TITLE: **PHASE II OPEN LABEL INVESTIGATION OF THE SAFETY AND EFFICACY OF PRE-OPERATIVE PROSTATE ARTERY EMBOLIZATION (PAE) BEFORE RADICAL PROSTATECTOMY IN PROSTATE CANCER PATIENTS.**

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1 Introduction

1.1 Background

Prostate cancer is the most common non-skin cancer diagnosis among men in the United States, and accounted for 29% of all new cancer diagnoses and 9% of cancer deaths among American men in 2012 (1). The American Cancer Society has estimated that 241,740 patients were diagnosed with prostate cancer, and that 28,170 deaths occurred due to the disease in that year (1). The National Cancer Institute further estimates that 238,590 incident cases will be identified in 2013, and that 29,720 deaths will be attributable to prostate cancer (2). Accounting for current screening processes and estimates of incidence trends, 1 in 6 men in the United States will be diagnosed with prostate cancer in their lifetimes, and 1 in 33 will die from the disease (3).

Trends in prostate cancer incidence have closely paralleled the dissemination of screening and diagnostic technologies. The incidence increased dramatically between the mid-1970s and late 1980s as transurethral resection of the prostate (TURP) to treat benign prostatic hypertrophy (BPH) became increasingly common; by the mid-1980s, 50% of prostate cancer diagnoses were incidentally detected as a result of TURP procedures (3). In the early 1990s, implementation of regular PSA screening corresponded with a dramatic increase in prostate cancer incidence, followed by a compensatory decline in the past decade (1,3). Prostate cancer mortality has decreased steadily since the early 1990s, and a cumulative decrease of 39% was observed between 1991 and 2007 (1,3). Between 2001 and 2007, age-adjusted 5-year survival rates were 100% for local and regional prostate cancers, and 29% for distant cancers (1).

Although prostate cancer is exceedingly common in North America and Western Europe, it is substantially less so in Asia and South America (1, 4). This discrepancy is thought to be at least partially due to genetic susceptibility, and familial predisposition is estimated to account for 5-10% of all prostate cancers (1,4). Of note, African Americans experience the highest known incidence of prostate cancer in the world, 241 per 100,000, in contrast to 149 per 100,000 among white American men (1,4).

Advanced age is the most significant risk factor associated with prostate cancer diagnoses: approximately 97% of prostate cancers are diagnosed in men 50 years of age or older, and 60% are diagnosed in men aged 65 and above (1,4). Since 2004, however, prostate cancer incidence among men aged 65 and older has decreased by 2.7% per year, and has remained stable among men under 65 years of age (1).

Although current evidence is minimal, preliminary research has suggested that additional risk factors may affect the risk of prostate cancer diagnosis and death. Numerous observational studies have identified associations between obesity and an increased risk of prostate cancer incidence and mortality (5-7). Occupational exposures have been associated with elevated risk of prostate cancer in firefighters and pesticide applicators (8-10). Dietary characteristics such as

high intake of polyunsaturated fats, calcium, dairy products, and processed meats have all been shown to increase risk of prostate cancer (1,4,11,12).

1.2 Status and Limitations of Current Therapies

Current treatment options for localized prostate cancer include active surveillance, radiation therapy (delivered as external beam radiation or brachytherapy), and radical prostatectomy (1,4,13,14). No statistically significant survival advantage has been reported with any one treatment option compared to the others, and treatment decisions are based on patients' symptomatic burden, comorbidities, stage of disease, and probability of treatment side effects (1, 4, 13-16).

Among patients with high-grade localized prostate cancer, radical prostatectomy is associated with substantial increases in overall survival (17). Over the past decade, robotic–assisted laparoscopic radical prostatectomy (RALRP) has surpassed open retropubic radical prostatectomy (RRP) as the most common surgical treatment for prostate cancer. RALRP now accounts for 80% of all radical prostatectomies performed in the United States (18,19). Although long-term outcomes data following RALRP are limited, available evidence suggests that mortality outcomes following RALRP and RRP are comparable (both are extremely low), and that RALRP may be associated with lower complication rates (19-21). Both perioperative (blood loss and transfusion requirements, postoperative pain, length of hospital stay, and 30-day mortality) and long-term follow-up (potency, continence, quality of life, biochemical recurrence, salvage therapy requirements, and overall and disease-free survival) outcomes associated with RRP have been well characterized (19,22,23).

Although there is no universal definition of a "large" prostate – threshold values in the published literature range from 50 to 100g – there is general consensus that large prostate size poses a therapeutic challenge for both surgeons and radiation oncologists (24-26). Of particular relevance to RALRP, larger prostate size limits mobility and visualization, and have been associated with longer procedure times and increased blood loss during surgery (22,23,27). Patients with larger prostate sizes are also more likely to experience poor postoperative functional outcomes, typically requiring more time to regain continence and achieving poorer sexual function (22,24).

The enhanced dissection capabilities of robotic surgery have the potential to mitigate the increased morbidity associated with operating on large prostate sizes (22). At present however, the technical challenges of operating on large prostates are compounded by poor visualization (22,23,27). Preoperative therapies that reduce prostate size may thus improve intraoperative visualization and consequently lead to reduced procedure times, decreased blood loss, and expedite return to continence and sexual function.

Androgen deprivation therapy (ADT) has been used to reduce prostate size prior to surgery and radiation treatment (28-32). ADT typically requires at least 3 months to achieve a reduction in

prostate size. However, there are significant side effects of treatment including bone and chest pain, rapid weight gain, cough, frequent/painful urination, headache, vision problems, depression and hormonal symptoms such as hot flashes, gynecomastia, testicular atrophy and impotence (28-32).

Although they allow better visualization and mobility, smaller prostates present challenges of their own. Numerous studies have reported statistically significant higher incidences of positive surgical margins in prostrates smaller than 50g (22, 25, 33). Improving intraoperative visibility by reducing blood loss during RALRP may have a positive impact on surgical margin status for smaller prostate sizes.

In this study, we explore a new methodology for volumetric reduction of prostate along with concomitant reduction of vascularity of the prostate gland. Our hypothesis is that the prostate volumetric reduction along with reduced gland vascularity will result in a reduction of blood loss and improved visualization translating into superior surgical outcomes with regard to both short-term morbidity and long-term oncologic and functional outcomes.

1.3 Prostate Artery Embolization (PAE)

Prostate artery embolization (PAE) was first reported in 2000 as a case study of a 76 year-old BPH patient with refractory hematuria (34). The patient underwent embolization with PVA particles, and by 5- and 12-month follow-up visits the patient's prostate was reduced by 52% and 62% of its pre-procedure size, respectively. This decrease in prostate size was accompanied by a decrease in PSA of approximately 90% by the 12-month visit.

The first animal trials of PAE were conducted in 6 beagles with Embosphere® Microspheres (BioSphere Medical, Roissy, France) (35). Immediately following the embolization procedures, retrograde urethrocystography and multiphasic, multislice, contrast-enhanced CT scans were obtained to document distribution of the microspheres and residual perfusion, and to perform 3-dimensional volumetric analysis. CT scans performed 1 month after PAE revealed appropriate distribution of the microspheres in the embolized territory with no evidence of non-targeted embolization. Stenosis of the prostatic urethra was reduced in all animals that received bilateral PAE, and decreased perfusion, cavitary necrosis and prostate volume reduction was evident following unilateral or bilateral PAE.

Sun and colleagues published the first animal study to evaluate the feasibility and safety of trans-arterial embolization (TAE) of the prostate in 16 healthy male pigs (36). All 16 animals underwent selective angiography, and 8 of the 16 then received PAE with Embosphere Microspheres. No significant difference in sexual desire or function was noted between the two groups ($p=0.328$). At necropsy, urinary bladder, ureters, urethra, sigmoid colon, and rectum appeared to be normal in all animals. The prostate volume of the embolization group on histopathology evaluation was significantly decreased compared to the control group ($p<0.001$).

Further studies in canine models yielded similar results. Jeon and colleagues showed that transcatheter arterial embolization with PVA particles can be used safely to reduce prostate volume in hormone-induced canine prostatic hyperplasia (37). In an additional study conducted in 7 dogs by the Sun group, 4 animals demonstrated significant reductions in prostate size while the other 3 appeared to have continued prostate growth (38). Intraprostatic cavities occupying 90-100% of the gland were identified in the 3 dogs that experienced an apparent increase in prostate size, and histopathological examination revealed little to no residual prostate tissue.

The first intentional treatment of BPH with PAE in humans was performed by Carnevale and colleagues (39). Two patients with acute urinary retention due to BPH refractory to selective α-blockers underwent PAE with Embosphere Microspheres under local anesthesia. Both had long-term indwelling catheters and were waiting for surgery. Prior to embolization, both patients underwent digital rectal examination, urodynamic testing, prostate biopsies, transrectal ultrasound (TRUS) and pelvic MRI. Post-PAE the patients underwent repeat urodynamic testing, TRUS and MRI at 30, 90 and 180 day follow up visits.

The first patient, aged 67 with a history of hypertension, had a prostate estimated at 63gm by TRUS and 69gm by MRI with an intravesical prostate protrusion (IPP) of 9mm. Bilateral PAE was performed successfully without complications. The patient experienced mild retropubic pain for 24 hours, which was treated with non-opioid analgesics. He experienced no fever or hematuria and was discharged 3 days after the procedure. The patient was able to urinate spontaneously when his catheter was removed 15 days post PAE. At one month of follow-up his prostate was reduced by 33.3% and 39.1% by TRUS and MRI, respectively, IPP was reduced to 4mm, and post void residual urine volume (PVR) was 8mL. At 3 months post PAE the patient was urinating normally, IPP was unchanged, Post void residual (PVR) was reduced to 5mL, and prostate size reduction was 39.7% and 44.9% by TRUS and MRI, respectively. By 6 months post PAE, PVR was absent and prostate size was similar to that at 3 months.

The second patient was aged 68 years, with a history of atrial fibrillation and hypertension. TRUS showed a prostate of 51g and asymmetric hypertrophy of the right lobe with an IPP of 16mm. Pelvic MRI estimated prostate size at 54g and revealed a discrete 1.1cm avascular cystic node on the right, protruding at the bladder neck. Unilateral PAE of the right prostate arteries was performed because the left arteries could not be visualized.

The patient had no post-PAE symptoms, was discharged 3 days after the procedure, and was able to urinate spontaneously when the catheter was removed 10 days after embolization. At 1 month of follow-up the patient reported occasional nocturia, PVR was measured at 110mL, IPP was unchanged from baseline (at 16mm), and prostate size was reduced 16.9% and 24.1% by TRUS and MRI, respectively. MRI revealed that the avascular nodule had increased to 1.3cm. By 3 months of follow-up the patient was voiding normally, IPP remained unchanged, PVR was reduced to 68mL, prostate size reduction was 25.5% and 27.8% by TRUS and MRI, respectively, and the cyst persisted. The patient's condition was similar at 6 months of follow-up.

For both patients urine stream increased with time, accompanied by reduction of PVR and prostate size shrinkage that was sustained at 6 months. Reduction was greater in the patient who received bilateral embolization.

The same investigators published midterm follow-up data for these 2 patients (40). The prostate of the first patient, who underwent bilateral PAE, continued to decrease in size over time, with a reduction of 53.6% by MRI at 18 month follow up. The patient was continuing to void normally at 30 months post embolization.

The second patient, for whom it had only been possible to perform unilateral PAE, demonstrated an increase in prostate size at 18 months compared to imaging done at the 6 month follow up visit. MRI showed a 12.2% reduction from baseline at 18 months compared to 27.8% at 6 months. PVR had increased to 200 mL and IPP was 17mm. At both the 18- and 30-month follow-up visits the patient was continuing to void normally.

More recently, Carnevale presented outcomes of 40 PAE procedures in 39 patients (41). Eleven patients with acute urinary retention treated with indwelling catheters were enrolled in a Phase I/II study and treated with PAE. This group included the first 2 feasibility cases (Phase I, discussed earlier) plus 9 other patients (Phase II). After completion of this study 28 additional patients who were not managed with indwelling urinary catheters were treated. Evaluations at baseline, 1, 3, 6, and 12 months post procedure were performed by MRI, TRUS, urodynamic testing (baseline and every 12 months), PSA, International Prostate Symptom Score questionnaire (IPSS) and International Index of Erectile Function questionnaire (IIEF). Embolization was performed with Embosphere Microspheres under local anesthesia. Clinical success was achieved in 10 of the 11 phase I/II patients (91%), with patients able to urinate spontaneously after catheter removal and no recurrence of lower urinary tract symptoms (LUTS) during 16-45 months of follow-up.

The single clinical failure was a patient who was embolized twice but still was not able to urinate spontaneously. He was referred for surgery and treated by TURP. Minor adverse events included diarrhea, light rectal bleeding (2-3 tsp), hematuria, anal burning sensation, retropubic pain and dysuria. Only non-opioid analgesics were required for pain management. Among the remaining 38 patients in whom PAE successfully reduced LUTS, one case of bladder ischemia was recognized retrospectively. The patient experienced no pain or urinary retention, but a defect was seen in the bladder wall by MRI at 30 days of follow-up. The ischemic area resolved spontaneously, and was not seen at future MRI surveillance.

Among the first 11 patients, average PSA levels dropped from 10.1ng/ml at baseline to 3.5ng/mL at month 3 ($p=0.003$), and average prostate size reduction was approximately 30% by MRI ($p=0.002$) and TRUS ($p=0.004$). It was not possible to obtain IPSS and IIEF scores at baseline because all patients had indwelling catheters prior to PAE, but these scores improved from first measurement at 30 days post PAE throughout a year of follow-up, with changes in the IPSS

being statistically significant (p=0.04). Average response from the quality of life question of the IPSS went from 6 (terrible) at baseline to 1.1 (pleased) at the 30 day follow-up, and continued at <1 (delighted) from 3-12 months of follow-up. Average changes in urodynamic tests from baseline to 12 months were as follows: urine flow (Qmax) improved from 4.2mL/sec to 10.8mL/sec (p=0.009), detrusor muscle pressure (Pdet) reduced from 85.7 to 51.5 (p=0.007), and PVR decreased from 160.6mL to 60mL (p=0.04).

In the subsequent 28 patients without acute urinary retention or indwelling catheters at time of treatment, average IPSS scores decreased from 20.3 (severe) at baseline to 1.7 (mild) at 90 days of follow-up, and prostate size reduction averaged 26.4% by MRI in the same period. Urodynamic test results were also notable in this group: Qmax increased from an average 8.0ml/sec at baseline to 17.4mL/sec at 90 days. Overall clinical success for all 39 patients, defined as LUTS improvement and ability to urinate spontaneously, was 97.5%.

None of the described studies reported new incidence of erectile dysfunction following PAE (39-41). This leads us to believe that sub-selective embolization of prostatic arteries does not cause embolization of feeding vessels to neurovascular bundles and hence does not lead to impotence or incontinence after the embolization procedure.

To date, no reported study has evaluated selective embolization of prostatic arteries as a pre-operative tool before radical prostatectomy.

The promising results described above led to development of this study, which aims to assess whether reduction in volume and vascularity of the prostate gland by pre-surgery prostate artery embolization improves surgical, functional and oncologic outcomes following robot-assisted laparoscopic radical prostatectomy (RALRP).

2 Study Objectives

2.1 Primary Objective

The primary study objective is to evaluate estimated blood loss (EBL) during robot-assisted laparoscopic radical prostatectomy (RALRP) among patients who receive pre-operative PAE using Embosphere Microspheres and those that do not.

2.2 Secondary Objectives

The key secondary objectives are to assess the outcomes listed below and to compare the results for patients who receive PAE and those that do not:

1. Change in hemoglobin on RALRP post operative day (POD) 1compared to baseline
2. Change in hematocrit on RALRP post operative day (POD) 1 compared to baseline
3. Change in prostate volume between baseline and Visit 3 (6 weeks $\pm$ 2 weeks post PAE) as determined by MRI in patients who receive PAE
4. Blood transfusion requirements during RALRP
5. RALRP duration in minutes
6. Length of hospital stay for RALRP
7. Presence or absence of a complete surgical margin around the entire tumor as determined by histopathology examination post RALRP
8. Biochemical recurrence of prostate cancer as determined by PSA levels post RALRP at 1 year follow up
9. Return to continence post RALRP as assessed by the pad weight test.
10. RALRP related adverse events
11. Erectile function compared to baseline as assessed by the IIEF post RALRP at 1 year follow up.

Additional secondary objectives are to assess outcomes listed below for patients that receive PAE:

12. Change in PSA between baseline and Visit 3 (6 weeks $\pm$ 2 weeks post PAE)
13. PAE related adverse events
14. Histologic changes in the prostate after PAE

3 PAE Patient Population

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria in order to be entered into the study:

1. Patient is 45-79 years old
2. Patient has signed informed consent
3. Patient must have biopsy-proven prostate adenocarcinoma with localized disease
4. Patient must be a candidate for robot-assisted radical prostatectomy (RALRP)
5. Patient has a prostate size >40 grams

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria may not be entered into the study:

1. Active urinary tract infection
2. History of life threatening allergy to iodinated contrast agents
3. Any known condition that limits catheter-based intervention or is a contraindication to embolization (eg shunt or adverse arterial anatomy)
4. Patient is unable to undergo MRI imaging
5. Cardiac condition including congestive heart failure or uncontrolled arrhythmia, uncontrolled diabetes mellitus, significant respiratory disease, or known immunosuppression which required hospitalization within the previous 6 months.
6. Baseline serum creatinine level > 1.8 mg/dL
7. Baseline hemoglobin < 8.0 g/dL
8. Active cystolithiasis or prostatitis
9. History of pelvic irradiation or radical pelvic surgery
10. Known major iliac arterial occlusive disease
11. Confirmed or suspected bladder cancer
12. Urethral strictures, bladder neck contracture, or other bladder or urethral pathology that could limit catheterization
13. Previous rectal surgery (other than hemorrhoidectomy) or history of rectal disease if the therapy or patient evaluation may potentially cause injury to sites of previous rectal surgery, e.g. if a transrectal probe is used
14. Previous pelvic irradiation or radical pelvic surgery
15. Previous prostate surgery, balloon dilatation, stent implantation, laser prostatectomy, hyperthermia, or any other invasive treatment to the prostate
16. Prior transurethral resection of the prostate or other invasive therapies
17. Coagulation disturbances not normalized by medical treatment
18. Acute urinary retention
19. Hypersensitivity to gelatin products
20. Any contraindication to embolization, including intolerance to vessel occlusion procedures, vascular anatomy/blood flow that precludes catheter placement or embolic agent injection, presence/likely onset of vasospasm, presence/likely onset of hemorrhage, severe atheromatous disease, feeding arteries smaller than distal branches, arteriovenous shunt, and collateral vessel pathways endangering normal territories during embolization or pelvic inflammatory disease

4 Study Design

This is a phase 2, prospective, non-randomized, matched-pair, single center study designed to evaluate the safety and efficacy of PAE using Embosphere Microspheres as a pre-operative tool in patients with biopsy-proven adenocarcinoma of the prostate with localized disease. A total of 10 patients with biopsy-proven prostate carcinoma with localized disease will be enrolled in the study to receive pre-prostatectomy PAE, and matched with 10 controls who will not receive pre-prostatectomy PAE, in order to evaluate the study objectives. Patient recruitment is anticipated to take approximately 2 years. Duration of participation is expected to be approximately 15 months from time of enrollment, including a minimum of 12 months follow up. This study will have a stop limit for re-evaluation after two patients with serious adverse events attributed to confirmed or suspected non-target embolization have been identified.

4.1 PAE Patients

The study will consist of a screening period in which patient eligibility will be determined. Consecutive eligible patients will be offered study participation to receive PAE with Embosphere Microspheres pre-RALRP. All patients will provide written informed consent before any study-specific assessments are performed. Patients will complete Expanded Prostate Cancer Index Composite (EPIC) and International Index of Erectile Function (IIEF) questionnaires, and undergo a baseline MRI with contrast to evaluate the size of the prostate gland and stage the cancer. Ten eligible patients will be enrolled and will undergo PAE with Embosphere Microspheres within 4 weeks of baseline imaging. After PAE treatment, patients will return for follow-up visits at 2 weeks ($\pm$ 4 days) and 6 weeks ($\pm$ 2 weeks) post embolization. Post- prostate artery embolization cystoscopy and rectoscopy will be performed during any visit up to 12 months post RALRP, if medically indicated especially if there is pain out of proportion to that which is expected, in all cases of bleeding per the rectum, and in cases of hematuria beyond that which is reasonably expected following prostatectomy At 6 weeks patients will complete the EPIC and IIEF questionnaires, receive a physical exam, and undergo laboratory assessments (including PSA levels), DRE, TRUS and an MRI of the prostate. The patients will undergo RALRP at 10 weeks (±2 weeks) post PAE, and will have first post-op follow up visit at 12 days +/- 7 days for urinary catheter removal. The impact of the embolization procedure on the perioperative, oncologic and functional outcomes will be evaluated at follow-up visits at 3, 6, 9 and 12 months post RALRP. Subsequent annual follow up will be performed as per standard protocol for the treating institution.

4.2 Control Patients

A similar cohort of patients who undergo RALRP without PAE will be treated as a matched control group. The controls will be matched using a 1:1 ratio to PAE treated patients based on AUA risk group. Risk stratification will be as follows, according to AUA guidelines:

- Low risk: Stage T1c to T2a tumors, AND PSA $\leq$ 10ng/mL, AND Gleason score $\leq$ 6

- Intermediate risk: Stage T2b tumors, OR PSA > 10ng/mL but ≤ 20ng/mL, OR Gleason score 7
- High risk: Stage T2c or higher tumors, OR PSA > 20ng/mL, OR Gleason score 8-10

Control patients will be selected after 10 patients for the PAE arm have been identified, such that the first potential control patient who matches the risk score of a PAE patient and agrees to participate in the study is matched to the appropriate member of the PAE arm. Once a match is identified, additional matches for a single PAE patient will not be sought. Because we are matching PAE and control patients based on AUA risk score only, we do not anticipate difficulty in finding a matched control for every PAE patient.

Control patients will sign written informed consent before any study-specific assessments are performed. Patients will complete EPIC and IIEF questionnaires within 12 weeks prior to RALRP, and will undergo MRI as a baseline study. Oncologic and functional outcomes will be evaluated by assessing PSA, EPIC, and IEFF at months 3, 6, 9, and 12 post RALRP, and then annually per standard follow-up protocol for the treating institution.

Safety will be evaluated for PAE patients throughout the study treatment and assessment periods by assessing adverse events, concomitant medications, changes in laboratory values, and findings on physical examination. Safety will be evaluated for Control patients during RALRP and the follow up period by assessing adverse events and concomitant medications.

The patients in both groups will continue to be followed post RALRP according to standard follow up protocol for the treating institution.

5 Treatment and Assessment

A Schedule of Study Events is provided in Appendix A, and a study flow chart is provided in Appendix B.

5.1 Visit -1: Screening/Baseline

PAE Patients (Visit -1 must be within 4 weeks before PAE):

Prior to treatment, patients in the PAE group will have the following assessments performed:

- Obtain Informed Consent
- Medical history, including demographics
- Physical exam, including vital signs, height (baseline only), weight, and genitourinary evaluation
- Recording of current medications
- Recording of concurrent medical conditions
- Prostate Specific Antigen (PSA)
- Urinalysis
    - Specific gravity, protein, glucose, blood, leukocytes, nitrites
- Baseline blood tests
    - Complete blood count (CBC) including red blood count (RBC), white blood count (WBC), platelets, hemoglobin, hematocrit, neutrophils
    - PT (Prothrombin Time)
    - Comprehensive metabolic panel
- Digital rectal exam (DRE) and transrectal ultrasound (TRUS)
- MRI of the prostate
- Expanded Prostate Cancer Index Composite (EPIC) Questionnaire
- International Index of Erectile Function (IIEF) Questionnaire

Patients meeting all the inclusion criteria and none of the exclusion criteria are eligible to receive pre-RALRP PAE.

Control Patients (Visit -1 must be within 12 weeks prior to RALRP):
Prior to RALRP patients in the Control group will have the following assessments performed:

- Obtain Informed Consent
- Medical History, including demographics
- Physical exam, including vital signs, height (baseline only), weight, and genitourinary evaluation
- Assessment that patient is a match for a PAE patient based on:
    - Low, intermediate or high risk prostate cancer based on AUA guidelines
- Recording of concurrent medical conditions
- Recording of current medications
- Prostate Specific Antigen (PSA)
- Urinalysis
    - Specific gravity, protein, glucose, blood, leukocytes, nitrites
- Baseline blood tests
    - Complete blood count (CBC) including red blood count (RBC), white blood count (WBC), platelets, hemoglobin, hematocrit, neutrophils
    - PT (Prothrombin Time)
    - Comprehensive metabolic Panel
- Expanded Prostate Cancer Index Composite (EPIC) Questionnaire
- International Index of Erectile Function (IIEF) Questionnaire
- Digital Rectal Exam (DRE) and TRUS of the prostate
- MRI of the prostate

5.2 Visit 1: PAE Study Treatment (PAE patients only)

PAE study treatment must be within 4 weeks of baseline MRI. PAE with Embosphere Microspheres will be performed following the procedure in Appendix C.

Treatment data recorded will include the following:

- Date of procedure
- Date and time of hospital admission and discharge
- Medications received immediately prior to and during the procedure
- Date and time of urinary catheter insertion and removal (if patient is discharged with catheter in place, catheter removal information will be collected at the first follow up visit)
- Medications at time of discharge
- Adverse events
- Fluoroscopy time and radiation dose

5.3 Visit 2: Post PAE, 2 weeks (± 4 days) from Visit 1 (PAE patients only)

Patients in the PAE group will have the following assessments performed:

- Cystoscopy and proctoscopy will be performed: 1) if medically indicated, especially if there is pain out of proportion to that which is expected, 2) in all cases of bleeding per rectum, and 3) in cases of hematuria beyond that which is reasonably expected following prostatectomy.

5.4 Visit 3: Post PAE, 6 weeks (± 2 weeks) from Visit 1 (PAE patients only)

Patients in the PAE group will have the following assessments performed:

- Physical exam including vital signs, weight, and genitourinary evaluation
- Blood and urine laboratory evaluations as at baseline
- Prostate Specific Antigen (PSA)
- DRE and TRUS
- MRI of the prostate
- Expanded Prostate Cancer Index Composite (EPIC) Questionnaire
- International Index of Erectile Function (IIEF) Questionnaire
- Adverse events
- Concomitant medications

Cystoscopy and proctoscopy will be performed: 1) if medically indicated, especially if there is pain out of proportion to that which is expected, 2) in all cases of bleeding per rectum, and 3) in cases of hematuria beyond that which is reasonably expected following prostatectomy.

5.5 Visit 4: Robot-Assisted Laparoscopic Radical Prostatectomy (RALRP) (10 weeks ± 2 weeks from Visit 1 for PAE patients and within 12 weeks of Visit -1 for Control patients):

Patients in the PAE and Control groups will undergo RALRP and the following parameters will be recorded at the time of surgery and during the post-operative period:

- Date and time of hospital admission and discharge
- Date of procedure
- Time of first incision and closure time
- Estimated blood loss (EBL) during surgery (cc)
- Need for blood transfusion during surgery, including amount of transfusion
- Weight of the prostate (in grams) after its removal
- Pathology: complete/incomplete histological margin
- Pathology: presence of viable tumor
- Date and time of urinary catheter insertion and removal (if patient is discharged with catheter in place, catheter removal information will be collected at the first follow up visit)
- Concomitant medications
- Adverse events
- Complete blood count on day of RALRP prior to surgery
- Hemoglobin and hematocrit 1 day post RALRP

Cystoscopy and proctoscopy will be performed: 1) if medically indicated, especially if there is pain out of proportion to that which is expected, 2) in all cases of bleeding per rectum, and 3) in cases of hematuria beyond that which is reasonably expected following prostatectomy

Patients in the PAE group will also have the following information recorded on pathology evaluation:

- Histology: distribution of embolic particles
- Histology: change in cancer morphology compared to pre-PAE biopsy
- Histology: change in normal prostate morphology compared to pre-PAE biopsy

5.6 Visit 5 (12 days +/- 7 days)

Patients in the PAE group and the Control group will have the following:

- Physical exam including vital signs, weight, and genitourinary evaluation
- Blood and urine laboratory evaluations as at baseline
- Concomitant medications
- Adverse events
- Urinary catheter removal

Cystoscopy and proctoscopy will be performed: 1) if medically indicated, especially if there is pain out of proportion to that which is expected, 2) in all cases of bleeding per rectum, and 3) in cases of hematuria beyond that which is reasonably expected following prostatectomy.**5.7 Visits 6, 7, 8, 9 (3, 6, 9, and 12 months ± 2 weeks for each visit post RALRP)**

Patients in the PAE group will have the following assessments performed:

- Physical exam including vital signs, weight, and genitourinary evaluation
- Prostate Specific Antigen (PSA)
- Expanded Prostate Cancer Index Composite (EPIC) questionnaire
- International Index of Erectile Function (IIEF) questionnaire
- Pad weight test
- Concomitant medications
- Adverse events

Cystoscopy and proctoscopy will be performed: 1) if medically indicated, especially if there is pain out of proportion to that which is expected, 2) in all cases of bleeding per rectum, and 3) in cases of hematuria beyond that which is reasonably expected following prostatectomy.

Patients in the Control group will have the following assessments performed:

- Physical exam including vital signs, weight, and genitourinary evaluation
- Prostate Specific Antigen (PSA)
- Expanded Prostate Cancer Index Composite (EPIC) questionnaire
- International Index of Erectile Function (IIEF) questionnaire
- Pad weight test
- Concomitant medications
- Adverse events

5.8 Annual Long-Term Follow-Up

After the 12 month visit, patients in both groups will continue to be followed according to the standard follow-up protocol for the treating institution.

6 Withdrawal of Patients

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse events
- Refusal of treatment
- Patient request
- Inability to complete study procedures
- Lost to follow up
- Noncompliance with study requirements

If a patient is withdrawn or discontinued from the study, the reason for withdrawal from the study will be recorded in the source documents and on the Study Termination CRF. All patients withdrawn from the study will be encouraged to complete, if possible, all clinical evaluations scheduled for the 12 month visit. All adverse events should be followed as described in Section 7. Patients who are withdrawn from the study for any reason will not be replaced.

7 Adverse Events

7.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject and does not necessarily have to have a causal relationship with the treatment. An AE therefore can be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product or procedure, whether or not considered related to the product or procedure. A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for an SAE as defined below.

Laboratory data are to be collected as stipulated in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (eg, diabetes mellitus instead of hyperglycemia).

Patients should be instructed to report any AE that they experience to the Investigator or Study Coordinator. AEs will be assessed at each visit. AEs occurring during the clinical trial and the protocol-defined 12-month follow-up period should be recorded on the appropriate AE CRF. In order to capture the most potentially relevant safety information during this study, it is important that the Investigator records AE terms accurately and consistently throughout the study. Wherever possible, a specific disease or syndrome should be reported on the CRF rather than the associated individual signs and symptoms. If observed or reported signs or symptoms are not considered a component of a specific disease or syndrome by the Investigator they should be recorded as separate AEs on the CRF.

All adverse events will be assessed for severity, relationship to study treatment, subsequent treatment required for the adverse event, and outcome/resolution. This information will be recorded on the Adverse Event CRF pages.

Adverse events that might occur in this study include, but are not limited to:

- For cystoscopy and PAE:
    - Burning in the urethra, urinary infection, hematuria, pain
- For PAE:
    - Hematospermia, hemorrhage, injury to bladder, including bladder neck, ureteral orifice or trigone, impact on future fertility, vasospasm, rectorrhagia, inguinal hematoma, bladder/bladder neck ischemia and necrosis, bladder resection, allergic reaction to microspheres or contrast agent, radiation exposure, vascular perforation

Serious Adverse Event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- **Results in death.**
- **Is life-threatening**, where life-threatening means that the subject was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- **Requires in-patient hospitalization or prolongation of existing hospitalization**. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- **Results in persistent or significant disability/incapacity,** where disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- **Is a congenital anomaly/birth defect.**
- **Is an important medical event as defined by the Investigator**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

  Clarification should be made between the terms "serious" and "severe" since they are not interchangeable. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject's life or functioning. A severe adverse event does not need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not constitute a SAE, unless the patient would be admitted to the hospital or the event would meet any other of the criteria for seriousness. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Under this protocol, scheduled hospitalizations or elective surgical procedures will not be considered SAEs. Prolongation of a scheduled hospitalization will be considered an SAE as defined above. Complications associated with surgical procedures or study treatments resulting in one of the outcomes above are considered SAEs.

7.2 Adverse Event Reporting

The Investigators are responsible for monitoring the safety of patients who have been enrolled in this study. All AEs considered to be related to study treatment will be followed until the event resolves or has reached a final outcome. Adverse events will be evaluated for severity using NCI CTCAE (Common Toxicity Criteria for Adverse Events) where applicable.

Investigators are required to document all AEs occurring during the study commencing with the date of PAE treatment for patients in the PAE group, and from date of RALRP for the Control group, and including the protocol defined post-treatment follow-up period (21 CFR §312.64[b]), which is defined as 12 months post day of treatment, on the designated CRF pages. AEs that occur following the signature of informed consent but prior to treatment will not be captured. SAEs that occur following the signature of the informed consent but prior to treatment will not be reported.

8 Symptom Assessments

8.1 Expanded Prostate Cancer Index Composite (EPIC) Questionnaire

EPIC is a validated 32-question tool that is self-administered by the patient, and evaluates male urinary function, bowel habits, sexual and hormonal function, and overall satisfaction. A copy of the EPIC questionnaire can be found in Appendix D.

8.2 International Index of Erectile Function (IIEF) Questionnaire

The IIEF is a validated 15-question tool that is self-administered by the patient, and evaluates male sexual function, sexual desire, and intercourse satisfaction. A copy of the IIEF questionnaire can be found in Appendix E.

8.3 Pad Weight Test

Continence will be assessed using the pad weight test. Patients will wear a special pad designed to capture urine leakage for 24 hours. After 24 hours the pad will be weighed to evaluate the amount of urine collected. An increase of <400g indicates continence and an increase of ≥ 400g indicates incontinence.

9 Statistical Analysis

9.1 General Considerations

In general, continuous variables will be summarized as n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized as the number and percentage of patients in each category.

Summary tables will present data for both treatment groups and overall, where appropriate. Data listings will include all data collected on the case report forms (CRFs), as well as any derived variables (study day, age, etc.). Data collected on patients who are screen failures will not be included in any summary tables, listings, or analyses.

For each parameter, baseline is defined as the value reported prior to the study procedure: PAE or RALRP for the PAE group (specified below for each outcome) and RALRP for the Control group. If multiple values were collected prior to the procedure, the value closest to the date/time of the initiation of the procedure will be used as baseline. This may include values collected earlier in the day on the date of procedure.

Any outliers detected during the review of the data will be investigated. If needed the data will be queried and corrected in the database prior to database lock and the generation of the final tables and listings.

All analyses will be performed on a locked database after all patients have completed Visit 7, died or been lost to follow up. Analyses will be performed using SAS® (Statistical Analysis System), version 9.1 or higher.

9.2 Sample Size Calculations

This is a proof of concept study and therefore, formal sample size calculations were not performed. Ten patients will be assigned in a non-randomized sequential manner to the PAE treatment group. Ten patients will also be assigned as matched controls in a 1:1 ratio to PAE treated patients based on risk group as defined in section 4.2. This sample size will provide sufficient data to assess the preliminary safety and efficacy of PAE treatment prior to RALRP.

9.3 Analysis Populations

All PAE patients who are treated with PAE and RALRP, and all Control patients who are treated with RALRP will be included in the Safety Population. This will be the population used for both safety and efficacy analyses.

9.4 Demographic and Baseline Characteristics

Patient characteristics will include the following:

- Patient demographics (age, gender; race, ethnicity)
- Medications
- Concurrent medical conditions
- Baseline PSA
- Prostate size, cancer staging, and Gleason score

9.5 Efficacy Analyses

9.5.1 Primary Efficacy Outcome – Estimated Blood Loss

The primary efficacy outcome is the estimated blood loss (EBL) during RALRP. The amount of EBL will be recorded in ccs, and the data will be summarized separately for both treatment groups, including 95% confidence intervals for the means. Treatment means will be compared using a matched pairs t-test.

9.5.2 Key Secondary Efficacy Outcomes

9.5.2.1 Changes in Hemoglobin

The change in hemoglobin between RALRP post-operative day one (POD1) and baseline (collected on day of RALRP prior to surgery) will be calculated for each patient. Data will be summarized for each time point, as well as the change from baseline, including 95% confidence intervals for the means. Treatment means for the change from baseline will be compared using a matched pairs t-test.

9.5.2.2 Changes in Hematocrit

The change in hematocrit between RALRP post-operative day one (POD1) and baseline (collected on day of RALRP prior to surgery) will be calculated for each patient. Data will be summarized for each time point, as well as the change from baseline, including 95% confidence intervals for the means. Treatment means for the change from baseline will be compared using a matched pairs t-test.

9.5.2.3 Blood transfusions during RALRP

The analysis of the blood transfusion requirements during RALRP will be performed in two ways. First, patients will be classified as requiring a transfusion or not. Proportions will be summarized, including 95% confidence intervals. Treatments will be compared using an exact binomial sign test. A second analysis will compare the amount of blood transfused between the two groups, where patients who did not receive a transfusion will be assigned a value of zero. This data will be summarized for both treatment groups, including 95% confidence intervals for the means. Treatment means will be compared using a matched pairs t-test.

9.5.2.4 RALRP Duration

The duration of the RALRP procedure in minutes will be recorded for each patient. Data will be summarized, including 95% confidence intervals for the means. Treatment means will be compared using a matched pairs t-test.

9.5.2.5 Length of Hospital Stay for RALRP

The length of stay (LOS) associated with the RALRP procedure will be calculated for each patient by counting the number of hours spent in the hospital from the time of admission to the time of discharge. Data will be summarized, including 95% confidence intervals for the means. Treatment means will be compared using a matched pairs t-test.

9.5.2.6 Surgical Margin Assessment

An analysis of the presence or absence of a complete surgical margin around the entire tumor as determined by histopathology examination post RALRP will be performed. Each patient will be classified as having a complete surgical margin or not, (presence or absence) and proportions will be summarized, including 95% confidence intervals. Treatments will be compared using an exact binomial sign test.

9.5.2.7 Biochemical Recurrence of Prostate Cancer

An analysis of the presence or absence of biochemical recurrence of prostate cancer as determined by PSA levels post RALRP at one year follow-up (Visit 9) will be performed. Each patient will be classified as having biochemical recurrence or not, and proportions will be summarized, including 95% confidence intervals. Treatments will be compared using an exact binomial sign test.

9.5.2.8 Return to Continence

An analysis of return to continence post RALRP will be performed using the pad weight test. Patients will be classified as being continent if the weight of the pad increase is insignificant; mild incontinence if the weight of pad increases by <400 grams over 24 hours and as incontinent if the weight of the pad increases by ≥400 grams over 24 hours. The pad weight test will be performed at the following post-RALRP timepoints: 12 days (if urinary catheter is removed), 3 months, 6 months, 9 months, and 12 months. The proportion of continent patients will be calculated for each treatment group at each timepoint. Treatments will be compared using an exact binomial sign test.

9.5.2.9 Erectile Function

The IIEF is a commonly used, validated instrument that consists of 15 items. Five subscales are calculated as follows:

- Erectile Function (items 1, 2, 3, 4, 5, 15)
- Orgasmic Function (items 9, 10)

- Sexual Desire (items 11, 12)
- Intercourse Satisfaction (items 6, 7, 8)
- Overall Satisfaction (items 13, 14)

Each subscale will be summarized separately for both treatment groups for the baseline (defined as pre-PAE for the PAE group and pre-RALRP for the Control group), 3 month, 6 month, 9 month, and 12 month timepoints, including change from baseline. Treatment means for the change from baseline will be compared using a matched pairs t-test.

9.5.3 Additional Secondary Efficacy Outcomes – PAE Patients Only

9.5.3.1 Change in Prostate Volume

An analysis of the change in prostate volume between baseline (pre-PAE) and Visit 3 as determined by MRI will be performed. Each PAE patient will have their prostate volume measured at both timepoints and the change will be calculated. Summary data will be presented for both timepoints and the change from baseline, including 95% confidence intervals.

9.5.3.2 Change in PSA

An analysis of the change in PSA between baseline (pre-PAE) and Visit 3 will be performed. Each PAE patient will have their PSA level measured at both timepoints and the change will be calculated. Summary data will be presented for both timepoints and the change from baseline, including 95% confidence intervals.

9.5.3.2 Histological Changes in Prostate After PAE

Histological changes in the prostate after PAE will be summarized.

9.6 Safety Analyses

9.6.1 Adverse Events

Safety summaries will include the incidence of treatment-emergent adverse events (TEAEs). Treatment-emergent adverse events (TEAEs) are defined as any event that began on or after the date of treatment or worsened in severity or frequency after treatment was initiated. Events worsening in severity should be considered new adverse events. Adverse events recorded on the CRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

- For PAE patients:
    - AEs starting on or after the date of the PAE procedure and up to the date of the RALRP procedure will be considered PAE TEAEs.
    - AEs starting on or after the date of the RALRP procedure will be considered RALRP TEAES

- For Control patients all AEs starting on or after the date of the RALRP procedure will be considered RALRP TEAES.

All TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summaries will present data for both treatment groups by System Organ Class (SOC) and Preferred Term. TEAEs will be evaluated for severity using the CTCAE when available. For the PAE group separate summaries will be generated for PAE TEAEs and RALRP TEAEs.

A summary of the number of reported TEAEs will be generated for both treatment groups. In addition, TEAEs will be summarized based on the number of patients experiencing an event, not the number of AEs experienced. For example, if a patient reports the same AE on 3 separate occasions that patient will be counted only once for that preferred term. Patients reporting more than one AE in a SOC will be counted only once in the SOC total. The denominator used for calculation of the percentages will be the number of patients in the Safety population in each treatment group.

Separate summaries will be generated for the following types of TEAEs for both treatment groups, as appropriate:

- Overall PAE & RALRP TEAEs
- Severe PAE & RALRP TEAEs (grade 3 or higher)
- PAE & RALRP TEAEs related to treatment
- Serious PAE and RALRP TEAEs (SAEs)
- Serious PAE & RALRP TEAEs related to treatment
- PAE & RALRP TEAEs resulting in death

Treatment groups will be compared on RALRP adverse event rates using an exact binomial sign test.

9.6.2 Concomitant Medications

Concomitant medications data will be presented in the data listings.

9.6.3 Physical Examinations

Data from physical exams (scheduled and unscheduled) will be presented in the data listings. All pre-treatment clinically significant findings, as determined by the Investigator, will be reported as concurrent medical conditions. All clinically significant findings on exams performed after treatment (PAE for PAE group and RALRP for Control group) will be reported as adverse events

9.6.4 Vital Signs

Summary statistics for baseline and change from baseline for each assessment timepoint for both treatment groups for the following vital sign parameters will be presented.

- Blood pressure (mmHg)
- Heart Rate (beats per minute)
- Respiration rate (breaths per minute)
- Temperature (°C)

9.6.5 Laboratory Evaluations

Summary statistics for baseline and change from baseline for each assessment timepoint for both treatment groups will be presented for all hematology and chemistry. Urinalysis data will be presented in the data listings only.

10 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be formed consisting of at least 3 individuals with expertise and experience in clinical trials and safety evaluations, but without direct involvement in the conduct of the study. The exact responsibilities, procedures, and guidelines used to manage the DSMB are described in a separate charter.

11 Records and Confidentiality

Each patient will be identified by study ID number and initials only in the trial records. Study data will be recorded on pre-printed CRFs. Monitoring of study data recorded on the CRFs to source documents will be conducted for all patients to ensure accuracy and completeness.

12 Good Clinical Practice and Ethical Considerations

The study will be conducted in accordance with FDA cGCPs, the International Conference on Harmonization (ICH) E6 for Good Clinical Practice (GCP): Consolidated Guidance and the appropriate regulatory requirement(s), and in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. Changes to the protocol potentially affecting safety or efficacy will require written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. Written informed consent will be obtained from the patients prior to any study specific procedures being performed. The informed consent form will be approved by the IRB prior to use. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

The Investigator will be thoroughly familiar with the appropriate use of the treatment procedure as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files will be established at the beginning of the study, maintained for the duration of the trial and retained according to the appropriate regulations.

13 Patient Confidentiality

In order to maintain patient privacy, all CRFs, study reports and communications will identify the patient by the assigned patient ID number and initials only. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

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Appendix A1: Schedule of Study Events for PAE Patients

	Visit -1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6, 7, 8, 9
	Screening / Baseline (within 4 weeks of PAE)	PAE (Day 1)	2 weeks ± 4 days post PAE	6 weeks ± 2 weeks post PAE	RALRP (10 weeks ± 2 weeks post PAE)	12 days (+/-7 days) post RALRP	Months 3, 6, 9, 12 ± 2 weeks post RALRP
Informed Consent	X						
Eligibility Assessment	X						
Demographics	X						
Medical History	X						
Concurrent Medical Conditions	X						
Physical Examination	X			X		X	X
Vital Signs	X			X		X	X
Complete Blood Count (CBC)	X			X	X[2]	X	
Serum Chemistry	X			X		X	
Prostate Specific Antigen (PSA)	X			X			X
Urinalysis	X			X		X	
Digital Rectal Exam (DRE)	X			X			
Transrectal Ultrasound (TRUS)	X			X			
MRI of the Prostate	X			X			
EPIC Questionnaire	X			X			X
IIEF Questionnaire	X			X			X
Pad Weight Test							X
PAE Procedure		X					
Post-PAE Evaluation		X[1]					
Cystoscopy, if medically indicated[5]			X	X	X	X	X
Rectoscopy, if medically indicated[5]			X	X	X	X	X
RALRP Procedure					X		
Post-RALRP Evaluation					X[3]		
Hematocrit & Hemoglobin					X[4]		
Adverse Events		X					
Concomitant Medications	X						
Protocol Violations	X						

[1] Post-PAE evaluation includes duration of hospital stay, fluoroscopy time, and catheterization duration

[2] CBC on day of RALRP must be performed prior to surgery

[3] Post-RALRP includes duration of hospital stay, post treatment catheter duration, and pathologic/histopathology assessment

[4] Hemoglobin and hematocrit will be measured 1 day post RALRP

[5] Cystoscopy and proctoscopy will be performed: 1) if medically indicated, especially if there is pain out of proportion to that which is expected, 2) in all cases of bleeding per rectum, and 3) in cases of hematuria beyond that which is reasonably expected following prostatectomy.

Appendix A2: Schedule of Study Events for Control Patients

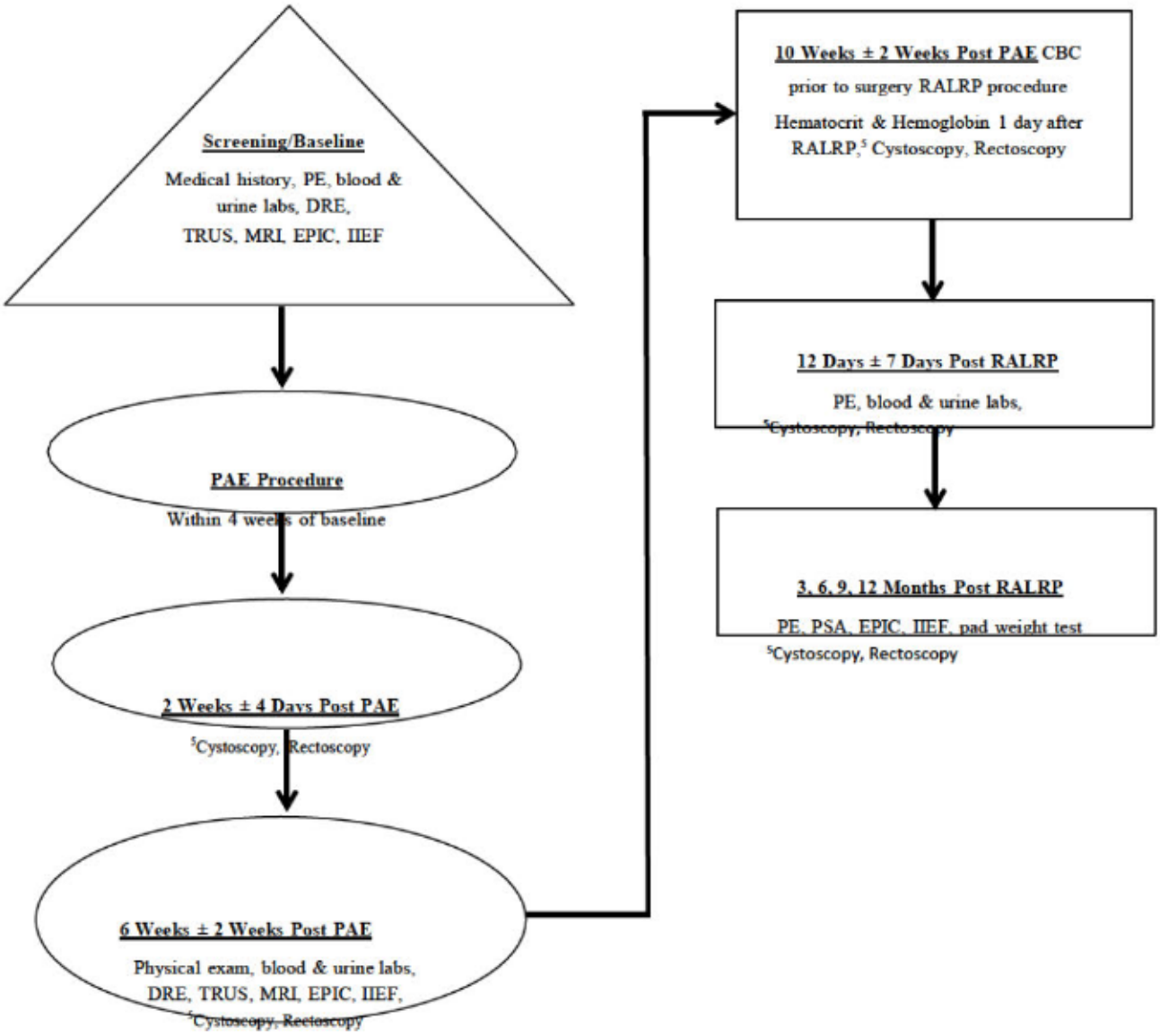
	Visit -1	Visit 4	Visit 5	Visits 6, 7, 8, 9
	Screening/ Baseline	RALRP (12 weeks ± 2 weeks from baseline)	12 days (+/-7 days) post RALRP	Months 3, 6, 9, 12 ± 2 weeks post RALRP
Informed Consent	X			
Matching Assessment	X			
Demographics	X			
Medical History	X			
Concurrent Medical Conditions	X			
Physical Examination	X		X	X
Vital Signs	X		X	X
Complete Blood Count (CBC)	X	X[1]	X	
Serum Chemistry	X		X	
Prostate Specific Antigen (PSA)	X			X
Urinalysis	X		X	
Digital Rectal Exam (DRE)	X			
Transrectal Ultrasound (TRUS)	X			
MRI of the Prostate	X			
EPIC Questionnaire	X			X
IIEF Questionnaire	X			X
Pad Weight Test				X
RALRP Procedure		X		
Post-RALRP Evaluation		X[2]		
Hematocrit & Hemoglobin		X[3]		
Adverse Events		X		
Concomitant Medications	X			
Protocol Violations	X			

[1] CBC on day of RALRP must be performed prior to surgery

[2] Post-RALRP includes duration of hospital stay, post treatment catheter duration, and pathologic/histopathology assessment

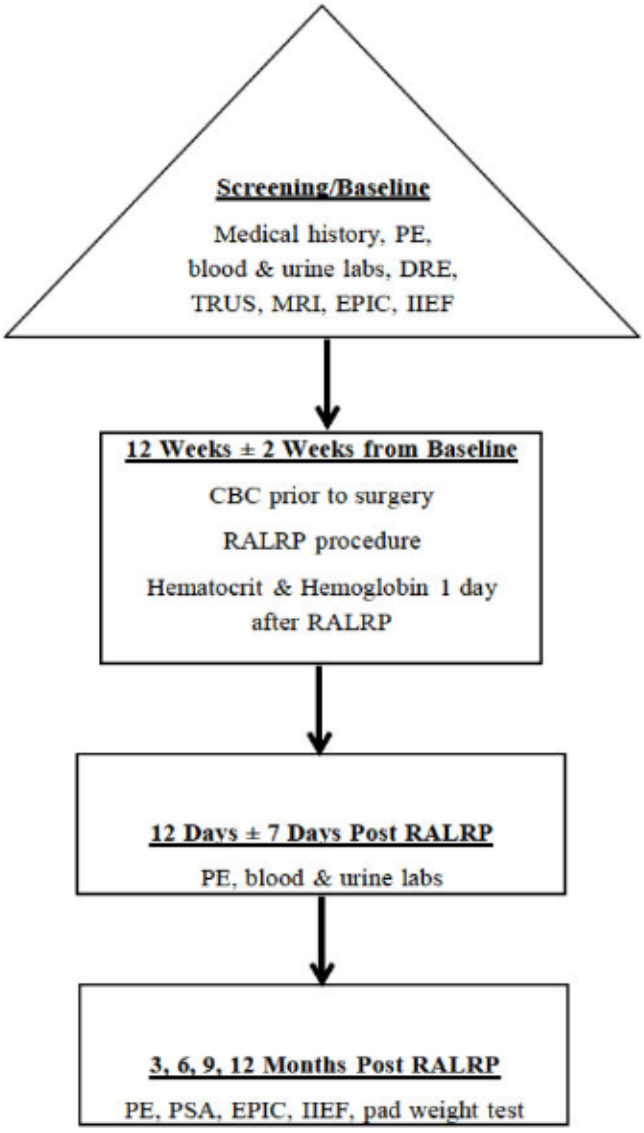
[3] Hemoglobin and hematocrit will be measured 1 day post RALRP

Appendix B1: Study Flow Chart for PAE Patients



[5]Refer to scheduled of Events for Cystoscopy and Rectoscopy Criteria

Appendix B2: Study Flowchart for Control Patients



Appendix C: Technical Protocol for Prostate Artery Embolization

- Administer prophylactic IV antibiotics, based on institution standard of care. Choice of antibiotic and sedation will be at the discretion of the interventional radiologist.
- Prior to embolization, insert a Foley catheter into patient's bladder and fill it with a mixture of 50% contrast agent and 50% saline. This will provide a visual landmark during angiography.
- Local anesthesia should be administered for a trans femoral approach on the side with the best arterial pulse.
- Conduct pelvic angiography with a 5Fr catheter to evaluate aortoiliac vessels and prostate arteries during the arterial and late phases.
- Observe closely for vascular conditions and blood flow that might preclude catheter placement or embolic injection, including severe atheromatous disease, arteriovenous shunt, or presence of feeding arteries that are too small to accept the microspheres. If these conditions are present and a viable feeding artery without these problems cannot be identified, embolization will be conducted on the contralateral side of the prostate. If these conditions are present on both sides of the prostate, do not embolize.
- If appropriate, anastomoses to non-targeted vessels and/or endangering collateral vessel pathways will be closed off with a larger size of embolic particles or embolic coils chosen to be appropriate to the size of the anastomosis or collateral vessel. If anastomoses or endangering collateral vessels cannot be closed off, the embolization will be performed only on the contralateral side of the prostate, if it is not affected by the condition. If anastomosis or endangering collateral vessels affect both sides of the prostate, no embolization will be performed.
- If vasospasm occurs, follow institution standard of care, which could include withdrawing the catheter slightly and waiting, or delivering a small amount of nitroglycerin. If the vasospasm cannot be resolved, conduct the embolization only on the contralateral side of the prostate.
- Ensure that the tip of the micro catheter is at or inside the ostium of the prostate arteries with additional angiography.
- Procedural endpoint is stasis of the terminal branches of the arteries feeding the prostate, while maintaining patency of the main artery branches.
    - Histopathology studies have demonstrated that intraprostatic vessels typically have diameters of approximately 300 µm, so embolic particles of 300–500 µm should be used unless an anatomic anomaly, such as anastomosis to a non-target vessel and/or endangering collateral vessel pathways, is identified. Only particles larger than 300-500 µm should be used to address these anomalies.
- Embolize each of the prostate arteries to stasis without reflux of the mixture to undesired arteries. Stasis is defined as persistence of contrast in the target artery for 5 heartbeats.
- Perform follow up angiography after each vessel is embolized to evaluate prostate devascularization and to identify any remaining collateral blood supply to the prostate. All feeding vessels should be embolized.
- When all apparent vessels feeding one side of the prostate are embolized, embolize the other side using the same technique.
- Once the embolization procedure is complete, follow institution's standard of care for

catheter and introducer removal and closure of femoral puncture.

- It is suggested to leave the Foley catheter in place for at least 6 hours after procedure. Catheter removal time is at the discretion of the interventional radiologist.
- It is suggested that patients be discharged with non-opioid analgesic, NSAID, omeprazole and antibiotics for 7 days.

Potential Risks Associated with PAE:

Adverse events that could occur during or as a result of PAE and associated procedures include, but are not limited to, burning in the urethra, urinary infection, hematuria, pain, hematospermia, hemorrhage, injury/ischemia/necrosis of bladder, including bladder neck, ureteral orifice or trigone, impact on future fertility, vasospasm, rectorrhagia, inguinal hematoma, bladder resection, allergic reaction to microspheres or contrast agent.

See Embosphere Microsphere IFU for complete product information.

Warnings on the IFU include:

- Embosphere Microspheres do not form aggregates, and as a result, penetrate deeper into the vasculature compared to similar size PVA particles.
- Some Embosphere Microspheres may be slightly outside of the labeled range so the physician should carefully select the size of Embosphere Microspheres according to the size of the target vessels at the desired level of occlusion in the vasculature after consideration of the arteriovenous angiographic appearance.
- Serious radiation induced skin injury may occur to the patient due to long periods of fluoroscopic exposure, large patient diameter, angled x-ray projections, and multiple image runs.
- Careful consideration should be given whenever use is contemplated of embolic agents that are smaller in diameter than the resolution capability of your imaging equipment. The presence of arteriovenous anastomoses, branch vessels leading away from the target area or emergent vessels not evident prior to embolization can lead to mistargeted embolization and severe complications.

Appendix D: Expanded Prostate Cancer Index Composite

URINARY FUNCTION

		More than once a day	About once a day	More than once a week	About once a week	Rarely or never	YOUR SCORE
1.	Over the **past 4 weeks**, how often have you leaked urine?	1	2	3	4	5	
2.	Over the **past 4 weeks**, how often have you urinated blood?	1	2	3	4	5	
3.	Over the **past 4 weeks**, how often have you had pain or burning with urination?	1	2	3	4	5	

		No urinary control whatsoever	Frequent dribbling	Occasional dribbling	Total control	YOUR SCORE
4.	Which of the following best describes your urinary control **during the last 4 weeks**?	1	2	3	4	

		None	1 pad per day	2 pads per day	3 or more pads per day	YOUR SCORE
5.	How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?	0	1	2	3	

		No problem	Very small problem	Small problem	Moderate problem	Big problem	YOUR SCORE
6.	How big a problem, if any, has each of the following been for you **during the last 4 weeks**?						
	a. Dripping or leaking urine	0	1	2	3	4	
	b. Pain or burning on urination	0	1	2	3	4	
	c. Bleeding with urination	0	1	2	3s	4	
	d. Weak urine stream or incomplete emptying	0	1	2	3	4	
	e. Waking up to urinate	0	1	2	3	4	

	f. Need to urinate frequently during the day	0	1	2	3	4	
		No problem	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	**YOUR SCORE**
7.	Overall, how big a problem has your urinary function been for you **during the last 4 weeks?**	1	2	3	4	5	

BOWEL HABITS

		More than once a day	**About once a day**	**More than once a week**	**About once a week**	**Rarely or never**	**YOUR SCORE**
8.	How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks?**	1	2	3	4	5	
9.	How often have you had uncontrolled leakage of stool or feces **during the last 4 weeks?**	1	2	3	4	5	

		Never	**Rarely**	**About half the time**	**Usually**	**Always**	**YOUR SCORE**
10.	How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks?**	1	2	3	4	5	
11.	How often have you had bloody stools **during the last 4 weeks?**	1	2	3	4	5	
12.	How often have your bowel movements been painful **during the last 4 weeks?**	1	2	3	4	5	

		Two or less	**Three to four**	**Five or more**	
13.	How many bowel movements have you had on a typical day **during the last 4 weeks?**	1	2	3	

		More than once a day	**About once a day**	**More than once a week**	**About once a week**	**Rarely or never**	**YOUR SCORE**
14.	How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks?**	1	2	3	4	5	

		No problem	Very small problem	Small problem	Moderate problem	Big problem	YOUR SCORE
15.	How big a problem, if any, has each of the following been for you **during the last 4 weeks?**						
	a. Urgency to have a bowel movement	0	1	2	3	4	
	b. Increased frequency of bowel movements	0	1	2	3	4	
	c. Watery bowel movements	0	1	2	3	4	
	d. Losing control of your stools	0	1	2	3	4	
	e. Bloody stools	0	1	2	3	4	
	f. Abdominal/pelvic/rectal pain	0	1	2	3	4	

		No problem	Very small problem	Small problem	Moderate problem	Big problem	YOUR SCORE
16.	Overall, how big a problem have your bowel habits been for you **during the last 4 weeks?**	1	2	3	4	5	

SEXUAL FUNCTION

		Very poor to none	Poor	Fair	Good	Very good	YOUR SCORE
17.	How would you rate each of the following **during the last 4 weeks?**						
	a. Your level of sexual desire	1	2	3	4	5	
	b. Your ability to have an erection	1	2	3	4	5	
	c. Your ability to reach orgasm (climax)?	1	2	3	4	5	

		None at all	Not firm enough for any sexual activity	Firm enough for masturbation and foreplay only	Firm enough for intercourse	YOUR SCORE
18.	How would you describe the usual QUALITY of your erections **during the last 4 weeks?**	1	2	3	4	

		I NEVER had an erection when I wanted one	I had an erection LESS THAN HALF the time I wanted one	I had an erection ABOUT HALF the time I wanted one	I had an erection MORE THAN HALF the time I wanted one	I had an erection WHEN-EVER I wanted one	YOUR SCORE
19.	How would you describe the FREQUENCY of your erections **during the last 4 weeks**?	1	2	3	4	5	

		Never	Less than once a week	About once a week	Several times a week	Daily	YOUR SCORE
20.	How often have you awakened in the morning or night with an erection **during the past 4 weeks**?	1	2	3	4	5	

		Not at all	Less than once a week	About once a week	Several times a week	Daily	YOUR SCORE
21.	**During the last 4 weeks**, how often did you have any sexual activity?	1	2	3	4	5	
22.	**During the last 4 weeks**, how often did you have sexual intercourse?	1	2	3	4	5	

		Very poor	Poor	Fair	Good	Very good	YOUR SCORE
23.	Overall, how would you rate your ability to function sexually **during the last 4 weeks**?	1	2	3	4	5	

		No problem	Very small problem	Small problem	Moderate problem	Big problem	YOUR SCORE
24.	How big a problem **during the last 4 weeks**, if any, has each of the following been for you?						
	a. Your level of sexual desire	0	1	2	3	4	
	b. Your ability to have an erection	0	1	2	3	4	
	c. Your ability to reach an orgasm	0	1	2	3	4	

		No problem	Very small problem	Small problem	Moderate problem	Big problem	YOUR SCORE
25.	Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?	1	2	3	4	5	

HORMONAL FUNCTION

		More than once a day	About once a day	More than once a week	About once a week	Rarely or never	YOUR SCORE
26.	**Over the last 4 weeks**, how often have you experienced hot flashes?	1	2	3	4	5	
27.	How often have you had breast tenderness **during the last 4 weeks**?	1	2	3	4	5	
28.	**During the last 4 weeks**, how often have you felt depressed?	1	2	3	4	5	
29.	**During the last 4 weeks**, how often have you felt a lack of energy?	1	2	3	4	5	

		Gained 10 pounds or more	Gained less than 10 pounds	No change in weight	Lost less than 10 pounds	Lost 10 pounds or more	YOUR SCORE
30.	How much change in your weight have you experienced **during the last 4 weeks**, if any?	1	2	3	4	5	

		No problem	Very small problem	Small problem	Moderate problem	Big problem	YOUR SCORE
31.	How big a problem **during the last 4 weeks**, if any, has each of the following been for you?	0	1	2	3	4	
	a. Hot flashes	0	1	2	3	4	
	b. Breast tenderness/enlargement	0	1	2	3	4	
	c. Loss of body hair	0	1	2	3	4	
	d. Feeling depressed	0	1	2	3	4	

	e. Lack of energy	0	1	2	3	4	
	f. Change in body weight	0	1	2	3	4	
		Extremely dissatisfied	**Dissatisfied**	**Uncertain**	**Satisfied**	**Extremely satisfied**	**YOUR SCORE**
32.	Overall, how satisfied are you with the treatment you received for your prostate cancer?	0	1	2	3	4	

Appendix E: International Index of Erectile Function (IIEF)

INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF) QUESTIONNAIRE							
	0	1	2	3	4	5	YOUR SCORE
1. Over the past 4 weeks, how often were you able to get an erection during sexual activity?	No sexual activity	Almost never/ never	**A few times (much less than half the time)**	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always	
2. Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?	No sexual activity	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always	
3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	Did not attempt intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always	
4. Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did not attempt intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always	
5. Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did not attempt intercourse	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult	
6. Over the past 4 weeks, how many times have you attempted sexual intercourse?	No attempts	One to two attempts	Three to four attempts	Five to six attempts	Seven to ten attempts	Eleven plus attempts	
7. Over the past 4 weeks, when you attempted sexual intercourse, how often was it satisfactory to you?	Did not attempt intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always	
8. Over the past 4 weeks, how much have you enjoyed sexual intercourse?	No intercourse	No enjoyment	Not very enjoyable	Fairly enjoyable	Highly enjoyable	Very highly enjoyable	

INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF) QUESTIONNAIRE							
	0	1	2	3	4	5	YOUR SCORE
9. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you ejaculate?	No sexual stimulation / intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always	
10. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	No sexual stimulation / intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always	
11. Over the past 4 weeks, how often have you felt sexual desire?		Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always	
12. Over the past 4 weeks, How would you rate your level of sexual desire?		Very low / none at all	Low	Moderate	High	Very high	
13. Over the past 4 weeks, how satisfied have you been with your overall sex life?		Very dissatisfied	Moderately dissatisfied	About equally satisfied and dissatisfied	Moderately satisfied	Very satisfied	
14. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?		Very dissatisfied	Moderately dissatisfied	About equally satisfied and dissatisfied	Moderately satisfied	Very satisfied	
15. Over the past 4 weeks, how do you rate your confidence that you could get and keep an erection?		Very low	Low	Moderate	High	Very high	

Appendix F: MRI Protocol for Prostate Imaging

INTRODUCTION

The following acquisition guidelines have been developed

Important Notes

- Regularly scheduled imaging for this study should be acquired consistent with these guidelines.
- Optimization of image acquisition protocols and consistency in the use of the same protocol throughout follow-up examinations are key for proper assessment.
- Imaging data, including raw/original data, shall remain archived for the duration of the study.
- Utilization of dynamic contrast-enhanced magnetic resonance (MR) imaging is mandatory if not medically contraindicated.
- In dynamic MR studies, it is mandatory to obtain high temporal resolution images (at least 12 sequential post-contrast phases, 30-35 seconds each, no interval).
- Signal-to-noise ratio (SNR) should be optimized to the extent possible.

PROSTATE MRI IMAGING

- Scanner type: 1.5 - 3.0 Tesla
- Phased array coil
- No breath-hold required
- T2-weighted imaging: turbo/fast spin echo sequences (TSE, FSE, FRFSE)
- Dynamic pre and post Gd T1-weighted imaging: volumetric interpolated sequences (LAVA, VIBE, THRIVE)
- Parallel imaging (ASSET, I-PAT , SENSE) can be used to reduce sequence time

SCAN 1 (PRE-CONTRAST T2 WEIGHTED)

Patient Orientation	Supine
Scan Locations/Coverage	From tip of seminal vesicles to apex of the prostate
Sequences	T2 axial and sagittal, turbo/fast spin echo sequences (TSE, FSE, FRFSE), without fat suppression,
Slice Thickness:	4 mm (1.5 Tesla) and;
Slice Thickness:	2.5- 3.0 mm (3 Tesla)
TE:	100-120
Skip/gap (slice spacing)	0.0 mm
Scan FOV	36 cm (use no-phase-wrap/phase oversampling to avoid wraparound)
Phase-encoding direction:	Anterior-posterior for axial acquisition, superior-inferior for sagittal acquisition
NEX/NSA:	2-4, maintaining good SNR

SCAN 2 (PRE AND POST CONTRAST, DYNAMIC-PHASE, T1 WEIGHTED)

Patient Orientation	Supine
Scan Locations/Coverage	From tip of seminal vesicles to apex of the prostate
Sequences	T1-weighted imaging: volumetric interpolated (LAVA, VIBE, THRIVE) with fat suppression
Slice Thickness	4 mm (1.5 Tesla), 2.5 mm (3Tesla)
TE:	Minimum
Flip angle:	10-12
Skip/gap (slice spacing)	3D sequence, no gap.
Scan FOV	36 cm (use no-phase-wrap/phase oversampling to avoid wraparound)
Phase-encoding direction:	Anterior-posterior
NEX/NSA:	1, maintaining good SNR
Acquisition timing:	1 pre contrast and 12 - 15 sequential post-contrast phases (no temporal gap), 15-25 seconds each phase, start contrast injection together with the sequence acquisition start. Total sequence time should be 4-6 min.

CONTRAST MEDIA INJECTION:

Gadolinium 0.1 mmol/kg or 0.2 ml/kg (20 ml maximum) should be injected by using a power injector followed by 20 ml saline flush.

Following sequences will be obtained whenever possible:

Prostate Fusion:

3 Plane Localizer

T2 weighted coronal haste Localizer

T2 weighted axial haste Localizer

T2 weighted Turbo spin echo coronal SFOV

T2 weighted Turbo Spin Echo SFOV

T2 weighted Fast Spin Echo axial

T2 weighted Fast Spin Echo Fat Saturation axial

T1 axial VIBE

T1 axial VIBE Fat Saturation pre

T1 ax VIBE Fat Saturation post contrast/dynamic

Prostate Diffusion weighted sequences with b_values of 50_500_1000