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MRI for prostate and gynecological brachytherapy is here to stay

Firas Mourtada, Ph.D.¹; Daniel G. Petereit, M.D.²; Sushil Beriwall, M.D.³; Joann I. Prisciandaro, Ph.D.⁴

¹Helen F. Graham Cancer Center & Research Institute, Christiana Care Health System, Newark, DE, USA

²Rapid City Regional Cancer Care Institute, Rapid City, SD, USA

³UPMC Hillman Cancer Center, Pittsburgh, PA, USA

⁴Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA

Key points

In this article, we describe the status of MRI utilization¹ for both gynecological and prostate cancer radiotherapy treatments using HDR brachytherapy in the United States. The current clinical evidence has demonstrated MRI should be incorporated in the standard of care for all gynecological and prostate brachytherapy patients. However, unlike Europe, in the U.S. we continue to look for ways to adapt MRI within our constraints (initial costs and reimbursement), and to provide our patients the best MRI based approach to manage their disease effectively and safely. We share what we have learned from our collective experiences.

Introduction

Brachytherapy has a long history in cancer therapy, with its initial applications performed shortly after the discovery and isolation of radium from pitchblende

by Pierre and Marie Curie in 1898. Two-dimensional radiographic films were used for treatment planning prior to the inception of 3D volumetric imaging in the 1970s. In particular, computed tomography (CT) and transrectal ultrasound (TRUS) were first implemented for several disease sites. More recently, magnetic resonance imaging (MRI) has demonstrated superior soft tissue contrast and spatial resolution, a clear advantage for accurate treatment planning using brachytherapy sources. Over the last few years, the use of MRI for patient selection and treatment planning has gained significant momentum with growing clinical experience. In the United States, MRI utilization for cervical cancers has increased from 2% in 2007 to 34% in 2014 [1]. MRI is superior to ultrasound and CT for visualizing intra-prostatic tumors and evaluating macroscopic extracapsular extension and/or seminal vesicle invasion that would preclude brachytherapy as a monotherapy option. In 2012, the American Brachytherapy Society (ABS) developed guidelines to use MRI for disease staging and treatment planning in “clinically relevant circumstances” by “experienced teams” [2]. In 2017 The American Association of Physicists in Medicine (AAPM) approved the formation of Task Group 303 – MRI Guidance in HDR Brachytherapy – Considerations from Simulation to

¹The product is not commercially available. Radiotherapy where MR data is the only imaging information is ongoing research. The concepts and information presented in this article are based on research and are not commercially available. Its future availability cannot be ensured. Not for clinical use.



1 (1A) MAGNETOM Aera (1.5T) Tim Dockable table at the Christiana Care Health System community hospital, Newark, DE, USA. (1B) Wide-bore MAGNETOM Skyra (3T) MRI with the Tim Dockable table at the University of Michigan, Ann Arbor, MI, USA.

Treatment – in response to the growing interest in MRI guided brachytherapy. The committee consists of brachytherapy physicists and clinicians from academic and community cancer centers, as well as MRI industry representatives. These experts have been charged with developing recommendations and guidelines for the commissioning, clinical implementation, and on-going quality assurance specifically for MRI-based prostate and gynecological HDR brachytherapy. Herein we present on key evidence to support the statement that MRI is here to stay for brachytherapy.

MRI future for prostate cancer brachytherapy

A special issue in the *Brachytherapy Journal* was recently published on the treatment of prostate cancer, including several pivotal articles on the use of MRI in the diagnosis, treatment, response assessment, and “the management of recurrent disease in the setting of rising prostate-specific antigen levels after low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy” [3]. The goal of the issue was to “bend the brachytherapy curve” by optimizing the therapeutic ratio through the utilization of MRI [3]. To highlight a few articles, Venkatesan *et al.* presented an overview of multi-parametric MRI (mp-MRI) techniques for high-resolution of prostate anatomy. They discussed the pros and cons of using an endorectal coil (ERC) with emerging evidence that it may not be necessary when using a 3T MRI [4]. In a second paper from Venkatesan *et al.*, they summarized prostate cancer findings, tumor staging, and presented an overview of the Prostate Imaging Reporting and Data System (PIRADS). In addition, they presented MRI findings observed in the post-therapy setting, including sites of recurrence, and MRI concepts pertinent to successful salvage brachytherapy [5]. Pugh and Pokharel reviewed MRI utilization in prostate brachytherapy and postulated future pathways for MRI integration. They detailed several advantages of MRI integration including “superior intra-prostatic soft tissue resolution, localization of the dominant intra-prostatic lesion, and improved anatomic visualization of the prostate apex, prostate-bladder interface, prostate-rectal interface, neurovascular bundles, and genitourinary diaphragm” [6].

LDR and HDR brachytherapy using TRUS or CT are commonly used in practice today. However, while the therapeutic ratio is largely favorable, ongoing dilemmas include ‘cold’ base and ‘hot’ spots in the apex, urethral strictures, bladder dysfunction, erectile dysfunction, and biochemical recurrences. The Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial demonstrated an unequivocal improvement in biochemical control rates

for intermediate to high risk patients treated with an LDR prostate brachytherapy boost, but with grade 3 late GU toxicities of 18.4% – half of which were urethral strictures, many of which resolved over time with a prevalence rate of 8.6% at five years [7].

MRI future for gynecological cancers brachytherapy

For gynecological cancer, the International Commission of Radiation Units and Measurements (ICRU) has recently updated their classical 1985 report 38 [8] with ICRU report 89 [9]. The updated report provides an excellent description of current volumetric imaging (MRI and CT) for the cervix with the addition of 4D adaptive target concepts and updated radiobiology and recommended dose volume histogram (DVH) parameters for target and organs-at-risk (OAR) [9]. Some of the ICRU updated guidelines were based on the Groupe Européen de Curie thérapie – European Society for Radiotherapy & Oncology (GEC-ESTRO) recommendations. GEC-ESTRO has taken the lead and recognized volumetric imaging for brachytherapy treatment planning for cervical cancer, with the formation of the gynecological (GYN) GEC-ESTRO work group. Over the last 18 years their work group has published a series of recommendations to assist in the standardization of image-based brachytherapy treatment planning. This has included the definition of a common language and means of delineating the target volumes (i.e., Intermediate Risk-CTV and High Risk-CTV for the definitive treatment of cervical cancer), discussions on issues related to applicator reconstruction, and suggestions on the appropriate MR imaging sequences utilized for treatment planning [10–13]. The outcome data with MRI-based planning is excellent in limited and well responding tumors demonstrating improved local control and decrease morbidities in comparison to historical 2D planning methods as demonstrated by the completed EMBRACE I (An International study on MRI-guided Brachytherapy in locally Advanced Cervical cancer) multicenter protocol [14]. Key findings include an improvement in local control by 10% when comparing limited to advanced image based brachytherapy planning for large tumors (three year local failures rates of 2%, 7–9%, 21–25% for stages IB, IIB, IIIB, respectively), and ongoing, detailed quality of life analysis of vaginal, bladder, and bowel morbidity [15, 16]. The late rectal morbidity appears to be lower when $D2cc \leq 65$ Gy versus ≥ 75 Gy, even though the HR CTV is dose escalated with Image Guided Advanced Brachytherapy (IGABT) [17]. Based on the positive outcomes from the RetroEMBRACE and EMBRACE I protocols, the EMBRACE research group has initiated the EMBRACE II protocol with the intention of

using state of the art treatment techniques for external beam and brachytherapy to enhance local, nodal, and systemic control while minimizing normal tissue toxicity [17].

How to navigate challenges transitioning to MRI-based brachytherapy

Often, we have the preconceived notion that MRI-based brachytherapy is resource intensive. Harkenrider *et al.* recently described their experience with transitioning from CT-based to MRI-based brachytherapy for cervical cancer at Loyola University Medical Center, Maywood, IL, USA) [18]. They suggest that the key to success is a multidisciplinary team approach involving radiation oncology, gynecologic oncology, radiology, and anesthesia. Once the 'big picture' was identified (e.g., MR applicator choice, dose fractionation schedule), they optimized their workflow to best suit their clinic [18].

MRI utilization for brachytherapy can be considered in three fundamental categories: pre-planning target diagnosis; implant guidance; MR-based treatment planning after implant insertion; and MRI-guided implant insertion and treatment planning. With this in mind, the basic requirements for the successful implementation of MRI in brachytherapy include:

1. Access to an MRI scanner (e.g., a diagnostic or dedicated radiation oncology simulator),
2. MR conditional ancillary equipment (e.g., leg straps, immobilization devices, transport table), and
3. an optimized clinical workflow, which involved input from all members of the multidisciplinary team involved in the patient's care.

Additionally, when integrating MR into brachytherapy, it is imperative to review and update the clinical workflow initially and on a periodic basis as your program matures. Considerations for MRI safety must also be a priority for a successful program with ongoing staff training to ensure patient and hardware safety.

At each of our four respective institutions, MRI has been utilized in the care of brachytherapy patients. Our departments are equipped with either the Siemens Healthineers MAGNETOM Aera (1.5T) or MAGNETOM Skyra (3T) MRI scanners (Figures 1A and 1B, respectively). Additionally, to minimize patient motion between planning simulation and treatment, MR-conditional transport systems, such as the Siemens Healthineers Tim Dockable table (Fig. 1C) and the Symphony™ (Qfix, Avondale, PA, USA) patient transport system²,



1C The Tim Dockable table detached from the Siemens Healthineers MRI simulator.



2 Example of a patient transport system (Symphony Patient Transport System, Qfix, Avondale, PA, USA) that can easily move the patient from our Siemens Healthineers Tim Dockable table for the MAGNETOM Aera 1.5T scanner with minimal motion of applicator or needles.
(A) Symphony patient trolley-integrated air pump, two batteries, and adjustable pillars.
(B) Symphony Brachytherapy Transfer Device and leg extension. All devices are MR Conditional.

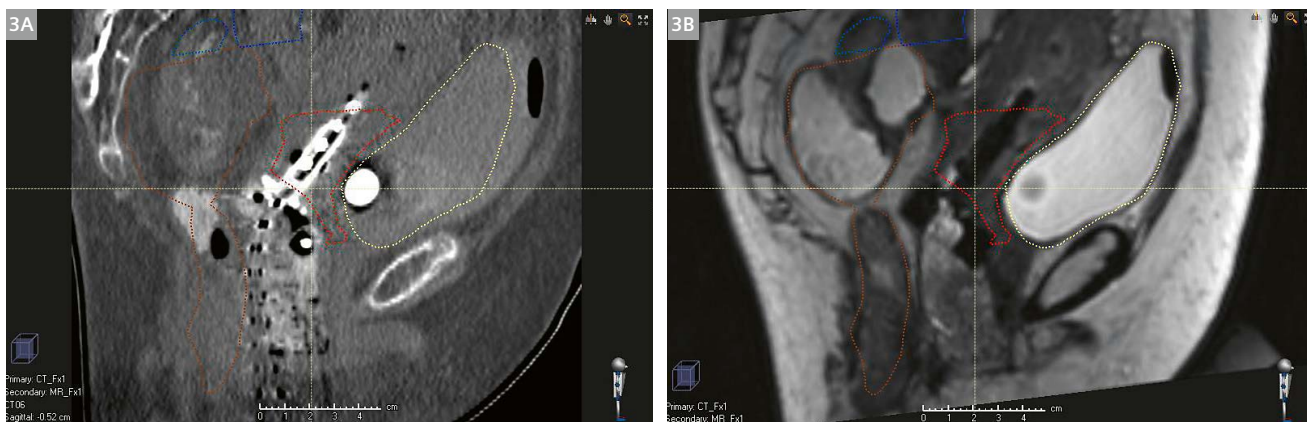
²The information shown herein refers to products of 3rd party manufacturer's and thus are in their regulatory responsibility. Please contact the 3rd party manufacturer for further information.

are being utilized (Fig. 2). However, each institutions approach to MR guided brachytherapy differs based on our resources, time, and financial constraints.

At one community-based cancer center (Helen F. Graham Cancer Center, Newark, DE, USA), for cervical cancer patients, applicator (plastic only) insertion is performed in a prep room that has OR lights and MR safe anesthesia equipment, adjacent to the MR scanner in our Radiology department. In the case of interstitial implants, diagnostic MR images are made available at the time of implant to assist in guiding needle/catheter placement. In general, the procedure starts with the patient lying supine on the Symphony patient trolley and Symphony Brachytherapy Transfer Device (Fig. 2). Once applicator insertion is complete using non-MR compatible stirrups, the patient is transferred onto the Siemens Healthineers Tim Dockable MR table. The patient is then transferred to the MAGNETOM Aera MRI scanner (Fig. 1A), and the 18-channel body coil (attached to Qfix Insight MR Bridge with Body Coil holder) is positioned about 1 cm above the patient's pelvis. MR scout images are taken (sagittal and coronal) to allow the physician to review the applicator placement quality, and if needed, make minor adjustments in the MR vault prior to the acquisition of the final T1- and T2-weighted 3D SPACE image protocols (< 10 min). Once the MR scans are complete, the patient is transferred back to the Symphony patient trolley and taken back to the HDR vault in Radiation Oncology. For MR-based treatment planning, the high risk clinical target volume (HR-CTV) and the organs at risk (OARs) are delineated on the T2-weighted 3D SPACE MRI dataset. MR-based planning is only performed for the first treat-

ment fraction and MR/CT rigid registration tools available in Raystation v 5.0 (Raysearch Labs, Stockholm, Sweden) are used for subsequent HDR fractions planned on CT images (Fig. 3). This rigid registration relies on the Smit Sleeve location (not bony anatomy). The Smit Sleeve is clearly visible on both MR and CT and is reliable to map the MR HR-CTV onto the subsequent fraction CT. The physician can then modify the registered HR-CTV on the CT if needed. For HDR treatment planning, *solid applicator* models provided by the Oncentra planning system (Elekta Inc., Stockholm, Sweden) (Fig. 4) are used to align the applicator on MR or CT images. Based on our commissioning data, the applicator model can map the first dwell position of the source within an uncertainty of 2 mm. The OARs are contoured on CT for each fraction since CT (with contrast) is fairly accurate to contour the bladder and rectum. This workflow has been found to be efficient since the procedure starts at the MR station, saving time for patient transfer under anesthesia. The entire process, applicator insertion, MR imaging, and the HDR fraction delivery is typically completed within 90 minutes.

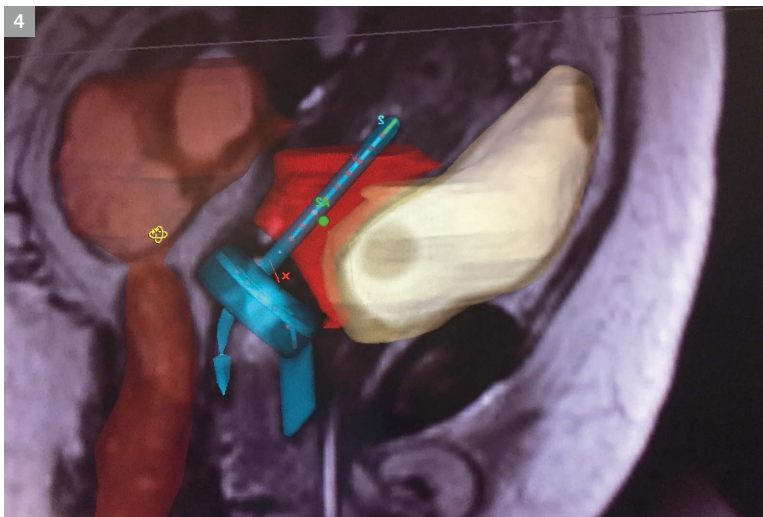
At an academic institution (University of Michigan), the extent to which we have adopted MRI-based brachytherapy varies based on treatment site and applicator. For all treatment sites, applicator insertion is performed either in a dedicated HDR suite or in an operating room. In the case of interstitial implants, diagnostic MR images are made available at the time of implant to assist in guiding needle/catheter placement. For gynecological cancers requiring cylindrical applicators (e.g., for the treatment of post-hysterectomy endometrial cancer),



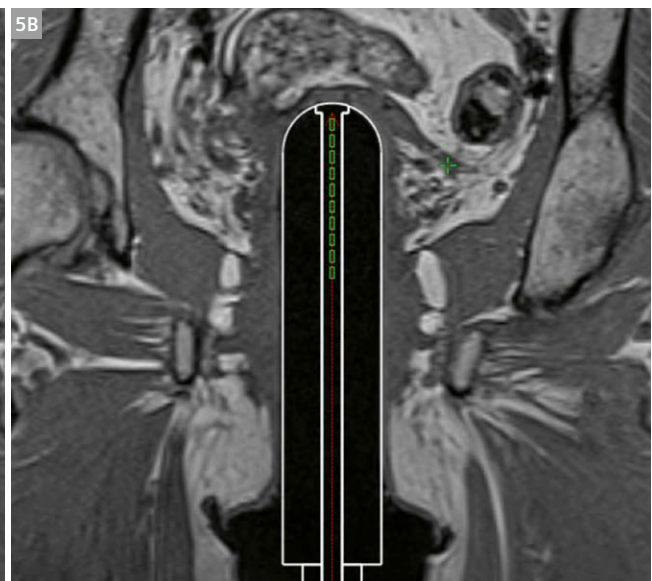
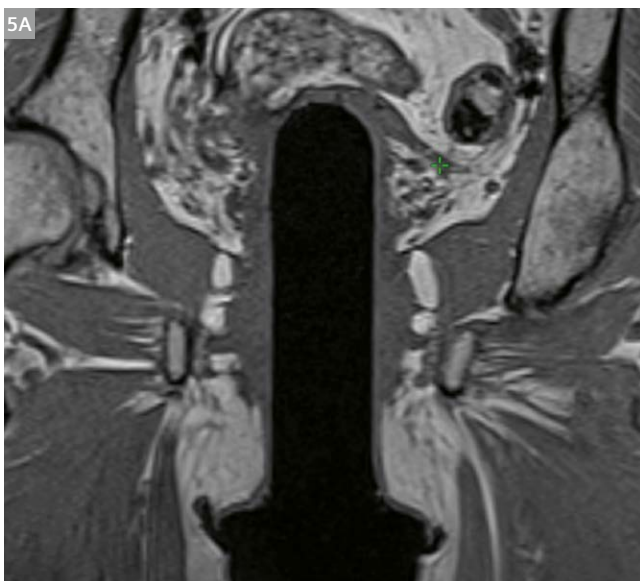
3 HR-CTV target (red dotted line) defined following rigid registration in Raystation planning system, using the Smith Sleeve for a tandem and ring gynecological case of a sixty-year-old patient with stage IV cervical cancer **(3A)** clinical standard CT pelvis protocol (Siemens Healthineers SOMATOM Sensation Open) vs. **(3B)** T2w 3D SPACE AX ISO 1.3 mm³ isotropic MRI (1.5T) MAGNETOM Aera. Coils used: Spine array coil in the Tim Dockable table and the 18-channel Body Matrix coil attached to the Qfix Insight MR Bridge with Body Coil holder. 3D distortion correction is turned on.

patients undergo MR (Fig. 1B) only planning simulations and a T1-weighted (VIBE) coronal image is used for treatment planning [19]. To expedite planning, an applicator model is overlaid on the outline of the applicator as visualized on the MR images (i.e., observed as a signal void) (Fig. 5). In the case of patient's treated with a ring and tandem applicator (e.g., for cervical cancer), we are still in transition to MR only planning simulations, following the purchase of new plastic brachytherapy applicators. At present, both CT and MR simulations are acquired for each treatment fraction, and rigidly registered. The HR-CTV is delineated on a T2-weighted MRI dataset, and the contour is then copied to the CT scan. Treatment plans are generated using the CT planning simulation.

In the future, we intend to transition to MR-only planning simulations, and in an attempt to reduce planning time (i.e., for subsequent treatment fractions), use deformable image registration to automate the contouring of the HR CTV and OARs [20]. For advanced gynecological cancers requiring an interstitial implant, both CT and MR planning simulations are acquired. The HR CTV is defined on a T2-weighted MRI and copied to the rigidly registered CT dataset for treatment planning. Lastly, in the case of prostate HDR brachytherapy, which is restarting following a three-year hiatus, the initial intent is to have diagnostic MR images available at the time of the US guided procedure to assist with dose escalation to intraprostatic lesions.



4 In Oncentra HDR treatment planning system, the tandem and ring *solid applicator* model is accurately registered (within 2 mm uncertainty) to the 3D MR images of patient anatomy shown Figure 3. Images obtained using T2w 3D SPACE AX ISO 1.3 mm³ isotropic MRI (1.5T) MAGNETOM Aera with spine array coil and 18-channel body coils, and 3D distortion correction is turned on.



5 (5A) Paracoronar 3D T1-weighted (VIBE) MRI of a patient with a plastic MR conditional vaginal cylinder in place. (5B) Alignment of the applicator model over the signal void representing the perimeter of the applicator for treatment planning purposes.

Conclusions

MR guided brachytherapy has strong supporting evidence that it will further improve the therapeutic ratio for prostate and gynecologic malignancies, and is feasible to implement in established brachytherapy practices. We believe more radiation oncology centers will and should begin implementing MR into their brachytherapy procedures. We look forward to seeing the future publication of the AAPM TG-303 report for further recommendations to aid brachytherapists in the expansion of MRI utilization in the United States for brachytherapy.

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Joann I. Prisciandaro,
Ph.D.



Sushil Beriwall,
M.D.



Daniel G. Petereit,
M.D.



Firas Mourtada,
Ph.D.

Contact

Firas Mourtada, Ph.D.
Chief of Clinical Physics
Radiation Oncology, Ste 1152
Helen F. Graham Cancer Center &
Research Institute
4701 Ogletown-Stanton Rd
Christiana Care Health System
Newark, DE 19713, USA
Tel: +1 302-623-4691
Fax: +1 302-623-4547
fmourtada@christianacare.org

Performing Gynecologic Brachytherapy in the Medical Innovation Technical Expert Center

Cindy P. M. Frentz¹; Ruud van Leeuwen²; Angelo van Wagendorff van Ryn³; Jurgen J. Fütterer¹; Lia Verhoef²

¹ Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, the Netherlands

² Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, the Netherlands

³ Siemens Healthineers, Siemens Healthcare Nederland B.V., The Hague, the Netherlands

Keypoints

In this article we describe our procedure of positioning brachytherapy applicators and catheters in cervical carcinoma. The procedure is performed with the support of intra operative MRI in the Medical Innovation Technical expert Center (MITeC) of the Radboud University Medical Center, Nijmegen.

Introduction

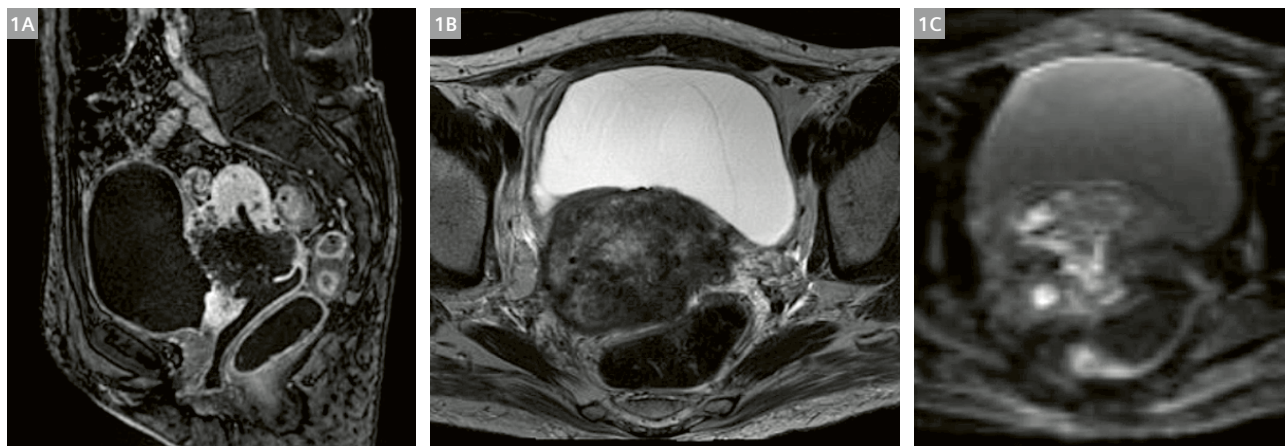
The Medical Innovation Technical expert Center (MITeC) of the Radboud University Medical Center is a multi-operation room setting utilized for minimal invasive surgical procedures supported by MRI, CT, or X-ray intervention technologies. In 2015 a wide-bore 3T MAGNETOM Skyra Combi Suite MRI scanner (Siemens Healthcare, Erlangen, Germany) was installed for MRI-guided procedures.

MR-guided adaptive brachytherapy (MRGABT) is a local radiotherapy treatment, employing after-loading techniques, that treats tumors by positioning a radioactive source, through hollow catheters placed in or near the

tumor. The radioactive source is programmed to stay at pre-specified positions in the applicator and catheters, during a varying time. In this way it is possible to give a high dose to tumor tissue while minimizing the radiation dose to the vital organs in the environment of the tumor.

For Radiation Oncology, one of the great opportunities of the combination of MRI in an operating room is the possibility to perform an MRI scan directly after positioning brachytherapy catheters into a tumor in order to reposition or return to the OR if additional intervention is necessary. MRGABT can be performed based on the MR images, as soft tissue contrast allows to customize treatment plans to accurately deliver therapeutic doses to tumor tissue, while minimizing dose to the normal structures in the vicinity of the tumor, potentially resulting in fewer treatment related complications.

In our hospital, cervical carcinoma patients routinely undergo MRGABT in the MITeC since October 2015. In this article we will describe the application procedure in a patient with cervical carcinoma and the way to perform MRI-scanning in an OR setting.



1 Diagnostic sagittal T1-weighted VIBE post Gd-contrast (**1A**) of a cervix carcinoma in situ. Transversal T2-weighted image (**1B**) showing a large tumor with extensive diffusion restriction on transversal TraceW diffusion-weighted image (**1C**).

Procedure

For patients with locally advanced cervical carcinoma, external beam radiotherapy combined with weekly cisplatin, followed by high dose brachytherapy is the treatment of choice [6–8].

A case in clinical routine: a 50-year-old woman with a large squamous cell carcinoma of the cervix uteri. The diagnostic abdominal MRI shows a tumor of 8.8 x 10 x 11 cm that penetrates through the bladder, the urethra, the cervix, the apical vagina, and the myo- and endometrium uteri and is also fixed to the sigmoid (Fig. 1). This unresectable tumor was treated by chemo- and radiotherapy: after 25 fractions of large-field external beam radiotherapy, combined with weekly cisplatin, the remaining tumor was treated with brachytherapy. By doing it this way the tumor could be treated with a much higher dose than would have been possible with external beam radiotherapy only. The healthy tissue in the area of the tumor received a much lower dose than it would with external beam radiotherapy, as the radiation source is positioned inside the tumor.

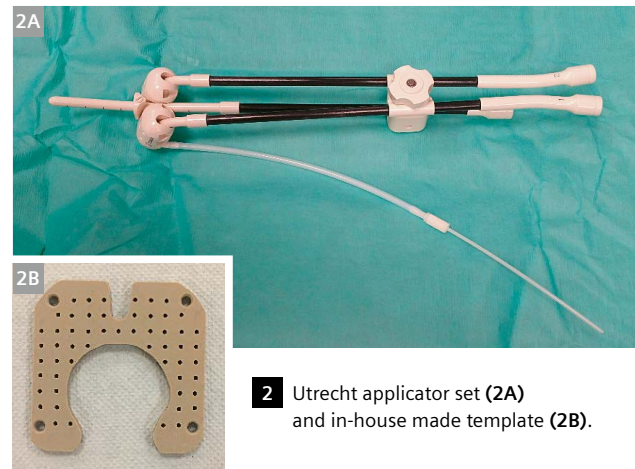
For this treatment an applicator with guided catheters (Elekta Utrecht Interstitial Applicator Set) was used. The applicator system consists of an intra-uterine catheter and two ovoid shaped devices that allowed the placing of additional needles in the tumor (Fig. 2A) [2]. A template made in-house was used to position and adjust the needles (Fig. 2B).

As tumor sizes vary in patients the addition of a template allows the placing of extra needles outside the range of the applicator and their catheters.

The insertion of the applicator, template, and catheters was done in the OR of the MITeC under general anesthesia. The catheters were positioned in the tumor using the applicator, its ovoids, and template to guide the needles. The needles could be individually repositioned and locked for treatment. After positioning and fixing the device an MRI took place next to the OR where the catheters were placed. The patient remained under general anesthesia during the transport to the MRI-room and during the scan. Transport of the patient was easily performed using the Combi Dockable MRI table [3].

The Combi Dockable MRI table is a trolley that can be undocked from the scanner in order to transport the patient. The trolley contains a rail and a sliding table top. Connecting the MRI table to the OR table enables you to slide the table top safely on to the OR table (Fig. 3A). The table top of this MRI table will stay under the patient throughout the procedure.

The table top will be on the OR table and can easily slide on the MRI table whilst the patient remains on the table top. The rails of the table top prevent the use of a conventional spine coil. As an alternative, to receive signal from the posterior side, a 4-channel Siemens flex large coil is positioned among the rails on the MRI table before



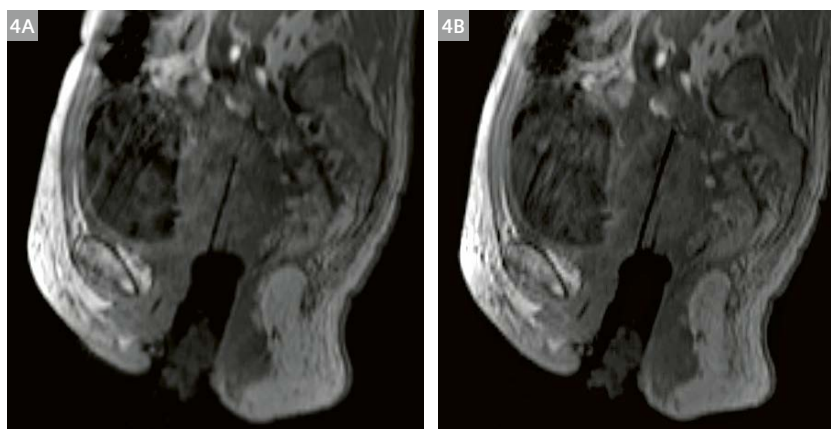
2 Utrecht applicator set (2A) and in-house made template (2B).



3 Patient transport from operation room (3A) to MRI room (3B) on the table top of the Combi Dockable MRI table.

shifting the table top on it. The coils are placed along the length of the patient to facilitate full field-of-view MRI of the anatomy and catheters.

We used markers on the MRI-compatible trolley to mark the position of the 4-channel flex coil so that we could easily position the pelvic region on top of the coil. After an MRI safety check, the team transported the patient through the MRI entrance and the table was docked to the MRI-scanner.



4 Example of repositioning of a catheter.
(4A) Sagittal reconstruction of 3D T1 VIBE: one of the catheters in situ.
(4B) Catheter placed 15 mm deeper in the tumor.

MRI-scans were made when the patient was still under general anesthesia using MRI compatible respiratory equipment and MRI-compatible monitoring equipment to monitor patient condition during scanning. The patient was positioned in feet first position to allow a good level of respiratory control. Over the abdomen an 18-channel body coil was placed for good signal of the lower abdomen.

The scanning protocol contains a transversal 3D T1-weighted VIBE sequence (TE 2.46 ms, TR 4.57 ms, voxel size 1.2 x 1.2 x 2.0 mm, acquisition time 2:08 min) to visualize the location and depth of applicator and catheters in the cervix and tumor. On both sides of the tunnel there is enough space for adapting the catheters in a sterile way.

After repositioning the catheters the 3D T1 VIBE was repeated in order to check the location and depth (Fig. 4). After obtaining the correct position high-resolution T2 TSE sequences (TE 90 ms, TR 5020, voxel size 0.6 x 0.6 x 3.0 mm, acq. time 5:13 min) were performed in 3 directions aligned to the tip of the applicator to obtain good image contrast between normal tissue and tumor. The T2 sequences were used for contouring of the tumor and organs, and for planning of the brachytherapy dose. Normally, water filled tubes (Elekta MR line marker set) can be placed inside the applicator to have a better visualization of the applicator on the T2w images [2].

Safety issues

Because of the strong magnetic field and the radiofrequency pulses in the MRI room it is important to double-check patient and personnel for ferromagnetic and conductive materials. The patient was screened for contra-indications on the day of the intake, and again at the arrival at the OR. Before entering the MRI room there was a safety check moment planned, where personnel were checked and ferromagnetic material was removed. The applicator is MRI safe. The needles used for the positioning and replacing of the catheters are safe to use in the MRI room, but not safe to leave inside the catheters during scanning. Therefore

the needles were taken out of the catheters before entering the MRI room. The template is MRI safe.

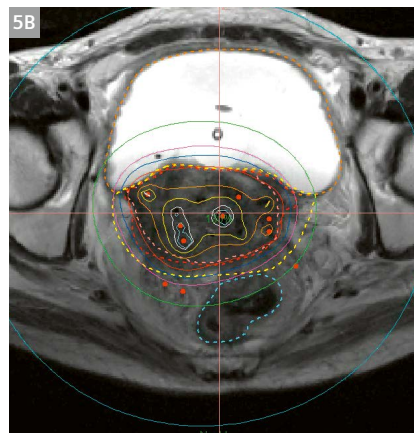
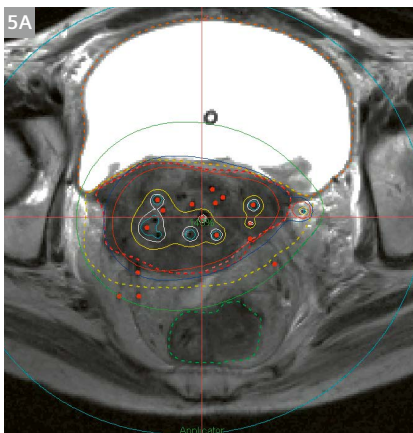
The door between the OR and the MRI room was locked. After the safety check the MRI technician unlocked the door and the patient could be transported to the MRI room. The door was automatically locked after a few minutes. To minimize risks, a minimal number of personnel were in the MR room: the anesthesiologist, the assistant anesthesiologist, and the MRI technician. All other personnel remained in the adjacent operation room or in the MRI control room.

Treatment

After the optimal placement of the applicator and catheters and the final MRI, the patient was transported back to the OR on the undocked MRI table. There she was brought to conscious, administered pain medication and transported to the recovery room. Meanwhile, dose planning was performed in the radiation oncology department. An accurate definition of the source positions relative to the anatomy is critical. Thus, evaluation of patient movements, artifacts of the applicator, and distortion should be taken into account. The bladder and bowel are organs in the direct area of the tumor. It is important for quality of life and tumor induction to spare these organs from as much radiation as possible. The optimal location of the radio-active source inside the catheters and applicator and the time they should stay inside were determined using Oncentra Brachy software (Elekta, Veenendaal, the Netherlands) [2].

After finalizing the optimal treatment planning the patient was transported to the treatment room in the department of radiation oncology, where the catheters and applicator were connected to the treatment device (Flexitron, Elekta, Veenendaal, the Netherlands) and radiation was performed [2]. After the radiation the applicator and catheters were taken out.

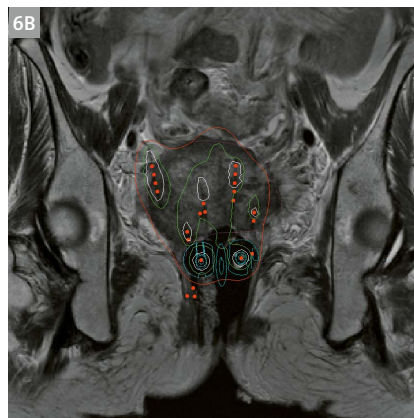
For effective treatment with high tumor dose and good recovery of healthy tissue the procedure of brachytherapy was carried out a total of four times during two consecutive weeks. Each time (fraction) the applicator and catheters



5 Dose plans of two sequential fractions in the same patient. The red line denotes 100% of the prescribed dose, the green line 50% of the prescribed dose, the red dotted line denotes the tumor. In an ideal situation the red line should exactly follow the red dotted line.

(5A) Utrecht applicator plus template, 15 needles, target dose 7.4 Gray. MRI after check position and MRI guided reposition.

(5B) Utrecht applicator and template, 5 needles; 2 free. Target dose 7.8 Gray. MRI after check position and repositioning using MRI.



6 Dose plans on coronal T2w image in Oncentra brachy treatment planning software. Pink dotted line: tumor. Red line: 100% dose, green line: 200% dose, white line: 300% dose. Insufficient radiation dose in the outer part of the tumor. Part of the tumor outside the red line **(6A)**. Good coverage of 100% radiation dose thanks to a catheter placed free-hand in the outer part of the tumor when conventional device is not applicable for large tumors **(6B)**.

were placed MRI-guided in the optimal way in relation to the tumor. In between the brachytherapy treatments two or three days were planned for recovery of healthy tissue [4, 5]. In Figure 5 the planned dose distribution of two fractions is shown, showing high dose inside the tumor and lower dose in the surrounding organs. Panel 5A shows insufficient coverage of the tumor, especially in the ventral and right side of the tumor; panel 5B shows markedly improved coverage after MRI-guided needle adjustment.

Future perspective

In the future real-time MRI during needle shifting would be an effective way of repositioning the catheters using MRI-safe needles. Real-time imaging also allows free-hand positioning or repositioning of needles, especially in large tumors where the applicator and guided catheters are not close enough to certain parts of the tumor, resulting in under dosage. In Figure 6A you find a part of the tumor (pink dotted line) outside the 100% radiation dose (red line). In this case this part of the tumor is out of reach of the applicator. A catheter was therefore positioned free-hand in this area (Fig. 6B). This extra catheter enables you to treat this part of the tumor as it should have been. To minimize risks such as perforation, MRI-guided positioning would be a great improvement of optimal positioning of free-hand placed needles. Good visualization of an MRI safe

needle needs to be available, but is not yet a clinical possibility in our hospital.

The MRI-guided procedure we described might also be applied for brachytherapy treatment in other cancer types, e.g. vagina, prostate or rectal tumors.

Conclusion and discussion

In order to prepare a patient for brachytherapy on cervix carcinoma it is good to have the availability of an MRI facility in the OR. This may offer the opportunity to effectively position and reposition applicator and catheters in a sterile way using MRI when the patient is in controlled general anesthesia. An additional advantage of the anesthesia is the reduction of motion artifacts caused by patient movement. The sliding table top of the Combi Dockable MRI table ensures easy patient transportation. Safety issues should be taken into account because of the high field strength, gradient field and radiofrequency pulses.

The option of real-time scanning during needle shifting would be an effective way of repositioning the catheters using MRI compatible needles. The treatment depends on size and position of the tumor. Different MRI compatible devices can be used. Real-time MRI can give you the ability to place or reposition needles free-hand in the tumor. This is not yet used in these procedures.

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Contact

Dr. C. G. Verhoef, Radiation oncologist
Department of Radiation oncology
Radboud University Medical Center
Geert Grooteplein zuid 32
6525GA Nijmegen
The Netherlands
Phone: +31(0)2436 86457
Lia.Verhoef@radboudumc.nl



Lia Verhoef

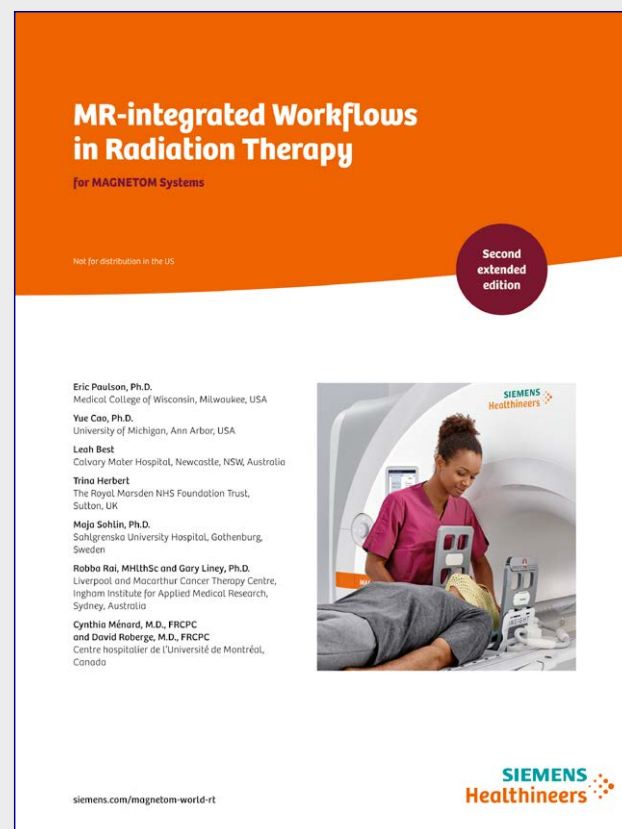


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MRI-Guided HDR Brachytherapy for Prostate Cancer

Cynthia Ménard^{1, 2, 3, 4}; Peter Chung^{1, 4}; Anna Simenov¹; Alejandro Berlin^{1, 4}; Alexandra Rink^{1, 3, 4}; Warren Foltz^{1, 3, 4}; David Jaffray^{1, 3, 4}

¹ Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, ON, Canada

² Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC, Canada

³ Techna Institute, University Health Network, Toronto, ON, Canada

⁴ Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada

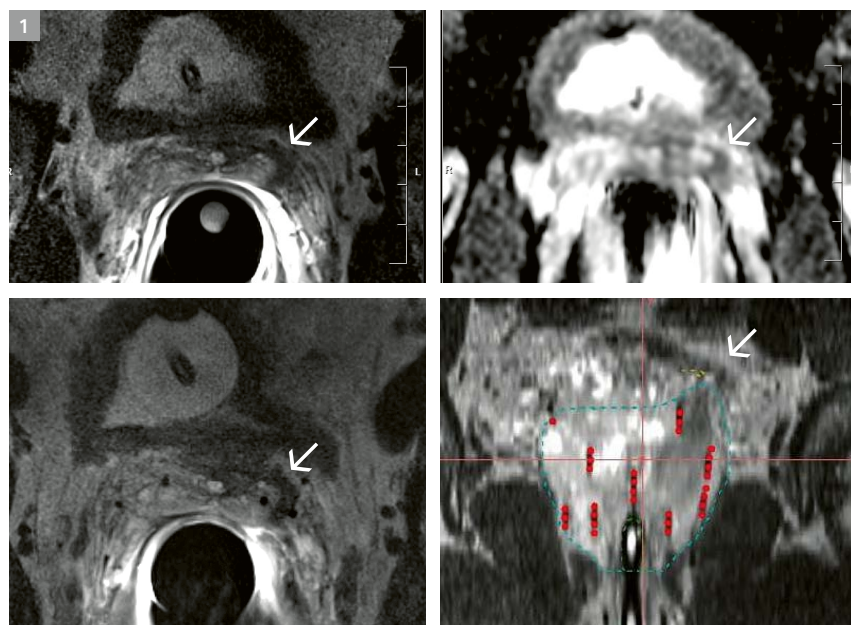
Introduction

Prostate brachytherapy, either as monotherapy or as a boost to external beam radiotherapy, can achieve unparalleled dose escalation, with doses (EQD2) upwards of 150 Gy when the dose gradient is taken into account [1]. As evidence mounts supporting the value of dose-escalation [2, 3], so has the adoption of high-dose-rate brachytherapy in clinical practice across the world.

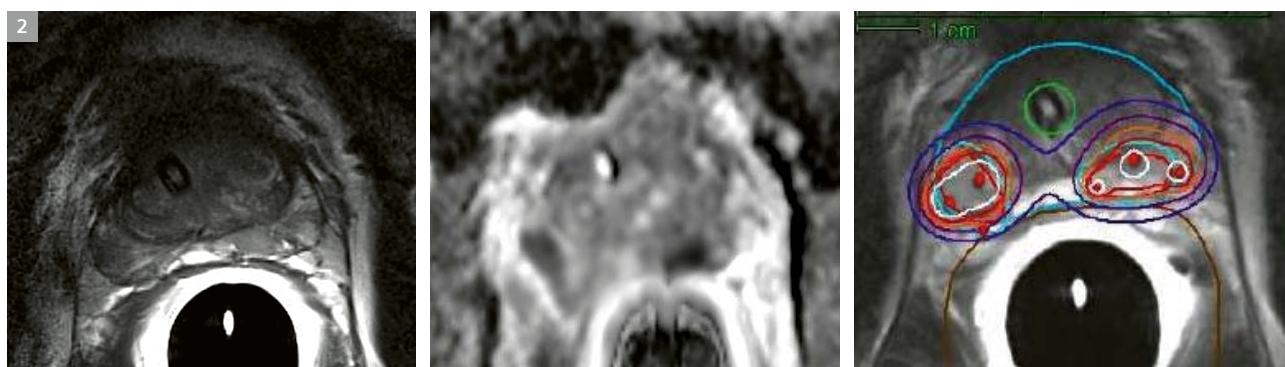
Although trans-rectal ultrasound (TRUS) remains the standard-care interventional imaging modality for guidance of prostate brachytherapy, it falters in its depiction of implanted devices, such as brachytherapy needles, and/or catheters due to substantial echogenic artifact that degrades image quality as the implant progresses. It also fails in depicting regions of tumor burden that should be considered in the implant and treatment.

MRI is considered state-of-the-art for local tumor staging and visualization. A diagnostic acquisition protocol that includes high-resolution T2-weighted FSE and diffusion-weighted imaging (DWI) with or without dynamic imaging during IV contrast injection, can accurately identify regions of gross tumor burden (GTV) and the presence of gross extracapsular extension or seminal vesicle invasion (stage T3) [4].

The prostate gland is a flawed surrogate target for cancer as a target for brachytherapy, as cancer is neither defined nor confined to the boundaries of the prostate gland. The gross target volume (GTV) should be considered in planning and executing brachytherapy for prostate cancer, and in this regard, MRI prior to implantation is paramount. The introduction of MRI to augment or replace the TRUS workflow has logically progressed over the past decades. Here we present our current state-of-the-art approach to interventional MRI applied to HDR brachytherapy for prostate cancer.



1 Patient with left seminal vesicle invasion (arrow). Catheters (signal void) are implanted deep and adjacent to extraprostatic disease (bottom), which can then be included in the target volume (turquoise) for HDR brachytherapy.



2 Patient with intermediate-risk prostate cancer and two gross target volumes in the right lateral peripheral zone, and left medial peripheral zone. Both targets are implanted for a boost to external beam radiotherapy in order to improve tumor control (isodose plan, right).

Why MRI after catheter placement?

Dose plans in HDR brachytherapy are generated after catheter insertion in order to prescribe the time that the radioactive source spends at each pre-defined 'dwell' position. Dwell-time optimization is a powerful variable after catheter placement by which dose is focused on targets at risk while reducing exposures to nearby organs and structures at risk of injury, such as the rectum. By replacing standard TRUS or CT with MRI for treatment planning, depiction of anatomic boundaries relative to implanted catheters is vastly improved [5].

In the absence of commercial MRI markers, catheter signatures can be accentuated as signal voids in a high-resolution FSE image using an intermediate echo-time (TE) (Fig. 1), or by using a dual-echo FSE acquisition in order to acquire a proton-density-weighted (PD) image for device reconstruction, and a matched T2-weighted FSE image for anatomic delineation. Although this approach presents an improvement in accuracy of delineating the prostate gland, blurring of the apical boundary can occur due to acute needle trauma and bleeding. Depiction of gross tumor is also degraded by edema and bleeding compared with MRI prior to catheter insertion.

Why MRI before catheter placement?

MRI acquired prior to brachytherapy is most critical, whereby the appropriateness of the treatment is confirmed, and images cognitively 'fused' or considered during the implant to avoid marginal miss of gross tumor. This approach results in a change in treatment plan in a substantial proportion of patients, either through the addition of hormonal therapy, the addition of external beam radiotherapy, and/or modification of the implant itself by including sites of extraprostatic extension and/or seminal vesicle invasion [6] (Fig. 1). Sites of tumor burden can also be considered when trading off target coverage and dose to adjacent organs at risk, such that undercoverage is permitted only in regions that do not harbor gross tumor.

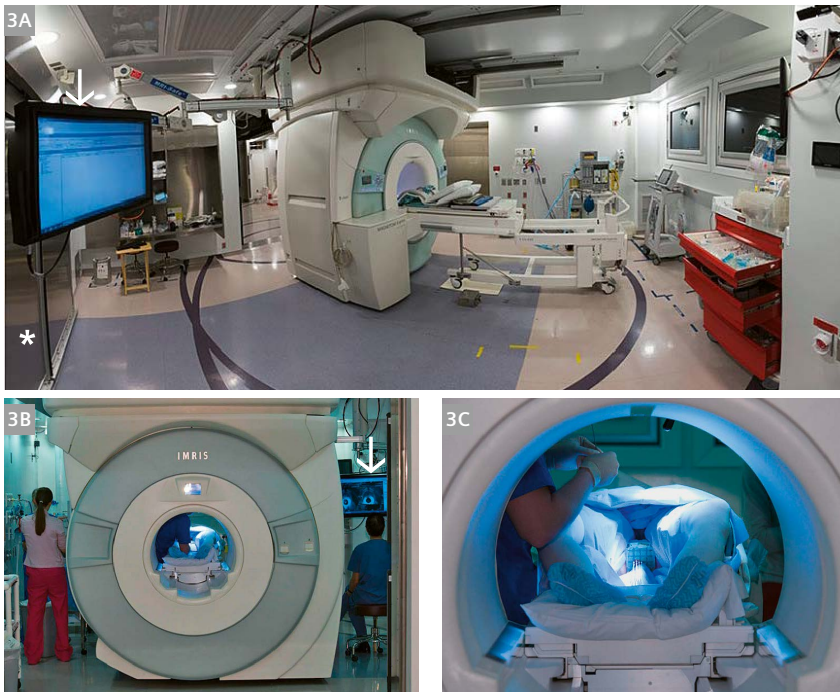
The next step is to differentially dose escalate visible tumor, and potentially de-escalate dose to microscopically involved prostate gland tissues distant to the GTV. A number of publications, predominantly in HDR applications, have demonstrated ease of escalating dose to tumors without incurring elevated dose to organs-at-risk (OARs) [7]. We await results of prospective trials to better ascertain the relative gain in effectiveness with this approach. It remains that the success or failure of tumor boost and/or focal-only therapies hinge on highly accurate techniques (Fig. 2). Sources of error and uncertainty introduced with MRI-TRUS registration remain to be addressed.

Why an MRI-only prostate brachytherapy workflow?

An MRI-only workflow permits MRI to be acquired prior to and during catheter insertion to aid in implant guidance, and after catheter insertion for MRI-based treatment planning. In this manner, registration errors are largely circumvented. The requirement for a separate visit for a diagnostic MRI prior to brachytherapy is also removed. We demonstrate our installation that integrates an MRI scanner (1.5T MAGNETOM Espree, Siemens Healthcare) with the HDR delivery (Elekta MicroSelectron HDR) suite, removing the need for patient transfer between treatment-planning MRI and delivery of HDR brachytherapy dose [8] (Fig. 3). Errors due to motion or swelling are thereby further mitigated, and imaging immediately after (or during) delivery can confirm delivered (in contrast to planned) dose.

The Interventional MRI procedure

Patients are placed in frog-leg on a patient positioning system atop the diagnostic table. An endorectal coil (Sentinelle Endocore Array, Siemens Healthcare) is secured and fixed perpendicular to a custom perineal template. The perineum is prepped and draped with patients under general anesthesia (continuous infusion propofol).



3 MRgBT suite at the Princess Margaret in Toronto. A 1.5T MRI scanner on rails is brought into the brachytherapy suite. Equipment that is not MRI safe (including HDR afterloader) is stored behind RF doors (3A, see *). Brachytherapy catheters are inserted stereotactically with patient in frog-leg fashion using a positioning system and endorectal coil (Sentinel Endocoil Array), and a custom perineal template. In-room navigation display (3A and 3B, arrow) improves workflow.

Diagnostic imaging ensues with the devices registered in MRI space for stereotactic targeting. For catheter insertion, the table is withdrawn, and needles inserted based on navigation software (Aegies, Hologic Inc.). The table is translated to isocenter for imaging verification every 1-3 catheters until the implant is complete. High-resolution images are then acquired for treatment planning of HDR brachytherapy. During treatment planning, the table is undocked, and the magnet driven out of the shielded brachytherapy suite. Once MRI safe, doors to the equipment room can be opened and the HDR afterloader can be connected to the catheters. Delivery proceeds with the patient under anesthesia, and all staff outside the treatment room. After radiation is delivered, catheters are removed and the patient is recovered. The overall procedure time is approximately 2 hours.

The imaging protocol includes diagnostic T2w TSE (TE: 103 ms; TR 5280 ms; 20 x 20 cm FOV with 320 x 320 matrix for 0.6 mm in-plane resolution; 2 mm slice thickness; 40 slices for 80 mm coverage; R/L phase encoding with 100% phase oversampling; iPAT factor 2; 200 Hz/pixel readout bandwidth; turbo factor 25; 2 averages; scan time 4 min 47 sec), and diagnostic DWI (TE 100 ms; TR 4000 ms; 20 x 20 cm FOV with 128 x 128 matrix for 1.6 mm in-plane resolution; A/P phase-encoding with 30% phase oversampling and 6/8 phase

partial fourier; 3 mm slice thickness; 10 slices for 30 mm coverage; iPAT factor 2; 1148 Hz/pixel readout bandwidth; fat saturation; isotropic diffusion sampling; 4 b-values of 0, 100, 600, 1000 s/mm²; 8 averages; scan time 5 min 34 sec). The transperineal template is also imaged for registration and navigation (TE 95 ms; TR 2000 ms; 18 x 18 cm FOV with 256 x 256 matrix for 0.7 mm in-plane resolution; A/P phase-encoding with 50% phase oversampling; 4 mm slice thickness; 5 slices for 20 mm coverage; iPAT factor 2; 199 Hz/pixel readout bandwidth; turbo factor 25; 3 averages; scan time 1 min 42 sec). Needle position is verified using short TSE imaging (TE 11 ms; TR 1300 ms; 20 x 20 cm FOV with 256 x 256 matrix for 1.0 x 0.8 mm in-plane resolution; R/L phase encode with 100% phase oversampling; 3 mm slice thickness; 14 slices for 42 mm coverage; iPAT factor 2; 190 Hz/pixel readout bandwidth; turbo factor 10; 1 average scan time 31 sec). Finally, images are acquired for treatment planning once catheters are locked in place. (Axial TSE: TE 108 ms; TR 5760 ms; 18 x 18 cm FOV with 320 x 320 matrix for 0.6 mm in-plane resolution; R/L phase encoding; with 80% phase oversampling; 2 mm slice thickness; 46 slices for 92 mm coverage; 200 Hz/pixel readout bandwidth; turbo factor 20; 3 averages; scan time 8 min 51 sec).

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Contact

Cynthia Ménard, M.D., FRCPC
Centre hospitalier de l'Université
de Montréal
Cancer Clinical Research Unit (CCRU)
Princess Margaret Cancer Centre
1560 Sherbrooke St E
Montréal, QC
Canada, H2L 4M1
cynthia.menard@umontreal.ca

Insights

In this section, you will learn more about the functionality and advantages of MRI and its special use in Radiation Therapy (RT).



Why MRI in RT? - The clinical motivation

Recently there is a growing interest in the use of magnetic resonance imaging in radiation therapy. This is due to the many attractive features for radiation therapy that MRI has to offer.



What is MRI and how does it work? - Part 1

In this session you will learn about the basic principles of an MRI signal and the different ways it is acquired.



What is MRI and how does it work? - Part 2

In this advanced module about MRI and how it works, you can have a closer look at how the different contrasts can be obtained, and how the MR image is generated from the Free Induction Decay signals.



Challenges in MRI in RT

In this module you will learn more about the challenges and their solutions in MRI for diagnostic imaging and RT planning.



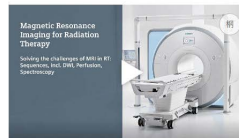
Solving the challenges of MR in RT: Signal, noise, distortion - 1.5T vs 3T

In this session, we focus on how the magnet and gradient design of an MRI system influences high resolution and low distortion combined with a large field of view as the key requirements for MR imaging in Radiation Therapy.



Solving the challenges of MR in RT: Gradients, RF system and coils

We will have a closer look at the gradient and Radio Frequency coils and how they can help to solve the specific challenges of using MRI in Radiation Therapy.



Solving the challenges of MR in RT: Sequences, incl. DWI, Perfusion, Spectroscopy

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MR-guided Gynecological High Dose Rate (HDR) Brachytherapy

Joann I. Prisciandaro¹; James M. Balter¹; Yue Cao¹; Katherine Maturen²; Amir Owringi¹; Shruti Jolly¹

¹ Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA

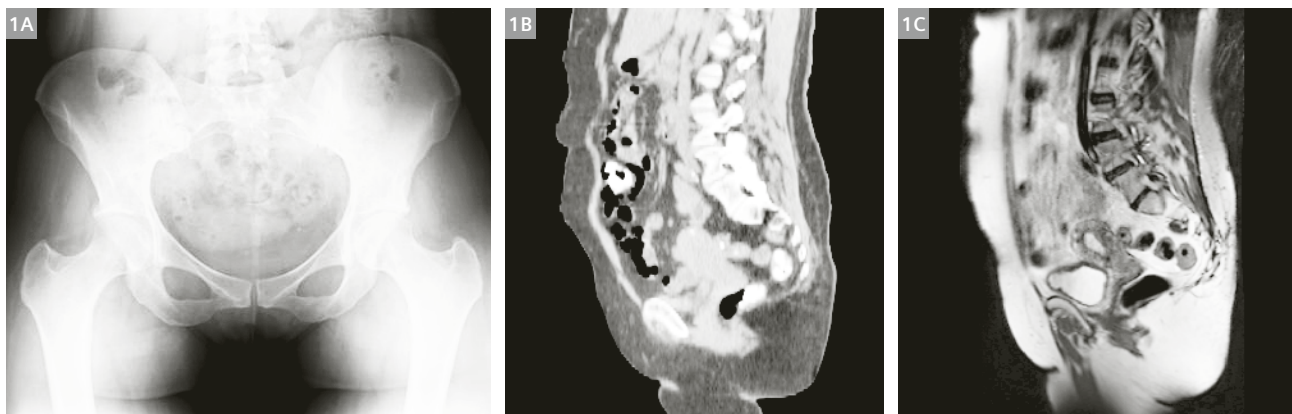
² Department of Radiology, University of Michigan, Ann Arbor, MI, USA

Introduction

Brachytherapy is a form of radiation therapy that is delivered using sealed radioactive sources positioned in close proximity to tissues with cancer. The term derives from the Greek meaning short distance therapy. It is one of the original forms of radiation therapy, and emerged shortly after the discovery of radium in the early 1900's. Up until the 1990's, little had changed in the way brachytherapy treatments were planned and delivered. The nominal workflow consisted of the selection and *in vitro* placement of the appropriate applicator (a device that contains the radioactive source(s)), acquisition of 2D radiographic images to determine the position of the applicator and sources relative to the patient's anatomy, determination of the desired dose to the cancerous tissues and dose limits to neighboring normal tissues, and development of a treatment strategy to deliver the dose. The last two steps are iterative, as one tries to optimize the position and length of time the radioactive source(s) may reside in the applicator to deliver the highest possible dose to the defined region of interest, while minimizing dose to neighboring normal tissues. However, 2D imaging presents limitations to the development of an optimal treatment plan. Although radiographs provide sharp subject contrast and detail between objects with highly

varying attenuation, such as bone and air, the limited differences in attenuation between different types of soft tissue make them difficult to discern (Fig. 1A). As a result, brachytherapy treatment plans have traditionally been designed to deliver the desired dose to a geometrically defined reference point relative to the applicator to which anatomic significance is attached. This approach limits the ability to individualize the patient's radiation to their specific tumor and normal tissues.

In the 1990's, as computed tomography (CT) and magnetic resonance imaging (MRI) became more widely available at clinics and hospitals, brachytherapy imaging began to transition from the use of planar to volumetric imaging. Unlike radiographs, volumetric images support some visualization of tumors and adjacent normal soft tissues (Figs. 1B, C). Compared to CT, MR images have the advantage of superior soft tissue resolution, and clear distinction of pelvic structures such as the uterus and cervix. Since local tumor control is strongly dependent on appropriately defined tumor volumes and the accurate delivery of radiation, the ability to visualize and delineate soft tissue is expected to improve target coverage and normal tissue sparing [1].



1 Example (1A) anterior pelvic radiograph [10], (1B) sagittal view of a pelvic CT simulation, and (1C) a sagittal reconstruction of a T2w 3D (SPACE) coronal image.

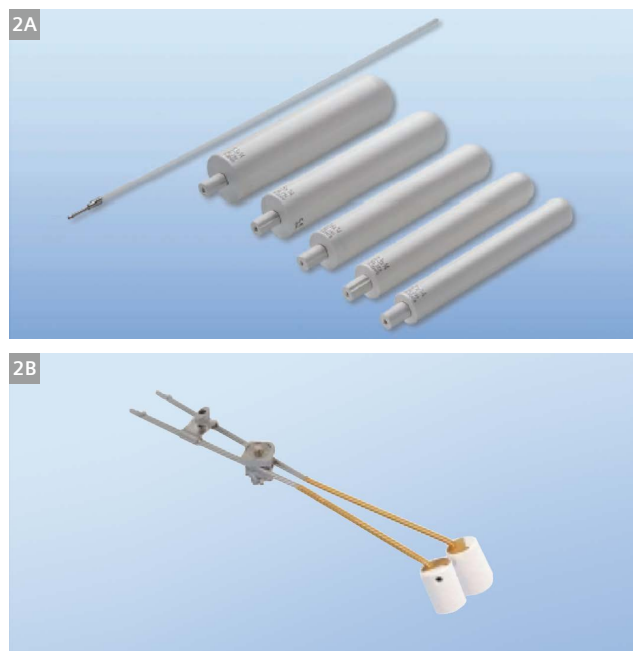
Beginning in 2000, GEC-ESTRO (the Groupe Européen de Curiethérapie – European Society for Radiotherapy & Oncology) recognized the significance of volumetric imaging in the movement toward 3D treatment planning for gynecological diseases, namely cervical cancer, with the formation of the gynecological (GYN) GEC-ESTRO work group [1]. In the fourteen years since its creation, the work group has released a series of recommendations to help standardize the approach to image-based brachytherapy treatment planning [1-4]. This has included the definition of a common language and means of delineating the target volumes (i.e., Low Risk-Clinical Target Volume (CTV), Intermediate Risk-CTV and High Risk-CTV for definitive treatment of cervix cancer), discussion on issues related to applicator reconstruction, and suggestions on the appropriate MR imaging sequences to utilize for treatment planning. Although these recommendations are helpful, there is a significant learning curve for each clinic during the clinical commissioning of MR-guided brachytherapy that is dependent on their specific MRI unit and brachytherapy applicators.

MR-simulator

In 2012, a 3T wide-bore MRI-simulator was installed in the department of Radiation Oncology at the University of Michigan (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). This unit was purchased for the express purpose of complementing, and at times, replacing CT treatment simulations, and has been outfitted with a laser marking system (LAP, Lueneburg, Germany) and detachable couch [5]. The couch supports imaging and treatment of brachytherapy patients, eliminating the need to transfer patients to other tables and the risk of inadvertently modifying the local geometry of the applicator and surrounding tissues. The brachytherapy suite is directly across the hall from the MRI-simulator, and an access door and path was built into the room design to permit wheeling the couch directly to the treatment suite following scanning.

Clinical commissioning

Prior to the clinical implementation of MR-guided brachytherapy, it is imperative to commission the process and workflow. Commissioning varies based on the desired treatment site, and involves the determination of the optimal imaging sequences for anatomical and applicator visualization. Care must be taken to ensure an MR conditional or compatible applicator is selected prior to the simulation. For treatment planning purposes, the images are imported into a software package (treatment planning system) that allows the user to identify the position of the applicator/potential source positions (a process known as applicator reconstruction) and the relevant patient anatomy. This software can then be used to optimize the length of time the

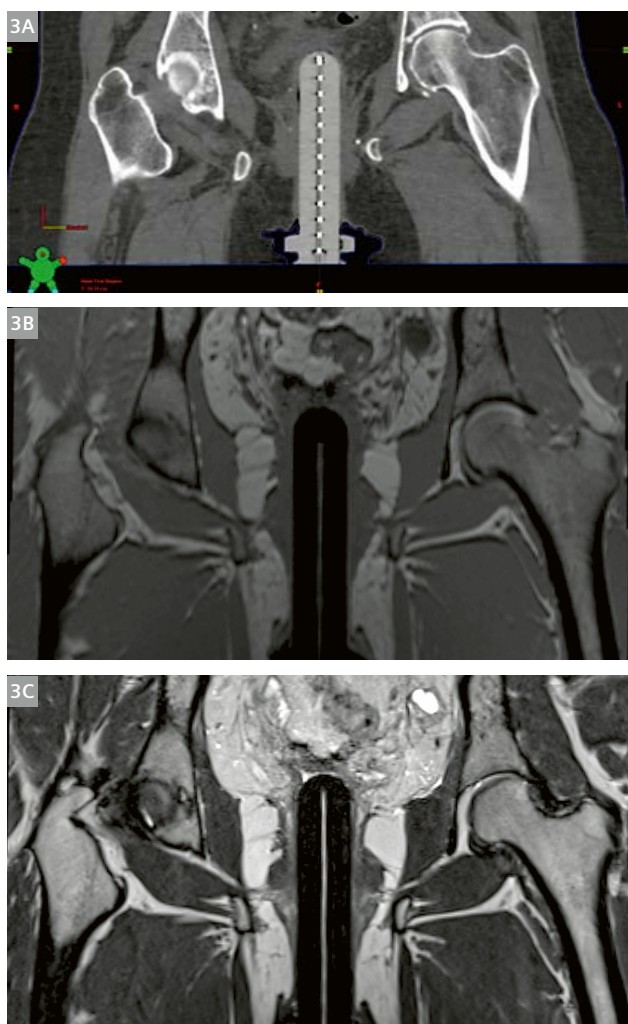


2 Common brachytherapy applicators used for vaginal brachytherapy delivery, **(2A)** vaginal cylinder (Varian Medical Systems, Palo Alto, CA, USA) and **(2B)** ovoids (modified from the Fletcher Williamson Applicator Set, Nucletron/Elekta, Veenendaal, The Netherlands).

radioactive source(s) should reside in various positions along the length of the applicator in order to deliver the desired dose and dose distribution to the patient. While the applicator, in particular the source channel (i.e., the hollow channel within the applicator where the source(s) may reside), is well-visualized in planar and CT imaging with the use of x-ray markers, this task is challenging with MRI. At present there are few MR markers that are commercially available to assist with applicator reconstruction. Additionally, the presence of the applicator, especially titanium applicators, produces image artifacts and distortions. Since dose calculations are dependent on the accurate definition of the applicator, namely the source position(s), relative to the patient's anatomy, geometrical uncertainties may result in dosimetric uncertainties to the target volume(s) and neighboring normal structures [3]. Thus, it is critical to evaluate these uncertainties prior to the clinical implementation of MR-guided brachytherapy.

a. Vaginal high dose rate (HDR) brachytherapy

Clinically, vaginal brachytherapy is most often used in the adjuvant treatment of uterine cancer post hysterectomy to reduce the risk of cancer recurrence in the vagina. Vaginal brachytherapy can also be used for treatment of other gynecologic cancers, including cervix, primary vaginal and vulvar cancer as clinically indicated. The typical applicators used for the delivery of vaginal brachytherapy are the vaginal cylinder and ovoids [6] (see Fig. 2).



3 Coronal view of a patient with a vaginal cylinder on (3A) CT, (3B) 3D T1w (MPRAGE) MR, and (3C) 3D T2w (SPACE) MR. To assist with the visualization of the central source channel, the appropriate marker (x-ray for CT and contrast filled for MR) was inserted in the applicator prior to simulations.

A vaginal cylinder is typically a smooth, plastic cylinder with a dome shaped apex that is available in diameters ranging from approximately 2.0–4.0 cm, depending on the patient's anatomy. The applicator typically has a single, hollow channel that runs along the center of the device; however, multi-channel variants are also available. Ovoids are hollow egg or cylinder-shaped capsules that are inserted into a patient's vagina and pressed up against the cervix if present or apex of the vaginal vault. Whereas the ovoids may be used to treat the upper portion of the vagina (known as the vaginal cuff), the vaginal cylinder offers the flexibility of treating the entire length of the vaginal vault [6].

During the clinical commissioning of MR-guided vaginal brachytherapy at the University of Michigan between August and September of 2013, three patients received a CT simulation preceding each HDR treatment with a Philips Brilliance CT scanner (Philips Medical, Chesterfield, MO, USA), followed by an MRI simulation using a Siemens MAGNETOM Skyra 3T scanner. The patients were positioned supine with their legs straight. The CT scan was acquired with a 1 mm slice thickness with an x-ray marker in place (see Figure 3A). The MRI was acquired with T1 and T2-weighted 3D imaging sequences. The following MRI sequences were used: 3D T2 (SPACE) coronal (FOV 320 × 320 × 176 mm, voxel size 0.94 × 0.94 × 1 mm, TR 1700 ms, TE 88 ms) and 3D T1 (MPRAGE) coronal (FOV 300 × 300 × 166.4 mm, voxel size 1.17 × 1.17 × 1.3 mm, TR 1900 ms, TE 2.35 ms, TI 900 ms, flip angle 9°). In order to identify the applicator channel, an MR marker was made in-house using a thin (0.046" outer diameter), hollow nylon tube (Best Medical International, Springfield, VA, USA) filled with gadolinium-doped water (T1 contrast) or either water or 0.2% Agarose Gel (T2 contrast), then sealed. Several different techniques were tested to seal the catheter ends including a heat seal with and without hot glue, bone wax with cyanoacrylate, and Water Weld™ with and without cyanoacrylate.

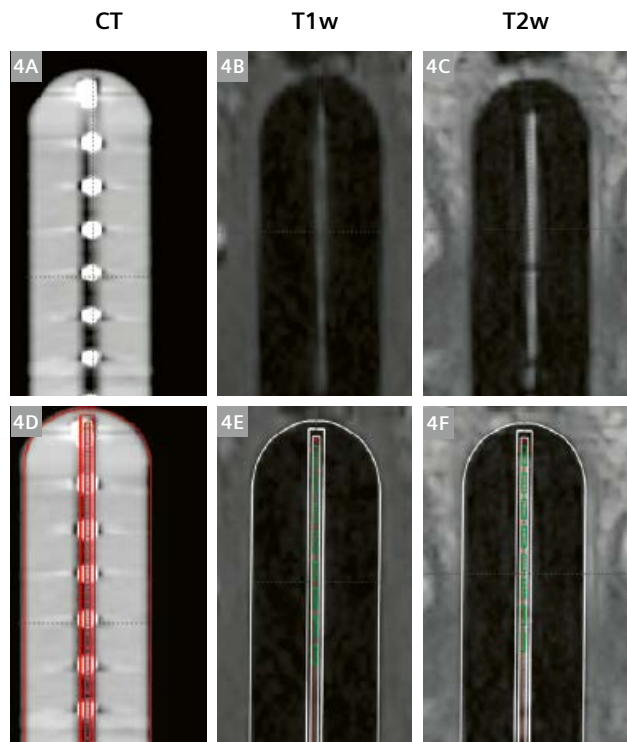
Although the applicator channel was easily visualized with the presence of the appropriate MR marker in both the T1w and T2w images as illustrated in Figures 3B and 3C, the applicator tip proved difficult to identify due to challenges in achieving a watertight seal. This resulted in observed displacements of the catheter tip, at times exceeding 1 cm. As such, an alternative method was investigated for applicator reconstruction using a solid model of the applicator available in the treatment planning software (BrachyVision 8.11, Varian Medical Systems, Palo Alto, CA, USA). Using T1w and/or T2w images, the solid model was aligned to the perimeter of the applicator (see Fig. 4). Deviations between the central source positions identified via aligning the applicator surface model to MR versus using the x-ray marker on CT to reconstruct the applicator (the conventional method) ranged from 0.07–0.19 cm and 0.07–0.20 cm for T1w and T2w images, respectively. Based on this study, vaginal brachytherapy patients at the University of Michigan now routinely undergo a single, T2w SPACE scan with approximately 1 mm isotropic voxel size. The applicator and related source positions for treatment planning are determined by alignment of the applicator model to the vaginal cylinder outline as observed on MRI.

b. Cervical HDR brachytherapy

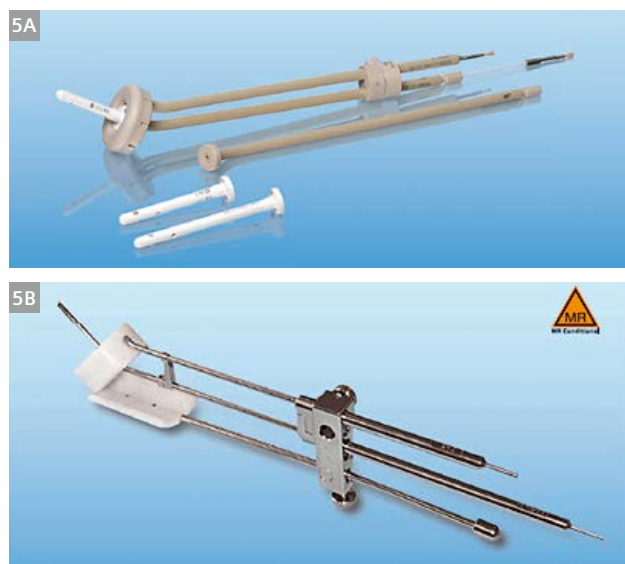
While cervical cancer remains the most common gynecologic cancer worldwide, in the United States, the incidence of cervical cancer has decreased significantly since the

widespread use of Papanicolaou (pap) smears in preventative care. Currently, approximately 12,000 new cases of cervical cancer are diagnosed per year. Treatment options are dependent on the stage of the disease upon clinical exam. Early stage cervical cancers are treated primarily by surgery. Occasionally, postoperative radiation or chemotherapy may be needed. When cervical tumors are not considered to be small enough to be removed by definitive hysterectomy, then curative or neoadjuvant radiation therapy with chemotherapy is the standard of care. In such situations, the patient undergoes combined external beam radiation with brachytherapy to provide high doses of radiation close to the tumor. Such treatments employ a variety of brachytherapy applicators. For most cases, the cervix can be treated using a combination of a tandem and ovoids, ring, or cylinder applicators [7]. However, when significant vaginal and/or parametrial involvement are present, then an interstitial brachytherapy implant may be needed to safely bring the required high doses of radiation to those areas.

At the University of Michigan, a plastic MR compatible ring and tandem applicator (GM11001220 and GM1100760, Varian Medical Systems, Palo Alto, CA, USA) has typically been used for HDR brachytherapy treatment of cervical cancer. This applicator system consists of an intrauterine catheter (tandem) and a circular, ring shaped device that allows the sealed source to be placed adjacent to the cervix (see Fig. 5A). During applicator commissioning which commenced in November 2013, 3D T2 (SPACE) sagittal images (FOV $300 \times 300 \times 79.2$ mm, voxel size $0.94 \times 0.94 \times 0.9$ mm, TR 1700 ms, TE 88 ms), 3D T1 (MPRAGE) sagittal images (FOV $300 \times 300 \times 79.2$ mm, voxel size $1.17 \times 1.17 \times 0.9$ mm, TR 1900 ms, TE 2.49 ms, TI 932 ms, flip angle 9°), and multi-planar 2D T2w images at 2–3 mm slice thickness, were acquired with in-house MR markers in each applicator. Although the tip of the tandem and ring was not visualized reproducibly due to the compromised seal of the MR markers, the source path and MR marker was discernable on the T1w images (see Fig. 6). As a result of the significantly higher acquisition time for the T2w versus T1w images (nearly twice the scan time), the source channel and MR markers were blurred due to patient and organ motion on the T2w images (see Fig. 6). To minimize scan time, multi-planar 2D T2w images as well as a 3D T1 (VIBE) sagittal scan with approximately 1 mm voxel size are acquired. Although the 2D T2w planar scans improve the quality of the resulting images, due to the large slice thickness of the 2D versus 3D MRI images, the MR marker was not visible on the 2D images. Therefore, 2D multi-planar T2w images as well as a small FOV 3D T2 (SPACE) sequence are acquired for soft tissue details, and 3D T1 (VIBE) sagittal images are acquired for applicator reconstruction. Prior to treatment planning, the registration of the T1w and T2w images is verified. If significant



4 Para-coronal view of the vaginal cylinder on (4A) CT, (4B) 3D T1w (MPRAGE) MR, and (4C) 3D T2w (SPACE) MR. Following alignment, the overlay of the solid applicator model is depicted for each imaging set in (4D–F).



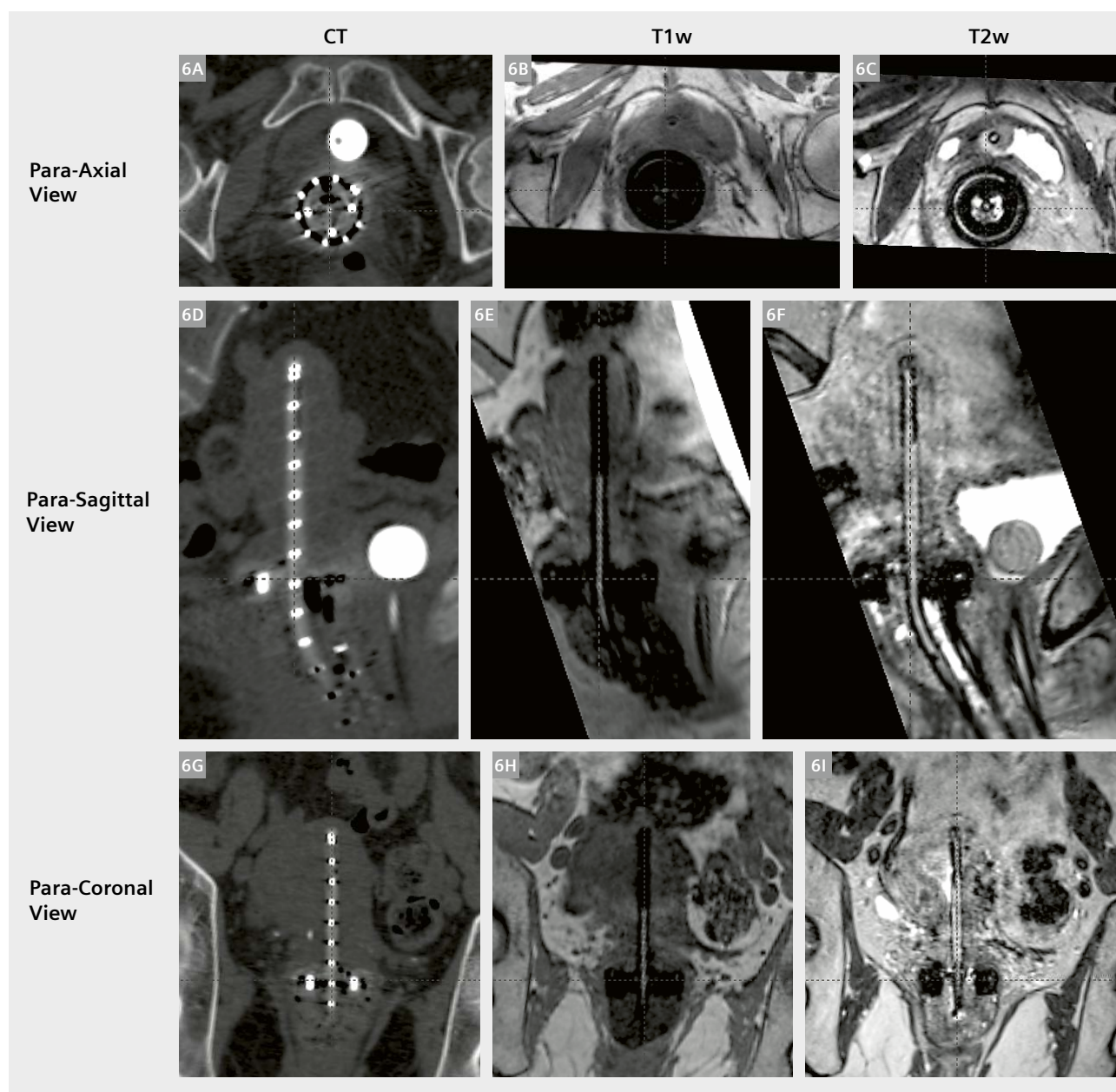
5 The (5A) plastic and (5B) titanium ring and tandem applicator system used at the University of Michigan (Varian Medical Systems, Palo Alto, CA, USA).

The MRI restrictions (if any) of the metal implant must be considered prior to patient undergoing MRI exam. MR imaging of patients with metallic implants brings specific risks. However, certain implants are approved by the governing regulatory bodies to be MR conditionally safe. For such implants, the previously mentioned warning may not be applicable. Please contact the implant manufacturer for the specific conditional information. The conditions for MR safety are the responsibility of the implant manufacturer, not of Siemens.

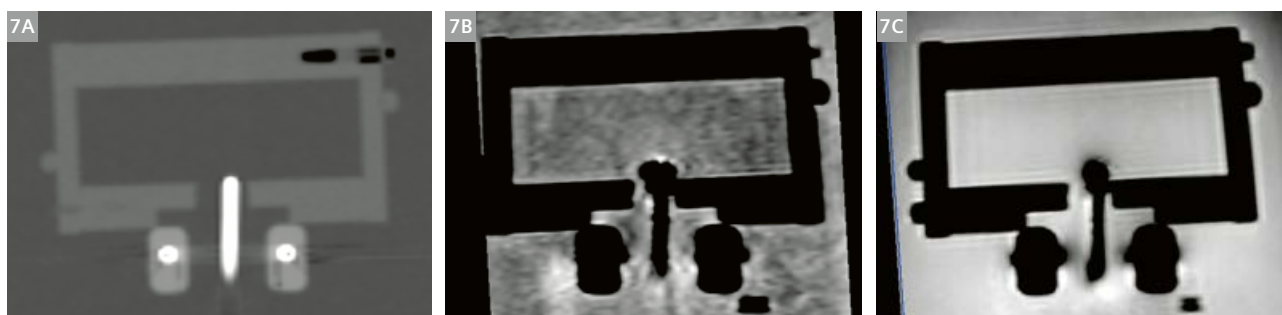
patient motion is observed, the images are manually registered in the treatment planning software.

Unlike the vaginal cylinder, a solid applicator model was not available in the treatment planning system for the utilized plastic ring and tandem system. As such, a user defined library plan and applicator model was developed based on the CT reconstruction of the applicator. When a new treatment planning simulation is acquired, the library plan is imported, and the applicator model is aligned based on the visible portions of the source channel, specifically focusing on the curvature of the tandem and/or ring.

Following a recent recall of the plastic ring and tandem system (PN BT-01366 Rev A, Varian Medical Systems, Palo Alto, CA, USA), a new titanium ring and tandem system (AL13017000, Varian Medical Systems, Palo Alto, CA, USA) has been purchased by the University of Michigan (see Fig. 5B). Due to susceptibility artifacts, the MR marker is not visible in the titanium applicator [8]. Additionally, these artifacts result in a mushroom effect off the tip of the applicator, making it challenging to accurately identify the applicator tip on MR (see Fig. 7). Kim et al. [9] have reported this effect to be considerably smaller when using



6 Comparison of CT, 3D T1w (MPRAGE), and 3D T2w (SPACE) images through the plastic ring and tandem system.



7 Comparison of (7A) CT, (7B) 3D T1w (MPRAGE), and (7C) 3D T2w (SPACE) sagittal images of the titanium ring and tandem system. The applicator set was scanned in a custom phantom designed to hold the applicator in a fixed position (based on [8, 9]). Prior to imaging, the phantom was filled with gadolinium-doped water. As compared to the CT image, magnetic susceptibility effects produce a mushroom effect off the tip of the tandem in the T1w and T2w images, resulting in uncertainties in the identification of the applicator tip on MRI.

a small slice thickness (i.e., 1 mm) T1w versus T2w MRI. With the recent arrival of the titanium ring and tandem system at our institution, the clinical commissioning of this applicator set is currently in progress.

Conclusions

MRI based image guided brachytherapy has the potential to significantly change the treatment planning process. Soft tissue contrast allows the user to customize treatment plans to accurately deliver therapeutic doses to the region-of-interest, while minimizing dose to the normal structures in the vicinity of the tumor, potentially resulting in fewer treatment-related complications. However, the transition from point to volume-based planning requires the user to perform a thorough set of commissioning tests to determine the geometric uncertainties related to their imaging and the associated dosimetric uncertainties.

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Contact

Joann I. Prisciandaro, Ph.D., FAAPM, Associate Professor
Dept. of Radiation Oncology
University of Michigan
Ann Arbor, MI
USA
Phone: +1 (734) 936-4309
joann@med.umich.edu



Joann Prisciandaro



Shruti Jolly

Optimizing MRI for Radiation Oncology: Initial Investigations

James Balter¹; Yue Cao¹; Hesheng Wang¹; Ke Huang¹; Shu-Hui Hsu¹; Martin Requardt²; Steven M. Shea³

¹Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA

²Siemens Healthcare, Erlangen, Germany

³Siemens Corporation, Corporate Technology, Baltimore, USA

Introduction

The superior soft tissue contrast, as well as potential for probing molecular composition and physiological behavior of tumors and normal tissues and their changes in response to therapy, makes MRI a tempting alternative to CT as a primary means of supporting the various processes involved in radiation therapy treatment planning and delivery. Obvious examples of the benefit of MRI over CT include target delineation of intracranial lesions, nasopharyngeal lesions, normal critical organs such as the spinal cord, tumors in the liver, and the boundaries of the prostate gland and likely cancerous regions within the prostate gland. For brachytherapy planning for cervical cancer, a recent GEC-ESTRO report directly recommends a change from traditional point-based prescriptions based primarily on applicator geometry, to volumetric treatment plans and prescriptions aided by soft tissue visualization, specifically improved by the use of MRI. MRI-based maps of diffusion and perfusion have demonstrated potential for predicting therapeutic outcome for tumors as well as normal tissues, and current clinical trials seek to validate their roles and performance as a means to individualize therapy to improve outcomes (minimize toxicity and improve local tumor control). In addition to these advantages, MRI has

been initially investigated as a means to better map the movement and deformation of organs over time and due to physiological processes such as breathing.

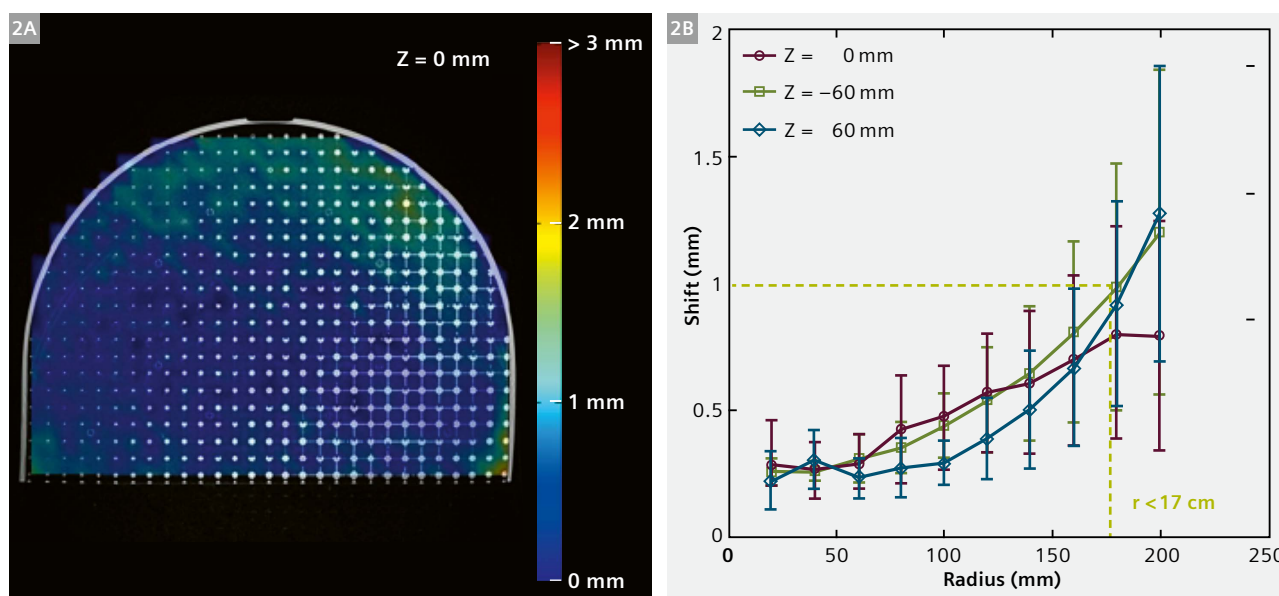
The historically accepted challenges in using MRI for primary patient modeling in radiation oncology have included distortion, lack of electron density information, and lack of integrated optimized systems to scan patients immobilized in treatment configuration.

MRI 'simulator' system

Over the past several years, we have investigated the feasibility of MRI systems to function in the same roles that CT scanners have for the past 10–15 years, that is as primary tools for patient modeling for radiation therapy. These efforts have accelerated in the past years with the installation of a dedicated MRI 'simulator' at the University of Michigan, based on a 3T wide-bore scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany), outfitted with a laser marking system (LAP, Lueneburg, Germany) and separate detachable couch tops supporting brachytherapy and external beam radiation therapy applications.



1 MRI simulation system shows a volunteer in position for initial setup wearing a customized face mask (**1A**). Close-up view of anterior coil setup and crosshairs from laser marking system (**1B**).



2 Colorwash of measured distortion through an axial plane of the distortion phantom (**2A**). Magnitude of distortion-induced shifts in circles of increasing radius from the bore center in axial planes at the center and ± 6 cm along the bore (**2B**).

The process of integrating MRI into the standard workflow of radiation oncology requires attention be paid to a number of specific areas of system design and performance. In our instance, we chose a system that could potentially support both external beam therapy as well as brachytherapy. The brachytherapy requirement played a specific role in some of our design choices. As the high-dose-rate (HDR) brachytherapy system was housed in a room across the hall from the MRI suite, a room design was created that permitted the direct transfer of patients from MRI scanning to treatment. Typically brachytherapy treatment has involved transferring patients to and from imaging systems, a process that could potentially influence the treatment geometry and changes the dose delivered away from that planned. Treating a patient directly without moving them has significant advantages for geometric integrity as well as patient comfort. To facilitate such treatments, a detachable couch was chosen as part of the magnet specifications, and two such couches were specifically purchased to support simultaneous treatment of patients on the couch used for MRI scanning and scanning of other patients for subsequent external beam treatments.

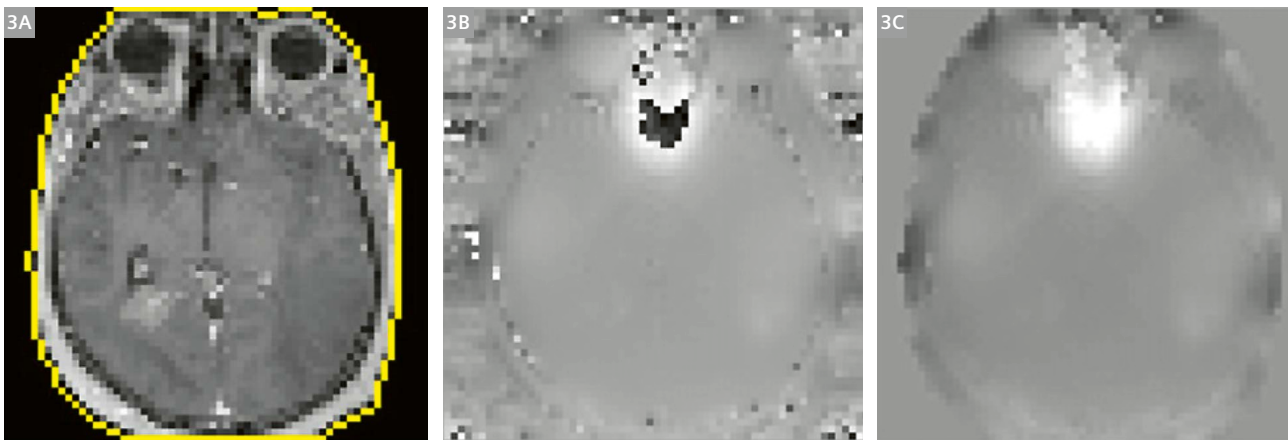
To support external beam radiotherapy, patients need to be scanned in positions and configurations that can be reproduced at treatment. In addition to necessitating a wide bore MRI scanner, an indexed flat table top insert was purchased from a company that specializes in radiation therapy immobilization systems (Civco, Kalona, IA, USA). A number of immobilization accessories were customized for use in the MRI environment, most notably a head and neck mask attachment system. To support high quality scanning of patients in treatment position without interfering with

their configuration for treatment, a series of attachments to hold surface coils (primarily 18-channel body coils) relatively close to the patient without touching are used.

Initial commissioning and tests

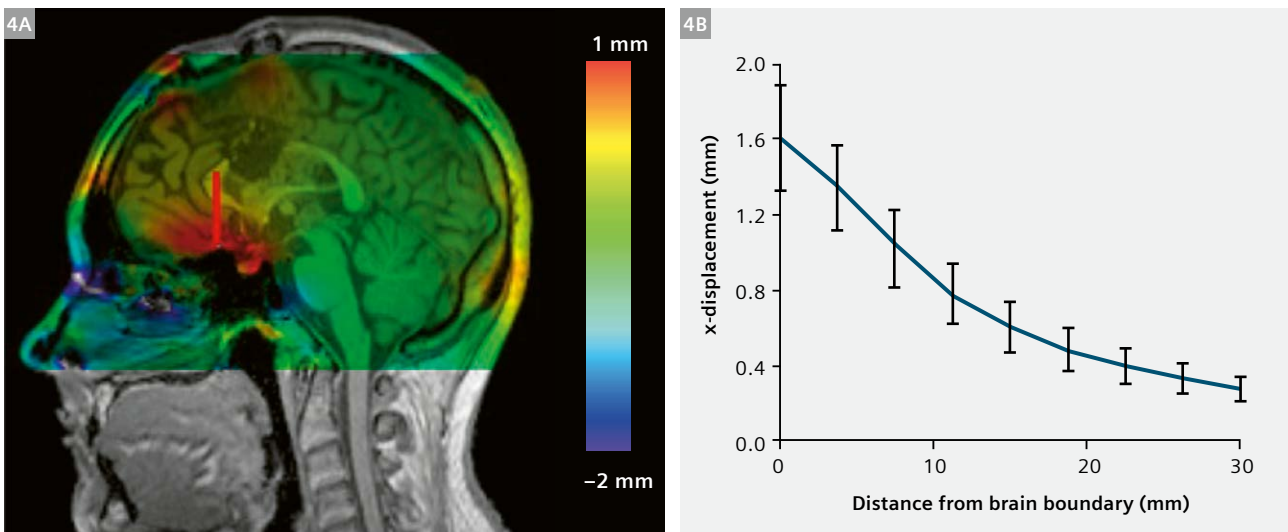
To commission the system, a number of tests were performed in addition to the standard processes for MRI acceptance and quality assurance. The laser system was calibrated to the scanner coordinates through imaging of a phantom with externally visible laser alignment markings and internal MRI-identifiable coordinates indicating the nominal laser intersection, and end-to-end tests were performed on phantoms and volunteers to establish the accuracy of isocenter marking using MRI scans as a source of input.

To characterize system-level distortion, a custom phantom was developed to fill the bore of the magnet (with perimeter space reserved for testing the 18-channel body coil if desired). The resulting phantom was a roughly cylindrical section with a sampling volume measuring 46.5 cm at the base, with a height of 35 cm, and a thickness of 16.8 cm. This sampling volume was embedded with a three-dimensional array of interconnected spheres, separated by 7 mm center-to-center distances. The resulting system provided a uniform grid of 4689 points to sample the local distortion. The phantom was initially scanned using a 3D, T1-weighted, spoiled gradient echo imaging sequence (VIBE, TR 4.39 ms and TE 2.03 ms, bandwidth 445 Hz/pixel) to acquire a volume with field-of-view of $500 \times 500 \times 170$ mm with a spatial resolution of $0.98 \times 0.98 \times 1$ mm. Standard 3D shimming was used for scanning, and 3D distortion correction was applied



3 T1-weighted image with external contour delineated as a mask (3A). The B_0 inhomogeneity map acquired from this subject (3B) was unwrapped within the boundaries of the mask, yielding the resulting distortion map (3C).

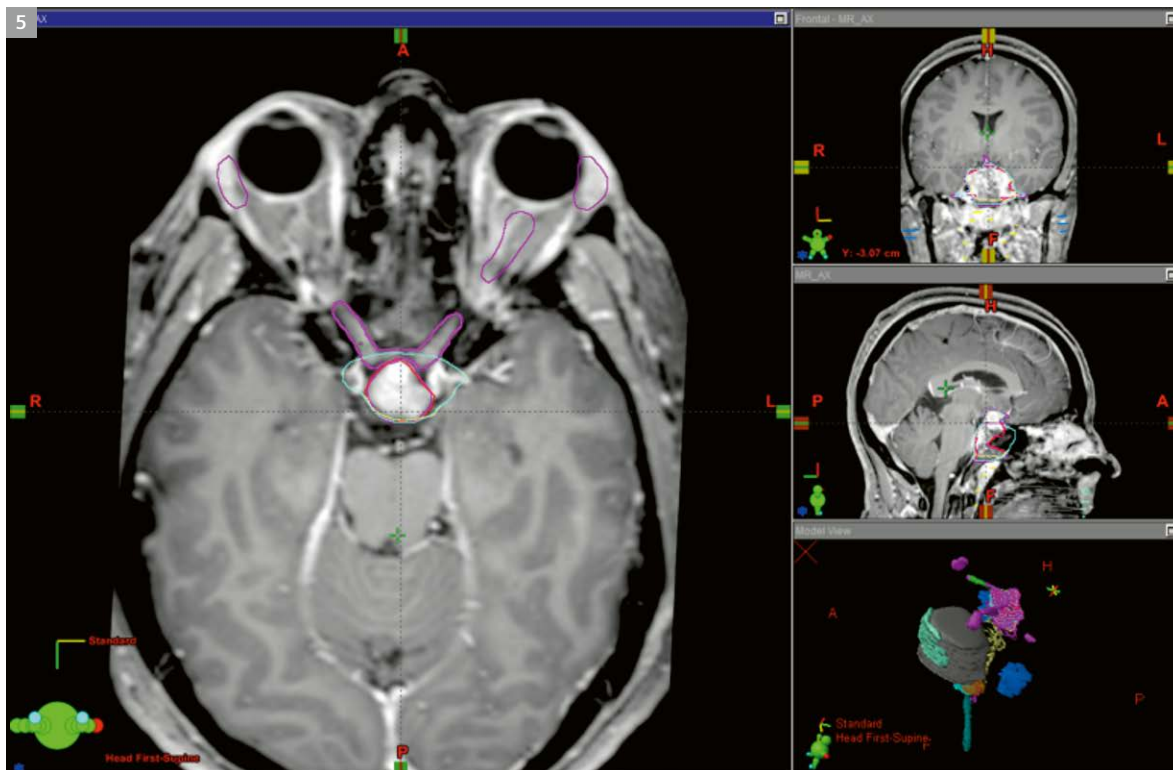
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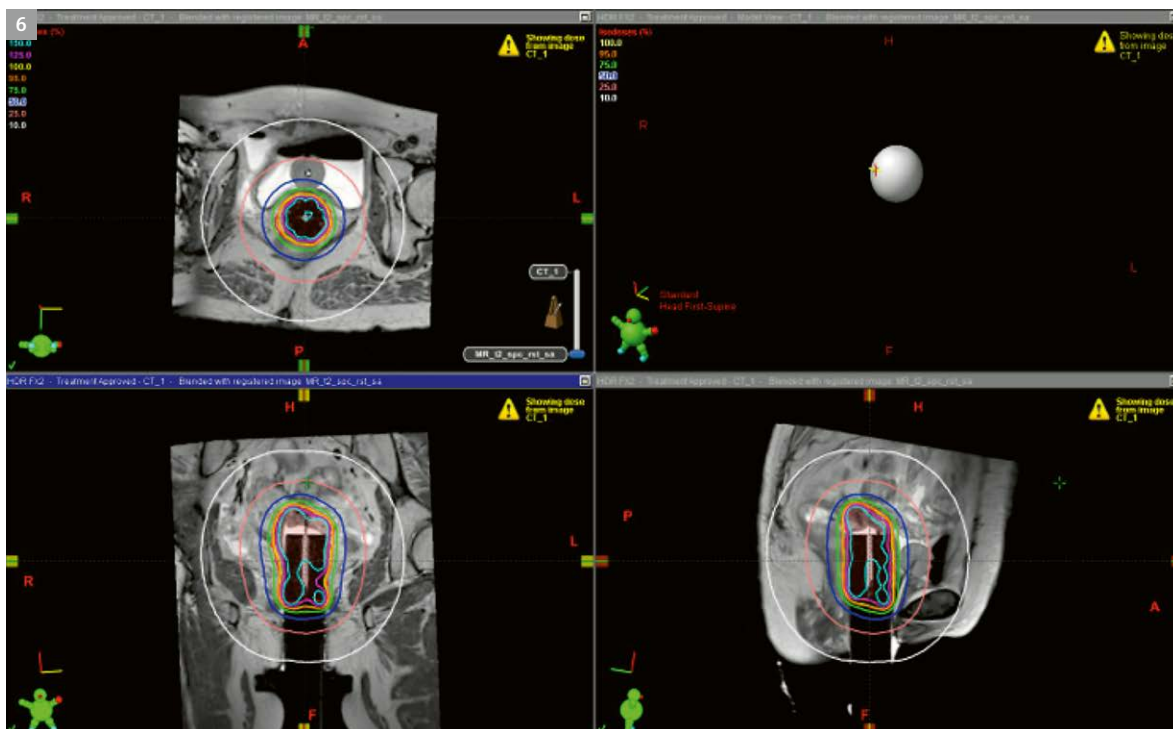
4 Colorwash of distortion-induced displacements through a sagittal plane of a subject (4A). Analysis of displacements along a line moving away from the sinus (red line in fig. 4A) shows the falloff of distortion due to susceptibility differences as a function of distance from the interface (4B).
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to the images prior to analysis. For this initial test, the body coil integrated into the magnet was used. Automated analysis of the images localized the sphere centers, yielding a deformation vector field that described the influence of system-level distortion on the measured sphere locations. This initial test demonstrated the accuracy of coordinate mapping via this scanning protocol, with average 3D distortions of less than 1 mm at radii of up to 17 cm in planes through the bore center as well as ± 6 cm along the bore length. Of note, scanning was performed using the *syngo* MR D11 software version. Future tests will be performed on the *syngo* MR D13 release.

To begin to assess the impact of subject-induced susceptibility on distortions, B_0 inhomogeneity maps were acquired during routine patient scanning and analyzed (for 19 patients) under an IRB-approved protocol. These maps were acquired using a 2D, double-echo, spoiled gradient echo sequence (GRE field mapping TE_1 4.92 ms, TE_2 7.38 ms, TR 400 ms, flip angle 60 degrees, voxel size $3.5 \times 3.5 \times 3.75$ mm), masked by the boundaries of the head acquired from T1-weighted images, and unwrapped using an algorithm from the Oxford Center for Functional Magnetic Resonance Imaging of the Brain [1]. The resulting maps showed homogeneity of 0.035 ppm or less over



5 Post-contrast T1-weighted images of a patient scanned in an immobilization mask using an anterior 18-channel body surface coil and a posterior 4-channel small soft coil and displayed in a radiation therapy treatment planning system (Eclipse, Varian, Palo Alto, CA, USA). Various delineated structures shown are used to guide optimization of intensity-modulated radiation therapy.



6 Display from a brachytherapy treatment planning system (Brachyvision, Varian, Palo Alto, CA, USA) showing orthogonal planes through cylindrical applicator implanted in a patient. Source locations (red dashes through the center of the applicator) are shown, as well as radiation isodose lines.

88.5% of a 22 cm diameter sphere, and 0.1 ppm or less for 100% of this volume.

These inhomogeneity maps were applied to calculate distortions from a typical clinical brain imaging sequence (3D T1-weighted MPRAGE sequence with TE 2.5 ms, Siemens TR 1900 ms, TI 900 ms, flip angle 9 degrees, voxel size $1.35 \times 1.35 \times 0.9$ mm, frequency-encoding sampling rate of 180 Hz/pixel). On these images, 86.9% of the volume of the head was displaced less than 0.5 mm, 97.4% was displaced less than 1 mm, and 99.9% of voxels exhibited less than 2 mm displacement. The largest distortions occurred at interfaces with significant susceptibility differences, most notably those between the brain and either metal implants or (more significantly) adjacent air cavities. In the location with the largest displacement (interface with the sinus), the average displacement of 1.6 mm at the interface falls to below 1 mm approximately 7 mm away.

Examples of clinical use

We have implemented a number of scanning protocols in our first year of operation. Routine scans are performed for patients with intracranial lesions of all forms, as well as for those with nasopharyngeal tumors, hepatocellular carcinoma, and certain spinal and pelvic lesions. Routine use of the system for MRI-based brachytherapy of patients with cervical cancer using a ring and tandem system is currently pending modification of part of the applicator for safety and image quality reasons, although patients undergoing other implants (e.g. cylinders) have had MRI scans to support treatment planning.

Summary

We have implemented the initial phase of MRI-based radiation oncology simulation in our department, and have scanned over 300 patients since operations began just over one year ago. The system demonstrates

sufficient geometric accuracy for supporting radiation oncology decisions for external beam radiation therapy, as well as brachytherapy. Work is ongoing in optimizing MRI scanning techniques for radiation oncology in various parts of the body and for various diseases. In addition to current and future work in optimizing MRI for use in routine radiation therapy, a variety of research protocols are underway using this system. A major current focus is on using MRI without CT for external beam radiation therapy. Results of these efforts will be presented in future articles.

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Contact

James M. Balter, Ph.D., FAAPM
Professor and co-director,
Physics division
Department of Radiation Oncology
University of Michigan
Ann Arbor, MI
USA
Phone: +1(734)936-9486
jbalter@umich.edu



Significant Benefit of Optimized 3D SPACE Sequences in Radiation Therapy Treatment

Maja Sohlin, Ph.D.¹; Karin Petruson, M.D., Ph.D.²

¹ Sahlgrenska University Hospital, Medical Physics and Biomedical Engineering, Gothenburg, Sweden

² Sahlgrenska University Hospital, Department of Oncology, Gothenburg, Sweden

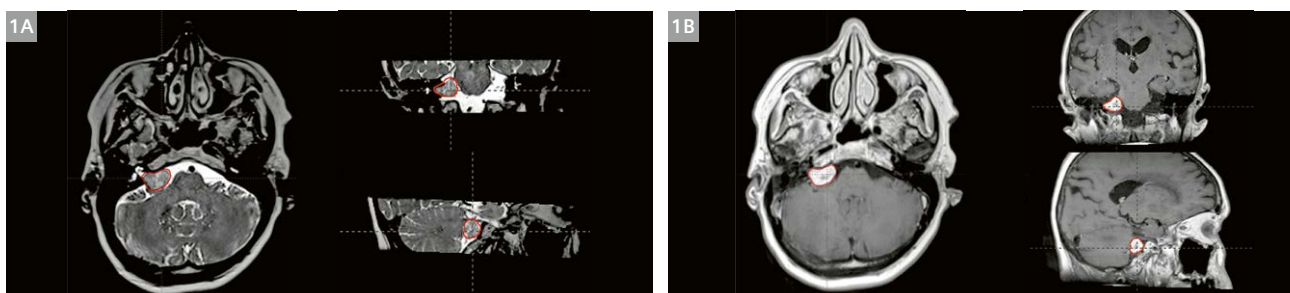
MR images used in radiation therapy have other requirements than conventional diagnostic MR images. In radiation therapy, the exact extent and position of lesions in relation to critical structures have to be determined in order to ensure an effective and safe treatment of the patient. This requires high in-plane spatial resolution, thin slices without slice gaps, and a minimal geometric distortion. In addition, due to image registration and patient fixation, a sub-optimal patient set-up is often required, including flexible coil solutions and a flat table top.

MR imaging struggles with system-related and patient-induced geometric distortions. For radiation therapy, the imaging protocols must be optimized to give minimal geometric distortions in the imaging volume. In general, the geometric integrity is best preserved by using spin-echo based sequences with high acquisition bandwidth. In the current workflow, MR images used for therapy planning have to be registered to a CT dataset. The imaging protocol must thus also be optimized to give sufficient image contrast and adequate spatial resolution to ensure an accurate image registration, with a trade-off between registration accuracy and image quality. Acquiring thin slices (<2-3 mm) without slice gaps using standard 2D multi-slice acquisitions results in either low signal-to-noise ratio or unreasonably long acquisition times, the latter not only inconvenient for the patient but also an increased risk of introduction of motion artefacts in the images.

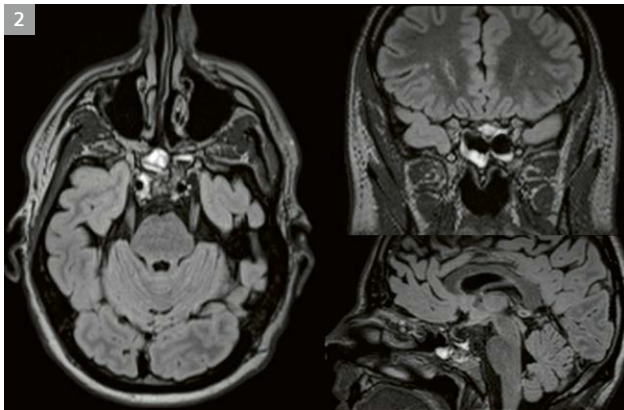
Although still not optimal for all applications, we found several examinations to benefit from the use of optimized fast isotropic 3D acquisitions. Utilization of the SPACE sequence for therapy planning has increased the possi-

bilities we have to delineate small tumors intended for treatment with high-dose radiotherapy. The sequence has shown to be very helpful in defining small benign as well as malignant brain tumors. At our clinic, these tumors are treated with stereotactic radiotherapy that involves a very narrow margin between the gross tumor volume and the planning target volume intended for treatment, which makes an exact tumor volume definition essential for successful treatment.

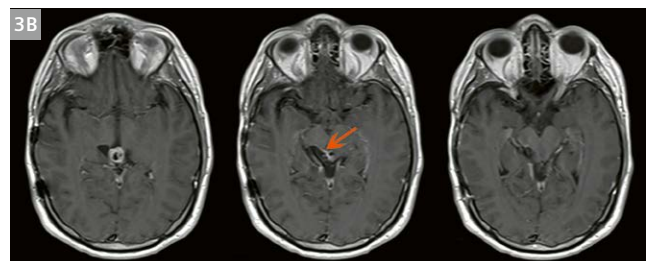
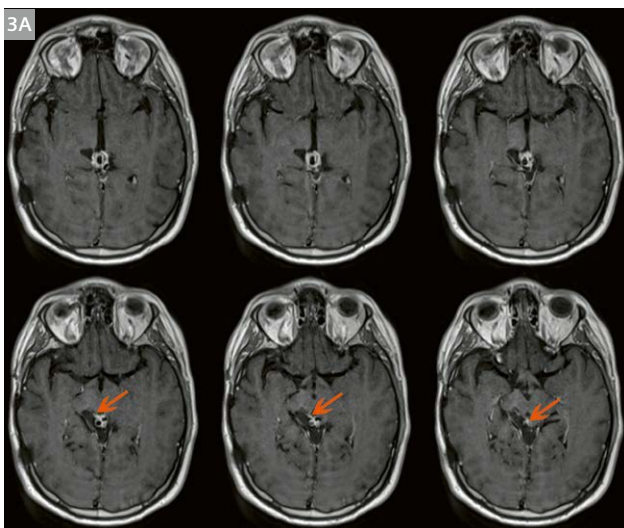
Further, we are in the initial stages of incorporating MRI in the workflow for brachytherapy for head-and-neck cancer patients. At our clinic, patients with cancer in the tongue and the base of tongue without nodal spread receive external radiotherapy combined with chemotherapy to the primary tumor site and to non-engaged lymph node sites. Some of the patients also receive an additional brachytherapy boost to the primary tumor site. The volume intended to receive the boost has been decided by the head-and-neck radio oncologist after a digital examination prior to brachy loop implantation. We have seen a great benefit of using a T1 3D SPACE MRI after the brachy loop implantation to reconstruct the loops and to verify that the tumor remnant is within reach of the radiotherapy. The possibility to reconstruct images in any arbitrary plane combined with the excellent image quality will increase the possibilities for us to offer patients a more exact treatment, sparing the salivary glands and mandibular bone. In conclusion, we are so far very satisfied with the SPACE sequence for several applications in radiation therapy and we see a great advantage of investing further optimization work to introduce the sequence in the treatment of other anatomical areas.



1 The gross tumor volume of a vestibular schwannoma on the T2-weighted SPACE (1A), and T1-weighted contrast enhanced SPACE (1B). The high (1 mm) and isotropic resolution of the SPACE sequence is highly beneficial for therapy planning of vestibular schwannoma as many schwannoma are as small as a few millimeters. The excellent image contrast on the T2-weighted SPACE may eliminate the need for contrast enhanced acquisitions.

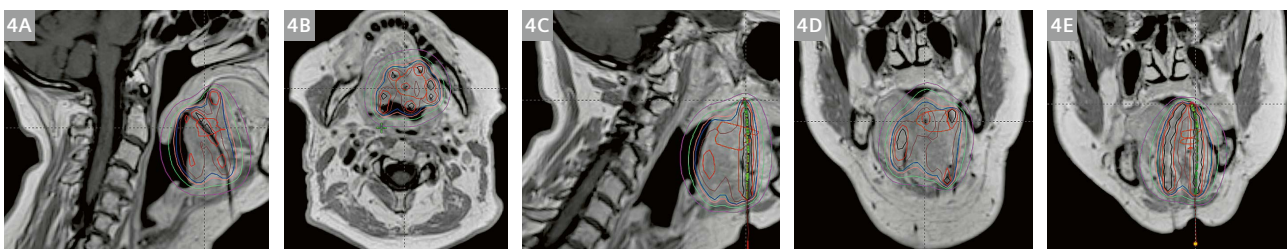


- 2** A patient diagnosed with a chordoma. Initial surgery was due to technical difficulties not completely radical and the patient will receive adjuvant radiotherapy to the remaining chordoma. Due to the close vicinity to the optical nerves it is extremely important to be able to define the exact volume of the tumor in order to minimize negative treatment effects of the radiotherapy. A T2-weighted SPACE dark fluid.



- 3** A patient who was diagnosed with a germinoma of the corpus pineale five years ago. He was initially treated with radio-chemotherapy and now shows a local recurrence. T1-weighted contrast-enhanced SPACE (**3A**) and standard T1-weighted contrast enhanced 2D TSE with a slice thickness of 3 mm (**3B**). The standard 2D TSE was not sufficient to determine the extent of the recurrent tumor.

- 4** Dose distribution for a brachytherapy patient on a T1-weighted SPACE (**4A-C**), and with an applicator reconstructed (**4D-E**).



Contact

Karin Petruson, M.D., Ph.D.
Radiation Oncologist
Sahlgrenska University Hospital
Department of Oncology
Blå stråket 2
413 45 Gothenburg
Sweden
karin.petruson@vgregion.se



Contact

Maja Sohlin, Ph.D.
Medical Physicist
Sahlgrenska University Hospital
Medical Physics and
Biomedical Engineering
Bruna stråket 13
413 45 Gothenburg
Sweden
maja.sohlin@vgregion.se



10 Years of Clinical Experience of MRI in Radiotherapy Treatment Planning: The Newcastle upon Tyne Story

Hazel McCallum, Ph.D.; Jonathan Wyatt, M.Sc.; Stephen Hedley, M.Sc.; Serena West, B.Sc.; Tim Dowling, B.Sc.; John Frew, F.R.C.R.; Rachel Pearson, F.R.C.R., Ph.D.; Christopher Walker, B.Sc

Northern Centre for Cancer Care, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

Introduction

The Northern Centre for Cancer Care installed its first MRI scanner dedicated for radiotherapy and oncology purposes in 2009, one of the first in the UK. Now with the hindsight of nearly ten years' experience, the evolution and development of MRI in radiotherapy planning in Newcastle upon Tyne will be described, from the first prostate patients planned with an MRI fused with a CT, extending to other treatment sites, to the first UK prostate patient to be treated with an MR-only pathway. In 2009, MRI was introduced as an important addition to the conventional CT planning process; it now forms an indispensable part of the radiotherapy service and paves the way for MR guided radiotherapy treatments with the introduction of MR-linacs.

Setting up the service

In 2007-08, when the hospital produced the specification for tender, there was only one wide-bore MRI scanner on the UK market, the Siemens MAGNETOM Espree 1.5T. An evaluation visit to Umea University Hospital, Sweden was a key influence, as the Newcastle team were able to observe an MRI scanner set-up for radiotherapy treatment planning, complete with laser bridge and in-house manufactured flat couch-top. Encouraged by the Umea University team, the purchase of a Siemens MAGNETOM 1.5T was confirmed in September 2008.

Multi-disciplinary collaboration was essential to the successful introduction of the service. Advice and guidance was provided by the Radiology Department throughout the planning, procurement installation and implementation stages. The appointment of an experienced MRI diagnostic radiographer was key, as their experience of sequence development as well as patient and staff safety provided some security in the early implementation phases.

Technical preparation

Commissioning for radiotherapy treatment planning

In 2009, there was little published data on performance standards for an MRI scanner for radiotherapy purposes. The radiotherapy department had access to a set of MagNet MRI QC phantoms, no longer commercially available and a large field of view geometric distortion phantom designed and built in Newcastle University [1].

An Evaluation Report on the Siemens MAGNETOM Espree, published by the NHS Purchasing and Supply Agency was used for much of the QC development and initial performance tolerances. Extensive experience of commissioning CT scanners and treatment imaging modalities was relied upon to develop additional tests which would consider radiotherapy aspects such as detailed geometric accuracy testing.

MRI commissioning tests

- Laser positional accuracy
- Couch level and scaling
- MRI compatibility of Immobilization devices
- Image quality
- Large FOV geometric distortion
- Geometric slice position and width
- Data transfer inter-operability
- Image fusion accuracy

MRI RT planning specific equipment

At the inception of our clinical service, there was no commercially available compatible flat couch top. We entered into a research collaboration with MediBord, Nottingham, UK to develop a bespoke flat couch top to fit with our scanner model and our preferred patient set-up. The couch top material is glass fibre which means the couch top is

extremely light, at less than 4 kg, and easy to maneuver. This is particularly important when the radiotherapy couch top needs to be replaced by the diagnostic couch top for clinical trials patient scanning or diagnostic scans for radiotherapy patients. The couch-top securing mechanism was designed to fit into the coil strap fittings on the Siemens MAGNETOM couch. The flat couch top was designed by NCCC staff and manufactured by Medibord. Figure 1 shows details of the couch top.

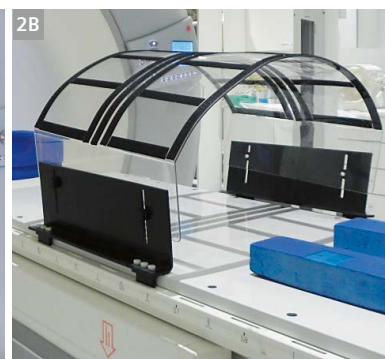
When acquiring diagnostic MR images, typically the surface coils are directly wrapped around the patient. This can compress the patient's skin, which is not appropriate for radiotherapy planning where an accurate image of the patient's external contour is essential.

To avoid any distortion of the patient skin contour, coil supports for pelvis and head and neck were designed and manufactured in-house by the Mechanical Workshop, Northern Medical Physics and Clinical Engineering. The pelvis coil support secures in position in the coil strap fittings, is manufactured from polyethylene terephthalate glycol (PTEG) and polyvinyl chloride (PVC) and is adjustable to suit a range of patient sizes. Hook and loop fastening is fixed to the PTEG surface to assist with securing the coils onto the support. The coil support for pelvic imaging is shown in figure 2.

The head and neck coil support is manufactured from PTEG and secured onto an in-house manufactured MRI compatible head board (Fig. 3).



1 (1A) Medibord RT flat couch top (1B) access to head coil fixtures (1C) retaining access to coil securing fixtures and utilizing these fixtures for securing the couch top in position.



2 (2A) In-house manufactured coils support for pelvis imaging (2B) showing the couch securing mechanism and adjustable size.



3 In-house manufactured coils support for brain and head and neck imaging.

MRI safety

From the outset, it was clear that education and adjustment was needed to safely introduce an MRI Suite in the center of a clinical radiotherapy treatment center. Considerations for access management to the MRI control area, were new concepts for radiotherapy staff who were more familiar with the model that any hazard was removed when the power was switched off. Management of projectile hazards was also of concern. The MRI Suite control room door is key-coded to enable controlled access to the MRI control room and so to the MRI examination room. Early incidents of wiped credit cards and stopped watches served to underline the new working practices required.

Clinical preparation

Development of radiotherapy specific MRI protocols was based heavily on those developed in Umea University, who provided extensive informal mentoring support in the set-up of our service.

Prostate

The first patient cohort to receive MRI RT planning acquisitions was prostate patients. Two acquisition sequences were used: a 3D T2-weighted Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE) sequence which was optimized to image the entire patient outline with a small voxel size ($1.2 \times 1.2 \times 1.7 \text{ mm}^3$) and a high bandwidth to minimize geometric distortion, and a small FOV T2-weighted Turbo Spin Echo (TSE) sequence. The SPACE sequences has since been further optimized and the TSE sequence replaced with a Multi-Echo Data Image Contribution (MEDIC) sequence which is acquired over a smaller field of view to assist with the definition of the in-slice boundary of the prostate capsule.

A typical patient set-up is shown in figure 4, with details of the current acquisition protocols.



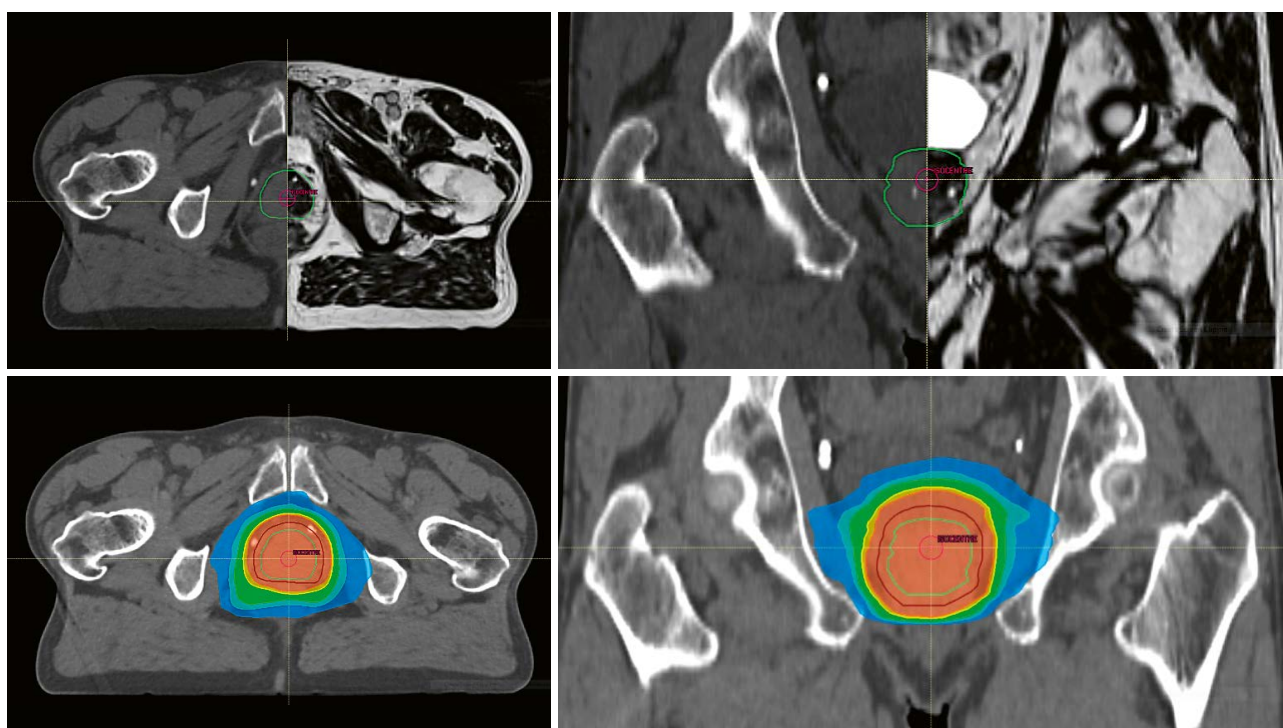
4 Typical patient set-up for prostate MRI acquisition and MRI acquisition parameters.

Prostate delineation protocols were developed with the help of Radiologist input. This inter-disciplinary team identified a difference in imaging task between diagnosis and delineation.

The experience of a radiologist identified the regions of disease within the prostate, but did not need to identify the boundary of the prostate gland, whereas a clinical oncologist needs to accurately delineate the boundary of the prostate gland. Cross disciplinary learning produced guidelines on prostate delineation based on MRI when fused with a planning CT. Methods of managing differences in patient anatomy between the MRI and CT scanning sessions were developed. There are inevitable patient set-up differences, both in posture and internal anatomy position. Rigid registration can take account of postural differences, but cannot completely compensate for differences in internal anatomy caused by changes in bowel and bladder filling. As the CT scan is used as the basis of the treatment plan and the reference image set for image guided radiotherapy, any differences in anatomy between CT and MRI tend to be compensated for by reverting to the CT anatomy as the gold standard. This inevitably compromises the added benefit of the MRI acquisition and results in an 'MRI guided CT delineation' for prostate GTV with OARs delineated on the CT scan. This means that the excellent MRI soft tissue image quality is not always able to be used to its full potential, providing experiential evidence of the benefit of an MR-only patient pathway. A typical CT-MRI image registration for a prostate patient, and the resultant dose distribution are shown in figure 5.

The clinical service was quickly extended to gynecological EBRT sites in January 2010. It was found that the same T2 3D SPACE acquisition protocol was suitable for cervix and uterus visualization. The acquisition sequences have now further developed and include two 2D sequences to assist with delineation, as shown in Table 1.

Sequence name	SPACE tse_vfl	MEDIC
Echo time	211 ms	22 ms
Repetition time	1500 ms	674 ms
Flip angle	150°	28°
Bandwidth	601 Hz/px	190 Hz/px
Orientation	Axial	Axial
Dimension	3D	2D
Field of View	450 x 447.3 mm ²	260 x 260 mm ²
Number of slices	120	34
Voxel size	1.4 x 1.4 x 1.5 mm ³	1.3 x 1.0 x 3.0 mm ³



5 CT-MRI image fusion with delineation and VMAT dose distribution.

Sequence name	SPACE tse_vfl	TSE	TSE
Echo time	165 ms	102 ms	101 ms
Repetition time	2000 ms	9840 ms	6300 ms
Flip angle	150°	150°	150°
Bandwidth	651 Hz/px	140 Hz/px	150 Hz/px
Orientation	Axial	Sagittal	Axial
Dimension	3D	2D	2D
Field of View	320 x 320 mm ²	290 x 280 mm ²	260 x 260 mm ²
Number of slices	144	28	45
Voxel size	1.3 x 1.3 x 1.5 mm ³	1.1 x 1.1 x 4.0 mm ³	1.0 x 1.0 x 4.0 mm ³

Table 1: MRI acquisitions for treatment planning of gynecological tumors.

Brain

MRI imaging for selected brain tumors was introduced in January 2011. Patients are scanned without the immobilization device so that the head coil can be used.

A T1 axial 3D sequence is used for delineation of the GTV. Typical patient images and the MRI sequence parameters are shown in figure 6.

Head and neck

The introduction of MRI imaging for oro and hypopharyngeal tumors began in April 2011. Two sequences

were developed to assist with GTV delineation and nodal and organ at risk delineation. A T1 VIBE post contrast acquisition was used to delineate GTV and a T2 sequence to delineate lymph nodes and organs at risk. Figure 7, shows a typical patient set-up and coil arrangement utilizing the in-house manufactured coil support. A second flex coil may be positioned over the patient's shoulders if required. The MRI acquisition parameters are also shown in figure 7 and typical patient images and dose distribution shown in figure 8.



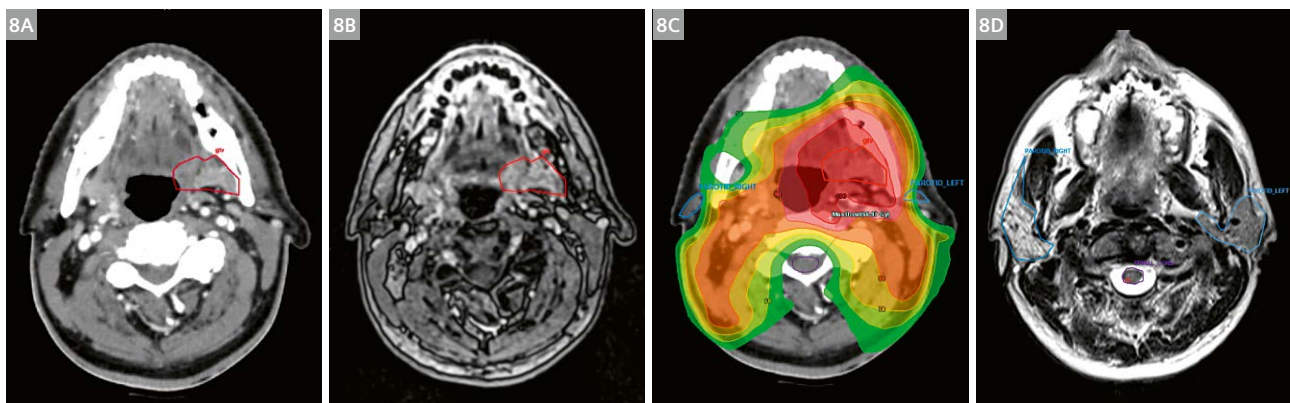
Sequence name	fl3d_vibe
Echo time	2.39 ms
Repetition time	9.00 ms
Flip angle	12°
Bandwidth	210 Hz/px
Orientation	Axial
Dimension	3D
Field of View	250 x 250 mm ²
Number of slices	192
Voxel size	1.1 x 1.0 x 1.0 mm ³

6 Soft tissue detail on MRI [LHS] and CT [Center] with MRI parameters shown on RHS.



7 A typical head and neck coil arrangement and MRI acquisition parameters.

Sequence name	fl3d_vibe	TSE
Echo time	2.39 ms	89 ms
Repetition time	9.00 ms	6000 ms
Flip angle	12°	150°
Bandwidth	210 Hz/px	159 Hz/px
Orientation	Axial	Axial
Dimension	3D	2D
Field of View	250 x 250 mm ²	310 x 271.25 mm ²
Number of slices	224	70
Voxel size	1.1 x 1.0 x 1.0 mm ³	1.1 x 0.8 x 3.0 mm ³



8 Typical image set **(8A)** CT, **(8B)** T1w VIBE **(8C)** dose distribution **(8D)** T2w TSE.

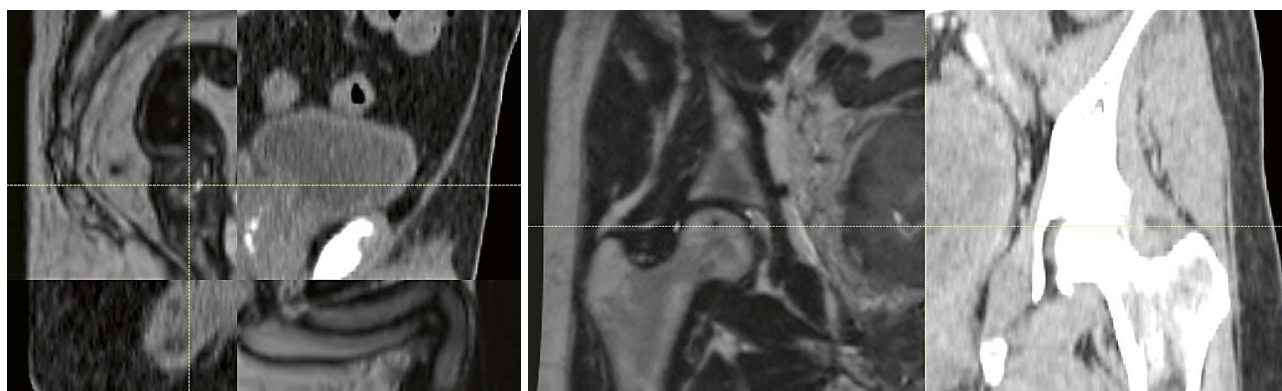
Rectum

Routine MR imaging for rectal cancer patients was introduced in April 2018. With MRI planning scans for anus patients then following in September, 2018. Patient set-up is similar to that for prostate patients.

The MRI acquisition parameters are shown for rectum patients in Table 2 and for anus patients in Table 3. A typical example of CT-MRI image registration for planning of a rectal cancer is shown in figure 9.

Sequence name	SPACE tse_vfl	TSE	TSE
Echo time	211 ms	102 ms	101 ms
Repetition time	1500 ms	9840 ms	6300 ms
Flip angle	150°	150°	150°
Bandwidth	601 Hz/px	140 Hz/px	150 Hz/px
Orientation	Axial	Sagittal	Axial
Dimension	3D	2D	2D
Field of View	450 x 447.3 mm ²	280 x 280 mm ²	260 x 260 mm ²
Number of slices	144	28	45
Voxel size	1.4 x 1.4 x 1.5 mm ³	1.1 x 1.1 x 4.0 mm ³	1.0 x 1.0 x 4.0 mm ³

Table 2: MRI acquisitions for treatment planning of rectal tumors.



9 MRI-CT fusion for rectum and anus.

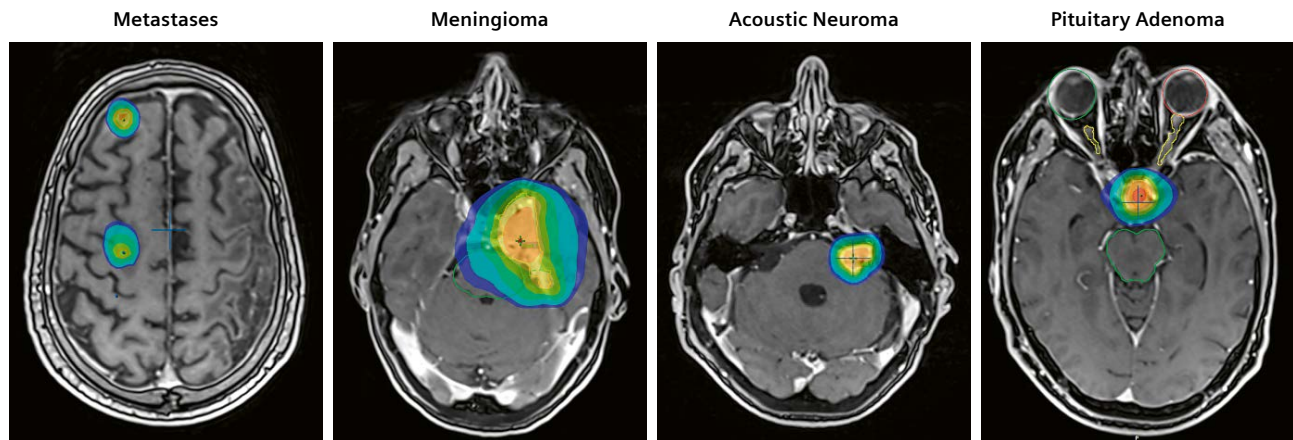
Sequence name	SPACE tse_vfl	TSE	TSE
Echo time	165 ms	102 ms	101 ms
Repetition time	2000 ms	9840 ms	6300 ms
Flip angle	150°	150°	150°
Bandwidth	651 Hz/px	140 Hz/px	150 Hz/px
Orientation	Axial	Sagittal	Axial
Dimension	3D	2D	2D
Field of View	320 x 320 mm ²	280 x 280 mm ²	260 x 260 mm ²
Number of slices	144	28	45
Voxel size	1.3 x 1.3 x 1.5 mm ³	1.1 x 1.1 x 4.0 mm ³	1.0 x 1.0 x 4.0 mm ³

Table 3: MRI acquisitions for treatment planning of anal tumors.

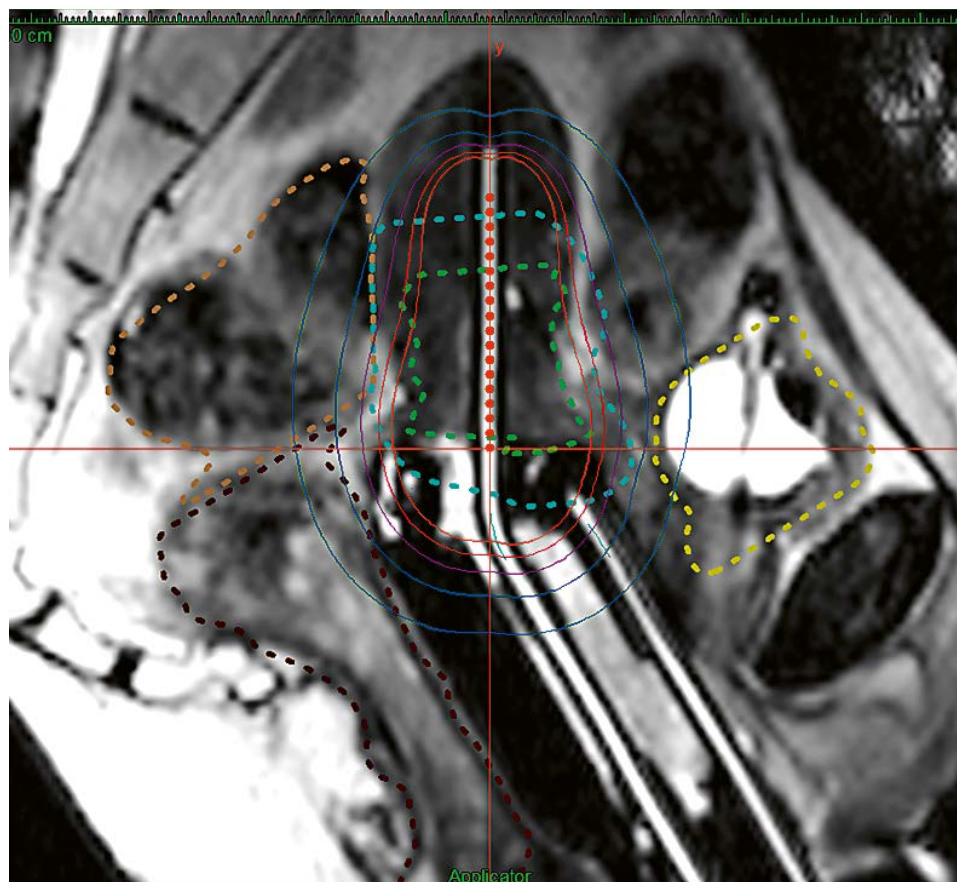
SRS Brain

Newcastle is one of 17 Cancer Centers in England commissioned by NHS England to deliver Stereotactic RadioSurgery (SRS) and has been treating SRS patients since June 2015. Rapid access to planning MRI scans is essential to delivery of this service, particularly for patients

travelling large distances. A range of MRI sequences are acquired, often tailored to the specific clinical presentation and vitally supported by neuroradiologists. Figure 10 shows a range of SRS brain tumors with the MRI acquisition image and the treatment dose distribution.



10 SRS brain treatments showing a range of treatment sites with the dose distribution.



11 MRI planning image showing a cervical ring brachytherapy treatment. The dashed lines show the clinical delineations and the solid lines the brachytherapy dose distribution.

Brachytherapy

MRI acquisitions for brachytherapy post-planning for prostate I-125 implants began in February 2010, with MRI-only planning for cervix brachytherapy being implemented in September, 2011. MRI-only planning for vaginal vault brachytherapy treatments was introduced in July, 2012 when MRI was also introduced as a position check for vaginal vault applicator insertions for patients with intermediate and high risk endometrial cancer. Figure 11 shows a brachytherapy treatment for cervical cancer.

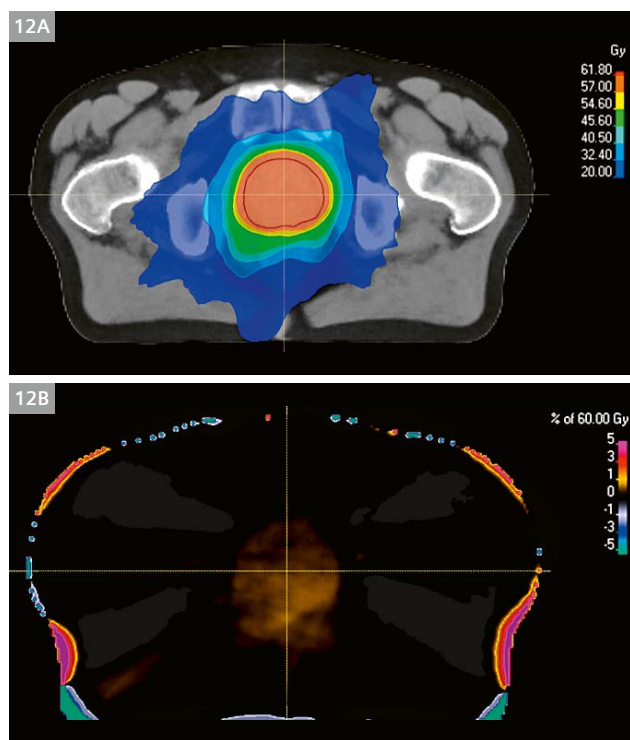
MRI-only planning

Our growing experience in CT-MR fusion for radiotherapy delineations emphasized the compromises that were necessary to account for differences in patient position and preparation between the CT and MRI imaging sessions. This was resulting in a limitation of the benefit of MRI as the CT image set was used as the standard where there were anatomical discrepancies between the CT and MRI. Feedback from Clinical Oncologists described increasing frustration at the compromises that were being imposed by limitations in the technique. NCCC has been investigating the technical development of an MR-only patient pathway

since 2016 with research partners in Australia, UK and Sweden. Conventional CT-MR based radiotherapy planning utilizes the superior soft tissue provided by the MRI for target and OAR delineation, and the CT image to account for different types of tissue in the dose calculation. An MR-only pathway requires an appropriate dataset for dose calculation, a synthetic CT, and the NCCC research group have investigated the accuracy of available algorithms [2].

MR also suffers from geometric distortion, which is of some concern in radiotherapy planning image sets. A dedicated large field of view distortion phantom and automated analysis software was evaluated [3] and is now used in monthly quality assurance. Radiotherapy specific Quality Control programmes have been developed to ensure adequate geometric fidelity and demonstrate consistent performance of the clinical MR scanner. MR-only pathways are available in some European radiotherapy centers using X-ray IGRT treatment machines, but there is an important difference in the treatment pathway between these centers and NCCC. Prior to radiotherapy treatment being delivered at each visit, an imaging session is performed on the treatment machine to ensure that the patient is set-up and aligned as accurately as possible. In the existing clinical centers in Europe, this is achieved using fiducial markers, whereas image matching using soft tissue anatomy is used in Newcastle, sparing the patient the procedure required to insert fiducial markers. This means that the MRI image used to develop the treatment plan can be used as a reference image for the on-treatment image verification.

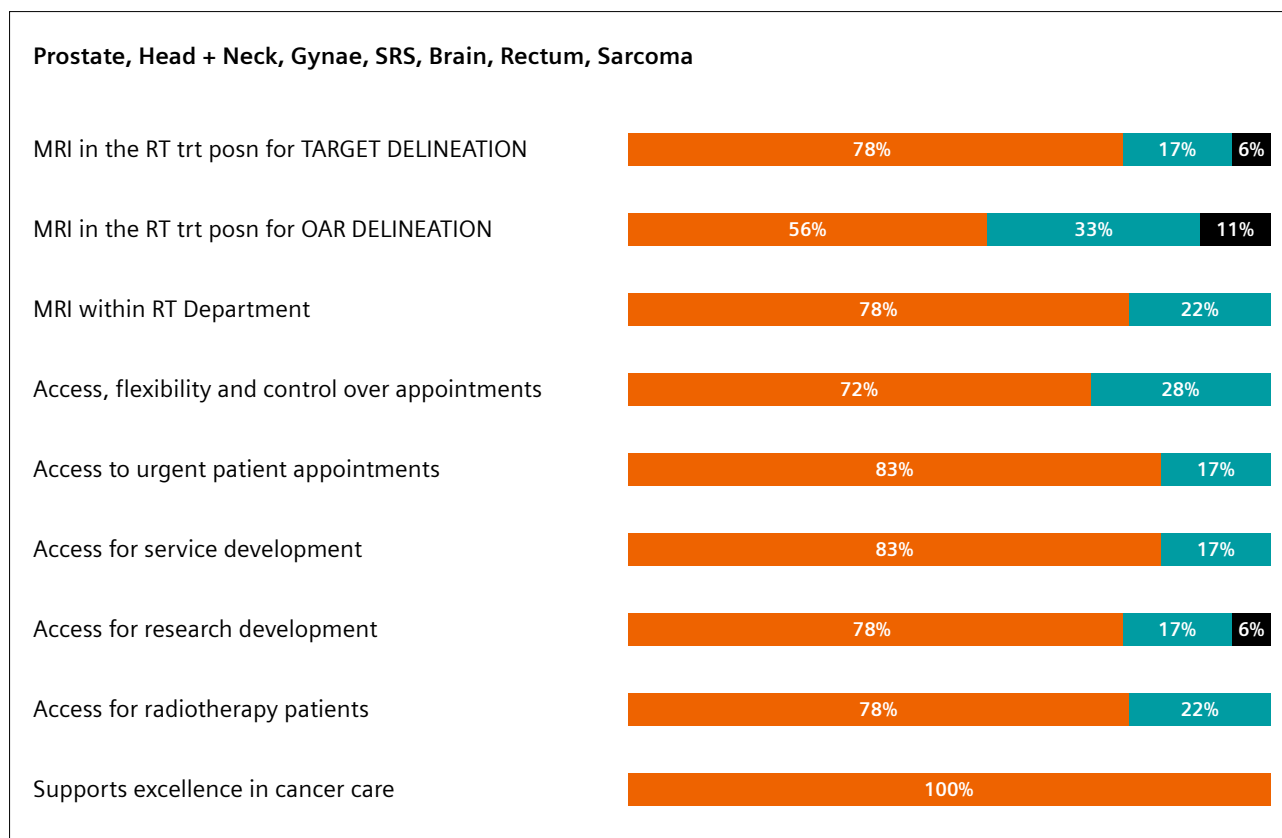
Our research experience coupled with our clinical experience means we felt confident in making the step from research to routine for MR-only planning for prostate patients. Our first MR-only prostate patients were treated in January 2019. Figure 12 shows the clinical dose distribution on the synthetic CT and the dose difference between the clinical plan and the QA plan calculated on the back-up CT.



12 First MR-only prostate patient – dose distribution (12A) and dose difference to CT (12B).

Planning for the future

As the replacement date of our radiotherapy MRI approached, MR acquisition activity was not enough to justify a second purchase and it was important to capture the clinical opinion of the role of MR in radiotherapy planning. A survey of Consultant Clinical Oncologists in NCCC was performed where participants were asked to score a range of statements on a five point scale for the treatment sites which were routine at the time of the survey [4]. The five point scale is shown on the next page.



13 Responses for external beam treatment sites where a planning MRI is acquired.

The response rate was 73% and figure 13 shows the results for external beam treatment sites which include a planning MRI.

The survey showed an overwhelmingly positive response for sites which currently receive planning MRI scans. When asked how important it is to acquire MRI scans in the treatment position for target and OAR delineation, no **Unimportant** or **Very Unimportant** responses were received. The **Neutral** responses referred to Brain cases, where it was felt that although MRI is **Very Important**, the patient position is less so, as rigid registration within the skull offers clinically acceptable results. There was also very strong support for the planning MRI scanner to be located within the radiotherapy department.

Summary

NCCC were one of the first UK cancer centers to install a dedicated MRI scanner for radiotherapy planning, in 2009. The clinical workload and clinical scope has significantly increased over the first 10 years so that over 35% of radical patients in Newcastle now receive an MRI to improve their planning pathway. Practices and equipment have developed greatly over the past ten years and manufacturers now offer commercial coil bridges and supports, however our experience with in-house developments may be useful on further developing commercial products. There was overwhelming clinical support to replace our radiotherapy MRI scanner and we are now looking forward to extending our MR-only pathway for prostate patients to other treatment sites, cementing MRI as indispensable to the radiotherapy pathway. The image (right) shows the NCCC MR in RT Team.

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The authors would like to acknowledge the contribution of Jill McKenna to the development and introduction of the NCCC MRI service.

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Contact

Dr. H. M. McCallum
Consultant Clinical Scientist
Radiotherapy Physics
Northern Centre for Cancer Care,
Freeman Hospital
Newcastle upon Tyne, NE7 7DN
UK
Tel.: +44 (0)191 213 8112
hazel.mccallum@nuth.nhs.uk

Dr. Rachel Pearson
Consultant Clinical Scientist
Radiotherapy Physics
Northern Centre for Cancer Care,
Freeman Hospital
Newcastle upon Tyne, NE7 7DN
UK
Tel.: +44 (0)191 213 8521
rachel.pearson@nuth.nhs.uk



The NCCC MRI Team [left to right] **Timothy Dowling** and **Steve Harris**, Senior MRI Imaging Radiographers; **Rachel Pearson**, Consultant Clinical Oncologist; **Rachel Brooks**, Research and Development Clinical Specialist Radiographer; **Iraje Ahmed**, MRI Imaging Radiographer; **Elizabeth Raven**, Superintendent Treatment Radiographer; **Hazel McCallum**, Consultant Clinical Scientist; **Karen Pilling**, Clinical Lead Superintendent Radiographer; **Serena West**, Imaging Superintendent Radiographer; **Jonathan Wyatt**, Clinical Scientist.

Siemens Healthineers' global MRI community offers peer-to-peer support and information. Radiation Oncologists, Radiologists, Medical Physicists, Technologists and Cardiologists have all contributed with publications, presentations, training documents, videos, case studies and more – all freely available to you via this unique network.

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The Importance of Collaboration between Clinical Radiology and Radiation Oncology in the Era of Precision Radiation Therapy

Amish Lakhani, MBBS MA (Cantab) FRCR¹; Yat Man Tsang, BSc MSc PhD²; Roberto Alonzi, BSc MBBS MRCP FRCR MD³; Anwar R. Padhani, MBBS FRCP FRCR¹

¹Consultant Radiologist, Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, Middlesex, UK

²Consultant Radiographer – Specialised Service Delivery, Mount Vernon Hospital, Northwood, Middlesex, UK

³Consultant Clinical Oncologist, Mount Vernon Hospital, Northwood, Middlesex, UK

Introduction

Radiation therapy is an essential component in the management of many cancer patients. It can be used for primary treatment, local control, and palliation in over 50% of cancer patients [1]. Radiation therapy has been shown to be an integral part of the treatment regime in 40% of patients who are cured of cancer, therefore making this treatment modality extremely cost-effective [2].

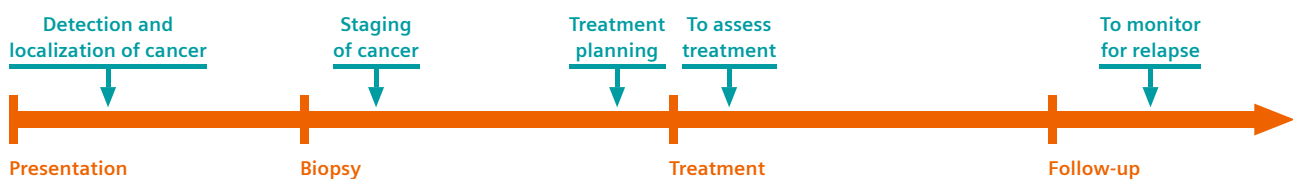
Key to the success of radiation therapy is the ability of the radiation oncologist to accurately delineate the tumor to maximize delivery of the radiation dose to the cancer whilst minimizing dose toxicity to the adjacent normal tissues. This has become increasingly possible with technological advances in highly conformal radiation therapy delivery methods such as intensity-modulated radiotherapy (IMRT) and stereotactic body radiation therapy (SBRT). Paralleling the advances in radiotherapy delivery methods are the technological advances in imaging with the development of next-generation techniques such as magnetic resonance imaging (MRI) with quantitative functional biomarkers, and positron emission tomography/computed tomography (PET/CT) with novel tracers. These

advances in imaging have improved the sensitivity and specificity of identifying tumor location and extent [3]. In this article we highlight examples of these advancements and demonstrate how collaboration between the clinical radiology and radiation oncology departments enhances treatment effectiveness.

Imaging in the cancer patient's pathway

Imaging is an integral component in almost every step of the cancer patient's pathway from detection and localization of cancer all the way to monitoring for recurrence once treatment is completed (Fig. 1). Using prostate cancer as an example, we will demonstrate how technological advancements in imaging are able to image the tumor microenvironment and normal tissues, and how we can use this to aid accurate and successful radiation treatments.

Multiparametric MRI (mpMRI) of the prostate is now routinely used in patients with suspected prostate cancer [4]. With mpMRI we can utilize multiple MRI sequences to depict different biological properties: Morphological T1 and



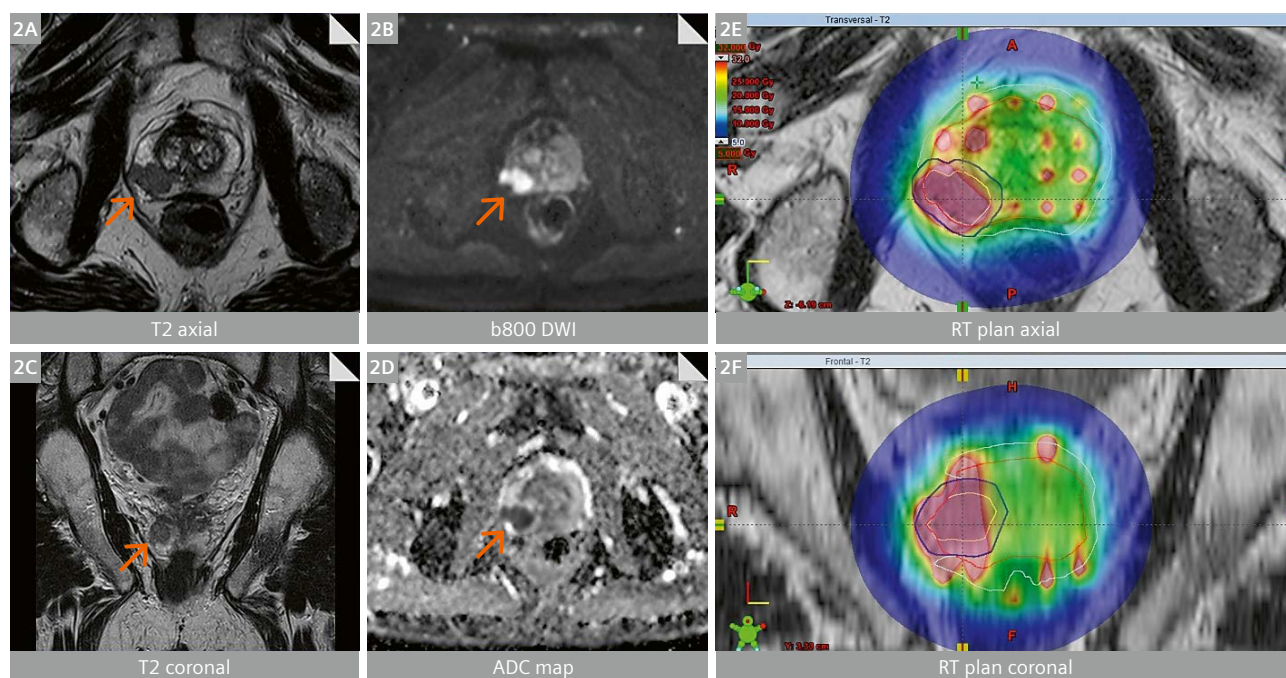
1 Imaging (green arrows) is integral throughout the cancer patient's pathway (orange arrow).

T2-weighted sequences give us information on anatomy; diffusion-weighted imaging (DWI) informs us of cellular density and necrosis; spectroscopy identifies cell proliferation and replacement of normal glandular tissues; and dynamic contrast enhancement (DCE) gives us information on perfusion and vascular permeability. Utilizing these properties it is possible to accurately detect, localize, and locally stage prostate cancer. mpMRI is also important to guide and/or direct biopsy via fusion techniques, and MRI may also be used to perform an in-bore biopsy if required.

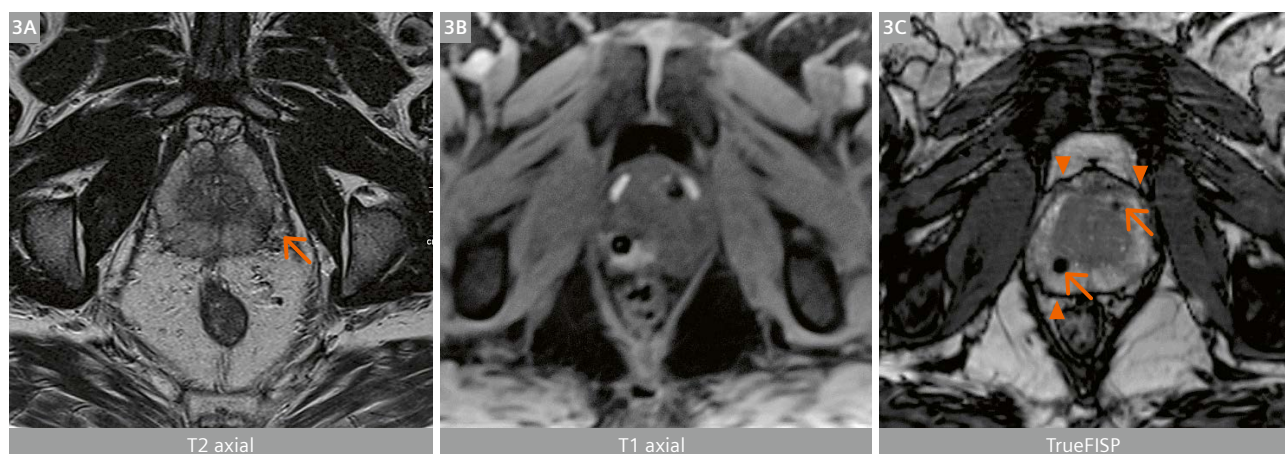
If a patient is diagnosed with prostate cancer localized to the pelvis, pelvic radiotherapy may be a suitable treatment option even in the presence of oligometastases. Even though mpMRI has been shown to yield high detection rates of clinically significant prostate cancer (csPC) [5], multiple studies have shown it can underestimate the volume and extent of intra-prostatic disease in patients with known prostate cancer [6]. This is why it is important to include the entire prostate gland in the gross tumor volume (GTV) when planning radiotherapy. However, we can also utilize the confidence of mpMRI in identifying the more aggressive index lesions which can be given a focal boost of radiation treatment (Fig. 2). In this example, the mpMRI clearly shows the dominant right-sided index lesion on the anatomical and DWI, allowing this patient to undergo biologically optimized radiotherapy; the planning computer optimization software was programmed to maximize the radiation dose

to the dominant index lesion with a focal boost, and to limit the dose to the rest of the gland to a defined ceiling.

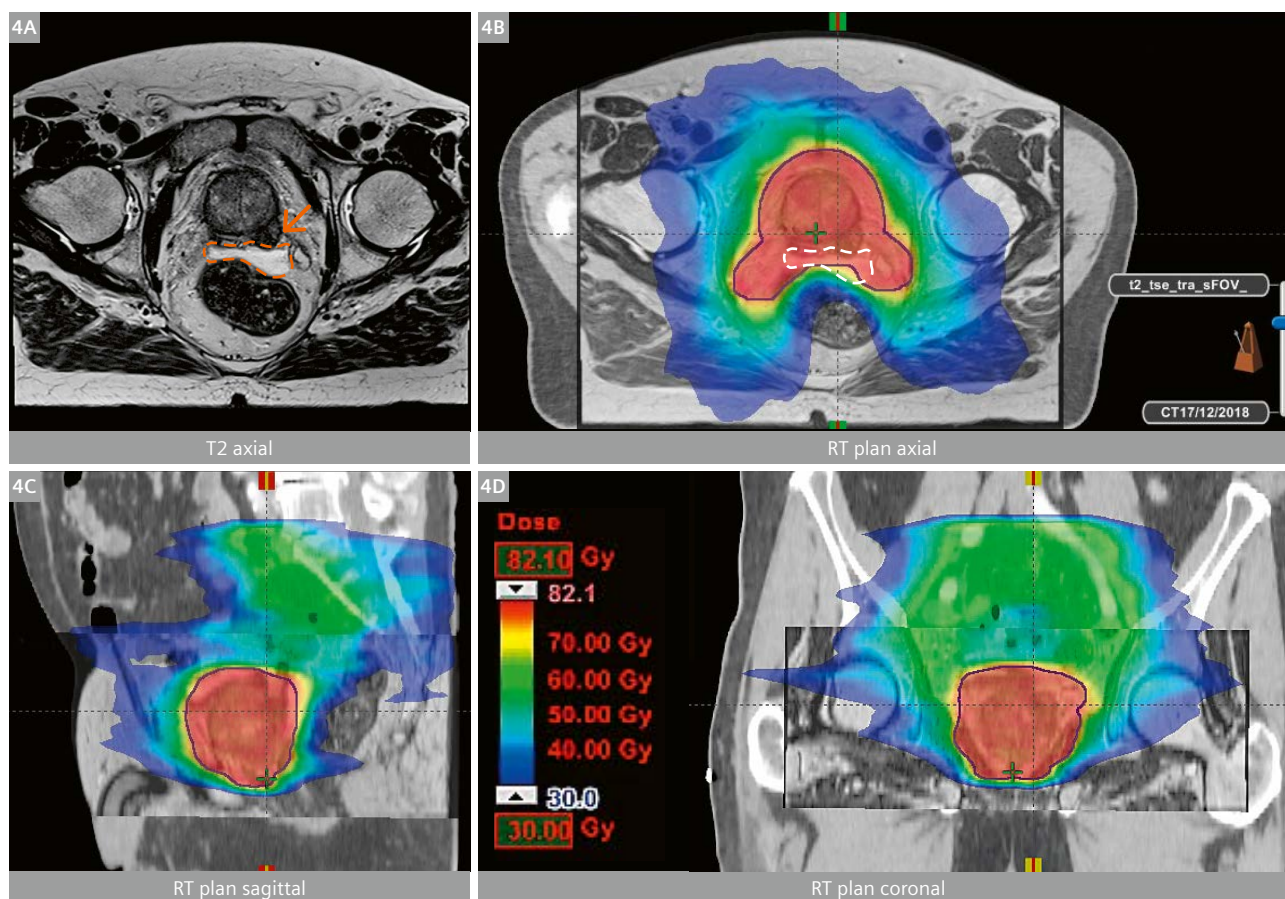
In another case example (Fig. 3), following a multi-disciplinary team (MDT) discussion, it was decided that a patient with organ-confined prostate cancer would be treated with highly conformal SBRT. At the MDT, the reporting radiologist described the prostate volume, index lesion location, and confirmed that the tumor was organ-confined. The radiation oncologist chose the optimal treatment plan. It is important for the radiologist to carefully assess the risk of gross extra-prostatic extension of tumor. Whilst the tumor may seem organ-confined, if there is increased tumor-capsule contact length, there is an increasing risk of microscopic extra-prostatic extension [7]. In fact, 20–50% of clinically organ-confined tumors ultimately have extra-prostatic extension (usually microscopic) at prostatectomy [8]. If this is a concern and the radiation oncologist is made aware, treatment margins at the site of the tumor can be extended and treatment margins elsewhere around the gland can be tighter, thereby helping to minimize potential side effects of including adjacent normal tissues in the radiotherapy field. An interventional radiologist inserted fiducial markers to aid with dynamic target tracking. Imaging with MRI was again subsequently employed to visualize the fiducial markers and prostate outline after insertion for radiotherapy planning purposes.



2 A 75-year-old man with raised PSA (18 ng/mL). Imaging with mpMRI (2A-D) and bone scan found a suspicious prostatic lesion in the right peripheral zone (arrows) with staging of T3a N0 M0 (extra-prostatic extension but no involved lymph nodes or distant sites of metastatic disease). The patient underwent an MR-directed and systematic biopsy which showed 5/12 positive biopsies (all right-sided) with a maximum Gleason score of 4+3. Brachytherapy catheters were inserted under general anesthetic and the patient received high-dose brachytherapy to the entire gland with a focal boost to the dominant right-sided index lesion (2E, F).



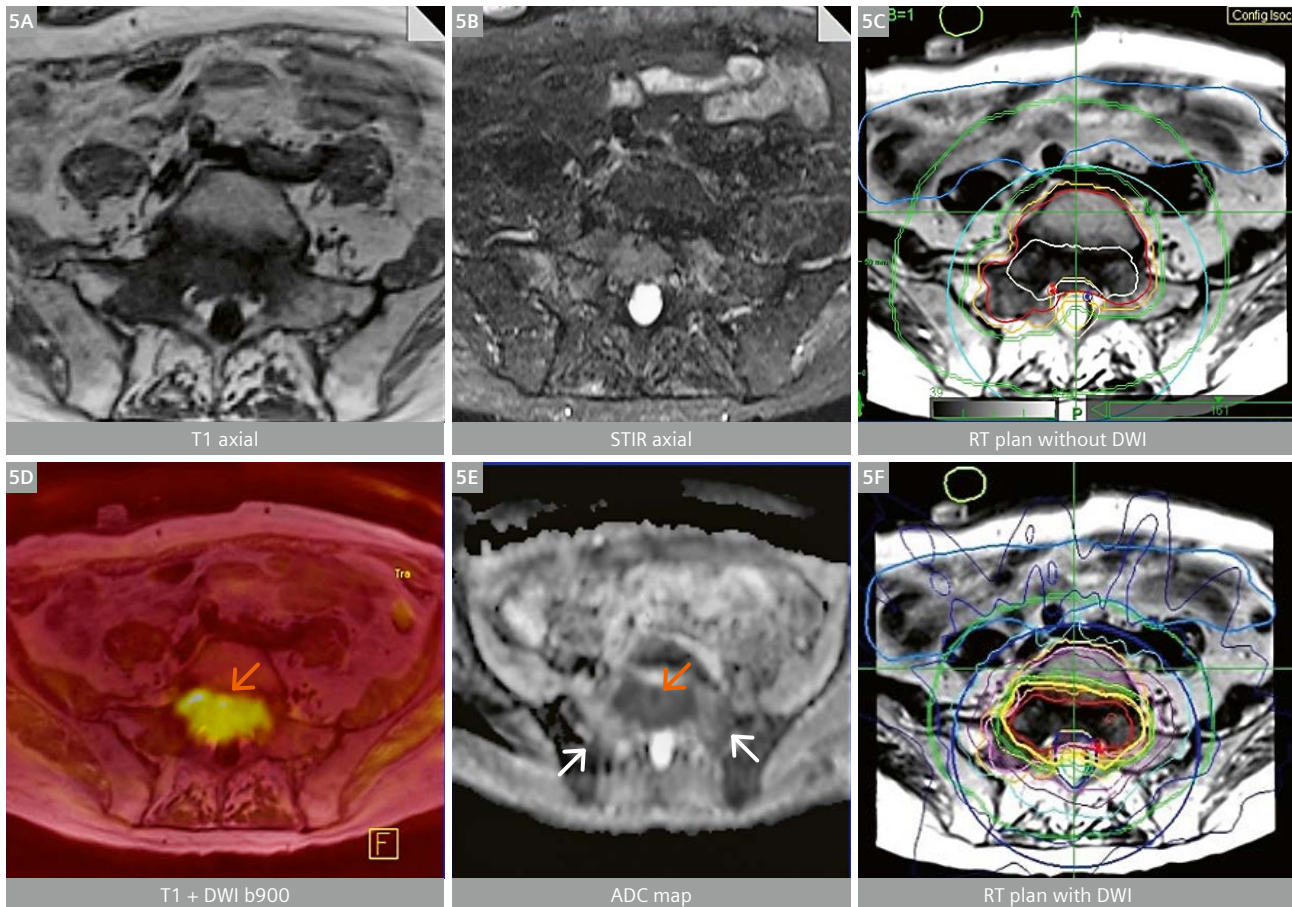
3 A 62-year-old man with raised PSA (9 ng/mL) underwent an mpMRI which demonstrated organ-confined index lesion (arrow) in the left peripheral zone (**3A**). The patient was discussed at the MDT, and SBRT was decided. Fiducial markers were inserted by an interventional radiologist, and a radiotherapy planning MRI was performed. T1-weighted axial imaging (**3B**) showed hemorrhage post fiducial marker insertion, and a TrueFISP sequence (**3C**) clearly delineates the prostatic outline (arrowheads) and the location of the fiducial markers (arrows) to aid with radiation treatment planning.



4 A 73-year-old man diagnosed with prostate cancer with iliac nodal involvement was referred for external beam radiotherapy (EBRT). (**4A**) The T2-weighted axial sequence demonstrates an index lesion in the left posterior peripheral zone (arrow), which was initially abutting the rectum. A rectal spacer (dashed outline) was inserted between the prostate gland and rectum, and the patient underwent radiation therapy planning scans (**4B-D**). These show how the rectal spacer allows for minimal dose to the rectum without compromising the dose intensity to the prostate gland.

With collaboration between radiation oncology and clinical radiology, reporting radiologists can tailor reports to give pertinent positive and negative findings that would be relevant for a patient undergoing radiation therapy. Figure 4 shows a case where the clinical radiologist noted that the posterior prostatic lesion was abutting the rectum and therefore the patient would be at higher risk of rectal toxicity if external beam radiation therapy was selected. This was flagged in the report and at the MDT, and the patient subsequently had a biodegradable balloon spacer inserted between the prostate and the rectum to allow the radiation oncologist to accurately treat the posterior prostatic tumor while reducing the risk of rectal toxicity. This patient was successfully treated with radiotherapy without developing rectal toxicity. Three years after treatment, the patient developed biochemical recurrence and

pain in the bony pelvis, so he underwent a pelvic MRI with morphological sequences only (Figs. 5A, B), which demonstrated a suspicious lesion within the S1 vertebral body extending to both sacral alar. Radiation therapy was considered and a CT-based radiotherapy treatment plan was performed. However, the MDT agreed that next-generation imaging with whole-body (WB) MRI using WB-DWI should be performed prior to radiation treatment (Figs. 5D, E) to exclude other sites of metastatic disease. Although no other sites of metastatic disease were identified, the DWI sequences demonstrated that the signal abnormality previously depicted in the posterior part of the vertebral body represented active hypercellular disease, whereas the signal change in both sacral alar was due to bilateral sacral insufficiency fractures, which are a well-recognized side effect of hormonal therapy, which the



- 5** The patient in Figure 4 presented three years later with increasing pelvic pain. An MRI of the pelvis with morphological T1W (5A) and STIR (5B) sequences was performed. This demonstrated a suspicious lesion in the posterior part of the S1 vertebral body extending to both sacral alar. A radiotherapy plan was created (5C) using the information from this standard pelvic MRI. After MDT discussion, it was decided that the patient should undergo a WB-MRI with DWI to rule out other sites of metastatic disease. Other metastatic sites were excluded, but the functional data gleaned from this advanced study demonstrated active disease posteriorly in the S1 vertebral body as high signal on the b900 DWI sequence (5D) and low signal on the corresponding ADC map (5E), indicating active hypercellular disease (orange arrows). However, the signal changes in both sacral alar demonstrated high signal (white arrows) on the ADC map (5E), indicating T2-shine-through due to edema from bilateral sacral insufficiency fractures, presumably secondary to previous hormonal therapy administered three years prior. The inclusion of the functional data from the WB-MRI led to a significant alteration of the radiotherapy plan (5F) and minimized dose to non-metastatic regions.

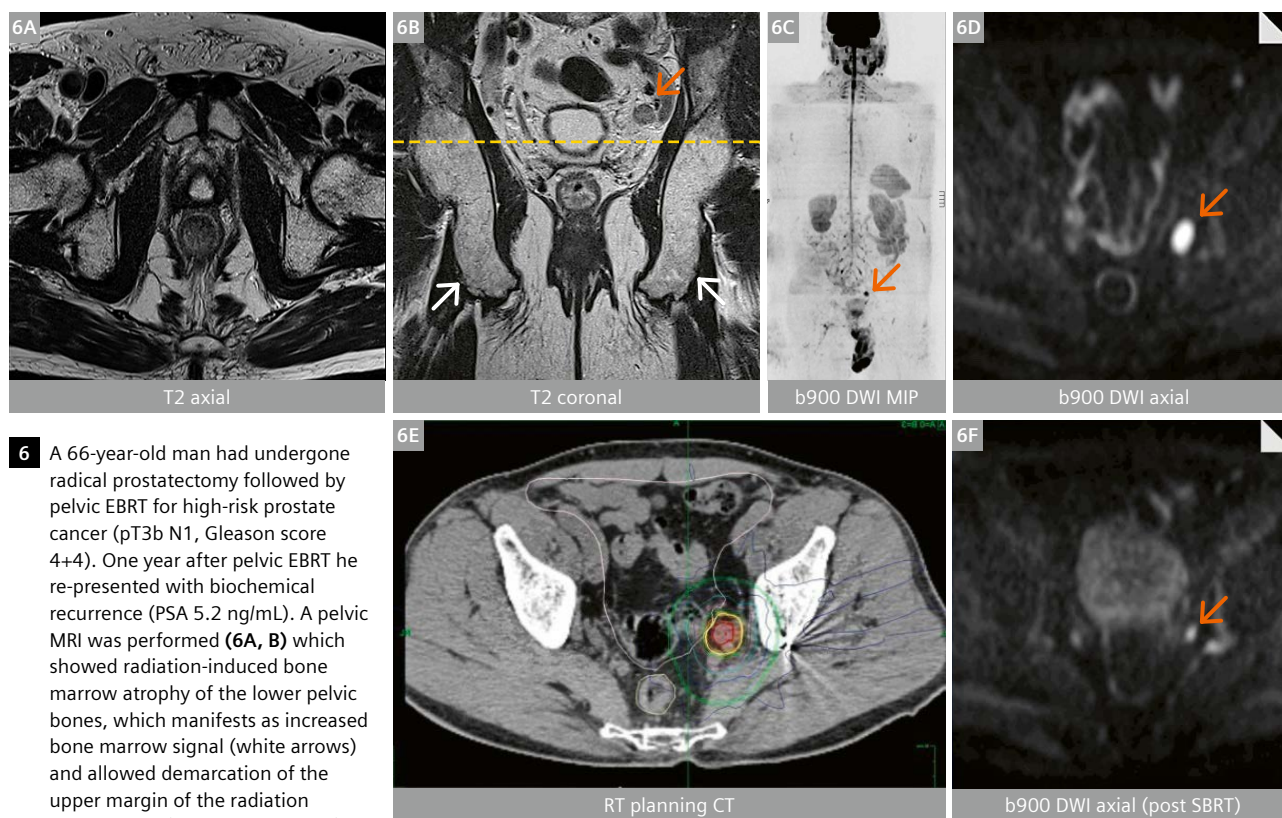
patient had previously received. This significantly altered the CT-based radiation therapy field and inappropriate dose administration to non-malignant tissues was avoided due to valuable information gleaned from advanced imaging techniques.

In our final example, we discuss a case of how highly conformal SBRT was successfully used repeatedly in a prostate cancer patient with oligorecurrent disease to postpone the use of androgen deprivation therapy (ADT) (Figs. 6, 7). The patient had previously undergone a radical prostatectomy followed by pelvic radiotherapy because of pathological extra-prostatic disease on post-operative histology. The patient presented one-year post pelvic EBRT with biochemical recurrence. Knowledge of previous radiation therapy and potential side effects is crucial for the clinical radiologist as the pelvic MRI demonstrated a suspicious lymph node just above the previous radiation therapy field visible as bone marrow atrophy (Fig. 6). Next-generation imaging with WB-MRI which includes WB-DWI confirmed no other sites of distant metastatic disease and,

following the MDT, the patient was selected for SBRT. A follow-up WB-MRI with DWI and drop in PSA confirmed successful treatment. Figure 7 demonstrates how the patient was followed with next-generation imaging techniques and PSA surveillance, and developed further oligometastatic disease which was treated with ablative radiation therapy techniques on three occasions over the subsequent years. Thus, the close collaboration between clinical radiology and radiation oncology colleagues with understanding and use of the technological advances in each other's fields successfully allowed the postponement of ADT use and therefore avoided the onset of potential side effects such as osteoporosis and metabolic syndrome [9].

Alternative radiation therapy techniques

Next-generation imaging techniques such as WB-MRI with DWI can also be extremely valuable in assessing a patient's suitability for different radiotherapy treatments. Radium-223 (^{223}Ra) is a calcium-mimetic alpha-particle



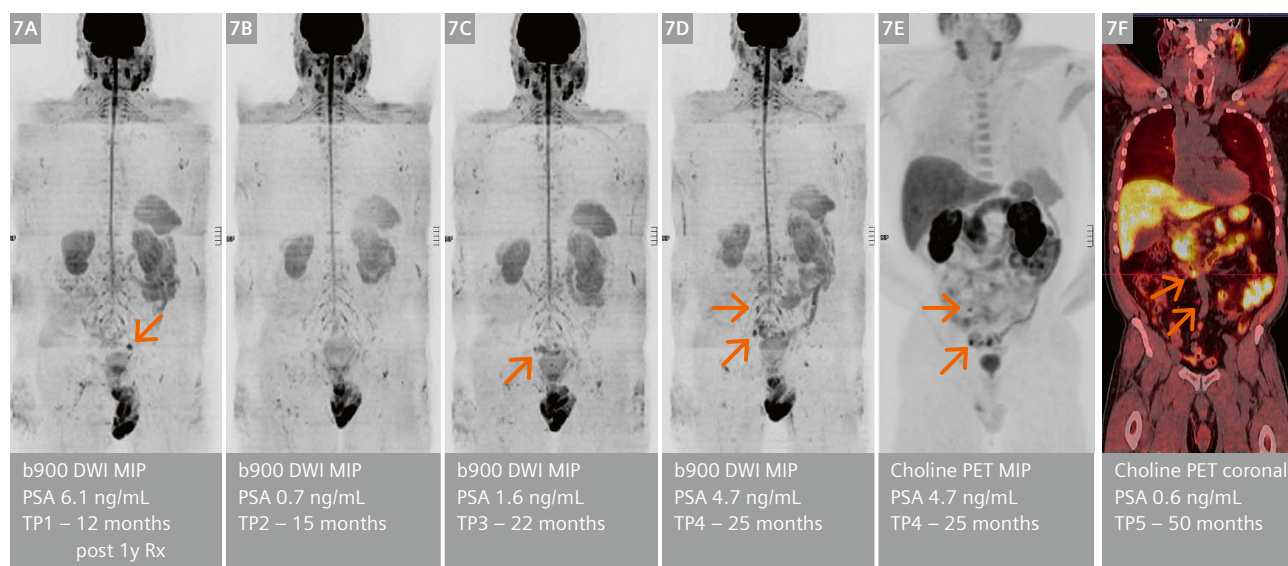
emitter which is taken up preferentially in areas of high bone turnover, particularly at sites of active bone metastases [10]. Thus, ^{223}Ra is a suitable treatment option in prostate cancer patients with bone metastatic disease and no soft tissue deposits >3 cm. WB-MRI with DWI and PET/CT with novel tracers such as gallium- and fluoride-labelled prostate-specific membrane antigen (PSMA) have been shown to have higher specificity and sensitivity to detect bone and soft tissue metastatic disease compared to conventional imaging techniques such as CT and bone scans [12, 13]. Therefore, these more advanced imaging techniques can be vital in accurate patient selection for these alternative radiation therapy techniques.

Conclusions and future directions

As advanced radiation therapy and imaging techniques are becoming more widely adopted, clinical radiologists and radiation oncologists should be aware of novel imaging

and treatment developments in each other's specialties. To deliver the promise of precision radiation therapy for improved patient outcomes and decreased side effects, increased precision of imaging is needed. This is enabled with multiparametric functional imaging methods where quantitative imaging biomarkers can be mapped onto radiation planning imaging to show tumor probability maps and areas of heterogeneity. Imaging is also used to assess the effectiveness of radiation therapies and their potential side-effects.

The use of next-generation imaging techniques will be key to facilitate the use of novel treatment developments such as theranostics, which combines specific targeted pharmacotherapies based on specific targeted diagnostic tests such as ^{177}Lu -PSMA treatment [13]. Close collaboration between clinical radiology and radiation oncology departments will assist in these high-precision treatment advancements to allow personalized medicine for cancer patients.



7 This series of images demonstrates how next-generation imaging techniques were used to enable advanced radiation therapy techniques for the patient from Figure 6 to postpone the use of ADT.

(7A) The WB-DW MRI MIP 12 months after prostatectomy and pelvic EBRT demonstrated a solitary left internal iliac lymph node (arrow) above the radiotherapy field which was treated with SBRT.

(7B) WB-MRI three months after SBRT shows successful treatment of the left internal iliac lymph node with a corresponding reduction in PSA.

(7C) WB-MRI performed seven months later due to a rise in PSA demonstrated a subtle focus in the right internal iliac region (arrow), which was reported as indeterminate but warranted close surveillance.

(7D) WB-MRI follow-up performed three months later showed an increase in size of the previous indeterminate right internal iliac lymph node and a new right common iliac lymph node in keeping with two nodal metastases (arrows).

(7E) A concurrent choline-PET/CT study confirmed these findings (arrows), which also correlated with the PSA rise. Two further SBRT treatments were performed and subsequent WB-MRI and choline-PET/CT studies showed no sites of active disease, and the PSA dropped to 0.02 ng/mL.

(7F) Two years after the previous SBRT treatments, the patient's PSA rose to 0.6 ng/mL and a choline-PET/CT study detected two new avid retroperitoneal lymph nodes (arrows), which were also treated with SBRT.

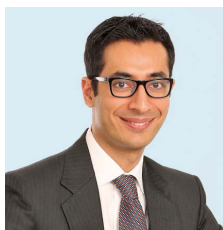
One year following the third SBRT treatments, there was new biochemical failure and imaging did not reveal any unequivocal sites of disease. After discussion with the patient, treatment with ADT was finally commenced after being postponed by over four years due to these advancements in imaging and radiation therapy techniques.

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Contact

Amish Lakhani, MBBS MA (Cantab) FRCR
Paul Strickland Scanner Centre
Mount Vernon Hospital
Northwood
Middlesex HA6 2RN
UK
amish.lakhani@stricklandscanner.org.uk



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Siemens Healthineers Headquarters

Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen, Germany
Phone: +49 9131 84-0
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