Title: Early changes in multiparametric MRI in response to neoadjuvant androgen deprivation and external beam radiation therapy for prostate cancer

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Closed to New Accrual

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No new subjects may be enrolled in the study as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

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OUTLINE

I Background and Significance

a. **Multiparametric MRI (mpMRI) and it's role in prostate cancer**

Prostate MRI is known to play an important role in prostate cancer detection and localization, and indeed prostate cancer staging[1]. It also aids in tumor detection when there is a biochemical suspicion of residual or recurrent disease after treatment[2],[3]. Compared to conventional prostate MR techniques from 5-10 years ago, which relied on morphology for tumor characterization, standard of care prostate MR in 2013 provides a wealth of information regarding tumor functionality[1]. mpMRI includes functional quantitative sequences such as Diffusion Weighted Imaging (DWI) and high temporal resolution Dynamic Contrast Enhanced (DCE) imaging. DWI is reflective of the random motion of water molecules at a cellular level, and is thus sensitive to cell membrane integrity, hypercellularity, enlargement of the nuclei and hyperchromatism. DWI (and more specifically, Apparent Diffusion Coefficient (ADC) derived from DWI) has been demonstrated on multiple occasions to correlate with Gleason score and serve as a biomarker for prostate tumor aggressiveness [4–9]. On DCE, prostate cancer shows early strong enhancement compared to surrounding normal prostate tissue. This enhancement pattern is thought to represent tumor angiogenesis and is necessary for further tumor growth[10],[11]. As a result, the number of vessels increases and these newly formed tumor vessels have higher permeability than do normal vessels because of weak integrity of the vessel wall. Studies have suggested that as the number of abnormal vessels in prostate cancer increases, the prognosis worsens[12][13]. Microvessel density in prostate cancer, an established independent predictor of pathologic stage, has been shown to correlate with DCE-MRI results[14].

b. **EBRT and ADT for intermediate-high prostate cancer**

In the era of PSA screening, many men are diagnosed with early-stage prostate cancer and have a good chance of cure. However, there are some patients, specifically those who present with unfavorable cancer based upon well-established features such as high prostate specific antigen (PSA), high Gleason score and/or those with advanced local disease (T-stage T2b or higher) who remain at high risk for prostate- cancer mortality. Androgen deprivation therapy (ADT) is very effective in controlling metastatic prostate cancer and improves survival when added to radiotherapy for localized disease. A significant gain in overall survival in those with locally advanced prostate cancer using a combination of external beam radiotherapy (EBRT) and ADT has been demonstrated by both the European Organization for Research and Treatment of Cancer (EORTC)[15] and the Radiation Therapy Oncology Group (RTOG)[16] and in others[17]. These randomized trials evaluated ADT given from six to thirty-six months. Long term (≥2 years) of ADT confers a modest survival benefit in men treated with radiotherapy for locally advanced prostate cancer compared with 6 months of ADT, but it is associated with increased toxic effects[18]. Therefore, identification of men in whom 6 months of ADT is sufficient for cure is important as is early identification of those who are not responding well to standard ADT.

i. ***Predicting those who will fail ADT therapy***

Time to PSA failure and the rate at which PSA rises are surrogates for prostate cancer specific mortality (PCSM). Very recently[19], PSA nadir of ≤ 0.3 ng/ml after 2-3 months of neoadjuvant ADT (prior to initiation of EBRT) has been shown to be associated with improved long-term biochemical prostate tumor control, reduction in distant metastases, and prostate cancer-related death. This initial PSA response during ADT may reflect the sensitivity of the prostate tumor to androgen deprivation and in turn to the radio-sensitivity bestowed by ADT on the subsequently irradiated prostate tumor. Pre-EBRT PSA nadir may therefore represent a valuable early predictor for improved outcomes after radiation therapy for prostate cancer.

ii. ***Predicting those who will fail ADT/EBRT therapy***

Looking further along the course of treatment with neoadjuvant ADT and 4 months of EBRT, D'Amico et al[20] used the Prentice criteria to assess whether measured lowest PSA concentrations (PSA nadir) or PSA immediately after treatment (PSA end) were early surrogates for prostate cancer-specific mortality, as both PSA end and nadir PSA are available before PSA failure. In this study they retrospectively reviewed 2 randomized controlled trials (cohort of 734 men), that showed improved overall and prostate cancer specific survival with radiotherapy and 6 months of androgen suppression compared with radio therapy alone. They found that men with PSA end values exceeding 0.5 ng/ml after EBRT and androgen suppression should be considered for long-term androgen suppression. Furthermore, an early endpoint such as PSA nadir after radiotherapy and at least 6 months of androgen suppression could identify men who are good candidates for future trials of additions of proven systemic therapies (i.e, one that extends survival in men with castration-resistant metastatic prostate cancer).

c. **mpMRI as a biomarker for response to therapy in prostate cancer**

A role for mpMRI as a non-invasive biomarker in assessing response to treatment options is currently an evolving area of great interest. In patients with low-risk prostate cancer on active surveillance, DWI

has been proposed to be a useful marker of prostate cancer progression and may help in identifying patients who may benefit from radical treatment [21],[22]. Recent studies have also investigated the use of mpMR to assess response to ADT[23] and radiotherapy[24],[25], with promising results.

After ADT, prostate gland shrinkage and fibrosis makes tumor difficult to detect on routine T2WIs. A feasibility study[23] evaluated the use of mpMR in monitoring response to ADT, and suggested that DCE as a marker of angiogenesis may help demonstrate ADT resistance, and DWI may help determine tumor cell death vs. residual tumor. In contrast to cytotoxic therapy, where ADC values increase (due to a lessening of the restriction of water molecules), ADT may not result in significant necrosis of prostate cancer cells, and in fact ADC values of prostate cancer post 3 months of ADT have been shown to remain the same[23]. In contrast, ADC values of areas where focal tumor was not suspected were significantly reduced with ADT, possibly due to acinar hypertrophy, fibrosis and basal cell hyperplasia.

Foltz et al. have looked at the very early post-radiotherapy changes in the prostate every 2 weeks up until 8 weeks of EBRT, and found that ADC was a possible candidate for early response to therapy, the optimal scan time being week 6 of EBRT[24]. Park et al have shown that ADC values in regions of tumor increased 1 and 3 weeks after initiating EBRT, and one month after completion of EBRT[25].

Specific to DCE, there is known to be an anti-angiogenic role for ADT in the prostate (androgen ablation has been shown to suppress glandular epithelial production of VEGF and induce apoptosis of endothelial cells). As PSA gene expression is down-regulated by ADT, PSA reduction post ADT may be secondary to androgen suppression rather than tumor cell death. It is therefore possible that DCE may act as a stronger surrogate for angiogenesis, rather than PSA.

There has been a pre-clinical study (on prostate zenograph models) evaluating a combination of parameters (ADC, DCE, tumor volume and PSA) which successfully predicted treatment response to a combination of ADT and radiotherapy, with a correlation coefficient of 0.85[26]. However, to our knowledge, no study has yet looked at a role for mpMRI in evaluating the effect of combined ADT and EBRT on prostate mpMR in humans. Nor has there been any work published on correlating PSA end with prostate mpMR, to determine if mpMR may act as an early biomarker in determining those who would benefit from long-term androgen suppression. We therefore propose to evaluate mpMR in response to combined therapy (ADT and EBRT), and to correlate quantitative mpMR parameters at early timepoints, with PSA end and PSA nadir.

II Specific Aims

1. The primary aim of this study is to explore the feasibility of mpMR as an early imaging biomarker to assess response of intermediate- and high-risk prostate cancer during treatment with neoadjuvant ADT.
2. A secondary aim is to explore the feasibility of mpMR as an imaging biomarker to assess response of bulky localized prostate cancer to combined ADT/EBRT.

3. To ascertain if the information provided using the non-ecoil 3 Tesla MRI images prior to starting EBRT can supplement CT information for Radiation Treatment (RT) planning purposes in men who are planning to undergo RT for prostate cancer.

III Study endpoints

1. The primary endpoint of this study is whether mpMR parameters measured after 2 months of neoadjuvant ADT therapy (TP1) correlate with nadir PSA post 8-weeks of ADT. In addition, we will determine whether mpMR parameters in areas of tumor (T) in those who fail neoadjuvant ADT (defined as PSA end ADT values >.3 ng/ml) are different to those who respond to ADT (defined as PSA end ADT ≤.3ng/ml).
2. A secondary endpoint of this study is whether mpMR parameters measured after 6 weeks of EBRT (TP2) and 8 weeks after completion of EBRT (TP3) correlate with end PSA (defined as PSA level immediately after EBRT treatment). In addition, we will determine whether mpMR parameters in areas of T in those likely to fail combined ADT/EBRT (defined as PSA end values >.5ng/ml) are different to those of responders (PSA end values ≤.5ng/ml).

IV Subject selection

1. Inclusion criteria:
    a. Adult males with unfavorable intermediate- to high-risk localized disease identified as one of the following three categories for unfavorable intermediatehigh risk factors, but must have visible disease on baseline MRI.
        i. Clinical or radiographic T2b-T4 primary tumor
        ii. Gleason score 7-10 in any core
        iii. PSA ≥ 10 prior to initiation of therapy
    b. Patients are deemed suitable for therapy with ADT and EBRT.
    c. Subjects must to able to provide informed written consent prior to study entry.

2. Exclusion criteria:
    a. The standard exclusion criteria for MRI exams will apply which include patients with pacemakers, non-compatible intra-cranial vascular clips, inner ear implants, and severe claustrophobia.
    b. Patients who because of age, general medical or psychiatric condition, or physiologic status unrelated to the presence of prostate cancer are unlikely to be candidates for repeat MRIs, or cannot give valid informed consent.
    c. Patients unwilling or unable to undergo the ecoil placement or multiparametric MRI exam.
    d. Patients with a history of allergic reaction to latex or Gadolinium containing intravenous contrast agents.

e. Individuals with renal disease or other contraindications to gadolinium will be excluded. The BWH standard MRI contrast screening criteria will be used to establish renal status.
f. Patients who have had prior prostatectomy or prior androgen therapy.
g. Patients with hip implant or any other metallic implant or device that results in significant distortion of the local magnetic field and compromise of the quality of the multiparametric MRI data.

V Subject recruitment/enrollment

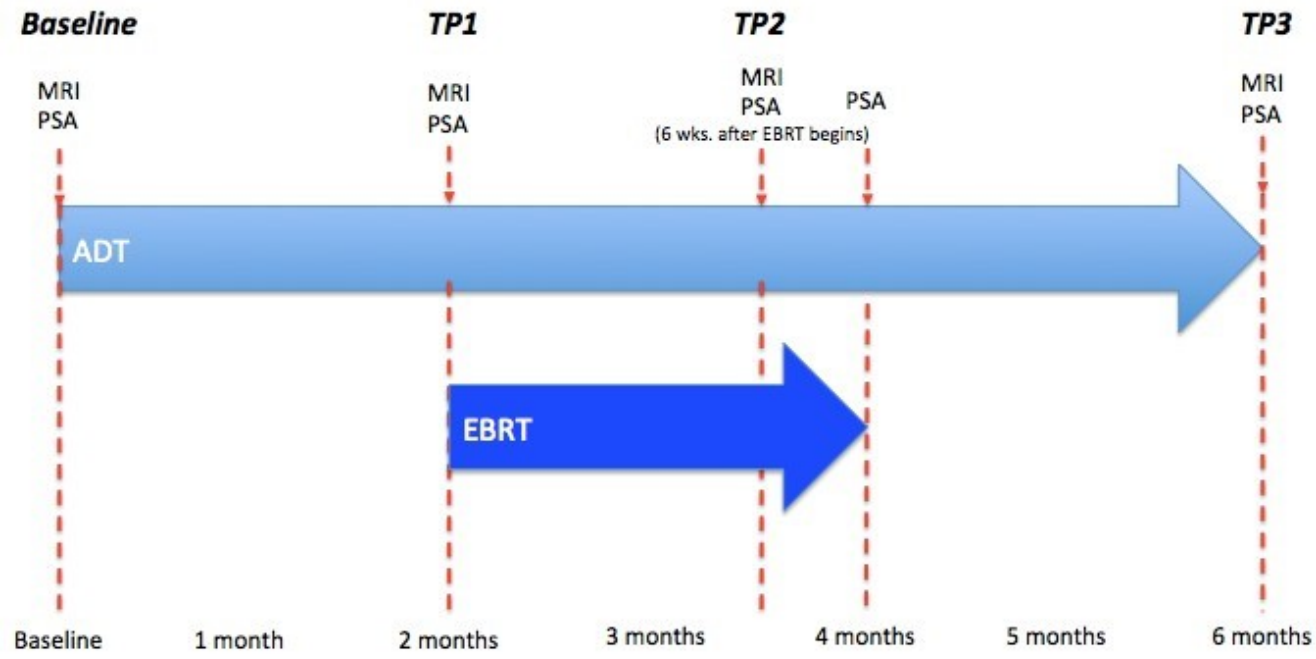
Men with unfavorable intermediate-to high-risk prostate cancer are routinely seen at the multidisciplinary Lank Center for Genitourinary Oncology by a urologist,medical oncologist and radiation oncologist. The standard of care for this patient population is combination therapy consisting of complete androgen blockade and EBRT. Patients meeting eligibility criteria and choosing to have their ADT/EBRT care at Brigham and Women's Hospital will be recruited by the treating radiation oncologist, and asked if they wish to participate in the study. The study staff (PI and study coordinator) will obtain a list of new patients to be seen in GU radiation oncology clinic for prostate cancer. They will review the clinic note in EPIC to determine which treatment option for prostate cancer was decided upon, if the patient meets inclusion criteria for the study, andif the patient had a baseline MRI prior to starting treatment. If eligible for the study, the treating radiation oncologist/oncologist will be emailed by the study PI (see attached email template) to ask their permission to approach the patient to determine if the patient is interested in being part of the study, or the treating radiation oncologist can ask the patient directly if interested in being part of the study, and obtain consent.

To facilitate awareness of the study and to help with recruitment, we will post a flyer about the study in the physician and nursing radiation oncology clinical office for staff to see.
If the patient expresses interest in the study, they will be given a recruitment letter and a study consent form, which the radiation oncologist will review with them. Consent can be obtained at this time by the radiation oncologist. If so, the patient will be given a copy for their own record. However, there will be a second opportunity to consent the patient at the time of treatment planning for radiotherapy which occurs six weeks after the first LHRH injection. Patients who are consented at six weeks will already have undergone their baseline MRI and PSA, which is the standard of care for all intermediate- and high-risk prostate cancer patients. At this time, the radiation oncologist may review the study with the patient and obtain consent or the study radiologist may review the study with the patient and obtain consent. Either way, the physician who obtains consent will inform the study staff (Fiona Fennessy, MD PhD and the study coordinator) of the patient's interest in the study. Those patients who elect to participate in the study with be contacted by the study coordinator to schedule the study MRIs and the serum PSAs, and to answer any remaining questions.

Any study patient may elect not to proceed with the study at any time.

VI Study Procedure

The timeline of the study is outlined below.



Baseline Standard of care prostate MRI and serum PSA will be obtained prior to starting ADT, as standard of care.
After an 8-week course of neoadjuvant ADT, serum PSA nadir and a prostate MRI will be obtained (**TP1**). EBRT will commence after an 8-week course of ADT for an 8-week period. However, 6 weeks into EBRT, subjects will undergo serum PSA level and a prostate MRI (**TP 2**). An end PSA at the end of EBRT will also be obtained. Six months after starting ADT, they will have a final prostate MRI and serum PSA level (**TP 3**). (*Please see section a, b, c, and d below for protocol on ADT, PSA, prostate MRI and EBRT respectively*).

1. ADT

Androgen suppression therapy consists of combined androgen blockade. Patients receive an antiandrogen, typically biaclutamide (Casodex) and an LHRH-agonist, typically Lupron. AST is given for two months prior to radiotherapy and then continued for a total of six to 36 months, depending upon the treating physician and overall health of the patient.

2. PSA

Serum PSA will be checked at baseline by treating physician, prior to commencing therapy. Serum PSA will also be subsequently checked on the same day as each follow-up MR is performed, i.e. TP 1,2 and 3, and right after finishing EBRT.

Parking at BWH for time spent for all 4 follow-up serum PSAs will be paid for.

3. Prostate MRI

The baseline prostate MRI is standard of care management, ordered by the radiation oncologist for staging and for EBRT planning. The 3 follow-up MRIs (at TP 1,2 and 3) are not standard of care management, and will be paid for by an NIH grant. However, all of the follow up prostate MRIs will use a standard BWH Radiology Department prostate non-endorectal coil MRI protocol. Subjects will need, to complete health screening and renal assessment forms completed prior to the MRI to determine if the patient is able to receive gadolinium. Blood results measuring renal function within a 3-week window prior to MR must be available, and if necessary, blood will be drawn to measure kidney function prior to administration of gadolinium. Subjects will be positioned lying on their back within the MRI magnet, which is a large cylindrical tube that allows strong magnetic fields to pass through the body. Earplugs and a padded table will be provided for the subject's comfort. A radio frequency receiver coil encased in a plastic mold called a phased-array coil will be positioned around the subject's pelvis. An endorectal coil will NOT be used for this study, as the endorectal probe will distort the prostate (making correlation with CT for planning difficult) and because of the risk of proctitis during EBRT.

The standard imaging protocol will include fast spin echo (FSE) for T2WI, fast spoiled gradient (FSPGR) for T1WI and (Dynamic Contrast Enhanced) DCE-maps, and diffusion imaging for ADCmaps. If renal function is normal, the MR contrast agent gadopentetate dimeglumine (Magnavist) will be used for DCE. A dose of 0.1 mmol/kg is administered intravenously using an MR compatible power injector immediately before beginning the dynamic contrast enhancement (DCE) portion of the MRI exam. Magnevist is not given to patients with a history of prior allergic reaction, which is extremely rare. Possible use of light sedation for anxiety associated with the MRI exam should be discussed between the patient and referring physician prior to the MRI exam. If any anti-anxiety medication is prescribed, subjects should bring it to the examination and use as directed. Subjects will also be told to take all of their prescribed medications as regularly scheduled.

Parking at BWH for time spent for 3 follow-up prostate MRIs will be paid for.

Following the multiparametric MRI exam, the imaging data will be collected and archived. A standard clinical prostate MRI staging report will be issued in a timely fashion. The quantitative MR-based information (ADC-maps and DCE pharmokinetics) will be analyzed separately using Oncoquant software (GE Healthcare) and will not be included in the standard MRI report. Should the results of this additional analysis impact the interpretation rendered in the standard prostate report, the referring physician will be contacted and advised. Individual results will not be discussed with or returned to the participating patients.

4. EBRT

Intensity-modulated EBRT will be given using daily pre-treatment imaging on implanted fiducials according to Brigham and Women's standards. This is referred to as image-guided, intensity modulated radiotherapy, or IGRT. The IGRT targets the prostate and seminal vesicles and in some cases, the pelvic nodes as well according to well standardized department protocols. Each daily treatment, or fraction, delivers 1.8 Gy to a total of 75.6 Gy over 42 treatment days. Treatments are given five days per week.

5. Fusion of the CT and 3T MRI images

3Tesla MRI is known to have a superior ability to visualize the prostatic apex and the prostatic rectal interface compared to CT. Therefore we seek to ascertain if the information provided using 3Tesla MRI images can supplement CT information for Radiation Treatment (RT)planning purposes in men who are planning to undergo RT for prostate cancer. This protocol is acquiring 3T MRI images without an endorectal coil in men planning to undergo RT for prostate cancer after fiducial marker placement and CT simulation but prior to the start of RT. We will perform a fusion of the CT and non-endorectal coil 3T MRI images using the intraprostatic fiducial markers. The fusion will allow us to assess if improved delineation of the prostatic apex and prostatic rectal border translates into not losing any target (i.e. prostate gland) coverage but reduces the volume of rectum receiving radiation in excess of 70 Gray. We will use the validated rectal metrics of a rectal V70 < 20% and also <10cc as the measurement to make this assessment. If the rectal V70 can be reduced with MRI information then the risk of late RT induced rectal bleeding would be expected to decrease. The MR data will not be used in the RT treatment planning of these men but only for the assessment of whether the rectal V70 could be reduced.

VII Biostatistics

1. Correlation of ADC Change With PSA Nadir

Zelefsky et al. report that 10-year relapse-free survival among patients with PSA nadir $\leq$ 0.3 was 74.3%, compared with 57.7% for patients with higher PSA nadir values (P = 0.001, N = 1045). In order to assess power for a test of whether mpMR parameters measured after 2 months neoadjuvant ADT therapy alone correlate with nadir PSA post 8-weeks of ADT therapy, we will make use of published data on the correlation between ADC change and nadir PSA. Foltz et al.[24] observed a correlation of 0.25 for nadir PSA with ADC percent change, between 6 weeks and the pre-RT baseline (N = 10). With 30 subjects, we anticipate 80% power to detect an absolute correlation of 0.49 or greater. Although this is greater than the correlation Foltz observed, we note that with a sample of size 10, using Fisher's transformation, an approximate 95% confidence interval for Foltz's estimate is (-0.45, 0.76), a wide interval which includes 0.49.

2. Within-Patient ADC Changes

Foltz et al.[24] reported a change in ADC between six weeks RT and baseline of -0.29 in tumor (2.8%, N = 36) and -0.56 in healthy tissue (N=10), with SDs of 0.23 and 0.18, respectively (in units of 10^ (-3) mm^2/s). Using the average variance above, we estimate a SD for ADC of 0.20. With N = 30 subjects, using this SD, we expect to have 80% power to detect a significant within-subject absolute difference in ADC between two time points of 0.14 or greater, based on a paired t-test at the 0.05 twotailed significance level, corrected for the 6 pairs of time points to be considered. This is much smaller than the difference of 0.81 observed in healthy tissue described by Barrett et al.[23], but larger than the very small difference of 0.03 that they observed in tumor. Foltz et al. observed changes in ADC between 4 weeks and baseline of 0.107 (B = 600) and 0.117 (B = 1200), both of which are less than 0.14.

3. Comparison of Normal Tissue ADC With Tumor

For comparisons between tumor and normal tissue, with 30 subjects we expect 80% power to detect an absolute difference in mean ADC of 0.19 or greater, based on a two-tailed two-sample t-test, adjusted for multiple comparison of time-points. Barrett's group observed a mean difference in ADC between tumor and healthy tissue of 0.20.

4. **Comparison of ADC Changes between Patients who Fail Treatment and Those who do not.**

We estimate that 25% of men with grade T2c or greater cancer will have end PSA greater than 0.5, and will fail therapy. Barrett et al. reported a change in ADC between three months of ADT and a preADT baseline in tumor of -0.028 with a SD of 0.227 (N = 35), in 20 patients with tumor of stage T2c or greater. We therefore estimate that ultimately 25% of these patients failed. We assume that the ADC changes in patients who fail and patients who do not fail are both normally distributed, with the same SD but different means. We estimate this SD from the Barrett et al. data as 0.227/sqrt (0.25^2+0.75^2) = 0.287. In our study, with 30 patients, we expect approximately 8 treatment failures. Assuming 8 failures and a SD of 0.287, we will have 80% power to detect an absolute difference between the mean ADC change among those who fail treatment and those who do not of 0.51 SDs, or 0.51*0.287 = 0.15 x 10^ (-3) mm^2/s change in ADC. Barrett observed a baseline ADC mean in tumor of 1.006, hence we expect to be able to detect a change from baseline and 3-months ADT in ADC of approximately +/- 15% or greater.

5. **Descriptive statistics will be used to enumerate the rectal V70's achieved using MRI versus CT data**.

VIII Risks and Discomforts

Participants in this study will undergo a total of 3 follow up prostate MRIs. (Baseline standard of care prostate MRI prior to initiating therapy will be ordered by the treating physician). All MRIs will use a standard routine prostate MRI protocol without the use of an endorectal coil. Patients will receive Magnavist 0.1mmol/kg intravenously for each study, so renal function will need to be checked prior to

each study to confirm normal function. If renal function is abnormal, the contrast agent will not be administered. Unlike CT (which uses radiation to produce images), MRI uses powerful magnetic fields and radio waves to produce images. There are no known health risks associated with this exposure. The radio waves used can cause a warming sensation to the body, similar to exposure to hot weather, or localized heating adjacent to the torso coil or ecoil. Body temperature can be expected to rise temporarily, but less than 1^{o} Centigrade or about 2^{o} Fahrenheit. In the event of a localized heating sensation, the subject will be instructed to notify the MR technologist immediately. However, the MRI scanner and the coils used have been designed to prevent localized heating from happening and there have been no reports of localized heating in patients scanned to date.

The MRI scanner also uses rapidly switched magnetic field gradients that make loud banging noises as it collects the information used to create images. Earplugs will be used to reduce this noise and will be offered to each subject. The switched gradients can, under certain circumstances, cause peripheral nerve stimulation that may be experienced as a mild twitching in the limbs and/or lower back muscles. Such effects are rare and scan settings are kept well below the levels where such effects are known to occur.

Subjects will be carefully screened at the time of enrollment to make certain that they do not have any unsafe metal implants. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable lying in the narrow cylinder of the MRI magnet. Subjects will be able to communicate with the MRI technologist for the entire time they are in the magnet. The MRI will be stopped at the subject's request at any time he so wishes. In addition, all patients will be offered Ativan (.5-1 mg) by their treating radiation oncologist. They also have the option to take a second dose upon arrival if they feel tense. All are driven home by a friend or relative.

IX Potential Benefit

No direct benefits from the study should be expected by individuals participating in this study. Results from this study, however, may indicate that mpMRI is an early non-invasive biomarker that may predict those that will respond to ADT/EBRT and in particular, determine those who may benefit from long-term androgen suppression or use of non-standard hormone therapies that are now being explored in patients with metastatic disease. As mpMRI of the prostate evaluates tumor physiology and functionality within the entire prostate gland, it offers information about underlying tumor heterogeneity and how these tumors respond to ADT alone and in combination with EBRT. The hope is that results from this study may offer preliminary information on how functional evaluation of the entire prostate could aid in strategizing patients for an optimal patient-specific therapy plan.

X Monitoring and QA

All subjects will complete the safety screening form, which will be reviewed by the MRI technician. During the multiparametric MRI exam, the subject will be monitored for safety in the MR environment by the MRI technologist. The quality of the MR data will be monitored by the MRI technologist as it is being acquired and by the study doctors on an ongoing basis.

All patient records will be kept on site and confidential. No individual identifiers will be used in any reports or publications resulting from this study. Data security will be controlled by limiting its electronic transmission and storage using secure networks and protected data archives at Brigham and Women's Hospital.

Standard monitoring software supplied by the manufacturer of the MR scanner will be used to insure compliance with specific FDA guidelines regarding power deposition, gradient slew-rates, and field strength. MRSI quality assurance will be monitored using phantom studies performed within one week prior to any patient study to assure the MR scanner is functioning properly for reproducible data acquisition.

All serious adverse events will be reported directly to the DFCI Office for Human Research Studies(OHRS).These include any serious adverse events such as an untoward medical occurrence that results in death or is life threatening (at the time of the event) or requires inpatient hospitalization or results in persistent of significant disability or incapacity. Expected adverse events from MRI are not serious and include claustrophobia while in the MRI magnet, a warming sensation while in the MRI magnet, or infiltration of intravenous contrast in the subcutaneous tissues at the time of its administration. All reasonable measures will be taken to avoid these adverse events.

XI: Registration with QACT

The registration procedure will be as follows:

1. Obtain written informed consent from the participant prior to the performance of any non0standard of care prostate MRI.
2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility**
3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at **checklist.** [redacted]
4. The QACT Registrar will (a) validate eligibility and (b) register the participant on the study
5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

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Protocol 13-343:

Early changes in multiparametric MRI in response to neoadjuvant ADT and EBRT for prostate cancer

Aim of Study: To determine if there are measurable changes in prostate MRI that will help predict those who will or will not respond to ADT/EBRT

Eligibility Criteria:

1. Unfavorable intermediate- to high-risk localized disease:
   - Clinical or radiographic T2b-T4 primary tumor or
   - Gleason score 7-10 in any core or
   - PSA ≥ 10 prior to initiation of therapy
2. Patients deemed suitable for therapy with ADT and EBRT and able to provide informed consent

What This Study Involves:

After confirming eligibility and obtaining consent:

- Baseline non-coil prostate MRI prior to the start of ADT/EBRT
- 3 additional non-coil prostate MRIs over the next six months
- PSA testing
  - *The patient will not be charged for the MRIs, PSA levels, or for parking*.

For more information, please contact: Study Coordinator: [redacted] or

Study PI: Fiona [redacted]ssy, M.D., Ph.D.

MRI protocol schedule
For patient: XXX

	Baseline (Time point 1)	**Time Point 2**	**Time Point 3**		**Time Point 4**
MRI Date (time)	Nov 1, 2013 (11 AM)	Dec 27, 2013 (10AM)	Feb 7, 2014 (11 AM)		April 18, 2014 (10AM)
PSA Date	Nov 1, 2013	Dec 27, 2013	Feb 7, 2014	Feb 21, 2014	April 18, 2014
(Notes)	Baseline, prior to any therapy	8 weeks into ADT; Friday before XRT begins	Friday of week 6 of XRT	Last OTV day of XRT	Day of 3rd hormone injection *OR* day when 3rd hormone injection *WOULD HAVE BEEN*

Recruitment letter for study entitled "Early changes in multiparametric MRI in response to neoadjuvant androgen deprivation and external beam radiation therapy for prostate cancer"

Dear Patient,

I would like to invite you to be part of a research study for which I am the principal investigator. This study is for patients with intermediate- to high-risk prostate cancer who are going to be treated with hormone therapy and radiotherapy. The purpose of this study is to evaluate whether MRI scans of the prostate can predict who will or will not respond to these treatments. It is expected that about 30 patients will take part in this study.

As outlined in detail in the consent form, this study involves a total of 3 follow up prostate MRI scans during the course of hormone therapy and radiotherapy. The study also requires providing a small blood sample (about ½ teaspoon) for PSA measurement on the same day as the prostate MRI, and an additional PSA blood test on the last day of radiotherapy. Should you decide to enroll in this research study, your participation will last 6 months.

Your participation in this study is voluntary. You may withdraw from this study at any time. Whether you participate or not will not affect your care. You will have access to the MRI reports as a result of your participation in this research study, but the MRIs will not affect your clinical care and participating in the study will not contribute to your health.

Please contact the study coordinator [redacted] or by email at [redacted], if you have any questions or would like to learn more about the study.

Thank you in advance for considering this protocol.

Sincerely,

Fiona Fennessy, M.D., Ph.D.

[redacted]

Email script from PI Radiologist to treating Radiation Oncologist:

“Dear Dr _____

Upon review of the medical records of your patient XX, DOB X/X/X, it would appear that he meets the eligibility criteria for our MRI research study protocol entitled "Early changes in multiparametric MRI in response to neoadjuvant androgen deprivation and external beam radiation therapy for prostate cancer”.

SCENARIO 1: He is due to be seen by you in clinic on X/X/X. If you deem him to be an acceptable candidate, can you please discuss this study with him, and provide him with the attached recruitment letter. If he is interested and willing to be part of the study, can you obtain consent? I am available by phone to answer any questions you or he may have [redacted]

SCENARIO 2: He was seen by you in clinic on x/X/X. Do you think he is an acceptable research candidate for this study, and do I have your permission to contact him to discuss the study with him and determine his interest in participating, and if possible to obtain his consent?

For your convenience, the aim of the study, eligibility criteria, and what the study involves for your patient are as follows:

Aim of Study: To determine if there are measurable changes in prostate MRI that will help predict those who will or will not respond to ADT/EBRT

Eligibility Criteria:

1. Unfavorable intermediate- to high-risk localized disease:
- Clinical or radiographic T2b-T4 primary tumor or
- Gleason score 7-10 in any core or
- PSA ≥ 10 prior to initiation of therapy
2. Patients deemed suitable for therapy with ADT and EBRT and able to provide informed consent

What This Study Involves:

After confirming eligibility and obtaining consent:

Baseline non-coil prostate MRI prior to the start of ADT/EBRT

3 additional non-coil prostate MRIs over the next six months

PSA testing

The patient will not be charged for the additional MRIs, PSA levels, or for parking.

Sincerely,
Fiona Fennessy