Use of contemporary prostate brachytherapy approaches in clinical trials

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Abstract. A number of clinical trials are investigating the role of prostate focal brachytherapy as an alternative treatment to whole gland therapy, offering the opportunity for tumour dose escalation and/or reduced toxicity. Brachytherapy, either low dose rate or high dose rate, offers a treatment choice with both precision in dose delivery and opportunity for a highly conformal, non-uniform dose distribution. Whilst multiple consensus documents have published clinical guidelines for patient selection, there are insufficient data to provide clear guidelines for treatment planning approaches along with many other technical issues when practicing focal brachytherapy. Without consensus guidelines there is the potential for a diversity of practices to develop, leading to challenges in interpreting outcome data from multiple centres. We provide a quantitative framework for prostate focal brachytherapy that incorporates a personalized, biological approach that can be used as the foundation for future prostate focal brachytherapy trials.

1. Introduction

Prostate cancer (CaP) is globally the most commonly diagnosed cancer in men [1]. Randomised trials have demonstrated that radiotherapy is an effective form of treatment for localised CaP and that escalating the dose improves biochemical control [2-5]. Dose escalation however, also results in increasing doses of radiation being delivered to surrounding healthy tissue and is therefore limited by a threshold when rates of gastrointestinal and genitourinary toxicity become unacceptable [2]. Brachytherapy [BT] offers an opportunity to accurately deliver higher doses of radiation than can typically be delivered with external beam radiotherapy (EBRT) [6]. This is due to the high dose gradients that surround the radioactive source creating an opportunity to tightly conform the radiation dose to the target volume whilst controlling radioactive source placement [7]. Furthermore, when BT is delivered in a small number of high-dose fractions, the radiobiological benefits due to the low alpha/beta ratio for prostate cancer can be exploited [8]. BT dose escalation however, using a whole-gland approach is limited by normal tissue toxicity, in particular, urinary toxicity associated with dose to the urethra [9].

A number of studies have investigated "focal" or "focussed" approaches to BT treatments, whereby the aim is to deliver very high doses of radiation to only tumour bearing regions of the prostate, with lower doses delivered to the remainder of the gland in an effort to maximise tumour control and minimise side effects [10,11]. Whilst a number of clinical trials report promising results, heterogeneity in treatment approaches may lead to difficulties in interpreting inconsistencies or unexpected results. Furthermore, technical challenges may prohibit rapid translation to routine clinical care [12].

We propose a focal BT approach that applies quantitative imaging (radiomics) to not only standardise target volume definitions but also non-invasively quantify and classify tumour phenotype [13,14]. The biofocussed BT approach uses advanced imaging techniques to characterise the biological nature of tumours using a 3D, voxel-by-voxel spatial representation, described by Haworth et al [15]. Using a mathematical model, the radiation dose needed to destroy the tumour cells within each voxel can be calculated; with knowledge of the ideal dose distribution a treatment plan can then be generated using either a low-dose-rate (LDR) or high-dose-rate (HDR) approach. We hereby describe a framework for Biologically Optimised RadioTherapy (BiRT).

2. Methods

The framework for BiRT, that incorporates multiparametric MRI (mpMRI), is shown in Figure 1. The framework presents a personalised medicine approach to treatment whereby knowledge of the spatial distribution of tumour heterogeneity is first quantified following imaging. Treatment is then prescribed based on 3D maps of the spatial heterogeneity and a dose-painting approach [16]. The treatment is delivered under the control of image guidance techniques, and quantitative imaging at regular intervals following treatment is compared with the pre-treatment imaging data to monitor treatment response.

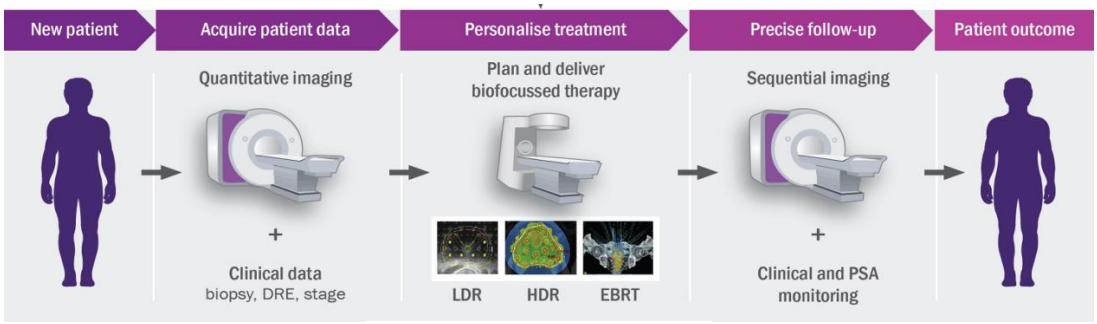

Figure 1. The BiRT framework

2.1 Acquire patient data

Multiparametric MRI is widely used in the staging and grading of newly diagnosed prostate cancer, and the PI-RADS system provides recommendations for scanning sequences and for reporting clinically significant cancers [17]. Regarding focal therapy, mpMRI may be used to guide biopsy, and has the potential to improve the detection of clinically significant cancers [18]. Similarly, mpMRI is the most commonly suggested method for defining the focal treatment volume within the prostate due to its high sensitivity and specificity [19]. Previous focal BT approaches however, have used an empirical or subjective approach to define target volumes, with definitions typically ranging from a geometric sub-division of the prostate (e.g. hemigland and sector-based approaches [20]), regions of positive biopsies [21] or a subjective delineation on MRI [22]. In contrast we suggest the use of computer aided detection (CAD) systems to delineate PCa from mpMRI [23,24] to improve consistency compared to manual delineation, which can suffer from inter-observer variability and low detection rates of satellite lesions [25]. A recent study by Sun et al for example, described the development of Gaussian kernel support vector machines (SVMs) and reported a prediction accuracy ranging from 70.4% to 87.1% as well as area under the curve (AUC) of the receiver operating characteristic (ROC) curve ranging from 0.81 to 0.94 [26].

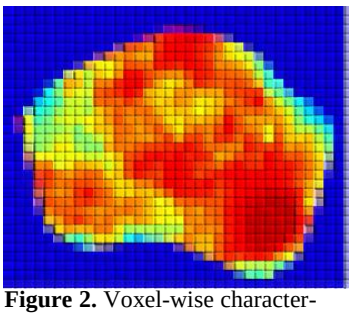

Figure 2. Voxel-wise characterisation of tumour biology to be used with biologically based inverse planning treatment methods [8].

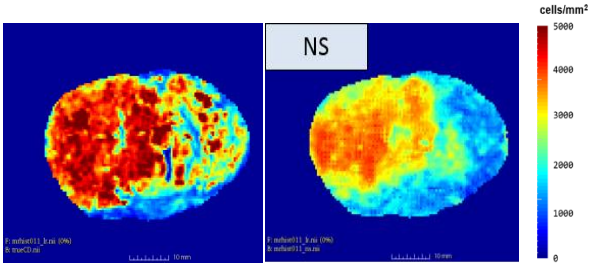

Figure 3. Cell density derived from histology (right panel) is compared with the predicted cell density derived using natural spline algorithm (left panel).

In addition to using mpMRI to define volumes for targeted treatments, mpMRI can also provide voxel-wise characterisation of the tumour phenotype [27]. Whilst radiogenomics analysis has been widely reported for its ability to capture intratumour heterogeneity in head and neck and lung cancers, the application in prostate cancer is less well developed. For the proposed biological approach to treatment planning, we have investigated the use of machine learning techniques to quantitate the spatial distribution of tumour cell density, tumour aggressiveness and hypoxia. Promising results indicate cell density prediction with a root mean square error of 1. 06 x 10^3 cells / mm^2, and differentiation of low and high-grade tumour with an AUC of 0.91 (Figure 2, *submitted*). Data were derived from a clinical study where in vivo mpMRI data was co-registered with histology using a sophisticated co-registration framework [28]. Mapping the spatial distribution of hypoxia in prostate cancer is challenging due to the difficulty in providing ground truth data from histology. Radiogenomics approaches offer apromising solution to this problem [29].

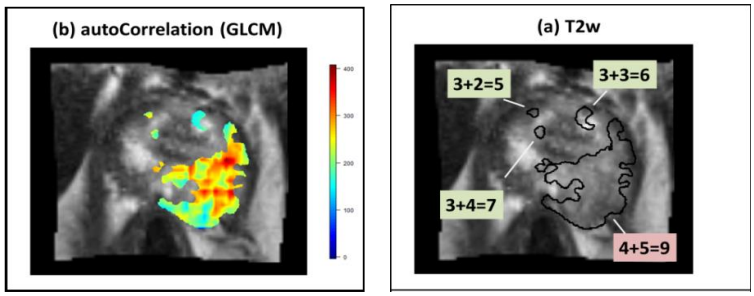

Figure 4. Predicting tumour grade using one of several methods described by Sun et al (submitted). GLCM: gray-level co-occurrence matrix. Left panel shows pathologist annotation overlaid on T2w MRI.

2.2 Personalised Treatment

With a voxel-wise representation of tumour location and characterisation of intratumour heterogeneity, treatment planning can be carried out using an inverse optimisation approach with biological objective functions. In the planning study of Haworth et al it was shown that by using an objective function based on tumour control probability (TCP), urethral doses could be reduced by up to eight-fold when compared with conventional, whole-gland treatment approaches and dose-based planning objectives [29]. It should be noted that in contrast to previous approaches to maximise radiation dose to the tumour bearing regions, the biological approach instead attempts to find the plateau on the TCP curve (Figure 3). With this approach, the normal tissue complication probabilities for each of the organs-at-risk can be minimised. Whilst we have shown that LDR treatment plans can be developed that are robust to seed placement uncertainty [30], more work in this area is required for HDR treatment planning. However, using the same principles, HDR treatments, when delivered using 3D source tracking technology to verify accurate delivery, offers the potential for a relatively simple but highly effective form of treatment for all prostate cancer risk groups.

2.3 Precise Follow-up

The current standard method for assessing treatment response following prostate radiotherapy is measurement of prostate specific antigen (PSA) [31]. However, its role in determining treatment response in BT is challenging due to the frequent “bounce” phenomenon [32], and its role for focused therapies is unclear. Instead, utilisation of mpMRI and PET imaging has the potential to offer improved outcome assessment after prostate therapy and has been previously reported by several researchers, though the approach is largely qualitative with conflicting results [33]. With the BiRT framework, we propose that quantitative biological and functional imaging methods will provide more reliable and reproducible methods for accurate assessment of PCa radiotherapy treatment response. Technical challenges include

standardization of scanning protocols and quantitative measures to account for inter- and intra-scanner variability [34].

3. Conclusion

We propose a quantitative, biologically-based, image-guided approach to focal therapy using imaging protocols that could be standardly incorporated into clinical trials delivering outcomes that can be rapidly translated into clinical practice. This method provides an objective process, using imaging as a guide for mapping spatial tumour characteristics to the non-uniform dose distributions required for optimal treatment, realising the goal of voxel-level dose painting. The methods used to map those tumour characteristics from imaging data allow quantification and consideration of the underlying uncertainties. With this approach, BT offers an ideal treatment option, exploiting the ability to tightly conform dose distributions under controlled treatment delivery techniques.

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