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MRI-Guided Active Selection for Treatment of Prostate Cancer: The Miami MAST Trial

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SCHEMA

MRI-Guided Active Selection for Treatment of Prostrate Cancer: The Miami MAST Trial

- Accrual Goal n = 230
- Primary Endpoint = Rate of progression on the first and second surveillance biopsies

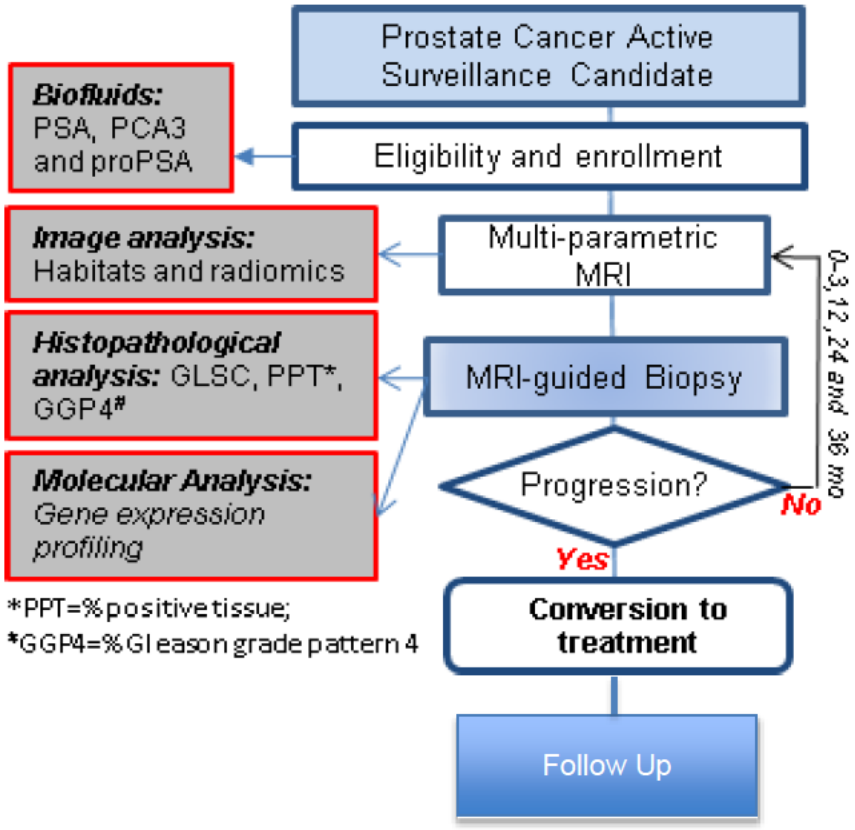

Figure 1: Prospective Trial Schema. Patients will have MRI-US fusion biopsy of the prostate within 3 months of study enrollment and then annually thereafter to assess for rate of tumor progression.

MRI – Magnetic Resonance Imaging, PSA – Prostate Specific Antigen, PCA3 – Prostate Cancer Antigen, GLSC – Gleason Score, PPT – Percent Positive Tissue, GGP4 – Gleason Pattern 4 or Above.

1. BACKGROUND

1.1 Study Disease

Prostate cancer is the most common malignancy and second most common cause of cancer related death among men in the United States.[1] Despite excellent cancer control for low-intermediate risk disease, treatment results in a significant detriment to health related quality of life.[2-4] Since the advent of prostate cancer screening, many men are diagnosed with indolent tumors which are unlikely to become symptomatic or result in metastasis or mortality, questioning whether the risks of treatment outweigh the benefits.[5,6] As a result, active surveillance (AS) has emerged as an attractive alternative to immediate treatment. This is a process in which a man defers immediate treatment, and undergoes monitoring with the intent of timely curative intervention at the point where a higher risk of tumor progression is indicated.[7,8] Research has shown active surveillance to be safe in carefully selected men allowing many men to defer treatment and its burden to quality of life for over 5 years.[9-11] The preservation of quality of life is of primary importance, particularly for men in their 50's and 60's. However, since men in these age ranges have a long-life expectancy, it is imperative that they be carefully selected for active surveillance to ensure the window of opportunity for cure is preserved.

Despite a worldwide acceptance of active surveillance in men with low risk tumors, nearly a third of men will progress to requiring treatment within the first three years.[7,12] Most active surveillance protocols select patients with low volumes of low grade tumor seen on diagnostic biopsy. However, unlike other solid tumors where a lesion is visualized on imaging and a needle is inserted directly into it, most methods of visualizing the prostate cannot reliably identify lesions that are localized to the prostate. As a result, the current standard for diagnosis involves visualizing the prostate via transrectal ultrasound and performing segmented biopsies of the gland for cancer detection because the tumor(s) is not usually identified clearly. Given the heterogeneous nature of prostate cancer, where both indolent and aggressive tumors may be found in the same gland and some tumors are located in regions of the prostate (e.g., anteriorly) not thoroughly sampled, this "sampling" approach may miss the dominant or high grade tumors, which are likely to be the drivers of progression.

This is confirmed by a 20-30% chance of seeing a higher grade or volume of tumor when a second biopsy is performed.[13] Furthermore, data from surgical patients suggest that 20-30% of patients who appear to be good candidates for surveillance may harbor high-risk features within their prostates suggesting that their biopsy may have underestimated the aggressiveness or volume of tumor present.[14,15] This highlights the need for serial biopsy, but also suggests that those patients who are likely to progress early are not truly progressing, but more likely to harbor higher risk tumors that were missed on initial biopsies; a process referred to as "reclassification". Therefore, men choosing active surveillance must understand that the biopsy may not reflect the true biology of their disease, and there is some inherent risk involved that they may lose their opportunity for cure while their tumor is being monitoring.

The primary goal of active surveillance is to monitor tumors that are deemed not to require immediate treatment with the goal of timely intervention at the point of tumor

progression. However, without careful selection of patients for surveillance this approach can compromise oncologic outcomes. Better tools are critically needed to improve risk stratification in men choosing between surveillance and immediate treatment to allow improved outcomes in men who truly harbor aggressive tumors so they can be offered necessary treatment earlier, before outcomes can be compromised.

1.2 Study Interventions

Single arm therapeutic trial investigating the impact of MRI and MRI-US fusion biopsy to identify higher grade or volume tumors early on for better selection of patients for active surveillance versus immediate treatment. We suspect that use of MRI and MRI-US fusion biopsy will allow the detection of men who are not ideal candidates for observation (based on a higher grade or volume of tumor that was missed on initial diagnostic biopsy) earlier in the surveillance process, so they can be offered timelier treatment rather than initial observation with delayed therapy after the tumor has progressed. MRI–US fusion biopsy will include targeting of suspicious areas seen on MRI as well as segmented sampling of the remaining gland. Patients will undergo MRI and MRI-US fusion biopsy within 3 months of enrollment in the trial and have repeat MRI-US fusion biopsies every year to assess overall rates and the temporal distribution of progression. Serum, urine and prostate biopsy tissue will be serially collected to investigate the association between various molecular biomarkers and radiologic and histological progression.

1.3 Other Interventions

Currently, there are no urine, serum or tissue markers that have been validated to reliably discern between men who are ideal candidates for active surveillance and those who are not. Previous studies have suggested that post digital rectal exam expressed prostatic secretions for prostate cancer antigen 3 (PCA3) and TMPRSS2:ERG (gene fusion related to promotion of prostate cancer) had a modest effect at best in predicting patients who would not be suitable for active surveillance.[16] Various prostate specific antigen isoforms, which can be collected in the serum, have shown some association to helping predict patients who are likely to progress on active surveillance.[17]. Recently, new genomic signature panels performed on biopsy tissue has shown promising results in helping to stratify risk among patients selecting active surveillance.[18] However, these tests still require further validation to evaluate their true benefit in treatment decision-making. Although each of these biomarkers may add some information regarding risk stratification, none of them can reliably guide or significantly facilitate treatment decision-making process. As a result, most protocols must rely on clinical (serum PSA) and histopathological factors on biopsy (Gleason score, percent of cores positive, percent of each core with cancer) to help select patients who may be suitable for active surveillance. However, as mentioned before there is an inherent risk in using these parameters as they will only be informative about the portion of the gland that was sampled.

1.4 Rationale

1.4.1 Rationale for Studying Active Surveillance Patients

Radical prostatectomy and radiotherapy, the two most common and potentially curative treatment options for prostate cancer come at a significant impact to health related quality of life.[2-4] With earlier diagnosis from PSA screening, there may be as much as a 15 year lead time before the majority of patients progress and metastasize. Active surveillance has emerged as an appropriate and safe alternative to immediate treatment and is supported by both the American Urological Association and the European Urological Association.[19,20] Our center has one of the largest active surveillance cohorts in the world. With a median follow up of 3 years about 30% of patients experienced progression of tumor. However, no patient in our series has developed metastasis or mortality. Given the success and emerging popularity of active surveillance, there is a consideration to expand the criteria for surveillance to allow intermediate risk patients to be considered eligible. However, some patients who undergo delayed surgery after initial surveillance have adverse histological findings that may portend worse outcomes or require further secondary treatments to establish cure.[21,22] It is likely that many of these patients harbored higher risk disease that was missed on initial evaluation of their prostate. Therefore, any biomarker, predictive tool, or imaging modality that could identify these patients early would be a welcome addition to reduce the likelihood of an adverse outcome due to poor selection of suitable patients.

1.4.2 Multiparametric MRI and MRI-US fusion for Identifying Tumor Areas with Aggressive Characteristics

As mentioned before transrectal ultrasound has poor sensitivity and specificity in visualizing tumors within the prostate making it difficult to target areas of the gland that are likely to harbor the most aggressive lesions. Multiparametric MRI, when applied to the prostate, provides much better tissue resolution and improved sensitivity and specificity in detecting aggressive cancers of prostate.[23,24] The individual parameters include T2 weighted images, which provides excellent depiction of prostatic anatomy with prostate tumors having a lower signal intensity than the surrounding tissue.[25] Diffusion weighted MRI (DWI) displays information on the diffusion of water molecules through the tissue and measures the resistance of the tissue using an apparent diffusion coefficient (ADC), which is often lower in higher Gleason score tumors.[26,27] Dynamic contrast enhanced (DCE)-MRI has also been applied to discriminate normal from malignant prostate tissues, with earlier and greater enhancement followed by washout seen in the latter. DCE-MRI measures vascularity and hence angiogenesis. Both DWI and DCE have a relatively high sensitivity and specificity for prostate cancer.[23,24]

Due to its improved accuracy to detect aggressive tumors of the prostate, many groups have advocated for the use of MRI to select patients who may be suitable for active surveillance. A recent study of 298 men with low risk cancer on biopsy who underwent MRI prior to removal of the prostate found that those with a lesion on MRI were more likely to have a more aggressive or larger tumor then initially perceived, suggesting they would not have been good candidates for surveillance.[28] Similarly, another study of 85 patients who qualified for active surveillance found that a suspicious lesion, lesion density and the number of lesions on MRI correlated with the likelihood of finding a higher grade or volume of tumor on repeat biopsy.[29] These studies speak to

the emerging role of MRI in selecting and following patients on active surveillance for low risk tumors.

Despite the increased accuracy of MRI to detect suspicious lesions within the prostate, targeting these areas on MRI can be cumbersome since the patient will have to be in the MRI suite for a prolonged period of time. However, recent technology that fuses MRI images with real time transrectal ultrasound has allowed the clinician to target lesions seen on MRI using transrectal ultrasound, allowing the biopsy to be performed quickly in the office seting.[30] Recent studies have revealed that MRI-US fusion biopsy results in a higher detection of cancers and significant cancers (that would exclude a patient from active surveillance) compared to the current standard of random biopsy using just transrectal ultrasound.[31,32] A prospective, blinded study compared MRI-US fusion biopsy and random sampling of the prostate on transrectal ultrasound.[33] Among the 172 patients in the study, fusion biopsy was more often informative then random sampling by the standard approach with a higher detection of all prostate cancers and aggressive prostate cancers. This improved accuracy for detection was robust to all subgroups of patients, prostate sizes, and lesion sizes.

Our group has developed semi-automated tools for compartmentalizing the prostate into "**habitats**" based on the combined analysis of the multiparametric data from T2w, DCE and ADC maps. This new tool will be applied to our protocol patients to better direct prostate biopsies based on MP-MRI.

There is emerging data that the application of this technology to selecting patients for active surveillance will contribute to the earlier identification of patients who are not good candidates for such an approach.[34] However, this data is in its infancy and requires further validation in larger prospective studies. Furthermore, due to the improved detection of more significant cancers with a fusion biopsy technique the histology is more likely to reveal higher grades and volumes of tumor compared to traditional biopsy methods. As a result, the grade and volume thresholds which currently serve as criteria for selection of active surveillance patients will have to be revisited.[35] Finally, the role of MRI-US fusion biopsy and MRI alone in following patients on surveillance will require further investigation to see if certain features on MRI alone can predict the outcome of biopsy. Therefore, although MRI-US fusion technology provides a more accurate way of identifying risk within the prostate, its role in the selection and management of active surveillance patients requires further validation.

1.4.3 Radiomics to provide more Quantitative Risk Assessment in Active Surveillance Patients

"Radiomics" refers to the extraction and analysis of large amounts of advanced quantitative MP-MRI features using high throughput methods.[36] Radiomics data are in a format that is amicable for building descriptive and predictive models relating image features to outcome, as well as gene–protein signatures. Resultant models may include imaging, molecular, and clinical data, and provide valuable diagnostic, prognostic or predictive information. Dr. Gillies's group at Moffitt Cancer Center have pioneered the use of image texture features in CT of the lung that are prognostic of survival.[37]

These methods are semi-automated wherein the radiologist identifies the lesion and computer software proceeds to segment, render and generate a report of quantitative features. These reports are pertinent to the questions: Which features are

informative (e.g. have a wide range and are measureable in all samples)? What is the variance from one measurement to another and what are the critical sources of that variance? Are the features with largest dynamic range related to outcomes?

The use of image features has been elevated to a new level through the work of Kuo and colleagues, who have associated extractable features from MRI or CT to global gene expression patterns in glioblastoma multiforme (GBM) and hepatocellular carcinoma (HCC).[38,39] In GBM, there are clear correlations between histopathology grade and MR imaging features.[40] However, the diversity of MR phenotypes is greater than that of histology, e.g. tumors of similar histopathology can exhibit distinctly different MR imaging patterns.[41] In HCC, Kuo quantified 138 features from contrast-enhanced CT images in a training set from 28 patients. These features were individually filtered by frequency in the datasets, interobserver agreement, and independence from other features, resulting in a subset of 32 highly informative features. A modified neural network was then used to identify 116 gene "modules" that contained sets of genes (out of 6732 total) whose variation was coherent. The algorithm then identified combinations of imaging features that were highly correlated with each gene module. This training set was then tested using a permutation of the original data and a completely independent data set. Only 28 of the imaging features were needed to explain all 116 gene modules, and 9 features could explain half of them. For each gene module, only 3-4 imaging features were needed. Thus, the CT feature data was predictive of global gene expression.

Gillies and Gatenby have recently pioneered the concept and practice of defining specific "habitats' from radiological images, which we will use to facilitate applying radiomics to prostate cancer analysis.[42] This approach requires the combination of co-registered images from multiple modalities, with each one contributing a piece of orthogonal information. For this reason, MRI is a technique of choice because multiple pieces of co-registered orthogonal data can be generated in a single exam. For example, DCE-MRI is a powerful method to identify regional distributions of blood flow, and lack of blood flow. The texture of these enhancements has proven to have significantly higher prognostic value than simple region-of-interest (ROI) measures. Diffusion MRI measured ADCs is a powerful method to interpolate the density of diffusion barriers (i.e. cells) and hence provides information that may be biologically, but not physically, related to DCE. T2 is sensitive to microscopic perturbations in the magnetic field; this is affected by blood flow and cell density, but in a non-linear fashion. Hence, T2 information is not strictly orthogonal to DCE and ADC and this correlation is accommodated in habitat imaging as described below.

1.4.4 Biomarker Validation for Active Surveillance

Biomarkers, be they from blood, urine or tissue, have the potential to contribute meaningfully to the decision of whether to recommend treatment or AS, and perhaps when to convert to treatment for men undergoing AS. The most promising of these biomarkers include genomic signature panels that can be tested on biopsy tissue to provide important information on risk stratification and prognosis.[18] Previous validations of these tissue markers have been performed using biopsy tissue from random sampling of the prostate. However, we plan to examine tissue biomarkers in two unique methods that may allow for a more enhanced prediction. First, we will be testing tissue

attained from MRI-US-guided biopsies, which will sample suspicious regions of the prostate most likely to harbor the dominant tumor. To the best of our knowledge, there have been no publications on biomarker assessment using tissue obtained from targeted biopsy. Biomarker testing from these tissue cores will be compared to cores from segmental sampling of the prostate to assess for any differences in risk assessment. Secondly, these biomarkers will be attained serially to assess the change over time in genomic risk assessment.

We have previously collaborated with GenomeDx who has developed techniques for the analysis of RNA-based gene expression in formalin fixed paraffin embedded (FFPE) tissues from prostate biopsy. Using their system, gene expression profiling will be performed using a high-density 1.4 million-feature expression microarray. Although previous genomic signatures have been limited in assessing risk among patients on active surveillance this study allows us to explore various combinations of genetic alterations seen in the tumor region most likely to be driving progression. Therefore, we can expand on previous findings[43,44] and facilitate the development of other genomic alterations that may have more significant prognostic implications. We believe that the radiomic and genomic characterization of various regions within the prostate will complement each other as well as the histological assessment to help select patients who are likely to harbor tumors that will portend an unfavorable outcome on active surveillance.

Other biomarkers to be investigated include the Four-Kallikrein Panel or OPKO test. The test is an algorithm comprised of the quantitative measurements of four kallikrein protein markers that can be measured in the blood: total PSA, free PSA, intact PSA, and human kallikrein protein. The OPKO test is derived from the measurement of these proteins in the blood as well as the patient age and digital rectal exam findings. The test provides a percent probability that the patient would have cancer, and high-grade cancer on prostate biopsy. Multiple studies have shown that the test improves the ability to discern between pathologically indolent versus aggressive tumors.[45-47] However, this test has not been validated in the active surveillance population to see whether it can improve the selection of patients who are unlikely to progress while monitoring their tumors.

Urinary PCA3 has emerged as another biomarker that assists in differentiating between patients with indolent versus aggressive tumors.[48] PCA3 mRNA is detected in the first amount of urine after prostatic massage. Although initially used to help in the detection of prostate cancer, this test has expanded its role and has shown promising results in selecting patients who are well suited for active surveillance.[16,49] While surveillance patients are at the extreme in terms of being favorable, we still may identify high risk patients not previously identified based on standard factors (Gleason score and tissue burden) and biomarker patterns that are associated with men in other stages of the disease. Finally, we will assess urine and serum based molecular markers to investigate their associations to tissue-based markers, radiological findings and histological progression.

1.5 Preliminary Studies

1.5.1 Experience with active surveillance

The Department of Urology at the University of Miami has a significant experience in active surveillance. Currently the clinical and histological criteria for surveillance include Gleason ≤ 6 (3+3), PSA ≤ 20ng/mL, and two or fewer biopsy cores with no more than 20% tumor present in each core. All patients had at least one confirmatory surveillance prostate biopsy. At diagnosis, the mean age of the AS patients was 62 years (range 33-79 years) with a mean PSA of 5.1 ng/mL. The mean follow-up for the cohort was 2.9 years (interquartile range (IQR) 1.4-24.0 years). On the first re-biopsy, 52% of the patients had no tumor. Only 7% of the AS patients had tumor progression (to some component of Gleason 4 disease) on first re-biopsy. In the second and third surveillance biopsies, 18% and 17% of the patients respectively progressed. Of the 249 men in the AS cohort as of this analysis in 2011, 64 (26%) demonstrated biopsy progression and 61 of them have been treated. No patient died of prostate cancer. Among the 61 treated patients, 32 had radical prostatectomy, 27 had interstitial or external beam radiation, and for 2 patients the type of treatment was unknown. Three men with an increase in tumor burden in follow-up biopsies elected to continue active surveillance despite the biopsy progression. However, the Miami criteria for active surveillance is very conservative and may exclude many men for whom surveillance would be acceptable. These criteria have been expanded in current clinical practice.

Similar outcomes have been reported in other cohorts of low risk patients on active surveillance.[11] Given the global success of active surveillance in low risk men, there has been a growing body of literature supporting the expansion of active surveillance to men with higher tumor burden or intermediate risk features.[8] As mentioned, we are also expanding our criteria in a similar fashion. Studies comparing intermediate and low risk patients on active surveillance have shown similar rates of progression between the two groups.[9] Although follow up is shorter in the intermediate risk group of men, we are not seeing a higher rate of metastasis or mortality. However, a proportion of men placed on active surveillance harbor a high-risk tumor that was missed on initial sampling. For these men, cancer outcomes may be compromised by failure to recognize this high-risk tumor and offer immediate treatment. We believe the emergence of MRI targeted biopsy will allow detection of higher volumes and grades of cancer due to more accurate targeting of suspicious lesions. As a result, this proportion of men, who truly aren't candidates for surveillance, will be reclassified earlier and be offered treatment before their oncologic outcomes can be compromised.

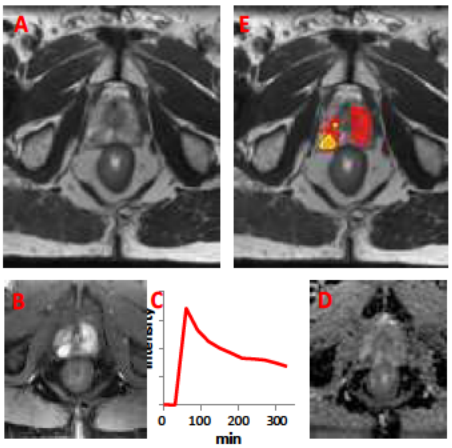

Figure 4: (A) T2w Axial slice (B) Early enhancement DCE (C) tumor contrast-to-time pattern; (D) ADC map; (E) Volumes of high perfusion (red) and low ADC (yellow) displayed in MIM.

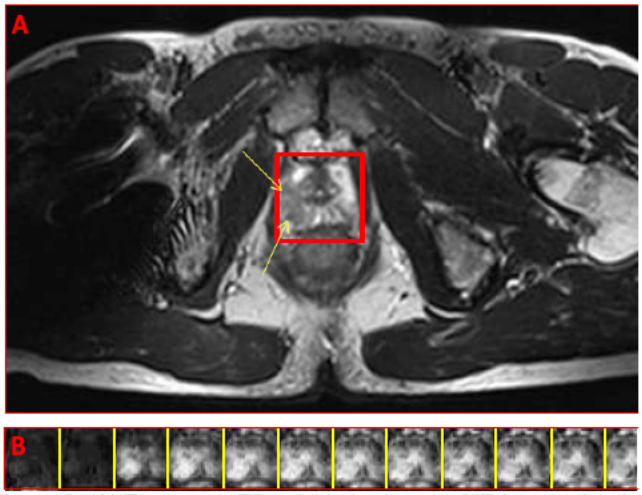

Figure 3. (A) Transverse T2-weighted spin-echo MR image of male pelvis. The red box surrounds the prostate; arrows indicate hypointense area in the right peripheral zone, suspicious for tumor. (B) Prostate area in the series of T1-weighted gradient echo sequence images, following contrast administration.

1.5.2 Multiparametric MRI

Our group, in collaboration with diagnostic radiologists, has considerable experience with using functional MRI in the routine assessment of prostate cancer prior to definitive therapy, especially prior to radiation therapy. Routine sequences are T2w, T1 non-contrast, T1 DCE-MRI and DWI obtained at 2.5 mm intervals. These sequences are acquired via a 3.0T magnet using a body coil. For the purposes of the studies outlined, MRS will also be performed, but we anticipate that DCE-MRI and DWI-derived ADC maps will be more important sequences in this population.

In **Figure 3** an axial T2w MRI of a male pelvis is shown: resolution 0.7 × 0.7 × 2.5 mm; Rectangular Field of View: 360 × 264 mm; slice thickness - 2.5 mm (no gap); 72 slices; repetition time (TR) 6300 ms/echo time (TE) 112 ms; flip angle 120º. The arrows point to a hypointense area in the right peripheral zone suspicious for tumor (**Figure 3A**). The prostate, centered in the red box, is presented in the series of T1-weighted gradient echo sequence MR images (**Fig 3B**), acquired with identical spatial resolution, spacing and image size as the T2w MRI. Prior to contrast material injection, one set of MR images were acquired as a pre-contrast image T1 data set. The rest of the data were acquired following intravenous bolus injection of a paramagnetic gadolinium chelate - 0.1 mmol of gadopentetate dimeglumine (Dotarem; Guerbet, Paris, France) per kilogram of body weight. The contrast was administered with a power injector (Spectris; Medrad) at 2.5 mL/s and followed by a 15-mL saline flush. The image sequence parameters were TR/TE 5.1/2.3 ms; flip angle 10º. Eleven post-contrast imaging datasets (34 sec each) were collected. Using DCE-MRI, contrast enhancing lesions are seen in the vast majority of patients; although, little work has been done in men who are candidates for active surveillance, so the proportion of these men who will display enhancing lesions is less certain.

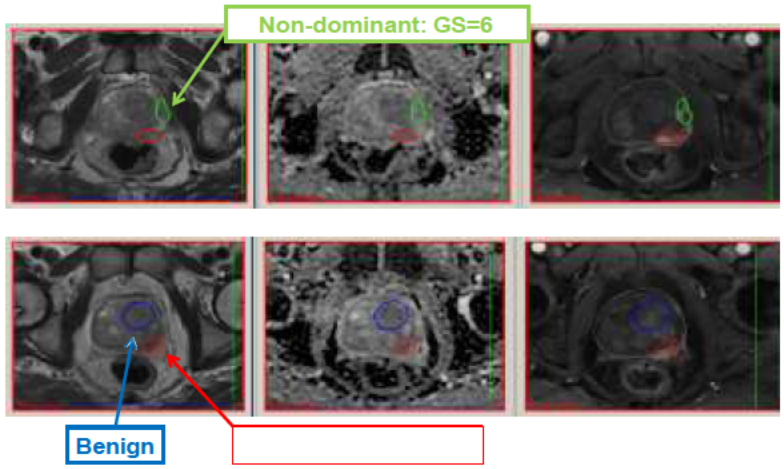

Figure 5. Regions of the prostate in the same patient were biopsied using MRI-guidance. The suspected dominant region contained Gleason score 7 disease, while the nondominant areas had Gleason 6 or no tumor.

Figure 4 shows a simple approach that we had adopted in clinical trials involving the targeting of high risk prostate subregions with radiotherapy by combining analyses of the DCE intensity and ADC maps showing the highest region of risk of Gleason score 7 or above, those with high perfusion and low ADC values (dominant lesion), in yellow. Our preliminary biopsy data bear this out; there is a higher risk of Gleason score 7 from dominant regions and a higher risk of Gleason 6 or benign prostate from non-dominant areas **Figure 5**.

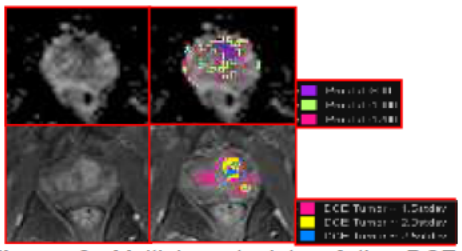

Figure 6. Multiple cutpoints of the DCE intensity and ADC values were used to characterize habitats in the prostate that will be targeted with MRI-guided biopsies.

Taking the analysis to another level, we have introduced selectable cutpoints in the in the MP-MRI analyses, as displayed in **Figure 6**. The result is many more defined "habitats" identified, from which targeted MRIus or MRI-directed prostate biopsies will be used to construct probability maps for histopathologic characteristics and gene expression signatures.

1.6 Quality of Life

The Quality of Life (QOL) assessment will provide unique data on the effects of MRI monitoring for patients undergoing active surveillance on QOL. We have selected a group of measures that have been used extensively in prostate cancer populations. To assess Health-Related Quality of Life (HRQOL) we will use the SF-12, a short form version of the commonly used SF-36, which is a health survey designed to assess multiple dimensions of HRQOL. The SF-12 captures approximately 85% of the variance in the SF-36 and was developed as a brief measure to address general aspects of quality of life. This brief instrument provides both physical and mental health summary scores. The physical summary score is comprised of physical functioning, role limitations due to physical functioning, bodily pain and general health subscales. The mental summary score is comprised of vitality, social functioning, role limitations due to emotional functioning and mental health subscales. The SF-36 and SF-12 both

demonstrate good internal reliability, with Cronbach's alphas exceeding 0.80. The SF-12 has been used extensively in cancer populations, and has been validated with prostate cancer patients.[50] As an index of Prostate Cancer-Specific Anxiety, we will administer the Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC). The MAX-PC is an 18-item instrument designed to detect symptoms of anxiety in prostate cancer patients. It is designed to evaluate three separate aspects of prostate cancer specific anxiety on 3 subscales: anxiety related to prostate cancer in general (prostate cancer anxiety subscale), anxiety specifically centered around PSA testing (PSA anxiety subscale) and fears of cancer recurrence (fear of recurrence subscale). The MAX-PC9 demonstrated high internal reliability with a Cronbach's alpha of 0.89, with subscale reliabilities between 0.59-0.90 and has been validated in prostate cancer patient samples.[51] Finally, we will evaluate Prostate Cancer-specific Quality of Life. Prostate-specific QOL will be measured with the Expanded Prostate Cancer Index Composite (EPIC-SF12).[52] Development of the EPIC was based on the widely used University of California Los Angeles Prostate Cancer Index and has been used extensively to assess post-treatment related dysfunction among prostate cancer patients. The EPIC has demonstrated excellent reliability (i.e., Cronbach's α>.91) across sexual function and sexual bother composites. The EPIC questionnaire will be used to measure changes in QOL over time. For this study, a combined EPIC-SF12 questionnaire will be used. There has been a significant amount of research showing a link between lifestyle modifications pertaining to diet and exercise and improved prostate cancer outcomes. As a result, we would like to collect information on patient's diet and exercise habits to see how changes in these modifiable factors can impact progression on active surveillance. For this purpose we will use the food frequency questionnaire (FFQ). The FFQ forms are optional for the patient and can be refused. All questionnaires will be available in English and Spanish.

2. HYPOTHESES

1) Multiparametric MRIus-guided or direct MRI-guided biopsies will allow for more directed sampling of the tumors from compartments with distinct MP-MRI characteristics, termed habitats, that will increase the rate of "progression" on early (first and second) surveillance biopsies and decrease the rate of "progression" on late (third and further) surveillance biopsies compared to historic TRUS-guided biopsy rates.
2) Identifying higher risk tumor early on will reduce the proportions of patiens with poor response to delayed primary treatment
3) Radiomics signatures from MP-MRI will define patterns that are associated with progression
4) Genomic signatures based on RNA from tumor tissue will define patterns that are associated with habitats and radiomics signatures, as well as progression.

3. OBJECTIVES

3.1 Primary Objective

To determine if multiparametric MRI and MRI-US fusion biopsies increase the rate of progression (conversion to treatment) within the first two non-diagnostic biopsies after undergoing active surveillance as compared to historical cohorts using standard ultrasound guided biopsies.

3.2 Secondary Objectives

1) To identify whether earlier identification of progression with MRI and MRI-US fusion biopsy will portend improved outcomes of patients undergoing delayed primary surgery or radiation after initial surveillance at the University of Miami
2) To determine the effect of multiparametric MRI and MRI-US fusion biopsy on health related quality of life and cancer specific anxiety using patient reported validated questionnaires.
3) To determine the incremental benefit of mpMRI, genomic risk test, and molecular marker at baseline compared to NCCN risk class for predicting progression on Active Surveillance

3.3 Exploratory Objectives

1) To define radiomic signatures on multiparametric MRI that select regions of the prostate that are likely to harbor more aggressive disease.
2) To molecularly characterize tissue from the muliparametric habitat-directed prostate biopsies and develop genomic signatures of indolent versus progressing prostate cancer using a 1.4 million feature oligonucleotide microarray capable of global high throughput analysis of formalin fixed paraffin embedded specimens.
3) To relate radiomics and genomics signatures to existing urine, serum and tissue biomarkers that have been associated with prostate cancer diagnosis and/or progression.
4) To determine the incremental benefit of mpMRI, genomic risk testing, and molecular markers at baseline compared to NCCN risk class for predicting reclassification on confirmatory baseline biopsy.
5) To evaluate serial changes in mpMRI, genomic risk scores and molecular markers and relate them to progression on active surveillance.

4. STUDY DESIGN

Single arm therapeutic trial investigating the impact of MRI and MRI-US fusion biopsy to identify higher grade or volume tumors early on for better selection of patients for active surveillance and improved outcomes for those undergoing delayed treatment after initial observation. MRI–US fusion biopsy will include targeting of suspicious areas seen on MRI as well as segmented sampling of the remaining gland. Patients will

undergo MRI and MRI-US fusion biopsy within 3 months of enrollment in the trial and have repeat MRI-US fusion biopsies every year to assess overall rates and the temporal distribution of progression. Serum, urine and prostate biopsy tissue will be serially collected to investigate the association between various molecular biomarkers and radiologic and histological progression.

Patients who are found to have cancer progression will undergo either radical prostatectomy or prostate dose escalated (EQD_2 >78Gy) image guided radiotherapy of the prostate. Although patients will be encouraged to seek treatment at the University of Miami to continue follow up on trial, we understand that patients may select to be treated elsewhere and this would not be considered a deviation from the protocol. Men undergoing surgery will have their pathology specimen compared to men in the University of Miami active surveillance database who had surgery after initial surveillance without MRI. After surgery men will be followed every 3-6 months (+/- 2 months) for the first year, every 6-12 months (+/- 3 months) in the second year, and annually (+/- 6 months) thereafter up to 5 years post surgery. Any adjustments to this schedule will be permitted under the discretion of the clinician. A PSA of 0.2 ng/ml with a repeat value showing the same or higher will be used to define biochemical recurrence post radical prostatectomy. For men undergoing radiation therapy, the method and dose of radiation that will be delivered will be left to the discretion of the treating physician. For men undergoing radiotherapy of the prostate, follow up serum PSA testing should occur every 6 months (+/- 3 months) for the first 3 years and then annually thereafter (+/- 6 months) for up to 5 years post treatment.

A PSA of 2 ng/ml above the nadir will be used to define biochemical failure post radiation. Rates of biochemical recurrence post surgery or radiation will be compared to historical data of men being treated after initial surveillance at the University of Miami. The choice to use androgen deprivation therapy will be left to the discretion of the treating physician. Follow up and treatment protocols have purposely been made broad to allow enrollment on other interventional trials for which a patient may be eligible. If the patient enters a radiation oncology clinical trials, then the timing of PSA and other labs will be timed in accordance with the radiation treatment protocol.

The flow chart shown in **Figure 1** illustrates the surveillance portion of the sequence that patients will go through if entered in the study. The post treatment flow chart for those who progress has purposely been left out to avoid prevention of patients enrolling on other intervention trials for which a patient may be eligible. Patients will be recruited for protocol participation from the pool of men seen for management of prostate cancer by physicians at the University of Miami. Those patients that sign an informed consent form for the study will be screened by the study investigators for fulfillment of eligibility criteria. Once the University of Miami Pathologic review is completed and all eligibility requirements are met, the patient will be registered in the study. Additionally, the patient will be asked to participate in the Urology Active Surveillance database for comparison with other active surveillance patients available in that database.

4.1 Accrual goal

The accrual goal for this study is 230 patients or approximately 46 patients per year for 5 years.

4.2 Duration of Study Participation

The research study will end at 36 months from the initial protocol biopsy.

Duration of study treatment will be a maximum of 60 months from enrollment and four biopsies for patients who do not progress. After the end of study, the patient will be followed, if consented, in the department of Urology active surveillance database as per their clinician's standard of care.

5. STUDY ENTRY AND ENROLLMENT AND WITHDRAWAL

5.1 Study Entry

Study entry, as used in this protocol, will be defined as a subject signing informed consent. Study enrollment, as used in this protocol, will be defined as the investigator's confirmation of the subject's eligibility by signing an eligibility checklist.

5.2 Enrollment Procedures

As per UM/SCCC Clinical Research Services policy, eligibility must also be reviewed by a CRS director or designee. The investigator or study coordinator will provide the following to a CRS representative:

1) Completed and signed protocol-specific eligibility checklist;
2) All pages of the original signed informed consent forms (ICFs), including HIPAA Form B;
3) Relevant source documents such as: subject medical history and physical exam, admission or discharge notes, diagnostic reports, pathologic confirmation of diagnosis, and relevant subject-specific written communication.

5.3 Cancellation Guidelines

The following are reasons for withdrawal of subjects from the study:

- a subject does not meet the eligibility criteria, (the subject will be considered a screen failure).
- a subject withdraws consent,
- a subject dies during protocol participation or
- a study investigator decides the subject should be withdrawn from the study (e.g. subject non-compliance)

Contact the CRS representative, or e-mail the information including the reasons for withdrawal as soon as possible, but no later than 48 hours after the event/decision.

6. PATIENT SELECTION/ELIGIBILITY CRITERIA

Patients with low to low-intermediate risk prostate cancer are eligible for the study. Eligibility criteria for involvement in the study have been made broad enough to allow for most men who have relatively low volume Gleason score 6-7 disease to participate. Patients will be recruited from the pool of men seen for management of prostate cancer by physicians at the University of Miami.

6.1 Inclusion (Eligibility) Criteria

1) Biopsy confirmed adenocarcinoma of the prostate within 18 months prior to enrollment;
2) Pre-enrollment prostate biopsy must consist of at least 8 cores;
3) Biopsy reviewed by a University of Miami Pathologist;
4) Serum PSA ≤20 ng/ml within 3 months of study enrollment;

5) Age ≥35 and ≤85 years;
6) Ability to understand and willingness to sign a written informed consent document;
7) Patients must agree to undergo serial multiparametric MRI and MRI-guided biopsy;
8) Patients must agree to fill out the longitudinal psychosocial questionnaires assessing health related quality of life.

6.2 Exclusion (Eligibility) Criteria

1) Greater than 4 cores positive, of any Gleason score, on the UM review,
2) Greater than 2 cores positive for Gleason 3+4 cancer,
3) Gleason 4+3 or higher cancer in any single biopsy core.
4) Extracapsular extension suspected on digital rectal exam with confirmation on MRI. Suspicion of extracapsular extension on MRI alone is not an exclusion for study enrollment.
5) Subject is not a candidate for multiparametric MRI with contrast. Some reasons may include (but are not limited to): renal insufficiency, foreign body or pacemakers.
6) No prior pelvic radiotherapy
7) No prior surgery to the prostate, other than transurethral procedures for benign prostatic hyperplasia (e.g., transurethral resection, green light laser treatment)
8) No concurrent, active malignancy, other than non-metastatic skin cancer of any type, superficial bladder cancer, or early stage chronic lymphocytic leukemia (well-differentiated small cell lymphocytic lymphoma) or <stage IV follicular lymphoma. If a prior malignancy is in remission for ≥ 3 years then the patient is eligible.
9) Bilateral hip replacement.

6.3 Gender and Ethnicity

Prostate cancer is a disease of adult men, with exceptionally few diagnosed at 35 years of age. Therefore, women and children are not candidates for this protocol. Based on standard NIH definitions, we estimate that approximately 40% of patients will be White, 24% African American, 35% Hispanic and 1% other at the University of Miami.

7. CLINICAL, RADIOLOGICAL AND LABORATORY EVALUATIONS

7.1 Screening Evaluations

- History and physical exam, within 12 months prior to protocol enrollment.
- Serum PSA (+/-) 3 months of protocol enrollment.
- Pathology review at the University of Miami of the outside biopsy material, prior to enrollment.

7.2 Evaluations During Intervention*

- Multiparametric MRI obtained at the University of Miami (+/-) 3 months of enrollment and at 12, 24, and 36 months from initial protocol prostate biopsy.

- MRIus-guided biopsies will be obtained at 0 to 3 months from enrollment ("initial biopsy") and at 12, 24 and 36 month from initial biopsy.
- History and physical at the discretion of the treating physician. Treating physician can be outside of UM..
- Serum PSA will be done preferably every 6 months or at least once a year up to 36 months from the initial biopsy. If the subject progress, PSA should be done every 6 months (+/- 3 months) or at the discretion of the clinician for the first 3 years and then annually thereafter (+/-6 months) for up to 5 years post treatment.
- If possible, plasma and/or serum (up to 5 tubes)) for research purposes (biomarkers) may be obtained at 0 to 3 months from enrollment and at 12, 24, and 36 months from initial biopsy (optional - patient may refuse),
- If possible, post prostate-massage urine (approximately 50 mL) may be collected for research purposes at 0 to 3 months from enrollment and at 12, 24, and 36 months from initial biopsy (optional - patient may refuse). Urine research collection will not be done if research funds are not available.
- Quality of Life surveys obtained 0 to 3 months after enrollment and every 12 months from initial biopsy:
  - Expanded Prostate Cancer Index Composite Questionnaire (EPIC+SF12)
  - Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC)
  - Optional - Food Frequency Questionnaire (FFQ) will be collected only atbaseline.

** Follow-up evaluations and visits may occur ± 1.5 months around each scheduled 6-month timepoint. For example, for the 6 month follow-up, the patient may be seen anytime between 4.5 and 7.5 months from the time of the first prostate biopsy. For the 12-month follow-up, the patient may be biopsied between 10.5 and 13.5 months from the time of the first prostate biopsy. Since the first biopsy may be from between 0-6 months from the day the patient is enrolled, each subsequent calendar event is timed in reference to the time of that first biopsy.*

7.3 Early discontinuation of study participation

Patients who experience protocol-defined progression will have attained the primary study outcome and will undergo treatment either with radical prostatectomy or whole gland image guided radiotherapy of the prostate at the University of Miami. Their histopathology (for surgery patients) and rates of biochemical recurrence will be followed and compared to historical series for comparison with cohorts not undergoing MRI guided selection for surveillance versus immediate treatment. However, those who refuse the recommendation for treatment will continue to be followed per active surveillance standard of care guidelines. Furthermore, those who seek treatment outside UM will be contacted for information on histopathology (for those undergoing surgery) and rates of biochemical recurrence. Patient refusal of the recommendation for treatment or further follow-up beyond progression will not be a protocol deviation. Patients who are without progression upon completion of the third annual biopsy will be censored without progression.

7.4 Multiparametric MRI

Multiparametric MRI exam of the pelvis and prostate, including T2, T1 non-contrast, T1 DCE and DWI MRI scans will be carried out at the GE Discovery MR750 3T MRI unit located at the University of Miami on 3T MRI at the University of Miami. The GE Discovery MR750 3T in the department of Radiation Oncology is preferred, but not mandated. Standard contraindications to MRI, such as ferromagnetic metal in body/eye, pacemaker, defibrillator, other mechanical device, or extreme claustrophobia (medication with anti-anxiety agents, such as Ativan, may be attempted) will prevent eligibility and will be applied for all protocol-related MRIs. Since the DCE-MRI scan involves the use of gadolinium, renal function should be assessed per routine policies.

A preparation procedure protocol has been developed to optimize the multiparametric MRI (see Appendix III) and will be recommended to the patient, but not mandated. A diet designed to reduce bowel gas will also be recommended to begin the day before the diagnostic MP-MRI. This protocol is a guide and slight variations are acceptable. Imaging parameters will be recorded on each patient in the CRFs. As a quality control measure, every MP-MRI will be reviewed by the study team within 45 days for adequacy. If the MP-MRI is deemed inadequate, another MRI will be requested within 30 days. An inadequate exam at that point will be deemed a protocol deviation. De-identified data will be sent to Moffitt Cancer center for radiomics as described below.

7.5 Prostate Biopsy

Standard antibiotic prophylaxis of will be at the discretion of the physician managing the biopsy. Aspirin, anticoagulants and vitamin supplements will be temporarily discontinued at least one week prior to the procedure, per routine; these drugs may be restarted per standard practice for prostate biopsies (typically a day or two later if there is no bleeding). The typical and recommended procedure involves placement of the patient in the left lateral decubitus position. Immediately prior to the procedure, 10 cc of 1% Lidocaine may be injected into the periprostatic nerve plexus under ultrasound guidance, typically using a 22 gauge 7-inch needle. The syringe is aspirated before the lidocaine injection to prevent unintentional injection into the vascular compartment. An ultrasonographic wheal may be viewed in the sagittal plane between the rectal wall and base of the seminal vesicles.

Transrectal ultrasound biopsies will be performed on an FDA-approved device using standard techniques. Twelve to fourteen needle core biopsies are desired, but the managing physician may opt for fewer, if there are complications or other indications, or more, if an area of interest was felt to be inadequately biopsied (needle misdirection or other reason). The managing physician will be a co-investigator and will understand the protocol goal of 12-14 cores per prostate biopsy. The arrangement that is recommended (not mandatory) will be left lateral base (LLB), left lateral mid (LLM), left lateral apex (LLA), left medial base (LMB), left medial mid (LMM), left medial apex (LMA), right lateral base (RLB), right lateral mid (RLM), right lateral apex (RLA), right medial base (RMB), right medial mid (RMM) and right medial apex (RMA). Transition zone biopsies may be acquired. The MRIus biopsies will be performed in the same fashion, but corresponding needle cores will be targeted towards the suspicious areas (see Figure 6). During the course of the procedure, hemorrhage may be visualizedwithin the bladder following needle

biopsy. If this is the case, or if gross blood is noted
at the urethral meatus, bladder catheterization and clot irrigation may be indicated, as determined by the urologist.

The procedure will be performed by an urologist in the Department of Urology (SP) at the University of Miami. For patients with MRI visible lesions, an MRI-US fusion biopsy will be performed in addition to the standard template (above). MRI-US fusion biopsies will be performed preferably using the Uro-Nav system from Invivo, Philips; although, the Artemis system is available in the department of urology and may be used.

7.5.1 MRI-Ultrasound (MRI-US) Registration for Targeted Prostate Biopsy

MRI-US fusion biopsy will be performed on an FDA approved platform (e.g., UroNav, In Vivo). The approach begins with multiparametric MRI of the prostate as described above. Expert radiologists will interpret the MRI with the assistance of in-house and/or commercially available software. Suspicious lesions will be determined based on multiple parameters and delineated on the MRI by a panel of expert radiologists with experience reading prostate MRI. Biopsy needle localization and tracking is recorded by an external magnetic field while the biopsy is performed using freehand transrectal ultrasound. Once the MRI is loaded onto the software platform, an initial transrectal ultrasound sweep of the prostate of the prostate is performed, and a rigid image fusion is performed allowing clinicians to see both the MRI and ultrasound images moving together in real time. The lesion on MRI is then targeted using ultrasound to ensure the correct depth and course of the needle to ensure the needle enters the suspicious area. By using freehand ultrasound, a technique familiar to urologists, the learning curve for the procedure is steep and the workflow preserved allowing a quick procedure for the patient.

7.6 Biopsy Tissue Handling

Immediately following each biopsy core, the tissues will be fixed in 10% formalin per routine. The formalin fixed tissues will be delivered to the Department of Pathology for paraffin embedding and sectioning.

The biopsies are to be placed in the tissue processor and processed routinely, and embedded in paraffin. Biopsies will be reviewed by a pathologist and the results (Gleason scoring and percent of tumor tissue) recorded in the patient’s record per routine. The remainder of the block will be stored per institutional policy in the Department of Pathology and requests for the biomarker analyses made at a time batched staining is possible (after a number of cases have been accrued).

When the tissue is sectioned for biomarker analyses, the slides will be labeled with a research ID number and will not contain patient information. Biomarker data will be entered into the Active Surveillance Database, which links the patient Medical Record number to a participant's Research ID number and in which data on each patient related to biopsies and treatments will be recorded. De-identified data will be sent to Genome Dx for gene expression profiling as described below.

7.7 Molecular Analyses of Blood and Urine

The objectives are to identify and examine molecular and genomic biomarkers in blood products and the urine that predict for disease progression and see how they correlate with radiomic and genomic signatures from distinct regions of the prostate.

Blood may be collected at baseline, and at 12, 24 and 36 months after initial biopsy. Urine post prostate massage may be collected at baseline and 12, 1,24 and 36 months after initial biopsy. Note that the collection of research fluids is optional – the patient can refuse the procedure. While these are exploratory studies, of key importance is to have such samples collected prospectively on a well-defined group of patients. Any urine or blood that is not used for specific biomarker testing will be stored for biomarkers development or validation.

7.8 Quality of Life and/or Outcomes

Psychosocial assessments will be conducted by a trained and fully-bilingual clinical coordinator/research nurse with experience in conducting psychosocial assessments in prostate cancer populations. We will make every effort to pair our psychosocial assessment visits with scheduled clinic appointments to reduce participant burden. The psychosocial battery will last between 30-40 minutes. All assessments will be conducted in private rooms in our clinics. All psychosocial data will be de-identified and only coded by participant number. Should a participant display any significant signs of distress (e.g., high levels of anxiety, depressed mood or spontaneous comments suggesting a need for psychosocial care), we will refer participants to appropriate psychosocial resources within our medical center.

7.9 Treatment

Men undergoing protocol defined progression will undergo for radical prostatectomy, prostate dose escalated (EQD2 >78Gy) image guided radiotherapy of the prostate, HiFu or any other prostate treatment. Although patients will be encouraged to seek treatment at the University of Miami to continue follow up on trial, we understand that patients may select to be treated elsewhere and this would not be considered a deviation from the protocol. Both treatment modalities are offered at the University of Miami and portend excellent cancer control in men with localized tumors. Patients will be counseled regarding with risks and benefits of both approach’s to allow for informed decision-making between the two options. Men undergoing surgery will have their pathology specimen compared to men in the University of Miami active surveillance database who had surgery after initial surveillance without MRI. After surgery men will be followed every 3-6 months (+/- 2 months) for the first year, every 6-12 months (+/- 3 months) in the second year, and annually (+/- 6 months) thereafter up to 5 years post surgery. Any adjustments to this schedule will be permitted under the discretion of the clinician. A PSA of 0.2 ng/ml with a repeat value showing the same or higher will be used to define biochemical recurrence post radical prostatectomy. For men undergoing radiation therapy, the method and dose of radiation that will be delivered will be left to the discretion of the treating physician. For men undergoing radiotherapy of the prostate, follow up serum PSA testing should occur every 6 months (+/- 3 months) for the first 3 years and then annually thereafter (+/- 6 months) for up to 5 years post treatment. A PSA of 2 ng/ml above the nadir will be used to define biochemical failure post radiation.

Rates of biochemical recurrence post-surgery or radiation will be compared to historical data of men being treated after initial surveillance at the University of Miami. Androgen deprivation will be prescribed at the discretion of the treating physician. Men who decline treatment despite progression and recommendation for treatment will be followed as per standard of care active surveillance criteria. Men who desire to undergo their treatments at centers outside the University of Miami will be contacted to attain post treatment oncologic data, as described above. Patient refusal to undergo treatment based on the protocol will be follow as per the treated physician. If the patient chose to seek treatment elsewhere will be left to the clinician and patients discretion and will not be considered a deviation of the protocol.

If the patient enters a radiation oncology clinical trial, then the timing of PSA and other labs will be timed in accordance with the radiation treatment protocol.

8. ADVERSE EVENT REPORTING

During the active surveillance part of the study, the only difference is the addition of a multiparametric MRI and MRI-US fusion biopsies in addition to random biopsy. The only adverse events expected from obtaining an MRI would include allergic reaction to the contrast, renal toxicity, or claustrophobia. Other than guidance by MRI, the prostate biopsy will be performed in the same fashion as standard biopsy of the prostate and therefore carries no increased risk from bleeding or infection. The addition of MRI guided biopsy has not been shown to increase the risk of infection or bleeding, compared to random biopsies alone.[53] These procedures are standardized and the risks well-documented. In the unlikely event that a study patient experiences an adverse reaction to a study related procedure, this will be reported the University of Miami Institutional Review Board as per their policies and using the grading scales of the NIH CTCAE version 4.0.

If the patient progress and decide to undergo either radical prostatectomy or radiotherapy or any other procedure:

8.2.1 Recording Abnormal Findings

In any clinical assessment, a value outside the normal or reference range (such as a clinical laboratory, vital signs, imaging findings or EKG findings) will not be recorded or assessed as an adverse event unless that value is considered to be of clinical significance by the investigator

8.2.2 Recording Signs and Symptoms

Sign, symptoms, or procedures resulting from an underlying clinical diagnosis should be documented as one comprehensive adverse event. If no underlying clinical diagnosis can be identified, each sign and symptom should be recorded as a separate independent event.

However, a new or worsening event resulting from an underlying clinical diagnosis or a reaction to concurrent medications should be documented as a separate independent adverse event unless it is within the normal range of fluctuation for that patient.

8.2.3 Recording Grade Changes

Adverse events will be recorded at the maximum grade/severity experienced for the duration of the event. Should one particular AE warrant further investigation, additional details may be collected at the discretion of the adverse event;

8.2.4 Reporting Period

Adverse Events relating to radical prostectomy and radiotherapy that are not related to MRI or MR biopsy, will not be documented in the adverse event log. Concominant medication will not be recorded after the subject progress.

8.2.5 IRB Reporting

All adverse events that are serious adverse events **and** are unexpected **and** are related or possibly related IRB within ten (10) working days of being made known to the Principal Investigator. Events that are more frequent than anticipated or more severe than expected must be reported to the IRB within ten (10) working days of being made known to the Principal Investigator.

All **unanticipated** deaths or life-threatening problems suspected as being a direct outcome or possibly an outcome of the study intervention must be reported to the IRB within 24 hours of being made known to the Principal Investigator.

For all SAE's, the investigator is obligated to pursue and provide follow-up reporting information until the event has resolved or until an acceptable medical endpoint has been reached or the patient is lost to follow-up.

9. DATA AND SAFETY MONITORING PLAN

The study investigators will report to the Sylvester Comprehensive Cancer Center Data and Safety Monitoring Committee (DSMC) to ensure data quality and subject safety. The investigators will conduct continuous reviews of the data and subject safety, keeping track of the number of subjects, significant toxicities in accordance with the protocol and observed responses, which will be discussed at DSMC committee meetings. All grade 3-5 adverse events will be entered into Velos and reviewed at DMSC meetings. In addition, all adverse reactions considered "serious" will be entered into Velos and reviewed by the DSMC on an ongoing basis. If an increase in the frequency of grade 3 or 4 adverse events is noted in the study, a report will be submitted to the DSMC at the time the increased rate is identified. If at any time the principal investigator stops enrollment or stops the study due to safety issues, the DSMC chair and manager will be notified within 1 business day and a formal letter will be sent to the DSMC to be received within 10 business.

10. STATISTICAL CONSIDERATIONS

This is a single-arm trial with the primary objective of determining the rate of progression over 2 years in men undergoing AS who are managed with multiparametric-

MRI and MRI-US fusion prostate biopsies, as compared to historical controls. The primary study endpoint is the 24-month cumulative progression rate based on biopsy criteria.

10.1 Primary Study Endpoints

10.1.1 Progression

The main study endpoint will be the 24-month cumulative progression rate. In the context of this trial, progression refers to a repeat surveillance biopsy indicating any one of the following: (i) more than 4 positive cores involving any grade of cancer, (ii)) three or more cores with Gleason 3+4 cancer, (iii) any single core with Gleason 4+3 cancer or higher, (iv) a Gleason 3+3 at diagnosis that is upgraded to Gleason 3+4 or (v) undergoing treatment, regardless of histological progression. Although many existing active surveillance protocols incorporate volume of cancer in their definition of progression, these are based on random biopsy of the prostate. Critical volumes of cancer based on targeted biopsy have not been defined and will be explored in this analysis.

- Progression rate will be estimated for each scheduled surveillance biopsy as the proportion of study patients without prior progression for whom the biopsy indicates progression.
- Cumulative progression rate will be estimated for each of the four planned biopsies as the proportion of patients with progression among those having had all planned biopsies to date, or a previous biopsy indicating progression.

10.1.2 Histological progression

In the context of this trial, histological progression refers to a surveillance biopsy that indicates any one of the following: (i) more than 4 positive cores involving any grade of cancer, (ii) three or more cores with Gleason 3+4 cancer, (iii) a Gleason 3+3 at diagnosis that is upgrade to Gleason 3+4, or (iv) any single core with Gleason 4+3 cancer or higher.

- Histological progression rate will be estimated for each scheduled biopsy as the proportion of study patients without prior GS progression for whom the biopsy indicates GS progression.
- Cumulative histological progression rate will be estimated for each scheduled biopsy as the proportion of patients with histological progression among those having had all planned biopsies to date, or a previous biopsy indicating Gleason score progression.

10.2 Secondary Study Endpoints

10.2.1 Time-to-Biochemical recurrence

Biochemical recurrence (BCR) is defined as PSA of 0.2 or higher on two or more separate measures after surgery or an increase of nadir + 2ng/ml or more after radiation. Time-to-BCR is defined as duration between date of treatment and date of BCR if BCR occurs.

10.2.2 QOL scores

Three contemporary instruments will be utilized to assess patient function and bother (Expanded Prostate Cancer Index Composite (EPIC), physical and mental health (SF12) and prostate cancer-specific anxiety Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC). Each of these measures will be assessed via the specific scoring instructions for each instrument. Given that this is a single arm trial, we will compare patient reported quality of life to historical active surveillance cohorts to see if MRI and MR targeted biopsy of the prostate improves patient quality of life.

10.2.3 Area under ROC curves as predictive measure and incremental prediction improvement for progression

Patients will be categorized at baseline by NCCN risk class ranging from very low risk to intermediate risk and into those who progressed while on the trial and those who did not. Logistic regression will be used to model the association between NCCN risk class and progression using AUC for ROC curves. The incremental benefit of mpMRI, genomic testing and molecular markers compared to NCCN risk alone will be evaluated by comparing AUC using a likelihood ratio test. MRI will be categorized from 1-5 using PIRADS, while genomic test scores and molecular markers can be used as continuous scores or categorized into levels of risk (low/ intermediate/high).

10.3 Exploratory Study Endpoints

10.3.1 Radiomic signatures extracted from MP-MRI prostate exam

The MP-MRI prostate exam is composed of three modalities which represent anatomy, cellularity and blood flow. *The contiguous regions across a modality based on a given criterion are referred to as habitats.* Here we propose a computational method to connect three modalities (T2, DWI and DCE) to find regions of interest that will characterize the prostate beyond the tumor location. The three modalities are registered with MIM Software which provides high level of accuracy of alignment. Two Regions of Interest (ROIs): Prostate and Peripheral Zone (PZ) are manually contoured in MIM. The pixels within the prostate are classified in three groups based on the distribution of the pixel intensity. In our approach, the subpopulation obtained by the categorization will be called high, low and uncertain with respect to the pixel intensities. Prostate biopsies will be placed in reference to the dominant and non-dominant SImTVs identified. The biopsy histopathologic results (i.e., percent core tumor tissue, Gleason score and percent Gleason grade 4) will then inform us on the relevance of the habitat(s).

10.3.2 Genomic signatures extracted from biopsy

493 genes in 16 pathways that include apoptosis, base excision repair, DNA double strand break repair, homologous recombination, mismatch repair, non-

homologous end joining, hypoxia, p53 signaling, prostate cancer signaling, androgen receptor signaling, and cell cycle checkpoint (including G1/S, G2/M & mitotic spindle checkpoint) will be assessed using a 1.4 million feature oligonucleotide microarray by GenomeDx as discussed above. Some of these pathways might also be useful in determining response to treatment and it would be beneficial to understand the timing of gene expression changes occur during the AS period and how such changes relate to alterations in imaging features. We will develop a predictive model including 493 genes in 16 pathways.

10.3.3 Area under ROC curves as predictive measure and incremental prediction improvement for progression on baseline biopsy.

Patients will be categorized at baseline by NCCN risk class ranging from very low risk to intermediate risk and into those who progressed on the baseline biopsy and those who did not. Logistic regression will be used to model the association between NCCN risk class and progression using AUC for ROC curves. The incremental benefit of mpMRI, genomic testing and molecular markers compared to NCCN risk alone will be evaluated by comparing AUC using a likelihood ratio test. MRI will be categorized from 1-5 using PIRADS, while genomic test scores and molecular markers can be used as continuous scores or categorized into levels of risk (low/ intermediate/high).

10.3.4 Serial changes in markers related to progression

mpMRI, genomic scores and molecular marker scores will be assess and associated to the risk of progression on trial using mixed model repeated measures adjusted for relevant demographic and clinical factors.

10.4 Sample size, accrual rate and study duration

We plan to accrue approximately 55 patients per year for the first three years of the study; this assumes a 10% dropout rate. The power (97.3%), is based on 150 patients, using a two-sided binomial test at the 5% significance level to detect an increase in the 24-month cumulative progression rate from 12.5%, as expected for AS historically, to 25% for MRI-AS. Enrollment will occur during the first 3.25 years. Enrollment will be completed at < 3.33 years from the enrollment of the last patient.

10.5 Statistical Analysis

Descriptive statistics will be done for patient demographics and baseline disease characteristics. Counts and percentages will be used to summarize the distribution of categorical variables while median, range, mean and standard deviation will be used for continuous variables. Baseline characteristics will include age, race/ethnicity, T-stage, Gleason score, PSA, PSAD and performance status. Continuous scores will be compared using ANOVA and linear regression controlling for common demographic and clinical variables.

For each scheduled surveillance biopsy session, we will tabulate patients and the following status categories: biopsy indicating progression, biopsy negative for progression, biopsy not performed for progression detected on earlier biopsy, biopsy not performed because patient refused, or biopsy not performed because patient dropped out of study.

Time to event endpoints such as progression and BCR will be analyzed by Kaplan-Meier (KM) or competing risk (CR) methods. Where the Kaplan Meier method is used, point estimates and two-sided 95% confidence intervals for rates will be reported for selected times using Greenwood's variance and the log-log transform method. Median survival time, if attained, will also be reported. We will report the progression rate and the cumulative progression rate for each surveillance biopsy. Taking the third scheduled biopsy at the end of 2 years as illustration, the progression rate at 24 months is the proportion of biopsied patients indicating progression among the total number of biopsied patients over the 24 month period. The 24-month cumulative progression rate is the primary endpoint, which will include those who complete the first three biopsies or have progression from the first or second biopsy. The primary endpoint, 24-month cumulative progression rate, will be estimated and reported with corresponding 95% confidence intervals. Groups will be compared by the log rank test. In addition, we will report and plot the cumulative progression rates in each arm for the four scheduled surveillance biopsies. It is expected that the early difference with historical values and those obtained with MRI-guided biopsies will not be sustained; that is, the 36-month cumulative progression rates will be approximately equal. Similar estimation of time-specific and cumulative rates will be done for Histological progression.

For radiomic signatures, gene signatures, and other biomarkers such as Gleason score and percent positive tissue (PPT), descriptive statistics (counts and percents; median and range; mean and standard distribution) and box plots will be used to summarize the distribution of the variables. In particular, once the habitats are defined, imaging features may be extracted. These features describe characteristics of the image intensity histograms (e.g., high or low intensity), tumor shape (e.g. round or spiculated), texture patterns (e.g. homogeneous or heterogeneous), as well as tumor location. We will consider a two-stage feature selection approach. In the first step, we will filter out "radiomics" variables using standard t-test or ANOVA and in the second step; we will perform random forests to identify radiomics signatures of habitats in relation to risk groups. Genes will be selected using Significance Analysis of Microarray (SAM) in R package, which allow the determination of significantly differentially expressed genes between classes (HP-Risk 1-4) controlling the Benjamini-Hochberg false discovery rate (FDR). The augmented classifiers predictive model will be developed using multivariate ordinal logistic regression. We will use area under the

receiver's operating characteristic curve (AUC) with 10-fold cross-validation approach to evaluate performance of prediction model. Radiomic profiles on multi-parametric MRI that suggest regions of the prostate that are suspicious for more aggressive prostate cancer will be correlated to histopathologic findings from biopsy of these regions. Genomic profiles from tissue cores in each region will be correlated to radiomic profiles and histopathology from that region to see what each adds to improving the ability to predict patients who are likely to harbor more aggressive tumors that would portend poor outcome on active surveillance. Radiomic and genomic profiles from MRI targeted biopsies will be compared to segmental biopsies to see if profiles from targeted biopsies are more informative for risk assessment compared to segmental biopsy using longitudinal analysis approach. We will also assess how these profiles change over time in serial imaging and biopsy and see if/ how these profile changes correlate to change in histopathology. We will also relate genomic and radiomic profiles of the prostate to common serum and urinary markers that have been used predict progression on active surveillance. For continuous outcomes, association between outcome and other covariates will be examined using linear regression model and correlation coefficient. For binary outcomes and time-to-event outcomes, logistic regression and Cox proportional hazards regression will be used, respectively. All tests will be two-sided and statistical significance will be considered when $p<.05$ after multiplicity adjustment.

10.6 Interim monitoring

Since this is a single arm trial, we do not propose any planned interim analysis or early stopping guidelines.

11. INVESTIGATOR'S RESPONSIBILITIES

11.1 Investigator Responsibility/Performance

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects.

The investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

11.2 Confidentiality

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. The investigator will maintain all documents related to this study in strict confidence.

11.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative

conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian.

The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

11.4 Source Documentation and Investigator Files

The investigator will maintain adequate and accurate records to document the conduct of the study and to ensure that study data can be subsequently verified. These documents will be classified into two separate categories: (1) investigator study file and (2) subject clinical source documents that corroborate data collected on the CRF's. Subject clinical source documents would include hospital/clinic patient records; physician's and nurse's notes; original laboratory, radiology, pathology, and special assessment reports; QOL forms, signed informed consent forms. When the CRF or any form is used as the source document, this will be clearly stated in the investigator study file.

At a minimum, the following be documented in source documents:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study)
- Progress notes for each subject visit
- Laboratory test results
- Condition and response of subject upon completion of or early termination from the study
- Quality of Life Surveys
- DCE-MRI tumor size and location generated by the in-house developed software

11.5 Recording and Processing of Data

Data for this study will be entered into electronic CRFs in REDCap A CRF is required for every patient who received any study intervention. The investigator will ensure that the CRF's are accurate, complete, legible and timely. All corrections to study data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. **Do not use "white-out" or obscuring correction tape.**

11.6 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

11.7 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and

standard of ethics.

11.8 Essential documents for the conduct of a clinical trial

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. The following documents will be on file:

- CV's and license of all investigators
- IRB documentation/correspondance
- Documentation of IRB certification

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APPENDIX I: LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	MAX-PC	1Jun2003	The Modified 18-Item Memorial Anxiety Scale for Prostate Cancer
2	EPIC-SF12	Feb2002	The Expanded Prostate Cancer Index Composite + SF12 and AUASI
3	FFQ		Food Frequency Questionnaire (Optional-collected at baseline only)

APPENDIX II: STUDY CALENDAR

Assessment	Screening (within 3 months of enrollment)	Baseline (within 3 months of enrollment unless otherwise specified)	Post-initial study biopsy (+1.5 months)						FU
			6 mo	12mo	18mo	24 mo	30 mo	36 mo	
Diagnostic biopsy (consisting of at least 8 cores)	X (within 18 months of enrollment & reviewed by UM Pathology)								
History & Physical Exam	X		X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	
PSA	X	X (if not done within 6 mos [+1.5 mos] of initial study biopsy)	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[A]
MP-MRI of prostate/pelvis		X (+/- 3months of enrollment)		X		X		X	
MRI-guided prostate biopsy		X		X		X		X	
EPIC-SF12 & MAX-PC		X		X		X		X	
FFQ		X (optional)							
Plasma and serum collection for research (five tubes of blood, if patient has consented)		X		X		X		X	
Urine collection for research (Approximately 50 mL, post prostate massage, if patient has consented and if research funds are available)		X		X		X		X	

[A]: Men undergoing protocol defined progression

- Men undergoing surgery: will be followed every 3-6 months (+/- 2 months) for the first year, every 6-12 months (+/- 3 months) in the second year, and annually (+/- 6 months) thereafter up to 5 years post surgery. Any adjustments to this schedule will be permitted under the discretion of the clinician.
- Men undergoing radiation therapy: follow up serum PSA testing should occur every 6 months (+/- 3 months) for the first 3 years and then annually thereafter (+/- 6 months) for up to 5 years post treatment. If the patient enters a radiation oncology clinical trial then the timing of PSA and other labs will be tmed in accordance with the radiation treatment protocol.

[B] History and Physical Exams will be done at the discretion of the treating physician
[C] Serum PSA will be done preferably every 6 months or at least once a year up to 36 months from the initial biopsy.