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Pilot study using multi-parametric magnetic resonance imaging for organ delination and tumor response assessment of prostate cancer patients being treated with radiation therapy.

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Pilot study of using multi-parametric magnetic resonance imaging for organ delineation and tumor response assessment of prostate cancer patients being treated with radiation therapy

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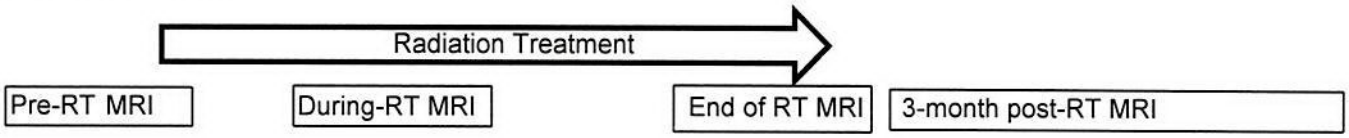
Eligibility:

- Histologically confirmed prostate adenocarcinoma
- Patients must sign study-specific informed consent form prior to registration

Eligibility Checklist:

_____(Y)	1. Is there histologically confirmed prostate adenocarcinoma?
_____ (2-7)	2. What is the combined Gleason Score Classification?
_____ (≤15)	3. What is the PSA level?
_____ (T1-T3)	4. What is the T stage?
_____ (≥ 70)	5. What is the Karnofsky Performance Status?
_____(Y)	6. Were pre-treatment evaluations completed per Section 4 of the protocol?
_____ (N)	7. Are there any major medical or psychiatric illnesses, which would prevent completion of treatment and/or interference with follow up?
_____(Y)	8. Has the patient signed a study-specific informed consent?

STUDY SCHEMA



STUDY SYNOPSIS

Title	Pilot Study of using multi-parametric magnetic resonance imaging (MRI) for organ delineation and tumor response assessment for prostate cancer patients being treated with radiation therapy
Phase	Pilot
Methodology	Single arm
Study Duration	4-year
Study Center(s)	Henry Ford Health System
Objectives	To generate intraprostatic lesions maps based on multi-parametric MRI, and characterize longitudinal changes in imaging characteristics
Number of Subjects	20 evaluable patients
Inclusion Criteria	Patients who will receive RT for prostate cancer and can have a contrast-enhanced MRI are eligible.
Exclusion Criteria	Patients who have a contraindication to contrast-enhanced MRI are not eligible. Patients with implanted device such as pace marker or metal fragments are not eligible.
Study Product(s), Dose, Route, Regimen	Patients will have multiple MRIs (before RT, during RT, immediately post-RT, 3-months post-RT).
Duration of Participation	6 months
Statistical Methodology	For this pilot study, statistical comparisons will be made between before, during, and after RT imaging, using the paired t-test, or the time course may be modeled using linear and non-linear mixed effects models with random effect for each subject (random intercept and slope as appropriate).

1.0 INTRODUCTION

With wide-spread Prostate-Specific Antigen (PSA) screening, the overall age-adjusted incidence of prostate cancer has increased gradually since 1986 and stabilized after the late nineties [1]. A combination of PSA, clinical stage and Gleason score have also increased the detection of prostate cancers at earlier stage. A study from the Mayo Clinic showed that the percentage of men diagnosed with T1c prostate cancer increased from 2.1% to 36.4% among 5,568 men with prostate cancer between 1987 and 1995 [2]. The proportion of patients diagnosed with low risk prostate cancer was 29.8% between 1989 and 1992 and increased to 45.3% between 1999 and 2001, according to the study from Cooperberg et al. [3]. The

systematic radical approaches including surgery and radiation have been the gold standard for prostate cancer treatment and have very effectively controlled low-risk, localized diseases. Multiple clinical trials have demonstrated improved tumor control with higher radiation dose to the entire prostate [4, 5]. However, dose escalation increases treatment toxicity, which also diminishes quality of life (QOL) outcomes. A survey in the Netherlands even showed that 75% of prostate cancer patients would choose to be treated with a lower dose for a lower cure rate to avoid toxicity, and have better QOL [6]. Data from several studies also question whether it is necessary to have immediate treatment for low risk cancers detected by PSA screening [7, 8]. Active surveillance and focal therapy have been proposed as alternatives to manage low risk prostate cancer. Active surveillance can spare men with indolent prostate cancers from radical treatment. However, there is currently no consensus regarding the patient selection criteria, optimized protocols trigger conditions for intervention. Clinical trial dropout rates were also found to be very high, with patients then choosing radical treatment despite late evidence of disease progression [9]. Focal therapy is a strategy to treat the DIL only to reduce gastrointestinal (GI) or genitourinary (GU) toxicities associated with whole prostate gland treatment. However, there are many hurdles associated with this strategy including the efficacy of focal therapy, uncertainties in characterizing the dominant lesion, and post treatment monitoring.

Prostate cancer is a multi-focal disease in up to 87% of cases [10]. Focal therapy alone can potentially miss cancer foci. External beam radiotherapy, on the other hand, is effective at controlling localized prostate cancer by treating the entire gland. There has been increased evidence from pathologic studies that DILs play an important role in prostate cancer progression and may be considered the epicenter of local recurrence post-treatment [12, 13].

MR imaging for prostate cancer has increased in significance over the past decade. Multiple MR Imaging techniques have shown promise for the detection and localization of prostate cancer including Diffusion Weighted Imaging (DWI), Perfusion Weighted Imaging (PWI), permeability imaging and ^{1}H MR Spectroscopy Imaging (MRSI). Combining these MR sequences into a multi-parametric format has improved the performance characteristics of prostate cancer detection and localization by evaluating area under curve (AUC) values, sensitivities, specificities, and positive predictive values. However, in a review of over 30 articles published over the past five years using multi-parametric MRI for prostate cancer [14], only one of these studies used a combination of imaging sequences [15]. Therefore our approach, using a combination of four quantitative MR examinations to access the location and volume of DILs, is indeed quite novel.

2.0 OBJECTIVES

This is a pilot study of implement multi-parametric MR imaging for organ delineation and tumor response assessment of prostate cancer patients being treated with radiation therapy. The study aims to generate intraprostatic lesions maps based on imaging, perform the treatment planning to compute the highest feasible simultaneous boosting dose to intraprostatic lesion and characterize longitudinal changes in imaging characteristics.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Histologically confirmed prostate adenocarcinoma.

3.1.2 Pretreatment evaluations must be completed as specified in Section 4.0

3.1.3 Patients must sign a study-specific informed consent form prior to study participation.

3.1.4 Patients with metal fragments or implanted devices such as pacemakers and aneurysm clips are not eligible for the study considering

4.0 PRETREATMENT EVALUATIONS

4.1 Complete history and physical examination.

4.2 Histological evaluation of prostate biopsy with assignment of a Gleason score to the biopsy material

4.3 Baseline prostaticspecific antigen *(PSA)*.

4.4 Quality of life evaluations using Abbreviated Version of the Expanded Prostate Cancer Index Composite Instrument (EPIC-26).

4.5 Symptom evaluation using RTOG common toxicity criteria

This evaluation will be carried out pre-treatment (baseline), end of treatment, and with each routine F/U visit for the first five years after treatment.

5.0 REGISTRATION PROCEDURES

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met.

6.0 Study Procedures

6.1 Multi-parametric MR imaging

6.1.1 MRI tests: Patients will undergo MRI tests at four different time points: pre treatment, half way through the treatment, right after treatment, 3-month post-treatment.

6.1.2 MRI imaging will be performed using a standardized protocol on a 3T/1.5T wide bore MRI scanner. Gadolinium will be administered intravenously. The MRI may include sequences such as T_1 and T_2 weighted imaging, diffusion weighted imaging, perfusion/permeability imaging including arterial spin labeling, dynamic contrast enhanced imaging and dynamic susceptibility contrast enhanced imaging, MR spectroscopy, Dixon and ultra-shot TE imaging.

6.1.3 Patient information will be obtained from the medical record to correlate patient, tumor, and treatment information with imaging findings.

6.1.4 We will also retrospectively evaluate the CT or MRI data and patient information acquired on a large cohort of patients and to incorporate this information into the image analysis.

6.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.
The screening procedures include:
6.2.1 Informed Consent
6.2.2 Review subject eligibility criteria

6.3 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. Patients will be considered off study after completion of protocol treatment and follow-up criteria. The reason(s) for discontinuation from study will be documented and may include:
6.3.1 Patients may be removed from study at any time by patient request.
6.3.2 Patients can be removed from study if they are unable to comply with protocol requirements.
6.3.3 Patients can be removed from study if the treating physician judges continuation on the study would not be in their best interest.

6.4 Treatment Planning Simulation, Image guidance and Localization Requirements

6.4.1 Planning simulations specifications

A treatment planning CT scan will be required to define tumor, clinical and planning target volumes and the critical structures *(See Section 6.4.5)*. The patient should be simulated and treated with full or partially full bladder and empty rectum. Each patient will be positioned in the supine position. The CT scan of the pelvis should start at or above the iliac crest down to the perineum. All tissues to be irradiated must be included in CT scan. CT scan thickness should be $\leq$ 0.3 cm. The target volumes and normal tissues must be outlined on all CT slices in which the structures exist. Patients will be simulated and treated in supine position with empty rectum and full bladder.

6.4.2 Volume and ICRU Reference Point Definitions

The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

6.4.2.1 *The Gross Tumor Volume **(GTV)*** is defined by the physician as all known disease as defined by the planning CT, and clinical information. GTV= prostate. The DIL indicated by all imaging modalities are identified as gross target volume (GTV) for the boost.

6.4.2.2 *The Clinical Target Volumes **(CTV)*** are the GTV plus areas considered to contain microscopic disease, delineated by the treating physician.

6.4.2.3 *The Planning Target Volume **(PTV)*** will provide a margin around the CTV to compensate for the variabilities of treatment set up and internal organ motion. For this study, PTV = CTV plus a uniform

5 mm margin except at prostate/rectum interface where 4 mm are used. A 3 mm margin will be applied to boost GTV to create a boost PTV.

6.4.2.4 *Critical Normal Structures*

The normal tissue volume to be contoured will include bladder, rectum, femoral heads, and penile bulb. The normal tissues will be contoured and considered as solid organs. The bladder should be contoured from its base to the dome, and the rectum from the anus (*at the level of the ischial tuberosities*) for a length of 15 cm or when the rectosigmoid flexure is identified.
The penile bulb will be outlined as a reference structure.

6.4.3 Treatment Planning

6.4.3.1 *Planning Target Volume (PTV)*

Treatment will be given only to the PTV using radiation beams where fields shaped to exclude as much of the bladder and rectum as possible. Field arrangements will be designed to produce the optimal conformal plan in accordance with volume definitions. The highest feasible isotoxic simultaneous boost dose to MRI-defined intraprostatic lesions without compromising bladder and rectum dose constraints will be investigated in the treatment planing. The treatment plan used for each patient will be based on an analysis of the volumetric dose including dose-volume histogram *(DVH)* analyses of the PTV and critical normal structures.

6.4.3.2 *Critical Normal Structures*

Dose-volume histograms *(DVHs)* must be generated for all critical normal structures and the unspecified tissues *(see Section 6.4.5).* Portions of the bladder and rectum will, by necessity, receive the full dose to the PTV; however, our goals are to follow RTOG0126[16] and RTOG0938[17] toxicity criteria for rectum, bladder, and penile bulb.

6.5 Radiation Toxicity

6.5.1 All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded.

6.5.2 Acute toxicity monitoring: Acute *($\leq$ 90 days from RT start)* side effects of radiation therapy will be documented using the NCI Common Toxicity Criteria version 4.0 *(see 8.2).*

6.5.3 Late toxicity monitoring *(> 90 days from RT start)* will be evaluated and graded according to the NCI Common Toxicity Criteria version 4.0 *(see 8.2).*

7.0 PATIENT ASSESSMENTS

7.1 Study Parameters

			Months after treatment completion*							
Parameters	Pre-Entry	Performed During RT	3	6	12	18	24	36	48	60
History, Physical Exam	X	weekly	X	X	X	X	X	X	X	X
MR Imaging	X	Two	X							
Prostate biopsy with Gleason score	X									
PSA	X		X	X	X	X	X	X	X	X
Toxicity Evaluation		weekly	X	X	X	X	X	X	X	X
EPIC Quality of Life Index	X	Last week	X	X	X	X	X	X	X	X

* Patients will be routinely followed every 3-6 months as per the standard for at least 1 year. At each visit, routine history, physical examination, blood work (PSA), and toxicity evaluation will be conducted.

7.2 Evaluation during Treatment

Patients will be seen and evaluated at least weekly during radiation therapy with documentation of tolerance, including acute reactions (e.g. # of BM per day, rectal tenesmus or abdominal cramping, rectal bleeding and general well-being). Treatment-related toxicities will be scored using NCI common toxicity criteria version 4.03. Patients should be scored at baseline before starting treatment as well.

For radiation proctitis:

Grade 1: Rectal discomfort, intervention is not indicated

Grade 2: Symptoms (e.g. rectal discomfort, passing blood or mucus); limited instrumental ADL; medical intervention indicated

Grade 3: severe symptoms; fecal urgency or stool incontinence; limiting self care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death

For radiation-induced cystitis:

Grade 1: Macroscopic hematuria; minimal increase in frequency, urgency, dysuria or nocturia; new onset of incontinence

Grade 2: Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL.

Grade 3: Gross hematuria, transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic operative intervention indicated.

Grade 4: Life-threatening consequences; urgent radiologic or operative intervention indicated

Grade 5: Death

7.3 Evaluation Following Treatment

7.3.1 At each visit the patient will have an interval history, complete physical examination and assessment of specific GU and GI morbidity.

7.4 Criteria for Local Control

7.4.1 *PSA failure* is defined as Phoenix definition as nadir + 2 ng/ml elevations of post-treatment PSA or starting hormones after one or more elevations in post-treatment PSA are documented.

7.4.2 *Clinical criteria* for local failure are progression (increase in palpable abnormality) at any time, failure of regression of the palpable tumor by two years, and redevelopment of a palpable abnormality after complete disappearance of previous abnormalities. Prostate needle biopsy may be recommended as clinically indicated any time after one year.

7.5 Criteria for Nonlocal Failure

Other types of failure will be documented as follows:

7.5.1 *Distant metastasis* will be documented if clinical or bone scan evidence is demonstrated.

7.5.2 *Time to Distant Failure*: The time to distant failure will be measured from the date of study registration to the date of documented regional nodal recurrence or distant disease relapse

7.5.3 *Disease-Specific Survival*: Disease-specific survival duration will be measured from the date of registration to the date of death due to prostate cancer.

7.5.4 *Overall Survival*: Survival duration will be measured from the date of registration to the date of death from any cause.

8.0 Adverse Event Reporting

8.1 All serious adverse events will be reported according to the standard reporting guidelines of Henry Ford Health System (HFHS)

8.2 Additionally, adverse events will be reported to the HFHS Institutional Review Board (IRB) according to their Standard AE Reporting guidelines except for as outlined below.

The following adverse events are excluded from SAE reporting:

- Moderate events (grade 2) due to the patient's cancer or the treatment which are common toxicities and expected. These will be noted in the patient's medical records
- Social or psychological trauma which is typical for patients undergoing treatment for cancer and/or the people with whom they have relationships. Events of this type that are severe in nature will be reported per the guidelines.
- Hospitalization secondary to expected cancer morbidity:
- Admission for palliative care or pain management

- Admission for management of non-protocol related deep venous thrombosis or pulmonary embolism.
- Planned hospitalizations for surgical procedures either related or unrelated to the patient's cancer

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Endpoints

9.1.1 Primary Endpoints

This is a pilot study of implement multi-parametric MR imaging for organ delineation and tumor response assessment of prostate cancer patients being treated with radiation therapy. The study aims to generate intraprostatic lesions maps based on MRI, perform the adaptive treatment planning to compute the highest feasible simultaneous boosting dose to intraprostatic lesion and characterize longitudinal changes in imaging characteristics. Additional MRI endpoints may be included as the research in those fields progresses during the conduct of this clinical trial.

9.1.2 Statistical Analysis

We set target enrollment at a minimum of 20 patients. Sample size has been determined based upon the feasibility and low risk to patients, funding, and the consideration of the statistical power to measure detectable changes in endpoints from. Patients will complete the Abbreviated EPIC questionnaire in writing, at home or in the clinic, per Radiation Therapy Oncology Group guidelines. Differences between pretreatment and post-treatment MR Imaging/EPIC scores will be compared in a patient-level regression analysis, accounting for pretreatment score, age, race, education, body mass index, prostate volume, and cancer risk (based on prostate-specific antigen, Gleason score, and T-stage). p-values <0.05 will be considered statistically significant. Reported p-values are 2-sided. A clinically relevant change in HRQOL is defined as a difference from pretreatment to post-treatment that exceeded half of the standard deviation of the pretreatment value.

9.1.3 Secondary Endpoints

Tumor control: local recurrences & distant metastasis: collect dose and volume data to allow tumor control probability and normal tissue complication probability modeling with the imaging data. These data will be correlated with treatment-related side effects and quality of life data.

9.2 Patient Accrual

The accrual goal for this study is 20 evaluable patients. This study will require about four years' accrual period with approximately 5 patients enrolled per year. Any subject who completes radiation therapy and has at least 3-month follow-up visit will be considered evaluable.

9.3 Reporting to monitor the study progress

Interim analyses and one final analysis will be performed for reporting of patient's quality of life.

Statistical Plan

Sample size has been determined based upon the feasibility and low risk to patients, funding, and the consideration of the statistical power to measure detectable changes in endpoints. Patients will complete the Abbreviated EPIC questionnaire in writing, at home or in the clinic, per Radiation Therapy Oncology Group guidelines. Differences between pre-treatment and post-treatment MR Imaging/EPIC scores, age, race, education, body mass index, prostate volume, and cancer risk (based on prostate-specific antigen, Gleason score, and T-stage). p-values < 0.05 will be considered statistically significant. Reported p-values are 2-sided. A clinically relevant change in HRQOL is defined as a difference from pre-treatment to post-treatment that exceeds half of the standard deviation of the pre-treatment value.

APPENDIX I

American Joint Committee on Cancer

Prostate Cancer Staging

7th EDITION

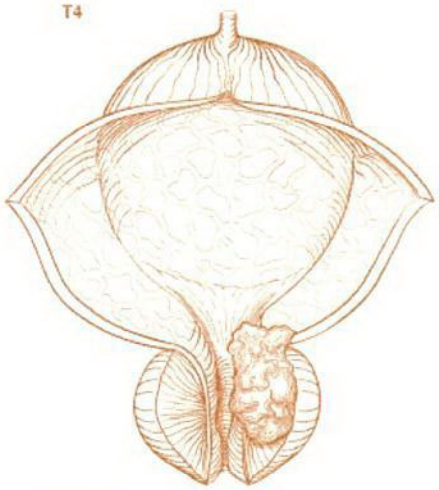


Figure A. T4 tumor invading adjacent structures other than seminal vesicles, such as bladder, rectum, levator muscles, and/or pelvic wall.

ANATOMIC STAGE/PROGNOSTIC GROUPS[6]					
Group	T	N	M	PSA	Gleason
I	T1a–c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA <20	Gleason 7
	T1a–c	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason 7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA ≥20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥8
III	T3a–b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

Definitions

Primary Tumor (T)

CLINICAL

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **T1** Clinically inapparent tumor neither palpable nor visible by imaging
- **T1a** Tumor incidental histologic finding in 5% or less of tissue resected
- **T1b** Tumor incidental histologic finding in more than 5% of tissue resected
- **T1c** Tumor identified by needle biopsy (for example, because of elevated PSA)
- **T2** Tumor confined within prostate[1]
- **T2a** Tumor involves one-half of one lobe or less
- **T2b** Tumor involves more than one-half of one lobe but not both lobes
- **T2c** Tumor involves both lobes
- **T3** Tumor extends through the prostate capsule[2]
- **T3a** Extracapsular extension (unilateral or bilateral)
- **T3b** Tumor invades seminal vesicle(s)
- **T4** Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall (Figure A)

Pathologic (pT)[3]

- **pT2** Organ confined
- **pT2a** Unilateral, one-half of one side or less
- **pT2b** Unilateral, involving more than one-half of side but not both sides
- **pT2c** Bilateral disease
- **pT3** Extraprostatic extension
- **pT3a** Extraprostatic extension or microscopic invasion of bladder neck[4]
- **pT3b** Seminal vesicle invasion
- **pT4** Invasion of rectum, levator muscles, and/or pelvic wall

Regional Lymph Nodes (N)

CLINICAL

- **NX** Regional lymph nodes were not assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in regional lymph node(s)

PATHOLOGIC

- **pNX** Regional nodes not sampled
- **pN0** No positive regional nodes
- **pN1** Metastases in regional node(s)

Distant Metastasis (M)[5]

- **M0** No distant metastasis
- **M1** Distant metastasis
- **M1a** Nonregional lymph node(s)
- **M1b** Bone(s)
- **M1c** Other site(s) with or without bone disease