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

Amish Lakhani, MBBS MA (Cantab) FRCR[1]; Yat Man Tsang, BSc MSc PhD[2]; Roberto Alonzi, BSc MBBS MRCP FRCR MD[3]; Anwar R. Padhani, MBBS FRCP FRCR[1]

[1]Consultant Radiologist, Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, Middlesex, UK
[2]Consultant Radiographer – Specialised Service Delivery, Mount Vernon Hospital, Northwood, Middlesex, UK
[3]Consultant 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
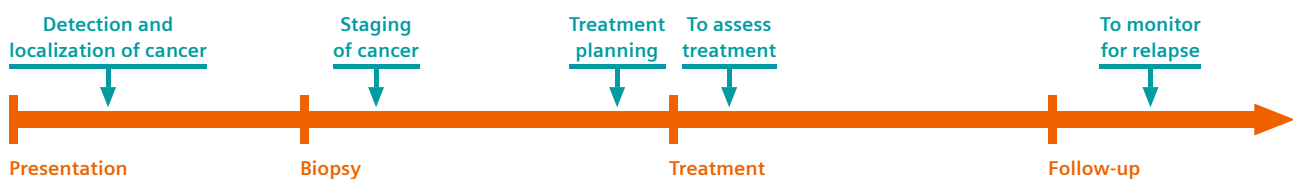

1 Imaging (green arrows) is integral throughout the cancer patient's pathway (orange arrow).

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.
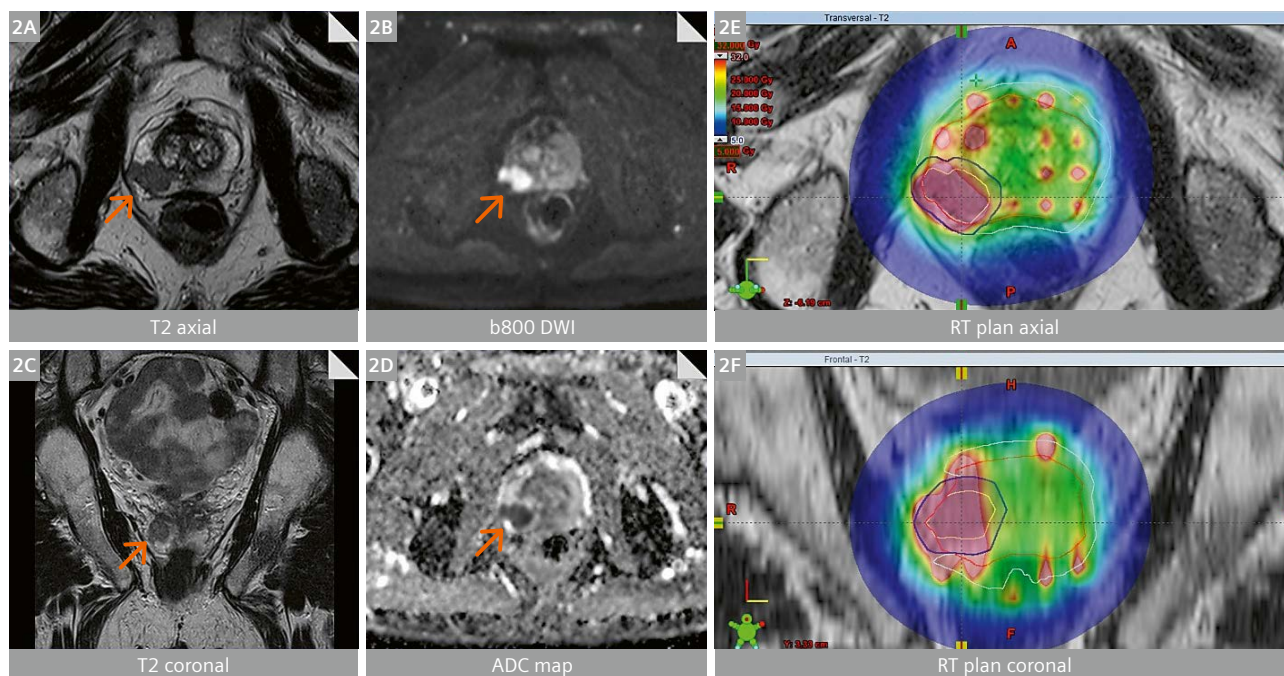
2 A 75-year-old man with raised PSA (18 ng/mL). Imaging with mpMRI **(2A-D)** and bone scan found a suspicious prostatic lesion in the right peripheral zone (arrows) with staging of T3a N0 M0 (extra-prostatic extension but no involved lymph nodes or distant sites of metastatic disease). The patient underwent 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)**.
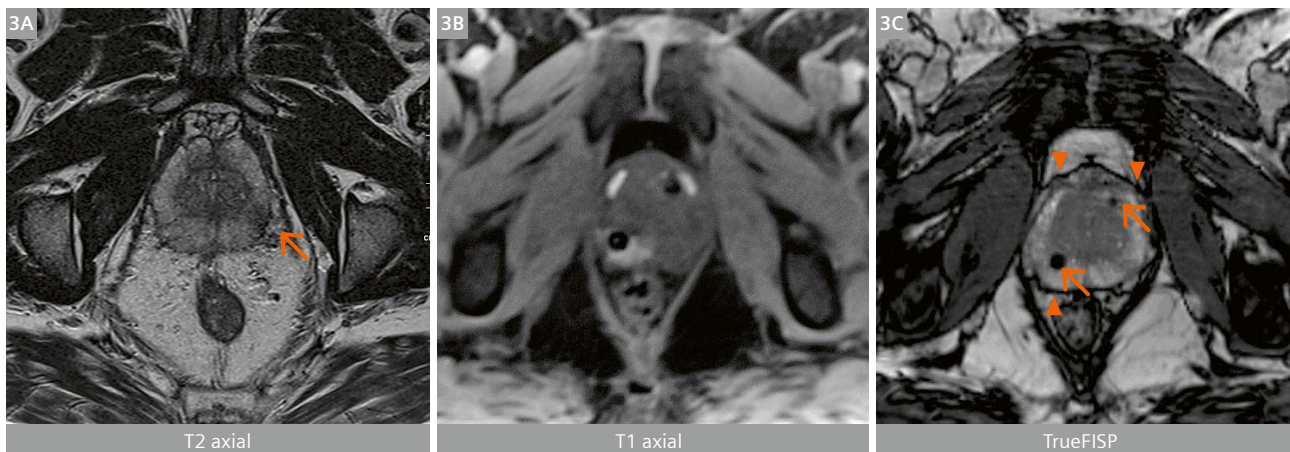
3 A 62-year-old man with raised PSA (9 ng/mL) underwent an mpMRI which demonstrated organ-confined index lesion (arrow) in the left peripheral zone **(3A)**. The patient was discussed at the MDT, and SBRT was decided. Fiducial markers were inserted by an interventional radiologist, and a radiotherapy 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.
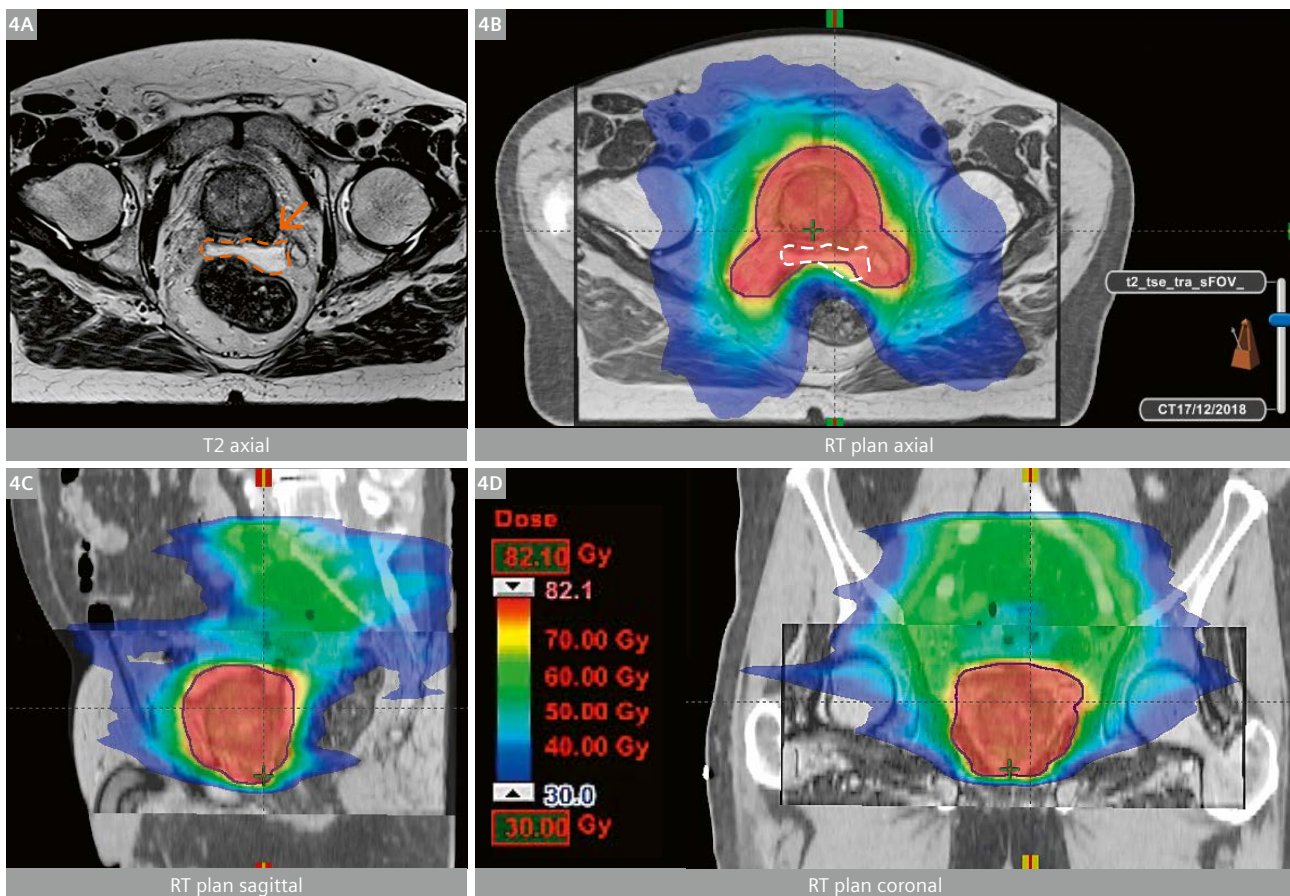
4 A 73-year-old man diagnosed with prostate cancer with iliac nodal involvement was referred for external beam radiotherapy (EBRT). **(4A)** The T2-weighted axial sequence demonstrates an index lesion in the left posterior peripheral zone (arrow), which was initially abutting the rectum. A rectal spacer (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

5A	5B	5C
T1 axial	STIR axial	RT plan without DWI
5D	5E	5F
T1 + DWI b900	ADC map	RT plan with DWI
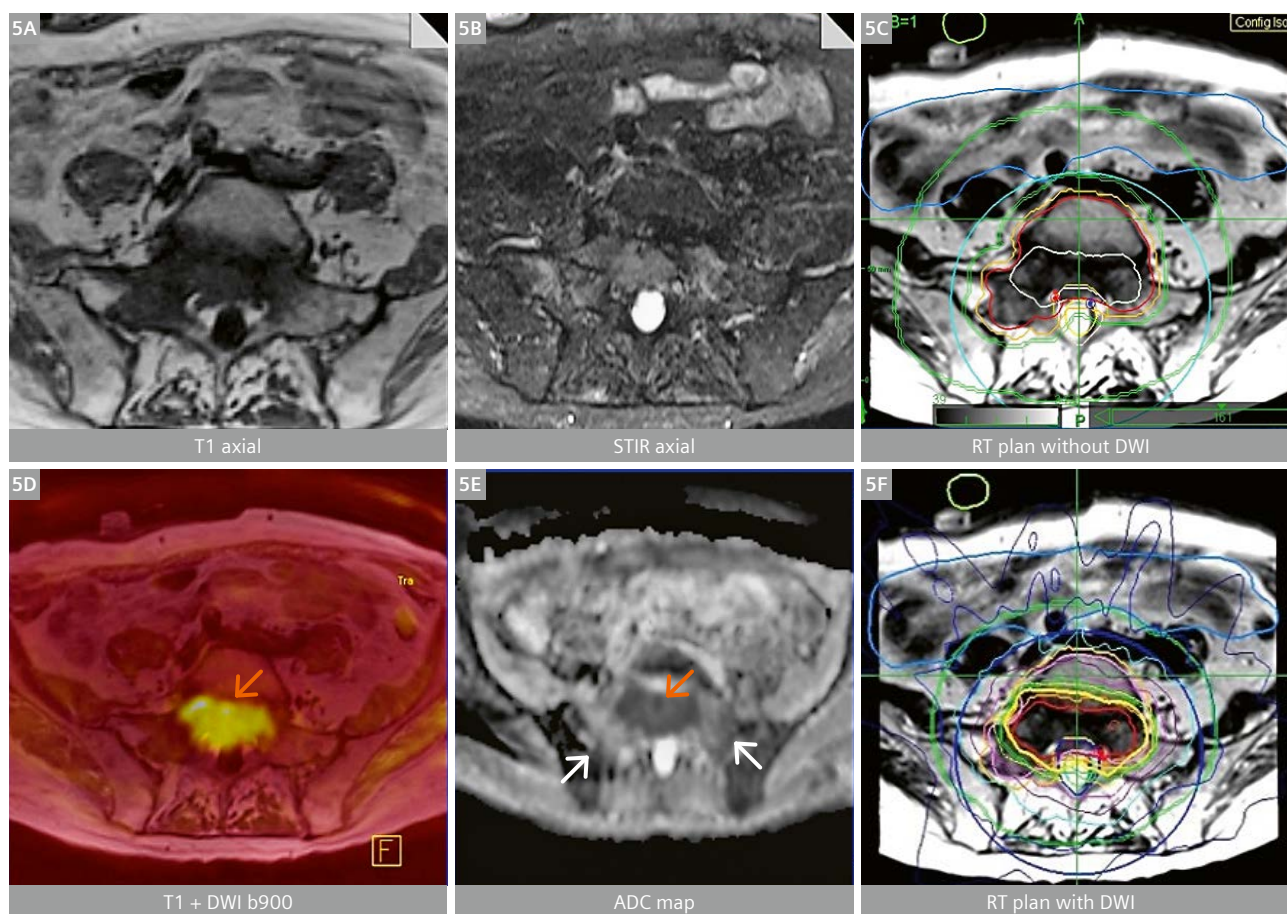
5 The patient in Figure 4 presented three years later with increasing pelvic pain. An MRI of the pelvis with morphological T1W **(5A)** and STIR **(5B)** sequences was performed. This demonstrated a suspicious lesion in the posterior part of the S1 vertebral body extending to both sacral alar. A radiotherapy 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.
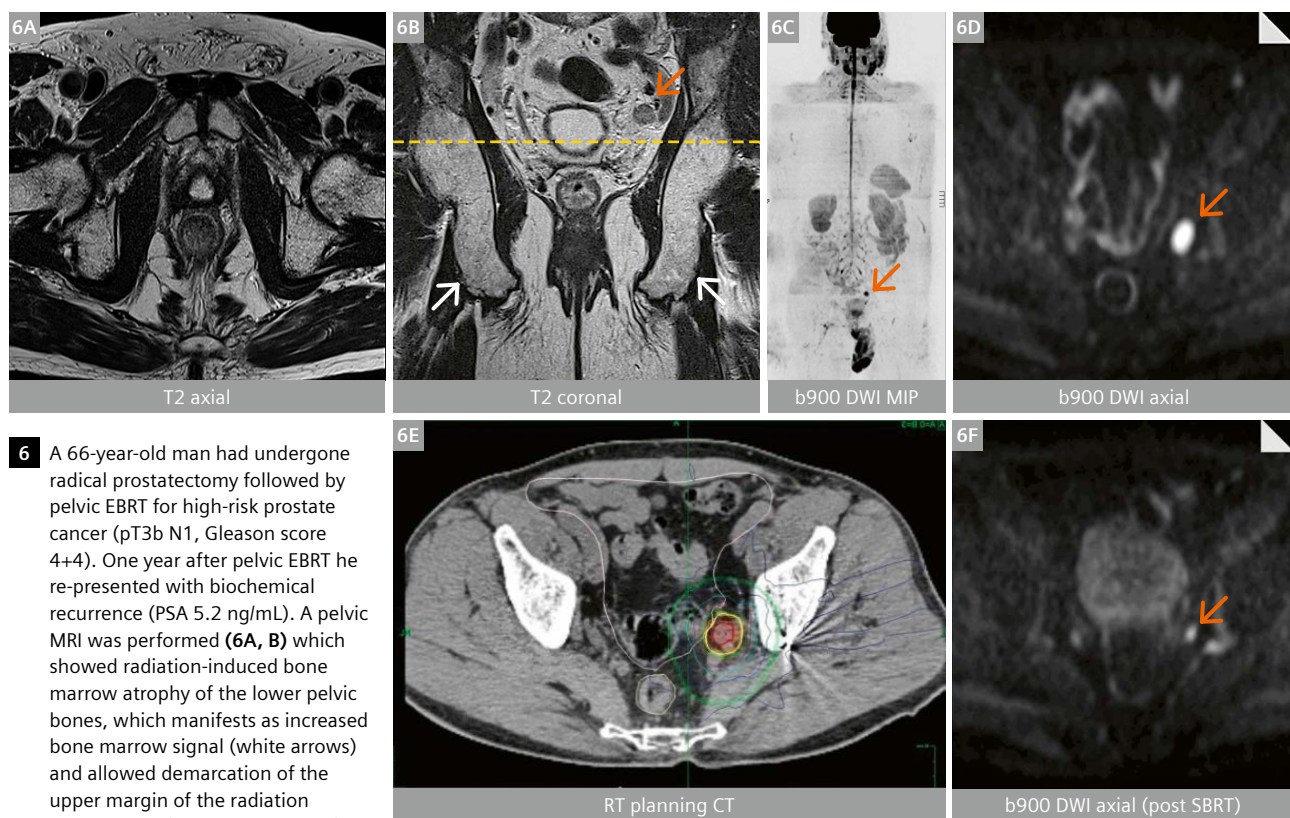
patient had previously received. This significantly altered the CT-based radiation therapy field and inappropriate dose administration to non-malignant tissues was avoided due to valuable information gleaned from advanced imaging techniques.

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

T2 axial | T2 coronal | b900 DWI MIP | b900 DWI axial

6 A 66-year-old man had undergone radical prostatectomy followed by pelvic EBRT for high-risk prostate cancer (pT3b N1, Gleason score 4+4). One year after pelvic EBRT he re-presented with biochemical recurrence (PSA 5.2 ng/mL). A pelvic MRI was performed **(6A, B)** which showed radiation-induced bone marrow atrophy of the lower pelvic bones, which manifests as increased bone marrow signal (white arrows) and allowed demarcation of the upper margin of the radiation therapy field (dashed yellow line).

RT planning CT | b900 DWI axial (post SBRT)

There was no suggestion of local recurrence at the prostatectomy bed. However just above the previous radiotherapy field there was a rounded left internal iliac lymph node (orange arrow) highly suspicious for a site of disease.

A WB-MRI with DWI was performed (**6C**: b900 DWI MIP, **6D**: b900 DWI axial) which confirmed that this was the only site of active disease (arrow) and therefore, the patient underwent SBRT following fiducial marker insertion (**6E**: planning CT). A follow-up WB-MRI three months post treatment (**6F**: b900 DWI axial) demonstrated successful ablative treatment with SBRT, which was in concordance with a reduction in PSA.
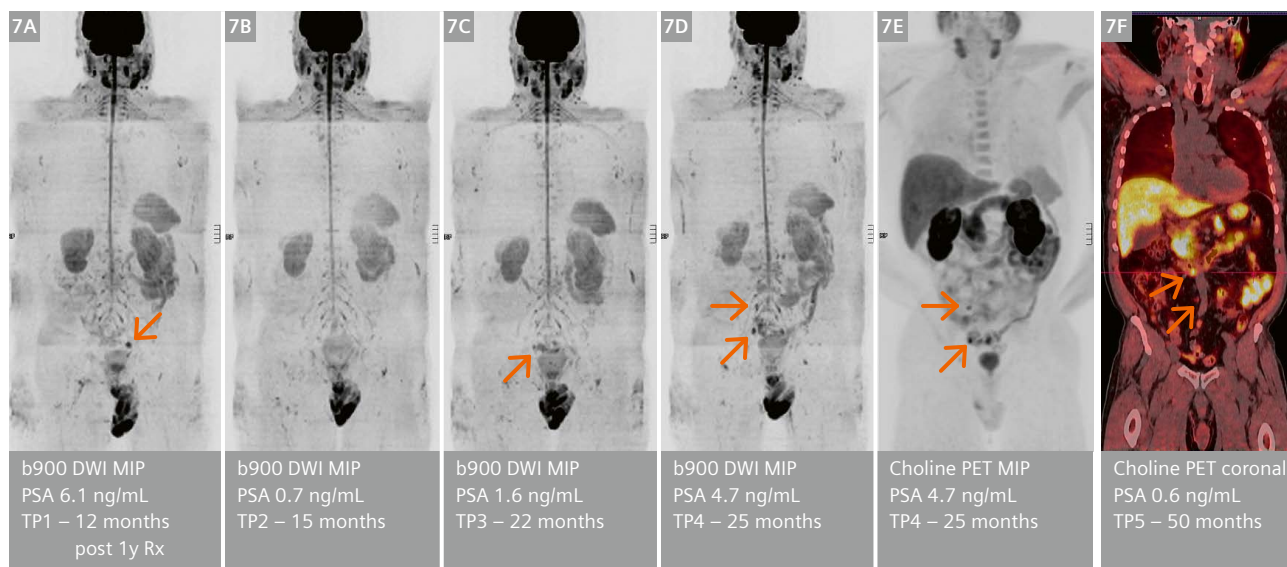
emitter which is taken up preferentially in areas of high bone turnover, particularly at sites of active bone metastases [10]. Thus, ^{223}Ra is a suitable treatment option in prostate cancer patients with bone metastatic disease and no soft tissue deposits >3 cm. WB-MRI with DWI and PET/CT with novel 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}Lutetium-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.

7A b900 DWI MIP / PSA 6.1 ng/mL / TP1 – 12 months post 1y Rx

7B b900 DWI MIP / PSA 0.7 ng/mL / TP2 – 15 months

7C b900 DWI MIP / PSA 1.6 ng/mL / TP3 – 22 months

7D b900 DWI MIP / PSA 4.7 ng/mL / TP4 – 25 months

7E Choline PET MIP / PSA 4.7 ng/mL / TP4 – 25 months

7F Choline PET coronal / PSA 0.6 ng/mL / TP5 – 50 months

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.

References

1 R. Atun, D. A. Jaffray, M. B. Barton, F. Bray, M. Baumann, B. Vikram, T. P. Hanna, F. M. Knaul, Y. Lievens, T. Y. M. Lui, M. Milosevic, B. O'Sullivan, D. L. Rodin, E. Rosenblatt, J. Van Dyk, M. L. Yap, E. Zubizarreta, and M. Gospodarowicz, "Expanding global access to radiotherapy," Lancet Oncol. 2015; 16(10):1153-86.

2 R. Baskar, K. A. Lee, R. Yeo, and K. W. Yeoh, "Cancer and radiation therapy: Current advances and future directions," Int. J. Med. Sci. 2012;9(3):193-9.

3 A. R. Padhani, F. E. Lecouvet, N. Tunariu, D. M. Koh, F. De Keyzer, D. J. Collins, E. Sala, S. Fanti, H. A. Vargas, G. Petralia, H. P. Schlemmer, B. Tombal, and J. de Bono, "Rationale for Modernising Imaging in Advanced Prostate Cancer," Eur. Urol. Focus. 2017;3(2-3):223-239.

4 H. U. Ahmed, A. El-Shater Bosaily, L. C. Brown, R. Gabe, R. Kaplan, M. K. Parmar, Y. Collaco-Moraes, K. Ward, R. G. Hindley, A. Freeman, A. P. Kirkham, R. Oldroyd, C. Parker, and M. Emberton, "Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study," Lancet. 2017;389(10071):815-822.

5 N. L. Hansen, T. Barrett, C. Kesch, L. Pepdjonovic, D. Bonekamp, R. O'Sullivan, F. Distler, A. Warren, C. Samel, B. Hadaschik, J. Grummet, and C. Kastner, "Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer," BJU Int. 2018,122(1):40-49.

6 S. Borofsky, A. K. George, S. Gaur, M. Bernardo, M. D. Greer, F. V. Mertan, M. Taffel, V. Moreno, M. J. Merino, B. J. Wood, P. A. Pinto, P. L. Choyke, B. Turkbey, "What Are We Missing? False-negative Cancers at Multiparametric MR Imaging of the Prostate," Radiology. 2018,286(14):186-195.

7 E. Baco, E. Rud, L. Vlatkovic, A. Svindland, H. B. Eggesbø, A. J. Hung, T. Matsugasumi, J.-C. Bernhard, I. S. Gill, and O. Ukimura, "Predictive Value of Magnetic Resonance Imaging Determined Tumor Contact Length for Extracapsular Extension of Prostate Cancer," J Urol. 2015 Feb;193(2):466-72.

8 A. Gallina, F. K. Chun, N. Suardi, J. A. Eastham, P. Perrotte, M. Graefen, G. Hutterer, H. Huland, E. A. Klein, A. Reuther, F. Montorsi, A. Briganti, S. F. Shariat, C. G. Roehrborn, A. De Taille, L. Salomon, and P. I. Karakiewicz, "Comparison of stage migration patterns between Europe and the USA: an analysis of 11 350 men treated with radical prostatectomy for prostate cancer," BJU Int. 2008 Jun;101(12):1513-8.

9 P. Sountoulides and T. Rountos, "Adverse Effects of Androgen Deprivation Therapy for Prostate Cancer: Prevention and Management," ISRN Urol. 2013 Jul 25;2013:240108. doi: 10.1155/2013/240108.

10 S. Dadhania, R. Alonzi, S. Douglas, A. Gogbashian, R. O. B. Hughes, D. Dalili, N. Vasdev, J. I. M. Adshead, and T. I. M. Lane, "Single-centre Experience of Use of Radium 223 with Clinical Outcomes Based on Number of Cycles and Bone Marrow Toxicity," Anticancer Res. 2018 Sep;38(9):5423-5427.

11 G. Shen, H. Deng, S. Hu, and Z. Jia, "Comparison of choline-PET / CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis," Skeletal Radiol. 2014 Nov;43(11):1503-13.

12 M. Eiber, T. Maurer, M. Souvatzoglou, A. J. Beer, A. Ruffani, B. Haller, F. Graner, K. Hubert, U. Haberhorn, M. Eisenhut, H. Wester, J. E. Gschwend, and M. Schwaiger, "Evaluation of Hybrid 68 Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy," J Nucl Med. 2015 May;56(5):668-74.

13 L. Emmett, K. Willowson, J. Violet, J. Shin, A. Blanksby, and J. Lee, "Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy," J Med Radiat Sci. 2017 Mar;64(1):52-60.

Contact

Amish Lakhani, MBBS MA (Cantab) FRCR
Paul Strickland Scanner Centre
Mount Vernon Hospital
Northwood
Middlesex HA6 2RN
UK
amish.lakhani@stricklandscanner.org.uk
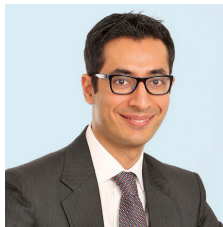
We are looking forward to hearing from you

The essence of *MReadings: MR in RT* is education and best practice sharing by MAGNETOM users. Along with the MAGNETOM World Internet site it is a platform to share experience around the globe.

In times of online media and digitalization we would value your feedback to ensure that the magazine continues to fit your interests and professional needs.

Please take a moment to complete a brief reader survey at
www.siemens.com/magnetom-world-rt