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His research interests include functional imaging and the microenvironment of tumors. Professor Padhani has a passion for teaching and has an impressive record of publications and lectures. His work involving whole-body and multi-parametric MRI is internationally renowned.

Advancing Cancer Care with Modern MRI

Many aspects of cancer care remain on 'red alert' as we enter the second decade of the 21st century. There are many times when we healthcare professionals cannot confidently answer questions that directly affect patient care. Seemingly simple questions such as "Do I have cancer?", "Is the cancer going to kill me?", "Is my cancer responding to therapy?", "Is the cancer back?" and "How long do I have to live?", "Will I make it to my daughter's wedding?" evade us on a daily basis. While we struggle to respond to the needs of our patients, we remain aware that progress is being made every day in cancer diagnosis and therapy, and within this, is the role being played by MRI as highlighted by articles in this Oncology edition of MAGNETOM Flash magazine.

MRI has become an integral part in management of cancer patients with distinct decision making roles in the clinic and for drug development. Clinical questions that can be addressed by MRI are highly dependent on the point of the patient journey. Many cancer-afflicted patients comment on the loss of control of their destiny which makes their progress through life more like a 'roller coaster'. The

optimal use of MRI requires very close interactions between oncologists and their radiologists and physicists. This is because MRI technologies (hardware, data acquisition sequences, post-processing etc) are continuously being developed and refined, validated and adopted for use in the clinic, but at different rates which makes cross platform standardisation and validation problematic. Oncologists need to define specific questions/ problem areas in order for radiologists/physicists to choose or develop appropriate technologies to answer the clinical need. If this is done successfully, both morphologic and generated functional MRI biomarkers have the power to transform the way that some patients are managed in the clinic. This issue of MAGNETOM Flash is full of examples where MRI is being developed to meet clinical needs of cancer patients.

Early cancer detection

When MRI is employed for early cancer detection in subjects with a high lifetime risk of developing cancer, either due to germline mutations or exposure to carcinogens, this is typically organ-based. Examples of organ-based

MRI screening include evaluation of those at increased risk of developing breast cancer (BRCA mutations, TP53 deletions, previous mantle radiotherapy). The biology being exploited in breast cancer detection and characterization is tumor neovascularization and hyperperfusion, which is done by using dynamic contrast-enhanced sequences (DCE-MRI). A key requirement for early breast cancer detection is very high spatial and temporal resolution of DCE sequences. High spatial resolution is important because lesions detected need characterization which in turn depends on the evaluation of fine morphologic features such as distinctness of margins and the patterns of internal structure. How this can be achieved using ultrahigh field, 7T* MRI scanners is discussed in the article by Siegfried Trattnig et al. in this issue. The challenges of working at 7T, particularly of achieving uniform fat suppression over both breasts are highlights.

Another area where MRI is increasingly used is for the detection (localization) of suspected cancer when another test(s) suggests that a tumor may be present. Examples include persistently raised serum prostate specific antigen (PSA) levels or when monoclonal bands

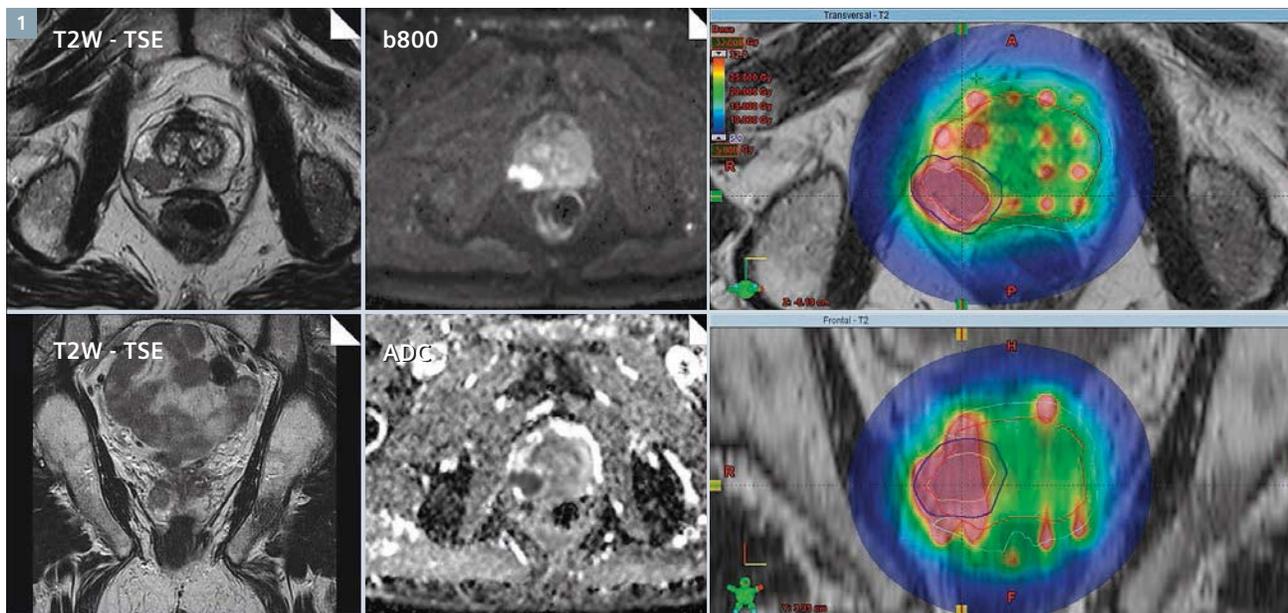
(M component) are found in older patients referred for the investigation of osteoporosis; when respectively prostate cancer and multiple myeloma may be suspected. Prostate cancer diagnosis is particularly problematic because many men with raised PSA will never be diagnosed with prostate cancer in their life (false alarms), with the flip side also being true that many men with diagnosed prostate tumors having normal PSA levels (false reassurance). Even in men with prostate cancer diagnosed from histologic samples, the question “Is the cancer going to cause patient harm?” cannot always be confidently answered, because the misclassification rate concerning risk status is too high (poor characterization). Often there is insufficient confidence to distinguish non-aggressive disease (only needing careful monitoring – active surveillance program) from virulent cancers (requiring definitive treatment). Such diagnostic uncertainty contributes to over-treatment of patients with low-grade cancers and under-treatment of patients with aggressive disease.

Multiparametric MRI (mpMRI) is now incorporated into many guidelines for the detection of prostate cancer particularly in men with persistently raised PSA levels and negative systematic transrectal prostate biopsies, who are considered to harbor cancer that has not yet been diagnosed. Diffusion MRI is a cornerstone of any mpMRI prostate examination as highlighted in the article by Liang Li and colleagues, who demonstrate high resolution, dedicated prostate diffusion MRI. Beyond detection of suspected lesions, better targeted biopsies from cancer suspicious regions at highest risk of harbouring the most aggressive lesion (dominant intra-prostatic lesion (DIL) or index intraprostatic lesion) is needed (Fig. 1). The article by Lars Schimmöller et al. provides practical examples of how this is achieved by in-bore MRI targeted biopsy. Of course mpMRI usage is not only confined to the characterization of prostatic lesions. mpMRI is also being routinely used in the brain and other organs, including gynaecological tumor characterization as highlighted by Hamidreza Sligheh Rad.

Diagnostic workup

Once patients are diagnosed with cancer, accurate workup of disease extent is key for therapy planning and prognostication. For this, the relationship between the primary tumor and adjacent normal tissues as well as the accurate determining of nodal and metastatic disease status are key requirements. A particularly venerable group of patients that can benefit from multisystem MRI assessments of metastatic disease are children* with cancer as shown by the case example of Maren Asmussen and Peter Reimer. Of course diagnostic workup of cancer patients goes beyond MRI, using other imaging modalities including PET scans. The hybrid imaging platform PET/CT has already established itself in the cancer evaluation arena but we now see the

*MR scanning has not been established as safe for imaging fetuses and infants under two years of age. The responsible physician must evaluate the benefit of the MRI examination in comparison to other imaging procedures.



1 Biologically optimized radiotherapy.

75-year-old male with prostate cancer (Gleason 4+3; PSA18 ng/mL; T3a; N0; M0). A dominant intra-prostatic lesion (DIL) in the right postero-lateral peripheral zone has been defined using multi-parametric MRI (T2-weighted and diffusion images (b800 and ADC maps) are shown). High dose rate brachytherapy catheters were inserted under general anaesthetic. The planning computer optimization software has been programmed to maximize the radiation dose to the DIL and limit the dose to the rest of the prostate to a defined ceiling. The DIL and DIL planning treatment volumes (PTV) (yellow and dark blue lines) receive a higher dose as a proportion of their volume than the non-dominant prostate and the non-dominant prostate PTV (light blue and red lines). *Courtesy of Dr. Roberto Alonzi, Mount Vernon Cancer Centre, Northwood, UK.*

“Morphologic and generated functional MRI biomarkers have the power to transform the way that some patients are managed in the clinic.”

Professor Anwar R. Padhani, MB BS, FRCP, FRCR

emergence of PET/MRI for improving lesion characterization as highlighted by the article of Amy Melsaether in women with breast cancer. Potential advantages of the hybrid PET/MRI approach include more precise registration and anatomic localisation of the PET uptake, the potential for simultaneous quantitative dynamic PET and contrast-enhanced perfusion MRI and shorter scan times (less sedation/anaesthesia). But MRI is not there to just to make PET scanning better! Unlike the situation with PET/CT (where low dose, non-contrast-enhanced CT is used principally for rough anatomic localisation and attenuation correction), the position of MRI in PET/MRI systems is that of an equal partner because of its own uniqueness. MRI strengths include excellence in anatomic imaging and multiparametric imaging capability which, combined with the high sensitivity of PET, have the potential to greatly improve the care of cancer patients, although evidence for the latter is still lacking. Watch this space!

Transforming treatment

MRI information has to be able to transform what we do for our patients. The article by Marymol Koshy highlights how breast MRI is transforming the surgical approach for breast cancer patients in Malaysia. An impressive article by Simon Robinson and colleagues highlights how functional MRI at 7T* can aid in the presurgical planning of brain cancer patients. The quality of fMRI is simply astonishing but 7T is not simply about creating pretty pictures! It is about much

more. It is about identifying the precise location of vital brain functions that must be preserved in complex brain surgery. It's about preserving a patient's uniqueness, what makes them human. The article suggests that millimetre precision is required for localizing eloquent brain areas in order to mitigate against severe post-operative deficits which are inevitable with brain tumor surgery without fMRI. You have to admire the efforts of Robinson and colleagues who are trying to make a difference in this very challenging area.

Just as we have seen advances in MRI diagnosis, so we have seen marked progress in image-guided treatment. A striking example is high precision, minimally invasive tumor ablation as highlighted by Kemal Tuncali who shows several case examples of tumor ablation guided by MRI. Another large field of advancement is in image guided radiotherapy. Advances in imaging hardware related to radiation delivery, have improved the physical conformality of radiation planning, treatment and delivery to tumors and organ boundaries using conformal and intensity modulated techniques. Articles by Gary Liney and Joann Prisciandaro highlight how MRI information can offer these advantages when radiation is delivered as external beam radiotherapy and internal high dose rate brachytherapy respectively. The authors reflect on the challenges of incorporating MRI data into the radiotherapy planning processes including the lack of electron density information and image distortion.

When considering further roles for MRI in radiation planning we can also look towards additional advantages that functional imaging, in general, can bring to radiation therapy. The ability to combine image-depicted biology with image-guided radiotherapy techniques opens the way for further refinements of target delineation and dose delivery, such that it is now possible to shape dose volume distributions not only to the geometry of targets but also to differences in the radiobiology across tumors. So it is possible to define additional 'targets-within-targets' as 3D maps of prescribed dose incorporating biological information derived from functional imaging; this is sometimes called 'dose painting by numbers'. An example of such an approach is shown in Figure 1. When considering these additional opportunities, it should be remembered that the perceived advantages of such approaches are currently without a sound evidence base regarding selection of patients who would benefit from these more complex approaches and whether improved patient outcomes will ultimately be seen; there remains incomplete clinical validation of these novel approaches.

Therapy monitoring

Lastly I would like to mention another challenging area in cancer care, that of treatment monitoring. There is an increasing awareness that the evaluation of tumor response to oncologic treatments based solely on anatomic imaging faces many limitations, particularly in the era of novel biologic targeted therapies. This is illustrated by the difficulty of response assessments in metastatic skeletal disease which unlike soft tissues, are exceptionally difficult to assess morphologically, and in brain tumors where increasing enhancement following chemoradiation therapy may be unduly misinterpreted as disease progression (so-called pseudoprogression). These limitations have hampered the development of new generations of cytostatic drugs also. It was thought that progression free survival (PFS) would serve as a suitable surrogate for overall therapeutic efficacy for the development of cytostatic compounds. However, it is increasingly being recognized that PFS

(most often anatomically determined) is often times disconnected from overall survival, as reported in large scale trials of bevacizumab therapy for metastatic solid tumors and brain gliomas [1, 2].

A particularly problematic area is monitoring response of patients with bone metastases because measureable bony soft tissue disease occurs infrequently. Symptom assessments and development of skeletal-related events (fractures, cord compression, skeletal pain requiring radiotherapy) are preferred markers of therapeutic efficacy in clinical trials but should not be used in routine clinical practise. Regardless of the method(s) used, current response biomarkers focus on assessing disease progression rather than positively addressing therapy benefit. The clinical consequences of using progression criteria can be detrimental for patients, including “prolonged exposure to potentially ineffective medications” and “all patients potentially getting all drugs – often too late”. Thus, currently available assessment methods can have negative impacts on oncologists’ thinking regarding therapy choices for patients with metastatic bone disease. The case example of Anwar Padhani shows a potential new approach by using whole-body diffusion MRI which

is able to positively assess therapy effectiveness even when morphology is unhelpful. This case also highlights how image post-processing of diffusion data can help to increase confidence regarding the effectiveness of therapy in patients with predominantly bone disease.

Future challenges

Clearly there are many professional challenges for incorporating advanced anatomic and multi-functional MRI methods into the care pathways of cancer patients as highlighted by many of the articles within this issue of MAGNETOM Flash. These include integration of the information of multiple individual tests all of which can be done at a single patient visit (new bioinformatics challenge), dealing with heterogeneity that exists between patients, between lesions (in the same patient) and within lesions (at baseline and in response to therapy). We also need to better understand the biology behind the image at multiple scales (physiology or pathologic processes, gene expression profiles, proteomics) and how imaging features correlate with other therapeutic efficacy biomarkers. An ongoing challenge is the need to

develop common measurements and analysis methods, uniform data displays and standardization across imaging vendor platforms. Documentation of reproducibility particularly across multiple centers also needs to be undertaken. Finally developing roadmaps for imaging biomarkers qualification and high precision medicine need to be developed. I hope you enjoy reading about the many new advances in oncologic MRI that we present to you in this magazine.

Anwar Padhani

- 1 Amit L, Ben-Aharon I, Vidal L, Leibovici L, Stemmer S. The impact of Bevacizumab (Avastin) on survival in metastatic solid tumors – a meta-analysis and systematic review. *PLoS One*. 2013;8(1):e51780.
- 2 Fine HA. Bevacizumab in glioblastoma – still much to learn. *N Engl J Med*. 2014; 20;370(8):764-5.

*MAGNETOM 7T is ongoing research. All data shown are acquired using a non-commercial system under institutional review board permission. MAGNETOM 7T is still under development and not commercially available yet. Its future availability cannot be ensured.

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