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**MRI-Guided Pelvic Radiotherapy: A Primer for Radiologists**


## Abstract

Radiation therapy (RT) is a core pillar of oncologic treatment and half of all patients with cancer receive RT, as curative or palliative treatment. Recent integration of magnetic resonance imaging (MRI) into the RT workflow, led to the advent of MRI-guided RT (MRIgRT). Using MRI as the imaging technique rather than computed tomography has clear advantages for guiding RT to pelvic tumours: superior soft-tissue contrast, improved organ motion visualization, and the potential ability to image tumor phenotypic characteristics to identify the most aggressive or treatment resistant areas which can be targeted with a more focal higher RT dose. Radiologists should be familiar with the potential uses of MRI in planning pelvic RT, the varied RT techniques used such as brachytherapy and external beam radiotherapy and the impact of MRIgRT on treatment paradigms.

The current clinical experience and evidence base for MRIgRT in prostate, cervical and bladder cancer will be discussed, and examples of treated cases will be illustrated. The benefits of MRIgRT such as real-time online adaptation of RT (during treatment) and inter-fraction and/or intra-fraction adaptation to organ motion will be highlighted along with how MRIgRT can improve toxicity and oncologic outcomes. MRIgRT is particularly beneficial for treating mobile pelvic structures and real-time adaptive RT treatment for tumors can be achieved using novel MRI-guided linear accelerator (MRI-LINAC/ MRL) systems in order to spare organs at risk. Future opportunities for the development of biologically driven adapted radiotherapy (ART) using functional MRI sequences and radiogenomic approaches will be outlined.


## Summary Statement

Magnetic resonance imaging guided radiation therapy (MRIgRT) for treating pelvic tumours offers superior soft-tissue contrast, improved organ motion visualization, and the potential

ability to image tumor phenotypic characteristics with real-time online adaptation of treatment plans to potentially improve toxicity and oncologic outcomes.

**Teaching points [marked in main text]**

- Currently CT is used throughout the RT pathway however using MRI as the imaging modality has clear advantages: Superior soft-tissue contrast allows for more accurate delineation of the tumor target and organs at risk, improved organ motion visualization, and the ability to image tumor phenotype characteristics using quantitative multi-parametric MRI (mpMRI) sequences
- The availability of hybrid systems incorporating MRI with a linear accelerator (MR-LINAC/ MRL) offers the opportunity for real-time MRI at each RT fraction, allowing for modification of patient position and treatment plan while the patient is on the treatment table
- Each RT fraction starts with acquisition of an online MRI which is used to perform RT plan adaptation through two different workflows, either adapt to position (ATP) or adapt to shape (ATS)
- The ATS workflow is used to treat structures that are mobile and may change shape e.g. bladder and cervix
- The ATP approach is used to treat prostate tumours where there is little day to day variation in size or shape

## Introduction

Radiation therapy (RT) is a core pillar of oncologic treatment. Approximately half of all the patients with cancer will receive RT, as curative or palliative treatment [1]. Quality of RT is critically affected by imaging, during the planning (pre-treatment) as well as delivery (treatment) phases. Transition from traditional 2-dimensional X-ray to three-dimensional computed tomography (CT) based RT planning laid the foundation of modern conformal RT. Improved visualisation of target in relation to normal tissues led to higher conformity of RT dose distribution to the target volume, with decreased normal tissue irradiation and better clinical outcomes [2,3]. It facilitated evolution of advanced techniques such as image-guided RT (use of imaging during treatment to direct radiation beam), and adaptive RT (ability to change a treatment plan and ensure accurate RT delivery by correcting for positional changes in the target following imaging taken at the time of RT). Advancements in imaging also allowed for development of hypofractionation RT schedules, which rely on accurately targeting the tumor to deliver high dose within fewer fractions. Especially for pelvic malignancies, considerable improvement in early and late genitourinary (GU) and gastrointestinal (GI) toxicities has been observed with use of conformal RT techniques [4,5]. However, the morbidity of pelvic radiotherapy still remains a cause of concern, with up to 10% experiencing moderate or severe side effects over five years post treatment[6].

Recent technologic developments, with the integration of magnetic resonance imaging (MRI) into the RT workflow, led to the advent of MRI-guided RT (MRIgRT). **TP[**Currently CT is used throughout the RT pathway however using MRI as the imaging modality has clear advantages: Superior soft-tissue contrast allows for more accurate delineation of the tumor target and organs at risk, improved organ motion visualization, and the ability to image tumor phenotype characteristics using quantitative multi-parametric MRI (mpMRI) sequences**]** [7].

Clinical implementation of MRIgRT includes use of offline MRI (outside the RT treatment session) for planning, or real-time online adaptation of RT (during treatment). Using online

MRIgRT allows for inter-fraction and/or intra-fraction adaptation to organ motion (particularly bladder, cervix and rectum in the pelvis, which are mobile structures) and real-time adaptive treatment to tumors. This is achieved using a MRI-guided linear accelerator (MRI-LINAC or MRL) system, which combines MRI with a linear accelerator (LINAC) for irradiation.

**Key concepts in radiotherapy planning and delivery**

The entire tumoricidal dose of radiation is divided into smaller 'fractions', to balance the tumor cell kill against adverse effects on surrounding normal tissues. Radiotherapy treatment can be delivered in two ways: External beam RT (EBRT, where the radiation source is located outside the body), and brachytherapy (BT, where a sealed radioactive source is placed inside the body). EBRT is delivered using a LINAC machine, which generates a therapeutic X-ray beam and directs it to the desired target. For EBRT planning, the first step is 'simulation' – the patient is positioned as for treatment and the relevant site is imaged, usually in the form of CT scan. These images are then transferred to a treatment planning system, and the visible tumour is drawn or delineated as 'gross tumour volume (GTV)' using all the available clinical radiological investigations. Depending on the tumour site and clinical setting, a margin around the GTV is given to account for subclinical micrometastatic disease, and labelled as 'clinical target volume (CTV)'. Finally, an additional margin around the CTV is given to generate 'planning target volume (PTV)', to account for uncertainties in daily positioning and variations in target and normal organ positions over the entire course of RT. Depending on the tumour site, CTV may need to include an additional 'internal target volume (ITV)', to allow for internal physiological motion affecting daily position of CTV (for example, variable bladder filling affecting uterine position in case of cancer of cervix). Examples of MRIgRT prostate (**Figure 1**), bladder (**Figure 2**) and cervical (**Figure 3**) RT plans are shown.

In contrast, brachytherapy involves placement of radioactive source(s) directly inside the tumour (or target organ). Due to the physical properties of the radioactive sources (sharp drop off in dose over millimetres) and better certainty in dose delivery, it provides a highly

conformal method to deliver high radiation dose to the tumour. Sparing of surrounding normal organs in brachytherapy is ensured by choosing an isotope which generates high radiation energy with limited tissue penetration [8]. These sources can be placed either permanently or temporarily, using appropriate applicators depending on the tumor site. Placement of applicators is guided by x-ray, ultrasound, CT scan, or MRI. Pelvic tumours are relatively accessible for brachytherapy, and this RT modality plays a major role in curative-intent treatment of cancers of cervix, prostate, and endometrium.

Improving the efficacy of RT entails maximising the dose to target volumes while minimising the amount of normal tissue irradiated. This is directly affected by the imaging technique used during RT planning and treatment. Enhanced visibility of tumour by functional imaging methods such as MRI and PET aids in more accurate delineation of GTV. Incorporation of imaging on modern LINACs allows verification of target volume before beam delivery, resulting in more precise irradiation and smaller PTV margins. Consequent sparing of normal tissues leads to reduction in RT-related morbidity[9]. Another advantage with improved reliability of tumour targeting is the use of hypofractionated RT, whereby larger dose per fraction can be safely delivered using fewer fractions. Such treatment delivered to a highly conformal target volume with a steep dose gradient in a small number of fractions, is referred to as Stereotactic Ablative Body Radiotherapy (SABR) or Stereotactic Body Radiotherapy (SBRT).

**Role of MRI in pelvic radiotherapy**

**A) Treatment planning**

Traditionally RT has been delivered using CT-guidance given the rapid image acquisition, inherent electron density information used for calculating the RT dose, no spatial distortion within the effective field-of-view (FOV), and a digitally reconstructed radiograph used for position verification.

Incorporation of MRI in radiotherapy planning evolved from side by side cognitive fusion, to co-registration of diagnostic MRI sequences with radiotherapy simulation CT images within

the radiotherapy treatment planning system, to acquiring only MRI scans specifically for RT planning without the need for CT. These MR sequences can then be converted into a synthetic CT dataset that is used for the Hounsfield unit calculations required to assign tissue densities for radiotherapy treatment planning. Using MRI improves the quality of target and normal tissue delineation in the pelvis. Major differences between diagnostic and RT planning MRI are highlighted in **Table 1**.

**B) Treatment delivery:**

**TP[**The availability of hybrid systems incorporating MRI with a linear accelerator (MR-LINAC/ MRL) (**Figure 4**) offers the opportunity for real-time MRI at each RT fraction, allowing for modification of patient position and treatment plan while the patient is on the treatment table**]**. MRL enables high quality imaging before treatment delivery, and guides adaptation accounting for daily anatomic changes that could affect planned dose distribution. Two commercially available operational systems currently exist, the Elekta Unity® (Elekta, Stockholm, Sweden) and ViewRay MRIdian® (ViewRay, Oakwood Village, Ohio)[10]. The Elekta system is composed of a 7 MV LINAC mounted circumferentially around a modified 1.5T MRI system. The ViewRay MRIdian combines a 6MV LINAC with an onboard MRI that is lower in field-strength (0.35 tesla) which results in a lower signal-to-noise ratio and lower electron return effect [11]. The MRIdian operates at a higher dose rate (550-600 cGy/ minute compared to 350 cGy/ minute on the Elekta). Both systems allow for a fully integrated on-table adaptive workflow however the MRIdian is capable of real-time tracking. Treatment delivery is automatically breath-hold gated so RT is only delivered once patient positioning is optimal. This removes the need for an ITV and reduces the PTV margin and volume of normal tissue irradiated. A cine MR function on the MRIdian enables automated beam gating based on live anatomy. The benefits of both MRL systems are expectedly higher in treating pelvic tumours such as prostate, cervix, and bladder, which are affected by significant inter and/or intrafraction motion of bladder and rectum. An exampleMRL workflow is shown in **Figure 5**.

**Adapt to Shape vs Adapt to Position**

**TP[**Each RT fraction starts with acquisition of an online MRI which is used to perform RT plan adaptation through two different workflows, either adapt to position (ATP) or adapt to shape (ATS)**]** [12]. The ATS workflow is used for tumours that deform from day to day. It is more time intensive as the online MRI must be re-contoured and the RT plan adapted often using a *deformable registration* approach. This may impact the RT dose calculations which are based on Hounsfield units calculated from the synthetic CT and re-planning is required. **TP[**The ATS workflow is used to treat structures that are mobile and may change shape e.g. bladder and cervix**]**. **Figure 6** shows the bladder shape changes between RT fractions due to changes in bladder volume which requires an ATS approach. For cervical cancers treated with MRIgRT on an MRL, the images acquired at each fraction are matched using the posterior vaginal wall as a consistent, stable and well-defined position. Other structures can move with bladder filling which also results in changes in the position of the cervical cancer (**Figure 7**). Using a consistent anatomical landmark reduces intra- and inter-observer variability in image registration.

The ATP approach is quicker and does not require daily delineation as only the tumour position is updated using the online-treatment MRI. *Rigid registration* can be performed on the entire image sets, or using a smaller region of interest (clipbox). **TP[**The ATP approach is used to treat prostate tumours where there is little day to day variation in size or shape**]**.

**MRIgRT for prostate cancer**

MRIgRT for prostate cancer provides excellent visualisation of the prostate gland and the tumour extent, resulting in more precise delineation compared to when using CT for planning and also allowing margin reduction resulting in less rectal irradiation (**Figure 8**). This is particularly important with increasing popularity of SABR for prostate cancer [13,14]. Visualising normal organs is also superior [14]. MRIgRT provides real-time prostate imaging therefore invasive fiducial markers are not required [14]. Daily plan re-optimization allows

compensation for interfraction prostate motion caused by rectal and bladder filling [14,15]. Accurate assessment of rectal and bladder tissue within the irradiation field also helps predict toxicity and optimise treatment accordingly. In addition, utilizing MRL for neurovascular bundle sparing RT may help to preserve erectile function [14,16]. **Figure 9** shows changes seen in the prostate and rectum at each RT fraction following MRIgRT. Published studies of MRIgRT for treating prostate cancers report a low incidence of acute GI and GU toxicity. The first prospective phase II study of prostate MRIgRT by Bruynzeel et al. found grade ≥ 2 acute GI and GU toxicity rates (both clinician- and patient-reported outcome measurements) of 5% and 24% [17]. This low incidence of acute GI toxicity, despite including the seminal vesicles in 96% of patients, was likely due to the smaller CTV to PTV margin made feasible by the superior tissue contrast in MRIgRT, along with online CTV monitoring and daily plan reoptimization.

Despite the routine plan reoptimization with selective relative sparing of the urethra, incidence of acute GU toxicity was still 24% but this was still lower than other trials that involved similar hypofractionation RT schedules using CTgRT rather than MRIgRT and reported GU toxicities of 46-61% [18,19]. At 1-year follow-up, the majority of these described GI and GU symptoms had resolved with no grade ≥ 3 toxicity observed [20]. A further prospective observational study by Alongi et al. found lower grade 2 or higher acute GI and GU toxicity rates of 4% and 12%, respectively with no grade ≥ 3 toxicity [21].

The MIRAGE trial, the first phase 3 randomized clinical trial comparing MRIgRT against CT-guided RT for prostate cancer, found that MRIgRT was superior to CT-guided RT in terms of acute toxicity and patient-reported quality of life [9]. With MRIgRT, incidence of acute grade 2+ urinary adverse effects was 24% vs 43% for standard CT-guided RT, while acute grade 2+ gastrointestinal toxicity was 0% vs 10.5%. This benefit was also reflected in the lower proportion of patients reporting clinically significant worsening of bowel symptoms (25% vs 50%) as well as urinary symptoms (7% vs 19%). Lower toxicity in the MRIgRT arm was attributed to the reduced PTV margin of 2mm with MRI as compared to 4mm in the CT arm, achievable due to more accurate intrafraction monitoring with MRI. While the relative impact

of smaller margins with regard to the enabling technology may be argued, it has also raised concerns of possible under coverage of the target. Longer follow-up data for these trials is needed to evaluate long-term cancer control and toxicity outcomes.

**MRIgRT for bladder cancer**

MRI is increasingly being integrated into management of bladder cancer, from staging evaluation at diagnosis to treatment planning[22]. Although transurethral resection of bladder tumor (TURBT) is the method of choice for bladder cancer diagnosis, almost 50% of cases show clinical–pathologic stage discrepancy [23]. MRI including T2-weighted MRI, diffusion-weighted imaging and dynamic contrast enhancement offers a high accuracy in the assessment of muscle involvement [24]. Created in 2018, Vesical Imaging-Reporting and Data System (VI-RADS) (**Table 2**), is a five-point scoring system based on T2w MRI, diffusion weighted imaging (MRI) and dynamic contrast enhanced (DCE) MRI findings to detect the likelihood of clinically significant cancer and the presence detrusor muscle invasion[25]. Scores 1 and 2 are assigned to tumors unlikely to invade the muscularis propria, scores 4 and 5 are assigned to tumors likely to invade the detrusor muscle layer. Score 3 represents the equivocal category. Studies have validated the VI-RADS score with high sensitivity and specificity values of 87.1% and 96.5% for detecting detrusor muscle invasion in bladder cancer [26].

For muscle-invasive bladder cancer, trimodality treatment consisting of TURBT followed by chemoradiotherapy offers a bladder-sparing alternative achieving overall survival rates similar to the conventional standard of radical cystectomy [27]. However, RT is challenging due to poor tumor visualization and the mobile nature of the bladder. Currently, this is tackled by employing various adaptive techniques, which utilise anisotropic margins (Utilising larger margins where most motion occurs e.g. superior and anterior direction instead of the inferior direction vs isotropic margin expansion where a symmetrical margin is used in all directions), patient-specific RT plan libraries, or daily adaptation to accurately cover the

bladder and spare surrounding bowel[28]. All of these techniques being imaging-dependent, MRIgRT has much potential to optimise bladder radiotherapy. The first clinical experience by Hunt et al. demonstrated the feasibility of MRgRT for bladder cancer and acceptable patient tolerance [29]. MRI-guided online adaptive re-optimisation using anisotropic margins achieved a significant reduction of average PTV by median 304 cc when compared to daily plan selection from CT-based plan library [30]. Another important application is for partial bladder irradiation, which has shown tumor control comparable to whole bladder irradiation [31]. The MRL can assess the tumor movement related to the bladder filling and determine the adequate intrafraction margins for partial bladder RT [32]. It also offers the potential for focused dose escalation to the tumor beyond that limited by the whole bladder tolerance [33]. Recently reported results from the RAIDER multi-centre clinical trial showed that focal escalation was feasible to partial bladder without resulting in increased toxicity[34]. The utility of MRIgRT can also be realised in safer implementation of hypofractionated bladder radiotherapy, from purely palliative setting towards more curative intent[35].

**MRIgRT for cervical cancer**

Standard of care for locally advanced cervical cancer (LACC) remains RT combined with chemotherapy followed by brachytherapy [36,37]. **Figure 10** and **Figure 11** show examples of cases of cervical cancer treated with BT and post-treatment imaging changes. While BT has conventionally been planned with X-ray based 2D technique, the potential of MRI guided BT (MRIgBT) for optimising target delineation was recognised quite early[36].

Remission rates following this treatment combination are 95% for patients Stage ≥II disease [38]. For patients with large tumors (> 5cm), local control (LC) is significantly correlated with the tumor dose with local recurrence (LR) rates ranging from 4% to 20% for high-risk clinical target volume doses of >87Gy vs <87Gy respectively [38]. The reported late rectal- and bladder toxicity rate was 8% and 16% respectively and both were related to the dose delivered[39].

Guidelines from GEC-ESTRO recognised the pivotal role of MRI in successful transition of cervix brachytherapy from 2D to 3D era[37]. Two MRI scans are recommended for accurate identification of tumour extent – first at diagnosis, prior to initiating RT, and second after EBRT, prior to BT boost. Composite information is used to escalate BT dose to residual gross tumour after EBRT, while optimising dose to pre-RT volume which has responded to EBRT. The advantage of MRIgBT over 2D x-ray-based BT for treating LACC was demonstrated by Lindegaard et al. in a single centre cohort study where an improvement in OS of 15% was observed following introduction of MRIgBT along with a relative reduction of moderate and severe morbidity by about 50% [40]. A recent prospective multicentre cohort study (EMBRACE-I) with 1341 patients has shown excellent results of MRIgBT for LACC with 5-year LC and OS rates of 92% and 74%, respectively [6].

BT provides the best outcomes in LACC but if not technically feasible or patient unfit for an invasive procedure then with higher doses delivered more precisely and non-invasively, MRI-guided SABR can help substitute BT boost treatments.[41]. Although MRIgBT for LACC has been successfully implemented in clinical practice, cone-beam CT is still routinely used for EBRT. The EBRT-CTV includes the visible tumour extent (GTV) along with the entire cervix and uterus. Variability in uterine anteflexion and anteversion make this CTV subject to significant inter- and intrafraction changes [42]. Bladder filling impacts the uterine position, while rectal filling affects the cervical position. Moreover, a significant reduction of tumor volume of up to 60-80% during the course of treatment has been observed affecting the GTV [43,44]. Adaptive MRI-guided EBRT with its superior soft-tissue contrast and daily-reoptimization is hence a promising approach for inter- and intrafractional motion mitigation [45]. Moreover, high accuracy of MRI in assessing uterus involvement can help exclude the uninvolved uterus. This would reduce the dose to bowel loops superior to uterus, and consequently minimise radiation-induced toxicity [45–47]. Kozak et al. showed a low rate of local failure and a significantly reduced radiation dose to bowel in patients with <90% vs.

≥90% of the uterus included in PTV [48]. Use of daily adaptation using MRIgRT (better target visualisation) potentially leads to a reduction in OAR dose, by facilitating improved accuracy of treatment delivery to the tumor and enabling margin reduction [46].

Another important role of MRIgRT is emerging in patients with local recurrence after primary radical treatment for gynaecological cancers, especially for reirradiation[49]. Future potential also includes functional MRI, which may enable higher doses of radiation to be delivered to the hypoxic tumor regions, which are more radio-resistant[50]. Clinical experience of MRIgRT for LACC is emerging, and future clinical trials are needed to evaluate oncological and toxicity outcomes.

**Limitations of MRIgRT**

Limitations of MRIgRT have to be recognised and addressed in order to successfully implement this technique in clinical practice. One of the main concerns regarding MRL is the high cost and therefore limited access. MRL capital are 3-4 times that of a conventional LINAC and also requires additional MRI competent staff members [51]. MRIgRT is time intensive, with the average treatment length being 45 minutes compared to 15 minutes for conventional LINAC [15]. The other logistic problem is providing backup for MRI-only pathway in case of machine downtime. This restricts current availability of MRL to larger referral centres. Moreover, some patients may have implanted MR incompatible devices or suffer from claustrophobia, severe anxiety or pain [46].

From the radiotherapy planning perspective, electron density information from a CT scan is required for accurate dose calculation. In MRIgRT, a synthetic CT is generated using MRI images. However, the fidelity of this solution is not well established for all clinical scenarios, and there are few options with full regulatory approval. MR images may also be affected by geometric distortion, especially in the case of the large field of view MRI scans, which can decrease the accuracy of RT dose delivery. For larger treatment areas, the maximum size of 22-24 cm will preclude the MRIgRT application for pelvic cancers where both the primary

and pelvic lymph nodes need to be treated. Although MRIgRT may allow a more precise tumor-focused radiation delivery, the PTV reduction may result in missing of an area potentially including microscopic disease and therefore lead to unintended under-treatment[7]. One additional issue that affects all RT delivery is respiratory motion artefact and MRIgRT is no different. However, MRI-compatible abdominal belt devices can be used during treatment on MRL systems to reduce the cranial-caudal movement of organs (**Figure 12**) during respiration allowing for treatment adaptation.

**Biological image-guided adaptive radiotherapy**

Functional MR highlighting different tissue characteristics provides a means of non-invasively probing the microenvironment of primary pelvic tumours and surrounding OARs. A range of functional MR techniques can be used to investigate tissue characteristics such as cellular microstructure, perfusion, and oxygenation status, and these techniques can yield quantitative imaging biomarkers[52]. Such biomarkers may be sensitive to early treatment-induced changes in tumours and OARs, providing a quantitative assessment of treatment response. In addition, spatial and temporal heterogeneity in such biomarkers may be used to identify and track aggressive tumour sub-regions, which could be targeted with an increased dose[53]. Quantitative MR may therefore inform treatment planning, an example of biological image-guided adaptive radiotherapy (BIGART)[54]. This section focuses on experimental applications of quantitative MR in MRIgRT and how they could be used to improve treatment outcomes in the future.

Diffusion weighted MRI (DW-MRI) is a functional imaging technique where image contrast depends on the magnitude and direction of water molecules' Brownian motion in tissue. As this motion is influenced by cellular structures such as cell membranes, the technique provides a non-invasive probe of tissue microstructure. DW-MRI is often interpreted in terms of cell density, for example with higher cellular density in tumors leading to hindered/restricted diffusion compared with normal, less cellular, tissue. Such

hindered/restricted diffusion results in higher signal intensity on DW images, corresponding to a lower apparent diffusion coefficient (ADC), a quantitative value derived from DW images. Escalating dose to the tumor regions of highest cellularity in theory could improve local control rates, providing a rationale for using DW-MRI to guide treatment planning[55]. Early increases in tumour ADC values following prostate RT has been associated with good treatment response, highlighting the potential value of DW-MRI in monitoring RT response [56].

Intravoxel incoherent motion (IVIM) is a DW-MRI technique which provides information about tissue perfusion as well as diffusion[57]. By modelling diffusion data with a perfusion component, a surrogate for tissue perfusion can be calculated (perfusion fraction or *f*). Early increases in *f* are associated with good response [58], and recent work provides evidence linking IVIM parameters to tumour hypoxia[59]. **Figure 13-15** show examples of where quantitative imaging has been implemented on a MRL for prostate (**Figure 13**) and cervical cases (**Figure 14 and 15**). This offers the potential for BIGART where hypoxic areas or regions of higher cellularity can be treated with higher radiation doses to improve local tumor control. It also allows for such biological characteristics to also be monitored longitudinally throughout treatment with early identification of non-responders who may benefit from a change in treatment approach.

Dynamic contrast–enhanced (DCE) MRI involves the acquisition of T1-weighted (T1W) fast spoiled-gradient echo images before, during, and after intravenous injection of a low molecular-weight gadolinium chelate. In tumours, contrast enhancement followed by wash-out tends to occur more rapidly than in normal tissue, reflecting the higher perfusion of the tumor. Pharmacokinetic analysis of DCE MRI data models the transfer of the contrast agent between the vascular space and the extravascular extracellular space [60]. It generates parameters related to perfusion including the volume transfer constant, $K^{trans}$, and the rate constant, $k_{ep}$, which are associated with tumor response to RT for pelvic tumors[61–63].

Tumour hypoxia, a low oxygen environment, is associated with RT resistance and metastatic disease [64–66]. Identifying tumour hypoxia may help with patient selection for radiation boosting however current methods of assessing hypoxia are invasive, requiring biopsies to identify gene-based hypoxia biomarkers, or oxygen electrodes, and are further hindered by sampling errors due to multi-focal tumours and intra-tumoral heterogeneity[67]. MRI offers a potential non-invasive method of assessing hypoxia that allows the whole tumor to be measured and assessed over time, i.e. before, during and following treatment to monitor response. One potential imaging technique for hypoxia is intrinsic susceptibility weighted or blood oxygenation level dependent MRI (BOLD; $R2^*$ biomarker), which exploits the difference in magnetic susceptibility of oxyhaemoglobin and deoxyhaemoglobin to generate contrast and identify regions of hypoxia [68,69]. Most BOLD imaging hypoxia studies utilise an experimental design where hyperoxic gas (typically 100% $O_2$) breathing is used to augment the signal to detect hypoxic subregions within a tumour[70]. Despite initial promise, BOLD imaging has failed to translate into clinical pelvic imaging since its inception 30 years ago. This is largely due to image artefacts arising from air/tissue interfaces in the pelvis and lack of specificity because R2* is not solely related to hypoxia. A newer technique popularised in the last decade is tissue oxygenation level dependent (TOLD MRI). Following a hyperoxic gas challenge, the change in longitudinal relaxation rate ($\Delta R1$) has a direct relationship with tissue oxygenation[71]. TOLD-MRI, also known as oxygen-enhanced MRI, has recently been successfully translated onto the MR-LINAC in head and neck patients[72]. The same group of researchers are also working towards applying the OE-MRI technique (**Figure 15**) to uterine and cervical cancer tumours (Clinical Trials. Gov ID: NCT05029258)

Recently, a new area of imaging-based cancer research, termed radiogenomics or imaging genomics, has emerged[73]. It is based on radiomics, a quantitative method of imaging analysis using data-characterisation algorithms to derive imaging biomarkers[74]. Imaging-based radiogenomics offers promise in bridging the gap between medical imaging and

histopathological or molecular/gene signatures, by focusing on the relationship between imaging features and genomic characteristics of the tumor [75]. Incorporating imaging radiogenomics into MRI-guided focal boosting of hypoxic tumours may further improve clinical outcomes given that hypoxic cells are more resistant to radiation than normoxic ones[64–66].

**Conclusion**

MRIgRT is a major advance in RT treatment for pelvic tumours, offering superior visualisation of pelvic soft tissue and overcoming the main limitations of CT guidance whilst improving interfraction and intrafraction adaptation to improve the accuracy of RT delivery. Integrating functional MRI sequences and radiogenomic approaches to RT delivery allows for biologically driven adapted RT which has the potential to improve local control. Using these quantitative imaging capabilities on the MRL will possibly help in early response assessment and treatment adaptation. A collaborative approach is required amongst radiation oncologists, radiologists, medical physicists, data scientists, engineers, and biologists in order to translate these developments to clinical RT on a larger scale. The clinical benefits of MRIgRT warrant further study and validation.

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**Tables**

**Table 1**: Differences between MRI sequence requirements for diagnostic radiology imaging vs radiotherapy planning imaging.

| | **Radiology** | **Radiotherapy Planning** |
|---|---|---|
| **Purpose** | Detection/ Characterisation/ Staging | Target and Organ at Risk (OAR) contours |
| **Field of view (FOV)** | Can use reduced FOV | Need bony contours and bone anatomy in FOV |
| **Slice thickness/ gaps** | 3-5 mm slices with gaps of 0-2 mm | Comparable to CT planning scan e.g. 2 mm slices with no gaps/ isotropic 3D ~ 1 mm |
| **Geometric distortion** | < 3 mm | < 2 mm over Volume of Interest, 3D sequences preferred |
| **Uniformity** | Tolerated | Important for intensity based image registration |
| **Bandwidth (readout)** | Trade off – fat/ water shift and signal to noise (SNR) ratio | High bandwidth to minimise fat/ water shift and susceptibility effects |
| **Imaging Plane** | Planes dependent on organ of interest and required information | Generally transverse (to align with CT) |

**Table 2**: Summary table of Vesical Imaging-Reporting and Data System (VI-RADS) scoring. The dominant sequences for VI-RADS risk estimates are DWI (first) and DCE (second; especially if the DWI is suboptimal). The T2 sequence is helpful as a first pass guide, especially for categories 1–3. CE = contrast-enhanced category; DCE = dynamic contrast enhancement; DW = diffusion-weighted category; DWI = diffusion-weighted imaging; MP = muscularis propria; SC = structural category; SI = signal intensity; T2w = T2 weighted.

| VI-RADS Score | Structural Category (T2w MRI) | Contrast-Enhanced Category (DCE-MRI) | Diffusion-weighted Category (DWI) |
|---|---|---|---|
| 1 | Uninterrupted low SI line representing the integrity of MP (lesion <1 cm; exophytic tumor with or without stalk and/or thickened inner layer) | No early enhancement of the MP (lesions corresponding to SC 1 findings) | MP with intermediate continuous SI on DWI (lesion <1 cm, hyperintense on DWI and hypointense on ADC, with or without stalk and/or low SI thickened inner layer on DWI) |
| 2 | Uninterrupted low SI line representing the integrity of MP (lesion >1 cm; exophytic tumor with stalk and/or high SI thickened inner layer, when present, or sessile/broad-based tumor with high SI thickened inner layer, when present) | No early enhancement of MP with early enhancement of inner layer (lesions corresponding to SC 2 findings) | MP with continuous intermediate SI on DWI (lesion >1 cm, hyperintense on DWI and hypointense on ADC, with low SI stalk and/or low SI thickened inner layer on DWI, or broad-based/sessile tumor with low/intermediate SI thickened inner layer on DWI) |
| 3 | Lack of category 2 findings with associated presence of an exophytic tumor without stalk, or sessile/broad-based tumor without high SI thickened inner layer but with no clear disruption of low SI MP | Lack of category 2 findings (lesions corresponding to SC category 3 findings) but with no clear disruption of low SI MP | Lack of category 2 findings (lesions corresponding to T2 category 3 findings) but with no clear disruption of low SI MP. |
| 4 | Interruption of low SI line suggesting extension of the intermediate SI tumor tissue to MP | Tumor early enhancement extends focally to MP | High SI tumor on DWI and low SI tumor on ADC extending focally to MP. |
| 5 | Extension of intermediate SI tumor to extravesical fat, representing the invasion of the entire bladder wall and extravesical tissues | Tumor early enhancement extends to the entire bladder wall and to extravesical fat | High SI tumor on DWI and low SI tumor on ADC extending to the entire bladder wall and extravesical fat. |