The Role of Multiparametric MRI in Contemporary Radiotherapy of Prostate Cancer

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Target Audience: Physicians and scientists interested in prostate cancer imaging research.

Purpose: Radiotherapy dose escalation results after primary or salvage radiotherapy (RT) of prostate cancer indicate that local persistence remains a problem. Three clinical trials are initiated for targeted treatment of prostate cancer, based on the hypothesis that: ***(i)*** the dominant lesions recognized on multiparametric MRI (MP-MRI) determine outcome; ***(ii)*** MP-MRI-directed biopsies are critical to accurately assessing pre-treatment (pre-Tx) histopathologic and molecular characteristics; ***(iii)*** MP-MRI parameters are related to tumor response and molecular abnormalities; ***(iv)*** early MP-MRI changes after treatment will correlate with response and ***(v)*** targeting these lesions will improve control rates without increasing toxicity.

Methods: MP-MRI is incorporated in prostate cancer RT by utilizing novel methods of analysis for seamless translation of imaging tumor volume(s) (ImTV(s)) for the treating physician. MP-MRI is performed on GE Discovery MR750 3T MRI unit using image acquisition parameters with image size and spacing suitable for fusion with the CT for RT planning purposes. The unit is equipped with a flat tabletop, like that in RT simulators. A typical exam consists of: ***(i)*** Axial T2w-MRI of the male pelvis: resolution 1.25×1.25×2.5 mm; Field of View (FOV): 320×320 mm; slice thickness=2.5mm (no gap); 72 slices; ***(ii)*** Axial T1w gradient echo MR images with identical spatial parameters as the T2w images; ***(iii)*** Dynamic Contrast Enhanced MRI (DCE-MRI)–12 series of T1w at 30s temporal resolution; ***(iv)*** Diffusion Weighted Imaging (DWI)-Single-shot echo-planar imaging performed with *b*=50, 500, and 1000 s/mm^2. MP-MRI is an integral part of the following clinical trials: ***(i)*** A Phase I Trial of MRI-Guided Lattice Extreme Ablative Dose Radiotherapy for Prostate Cancer (the **LEAD** trial) in which a high RT dose is given on day 1 to the ImTVs and standard fractionation RT treatment for 38 treatments subsequently; ***(ii)*** A Phase III Randomized Trial of Hypofractionated External Beam Image-Guided Highly Targeted Radiotherapy (the **HEIGHT** Trial) in which half the men receive a daily RT dose-painted boost to the ImTVs and half - standard RT; ***(iii)*** A Phase III Randomized Trial Of MRI-Mapped Dose-Escalated Salvage Radiotherapy *Post-Prostatectomy* (The **MAPS**) in which half the men receive a daily RT dose-painted boost to the ImTVs and half - standard RT. The role of MP-MRI is highlighted in red on **Figure 1**: ***(i)*** delineation of ImTVs for ultrasound/MRI fusion in the Artemis^{TM} system (Eigen, CA) for targeted biopsy; ***(ii)*** ImTVs RT boost target; ***(iii)*** post-Tx MP-MRI at 3, 9 and 24 mo.

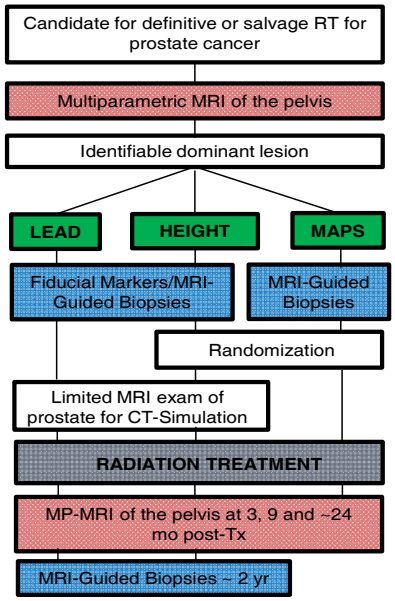

Figure 1. General schema of the trials.

Results: Currently 18 patients are enrolled in **LEAD**; 12 in **HEIGHT** and 7 in **MAPS**. An integrated platform is developed for ImTV visualization using MIM Software Inc (Cleveland, OH). MP-MRIs from the prostate/prostate bed are transferred to MIM from PACS and coregistered. An unsupervised pattern recognition technique is implemented for identification and automatic delineation ImTVs in the DCE-MRI (**Figure 2**). The approach is based on non-Negative Matrix Factorization (NMF).[1] The tumor area is characterized with rapid uptake followed by continuous washout of the contrast (**Fig 2C**). The weights, corresponding to this contrast-to-time pattern represent the DCE-tumor map (**Fig 2E**, red). Low ADC values (<1000 s/mm^2) are also auto-contoured in MIM (**Fig 2E,** red-green overlap is yellow). The ImTV is used for biopsy target and RT boost. To date MP-MRI at 3 and 9 mo post-Tx are obtained from 11 patients in **HEIGHT** and **LEAD** and 2 in **MAPS**. A procedure for coregistration is implemented of the pre- and post-RT MP-MRIs. ROIs in the prostate/prostate bed are contoured in MIM (**Figure 3**). The graphs show the means of the associated DCE curves for pre-Tx, and 3 and 9 mo post-Tx. The DCE ImTV lesion shows the most rapid and highest uptake. By 9 mo all regions of the prostate have a similar slow uptake pattern. To illustrate quantitative changes, pre- and post-TX values of K^{trans} are shown in the bar graph in the upper right.

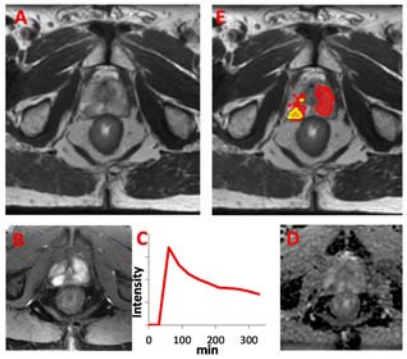

Figure 2. (A) T2w Axial slice (B) Early enhancement DCE (C) tumor contrast-to-time pattern; (D) ADC map; (E) Volumes of high perfusion (red) and low ADC (yellow) displayed in MIM.

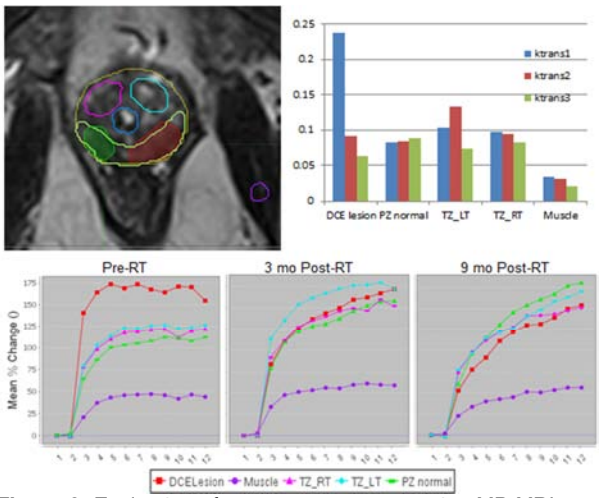

Figure 3. Evaluation of treatment response using MP-MRI pre- and post-RT for a patient in the experimental arm of **HEIGHT**. ROIs are outlined in 3 dimensions: prostate (orange); peripheral zone (PZ) – yellow; dominant tumor – red; normal PZ – green; urethra (blue); left (light blue) and right (pink) transition zone (TZ); muscle (purple). Below: DCE curves for ROIs pre-Tx, and 3 & 9 mo post-RT. K^{trans} (upper right corner).

Conclusions: MP-MRI is an integral part of several contemporary clinical trials for RT of prostate cancer both in patients treated primarily and post-prostatectomy. The outcomes of these trials will determine the contribution of MP-MRI for improved control rates without increasing toxicity, as well as the capacity of early MP-MRI changes after treatment to correlate with response.

References: [1]Stoyanova R, et al. Transl Oncol. 2012;5(6):437-47.