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Adaptive radiotherapy with the combination of MR imaging and linac

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Methods

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Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered current, but may change as more evidence becomes available if an update of the document is commissioned.

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Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Name of the technology/procedure: **Adaptive radiotherapy with the combination of MR imaging and linac**

Target population

People with cancer which could benefit from conventional radiotherapy treatment.

Description of the procedure and technology

The development of Image Guided Radiotherapy (IGRT) is a major step forward in radiation oncology. Before the use of IGRT, large margins to correct for geometric uncertainty were required with important associate toxicity [Kerkmeijer, 2016]. Currently, linear accelerators (linacs), are equipped with on-board online cone beam computed tomography (CBCT) with excellent bone visibility. CBCT is routinely used before radiation treatment and its use is motivated by the need to reduce treatment geometric uncertainties such that the practitioner could confidently reduce the volume of normal tissue being irradiated [Jaffray, 2012], reducing treatment toxicity and increasing treatment effectiveness. A major challenge is incorporating the level of soft tissue contrast in radiation delivery [Chiu, 2018]. Indeed, most tumors may be difficult to identify when surrounded by soft tissue. In conventional radiotherapy workflow, magnetic resonance (MR) images are usually obtained as well as computed tomography (CT) images (fusion process) in the planning phase.

The MR-linac (also known as MR-guided radiotherapy, MR-gRT) is a hybrid linac combined with a MR imaging scanner. MR-guided radiotherapy systems provide high and versatile soft-tissue contrast imaging during irradiation. Its use could ensure a better targeting precision (particularly in parts of the body where CT provides insufficient contrast), a localization of smaller radiation treatment targets, and an accurate assessment of morphological changes in the tumour over the course of therapy. Therefore, MR-gRT could be used to identify imaging biomarkers that could indicate a treatment response to adaptively modify the treatment avoiding changing the original treatment planning [Pollard, 2017].

This hybrid system should allow clinicians to provide more precise targeted treatments and cause fewer side effects due to decreased dose to organs at risk (OAR) and surrounding healthy tissue. Among the expected additional benefits of the MR-linac compared with existing technologies is an increased dose escalation to the tumor, aiming to eradicate the tumour and improve treatment outcomes while having equal or decreased toxicity rates [Kerkmeijer, 2016].

Clinical importance and burden of disease

Cancer is the second leading cause of death globally and is responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer [WHO, https://www.who.int/news-room/fact-sheets/detail/cancer]. The global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. One in 5 men and one in 6 women worldwide develop cancer during their

lifetime, and one in 8 men and one in 11 women die from the disease. Worldwide, the total number of people who are alive within 5 years of a cancer diagnosis (5-year prevalence), is estimated to be 43.8 million [WHO, https://www.who.int/cancer/PRGlobocanFinal.pdf].

In 2010, 2,637,975 persons were estimated to live in Italy after a cancer diagnosis, 1.2 million men and 1.4 million women, or 4.6% of the Italian population. A quarter of male prevalent cases had prostate cancer (n = 305,044), while 42% of prevalent women had breast cancer (n = 604,841). More than 1.5 million people (2.7% of Italians) were alive for 5 or more years after diagnosis and 20% since ≥15 years. It is projected that, in 2020 in Italy, there will be 3.6 million prevalent cancer cases (+ 37% vs 2010). The largest 10-year increases are foreseen for prostate (+ 85%) and for thyroid cancers (+ 79%), and for long-term survivors diagnosed for 20 or more years (+ 45%). Among the population aged ≥75 years, 22% will have had a previous cancer diagnosis [Guzzinati, 2018]. Approximately 50% of all cancer patients receive radiation therapy during their course of illness [Delaney 2005; Begg 2011] either for cure or as a palliative treatment to relieve the patients from symptoms such as pain caused by the cancer [Delaney, 2005]. The majority of patients are treated with the intent to cure [Barnett, 2009].

Products, manufacturers, distributors and approval

We identified two MR-linac systems: Elekta Unity by Elekta Limited and MRidian Linac by ViewRay Inc.

Elekta Unity

Elekta Unity received the CE mark in June 2018 and the FDA 510(k) clearance in December 2018. In Italy, Elekta Unity is classified according to the *Classificazione Nazionale dei Dispositivi Medici (CND)* under the class "*Z11010101 - ACCELERATORI LINEARI AD ENERGIA SINGOLA*" and registered within the Italian National medical device database (BD/RDM) with the number 1751024.

According to the manufacturer, Elekta Unity fully integrates two very different technologies in a single platform: high-field (wide bore 1.5 Tesla) MR imaging system, based on the Philips Ingenia MR scanner and a next generation Elekta linear accelerator (6MV). These two technologies are controlled and powered by integrated software with responsive workflow solutions. Using the high-field MR imaging, tumors can be precisely located, their movement tracked, and treatment delivery adapted in real-time in response to changes in tumor position, shape, biology and the relationship to sensitive organs over time. There are two workflow strategies for online adaptation: Adapt to Position (position compensation) or Adapt to Shape (shape compensation). The choice can be made by the operator based on the anatomical changes that are seen on the daily MR image [Technical information provided by Elekta SpA].

MRidian Linac

MRidian Linac received the CE mark in September 2016 and the FDA clearance in February 2017. In Italy, MRidian Linac is classified according to the *Classificazione Nazionale dei Dispositivi Medici (CND)* under the class "*Z11010101 - ACCELERATORI LINEARI AD ENERGIA SINGOLA*" and registered within the Italian National medical device database (BD/RDM) with the number 1663572.

According to the Italian distributor, MRIdian is equipped with a linac (6MV) and a Multi Leaf Collimator. MRidian Linac is able to deliver dose during the MR acquisition in cine modality of 8 images per second with automatic gating. The MR scanner can be used for daily volumetric images and the system is

designed in order to perform Adaptive Radiotherapy, which means a daily modification of the treatment plan basis on the patient anatomical changes to the ongoing treatment. Furthermore, particular MR sequences allow functional images (diffusion weighted imaging, DWI) in order to analyze the biological response of patients. The linac is mounted on a rotating gantry ring in between two split magnets, in this way the radiation beam has no interference with the magnet system and is possible to achieve a Source Axis Distance of 90 cm, optimal for good penumbra. The magnetic field intensity is set at 0.345 T, not to warp the dose distribution, have fast imaging during cine modality, not over irradiate the air-tissue interfaces anatomic site (e.g. head and neck or lung) due to Electron Return Effect, not to overheat the patient due to continue exposure to magnetic field (low SAR values). The MR is able to get images in cine mode during dose delivery, while the system is tracking in real-time the tumour (or organ at risk) position: if the target goes out of the margin, the beams automatically turn off and then on as soon the target is in the expected position [Technical information provided by Radiustech Srl].

Product name [Manufacturer]	Distributor	CE Mark	BD/RDM	FDA
Elekta Unity [Elekta Limited (UK)]	Elekta S.p.A. (Elekta group Business Unit)	☑	☑	☑
MRidian Linac [ViewRay Inc.]	Radiustech Srl	☑	☑	☑

Roll out in Italy

According to the manufacturer, seven Elekta Unity systems are in clinical use around the world: USA, UK, Denmark, Germany and the Netherlands. The first patient was treated in May 2017 as part of a pre-CE mark clinical trial. From the first clinical treatment (August 2018) to date, 175 patients have been treated. In Italy, one Elekta Unity system is under installation at the hospital Negrar - OSP Sacro Cuore Don Calabria (Veneto).

According to the Italian distributor, two MRIdian Linac systems are installed in Italy, one at Gemelli Hospital in Rome (which is treating patients), and the other one is being installed at San Pietro Fatebenefratelli in Rome. All over the world, there are 27 MRIdian Linac systems currently treating patients, and other 10 systems are under installation.

☐ Pre-marketing	☐ On the market for 1-6 months	☐ On the market for 7-12 months
☑ On the market for more than 12 months	☐ Not identified	

Setting

The MR-linac is used in radiotherapy units and needs of a shield known as “bunker”.

☐ Home	☑ Hospital	☐ Outpatient
☐ Accident and Emergency	☐ Other:	

Comparators

The standard of care is represented by cone-beam CT linac (linac with image guidance by a cone beam CT imaging system).

Effectiveness and safety

According to the purpose of this document, no inclusion criteria were set. The identification of studies of probable interest was aimed at either summary studies, even descriptive but updated, and trials or other studies completed or in progress. We identified a narrative review by Pollard et al. [Pollard, 2017] describing the state of art of IGRT in 2017. After explaining the rationale for the combining of MR and RT images in real time, the authors review the history and evolution of the technique and the first tests of association of the three technologies in a single device.
We identified 8 studies (Table 1). All studies are non-comparative, and none have results available. One study (NCT04075305) is a large multi center prospective cohort due to report in 2024.

Potential benefits to patients

Potential benefits of this modality include radiation therapy effectiveness and safety by enabling greater beam accuracy than external beam radiation therapy (EBRT) guided by CT and other types of IGRT [ECRI, 2018]. This technique may allow dose escalation to the tumor target volume while sparing the tumor-neighboring susceptible organs at risk, which has the potential to reduce treatment toxicity and improve outcomes as local control rate, quality of life and survival.

☐ Mortality reduction or increased survival	☐ Reduction of the morbidity	☐ Improved quality of life (patient/users)
☐ Improved patient monitoring	☑ Other: Reduction of the toxicity	☐ Not identified

Cost of the technology/procedure

According to the manufacturers and distributors of the identified systems, list price ranges between

€ 9,000,000 and € 10,000,000, depending on the system configuration (VAT excluded).

☑ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☐ Increased costs due to the required investments
☐ New costs	☐Other: Reduction of costs linked to the reduction of re-intervention rate	☐ Not identified

Potential structural and organisational impact

Structural impact

The MR-linac layout includes the treatment room, shielded with barriers (known as “bunker”) for radiation and magnetic shielding for radio waves, a control room ad an equipment room. Moreover, the site should be provided by all implants for the operation and the safety of any conventional MR system as a quench venting system that provided to vent the superconductive magnet's cryogenic gases outside the building, or the oxygen monitor or heating, ventilation, and air conditioning (HVAC) system [Site Planning Guide 2017].

☑ Increase in requirement of instruments	☐ Always be used	☐ Can be used only under specific circumstances
☐ Decrease in requirement of instruments	☑ Other: Building a bunker for shielding radiation and magnetic shielding for radio waves	☐ Not identified

Organisational impact

Currently, MRI-guided systems are operated by teams of physicians, radiographers, and physicists because of the diverse and complex tasks required to deliver treatment.

☐ Increase in the number of procedures	☐ Re-organisation required	☑ Training required for users
☐ Reduction in the number of procedures	☐ Other:	☐ Not identified

Conclusions

MR-linac is a promising technology as it allows real-time visual acquisition of treatment effects. It also focuses treatment on cancerous target cells saving healthy tissue from damage. However, costs and logistics are higher than non-MRI guided treatment. Evidence on the clinical benefits of the technology is now required across a wide spectrum of cancers. A substantial lack of evidence of clinical benefit, as typical of the initial phase of development and use of new equipment, means that the potential theoretical

benefit of the technique is not quantifiable. Radiation exposure should be less than CT-based imaging systems.

Future prospects

We are not aware of any further potential developments of the technology.

Table 1: Summary of the registered studies on clinicaltrials.gov.

NCT number and Title	Intervention / Control	Study type and design and estimated enrolment participants	Completion	Link
NCT03621644 Stereotactic MRI-guided On-table Adaptive Radiation Therapy (SMART) for Locally Advanced Pancreatic Cancer	ViewRay MRIdian or MRIdian Linac	Non comparative cohort (N=133)	2023	https://clinicaltrials.gov/ct2/show/NCT03621644
NCT03658525 Prostate Radiotherapy Integrated With Simultaneous MRI (The PRISM Study) (PRISM)	Elekta Unity	Non comparative cohort (N=30). Feasibility study	2020	https://clinicaltrials.gov/ct2/show/NCT03658525
NCT03284619 First-In Man (FIM) Study MR-Linac (FIM MR-Linac)	MR Linac	Non comparative cohort (N=5)	2017 (no results)	https://clinicaltrials.gov/ct2/show/NCT03284619
NCT02683200 MRI-Guided Stereotactic Body Radiation Therapy in Treating Patients With Liver Metastases or Liver Cancer	Stereotactic Body Radiotherapy for Liver Metastases and Hepatocellular Carcinoma Utilizing an MRI-Guided Tri-60Co Teletherapy System	Non comparative cohort (N=20). Feasibility study	2018 (no results)	https://clinicaltrials.gov/ct2/show/NCT02683200
NCT04075305 The MOMENTUM Study: The Multiple Outcome Evaluation of Radiation Therapy Using the MR-Linac Study (MOMENTUM)	MRI-Linac on a basket of major cancers	Prospective cohort. (n=6000)	2024	https://clinicaltrials.gov/ct2/show/NCT04075305?term=MR-Linac&draw=1&rank=2
NCT03727698 Prospective Evaluation of Radiotherapy Using Magnetic Resonance Image Guided Treatment (PERMIT)	MRI-Linac on a basket of major cancers	Non comparative cohort (n=200)	2025	https://clinicaltrials.gov/ct2/show/NCT03727698?term=MR-Linac&draw=1&rank=4
NCT02973828 PRIMER: Development of Daily Online Magnetic Resonance Imaging for Magnetic Resonance Image Guided Radiotherapy	Procedural study partly with non patient volunteers	Case series (n=173)	2020	https://clinicaltrials.gov/ct2/show/NCT02973828?term=MR-Linac&draw=1&rank=7
NCT03972072 MRI - Guided Adaptive RadioTHerapy for Reducing XerostomiA in Head and Neck Cancer (MARTHA-trial) (MARTHA)	Interventional study on head and neck cases to assess dosage to avoid xerostomia. Other outcomes OS, QoL.	Case series (n=44)	2023	https://clinicaltrials.gov/ct2/show/NCT03972072?term=MR-Linac&draw=1&rank=8

Searches performed on 24th September 2019

Evidence searches

Searches of the databases (Pubmed, Embase, and Cochrane Library) were carried out on September 2019 using the following keywords to indicate:

MEDLINE

ELEKTA AND UNITY[Title] MR[Title] OR MRI[Title] OR “Magnetic Resonance” [Title] OR MR-Linac[Title] OR MR-guided[Title] OR “MR guided” [Title] OR “MR combin*“[Title]	AND	Guided[Title] OR Imaging[Title] OR Scanner[Title] OR Integrat*[Title] OR Simultaneous[Title] OR linear accelerator [Title] combin*[Title] OR “real time” [Title] OR during[Title]	AND	Radiotherapy[Title] Radiation Therapy[Title] Radio-therapy[Title] “Radio therapy” [Title]

EMBASE
“MRI GUIDED RADIOTHERAPY “OR
“MRI-Guided Radiation Therapy” OR
“Magnetic Resonance Image Guided Radiotherapy”
“MR combin* scanner and a radiotherapy machine”

The keyword “MRI Linac” was searched on ClinicalTrials.gov.

For evidence searches on MRIdian we asked the distributor for studies comparing the technology with a suitable alternative.

Bibliography

Agenas http://www.agenas.it/images/agenas/hta/Manuale_procedure_HTA.pdf

Barnett GC, West CML, Dunning AM et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. (2009) Nat. Rev. Cancer 9, 134–142. 10.1038/nrc2587

Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. (2011) Nat. Rev. Cancer 11, 239–253.

Chiu TD. MR-CBCT image-guided system for radiotherapy of orthotopic rat prostate tumors. PLoS One. 2018; 13(5): e0198065.

Delaney G, Jacob S, Featherstone C et al. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer. 2005 Sep 15;104(6):1129-37.

ECRI Institute. Elekta Unity (Elekta AB) for magnetic resonance Radiation Therapy. Product Brief. November 2018. (available on subscription)

Guzzinati S, Virdone S, De Angelis R et al. Characteristics of people living in Italy after a cancer diagnosis in 2010 and projections to 2020. BMC Cancer (2018) 18:169

Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. Nature Reviews Clinical Oncology volume 9, pages 688–699(2012)

Kerkmeijer LGW, Fuller CD, Verkooijen HM et al. The MRI-Linear Accelerator Consortium: Evidence-Based Clinical Introduction of an Innovation in Radiation Oncology Connecting Researchers, Methodology, Data Collection, Quality Assurance, and Technical Development. Front Oncol. 2016; 6: 215.

Site Planning Guide. MRIdian Linac by Viewray. 6 June 2017. (internet, last access 08.11.2019 https://viewray.com/wp-content/uploads/2018/06/L-0077-MRIDIAN-LINAC-SITE-PLANNING-GUIDE.pdf)

Pollard JM, Wen Z, Sadagopan R, Wang J, Ibbott GS. The future of image-guided radiotherapy will be MR guided. Br J Radiol 2017; 90: 20160667.

Glossary

BD/RDM: Italian Medical device database (http://www.salute.gov.it/dispositivi/paginainternasf.jsp?id=499&menu=repertorio).

CND: Italian medical devices classification (Classificazione Nazionale dei Dispositivi Medici)

FDA: Food and Drug Administration.

HVAC: Heating Ventilation Air Conditioning

MV: Mega Volts

SAR: Specific Absorption Rate (Tasso specifico di assorbimento)