Biologically Targeted Radiation Therapy (BiRT): From Concept to Clinical Translation

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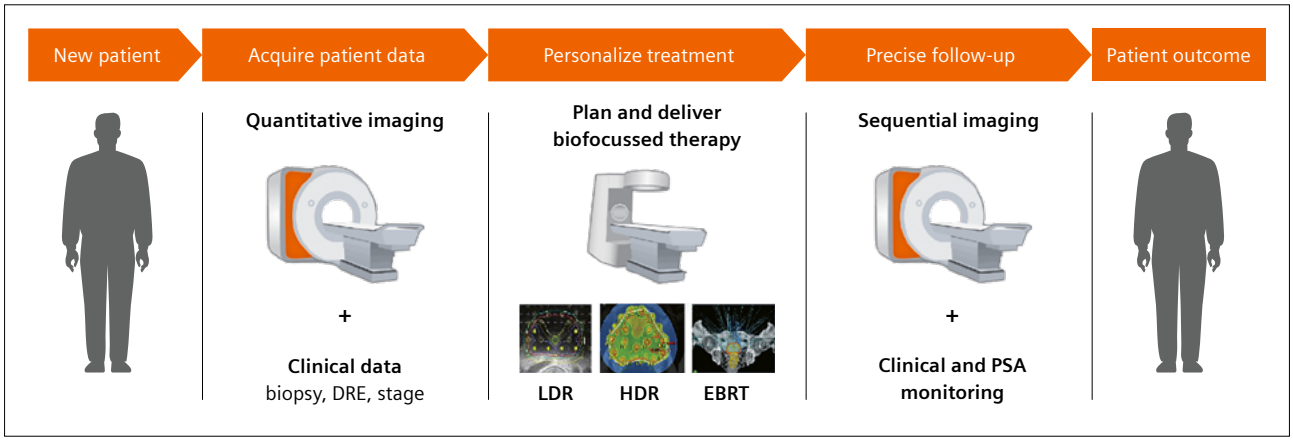
Introduction

Cancers are well known for biological heterogeneity between patients as well as within tumors in an individual patient. Conventional radiation therapy (RT) dose prescriptions are currently anatomy-based and assume all tumors of a given type respond to radiation in the same way, ignoring tumor heterogeneity. Biologically targeted radiation therapy (BiRT), on the other hand, uses knowledge of spatially heterogenous biological characteristics of tumors and their predicted response to radiation treatment to prescribe a heterogeneous dose through the tumor volume for a specific therapeutic objective. Non-invasive, three-dimensional mapping of tumor biological characteristics is key to the implementation of the BiRT approach.

Magnetic resonance imaging (MRI), with the capability to acquire both anatomical detail as well as biological, physiological, and metabolic information, is a promising solution. Whilst MRI is increasingly being used for RT planning for many cancers, its utility has typically been limited to providing anatomical definition. However, MRI can also help visualize spatial variations in tumor biology such as blood flow, cell growth and death, inflammation, and oxygenation. Combined with radiomics analysis, development of quantitative MRI biomarkers of tumor biological characteristics offers a pathway for personalized RT dose prescriptions [1].

Traditionally, in prostate cancer (PCa) RT, a uniform dose of radiation is prescribed to the entire prostate gland based on anatomy defined from CT. In contrast to CT, multi-parametric MRI (mpMRI) has the potential for visualization of the tumor within the prostate gland. Using mpMRI to delineate tumors within the prostate, a recently published Phase III clinical trial (the FLAME trial, [2]) has shown that, with a median follow-up of six years, there was an increase in biochemical disease-free survival in patients who received an escalated or 'boost' dose to the tumor compared with those who received the conventional (no boost dose) treatment. However, in this treatment paradigm, intra-tumor heterogeneity is ignored, with the entire volume prescribed at a single dose level. The FLAME trial has also shown that further dose escalation cannot be



1 Proposed clinical implementation of the BiRT workflow for prostate cancer. Treatment options include low-dose-rate brachytherapy (LDR), high-dose-rate brachytherapy (HDR), and external beam radiotherapy (EBRT). Although not shown here, intensity modulated proton/particle therapy may be indicated in some situations. DRE: Digital rectal examination; PSA: Prostate-specific antigen.

achieved without increasing radiation toxicity to surrounding organs. The BiRT approach presents a solution to this problem by redistributing the radiation dose so that radioresistant sub-volumes receive higher doses of radiation than less aggressive sub-volumes whilst maintaining or minimizing dose to surrounding organs at risk.

Within this publication, we present an overarching description of the BiRT project. We present our work in developing imaging biomarkers to guide biologically targeted radiation therapy. In addition, we describe our work that demonstrates the potential for biologically targeted adaptive RT and early detection of non-responding tumors through monitoring changes in mpMRI parameters and radiomic features during and post-treatment.

The BiRT project

The BiRT project aims to develop a mechanism for personalized dose prescriptions using a three-dimensional, voxelized description of tumor biological characteristics obtained using quantitative imaging. Previous studies have shown that tumor biological characteristics can be mapped in three dimensions at the voxel level using quantitative MRI and radiomics analysis [3]. Using artificial intelligence (AI) methods and sophisticated image registration techniques, we have developed population-based statistical models to obtain probabilistic predictions of tumor biological characteristics from patient imaging data [4]. The clinical workflow for the BiRT approach, applied to the case of PCa RT, is shown in Figure 1. In this workflow, quantitative imaging performed for each new PCa patient will be used to provide a spatial map of tumor characteristics that can be utilized in a tumor control probability (TCP) model to optimize dose prescriptions at a voxel level [5]. Through longitudinal imaging, changes in tumor characteristics during the course of the treatment will be monitored to adapt dose prescriptions, and at several time-points after treatment to predict tumor response, enabling early salvage treatments if required.

Predictive models of tumor characteristics and validation with histology

In developing the proposed BiRT framework, the first step was to develop predictive models that could be used to translate mpMRI data into spatially defined maps of biological characteristics, providing the input for creating biologically optimized treatment plans. To develop these predictive models, 63 PCa patients, who were scheduled for radical prostatectomy, were enrolled in a prospective Human Research Ethics Committee (HREC/15/PMCC/125) study at the Peter MacCallum Cancer Centre (Melbourne, Australia). In vivo imaging following PI-RADS and ESUR guidelines [6, 7] was carried out prior to surgical resection and ex vivo MRI. In vivo imaging included axial T2-weighted (T2w) imaging, diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI. A 3D T2-weighted (T2w) imaging sequence was included to allow co-registration of in vivo MRI with ex vivo T2w MRI and histology using a methodology developed by Reynolds et al. [8]. Radiomics analysis of the T2w images, as well as parametric maps derived from the DWI and DCE-MRI data, was performed to obtain feature sets highly correlated to histological ground-truth measures of tumor location, cell density, and tumor grade. Predictive models of these tumor characteristics were developed using machine learning techniques [9–11]. In more recent work, the addition of radiomic features derived from prostate-specific membrane antigen (PSMA) positron emission tomography (PET) images were found to further improve the performance of machine learning models in the prediction of tumor location and disease grade [12]. Additionally, using a radiogenomics approach, 16 candidate radiomic features were identified that were highly correlated with hypoxia gene signatures in a sub-cohort of the dataset [13]. Efforts are underway to extend this work to include the complete study data to obtain robust biomarkers of PCa hypoxia.

BiRT planning and delivery: Personalized dose prescriptions based on tumor characteristics derived from mpMRI

Several in silico planning studies have demonstrated the predicted value of the BiRT approach in PCa RT treatment planning. One of the earliest studies considered using low-dose-rate brachytherapy to modulate the dose distribution based on estimates of the distribution in cell density throughout the prostate [14]. This study demonstrated the potential to maintain high rates of tumor control whilst minimizing dose to surrounding organs at risk, such as the urethra, potentially reducing genitourinary side effects from these treatments. A similar study was performed to create BiRT plans for external beam RT (EBRT) for PCa using patient-specific clonogen density maps [5]. Data collected from five patients in the radical prostatectomy cohort described above were used to generate clonogen density maps for each patient using AI-derived tumor location and cell density predictive models [9, 10]. The study demonstrated an improved TCP with the BiRT approach when compared to the traditional uniform dose plans and focal "boost" plans as in the FLAME clinical trial, while simultaneously minimizing the normal tissue complication

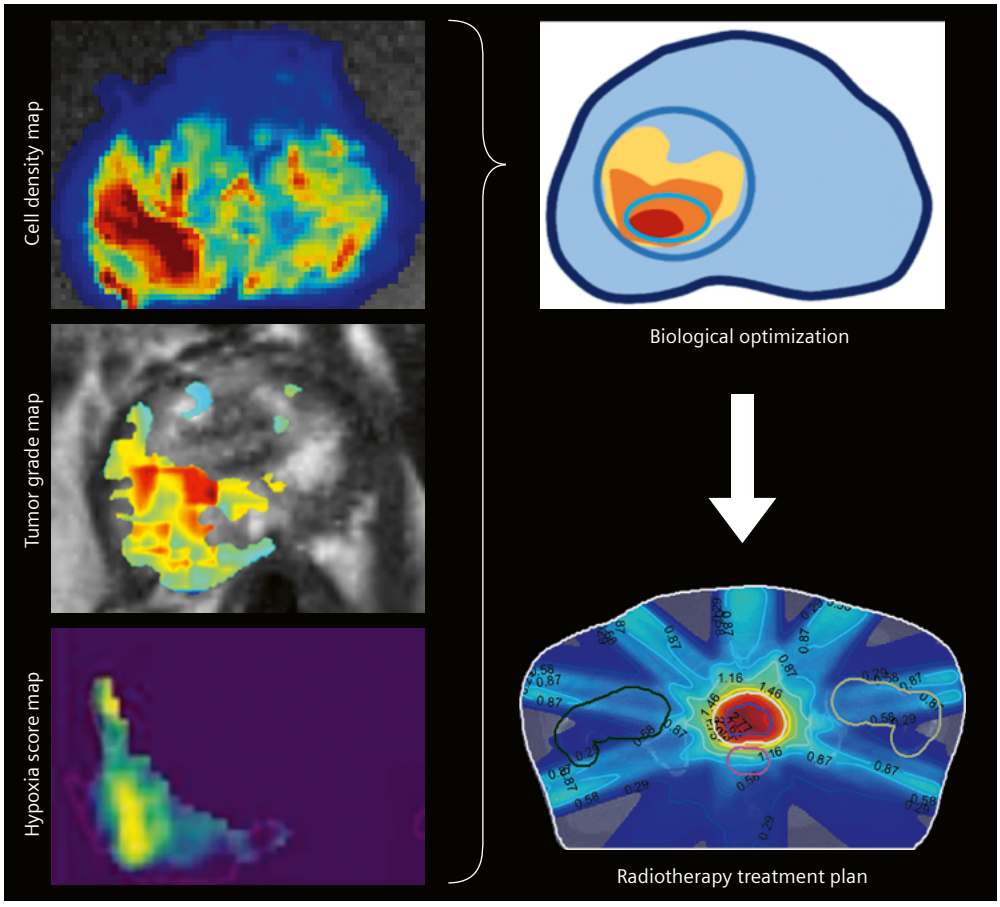
probability (NTCP) of the rectum and bladder. A later study incorporated patient-specific hypoxia score maps to provide evidence that the inclusion of a binary hypoxic status into the planning process can significantly improve the TCP (Fig. 2) [13, 15]. More recently, this work has been extended to incorporate a consideration of tumor grade and the value of including a statistical biological atlas to improve the overall predictive power of the cell density and tumor grade models [16, 17].

Our current work is focused on further development of robust imaging biomarkers of radioresistance. Whilst we have demonstrated an association of imaging features with hypoxia-related genetic signatures in a small study of just six patients, further work is required to develop predictive models using a larger cohort of patients and potentially novel imaging and image processing methods that may reveal reliable indicators of the presence of radioresistant sub-volumes [18, 19].

Imaging biomarkers of RT response

So far, we have described our work in developing spatial maps of tumor biology for the purpose of RT planning. In the work that follows, we describe how these pre-treatment maps provide baseline information that can be used to monitor response to treatment, both during and post-treatment, in an effort to develop biologically targeted adaptive RT techniques and detect recurrent disease, respectively. For this work, we recruited 23 patients to the Sequential Imaging for Biologically targeted RT (SI-BiRT) clinical trial, which was designed to identify mpMRI-derived treatment response biomarkers at a regional and voxel level in patients receiving RT. Initially, the trial included three Australian hospitals and acquired data from three 3T scanners (two MAGNETOM Skyra and one MAGNETOM Prisma, Siemens Healthineers, Erlangen, Germany). A fourth center has recently been added to this study and will collect imaging data in patients receiving low-dose-rate brachytherapy treatments. Data from this fourth center is premature and hence will not be included in this publication.

Longitudinal mpMRI in recruited patients was performed before, during, and after RT. Building on the previous BiRT studies, the SI-BiRT clinical trial imaging protocol was developed to enable extraction of additional quantitative parametric maps that have the potential to inform tumor hypoxia, a known driver for radio-resistance. The DWI protocol was modified to acquire nine b-values between 0 s/mm² and 800 s/mm² to enable the estimation



2 Framework for generating a biologically optimized dose distribution using cell density, tumor grade, and hypoxia score maps derived from mpMRI.

of diffusion coefficient (D) and perfusion fraction (f) using the intra-voxel incoherent motion (IVIM) model. The maps of D and f, correlating to cell density and relative volume of microvasculature, reflect the consumption and supply of oxygen in tissue and were used to derive maps of hypoxia score (HS) [20]. Radiomics analysis was applied to extract potential biomarkers of response, both during treatment to identify radio-resistance, and after treatment to predict response to treatment.

For radiation oncology, the AAPM Task Group 294 specifically defines an MRI biomarker as *"any anatomic, physiologic, biochemical, or molecular parameter detectable with MR imaging methods to identify the presence and/or severity of a malignancy and its response to therapy"* [21]. However, clinical translation of the majority of MRI-derived biomarkers is severely hampered by the uncertainty associated with their measurement. Measurement uncertainty in MRI can arise from differences in hardware and software within and between scanners, as well as day-to-day variation in the patient physiology. Therefore, in the SI-BiRT project, in addition to assessing the statistical significance of treatment-related changes in the quantitative imaging parameters, we also quantified the "detectability" of the change, defined as a treatment effect size larger than the measurement uncertainty in the parameter. Here, we present the three phases of this project.

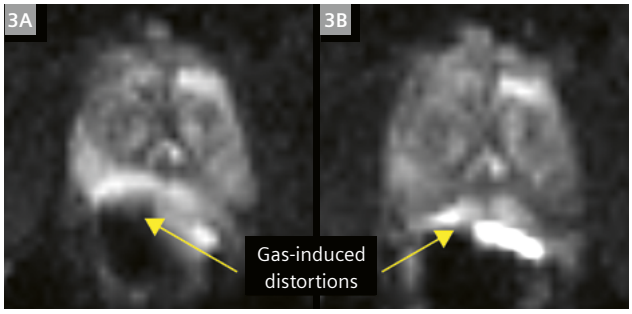
Phase 1: Longitudinal multi-scanner quality assurance program

The SI-BiRT project included a quality assurance (QA) program for all scanners and involved longitudinal scanning of two commercial phantoms (Diffusion and System phantoms, CaliberMRI, Boulder, CO, USA) and one inhouse-developed mpMRI phantom. Details of the SI-BiRT imaging protocol used for this study are included in the Appendix. The within-scanner accuracy and repeatability, and the reproducibility between scanners were quantified for maps of apparent diffusion coefficient (ADC), T1 with and without B1 correction, and R2*. The QA program was designed to provide assurance that the ADC, T1, and R2* maps were comparable across all time-points and between the scanners [22]. The ADC map was found to be the most repeatable and reproducible compared to T1 and R2*. Furthermore, this study showed that the correction of T1 maps with B1 mapping resulted in a higher accuracy error but improved the repeatability and reproducibility of T1 measurements. B1 mapping was therefore used for T1 mapping in the SI-BiRT trial, where repeatability within longitudinal scans of a subject to detect treatment-related changes is prioritized.

Phase 2: Measurement uncertainty thresholds

The second study in the SI-BiRT project aimed to quantify the combined uncertainty due to scanner variability and day-to-day biological variability in the prostate. Two cohorts of participants were imaged with the SI-BiRT imaging protocol, excluding DCE-MRI due to the requirement of repeated injection of the contrast media. In a sub-study of the SI-BiRT clinical trial, test-retest imaging was performed for ten PCa patients within a two-week period prior to receiving RT using the 3T MAGNETOM Prisma scanner. Test-retest imaging in six healthy volunteers with no known prostate disease was acquired with a 3T MAGNETOM Skyra scanner, with each participant receiving a minimum of two repeated scans within three months. In addition to the qMRI parameters investigated in the quality assurance study (Phase 1), the diffusion coefficient (D), perfusion fraction (f), and hypoxia score (HS) were also obtained from the DWI.

The repeatability of qMRI parameter measurements was calculated for average and voxel-wise measurement approaches across the regions of interest (ROI). The former is defined by the variability in average values of measurements within the ROI, whilst the latter accounts for the variability in measurements per voxel. The repeatability of voxel-wise measurements of all maps was consistently lower than the average (ROI) measurement approach. ADC, D, and HS measurements were found to be significantly less repeatable in the peripheral zone (PZ) compared to the non-peripheral zone, potentially arising from the presence of transient gas-induced distortions in DWI and the proximity of the PZ to the rectum (Fig. 3). The DWI-derived qMRI parameter measurements in tumor tissue were also significantly less repeatable than the benign tissue, potentially due to the relatively smaller volume of the ROI. The percentage repeatability coefficient (%RC), representing the threshold of change required to distinguish "true" treatment-related changes from measurement uncertainties in 95% of subjects, was computed for each qMRI parameter. The %RC for ADC, D, and HS was calculated separately for each anatomical zone and tissue type (tumor and benign). As the repeatability of T1 and R2* was found to be comparable between anatomical zones and between tumor and benign tissue types, one single %RC was computed for the entire prostate gland for these parameters.



3 Example axial view of test-retest (**3A** and **3B** respectively) diffusion-weighted images depicting varying severity of rectal gas-induced distortions.

Phase 3A: Post-treatment response monitoring with longitudinal mpMRI: Analysis of SI-BiRT clinical trial (in progress)

The SI-BIRT clinical trial aimed to

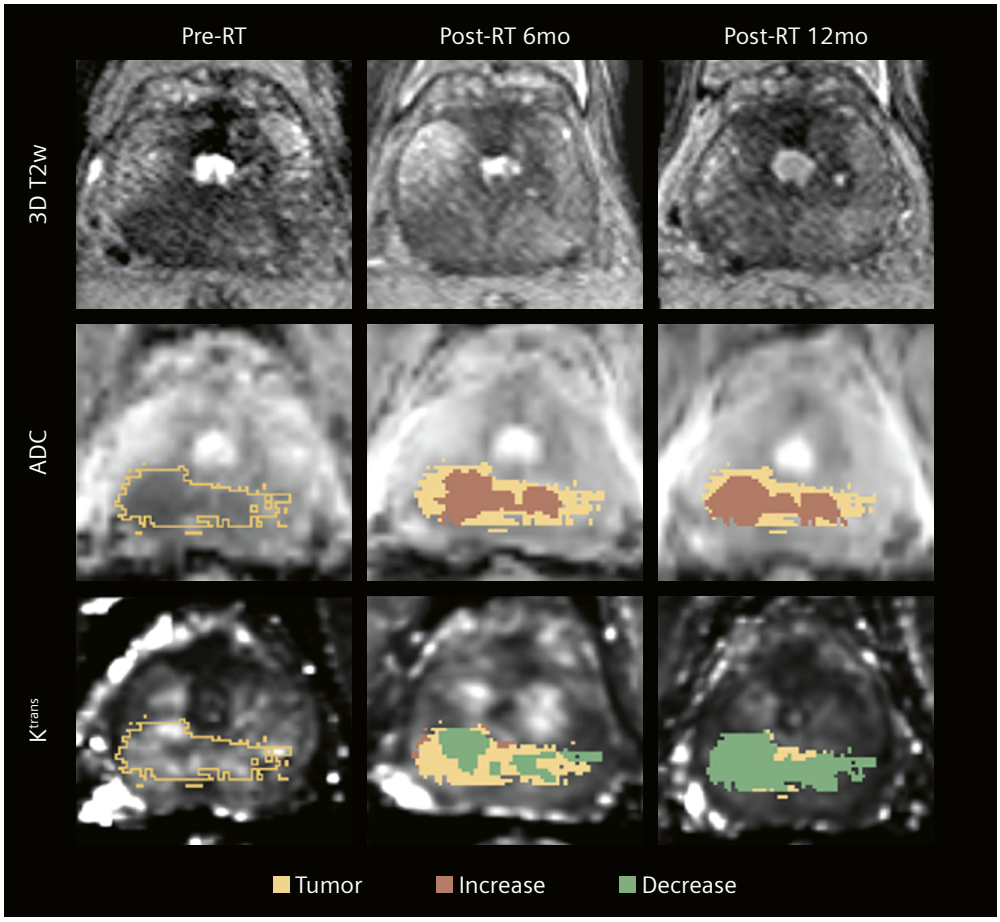
1) evaluate feasibility of spatial treatment response mapping with mpMRI;
2) identify robust quantitative imaging features that may predict response to RT;
3) determine optimal follow-up times to predict treatment response.

Whilst we continue to analyze the data from patients who received external beam RT, and to collect data in patients receiving brachytherapy, we present the preliminary results from the data collected to date.

Using the measurement uncertainty thresholds established from the repeatability study of the SI-BiRT project, we have identified sub-regions within tumors with detectable (larger than the uncertainty threshold) changes in each of the qMRI parameter maps. Figure 4 shows detectable sub-regions in ADC and K^{trans} maps for a single patient at 6 and 12 months post-treatment. The tumor subregion with detectable change was found to vary between the measurement timepoints and also between the parameter maps. Our findings suggest that a combination of multiple parametric maps provides complimentary information and may be of greater benefit than considering a single parameter in isolation.

Within the SI-BiRT (main study) patient cohort, 13 of the 23 patients received androgen deprivation therapy (ADT) for up to 4 months prior to treatment and for a further 1–22 months post-treatment. For patients receiving RT only, the most promising qMRI parameters for reliably detecting treatment response were K^{trans}, v_e, T1, and HS. The most promising qMRI parameters for treatment response in patients who received RT with ADT were found to be K^{trans}, v_e, and HS, but at different follow-up timepoints than the RT-only cohort. The dynamics and magnitude of treatment-related changes were different between the two patient groups, demonstrating that the relative value of each of qMRI parameter and the optimal timing of measurement is likely to be different depending on the use of ADT in combination with RT.

Our current focus is on the analysis of the radiomic features and eventually the development of a clinical tool that will predict the likelihood of recurrent disease.



4 Example of longitudinally acquired T2-weighted (T2w) images and apparent diffusion coefficient (ADC) and forward transfer constant (K^{trans}) maps at pre-radiation therapy (RT) and 6 and 12 months post-RT. The tumor region is delineated in yellow, with subregions of detected treatment-related changes in brown and green (increase and decrease in parameter value, respectively).

Phase 3B: During-treatment response monitoring: A step toward "real-time" biological treatment adaptation

A sub-study in the SI-BiRT clinical trial was designed to investigate the potential for qMRI to detect regions of radio-resistance during the course of RT. In the same way that PET has been proposed for head and neck cancers to identify regions of non-responding tumor and thus targets for dose-escalation [23], our goal is to investigate the potential for qMRI to identify sub-volumes at risk of recurrence and modify planned dose distributions, during the course of RT, to minimize risk of treatment failure. The SI-BiRT sub-study cohort of 10 patients were imaged at 2 and 4 weeks during the standard course of RT (60 Gy delivered in 20 treatments over a period of 4 weeks). All patients were imaged according to the SI-BiRT imaging protocol, excluding DCE-MRI due to the short interval between imaging sessions. We are in the process of applying our image analysis framework to identify reliable imaging biomarkers of response during RT. Our hypothesis is that by combining imaging biomarkers of treatment response and radioresistance, predictive models can be developed and used in future patients for early assessment of treatment efficacy and to inform intervention via treatment adaptation if necessary.

Conclusion and clinical translation

Access to MRI for patients undergoing radiation therapy has been increasing in recent years. Whilst the benefits of delineating soft-tissue-based surrounding healthy organs and tumors are well documented, the ability of MRI to define functional and biological characteristics of tumors is yet to be incorporated into mainstream RT. Our work so far has demonstrated that MRI can spatially define biological characteristics of tumors that may predict response to radiation. With this information, radiation therapy treatment planning can generate modulated dose distributions whereby the optimal dose of radiation for maximized tumor control and minimized treatment side effects can be determined on a voxel-wise basis. For clinical translation, generalizability of our results needs to be verified, and commercial treatment planning systems modified to enable spatial maps of tumor biology to be incorporated into the dose-optimization engines. We are currently exploring the possibility of mapping response during radiation therapy using quantitative MRI. However, our work so far has provided sufficient evidence that imaging following treatment has the potential to identify recurrent disease, offering the opportunity for early and targeted salvage treatments. Our goal is to incorporate routine imaging post-RT in prostate cancer patients enrolled in future clinical trials so that the link between clinical outcomes and detectable changes in qMRI and MRI radiomics features can be established.

Acknowledgments

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Appendix: Imaging protocol

The imaging protocol developed for the SI-BiRT studies consists of imaging sequences recommended by the Prostate Imaging—Reporting and Data System (PI-RADS v2) and prostate-specific qMRI protocols in the literature to enable extraction of a comprehensive range of qMRI parameters from the images.

- Axial 2D T2-weighted imaging (T2w) was acquired with the Turbo Spin-Echo sequence (TE: 80–120 ms, TR: > 7000 ms, resolution: 0.5 × 0.5 × 2.5 mm^3).
- Sagittal 3D T2w imaging was acquired with the SPACE sequence (TE: 100–110 ms, TR: > 1600 ms, isotropic resolution: 0.8 × 0.8 × 0.8 mm^3).
- Diffusion-weighted imaging (DWI) was acquired with the reduced field of view echo planar imaging sequence, ZOOMit (TE: 70 ms, TR: > 4000 ms, resolution: 1.9 × 1.9 × 4 mm^3, b-values: 0, 20, 50, 100, 200, 300, 400, 600, 800 s/mm^2).
- Transverse relaxation rate, R2*, mapping was performed with a multi-echo gradient echo sequence from the MapIt module (TE: 12 echoes from 4.9–73.8 ms, TR: 810 ms, resolution: 1.7 × 1.7 × 4 mm^3). Variable flip angle (VFA).
- T1 mapping with spoiled gradient echo was acquired with the VIBE sequence (TE: 1.38 ms, TR: 4.63 ms, resolution: 1.1 × 1.1 × 3 mm^3, flip angles: 2/5/10/15/20/30 degrees).
- Prior to the T1 map, B1 mapping was acquired with the TFL sequence to correct for inhomogeneity in the transmit frequency field (TE: > 2 ms, TR: > 8500 ms, resolution: 3.9 × 3.9 × 5 mm^3, flip angle: 8 degrees) in the VFA VIBE T1 mapping sequence.
- Dynamic contrast-enhanced MRI (DCE-MRI) was acquired with the improved VIBE sequence with inline Tofts modelling (TWIST acquisition, TE: 1.4–2.5 ms, TR: 4.1 ms, resolution: 1.1 × 1.1 × 3 mm^3, 4.9 s temporal resolution).

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