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Identifying quantitative *in vivo* multi-parametric MRI features for treatment related changes after laser interstitial thermal therapy of prostate cancer

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ABSTRACT

Laser interstitial thermal therapy (LITT) is a new therapeutic strategy being explored in prostate cancer (CaP), which involves focal ablation of organ-localized tumor via an interstitial laser fiber. While little is known about treatment-related changes following LITT, studying post-LITT changes via imaging is extremely significant for enabling early image-guided intervention and follow-up. In this work, we present the first attempt at examining focal treatment-related changes on a per-voxel basis via quantitative comparison of MRI features pre- and post-LITT, and hence identifying computerized MRI features that are highly sensitive as well as specific to post-LITT changes within the ablation zone in the prostate. A retrospective cohort of 5 patient datasets comprising both pre- and post-LITT T2-weighted (T2w) and diffusion-weighted (DWI) acquisitions was considered, where DWI MRI yielded an Apparent Diffusion Co-efficient (ADC) map. Our scheme involved (1) inter-protocol registration of T2w and ADC MRI, as well as inter-acquisition registration of pre- and post-LITT MRI, (2) quantitation of MRI parameters by correcting for intensity drift in order to examine tissue-specific response, and (3) quantification of the information captured by T2w MRI and ADC maps via texture and intensity features. Correction of parameter drift resulted in visually discernible improvements in highlighting tissue-specific response in different MRI features. Quantitative, voxel-wise comparison of the changes in different MRI features indicated that steerable and non-steerable gradient texture features, rather than the original T2w intensity and ADC values, were highly sensitive as well as specific in identifying changes within the ablation zone pre- and post-LITT. The highest ranked texture feature yielded a normalized percentage change of 186% within the ablation zone and 43% in a spatially distinct normal region, relative to its pre-LITT value. By comparison, both the original T2w intensity and the ADC value demonstrated a markedly less sensitive and specific response to changes within the ablation zone. Qualitative as well as quantitative evaluation of co-occurrence texture features indicated the presence of LITT-related effects such as edema adjacent to the ablation zone, which were indiscernible on the original T2w and ADC images. Our preliminary results thus indicate great potential for non-invasive computerized MRI imaging features for determining focal treatment related changes, informing image-guided interventions, as well as predicting long- and short-term patient outcome.

1. Introduction

Prostate cancer (CaP) is the most frequent malignancy diagnosed in men 50 years and older in industrialized countries [1]. However, while 1 in 6 men may be diagnosed with prostate cancer, only 1 in 36 will die from it [1]. There is thus an increasing clinical preference to put patients with more focal, lower grade CaP on active surveillance, where they are monitored for disease

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metastasis. Focal therapy options provide a useful adjunct to active surveillance, with significantly lower morbidity (urinary, sexual dysfunction) [2] compared to more radical treatment options (prostatectomy, radiation treatment). They additionally reduce the overtreatment of CaP in the general population, while allowing patients to have their disease treated once diagnosed [2].

Focal therapy strategies such as laser interstitial thermal therapy (LITT), high intensity focused ultrasound (HIFU), cryotherapy, and photo-dynamic therapy (PDT) are considered to be highly effective for targeting the *index lesion*, or the largest focus of CaP as measured by volume, within the prostate [3]. Most secondary (non-index) tumors tend to exhibit relatively smaller volumes and rarely have a higher Gleason score than the index lesion, making them unlikely to affect overall disease progression [4]. Thus, biologically speaking, most patients can be considered to have unifocal disease (*i.e.* the index lesion), by targeting which one can dramatically decrease the total tumor volume and eliminate the most likely source of metastasis [5].

The specific focal therapeutic strategy considered in this work is LITT, which involves thermal destruction of tissue via the Nd-YAG laser delivered by an interstitial fiber. Heat energy is delivered to raise the temperature within the targeted CaP region, where rapid coagulative necrosis and instant cell death occur above 60 °C. One of the major advantages enjoyed by LITT is its compatibility with magnetic resonance imaging (MRI), allowing for high resolution *in vivo* imaging to be used in LITT procedures [6]. MRI is also capable of monitoring temperature change in the tissue, which enables real-time monitoring of LITT. Further, multi-parametric MRI offers the ability to accurately denote the specific location of biopsy-proven CaP within the gland [1], which is very important for accurately delineating ablation zones within the prostate as well as for accurate guidance of the laser fiber during treatment.

In organs such as the liver, the extent of tissue necrosis due to LITT has been shown to be visible on MRI [7]. Rosenkrantz et al. [6] have described some of the primary imaging characteristics at the 6-month follow-up mark after most types of focal therapy (though this study was not limited to LITT). The most significant of these was a decrease in the prostate volume (leading to loss of differentiation between prostatic zones), as well as poor visualization of the capsule. Structural T2w MRI is considered to be of limited utility to evaluate focal therapy effects due to the presence of multifocal hypointensities that appear due to prostatic parenchyma [6], post-therapy. Diffusion weighted imaging (DWI) accurately visualizes tissue viability post-LITT (based on increased water diffusion), but its ability to differentiate between normal tissue, necrosis, and residual tumor has not been studied. Additionally, to our knowledge, the relative importance and utility of different MRI protocols in determining post-LITT effects has not been explored in detail.

There is thus relatively little information regarding the specific *in vivo* imaging characteristics of LITT-induced changes in the prostate. Further, the qualitative observations of LITT-related changes on prostate MP-MRI do not specifically address how to differentiate between the appearance of benign LITT-related changes (edema, necrosis) that can mask the presence of residual CaP, post-LITT. This implies a need for co-registration and image analysis methods to quantitatively compare pre- and post-LITT MRI in order to identify voxel-by-voxel changes in MRI parameters that can describe LITT-related changes within the prostate. Careful co-registration of pre- and post-LITT MRI can enable accurate overlays of the two acquisitions as well as voxel-wise comparison of the ablation zone (focally targeted index lesion) between pre- and post-LITT MRI acquisitions. Superposing the ablation zone from the pre-LITT MRI onto the post-LITT MRI can help identify imaging characteristics that correspond to residual disease (which would primarily occur within the ablation zone), as well as for benign LITT-related changes (edema, necrosis) that may appear external to the ablation zone.

In this work, we present the first attempt at quantitative image analysis of high-resolution (per-voxel) evaluation of treatment-related changes *in vivo* in CaP patients who have undergone LITT, via co-registration of pre- and post-LITT MRI acquisitions. Our approach is intended to form a precursor to building of a novel imaging-based predictor of early focal treatment response in CaP, to enable effective image-guided intervention. Our scheme may also find application in examining quantitative changes in non-invasive imaging markers as a function of time, to be correlated against long-term disease outcome and patient prognosis.

The remainder of this paper is organized as follows. Section 2 describes previous related work in quantitative treatment evaluation and Section 3 provides an overview of the methods used in the current work. Section 4 details the experimental design, while Section 5 summarizes the experimental results and discussion. Finally, Section 6 presents our concluding remarks.

2. Previous related work

Treatment evaluation of therapeutic options for prostate cancer has primarily been examined for radiation treatment in a number of qualitative studies [8–12]. Our group [13,14] has leveraged these qualitative characteristics within novel quantitative schemes for per-voxel evaluation and MRI signature construction to differentiate between possible radiation treatment outcomes (success, unsuccessful, recurrence). However, to our knowledge there is no similar work on evaluating treatment related changes due to LITT, via co-registration and quantitative analysis of pre- and post-LITT MRI.

MR thermometry measurements acquired during LITT have been utilized for predicting cell death using animal models [15–17]. These have involved construction of simulated mathematical models which can provide an estimate of cell death at a location, given the temporal thermometry information during treatment for that location and certain assumptions regarding temperature effects *in vivo*. Validation of these models has been done via rigid co-registration between thermometry images and post-LITT MRI [15] or histology [16,17], enabling comparison of actual regions of cell death against a simulated heatmap.

In studies involving prostate cancer patients, a Phase I LITT trial found good correlation between volumes of thermal damage that were visible on MRI and those determined via staining of *ex vivo* surgical prostatectomy specimens from patients who had previously undergone LITT [18]. Additionally while the ablated volume measured on MRI was marginally over-estimated compared to pathology, MR images demonstrated excellent capability in discriminating non-viable necrotic tissue, post-ablation. More recently, co-registration approaches have been proposed for planning [19] and guidance [20] of LITT for prostate cancer using MRI information. These methods involved the construction of a phantom to simulate focal treatment, as well as the application of the simulated information for accurate targeting of focal treatment via fusion of MRI and ultrasound.

3. Motivation and brief overview

In this work, we present the first results of utilizing careful co-registration and image analytic tools to enable high-resolution (per-voxel) evaluation of treatment-related changes *in vivo* in CaP patients who have undergone LITT, using MRI information. A retrospective cohort of prostate MRI data that comprises both pre- and post-LITT acquisitions, including T2-weighted (T2w) and