other two cohort studies, this was deemed to result in a serious risk of bias. [59, 97]

Table 6: Assessment of methodological quality using the Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool and risk-of-bias tool for randomized trials (RoB-2)

Author, year	Confounding	Randomisation process	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing Data	Measurement of outcomes	Selection of the reported result	Overall bias
	ROBINS-I tool								
Lee, 2022[96]	Critical		Serious	Low	Moderate	No Information	Serious	Serious	Critical
Nicosia, 2023[59]	Serious		Serious	Low	Moderate	Serious	Moderate	Moderate	Serious
Tallet, 2023[51]	Serious		Moderate	Low	Low	No Information	Serious	Moderate	Serious
Kang, 2022[97]	Serious		Serious	Low	Serious	Serious	Serious	Moderate	Serious
Ma, 2023[98]	Moderate		Moderate	Low	Low	No Information	Moderate	Moderate	Moderate
	ROB-2 tool								
Kishan, 2023[58]		Low			High	Low	High	Low	High

5.4 Prostate cancer

Three comparative prostate studies were identified which compared MRgRT with CTgRT delivered using kV CBCT; one RCT (Kishan et al.) and two prospective phase II cohort studies (Niscosia et al. and Ma et al.).[58, 59, 95, 98] Table 7 provides a summary of the findings of these studies. In short, Kishan et al. reported on a phase III RCT, known as the MIRAGE trial, which randomised patients in a 1:1 ratio to receive stereotactic body radiotherapy (SBRT) via either CT guidance (control; n=77) or MRI guidance (intervention; n=79). Nicosia et al. reported on a prospective phase II cohort study which compared patients who were treated with SBRT via either CT guidance (n=63) or MRI guidance (n=72). Ma et al. presented data from a prospective phase II trial, known as the SCIMTAR trial, which included patients treated with SBRT using CT guidance (n=69) or MRI guidance (n=31). The three studies were distinctly different in terms of their populations. Kishan et al. recruited those with intermediate, high- or very high-risk prostate cancer, Nicosia et al. recruited patients with low- or favourable intermediate-risk prostate cancer, and Ma et al. recruited post-prostatectomy patients.

None of these three publications reported on overall survival or mortality, although a four-year analysis of biochemical recurrence-free survival is planned for the SCIMTAR trial. Two of the three studies provided outcome data on quality of life,[58, 95, 98] all three studies provided outcome data on acute and late toxicity,[58, 59, 95, 98] while two reported on treatment duration.[58, 59]

Symptoms and quality of life

The studies reported by Kishan et al. and Ma et al. provided outcome data on symptoms and quality of life.[58] A pre-specified secondary analysis published by Kishan et al. as a brief report provided data on QoL outcomes at 24 months, which supplemented the original findings reported at one and three months post-SBRT.[95] There was 83% compliance with QoL surveys at the 24 month timepoint. Kishan et al. acknowledged that the MIRAGE RCT was not powered for any of the secondary analyses evaluated at 24 months. Ma et al. recorded outcomes at one month, three months and six months post-SBRT.

Both Kishan et al. and Ma et al. used two established, validated questionnaires to assess QoL: the International Prostate Symptom Score (IPSS) and the Expanded Prostate cancer Index Composite-26 (EPIC-26).[120] The IPSS contains seven questions which assess urinary symptoms (and also an additional question relating to QoL), with higher scores indicating more severe symptoms. The EPIC-26 comprises 26 questions with five domains (urinary incontinence, urinary irritation or obstruction, sexual, bowel, hormonal), which is scored from 0 (worst) to 100 (best).[121] Kishan et al. defined a clinically relevant decrement in EPIC-26 score as

greater than 18, 14, 12, and 24 points for urinary incontinence, urinary irritative or obstructive, bowel, and sexual domains, respectively. The same authors considered a clinically relevant increase in IPSS score as an increase of ≥15 points. In contrast, Ma et al. defined a clinically relevant decrement in EPIC-26 score as values greater than 6, 5, 4, and 10 points for the urinary incontinence domain, urinary irritative/obstructive domain, bowel domain, and sexual domain, respectively. Ma et al. did not define or report clinically significant differences in IPSS scores.

Kishan et al. reported no significant differences in total IPSS changes from baseline between the two groups at one month (p=0.06) or three months (p=0.20) post-SBRT.[58] However, a lower proportion of patients in the MRgRT arm had a clinically significant increase in IPSS score (≥15 points) at one month post-SBRT (6.8% [5 of 72] vs. 19.4% [(14 of 74] p=0.01). This statistical difference between groups was not observed at the three month timepoint (1.4% [1 of 72] vs. 4.1% [3 of 74] p=0.30), or at any point between six and 24 months post SBRT.[58].[95] There was no difference in the QoL subscore between the groups at one (p=0.50) or three months (p=0.30); IPSS QoL was not reported at 24 months.

Ma et al. reported a statistically significant increase from baseline in the IPSS summary score in the MRgRT arm (score +1.8, p=0.02), but not the CTgRT arm (score +1.0, p=0.12) at one month post-SBRT. Neither arm had a statistically significantly change in the IPSS summary score at three or six months post-SBRT. No significant changes in the IPSS QoL domain were reported in either the CTgRT or MRgRT arm at one, three, or six months post-SBRT.

Kishan et al. reported no significant differences in the following EPIC-26 subdomains from baseline at one month post-SBRT: irritative/obstructive sub-score (p=0.30) or overall urinary domain (p=0.30).[58] Neither of these outcomes were significantly different between the two groups at three months: irritative/obstructive sub-score (p-value not reported) or overall urinary domain (p=0.20).[58] Following completion of SBRT in the MIRAGE RCT, urinary incontinence EPIC-26 subdomain scores decreased significantly more (i.e., worse symptoms) with CTgRT versus MRgRT at one month (11.3-point vs. 6.2-point decrement; p=0.01), but not at three months. A significantly lower proportion of patients in the MRgRT arm reported a clinically relevant deterioration in urinary irritation at any point between six and 24 months (14/73 vs. 24/68 [19.2% vs. 35.3%] for urinary irritation, p=0.03). Ma et al. reported a significant deterioration from baseline in the urinary irritative/obstructive domain of EPIC-26 in the CTgRT arm (p=0.02), but not the MRgRT arm (p=0.11) at one month; this deterioration had reversed by three months. Compared with baseline, a statistically significant decline in the EPIC-26 urinary incontinence domain was reported in the MRgRT arm (p=0.04), but not the CTgRT arm (p=0.12) at one month, with no difference from baseline reported for either arm at three or six

months. There was no statistical difference in the percentage of patients with clinically relevant deterioration at the one-, three-, or six-month time points for either the EPIC-26 urinary irritative/obstructive domain or the urinary incontinence domain.

Kishan et al. reported that a significantly lower proportion of patients in the MRgRT had a clinically significant (≥12-point) decrease in EPIC-26 bowel scores (25.0% [17 of 68] vs. 50.0% [34 of 68]; p=0.001) at one month.[58] Patients in the MRgRT arm reported a significantly smaller decrement in EPIC-26 bowel domain sub-scores at one month (4.1 point vs. 18.2-point decrement; p<0.001) but not at three months. The proportion of patients reporting a clinically relevant deterioration in bowel function at any point between six and 24 months was lower for patients receiving MRgRT (19/72 vs. 30/71 [26.4% vs. 42.3%] for bowel function, p=0.046). MRgRT was associated with significantly lower odds of a clinically relevant deterioration in bowel function (odds ratio (OR) 0.44, 95% confidence interval (CI) 0.21–0.94; p=0.03). Ma et al. reported statistically significant decreases in the EPIC-26 bowel domain at one (p<0.0001, p=0.02), three (p=0.04, p=0.32), but not six months (p=0.06, p=0.34) for the CTgRT and MRgRT arms, respectively. CTgRT was associated with a higher probability of a clinically relevant decline in EPIC-26 bowel score upon multivariable analysis (OR 3.02, 95% CI, 1.12-8.17, p=0.03).

Analysis of EPIC-26 sexual domain scores were restricted to participants who did not receive androgen deprivation therapy in the Kishan et al. study. At three months, a greater decrement in EPIC-26 sexual domain scores was seen with CTgRT (13.2-point vs. 3-point decrement; p=0.04). Differences in clinically relevant decreases in EPIC-26 sexual domain scores from baseline were not statistically significant at one month post-SBRT (p=0.10), but were at three months (p=0.04) in favour of the MRgRT intervention. At 24 months post-SBRT, the difference was no longer statistically significant (OR 0.68, 95% CI 0.27-1.69, p=0.40). MRgRT was associated with significantly lower odds of a clinically relevant deterioration in the Sexual Health Inventory for Men (SHIM) score (OR 0.37 [95% CI 0.15–0.91] p=0.03) between six and 24 months post-SBRT. Ma et al. reported no statistically significant changes from baseline assessment of the EPIC-26 sexual domain at one, three or six months for either group.

Acute toxicity

All three studies provided outcome data on acute toxicity, assessed using the Common Toxicity Criteria for Adverse Events (CTCAE).

Kishan et al. reported no Grade ≥ 3 GU toxicity in the MRgRT group of the MIRAGE RCT while one patient (1.3%) in the CTgRT group experienced Grade 3 urinary retention.[58] The incidence of acute Grade ≥ 2 GU toxicity was significantly lower

with MRgRT versus CTgRT (19 of 78 patients, 24.4% [95% CI, 15.4-35.4] vs. 33 of 76 patients, 43.4% [95% CI, 32.1-55.3]; p=0.01). The incidence of acute Grade ≥ 2 GI toxicity was significantly lower with MRgRT (0 of 78 participants, 0.0% [95% CI, 0.0-4.6] vs 8 of 76 participants, 10.5% [95% CI, 4.7-19.7]; p=0.003).[58]

The primary outcome of the study reported by Nicosia et al. was incidence of acute toxicity scored using CTCAE, defined as any event that occurred within 90 days of the RT treatment.[59] Overall, any grade acute toxicity occurred in 63 (46.5%) patients. In terms of acute toxicity, at one month, while events were more frequent in the CTgRT arm, the difference was not statistically significant: 19 (26.4%) versus 20 (31.7%), Grade 1 events, 9 (12.5%) versus 11 (17.5%), Grade 2 events, and 2 (2.8%) versus 3 (4.7%) Grade 3 events in the MRgRT and CTgRT arms, respectively (p=0.52). Acute toxicity at three months included 11 (15%) versus 14 (22.0%) Grade 1 events, 6 (9.0%) versus 5 (8.0%) Grade 2 events and 0 versus 0 Grade 3 events in MRgRT and CTgRT groups, respectively (p=0.56).

Assessment of gastrointestinal (GI) toxicity showed a non-statistically significant difference favouring MRgRT compared with CTgRT: 6 (8.0%) versus 11 (17.5%) Grade 1 events and 5 (7.0%) versus 8 (12.5%) Grade 2 events (p=0.06). Similarly, no difference was seen between the two arms in terms of genitourinary (GU) toxicity when considered overall (p=0.82) or when limited to Grades 2 and 3 events (8 [11.0%] vs. 8 [13.0%] and 2 [2.5%] vs. 3 [4.7%] for the MRgRT and CTgRT groups respectively; p=0.75).

No patients receiving MRgRT in the SCIMITAR multi-centre phase II trial reported by Ma et al. had Grade 3 GU or Grade ≥2 GI toxicity.[98] Three patients all treated with CTgRT had Grade 3 toxicity (n=1 GU, n=2 GI) including haematuria due to radiation cystitis (n=1), diarrhoea (n=1) one week after SBRT, and proctitis (n=1) six months after SBRT. MRgRT was associated with significantly lower rates of any-grade acute GI toxicity compared with CTgRT (41.9% vs. 72.5%, p=0.006), or an estimated absolute reduction of 30.5% (95% CI, 11.6-49.5) and significantly lower rates of any-grade GI toxicity of up to 6 months after SBRT (41.9% vs. 73.9%, or an estimated absolute reduction of 32% [95% CI, 12.9-51.1]; p=0.002).

Late toxicity

A pre-specified secondary analysis of late GU and GI toxicity at two years was published by Kishan et al. as a brief report in late 2024.[95] MRgRT was associated with significantly lower cumulative incidence of physician-assessed late Grade ≥2 toxicity at two years for both GU toxicity, compared with CTgRT (27% [95% CI, 19–39] vs. 51% [95% CI, 41–63]; p=0.004) and GI toxicity (1.4% [95% CI, 0.2–9.6] vs. 9.5% [95% CI, 4.6–19]; p=0.025).

Nicosia et al. reported what was described as acute toxicity at six months; however, to be consistent with other studies, this was considered by the HIQA evidence review team to be late toxicity data.[59] Using this definition, the incidence of Grade 1 or 2 events was significantly lower (p=0.03) with MRgRT compared with CTgRT (4 [5.0%] versus 13 [21.0%] Grade 1 events; 2 [3.2%] versus 1 [2.0%] Grade 2 events). There were no Grade 3 adverse events observed at six months in either group.

In the phase II SCIMITAR trial reported by Ma et al., Overall late Grade 1 GU and GI toxicity rates were 40.0% and 34.0% in the combined groups, respectively. The incidences of late Grade 2 GU and GI toxicities were 9.0% and 0.0%, respectively. MRgRT was associated with a lower incidence of late any-grade GI toxicity than CTgRT, but this difference was not statistically significant (29.0% vs 37.7%; p=0.4).[98] MRgRT was also associated with lower rates of late (42.0% vs. 53.6%, p=0.28) and up to six months (48.4% vs. 60.8%, p=0.24) any-grade GU toxicity. However, none of these differences were statistically significant. Multivariable analysis indicated that compared with MRgRT there was no differences in the odds of any grade GU toxicity (OR 1.18, 95% CI, 0.44-3.16, p=0.75) but that CTgRT was associated with a significantly higher odds of any grade GI toxicity (OR 3.71, 95% CI, 1.38-9.99), p=0.009) within six months of SBRT.

Treatment duration

Kishan et al. reported a longer median fraction duration for the MRgRT group (1,133 seconds [interquartile range [IQR], 1,109-1,289 seconds] compared with the CTgRT arm (232 seconds; IQR, 198-272 seconds).[58] Similarly, Nicosia et al. reported a longer median time from pre-treatment imaging acquisition (MRI or CT) to the end of the treatment session, with median times of 38 minutes and 15 minutes for MRgRT and CTgRT, respectively.[59]

Table 7: Summary of findings table (prostate cancer)

Outcome	Narrative summary of effects	Number of participants	Certainty	Comments
Symptoms and QoL	**Urinary** Kishan et al. found the percentage of patients reporting a clinically relevant rise in IPSS (≥15 points) was significantly greater in the CTgRT arm at one month (19.4% [14 of 74] vs. 6.8% [5 of 72]; p=0.01), but not at three months (1.4% [1 of 72] vs. 4.1% [3 of 74]; p=0.30). Kishan et al. found the proportion of patients reporting a clinically relevant deterioration in EPIC-26 urinary irritation (≥14 points) at any point between six and 24 months was lower for patients receiving MRgRT (14/73 vs. 24/68 [19.2% vs. 35.3%] for urinary irritation, p=0.03). Ma et al found no statistically significant difference in the percentage of patients with clinically relevant deterioration at the one, three, or six month time points for either the EPIC-26 urinary irritative/obstructive domain or the urinary incontinence domain. **Bowel** Kishan et al. reported that a significantly reduced percentage of patients in the MRgRT had a clinically significant (≥12-point) decrease in EPIC-26 bowel scores (25.0% [17 of 68] vs. 50.0% [34 of 68]; p=0.001) at one month. The proportion of patients reporting a clinically relevant deterioration in bowel function at any point between six and 24 months was lower for patients receiving MRgRT (19/72 vs. 30/71 [26.4% vs. 42.3%] for bowel function, p=0.05). MRgRT was associated with significantly lower odds of a clinically relevant deterioration in bowel function (odds ratio [OR] 0.444, 95% CI, 0.21–0.94; p=0.03). Ma et al. reported CTgRT was associated with greater clinically relevant declines (≥4-point) in EPIC-26 bowel score upon multivariable analysis (OR 3.02, 95% CI, 1.12-8.17, p=0.03).	1 RCT + 1 Prospective cohort study n=256	Very low[a,b,c,d]	

	Sexual Kishan et al. reported a greater decrement in EPIC-26 sexual domain scores was seen with CTgRT (13.2-point vs. 3-point decrement; p=0.04) at three months. MRgRT was associated with significantly lower odds of a clinically relevant deterioration the SHIM score (OR 0.37 [95% CI, 0.15–0.91]; p=0.03). Differences in clinically relevant decreases in EPIC-26 sexual domain scores from baseline were not statistically significant at one month post-SBRT (p=0.10) but were at three months (p=0.04) in favour of the MRgRT intervention. At 24 months post-SBRT, the difference was no longer statistically significant (OR 0.68, 95% CI 0.27-1.69, p=0.40). Ma et al. reported no statistically significant changes from baseline assessment of the EPIC-26 sexual domain at one, three or six months for either group.			
Acute Toxicity	Kishan et al. reported no Grade ≥ 3 GU toxicity in the MRgRT group of the MIRAGE RCT while one patient (1.3%) in the CTgRT group experienced Grade 3 urinary retention. The incidence of acute Grade ≥ 2 GU toxicity was significantly lower with MRgRT versus CTgRT (19 of 78 patients, 24.4% [95% CI, 15.4-35.4] versus 33 of 76 patients, 43.4% [95% CI, 32.1-55.3]; p=0.01). The incidence of acute Grade ≥ 2 gastrointestinal (GI) toxicity was significantly lower with MRgRT (0 of 78 participants, 0.0% (95% CI, 0.0-4.6) versus 8 of 76 participants, 10.5% (95% CI, 4.7-19.7); p=0.003). Nicosia et al. reported no significant difference in overall acute toxicity in MRgRT and CTgRT groups within 90 days post-SBRT (p=0.52) or at three months post-SBRT (p=0.56). GI toxicity was less frequent with MRgRT, but this difference was not statistically significant (6 [8.0%] versus 11 [17.5%] Grade 1 events; 5 [7.0%] versus 8 [12.5%] Grade 2 events; p=0.06). GU toxicity did not differ significantly between the two groups (p=0.82).	1 RCT + 2 prospective cohorts n=391	Very low[a,c,d,e,f]	

	Ma et al. reported no Grade 3 GU or Grade ≥2 GI toxicity. Three patients all treated with CTgRT had Grade 3 toxicity (n=1 GU, n=2 GI) including haematuria due to radiation cystitis (n=1), diarrhoea (n=1) one week after SBRT and proctitis (n=1) six months after SBRT. MRgRT was associated with significantly lower rates of any-grade acute GI toxicity compared with CTgRT (41.9% vs. 72.5%, p=0.006), equating to an estimated absolute reduction of 30.5% (95% CI, 11.6-49.5). MRgRT was associated with significantly lower rates of any-grade GI toxicity of up to 6 months after SBRT (41.9% vs. 73.9%, or an estimated absolute reduction of 32.0% [95% CI, 12.9-51.1]; p=0.002).			
Late Toxicity	Kishan et al. reported MRgRT was associated with significantly lower cumulative incidence of physician-assessed late Grade ≥2 toxicity at two years compared to CTgRT for both GU toxicity, (27.0% [95% CI 19–39] vs. 51.0%[95% CI 41–63]; p=0.004) and GI toxicity (1.4%[95% CI 0.2–9.6] vs.9.5% [95% CI 4.6–19]; p=0.025). Nicosia et al. reported the incidence of Grade 1 or 2 events was significantly lower (p=0.03) with MRgRT compared with CTgRT (4 [5.0%] versus 13 [21.0%] Grade 1 events; 2 [3.2%] versus 1 [2.0%] Grade 2 events). There were no Grade 3 adverse events observed at six months in either group. Ma et al. reported MRgRT was associated with a lower incidence of late any-grade GI toxicity than CTgRT, but this difference was not statistically significant (29.0% vs 37.7%; p=0.4).(123) MRgRT was also associated with lower rates of late (42.0% vs. 53.6%, p=0.28) and up to six months (48.4% vs. 60.8%, p=0.24) any-grade GU toxicity. However, none of these differences were statistically significant. Multivariable analysis indicated that compared with MRgRT there was no differences in the odds of any grade GU toxicity (OR 1.18, 95% CI, 0.44-3.16, p=0.75) but that CTgRT was associated with a significantly higher odds of any grade GI	1 RCT + 2 prospective cohorts n=391	Very low[a,c,d,e,f,g]	

	toxicity (OR 3.71, 95% CI, 1.38-9.99), p=0.009) within six months of SBRT.			

Key: ADT – androgen deprivation therapy; CI – Confidence Interval; CTCAE – Common Terminology Criteria for Adverse Events; CTgRT – Computer Tomography Guided Radiotherapy; EPIC-26 – The Expanded Prostate Cancer Index Composite; GI – Gastrointestinal; GU – Genitourinary; HR – Hazard Ratio; HRQoL – Health-Related Quality of Life; IPSS – International Prostate Symptom Score; MRgRT – Magnetic Resonance Guided Radiotherapy; OS – overall survival; PFS – Progression-Free Survival; RCT – Randomised Control Trial; SBRT – Stereotactic Body Radiotherapy; QoL – Quality of Life; QLQ - Quality of Life Questionnaire.

Explanations:

[a] Very high risk of bias

[b] Reporting of this outcome varied greatly in terms of the time-point of assessment and the reporting of findings.

[c] Although the assessment and reporting this outcome differed between the studies, there was consistent finding of a relative improvements in quality of life using MRgRT despite not reaching statistical significance in some studies. The exact relative effect size however may be different between studies owing in part of the different prostate cancer populations studied.

[d] In the limited number of studies published, all with statistically significant results, the authors report a direct conflict of interest involving the manufacturer of an MRgRT system giving rise to potential concerns regarding publication bias.

[e] Both significant and non-significant estimates observed in these two studies, however consideration given to the fact that these are different prostate cohorts and there is differences in how the results are reported.

[f] Confidence intervals (where reported) are wide, and it is likely the decision-making would be impacted if the true effect was at the upper or lower bounds. There were also too few events in some cases.

[g] Differences in how results are reported made imprecision judgements difficult. Very small number of events in all studies, and the RCT noted the trial was not powered to address late toxicity outcomes.

5.5 Liver cancer

A single study, by Tallet et al., retrospectively evaluated the effectiveness and toxicity of SABR delivered via either MRgRT (n=18 patients; 19 tumours) or kV CBCT CTgRT (n=41 patients; 45 tumours) for the treatment of primary and secondary liver tumours.[51] Table 8 below summarises the main findings.[51] The median follow-up and imaging follow-up for the full cohort of patients was 16.7 months (range 1.2-73.0 months) and 8.2 months (range 0.3-73.0 months), respectively. Follow-up imaging included liver MRI and CT scan every three months.

Local control

At the last reported follow-up, 28 patients (47.0%) had died, eight (14.0%) were lost to follow-up (and deemed deceased), while 23 (39.0%) were still alive.[51] The local control (LC) rate was 76.6% for the full study cohort, with 23.4% experiencing progression or relapse within the radiation field. The LC rates between the two groups were similar-75.6% and 78.9% in the CTgRT and MRgRT groups, respectively (p=0.96).

Acute and late toxicity

The all-grade toxicity rate for the full study cohort was 31.25% (33.3% and 26.3% in the CTgRT and the MRgRT groups, respectively).[51] The Grade ≥3 toxicity rate was 4.7% overall, 4.4% in the CTgRT and 5% the MRgRT group. Grade 1 nausea was reported by seven (16.0%) and two (11.0%) patients in the CTgRT and MRgRT groups, respectively; no patients experienced Grade ≥2 nausea. Grade 1 abdominal pain was reported by three patients (7.0%) and one patient (5.0%) of CTgRT and MRgRT groups, respectively. Considering Grade 2 toxicity, one patient (5.0%) in the MRgRT group experienced Grade 2 abdominal pain, while in the CTgRT group one (2.0%) patient experienced Grade 2 duodenal ulcer and one (2.0%) patient had Grade 2 gastritis. Considering Grade 3 toxicity, one patient (2.0%) in the CTgRT group experienced Grade 3 gastric haemorrhage. One patient (2.0%) in the MRgRT group, whose portal trunk received a total dose of 30Gy in 5 fractions in 7.0% of the volume (far below the dose constraint), had Grade 3 portal hypertension; this patient, had a thermoablation procedure in segment I of the liver, which was potentially responsible for this adverse event. One case of Grade 5 radio-induced liver disease (in the CTgRT group) was reported in a patient with hepatocellular carcinoma and a Child-score A6, who experienced decompensated cirrhosis with a Child-score C11.

Table 8: Summary of findings table (liver cancer)

Outcome	Narrative summary of effects	Number of participants	Certainty	Comments
Local control	At the last reported follow-up, 28 patients (47.0%) had died, 8 (14.0%) were lost to follow-up (and deemed deceased), while 23 (39.0%) were still alive. The local control (LC) rate was 76.6% for the full study cohort, with 23.4% experiencing progression or relapse within the radiation field. The LC rates between the two groups were similar - 75.6% and 78.9% in the CTgRT and MRI groups, respectively (p=0.96).	1 retrospective cohort n=59	Very low[a,b,c,d]	
Acute and late toxicity	The all-grade toxicity rate was 33.3% and 26.3% in the CBCT and the MRgRT group, respectively. Grade ≥3 toxicity rate was 4.7% overall, 4.4% in the CTgRT and 5.0% the MRgRT group. 1 patient (2.0%) experienced Grade 3 gastric haemorrhage in the CTgRT group. 1 patient (2.0%) had Grade 3 portal hypertension in the MRgRT group whose portal trunk received a total dose of 30Gy in 5 fractions, in 7.0% of the volume (far below the dose constraint), and who had a thermoablation procedure in segment I of the liver, potentially responsible for this adverse event. 1 case of Grade 5 radio-induced liver disease (in the CTgRT group) was experienced in a hepatocellular carcinoma patient with a Child-score A6, who experienced decompensated cirrhosis with a Child-score C11. Ulcerous complications were less common in the MRI group (0.0% vs. 4.4% in the CTgRT group; gastric haemorrhage, duodenal ulcer).	1 retrospective cohort n=59	Very low[a,b,c,d]	

Key: CTgRT – computer tomography guided radiotherapy; LC – local control; MRgRT – magnetic resonance guided radiotherapy; MRI – magnetic resonance imaging.

Explanations:

[a] Very high risk of bias.

[b] Lack of confidence intervals, single study with no verification of findings from other studies.

c One small study with too few events.

d In the limited number of studies published, the authors or institution report a direct conflict of interest involving the manufacturer of an MRgRT system giving rise to concerns regarding potential publication bias.

5.6 Pancreatic cancer

Table 9 below summarises the findings from Lee et al. (n=50) which retrospectively compared the effectiveness and toxicity of MRgRT and CTgRT for the treatment of primary and secondary unresectable pancreatic tumours following induction chemotherapy. [96] The study compared adaptive SBRT using a 0.35T MRgRT delivery system (n=26) with non-adaptive SBRT delivered on a conventional linac with CBCT (n=24). Patients with locally advanced unresectable pancreatic adenocarcinoma, including oligometastatic disease were included.

Overall survival

Overall survival (OS) was calculated from the start date of SBRT until date of death.[96] Patients with non-metastatic disease had 1- and 3-year OS rates of 87.3% (95% CI, 69.6–95.1) and 37.0% (95% CI, 17.4– 56.8), respectively. Patients with oligometastatic disease had a 1- and 3-year OS rate of 61.6% (95% CI, 33.5–80.7) and 16.0% (95% CI, 2.7–39.5), respectively. On univariate analysis, no statistical difference in OS was seen between the two groups (adaptive MRgRT vs. non-adaptive CTgRT: HR 1.2 [95% CI, 0.54 -2.67] p=0.66).

Local progression-free survival

Local progression-free survival (LPFS) was calculated from the start date of SBRT to the date of local progression or death.[96] The 1- and 3-year LPFS rates of patients with non-metastatic disease were 90.0% (95% CI, 72.0– 96.7) and 57.4% (95% CI, 31.7–76.4), respectively. In patients with oligometastatic disease and partial response to the induction chemotherapy, the 1- and 3-year LPFS were 100.0% and 44.4% (95% CI, 6.6–78.5), respectively. In patients with stable or progressive oligometastatic disease after induction chemotherapy the 1- and 3-year LPFS were 45.7% (95% CI, 8.2–78.3) and 0%, respectively. While not statistically significant, the reported hazard rate (HR) favoured those who received the adaptive MRgRT intervention (HR 1.87 95% CI, 0.73-4.78, p=0.19).

Acute toxicity

There were no Grade 3 or higher acute adverse events in either patient group. Although 23 (46.0%) of patients reported a Grade 2 acute toxicity, these data were not reported per intervention group.

Late toxicity

Overall, patients treated with adaptive MRgRT showed non-statistically significant lower rates of late adverse events compared with those treated with non-adaptive CTgRT (Grade 2: 19.2% vs. 33.3%; Grade 3: 0.0% vs.8.3%; p=0.08). Two (6.0%)

patients treated with non-adaptive CTgRT experienced Grade 3 gastro-intestinal bleeding, both requiring endoscopic intervention.[96]

Table 9: Summary of findings table (pancreatic cancer)

Outcome	Narrative summary of effects	Number of participants	Certainty	Comments
Overall survival	The study found no statistical difference in OS between the adaptive MRgRT and non-adaptive CTgRT on univariate analysis (HR 1.2 [95% CI, 0.54 -2.67], p=0.66)).	1 retrospective cohort n=50	Very low[a,b,c,e]	
Local progression-free survival	The study found no statistically significant difference in LPFS between the adaptive MRgRT and non-adaptive CTgRT on univariate analysis (HR 1.87 [95% CI, 0.73-4.78], p=0.19)).	1 retrospective cohort n=50	Very low[a,b,,c,e]	
Acute toxicity	There were no Grade 3 or higher acute adverse events in either patient group. Although 23 (46.0%) of patients reported a grade 2 acute toxicity, this data was not reported per intervention group	-	-	Acute toxicity was not reported according to the assigned intervention.
Late toxicity	Overall, patients treated with adaptive MRgRT showed non-statistically significant lower rates of late adverse events compared with those treated with non-adaptive CTgRT (Grade 2: 19.2% vs. 33.3%; grade 3: 0.0% vs. 8.3%; p=0.08). Two (6.0%) patients treated with non-adaptive CTgRT experienced Grade 3 gastro-intestinal bleeding, both requiring endoscopic intervention.	1 retrospective cohort n=50	Very low[**a,b,d,e**]	

Abbreviations: CI – confidence interval; CTgRT – computer tomography guided radiotherapy; HR – hazard ratio; LPFS – local progression free survival; MRgRT – magnetic resonance guided radiotherapy.

Explanations:

[a] Very high risk of bias.

[b] Single study with no verification of findings from other studies.

[c] One small study with too few events, the decision to use MRgRT would likely vary at the extreme ends of the wide confidence interval reported.

[d] One small study with too few events. Lack of confidence intervals.

[e] Although the main aim of the study did not align with ours, the population included pancreatic cancer and oligometastatic cancer to the pancreases. These results were not broken down by primary versus secondary cancers, and hence may not be generalisable to either population.

5.7 Lung cancer

Table 10 below summaries the findings from Kang et al. (n= 81) which retrospectively evaluated effectiveness and toxicity of MRgRT and CTgRT for the treatment of lung tumours.[96] Outcomes for a total of 41 patients (50.6%) who received MR-guided SABR between March 2019 and December 2021 were compared with those for 40 patients who received CTgRT delivered using kV CBCT or MVCT on a conventional linac or a tomotherapy system between March 2013 and August 2021. Patients were followed up for a median of 19 months, with a median follow-up of 11 months (range, 3-32 months) and 34 months (range, 3-105 months) in the MRgRT and CTgRT groups, respectively.

Overall survival

Kang et al. defined OS as the time from the end date of treatment to death from any cause or last follow-up visit. No significant difference in the one-year OS rates was seen between the MRgRT (87.4%) and the CTgRT (87.0%) groups (p=0.30).

Progression-free survival

Kang et al. defined progression-free survival (PFS) as the duration from the end date of treatment to the date of disease relapse at any site, death from any cause, or last follow-up visit if a patient was free of disease. No significant difference in the one-year PFS rate was seen between the MRgRT (80.2%) and the CTgRT (80.4%) groups (p=0.50).

Local control

Kang et al. defined LC as the duration from the end date of SABR to the date of disease relapse in the initial involved site, death from any cause, or last follow-up visit if a patient was free of disease. The one-year LC rate was 92.1% and 75.4% in the MRgRT and CTgRT groups, respectively (p=0.07). In total, 17 out of 40 and 22 out of 41 patients in the MRgRT and CTgRT groups experienced disease recurrence during follow-up, respectively. There were four and 17 cases of local recurrence and 13 and five cases of distant recurrence in the MRgRT and CTgRT groups, respectively.

Acute and late toxicity

There was no significant difference in the frequency of any Grade toxicity (p=0.19), radiation pneumonitis (p=0.54), dyspnoea (p=0.59) or rib fracture (p=0.99) between the MRgRT and CTgRT groups. No toxicities of Grade ≥3 was observed in either group. Grade 2 toxicity was experienced by eight patients (19.5%) in the MRgRT group which included seven cases of radiation pneumonitis and one case of dyspnoea. In comparison, Grade 2 toxicity was experienced by 14 patients (35%) in

the CTgRT groups which included 10 patients with radiation pneumonitis, three patients with dyspnoea, and one patient with rib fracture without displacement.

Table 10: Summary of findings table (lung cancer)

Outcome	Narrative summary of effects	Number of participants	Certainty	Comments
Overall survival	1-year OS rates were 87.4 % for the MRgRT group and 87.0% for the control group, respectively (p=0.30).	1 retrospective cohort n=81	Very low[a,b]	
Progression free survival	No significant difference in the 1-year PFS rate was seen between the MRgRT (80.2%) and the CTgRT (80.4%) group (p=0.50).	1 retrospective cohort n=81	Very low[a,b]	
Local control	The 1-year LC rate in the MRgRT and control groups were 92.1% and 75.4%, respectively (p=0.07).	1 retrospective cohort n=81	Very low[a,b]	
Acute and late toxicity	There was no significant difference in the frequency of overall any Grade toxicity (p=0.19), radiation pneumonitis (p=0.54), dyspnoea (p=0.59) or rib fracture (p=0.99) between the MRgRT and CTgRT groups. No toxicities of Grade ≥3 was observed in either group. Grade 2 toxicity was experienced by eight patients (19.5%) in the MRgRT group and 14 patients (35.0%) in the CTgRT group.	1 retrospective cohort n=81	Very low[a,b]	

Key: CTgRT – computer tomography guided radiotherapy; HR – hazard ratio; LC – local control; MRgRT – magnetic resonance guided radiotherapy; OS – overall survival; PFS – progression free survival; SBRT – stereotactic body radiotherapy.

Explanations:

[a] Very high risk of bias.

[b] Single study with no confidence intervals or verification of findings from other studies.

5.8 Patient anxiety/experience

Three studies that used validated questionnaires to assess patient anxiety while undergoing treatment on a MR linac were identified during topic exploration or while screening the results of the database searches for this systematic review. While patient anxiety during imaging and treatment on a MR linac was not included in the search strategy or as an outcome in the PICOS for this systematic review a priori, a high-level summary of the findings of these studies is included below.

A 2024 prospective study reported the results from a 15-point MR-related anxiety questionnaire completed by 205 patients treated to the abdomen and pelvis.[122] Low median levels of anxiety were noted, with 87.0% and 11.0% giving a rating of 'not at all' or 'somewhat' respectively, in relation to their MR anxiety. However, it should be noted that this study excluded claustrophobic patients. Another 2024 prospective study included 66 patients treated as part of the MOMENTUM trial to various anatomical sites who completed a 17-item MR linac patient-reported experience questionnaire after their first and second treatments.[123] All patients (100%) reported after their first treatment that the noise level and lighting in the room were easy to tolerate and most (96.0%) found the treatment position and treatment bed to be comfortable. The results were similar after treatment two, except that 9.0% wanted to come out of the machine during treatment, compared with 1.8% during the first treatment. A final 2024 prospective study included 113 patients treated to various anatomical sites who completed the same 17-item MR linac patient-reported experience questionnaire.[124] Similarly, most patients found the treatment position and treatment bed to be comfortable (93.0% and 91.0%, respectively).

5.9 Ongoing research studies

The search of the trial registries identified 58 ongoing research studies (available from our Zenodo repository: https://zenodo.org/records/15518924). These studies comprise a range of cancers and anatomical sites: prostate (n=21),[101, 125-142] all patients suitable for MRgRT (n=6), oligometastatic and primary liver cancer (n=6), primary lung cancer and lung metastasis (n=5),[143-146] colorectal (n=4), primary brain cancer and brain metastasis (n=5), head and neck (n=4), pancreas (n=2), any metastatic solid tumours (n=2), gynaecological (n=2) and spinal metastasis (n=1) Only 12 of these trials, when reported, will provide comparative data.[125, 128, 136, 137, 147-154] Eight trials will compare standard CTgRT and MRgRT in EBRT or SBRT in the treatment of brain and spinal metastasis, cervical, endometrial, liver (primary or oligometastises), oropharyngeal, prostate and rectal cancer.[125, 147-151, 153, 154] Two trials are investigating the delivery of a simultaneous integrated boost using MRgRT compared with standard MRgRT in prostate and rectal cancer,[136, 152] while another

two trials are investigating standard versus differing fractionation schedules in prostate cancer.[128, 137]

5.10 Radiation dose to patients

Image guidance dose

IGRT is widely accepted as a requisite for the safe and accurate delivery of radiotherapy. The patient is imaged to ensure that the target volume can be localised, and the treatment can be delivered correctly. Each imaging technique delivers a different dose to the patient, and the actual dose delivered will depend on local optimisation practices and patient characteristics (for example patient size).[19] Diagnostic reference levels (DRLs) are not routinely developed for IGRT methods at present. This makes it difficult to provide estimates of 'typical' IGRT doses to patients.

While there are many modalities of IGRT including kV planar imaging and MVCT, SBRT is typically delivered using kV CBCT guidance, in Ireland. A 2024 survey conducted by the Institute of Physics and Engineering in Medicine (IPEM) proposed some DRLs for CBCT applications, including prostate (20.6 mGy), gynaecological (20.8 mGy), breast (5.0 mGy), 3D-lung (6.0 mGy), 4D-lung (11.8 mGy), brain (3.5 mGy), and head and neck (4.2 mGy).[155] It is important to note that these estimates are per image taken, and in the stereotactic setting patients may have three or more CBCT images per fraction plus an additional dose from any intra-fraction imaging taken to ensure the target remains localised during the delivery of these high dose prescriptions. The authors of this IPEM survey noted several important considerations when interpreting these estimates, including the large differences observed between different imaging systems and the effect of pro-active optimisation strategies in reducing dose. Hence, these estimates may be difficult to apply at a local level or to the Irish context.

Compared with the above CTgRT options, there is no imaging dose associated with MRgRT as it relies on a non-ionising technique to guide the radiotherapy treatment.

Therapeutic dose

Within the scope of the application for generic justification, MRgRT may be used to deliver existing prescriptions using established fractionation patterns. Therefore, the therapeutic dose is not expected to differ between MRgRT and a conventional linac.

However, registered trials which utilise MRgRT are investigating shorter courses and hypofractionated treatments.[126-128, 138, 156] Vendors have also marketed MRgRT for possible shorter treatment courses through hypofractionation.[157] In accordance with HIQA methods documents, these novel hypofractionated or ultra-

hypofractionated prescriptions under investigation may constitute a new class or type of practice, and if so would require generic justification prior to its adoption.

License for use

In accordance with regulatory requirements of S.I. 30 of 2019, all practices involving the use of ionising radiation must be authorised in advance by the Environmental Protection Agency (EPA).[158] All undertakings carrying out a radiological practice must fully comply with the relevant provisions of the regulations, and any conditions attached to a licence or registration are subject to compliance assessment, including inspection by the EPA. Undertakings carrying out radiotherapy, such as the practice outlined in this report, must hold a license for radiotherapy using a linac in a medical radiological installation from the EPA. Licensing is not linac specific; however, a prospective risk assessment is required prior to the installation and commissioning of all sources of ionising radiation. Information on legislative requirements is provided in guidance for undertakings issued by the EPA.[159, 160]

5.11 Public and occupational exposure

In accordance with Regulation 12(5) of S.I. No. 30 of 2019, all practices involving the use of ionising radiation must be authorised in advance by the Environmental Protection Agency (EPA).[158] All undertakings carrying out a radiological practice must fully comply with the relevant provisions of the S.I. No. 30 of 2019 and any conditions attached to an authorisation.

In the context of Ireland, exposure to staff, the public, carers and comforters under SI 256 of 2018, as amended, can be minimised through a carefully considered prospective risk assessment and use of a well-developed quality management system. The design stage of the risk assessment must be completed prior to the installation and commissioning of all sources of ionising radiation.

Local policies, procedures and guidelines must be in place to protect staff and members of the public. Procedures to be followed in the event of an incident liable to have radiation safety implications for workers and members of the public must be developed. It must be ensured that dose constraints and limits for occupational and public exposure as set out in Part 3, Sections 1 and 2 of SI 30 of 2019 are adhered to.[158] In assessing compliance with the dose constraints for medical applications, account should be taken of the principles and approach set out in the EPA's guidance document "The Design of Diagnostic Medical Facilities Where Ionising Radiation Is Used" (2009).[159]

Further information on the EPA requirements is provided in their guidance for undertakings on the application of the IRR19.[160] Information on the dose

constraints for carers and comforters, and individuals participating in medical or biomedical research is also available in guidance issued by HIQA.

No change in the risk of public and occupational exposure is anticipated from the use of the MRgRT compared to a standard linac, provided appropriate radiation protection safeguards are in place.

5.12 International guidelines and reports

Completed studies identified in this systematic review originated from a range of countries including Canada, China, Denmark, France, Germany, Israel, Italy, the Netherlands, Spain, South Korea, Switzerland, Turkey, UK, and USA.

Information included as part of the application for generic justification from Elekta indicated that their MR-linac was or is in use in the following countries: Australia, Bahrain, Belgium, Canada, China, Denmark, France, Germany, Hong Kong, Israel, India, Italy, Jordan, Lithuania, Malta, Mexico, New Zealand, Panama, Pakistan, Poland, South Korea, Spain, Sweden, Taiwan, Thailand, the Netherlands, Turkey, UK and USA.

In terms of international guidelines and reports, in addition to those described in the results above, five relevant records were identified as part of the targeted grey literature search. These included:

- A rapid response review of the MRgRT delivery systems by Canada's Drug and Health Technology Agency (CADTH) published in 2019.[14] This review of the clinical effectiveness, cost effectiveness and guidelines for the use of MRgRT delivery systems identified a single, retrospective, non-randomised cohort study involving patients with lung cancer. This review concluded that given the limited, poor quality evidence available, the clinical effectiveness of the MR-linac was uncertain. They also noted the challenges associated with implementing this technology, including: the development of new local processes, workflows and guidelines; requirements for staff training, close multi-disciplinary collaboration and quality assurance; and potential cost implications.

- A rapid review by the Institut National d'Excellence en Santé et en services Sociaux (INESSS) in Quebec, Canada published in 2019 concluded that the technology was not cost effective, as there were no data showing an incremental clinical benefit to justify the higher costs associated with introducing and using MR-linacs.[161]

- Recommendations on the clinical implementation of hybrid MR-linac systems

in radiation oncology from the European Society for Radiation Oncology (ESTRO) Advisory Committee for Radiation Oncology Practice (now known as the ESTRO Guidelines Committee) were published in 2021.[84] These recommendations noted the challenges before commencing clinical services with a MR-linac, including consideration of staff training and patient screening, in terms of MR safety. The report also noted the potential for the use of functional imaging, radiomics, deep learning and artificial intelligence to facilitate fast and reliable extraction of large amounts of data from multiple MR images, which will likely to change workflows in the field of MRgRT in the future.

- Guidelines on the optimal use of imaging in radiotherapy for lymphoma from the International Lymphoma Radiation Oncology Group (ILROG) published in 2019 noted the ongoing development of MR-linacs, including their ability to locate tumours precisely, tailor the shape of photon beams in real time, and deliver radiation accurately to moving tumours as well as the added advantage of avoiding the radiation dose from CBCT.[162] The guidelines also proposed that MR-linacs would play an important role in the field of lymphoma radiotherapy.

- In the UK, updated guidance for IGRT was published in 2021 by the radiotherapy board. This was a joint publication by the Society and College of Radiographers (SCoR), the Institute of Physics and Engineering in Medicine (IPEM) and The Royal College of Radiologists (RCR) to make evidence-based practice recommendations for IGRT. The updated guidance makes reference to the advantages of MRgRT delivery systems for the treatment primary and metastatic liver cancers due to the low soft-tissue contrast of liver tumours. MRI-guided radiotherapy is noted as a promising technique for liver cancers as MRI can be applied for localisation, gating and intra-fraction motion monitoring.[19]

6 Discussion

For the purpose of this report and to enable a decision on the generic justification of MRgRT, the HIQA Evidence Review Team conducted a systematic review of two research questions on the clinical effectiveness and safety of this practice. The evidence base for MRgRT varies greatly in terms of its quantity, quality, strength and utility depending on the anatomical site in question. Comparative data were narratively synthesised where available and all studies retrieved were organised into an evidence and gap map to visualise the existing evidence and gaps for this practice according to anatomical sites and patient outcomes. The findings of this review are broadly supported by similar reviews conducted on MRgRT.[94, 163, 164]

6.1 Summary of RQ1 findings

The clinical effectiveness outcomes included in this systematic review were quality of life, overall survival, progression-free survival, local response and local control. There is some weak evidence of very low certainty which suggests that MRgRT may be associated with smaller decreases in patient reported quality of life in prostate cancer compared with CTgRT.[58, 98] No statistically significant difference in OS, PFS or LC was observed between MRgRT and conventional IGRT in any study despite some studies also reducing PTV margins in the MRgRT groups.[51, 97] None of these studies were designed as non-inferiority trials. These outcomes were often limited by the short follow-up time (Table 5), the range of possible confounders and the high risk of bias which at times favoured the MRgRT intervention.

The evidence on the clinical effectiveness of MRgRT compared with more conventional IGRT methods is limited and of very low certainty. It is noted that a switch to MRgRT may facilitate additional optimisation, dose escalation or further hypofractionating treatments given its enhanced soft tissue visualisation, motion management and access to adaptive RT. Investigation of dose escalation or differing fractionation schedules was not the primary objective in any of the six comparative studies identified in this review; however, it is likely that ongoing and future studies will provide insight into whether these practices, when combined with MRgRT, can improve the efficacy and effectiveness of radiotherapy treatment.[126-128, 138, 156] Longer term follow-up data would help determine if a combination of MRgRT with dose escalation or the use of a boost results in improvements in clinical effectiveness.

6.2 Summary of RQ2 findings

All six comparative studies assessed toxicity outcomes; however, only the three prostate studies found a statistically significant difference in favour of the MRgRT

intervention compared with CTgRT.[58, 59, 98] These observations may be partly explained by the reduction in PTV margins in two of the studies, online adaptive techniques and/or the gating and motion management enabled by the MRgRT intervention. While the enhanced imaging capabilities of MRgRT are used to achieve such additional optimisation, it is possible that other devices with similar abilities could achieve the same results.[95] Other data identified in this review indicated a lower frequency of low-grade acute and late toxicities with MRgRT compared with CTgRT; however, these differences were not statistically significant and the evidence was assessed as being of very low certainty.[51, 59, 96] However, no safety concerns or unexpected toxicities were identified by these comparative studies. These findings must be caveated by the high risk of bias which often favoured the MRgRT intervention. Similar to the findings on RQ1, all outcomes were of very low certainty and none of these studies were designed as non-inferiority studies. Studies that examine de-escalation of radiation dose with MRgRT are ongoing to identify if acceptable local control can be achieved while minimising radiotherapy-related toxicities.[135, 137, 165]

6.3 Evidence gaps

After registering the systematic review and completing title and abstract screening, a decision was taken to focus on comparative data while also conducting a scoping exercise to map the evidence and knowledge gaps on MRgRT.

Non-comparative studies account for a large proportion of the existing evidence; however, they are limited in their usefulness as they provide poor insight as to how clinical effectiveness and toxicity differ from the available alternative (that is, conventional IGRT methods). These non-comparative studies may inflate the quantity of evidence without necessarily providing information that can help inform decisions on practice. There is a distinct lack of evidence for many cancers on how MRgRT may affect patient relevant outcomes, particularly quality of life. Figure 3 should be reviewed with the caveat that only treatment sites for which data are available are displayed, and that there are in fact a large number of other radiotherapy treatment sites and paediatric applications for which no evidence was identified. These observations follow on from existing calls in the literature for RCT data in MRgRT trials.[135, 165]

The largest studies identified in the evidence and gap map are registry studies. Such registry studies can provide important insights into unexpected safety or toxicity issues. However, given that many of the adverse events are expected with conventional radiotherapy, it is difficult to gain new insights without being able to make direct comparisons. Some prospective registries have attempted to overcome this through novel study designs, one of which is the Utrecht Prostate Cohort (UPC)

which uses a trial within a cohort (TWiC) design.[101] At present, only baseline data have been published for this study; however, it is envisaged that a number of ongoing trials identified by this systematic review will eventually add to the evidence base for MRgRT, and for MRgRT used in combination with other new types of practices.

6.4 Considerations

MR linacs have been assessed as a type of practice, in general within this report; however, differences in the technical characteristics between models and vendors exist. These include differences in the strength of the magnet which can determine the degree of soft tissue visualisation and differentiation between the volume of interest and adjacent structures within the body. Some of the non-comparative data in particular relates to an older tri-cobalt system which has been largely superseded by more modern linac technology.

MRgRT also introduces a heterogeneous set of optimisation techniques that are likely to vary greatly in clinical practice. Such optimisation techniques include adaptive radiotherapy, methods of gating and internal motion management, and the possibility of PTV margin reduction in some tumour sites. Because of these variations, it may be challenging to reproduce results from any given trial, as differences in optimisation techniques and other local practices may modulate the relative benefits seen in MRgRT comparative studies.

A strengths, weaknesses, opportunities and threats (SWOT) analysis conducted by Van Herk et al. argued that although MRgRT workflows may improve geometric accuracy, there is the possibility for overconfidence in the total planning and treatment chain accuracy and incorrect margin definition leading to local recurrences.[24] These concerns should be considered in tandem with the limited evidence on local control found by this systematic review. The SWOT analysis also highlighted that although new technologies can be attractive, patient selection will be paramount to ensuring that valuable time slots are offered to those with the greatest capacity to benefit.

MRgRT generally takes longer to deliver and is associated with higher upfront and ongoing costs in terms of the initial capital investment, maintenance and staffing. A cost-effectiveness and budget impact analysis was not within the scope of this report; however, MR linacs are generally many times more expensive than conventional linacs with X-ray based IGRT systems. MRgRT also generally requires longer treatment times as seen in the results of this review; however, it is hypothesised that using hypofractionated regimens to reduce the number of visits a patient is required to make to complete their course of treatment may offset some of these costs, as well as concerns about capacity within the system and current

waiting times. While trials investigating hypofractionated regimens delivered using MRgRT are ongoing, no evidence for same was identified for inclusion in this systematic review; all included comparative data used the same or similar prescriptions in the conventional and MRgRT arms.

MR linacs also introduce new patient-related complexities to the radiotherapy workflow, such as MR safety concerns and claustrophobia, as well as technical challenges for medical physicists, engineers and radiation therapists who will require additional training.[166, 167] This is particularly important given the current national staffing deficit in both public and private radiotherapy centres.[168, 169]

One area of concern with MRgRT technologies not fully captured within the scope of our evidence synthesis is the potential for increased skin dose due to an electron streaming effects. As noted above, studies that only reported surrogate dosimetric endpoints were excluded. However, there is non-comparative evidence to suggest that skin doses and skin toxicities (including poor cosmetic outcomes) are not as high as previously expected.[170, 171]

6.5 Limitations

Three main limitations are worth highlighting in this systematic review.

Firstly, the lack of randomised trial data means that there is a significant possibility of confounding in many of the studies which we have included. Patients often received other therapies, or were assigned to a particular arm of the study based on their breathing difficulties or performance status. This, combined with the high risk of bias in these studies, greatly decreased the certainty of the evidence. Comparative evidence was limited to adult patients with prostate, liver, pancreatic and lung cancer, making broad generalisations about this practice difficult. Although the evidence and gap map may provide insight into the current landscape of MRgRT evidence on patient relevant outcomes, care must be take not to infer that the volume of evidence available equates to a robust evidence base for its use across all treatment sites.

Secondly, the evidence and gap map displays one 'bubble' per reported outcome for each record included in our systematic review. Cohort studies may have published on sub-populations of the cohort a number of times, or alternatively may have periodically published retrospective cohort studies on a pool of participants which increased over time. For example, five studies from the MOMENTUM registry were included in this systematic review, and hence contributed one bubble per reported outcome for each study in the evidence and gap map.[25, 71, 99, 100, 172] These overlapping samples from a larger population may give the illusion that there are more data on non-comparative MRgRT studies than there truly are.

Finally, many relevant ongoing trials have not concluded or only have interim results available.[94, 163, 164] It is possible that these studies, when reported, will add higher quality evidence to the existing evidence base, and may highlight if MRgRT in combination with other new types of practices improves patient relevant outcomes.

6.6 Conclusion

The evidence identified in this systematic review is limited to six comparative studies at high risk of bias. Based on GRADE, evidence for all outcomes of interest is of very low certainty, and significant gaps in the evidence exist. However, it is noted that no safety concerns were found in the literature reviewed. Moreover, unlike conventional IGRT methods, there is no imaging dose associated with MRgRT.

7 Evidence to decision

A draft of this report was submitted to the MEIR EAG for their consideration and feedback. Following this, a discussion was held at a meeting of the EAG on 27 February 2025, in which the evidence summary and additional contextual factors were considered. As per the HIQA Methods for generic justification of new practices in ionising radiation, a modified version of the GRADE evidence-to-decision (EtD) framework was used to support the MEIR EAG in coming to a recommendation regarding the generic justification of MRgRT in patients with cancer who require external beam radiotherapy.

7.1 Overview of MEIR EAG GRADE EtD discussion

Informed by the review of the above evidence, the MEIR EAG completed judgements under a modified evidence-to-decision (EtD) framework to arrive at a recommendation to HIQA. The full EtD framework including a summary of the panel discussion and the final judgements can be found in Table 11 and Table B.2: Appendix B, respectively. In terms of benefits and harms, the MEIR EAG considered the evidence for the outcomes listed in terms of both the magnitude of the effect and the certainty of the evidence. The certainty of the evidence was assessed in accordance with GRADE guidelines and was considered to be 'very low'.[89]

In terms of the benefits of this practice, the MEIR EAG noted that the main benefits of MRgRT relate to the potential to reduce toxicity compared with conventional IGRT. This was thought to be consistent with the improved visualisation achieved with MRgRT, particularly for challenging anatomical areas. Given the very low certainty of the evidence, consideration was given to whether a judgement of 'don't know' was most appropriate. However, it was agreed that while the evidence was limited, the observed reductions in toxicity for prostate cancer patients were consistent with the incremental improvements observed with other changes to radiotherapy techniques that supported more precise targeting of the tumour site. From a radiation protection perspective, improved visualisation would enable reduced radiation exposure to healthy tissue with exposure also reduced given removal of the CT imaging component. While acknowledging the absence of evidence for paediatric populations, the EAG noted that this potential to reduce exposure would be particularly relevant for children. The EAG judged the desirable effects to be 'small'.

The evidence on undesirable effects was noted to be limited, with no identified safety concerns. The MEIR EAG also discussed potential challenges associated with MRgRT such as claustrophobia and the increased time on the treatment bed as these may represent significant issues for some patients. Moreover it was noted that

use of MRgRT may be contra-indicated in some patients with implantable medical devices or who require anaesthesia as the monitoring equipment may not be compatible with the magnet. As with other forms of radiotherapy, patient selection was noted to be important, with agreement that harms/risks could be minimised with careful patient selection. As such, the overall harms were judged to be 'trivial'.

The EAG highlighted that additional resources are required to implement MRgRT (education and training of personnel and adjustment of the bunkers for MR) with significant upfront capital investment. Moreover, they noted that current quality assurance techniques are still limited, and there is a need to refer to up-to-date guidelines, such as the ESTRO-ACROP guidelines. When considering variability or uncertainty in how much people value the main outcomes, the MEIR EAG noted that cost is likely an important additional consideration. It was also noted that the benefits associated with moving towards an IGRT method with no imaging dose were hard to quantify for the patient, and there may be more linac downtime for repairs and maintenance compared with standard linacs which could pose additional challenges for centres with only one MRgRT system. The EAG agreed that there was 'probably no important uncertainty or variability' in how patients value the outcomes.

While the certainty of evidence was very low, the EAG agreed that the potential for reduced toxicity and improved anatomical targeting likely outweighs the undesirable effects. These were considered manageable with appropriate patient selection and planning, highlighting the importance of individual justification for all patients. The EAG concluded that the balance of desirable and undesirable effects 'probably favours the use of MRgRT'. The MEIR EAG recommended to HIQA that MRgRT for patients with cancer who require external beam radiotherapy should be generically justified.

Table 11: Magnetic resonance-guided radiotherapy

	Summary of judgements						
Desirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable Effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know

7.2 HIQA Decision

Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified. The practice MRgRT in patients with cancer who require external beam radiotherapy is generically justified under SI 256/2018. The generic justification of this practice is effective from 30 May 2025. Under the regulations, HIQA may review the generic justification of this practice if new and important evidence about the practice emerges. HIQA may also review this practice if new and important evidence about alternative techniques and technologies (including non-ionising practices) emerges.

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9 Appendix A

Table A.1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Key Points, Overall approach & Methods
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	N/A – but do have Plain Language summary & Key Points.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Overall approach
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Methods/4.1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods/Table 3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods, including link to Zenodo project & Appendix A
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	A Methods, including link to Zenodo project & Appendix A
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods/4.4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods/4.5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods/Table 3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Limited data extraction tables on Zenodo

Section and Topic	Item #	Checklist item	Location where item is reported
			project. Full data extraction table in Appendix B.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods/4.6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods/Table 3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods/4.5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods/4.5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods/4.5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods/4.5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods/4.7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results/Figure 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	Results Table 5, Table B.1 in Appendix B
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results/Table 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results/Summary of Findings Tables
	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results/5.3

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results/Summary of Findings Tables
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion/6.1 & 6.2
	23b	Discuss any limitations of the evidence included in the review.	Discussion/6.5
	23c	Discuss any limitations of the review processes used.	Discussion/6.5
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion/6.4
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Prospero registration - Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	HIQA website - Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Protocol Deviations/4.2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A – HIQA report
Competing interests	26	Declare any competing interests of review authors.	No COI for review authors but see page 7 for EAG COIs
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Link to Zenodo project in Results

Table A.2 Full search strategy – Medline (EBSCO)

Database Name	Medline via Ebscohost			
Date search was run	15 May 2024			
#	Query	Limiters/Expanders	Last Run Via	Results
S12	S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	Limiters - Publication Date: 20180101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	3,637
S11	TX MRIdian	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	255
S10	TX "Elekta Unity"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	224
S9	AB (MRIgRT OR MRgRT OR MRgART OR MR-gRT MRg-A-SBRT OR MRgSBRT) OR TI (MRIgRT OR MRgRT OR MRgART OR MR-gRT OR MRg-A-SBRT OR MRgSBRT)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	394
S8	AB ((MR OR MRI) N3(Radiotherap* OR radiation OR RT OR ART OR SBRT)) OR TI ((MR OR MRI) N3 (Radiotherap* OR radiation OR RT OR ART OR SBRT))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	4,288

S7	AB ((MR OR MRI) N2 linear accelerator) OR TI ((MR OR MRI) N2 linear accelerator)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	268
S6	AB (MR OR MRI) N2 linac* OR TI (MR OR MRI) N2 linac*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	880
S5	AB Magnetic Resonance linear accelerator OR TI Magnetic Resonance linear accelerator	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	62
S4	AB (Magnetic Resonance N3(radiotherapy OR radiation OR RT OR ART OR SBRT)) OR TI (Magnetic Resonance N3(radiotherapy OR radiation OR RT OR ART OR SBRT))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	1,650
S3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	2,443
S2	(MH "Radiotherapy, Image-Guided") OR (MH "Radiotherapy Planning, Computer-Assisted")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	28,395
S1	(MH "Magnetic Resonance Imaging")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	486,290

Table A.3 Details of grey literatures

Organisation type	
Health Technology Assessment agencies	
Organisation	**Link to URL**
Canada's Drug and Health Technology Agency	www.cadth.ca
Choices In Health Care (COHERE) Finland	https://palveluvalikoima.fi/en/cohere-finland
Health Quality Ontario	https://www.hqontario.ca
Health Technology Wales	https://healthtechnology.wales/
International HTA database	https://database.inahta.org/
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/
NIHR Health Technology Assessment programme	Health Technology Assessment | NIHR
Norwegian Institute of Public Health (NIPH)	https://www.fhi.no/en/
Scottish Health Technologies Group	https://shtg.scot/
Swedish Agency for Health Technology Assessment and Assessment of Social Services	https://www.sbu.se/en/
International guideline groups/professional organisations	
Organisation	**Link to URL**

European Society for Radiology (ESR)	Guidelines & Recommendations | European Society of Radiology (myesr.org)
European Society for Radiotherapy and Oncology (ESTRO)	ESTRO - Guidelines
Guidelines International Network	https://g-i-n.net/)
International Atomic Energy Agency (IAEA)	https://www.iaea.org/
International Commission on Radiological Protection (ICRP)	https://www.icrp.org/

Country specific guideline groups/professional organisations		
Organisation	**Country**	**Link to URL**
ACR-AAPM	US	https://www.aapm.org/pubs/ACRAAPMCollaboration.asp
Agence Fédérale de Contrôle Nucléaire	Belgium	https://afcn.fgov.be/
Agency for Healthcare Research and Quality	US	https://www.ahrq.gov/)
American College of Radiology (ACR)	US	https://www.acr.org/
American Society for Radiation Oncology (ASTRO)	US	https://www.astro.org/
Autorité de Sûreté Nucléaire (ASN)	France	https://www.asn.fr/
Haute Autorité de Santé (HAS)	France	https://www.has-sante.fr/jcms/r_1455134/en/about-has
Health Products Regulatory Authority (HPRA)	Ireland	https://www.hpra.ie/
National Cancer Control Programme (NCCP)	Ireland	https://www.hse.ie/eng/services/list/5/cancer/

National Comprehensive Cancer Network (NCCN)	US	https://www.nccn.org/
Objective Health Canada	Canada	https://objectivehealth.ca/
Royal College of Radiologists (RCR)	US	https://www.rcr.ac.uk/guidelines
Scottish SIGN	Scotland	https://www.sign.ac.uk
Swiss Federal Office of Public Health	Switzerland	https://www.bag.admin.ch

Summary of web search	**Key words searched**
Google and Google Scholar	Key words: "MR guided radiation therapy" OR "MR guided radiotherapy" OR "MR linac" OR "MR linear accelerator"

Regulatory organisations	
Organisation	**Link to URL**
European Medicines Agency (EMA)	https://www.ema.europa.eu/en/homepage
European Database on Medical Devices (EUDAMED)	https://ec.europa.eu/tools/eudamed/#/screen/home
Food and Drug Administration (FDA)	https://www.fda.gov/
Health Products Regulatory Authority (HPRA)	https://www.hpra.ie/

Table A.4: Synthesis Without Meta-analysis (SWiM) reporting items

SWiM is intended to complement and be used as an extension to PRISMA			
SWiM reporting item	**Item description**	**Page in manuscript where item is reported**	**Other***
Methods			
1 Grouping studies for synthesis	1a) Provide a description of, and rationale for, the groups used in the synthesis (e.g., groupings of populations, interventions, outcomes, study design)	Data extraction and synthesis	
	1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	Protocol deviations	
2 Describe the standardised metric and transformation methods used	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen, and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	Protocol deviations	
3 Describe the synthesis methods	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	Data extraction and synthesis	
4 Criteria used to prioritise results for summary and synthesis	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question)	Protocol deviations	

SWiM reporting item	***Item description***	***Page in manuscript where item is reported***	***Other****
5 Investigation of heterogeneity in reported effects	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	Appendix 2 Table A.4	
6 Certainty of evidence	Describe the methods used to assess certainty of the synthesis findings	Grading of Recommendations Assessment, Development and Evaluation (GRADE)	
7 Data presentation methods	Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots). Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included.	Data extraction and synthesis Grading of Recommendations Assessment, Development and Evaluation (GRADE)	
Results			

8 Reporting results	For each comparison and outcome, provide a description of the synthesised findings, and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	Results	
Discussion			
9 Limitations of the synthesis	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis, and how these affect the conclusions that can be drawn in relation to the original review question	Discussion (Limitations)	

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

*If the information is not provided in the systematic review, give details of where this information is available (e.g., protocol, other published papers (provide citation details), or website (provide the URL).

10 Appendix B

Table B.1: Data extraction from studies that underwent full data extraction

Treatment site	
Prostate	
Author & year	**Nicosia 2023**
Title	Linac-based versus MR-guided SBRT for localized prostate cancer: a comparative evaluation of acute tolerability.
Country	Italy
Design	Prospective Phase II cohort study
Industry funding/ sponsorship	No industry funding, sponsorship or financial relationship declared for this study.
COIs	One author reported financial relationships with Elekta.
Radiotherapy target	Prostate (clinical target volume was the prostate gland and the first third of the seminal vesicles).
Primary tumour	Low or favourable intermediate risk prostate cancer.
Inclusion criteria	Patients with localised prostate cancer (PCa) were treated with SBRT either on MR-linac or conventional linac. Patients treated with MR-linac were included in an ongoing prospective clinical trial (Prot. n° 23,748). Patients treated with conventional linac-based SBRT with fiducial markers were those enrolled in a prospective phase II study, approved by the Ethical Committee (No. Prot. SBRT PROG112CESC). Patients' were included according to the following characteristics: age<85 years, the WHO performance status 2, prostate volume≤80 cc, PSA<20 ng/ml, histologically proven PCa at low or favourable intermediate risk, for which ADT was not mandatory, T1–T2 stage, no pathologic lymph nodes on computed tomography (CT) and magnetic resonance imaging (MRI), no distant metastases, no previous prostate surgery other than transurethral resection of the prostate (TURP) (at least a 6-month interval before RT initiation), no other malignant tumours in the last 5 years, and minimum follow-up of 6 months after SBRT.
Exclusion criteria	Exclusion criteria were clinical positive nodes or a lymph node involvement risk>15%, previous TURP less than 6 months before RT, previous prostate surgery other than TURP, previous pelvic irradiation, and previous ADT.
Intervention	SBRT delivered using 1.5T MR-linac. Patient immobilization was obtained using an abdominal thermoplastic mask and/or Combifix™ (CIVCO, Orange City, IA, USA).

Radiotherapy technique	Adapt to shape used for each MRgRT session, involving replanning and full optimisation at each fraction.
Control	Volumetric modulated arc (VMAT) with conventional linac. CBCT IGRT. Intraprostatic fiducial markers used. Immobilisation device: Combifx™ (CIVCO, Orange City, IA, USA). Not adaptive.
Radiotherapy dose	35Gy in 5 fractions every day or every other day
Number of participants	n=135, MRgRT= 72 (53.3%), CTgRT= 63 (46.7%)
Median age of patients (range)	Median age 72 years (54-84) for MRgRT. Median age 74 years (57-83) for CTgRT.
Other therapies	Some patients received ADT. Some patients had previous abdominal surgery but no previous prostate surgery other than transurethral resection of the prostate (TURP) at least a 6-month interval before RT initiation.
Outcomes reported	Toxicity (CTCAE, v5.0), PSA and international prostatic symptom score (IPSS).
Follow-up	Follow up was performed 60 days after the end of radiotherapy, then every 3 months in the 1st year, every 6 months in the 2nd and 3rd years, and then once a year.
Outcomes, any measure of clinical effectiveness	Not reported.
Outcome, any measure of potential harm: Acute toxicity	Overall, any grade acute toxicity occurred in 63 (46.5%) patients. Overall, acute toxicity in MRgRT and CTgRT groups was Grade 1: 19 (26.4%) versus 20 (31.8%), Grade 2: 9 (12.5%) versus 11 (17.5%), and Grade 3: 2 (2.8%) versus 3 (4.7%) (p=0.52). Acute toxicity at the end of SBRT treatment in MRgRT and CTgRT groups was Grade 1: 14 (19.0%) versus 17 (27.0%), Grade 2: 7 (10.0%) versus 8 (13.0%), and Grade 3: 2 (2.8%) versus 3 (4.7%) (p=0.51). Acute toxicity at 3 months in MRgRT and CTgRT groups was Grade 1: 11 (15.0%) versus 14 (22.0%) and Grade 2: 6 (9.0%) versus 5 (8.0%) (p=0.56). Acute toxicity at 6 months in MRgRT and CTgRT groups was Grade 1: 4 (5.0%) versus 13 (21.0%) and Grade 2: 2 (3.2%) versus 1 (2.0%) (p=0.03).

	Prostate volume≥61 cc correlated with overall acute toxicity (p=0.002) and overall acute toxicity at SBRT end (p=0.005). Other factors associated with increased overall acute toxicity were hypertension, and having received abdominal surgery before SBRT. Gastrointestinal toxicity showed a trend toward statistical significance favouring MRgRT group compared to CTgRT group as follows: Grade 1: 6 (8.0%) versus 11 (17.5%) and Grade 2: 5 (7.0%) versus 8 (12.5%) (p=0.06). Grade 3: 5 (7.0%) versus 8 (12.5%). Overall p-value (presumably for the differences in all grades of toxicity across both group) was 0.06. Genitourinary toxicity did not differ significantly between the two groups. In particular, Grades 2 and 3 MRgRT and CTgRT groups were as follows: 8 (11.0%) versus 8 (13.0%) and 2 (2.5%) versus 3 (4.7%) (p=0.75). At the univariate analysis, the only other clinical factor significantly associated with increased GI and GU toxicity was prostate volume ≥61 cc (p=0.02; p=0.03, respectively). Grade 2: 8 (11.0%) versus 8 (12.8%) for MRgRT and CTgRT respectively. Grade 3: 2 (2.5%) versus 3 (4.7%) in the MRgRT and CTgRT respectively. Overall p-value (presumably for the differences in all grades of toxicity across both group) was 0.82.
Late toxicity	No late toxicity reported, aim of this study was to compare acute toxicity.
Treatment time	The median time from pre-treatment imaging acquisition (MR or CBCT) to the end of the treatment session was 38 min and 15 min, for group 1 and group 2, respectively.
Surrogate outcomes	Dosimetry data not reported.
Authors' conclusions	Prostate SBRT with 1.5-T MR-linac is feasible and safe. Compared to conventional linac, MRgRT might to potentially reduce the overall G1 acute toxicity at 6 months, and seems to show a trend toward a lower incidence of Grade 2 GI toxicity. A longer follow-up is necessary to assess the late efficacy and toxicity.
Author & year	**Kishan 2023**
Title	Magnetic Resonance Imaging–Guided vs Computed Tomography–Guided Stereotactic Body Radiotherapy for Prostate Cancer.
Country	US
Design	Non-blinded single centre phase III RCT.
Industry funding/ sponsorship	No industry funding, sponsorship or financial relationship declared for this study.
COIs	Some authors reported financial relationships with ViewRay.
Radiotherapy target	Clinically localised prostate adenocarcinoma (i.e., cN0M0 on conventional imaging). Proximal 1cm of seminal vesicles included for all patients.
Primary tumour	Prostate

Inclusion criteria	Aged 18 or older standard-of-care workup men aged 18 years or older with histologically confirmed, clinically localized prostate adenocarcinoma (i.e., cN0M0on conventional imaging) were enrolled between May 5, 2020, and October 1, 2021. Participants must have had a standard-of-care workup. No evidence of disease beyond the prostate and/or seminal vesicles. Staging workup as recommended by the NCCN on the basis of risk grouping. Ability to understand, and willingness to sign, the written informed consent.
Exclusion criteria	Presence of non-MRI–compatible electronic devices or foreign objects and severe claustrophobia. Histolopathologically proven neuroendocrine or small cell carcinoma, clinical node-positive or metastatic disease, prior whole gland cryosurgery, HIF, or brachytherapy, prior pelvic radiotherapy, history of Crohn's disease, ulcerative colitis or ataxia telangiectasia.
Intervention	0.35T MR-linac Step-and-shoot IMRT. Non-adaptive.
Radiotherapy technique	Step-and-shoot IMRT, 2mm isotrophic CTV to PTV margin. For MRI-guided SBRT, the prostate was aligned prior to each fraction with a true fast imaging with steady state precession MRI. During SBRT, cine MRI was obtained 4 times per second in the sagittal plane. If greater than 10.0% of the prostate volume moved outside a 3-mm gating boundary placed around the prostate, an automatic beamhold would be initiated.
Control	CBCT linac with standard margins (4mm isotropic) plus fiducial implants, SBRT delivered with VMAT. Fiducial markers were placed transperineally on the day of the scan.
Radiotherapy dose	SBRT prostate: 40Gy in 5 fractions. SBRT pelvic nodes 25Gy in 5 fractions, simultaneous integrated boost to the dominant intra-prostatic lesion (42 Gy in 5 fractions), and a simultaneous integrated boost to a pelvic node deemed to be involved with metastatic disease on advanced functional imaging (35 Gy in 5 fractions) were allowed per investigator discretion. Treatments preferably delivered every other day or may be given consecutive days, with treatment within a period of time may not have exceeded 14 days.
Number of participants	n=156, CTgRT =77, MRgRT =79.
Median age of patients (range)	Median 71 (IQR 67-77) in the CT arm 71 (IQR 68-75) in the MRgRT arm.
Other therapies	ADT use in 57 (74.0%) of patients in the CT arm and 49 (62.0%) of patients in the MR arm. ADT may be prescribed with or without non-steroidal antiandrogen or second generation hormonal therapy agents.
Outcomes reported	The primary outcome was incidence of acute genitourinary (GU) Grade 2 or greater toxicity scored using CTCAE v4.03 evaluated from the start of SBRT to 90 days of fewer after SBRT. Secondary outcomes included acute CTCAE v4.03 Grade ≥ 2 gastrointestinal (GI) toxicities or changes in International Prostate Symptom Score (IPSS) and Expanded Prostate Cancer Index Composite-26 (EPIC-26).
Follow-up	All patients had three months or more of follow-up. Schedule: every 3 months year 1, every 6 months year 2-5 and yearly thereafter. Acute effects were evaluated from the start of SBRT up to days or fewer after SBRT.
Outcomes, any measure of	Not reported in this publication.

clinical effectiveness	
Outcome, any measure of potential harm	A pre-specified interim analysis was conducted on October 1, 2021, after 100 patients (51 patients in the CT guidance arm and 49 patients in the MRI guidance arm) were evaluable for the primary end point. The incidence of acute Grade 2 or greater GU toxic effects was significantly reduced in men receiving MRI-guided SBRT compared with men receiving CT-guided SBRT (24 of 51 (47.1%) versus 11 of 49 (22.4%); p =0.01). Thus, a revised power calculation was performed, and it was concluded that a conditional power of 89.0% could be maintained with only 154 patients. By this time, 156 patients had already been treated, and the trial was closed for further accrual.
Acute/late toxicity	Genitourinary (GU): There was no Grade 3 or greater toxicity in the MRI group. In the CT guidance group 1 patient (1.3%) experienced Grade 3 urinary retention. The incidence of acute Grade 2 or greater GU toxic effects was significantly lower with MRI versus CT guidance (19 of 78 patients, 24.4% (95% CI, 15.4-35.4) versus 33 of 76 patients, 43.4% (95% CI, 32.1-55.3); p=0.01). IPSS: No significant differences in urinary-irritative or obstructive sub-score or overall urinary domain score were seen. Differences in total IPSS and IPSS quality of life sub-score did not significantly differ. After SBRT, urinary incontinence subdomain scores decreased significantly more with CT guidance versus MRI guidance at 1 month (11.3-point vs.6.2-point decrement; p=0.01) but were no longer significantly different at 3 months. The percentage of patients with a clinically relevant increase in IPSS (>15 points) was significantly greater with CT guidance at 1 month (19.4% (14 of 74) vs.6.8% (5 of 72); p =0.01) but not at 3 months (1.4% (1 of 72) vs.4.1% (3 of 74); p=0.30). Differences in total IPSS and IPSS quality of life subscore did not significantly differ. Gastrointestinal (GI): The incidence of acute Grade 2 or greater gastrointestinal toxic effects was significantly lower with MRI versus CT guidance (0 of 78 participants, 0.0% (95% CI, 0.0-4.6) vs.8 of 76 participants, 10.5% (95% CI, 4.7-19.7); p=0.003). Magnetic resonance imaging guidance was associated with a significantly smaller percentage of patients with a 15-point or greater increase in IPSS at 1 month (6.8% (5 of 72) vs. 19.4% (14 of 74); p=0.01) and a significantly reduced percentage of patients with a clinically significant (12-point) decrease in EPIC-26 bowel scores (25.0% (17 of 68) vs.50.0% (34 of 68); p=0.001) at 1 month. EPIC-26 bowel domain sub-scores at 1month (4.1- point vs.18.2-point decrement; p<0.001) but not at 3 months. A significantly larger percentage of patients treated with CT guidance experienced a clinically relevant (≥12-point) decrement in EPIC-26 bowel domain scores (50.0% (34 of 63) vs.25.0% (17 of 63); p=0.001). A numerically greater decrement in EPIC-26 sexual domain scores was seen with CT guidance versus MRI guidance at 3 months (13.2-point vs.3-point decrement; p=0.04; analysis restricted to men who did not receive androgen-deprivation therapy). No differences in longitudinal hormonal or vitality domain score or proportions of patients with clinically relevant decrements in the sexual domain and the hormonal domain were seen (analysis restricted to men who did not receive androgen-deprivation therapy).
Treatment time	Median post-imaging delivery times were 1133 seconds (IQR, 1109-1289 seconds) with MRI guidance versus 232 seconds (IQR, 198-272 seconds) with CT guidance.

Surrogate outcomes	Statistically significant values CT-Guidance versus MRI guidance (volumes in cc) • PTV volume 55.90 (44.20-66.90) versus 50.60 (37.70-60.60); P <0.001. • PTV V42Gy 5.4% (0.4-14.9%) versus 18.6% (12.2-25.5%); P <0.001. • Bladder V40Gy 0.70 (0.20-1.60) versus 0.30 (0.10-0.44); P= 0.001 • Bladder V39Gy 3.70 (2.60-6.10) versus 1.90 (0.90-3.60); P <0.001 • Anal Canal D0.035cc 12.30 (10.20-16.40) versus 24.00 (18.90-28.00); P <0.001 • Anal Canal V20Gy 0.00 (0.00-0.00) versus 0.10 (0.02-0.30) ; P <0.001 No statistically significant different for CTV, urethra, rectum, small bowel or penile bulb.
Authors' conclusions	In this randomised clinical trial, compared with CT-guidance, MRI-guided SBRT significantly reduced both moderate acute physician-scored toxic effects and decrements in patient-reported quality of life. Longer-term follow-up will confirm whether these notable benefits persist.
Author year	**Ma 2023**
Title	Quality-of-Life Outcomes and Toxicity Profile Among Patients With Localized Prostate Cancer After Radical Prostatectomy Treated With Stereotactic Body Radiation: The SCIMITAR Multicenter Phase 2 Trial.
Country	US
Design	Multicenter Phase 2 Trial
Industry funding/ sponsorship	The trial was partially funded by ViewRay.
COIs	Some authors reported financial relationships with ViewRay.
Radiotherapy target	Prostate bed +/- bed boost +/- pelvic nodes RT at discretion of physician. For MRgRT the PTV was a 3mm isotrophic expansion of CTV, while CTgRT was 5mm isotropic expansion.
Primary tumour	Prostate.

Inclusion criteria	Patients with a history of clinical localised adenocarcinoma of the prostate, who had prostatectomy. Additionally, patients must have had at least one of the following: (1) adverse pathologic features at the time of prostatectomy (positive surgical margin, pathologic T3/ T4 disease, pathologic Gleason score 8-10 disease or presence of tertiary Gleason grade 5 disease), (2) rising prostate specific antigen (PSA) on at least 2 consecutive measurements, with both >0.03 ng/mL, or (3) a Decipher genomic classifier score >0.45. A CT scan, MRI of the pelvis and a bone scan within 120 days before enrolment were required. Positron emission tomography was strongly encouraged.
Exclusion criteria	Not described as exclusion, but 4 patients declined MRgRT due to claustrophobia or presence of pacemaker.
Intervention	MRgRT, 13 to 17 static gantry intensity modulated RT fields were used, and a set-up MRI was acquired before each treatment. During MRgRT delivery, sagittal cine MRI images were acquired at 4 frames per second to track the anterior rectal wall motion in real time. A gating boundary of 3 mm around the anterior rectal wall was set such that if >10% of the volume moved outside this window, beam delivery was automatically paused. Online adaptive RT was delivered in a minority of MRgRT fractions (4 fractions or 2.5%) owing to staffing restrictions during the COVID-19 pandemic in the setting of unclear clinical benefit.
Radiotherapy technique	MRgRT delivered with 0.35T system. Set-up MRI was acquired before each treatment. During MRgRT delivery, sagittal cine MRI images were acquired at 4 frames per second to track the anterior rectal wall motion in real time a gating boundary of 3 mm around the anterior rectal wall was set such that if >10% of the volume moved outside this window, beam delivery was automatically paused. Online adaptive RT was delivered in a minority of MRgRT fractions (4 fractions or 2.5%) owing to staffing restrictions during the COVID-19 pandemic in the setting of unclear clinical benefit.
Control	Computed tomography (CTgRT) therapy was used with a kilovoltage cone beam CT acquired before each treatment to verify anatomy. Treatment delivered on NovalisTx or TrueBeam linacs.
Radiotherapy dose	Patients received SBRT 30 to 34 Gy/5 fractions to the prostate bed (± bed boost ± pelvic nodes). Median dose 32Gy (range 30-34Gy). RT was delivered every other day.
Number of participants	n=100. (CTgRT, n=69; MRgRT, n=31).
Median age of patients (range)	Median age overall 69 (range 50-82), CTgRT arm 69 (range 52-79), MRgRT arm 68 (range 50-82).
Other therapies	Median 6 months (ranging from 1-8) of androgen-deprivation therapy (ADT) were used at the discretion of the treating physician, 16 (51.6%, median duration six months ranging from 4-8) of the MRgRT group had concurrent ADT, while 25 (36.2%, median duration six months ranging from 1-6) of the CTgRT group.
Outcomes reported	Co-primary endpoints were 4-year biochemical recurrence–free survival, physician-scored acute (<90days post-SBRT) and late (≥90days post-SBRT) GU and GI toxicities by the Common Terminology Criteria for Adverse Events (version 4.03) scale, and patient-reported quality-of-life (QOL) outcomes, as represented by the Expanded Prostate Cancer Index-26 and the International Prostate Symptom Score.

Follow-up	Median follow up was 29.5 months (CTgRT: 33.3 months, MRgRT: 22.6 months).
Outcomes, any measure of clinical effectiveness	Not reported in this paper (but is part of trial endpoints)

Outcome, any measure of potential harm : acute/late toxicity	Overall, late Grade 1 GU and GI toxicity rates were 40.0% and 34.0% respectively. The majority of worst acute toxicity events were Grade 1 for GU and GI toxicity, at 43.0% and 57.0%, respectively. Worst acute Grade 2 GU and GI toxicity rates were 9.0% and 5.0%, respectively. The incidences of late Grade 2 GU and GI toxicities were 9% and 0.0%, respectively. No patient receiving MRgRT had grade 3 GU or Grade ≥2 GI toxicity. Three patients all treated with CTgRT had Grade 3 toxicity (n=1 GU, n=2 GI). These included haematuria due to radiation cystitis (n=1), diarrhoea (n=1) one week after SBRT and proctitis (n=1) 6 months after SBRT. Compared with CTgRT, MRgRT was associated with significantly lower rates of any-grade acute GI toxicity (41.9% vs. 72.5%, p=0.006, or an estimated absolute reduction of 30.5% (95% CI, 11.6-49.5)) and significantly lower rates of any-grade GI toxicity of up to 6 months after SBRT (41.9% vs.73.9%, p=0.002, or an estimated absolute reduction of 32% (95% CI, 12.9-51.1)). Late any-grade GI toxicity was 37.7% for CTgRT and 29.0% for MRgRT (p=0.4). Though MRgRT was associated with numerically lower rates of acute (48.4% vs.55.0%, p=0.54), late (42.0% vs.53.6%, p=0.28) and up to 6 months (48.4% vs.60.8%, p=0.24) any-grade GU toxicity, none of these differences were statistically significant. In terms of patient reported outcomes, there was a consistent decline in EPIC-26 urinary irritative/obstructive domain score (mean, −2.9; 95% CI, −4.9 to −0.9; P = .049) and increase in IPSS sum scores (IPSS_S) (mean, 1.2; 95% CI, 0.2-2.2; P = 0.007) 1 month after SBRT; both normalized by 3 months post- SBRT. No statistically significant deterioration in the urinary irritative/obstructive domain was seen at any time in patients treated with MRgRT, and no significant changes in urinary incontinence or the IPSS QOL summary scale were seen with either treatment arm. A statistically significant decline in the EPIC-26 bowel domain score was observed at 1 month (mean, −8.6; 95% CI, −12.4 to −4.8; p<.0001), 3 months (mean, −2.6; 95% CI, −4.8 to −0.4; p=0.02) and 6 months (mean, −4.6; 95% CI, −8.4 to −0.8; p=0.04). However, the proportion of patients with clinically relevant deterioration improved from 1 month to 6 months, with the clinically relevant deterioration resolving earlier in men receiving MRgRT. In terms of predicators of toxicity, CTgRT (P = .002), elective nodal RT (P = .03), prostate bed boost (P = .04), and baseline EPIC-26 bowel domain score (p0=.02) were significantly associated with any-grade GI toxicity within the first 6 months in the univariable analysis while CTgRT was the only significant predictor (OR, 3.71; 95% CI, 1.38-9.99; p=0.010) in the multivariable analysis. Similarly, CTgRT (OR, 3.02; 95% CI, 1.12-8.17; p=0.03) and baseline EPIC-26 bowel score (OR, 1.08; 95% CI, 1.00-1.16; p=0. .047) were significant predictors of clinically relevant decline in EPIC-26 bowel scores within 6 months of SBRT. Three patients died during the follow-up period, all unrelated to prostate cancer treatment (n=1 each from congestive heart failure, myocardial infarction, and intracranial haemorrhage).
Treatment time	Not reported.

Surrogate outcomes	Not reported.
Authors' conclusions	Post-prostatectomy SBRT was well tolerated within the first 6 months as evaluated by both physician-scored toxicity and patient-reported outcomes. MRgRT was associated with significantly decreased GI toxicity and better-preserved bowel QOL compared with CTgRT. Long-term follow-up and randomized trials comparing conventional fractionation or moderate hypofractionation to SBRT are needed to further characterize the safety and efficacy of this technique.
Pancreas	
Author year	**Lee 2022**
Title	Consolidatory ablative stereotactic body radiotherapy after induction chemotherapy for unresectable pancreatic cancer: A single centre experience.
Country	South Korea.
Design	Retrospective study.
Industry funding/ sponsorship	No industry funding, sponsorship or financial relationship declared.
COIs	No conflict of interest declared.
Radiotherapy target	Pancreas.
Primary tumour	Pancreas and oligometastases.
Inclusion criteria	Patients with locally advanced pancreatic adenocarcinoma, including oligometastatic disease, who received induction chemotherapy followed by ablative dose SBRT between January 2017 and September 2021 were included. Locally advanced stage was defined as a tumour with greater than 180-degree involvement of the superior mesenteric artery or celiac axis or unreconstructable involvement of the superior mesenteric vein or portal vein. Oligometastatic disease was defined as less than four metastases to a single organ.
Exclusion criteria	Prior definitive treatment history, pancreatic tumour histology other than adenocarcinoma, or double-primary malignancies. Patients who were unable to breathe regularly, could not tolerate extended treatment times, or had any contraindications to MR (e.g., claustrophobic, metal implant) were assigned to non-adaptive SBRT (linac based).
Intervention	Daily adaptive MR-guided SBRT on a 0.35T system.

Radiotherapy technique	Patients were immobilised in the supine position with arms over head. A pneumatic abdominal compressor was used to reduce breathing-induced internal tumour movement. For MRgRT group, daily adapted plan constructed, and the best plan for an individual patient was chosen based on both OAR dose and target coverage. Each MRgRT fraction was delivered under MR-guided real-time gating.
Control	Non-adaptive linear accelerator (linac)-based SBRT was delivered using the TrueBeam-STX (Varian Medical Systems, Palo Alto, CA). In non-adaptive SBRT, image-guided RT using cone beam CT was performed for all fractions. To reduce inter- and intra-fractional variability, a 6-hour fasting period before simulation and each fraction was mandated.
Radiotherapy dose	The median prescribed dose was 50Gy (range, 40–50 Gy) in 5 fractions.
Number of participants	n=50 patients (linac-based SBRT=24, MR-guided SBRT=26).
Median age of patients (range)	Median age was 62 years (range, 39–78 years).
Other therapies	All patients received four or more cycles of induction chemotherapy before SBRT. Induction chemotherapy consisted of FOLFIRINOX (92.0%) and Gem/nab-paclitaxel (8.0%) regimens. A 3–4 week break from induction chemotherapy was required before SBRT delivery.
Outcomes reported	OS, disease response, LPFS, dosimetric outcomes, adverse events (CTCAE, v5.0).
Follow-up	Median follow-up period was 18.8 months (range, 4.1–61.0 months) for all patients and 21.1 months (range, 6.2–61.0 months) for survivors from the start date of SBRT.
Outcomes, any measure of clinical effectiveness	SBRT technique (adaptive vs. non-adaptive) also had no significant association with both OS and LPFS. Disease Response: After SBRT, eleven (22.0%) patients underwent resection, and all had R0 resection, with three (6.0%) achieving a pathologic complete response (pCR). There were no Grade ≥3 postoperative adverse events. Patients with resected tumours showed significantly improved survival outcomes compared with patients without resection (1-year OS: 90.9% (95% CI, 50.8–98.7) vs.75.1% (95% CI, 57.5–86.2); 3-year OS: 64.9% (95% CI, 24.9–87.4) vs.19.0% (95% CI, 6.7–36.0); p=0.01). At the last follow-up, 16 (32.0%) patients were in a progression free state with normalized CA 19-9 and without imaging evidence of progression. OS: In patients with non-metastatic disease, the median OS was 26.5 months (range, 4.1–61.0 months). 1- and 3-year OS rates were 87.3% (95% CI, 69.6–95.1) and 37.0% (95% CI, 17.4–56.8), respectively. SBRT technique (adaptive vs. non-adaptive) HR 1.2 (95% CI 0.54 -2.67) p=0.656.

	LPFS: 1- and 3-year LPFS were 90.0% (95% CI, 72.0–96.7) and 57.4% (95% CI, 31.7–76.4), respectively. SBRT technique (adaptive vs. non-adaptive) HR 1.87 (95% CI, 0.73-4.78) p=0.19. Patients with oligometastatic disease had inferior survival outcomes with a median OS of 12.5 months (range, 6.2-40.7 months), and the 1- and 3-year OS rates of 61.6% (95% CI, 33.5-80.7) and 16% (95% CI, 2.7-39.5) respectively. There was no survival difference among responders to induction chemotherapy. In the multivariable analysis, tumour size ≤4 cm, non-metastatic status, and good response to induction chemotherapy were associated with improved LPFS.
Outcome, any measure of potential harm : Acute/late toxicity	Acute Grade 2 adverse events occurred in 23 (46.0%) patients. There were no Grade 3 or higher acute adverse events. The most common acute adverse events were abdominal pain (32.0%), nausea/vomiting (28.0%), and poor oral intake (16.0%). Late toxicity: Regarding the late adverse events, Grade 2 or higher events occurred in 15 (30.0%) patients. A total of two (6.0%) patients experienced Grade 3 gastro-intestinal bleeding, both requiring endoscopic intervention, but were successfully managed. There were no Grade 4 or higher late adverse events. Patients treated with MR-guided adaptive SBRT showed a trend toward lower rates of late adverse events compared with those treated with non-adaptive SBRT (Grade 2: 19.2% vs.33.3%; Grade 3: 0% vs.8.3%; p=0.08).
Treatment time	Not reported.
Surrogate outcomes	The values of dosimetric parameters in patients with or without local progression within three years following SBRT are reported. The mean values were all higher in patients without local progression compared to those with local progression. Among dosimetric parameters, the difference between the two groups was significant for the prescribed dose (p=0.006), GTV Dmin (p<0.001), and GTV Dmean (p=0.008). According to the ROC analysis, GTV Dmin showed the highest AUC (0.789) as a predictor of local progression. Patients with GTV Dmin ≥50.5 Gy showed superior OS and LPFS compared to those with GTV Dmin < 50.5 Gy (1-year OS: 82.9% (95% CI, 60.6–93.2) vs.74.3% (95% CI, 51.4– 87.6), p=0.05; 1-year LPFS: 91.5% (95% CI, 70.0–97.8) vs. 77.3% (95% CI, 53.2–54.2), p=0.007).
Authors' conclusions	Consolidatory ablative dose SBRT following induction chemotherapy is an effective strategy for selected patients with unresectable pancreatic cancer. The SIP technique and MR-guided adaptive RT were attributed to minimizing the risk of adverse events. Further studies are needed to identify the best candidates for consolidatory SBRT in unresectable pancreatic cancer.
Liver	
Author year	**Tallet 2023**
Title	Is MRI-Linac helpful in SABR treatments for liver cancer?

Country	France.
Design	Retrospective study.
Industry funding/ sponsorship	No industry funding, sponsorship or financial relationship declared.
COIs	Conflict of interest: department and some authors report financial support from ViewRay.
Radiotherapy target	Liver.
Primary tumour	Primary or secondary liver tumours. MRgRT group: colorectal 8 (42.0%), breast 4 (21.0%), other 3 (16.0%). CTgRT group: colorectal 17 (38.0%), breast 8 (18.0%), other 15 (33.0%).
Inclusion criteria	Eligible patients were those with a Karnofsky Performance Status of more than 70.0%, no more than three lesions, with a maximum cumulative size of less than 60 mm, a Child-score A or B, and suitable biological liver-function, defined as hepatic-enzymes count inferior to three times the usual-values and a prothrombin time >70. Liver tumours were histologically proven either by previous surgery or by biopsy.
Exclusion criteria	Not described.
Intervention	0.35T MR-linac with respiratory gating.
Radiotherapy technique	MRgRT: 0.35T MR-linac with respiratory gating, with treatment delivered either in free-breathing or in early-inhale breath-hold using the respiratory gating functionality, with the percentage of PTV allowed outside the 5mm-gating boundaries set at 10.0%. MR-compatible all-fits-one contention device. PTV was obtained by isotropically expanding the GTV by 5 mm or 3 mm for tumours poorly or accurately distinguishable from the liver parenchyma, respectively. CTgRT: was carried out with three implanted fiducial markers and abdominal compression was applied. Free breathing. Immobilization devices consisted of a dedicated vacuum ball mattress and an abdominal compression system. The PTV margin was obtained by adding to the internal target volume (ITV) 5mm laterally and anterior/posteriorly by 7mm.
Control	Cone beam CT-guided (CTgRT) SBRT on Elekta Versa HD® linac using fiducials.
Radiotherapy dose	The median dose prescribed to the PTV was 40Gy (35–50) in 5 fractions (3–10). Organs at risk dose constraints fulfilled Timmerman's recommendations.
Number of participants	n=59, MRgRT: 18, CTgRT: 41. Tumours treated in the MRgRT group: 45 and in the CTgRT group: 19.
Median age of patients (range)	MRgRT: median age 70 years (range 38-89) CTgRT: median age 69 years (range 30-83).

Other therapies	No previous liver tumour-directed therapy delivered in 19 (42.0%) of the CTgRT arm and in 8 (42.0%) of the MRgRT arm. One previous liver tumour-directed therapy delivered in 11 (25.0%) of the CTgRT arm and in 4 (21.0%) of the MRgRT arm. Several previous treatments were delivered in 15 (33.0%) of the CTgRT arm and in 7 (37.0%) of the MRgRT arm.
Outcomes reported	Local response as per RECIST criteria, toxicity (CTCAE, v4.0), dosimetry parameters.
Follow-up	The median follow-up and imaging follow-up for all patients was 16.7 months (1.18-73.02) and 8.2 months (0.30-73.02), respectively. Patients were followed up by liver MRI and CT scan every three months.
Outcomes, any measure of clinical effectiveness	Local control and patients' outcome: At last follow-up, 28 patients (47.0%) had died, 8 (14.0%) were lost to follow-up (and deemed deceased), whereas 23 (39.0%) were still alive. The local control rate was 76.6% (75.6% and 78.9% in the CBCT and MRI groups, respectively, p=0.96), meaning that 23.4% of patients experienced progression or relapse within the radiation field.
Outcome, any measure of potential harm: Acute/late toxicity	The all-grade toxicity rate within the whole study population was 31.25% (33.3% and 26.3% in the CBCT and the MRI group, respectively). Grade ≥ 3 toxicity rate was 4.7% (4.4% and 5.0% in the CBCT and the MRI group, respectively). No patients experienced nausea Grade ≥2.No patients experienced Grade ≥3 abdominal pain, gastritis or duodenal ulcer, however 1 patient (5.0%) experience Grade 2 abdominal pain in the MRI group, 1 (2.0%) patient experienced Grade 2 duodenal ulcer in the CBCT group, and 1 (2.0%) patient had Grade 2 gastritis in the CBCT group. 1 patient (2.0%) experienced Grade 3 gastric haemorrhage in the CTgRT group. One patient (2.0%) had Grade 3 portal hypertension in the MRgRT group. This was the only unexpected Grade 3 toxicity observed in the MRI group was portal hypertension, occurring in a patient whose portal trunk received a total dose of 30Gy in five fractions, in 7.0% of the volume (far below the dose constraint), and who had a thermoablation procedure in the segment I, potentially responsible for this adverse event. One case of Grade 5 radio-induced liver disease (in the CBCT group) was experienced in a hepatocellular carcinoma patient with a Child-score A6, who experienced decompensated cirrhosis with a Child-score C11. Ulcerous complications were less common in the MRI group (0 vs.4.4% in the CBCT group; gastric haemorrhage, duodenal ulcer).
Treatment time	Not reported.
Surrogate outcomes	The dosimetry metrics provided by the RayStation TPS and a VMAT technique appeared statistically significantly superior to those from the MRIdian system with its step-and-shoot IMRT method, as outlined by the conformation number (CN, median CN 0.90 vs.0.83, p=0.0017), although other metrics were comparable. Hence, despite the superiority of the VMAT (using non-coplanar arcs) over the step-and-shoot method, both the tumour margins reduction and the gating function lead to similar target coverage with higher healthy tissue preservation.

Authors' conclusions	However, patient characteristics appeared similar in the two groups, except for median tumour size (higher in the MRI group). Hence, patients' outcomes have to be considered with caution, and the objective of reporting local control and toxicity was mainly to ensure the absence of both unexpected toxicity and worse tumour control. SABR was well tolerated in both groups, and margins reduction and the use of gating prevented ulcerous disease occurrence. The use of MRI as IGRT allows for the reduction of the amount of healthy liver parenchyma irradiated without any decrease of the tumour control rate, which would be helpful for dose escalation (SMART method) or subsequent liver tumour irradiation if needed. Tumour margin reduction and gating also appear to reduce gastrointestinal toxicity.
Lung	
Author year	**Kang 2022**
Title	Application of real-time MRI-guided linear accelerator in stereotactic ablative body radiotherapy for non-small cell lung cancer: one step forward to precise targeting.
Country	South Korea
Design	Retrospective study
Industry funding/ sponsorship	No industry funding, sponsorship or financial relationship declared.
COIs	No conflict of interest declared.
Radiotherapy target	Lung
Primary tumour	Lung cancers including adenocarcinoma, squamous cell carcinoma SCC, NSCLC-not otherwise specified.
Inclusion criteria	The inclusion criteria were: (1) non-small cell lung carcinoma; (2) tumours less than 4.5 cm in the longest diameter; and (3) treatment with SABR on a lung lesion with a BED10>100 Gy.
Exclusion criteria	The exclusion criteria were: (1) previous treatment on the same site with radiotherapy; (2) treatment with mediastinal lymph nodes, bronchial tree, or pleura; and (3) Eastern Cooperative Oncology Group (ECOG) performance status score of≥3. Patients who did not complete treatment or were lost to follow up were excluded. Patients who were simultaneously treated for multiple lung lesions were also excluded.
Intervention	0.35T MR-linac MRIdian Linac® from ViewRay MR-Linac system (MRIdian), with respiratory gating.
Radiotherapy technique	0.35T MR-linac with real-time tumor tracking, gated, breath-hold, Chest Vac-LokTM, not adaptive.

Control	CT based SABR delivered using Tomotherapy and Novalis Tx, BrainLAB. Whole-body Vac-LokTM. Abdominal compression with forced shallow breathing used for the control group.
Radiotherapy dose	48 to 60Gy in 3–5 fractions. The number of fractions were different between the experimental and control arm (p<0.001). However, all the patients in this study received a minimum BED10 of 100 Gy. There was no significant difference in the BED10 on PTV between the two groups (116.7 ± 20.1 Gy for the MR group vs. 116.2 ± 16.3 Gy for the CT group, p=0.915). No. of fractions: 3: MR group 6 (14.6%), CT group 1 (2.5%) 4: MR group 15 (36.6%), CT group 38 (95.0%) 5: MR group 20 (48.8%), CT group 1 (2.5%)
Number of participants	n= 81, MRgRT: 41, CTgRT: 40
Median age of patients (range)	Median age MRgRT: 75 years (range 46-87), CTgRT: 75years (range 45-88), p=0.682.
Other therapies	Not described but noted that patients received differing treatments prior to SABR.
Outcomes reported	Treatment response using Response Evaluation Criteria in Solid Tumors version 1.1, one-year progression free survival, one-year overall survival and treatment toxicity using CTCAE, v5.0.
Follow-up	Median follow up of 19 months (3-105 months). For most cases, the first follow-up was conducted 1 month after SABR. Chest physical examination and chest CT also were performed in addition to physical examination and laboratory workups. The patients were followed-up every 3 months for the first 2 years then every 6 months for up to 5 years thereafter.
Outcomes, any measure of clinical effectiveness	Overall survival: OS was defined as the time from the end date of SABR to death from any cause or the last follow-up visit. 1-year overall survival rates were 87.4 and 87.0%, respectively (p=0.30). Progression-free survival (PFS): Progression-free survival (PFS) was defined as the duration from the end date of SABR to the date of disease relapse at any site, death from any cause, or last follow-up visit if a patient was free of disease. 1-year PFS rate (80.2% for the MR group versus 80.4% for the CT group, p=0.50. Local control: LC was determined as the duration from the end date of SABR to the date of disease relapse in the initial involved site, death from any cause, or last follow-up visit if a patient was free of disease. In total, 17 and 22 patients in the MR and CT groups, respectively, experienced disease recurrence during follow-up. There were 4 and 17 cases of local recurrence and 13 and 5 cases of distant recurrence in the MR and CT groups, respectively. The LC rate in the MR group was superior to that in the CT group, with borderline significance (p=0.07). The 1-year LC rate in the MR and CT groups were 92.1 and 75.4%, respectively (p=0.07).

Outcome, any measure of potential harm: acute/late toxicity	Acute/late toxicity: There was no significant difference in the frequency of radiation-related toxicities between the MR and CT groups (p=0.19). Overall, eight patients (19.5%) in the MR group experienced Grade 2 toxicity. There were seven cases of radiation pneumonitis and one case of dyspnoea. In the CT group, 14 patients (35.0%) developed Grade 2 toxicity, including 10 (25.0%) patients with radiation pneumonitis, 3 (7.5%) patients with dyspnoea, and 1 (2.5%) patient with rib fracture without displacement. No other toxicities of Grade≥3 was observed in either group. The incidence of radiation-induced toxicity is not proportional to the radiation dose to the ipsilateral lung.
Treatment time	Not reported.
Surrogate outcomes	All the patients in this study received a minimum BED10 of 100 Gy. There was no significant difference in the BED10 on PTV between the two groups (116.7 ± 20.1 Gy for the MR group vs. 116.2 ± 16.3 Gy for the CT group, p = 0.91). There was no significant difference in GTV between the two groups (7.1±9.3 cm3 for the MR group versus 8.0±6.8 cm3 for the CT group, p=0.64). However, the PTV was smaller in the MR group by almost 40%, with a significant difference (20.8 ±18.8 cm^3 for the MR group vs.34.1 ± 22.9 cm^3 for the CT group, p=0.005). However, the reduction of PTV in the MR group did not result in lower low-to-moderate dose and mean dose to the ipsilateral lung compared to that in the CT group (V5 (percentage of volume receiving more than 5 Gy: 36.8±10.8% vs.32.4±11.7%; V10: 28.4±8.6% vs. 28.1 ± 11.1%; V20: 19.5 ± 6.5% vs.19.0 ± 10.1%; mean dose: 644.6±203.9 Gy vs.641.5±298.8 Gy for the MR group vs. CT group).
Authors' conclusions	MR-linac in SABR for lung cancer reduces the volume of the irradiated field without compromising the local control rate. With further follow-up, recruitment of additional patients, and improvements in our planning ability with more experience, we anticipate to report better results in the future.

Table B.2: Evidence-to-Decision Framework

Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Overall** • No evidence of a statistically significant difference in overall survival, progression-free survival or local control. There was some evidence of improvements in quality of life in prostate cancer, but these effects were sometimes transient and were only statistically significant for some sub-domains. • All six comparative studies assessed toxicity outcomes, however only the three prostate studies found some statistically significant differences in favour of the MRgRT intervention. **Prostate** • Higher proportion of patients in the CTgRT arm had a clinically relevant rise in **IPSS** (≥15 points) at 1 month (19.4% vs. 6.8%; p=0.01), but not at 3 months (1.4% vs. 4.1%; p=0.30). • Proportion of patients reporting a clinically relevant deterioration in **EPIC-26 urinary irritation** (≥14 points) at any point between 6 and 24 months was lower for patients receiving MRgRT (19.2% vs. 35.3%, p=0.03) . The SCIMITAR study found no statistically significant difference at 1, 3 or 6 months post-SBRT in these domains. • MRgRT was associated with significantly lower odds of a clinically relevant deterioration in **bowel function** at 24months (OR 0.44 95% CI 0.21–0.94). The SCIMITAR study found CTgRT was associated with a significantly higher odds of a clinically relevant decline in **EPIC-26 bowel score** upon multivariable analysis. • Considering clinical relevant scores, the reported MRgRT was associated with better **Sexual Health Inventory for Men** scores (OR 0.37, 95% CI 0.15–0.91) but not **EPIC-26 sexual domain** (OR 0.68, 95% CI 0.27-1.69) at 24 months. The SCIMITAR study found no clinically relevant differences in EPIC-26 sexual domain scores at 1, 3 or 6 months post-SBRT. • MRgRT was associated with significantly lower rates of **acute Grade 2+ genitourinary (GU) toxicity** (OR 0.37, 95% CI 0.15–0.91) but not EPIC-26 sexual domain (OR 0.68, 95% CI 0.27-1.69) & **acute Grade 2+ gastrointestinal (GI) toxicity** (0.0% vs. 10.5%; p=0.003).	

	• MRgRT was associated with significantly lower cumulative late **Grade 2+ GU** (27.0% vs. 51.0%; p=0.004) & **GI toxicity** (1.4% vs. 9.5%; p=0.02) at 2 years, and with less deterioration in **urinary irritation** (p=0.03) and **bowel function** (p=0.05). Other studies with varying follow-ups found no statistically significant differences. **<u>Liver</u>** • **Local control** rates between the 2 groups were similar - 75.6% (CTgRT) & 78.9% (MRgRT) (p=0.96). • **Grade 3+ toxicity rate** was 4.7% overall; 4.4% (CTgRT) & 5.0% (MRgRT). **<u>Pancreas</u>** • No statistical difference in **overall survival** between the adaptive MRgRT and non-adaptive CTgRT (HR 1.2 [95% CI, 0.54 -2.67], p=0.66). • No statistically significant difference in **local progression free survival** between the adaptive MRgRT and non-adaptive CTgRT (HR 1.87 [95% CI, 0.73-4.78], p=0.19). • Overall, patients treated with adaptive MRgRT showed non-statistically significant lower rates of **late adverse events** compared with those treated with non-adaptive CTgRT. **<u>Lung</u>** • 1-year **overall survival** rates were 87.4 % for the MRgRT group and 87.0% for the control group (p=0.30). • No significant difference in the 1-year **progression free survival rate** was seen between MRgRT (80.2%) & CTgRT (80.4%). (p=0.50) • 1-year **local control** rate in the MRgRT & control groups were 92.1% and 75.4%, respectively. • No significant difference in the frequency of **any Grade toxicity, radiation pneumonitis**, **dyspnea,** or **rib fracture** between the MRgRT and CTgRT groups. No **Grade 3+** toxicities were observed in either group.	

Panel discussion:

The EAG considered the evidence for the outcomes listed, both in terms of the magnitude of the effect and the certainty of the evidence.

The MEIR-EAG agreed that the evidence of benefits with MRgRT primarly relate to reductions in toxicity compared with conventional IGRT methods. This was thought to be consistent with the improved visualisation achieved with MRgRT particularly of challenging anatomical areas. Additionally, while noting

that it is not yet clear whether MRgRT will lead to improvements in clinical effectiveness, risk of harm may be reduced, even if this is limited to reduction of radiation exposure to healthy tissue by removal of the CT imaging component.While acknowledging the absence of evidence for paediatric populations, the EAG noted that this potential to reduce exposure would be particularly relevant for children.

Given the very low certainty of the evidence, consideration was given to whether a judgement of 'don't know' was most appropriate. However, it was agreed that while the evidence was limited, the observed reductions in toxicity for prostate cancer patients were consistent with the incremental improvements observed with other changes to radiotherapy techniques that supported more precise targeting of the tumour site. A judgement of 'small' was therefore recorded.

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	• No safety concerns were identified. • Some MRgRT patients report claustrophobia, anxiety and difficulties with the noise, though most tolerate treatment well.	Additional time on the treatment bed.

Panel discussion:

The EAG considered the evidence for the outcomes listed, both in terms of the magnitude of the effect and the certainty of the evidence.

The included evidence with respect to undesirable effects was noted to be limited, with no identified safety concerns. As for other forms of radiotherapy, patient selection was noted to be important. Use of MRgRT may be contra-indicated in some patients with implantable medical devices or who require anaesthesia as the monitoring equipment may not be compatible with the magnet. Initial discussions with patients about MRgRT should address issues such as claustrophobia and the length of time on the treatment bed, as these may represent significant issues for some patients. Clinical experience was that MRgRT was generally well tolerated suggesting that harm/risks could be minimised with careful patient selection. A judgement of 'trivial' was recorded by the EAG for this criterion.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
● Very low ○ Low ○ Moderate ○ High ○ No included studies	• The certainty of the evidence for all outcomes is **Very Low.** Main reasons for downgrading: high risk of bias, wide confidence intervals (where reported), low number of events predominatly due to the availability of only one estimate from a single small study for some outcomes.	
The finding for this criterion was noted to be based on the standard GRADE methodology, so no panel discussion around this criterion was required. As the certainty of evidence for all outcomes is 'very low', the overall certainty of the evidence is 'very low'.		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		Additional resources are required to implement MRgRT (education and training of personnel and adjustment of the bunkers for MR) with significant upfront capital investment. Current quality assurance techniques are still limited, and there is a need to refer to up to date guidelines such as the ESTRO-ACROP guidelines.

Panel discussion:

Given the requirement for significant upfront capital investment and the additional resources required to implement MRgRT, cost was noted as an important consideration. It was noted that the benefits associated with moving towards an image-guided radiotherapy method with no associated imaging (radiation) dose are hard to quantify for the patient. There may be more linac downtime for repairs and maintenance compared to standard linacs which could pose additional challenges for centres with only one MRgRT system. There was reference to a previous discussion under the 'Undesirable Effects' criterion about the increased time required on the treatment bed.

A judgement of 'probably no important uncertainty or variability' was recorded by the EAG for this criterion.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations

○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ favours the intervention ○ Varies ○ Don't know	See summary of findings tables in the report - Tables 7-10 (above)	

Panel discussion:

While the evidence base was noted to be limited and of very low certainty – particularly for lung, liver, and upper abdominal cancers – and that further trials comparing adaptive MRgRT with adaptive cone-beam radiotherapy are desirable, the EAG agreed that the available data suggests that MRgRT results in less treatment-related toxicity compared with conventional IGRT, with no evidence of additional undesirable effects.

While MRgRT is associated with improved imaging, the EAG noted that there is a lack of data to support reductions in treatment margins; such reductions may require a review under the generic justification process.

A judgement of 'probably favours the intervention' was recorded by the EAG for this criterion.

Recommendation

On consideration of the balance between the benefits and harms, the EAG found that this favoured the use of MRgRT. The EAG recommended that MRgRT be generically justified for patients with cancer that require external beam radiotherapy.

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