

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6659

MR IMAGING AND MR SPECTROSCOPIC IMAGING OF PROSTATE CANCER PRIOR TO  
RADICAL PROSTATECTOMY: A PROSPECTIVE MULTI-INSTITUTIONAL  
CLINICOPATHOLOGICAL STUDY

**PARTIAL PROTOCOL—  
CONTACT ACRIN  
PROTOCOL  
DEVELOPMENT AND  
REGULATORY  
COMPLIANCE FOR A  
COMPLETE PROTOCOL**

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**Version Date:** July 16, 2003

**Activation Date:** June 23, 2003

**Including amendments #1-5**

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## INDEX

### Schema

1.0	Abstract.....	1
2.0	Background and Significance.....	1
3.0	Specific Aims or Objectives.....	8
4.0	Study Overview.....	8
5.0	Patient Selection.....	8
6.0	Site Selection.....	9
7.0	Online Registration System.....	9
8.0	Data Collection and Management.....	10
9.0	Data Collection Forms.....	13
10.0	Pathology and Image Submission.....	13
11.0	Imaging Modalities.....	15
12.0	Statistical Considerations <b>REMOVED FROM WEB VERSION</b> .....	18
13.0	Adverse Event Reporting.....	18
14.0	Institutional Audits.....	19
	References.....	22
	Appendix I: Sample Consent Form.....	25
	Appendix II: Tissue Banking Consent.....	31
	Appendix III: Eligibility Checklist.....	33
	Appendix IV: Protocol Specific Application.....	36
	Appendix V: Diagram of the Prostate.....	37
	Appendix VI: QA Spectroscopy SNR Protocol.....	38
	Appendix VII: Procedure To Set Up the Prostate Exams Under Functool 2.....	42
	Appendix VIII: MRS/Imaging Test Case Submission and Approval Process.....	44

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SCHEMA

R  
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Pre-operative MRI/MRSI  
( $\geq 6$  weeks post-biopsy)



Radical Prostatectomy (*within six months of imaging studies*): Pathologic review to be performed at surgical institution followed by a central review by Dr. Thomas Wheeler

The primary objective of this study is to compare the diagnostic accuracy of MRI versus MRI combined with MRSI (called just MRSI hereafter) for the localization of prostate cancer in patients who are scheduled to have radical prostatectomy surgery. Reference information will be decided from the pathological examination of surgical specimens. Five core institutions will participate with a single reader at each institution; each reader will evaluate every participant on study regardless of institutional affiliation.

**Eligibility:** (See Section 5.0 for details)

- Biopsy-proven adenocarcinoma of the prostate.
- The patient is expected to undergo a radical prostatectomy at the participating institution within six (6) months of MRI/MRSI imaging.
- Interval between biopsy and protocol MRI/MRSI must not be less than six (6) weeks.
- Pathologic specimens from surgery must be provided for central analysis.
- Signed study-specific consent form prior to study entry.
- Consent to the administration of Fleet enema as part of preparatory procedures.
- Encourage retrieval of any outside biopsy reports and slides (medical release form with signature)

**Required Sample Size:** 134 patients to be recruited in seven (7) months

## **1.0 ABSTRACT**

Endorectal MRI is emerging as the most accurate modality for the local imaging of prostate cancer. MR spectroscopic imaging (MRSI) of the prostate depicts the altered metabolism associated with prostate cancer, and is performed in conjunction with standard endorectal MRI. Combined endorectal MRI and MRSI provides an integrated anatomic and metabolic depiction of prostate cancer, and appears superior to endorectal MRI alone. The primary aim of this protocol is to evaluate the accuracy of combined MRI/MRSI performed at multiple institutions in the localization of prostate cancer and its incremental benefit on diagnostic accuracy when compared to MRI alone. One hundred and thirty-four patients with documented prostate cancer who are planned for radical prostatectomy will undergo preoperative combined MRI/MRSI at 1 of 5 institutions. Five independent readers will interpret all scans. Reference information will be derived from central pathological examination of surgical specimens. Secondary objectives include determination of the incremental effect of combined MRI/MRSI on inter-observer agreement when compared to MRI alone and determination of the accuracy of combined MRI/MRSI when compared to other available information on tumor extent derived from digital rectal examination, prostate specific antigen (PSA) level, Gleason score, and Partin nomogram.

## **2.0 BACKGROUND AND SIGNIFICANCE**

### **2.1 Medical and Socioeconomic Importance of Prostate Cancer**

Prostate cancer is the most common non-cutaneous cancer and the second most common cause of cancer death in American men. In 1999, an estimated 179,300 new cases of prostate cancer were diagnosed in the United States, and an estimated 37,000 men died of the disease.<sup>1</sup> For 2001, 198,000 new cases are predicted. The rise in prostate cancer incidence appears partially due to an increase in screening with digital rectal examination (DRE), prostate-specific antigen (PSA), and transrectal ultrasonography (TRUS) with biopsy.<sup>2-5</sup> However, the age-adjusted mortality rose an estimated 39% from 1985 to 1997,<sup>5</sup> suggesting both a true increase in clinically important disease in addition to an increase in diagnostic sensitivity. Combined with an aging population, these factors have made prostate cancer a major medical and socioeconomic problem.

## 2.2 Staging of Prostate Cancer

Both the TNM and Jewett-Whitmore staging systems are in common usage, and are based on the local, nodal, and distant extent of disease (AJCC, Jewett manual).<sup>6,7</sup>

The staging systems are summarized below:

Jewett-Whitmore	TNM	Description
A	I (T1N0M0)	Organ-confined tumor. Clinically and radiologically inapparent.
B	II (T2N0M0)	Organ-confined tumor. Clinically or radiologically apparent. T2A: Unilateral T2B: Bilateral
C	III (T3N0M0)	Extracapsular extension, or seminal vesicle invasion. T3A: Extracapsular extension T3B: Seminal vesicle invasion
D*	IV (T4, N1, or M1)	Distant spread. T4: Invasion of the bladder, external sphincter or rectum N1: Regional nodal metastases M1A: Non-regional nodal metastases M1B: Bony metastases M1C: Other distant metastases

\*The Jewett-Whitmore classification divides stage D into D1 (microscopic nodal metastases only) and D2 (all other forms of distant spread).

## 2.3 Importance and Limitations of Staging Prostate Process

**2.3.1** For prostate cancer, tumor stage is critical in predicting prognosis and planning therapy. Organ-confined tumors (Jewett-Whitmore stages A and B, TNM stages I and II) have a relatively good prognosis and may be treated by surgery or radiotherapy. Conversely, tumors that have spread outside the gland (Jewett-Whitmore stages C and D, TNM stages III and IV) have a poorer prognosis and are generally not treated surgically.<sup>8</sup>

**2.3.2** Prognosis is closely related to stage. Despite the prevalence of prostate cancer, good prognostic studies are lacking. Because the mortality from unrelated causes is high in elderly men with prostate cancer, available studies often describe outcome only for highly selected patients undergoing specific treatment; follow-up of 10 to 15 years is required for meaningful long-term evaluation of organ-confined disease. Representative available data are summarized in the table below:<sup>9-13</sup>

Jewett-Whitmore	TNM	2-year mortality	5-year disease-specific mortality	10-year disease-specific mortality
A and B	I/II	*	10%	9-22%
C	III	*	18%	40%
D1	IV	*	34%	*
D2	IV	42%	*	*

**2.3.3** Surgery and radiation therapy are the mainstays of prostate cancer treatment. Nevertheless, clinical management remains controversial, in part due to the limitations of staging. Unlike many other types of cancer, which behave aggressively and are more rapidly and uniformly fatal if left untreated, the natural history of prostate cancer covers the wide spectrum of biologic activity. Some cancers are small, well differentiated, and unlikely ever to cause clinical disease, while others are larger, poorly differentiated, and likely to metastasize, leading to death. Autopsy and cystoprostatectomy specimen studies have shown that 30-46% of men older than age 50 have microscopic prostate cancer, yet less than 20% of men will develop clinically evident disease in their lifetime. Therefore, some patients with newly diagnosed prostate cancer will require some form of therapy, while others have indolent cancers not requiring aggressive treatment. Since most cancers (>85%) found by PSA screening programs represent clinically significant disease (5-8) and are detected at an earlier stage than in the past, they are more likely to be suitable for definitive therapy. The challenge is to correctly distinguish patients who need treatment from those who do not. While currently used methods for evaluating prostate cancer (digital rectal exam, PSA, Gleason score) can generally identify very aggressive or very indolent cancers, most patients fall into the intermediate category (PSA >10 to 20 ng/ml and an intermediate Gleason score of 5 to 7), where the probability of extracapsular extension is between 13% and 58% and it is difficult to distinguish with certainty those cancers likely to progress from those that can be safely observed. Thus, there is a need for tools that can more accurately assess risk and determine which patients can be safely observed and which require aggressive therapy, and to determine what type and intensity of treatment would be most appropriate for individual patients. Accurate risk stratification will also allow different treatment strategies to be directly compared in patient populations of similar disease severity, improving the quality of data derived from clinical trials of prostate cancer treatment.

**2.3.4** New and emerging minimally invasive treatments for prostate cancer, such as interstitial brachytherapy, cryosurgery, laser therapy, and high frequency focused ultrasound as well as watchful waiting require an extension of diagnostic imaging beyond staging to provide more precise information about tumor size and location within the gland so that treatment can be focused in areas of known cancer while sparing normal prostate tissue. The inability of DRE, initial PSA, Gleason score, sextant biopsy results, and MRI alone or in combination, to accurately localize clinically significant cancer in the prostate gland and assess pathologic stage limits prediction of prognosis and treatment planning. This has led to a growing interest in the role of tumor volume in prostate cancer assessment.

## **2.4 Traditional Methods of Evaluating Prostate Cancer**

Traditional methods of detecting prostate cancer and evaluating tumor extent include digital rectal examination, prostatic specific antigen level assay, sextant biopsy, transrectal ultrasound, and nomograms that combine these variables, such as Partin tables. All of these techniques may be used for both diagnosis and staging, with varying levels of accuracy.

**2.4.1** *Digital Rectal Examination (DRE)* was historically the primary test for the early diagnosis for prostate cancer, but has a sensitivity of only 30% and a specificity of 40%<sup>14</sup> for the diagnosis of organ-confined disease. In addition to limited accuracy in the diagnosis of early disease, DRE is also inaccurate in staging; 47% of patients with apparently organ-confined disease on DRE have extracapsular extension pathologically and 33% of patients with apparent extracapsular extension on DRE have organ-confined disease pathologically.<sup>15</sup>

**2.4.2** *Prostatic Specific Antigen (PSA)* is an enzyme secreted only by the epithelial cells of the prostate that most likely functions by liquefying the ejaculate.<sup>16</sup> PSA levels are elevated in prostate cancer and benign prostatic hyperplasia.<sup>17</sup> The normal serum PSA level is under 4

ng/ml. A PSA level of 4 to 10 ng/ml is considered borderline for abnormality; 20% of such patients have prostate cancer. Most patients with a PSA greater than 10 ng/l have prostate cancer. The identification of PSA in the 1980s revolutionized the diagnosis and surveillance of prostate cancer and has resulted in many more cases being detected at an earlier stage. In addition to diagnosis, PSA level is also correlated with pathologic stage. In a Mayo Clinic study of 945 radical prostatectomies, the percentage of patients with extraprostatic disease was related to PSA level: <sup>18</sup>

PSA (ng/ml)	< 2	2-10	10-25	25-50	> 50
<b>Extraprostatic disease</b>	30%	47%	67%	83%	93%

In another study, (25) 75% of the men with a serum PSA value of less than 4.0 ng/ml had organ-confined disease. In men with PSA between 4.0 and 10.0 ng/ml, only 53% had organ-confined disease. Only two men with PSA levels greater than 30 ng/ml had organ-confined disease.

Several refinements to the standard PSA measurement have been introduced to try and increase the accuracy of prostate-specific cancer identification. These refinements include PSA density (PSA divided by the prostate volume), PSA transition zone density (PSA divided by the volume of the transition zone), free to total PSA ratio (the fraction of unbound serum PSA), and PSA velocity (the rate of change in PSA over time). These new refinements have not yet entered into widespread clinical practice.

### 2.4.3 Sextant Biopsy

Non-targeted systematic sextant biopsies are performed by taking three cores equally spaced between the base and apex in the mid-parasagittal plane of each side of the prostate.<sup>16</sup> The biopsy needle is positioned under transrectal ultrasound (TRUS) guidance so that the full thickness of the peripheral zone is included. TRUS-guided sextant biopsy is the current standard of reference for the diagnosis of prostate cancer in a patient who has an abnormal DRE or PSA. Nonetheless, sextant biopsy has some limitations. Approximately 20% of patients with an elevated PSA and a negative initial biopsy will have a subsequent positive biopsy, presumably due to sampling error.<sup>19</sup> Additionally, the intraglandular localization of prostate cancer is often incorrect on sextant biopsy, which likely represents a combination of sampling error and technical problems in localizing the specimen site during biopsy.<sup>20-22</sup> Another drawback of sextant biopsy is that the true Gleason score may not be represented in the cores obtained due to sampling error. In a study of 72 patients who underwent sextant biopsy and radical prostatectomy, the biopsy and specimen Gleason scores matched in only 47% of cases. In 38%, the final grade was higher, and in 15% the final stage was lower.<sup>23</sup> In an effort to improve the results from biopsy, several investigators have advocated the routine use of up to twelve biopsies.<sup>24</sup>

### 2.4.4 Transrectal Ultrasound (TRUS)

Prostate cancer appears as a hypoechoic lesion in the peripheral zone on transrectal ultrasound (TRUS). However, many cancers are undetectable, and are presumably isoechoic. In the American Cancer Society prostate screening study of 2427 men, a total of 56 cancers were detected.<sup>25</sup> Of these, TRUS detected 43 (77%), indicating the limited sensitivity of the technique. In addition, TRUS is not specific. In this same study, 330 of 2427 men had a suspicious ultrasound, but only 56 of these men had prostate cancer. For these reasons, current practice is to perform targeted biopsies of any palpable or sonographically suspicious nodules, and non-targeted systematic sextant biopsy. Early studies with color Doppler sonography suggest that this may improve the capability of

identifying some nonpalpable hypervascular tumors.<sup>26</sup> TRUS has also been used for local staging of prostate cancer. Sonographic signs of T3 disease include bulging or irregularity of the prostate margin, asymmetry of the seminal vesicles, and obliteration of the ejaculatory duct or the fat plane between the seminal vesicles and the prostate.<sup>27</sup> However, despite initial enthusiasm, the results have been disappointing. In a multi-institutional prospective study, TRUS was no better than DRE in local staging.<sup>27</sup> Receiver operating characteristic (ROC) analysis showed no difference between the areas under the curve for TRUS (0.69) and DRE (0.72).

#### **2.4.5** Partin Tables

Because of the limited accuracy of any single traditional technique in the staging of prostate cancer, a number of studies have examined the utility of combining information derived from different techniques. One of the most frequently cited studies used the combination of clinical stage, Gleason score, and PSA level to assign probabilities for extracapsular extension, seminal vesicle invasion, and regional node metastases.<sup>15</sup> The tabulated risk assignments in these studies are popularly known as the Partin tables. Unfortunately, many patients have an assigned risk for extracapsular extension that is in the intermediate range, and the Partin tables are of limited practical benefit in choosing treatment.

### **2.5** MRI of Prostate Cancer

Limitations in evaluating the location, volume, local extent of disease, and the risk of progression by traditional methods of assessment are major roadblocks to improving the management of patients with prostate cancer. As a result, there is considerable interest in other assessment modalities, particularly MRI. MRI findings in prostate cancer were first described in the early 1980s.<sup>28</sup> Later studies established that prostate cancer is characterized by low T2 signal intensity in the normally high T2 signal intensity peripheral zone.<sup>29</sup> However, the presence of reduced T2 signal intensity in the peripheral zone is of limited sensitivity, presumably because some tumors are isointense. The finding is also of limited specificity, because there are other causes of low T2 signal intensity in the peripheral zone such as hemorrhage, prostatitis, scarring, radiotherapy, cryosurgery, and hormonal therapy. Because MRI is generally reserved as a staging study in patients with biopsy-proven prostate cancer, the accuracy of MRI in the diagnosis of prostate cancer is unknown. From the inception of prostate MRI, the hope has been that the modality would be more accurate in local staging and detection of extraprostatic disease. Disappointingly, an early multi-institutional study examining the detection of extracapsular extension showed no difference in the area under the ROC curve for MRI (0.67) compared to transrectal ultrasound (0.62).<sup>30</sup> This study was published in 1990 and had several major limitations: surface or endorectal coils were not used, MRI technology and pulse sequences employed are now obsolete, and imaging criteria for the diagnosis of extracapsular extension were not explicitly stated. Since that time, single institution studies have tended to show higher overall staging accuracy for prostate MRI (86 to 88%).<sup>31,32</sup> Multivariate feature analysis has shown that the MR imaging findings that are most predictive of extracapsular extension are a focal irregular capsular bulge, asymmetry or invasion of the neurovascular bundles, and obliteration of the rectoprostatic angle.<sup>33</sup>

### **2.6** Current Limitations in the Assessment of Prostate Cancer by MRI

To date, the primary role of MRI for prostate cancer has been to detect extracapsular spread of tumor. However, the inherent limitations in sensitivity, specificity, and interobserver variability for the detection of prostate cancer by MRI continues to constrain the widespread use of this technology. In one study, 21 palpable tumors were correctly identified in a study population of 53 patients, but focal abnormalities were incorrectly labeled as tumor in a



further 16 patients, resulting in a specificity of only 48%. As a result, MR imaging is not in widespread use for staging prostate cancer. In 1995, the consensus workshop on screening and global strategy for prostate cancer did not recommend MRI as a staging tool.<sup>34</sup> Another concern is that while microscopic extracapsular extension is considered by many to be as prognostically important as more established extracapsular extension,<sup>35</sup> “it is beyond the capability of any current imaging study to detect microscopic local tumor extension.”<sup>27</sup> Even with further technological developments, it seems unlikely that MRI alone can provide an assessment of prostate cancer stage that is of sufficient accuracy and reproducibility to achieve widespread clinical use.

## **2.7 Importance of Tumor Volume**

- 2.7.1** The importance of detecting extracapsular extension of prostate cancer is being challenged on the basis of reports of long-term survival (10-year survival, 60-67%) after surgery in men with extracapsular disease. Most urologists are unwilling to deny patients potentially curable resections even if the MR suggests extracapsular spread. Despite significant advances during the past 25 years that have greatly improved the ability to detect and stage malignancies, imaging has had a minor role in the care of prostate cancer. For prostate cancer imaging to advance, we must look beyond contemporary strategies.
- 2.7.2** A difference between the 40% lifetime risk of autopsy prostate cancer and the 8% lifetime risk of clinical prostate cancer lead to an analysis of the volume distribution of autopsy cancer, which showed that microscopic tumors were the most frequent, with an exponential decline in tumor frequency at increasing tumor volumes. This suggests that small indolent prostate cancers are common, and that only the larger tumors are of clinical significance. Furthermore, smaller tumors tend to be better differentiated, with lower Gleason scores, indicating that prostate cancer generally begins as a small well differentiated tumor, and become less differentiated and more aggressive with the passage of time and with increasing volume. Several studies support the concept of tumor volume as a prognostic indicator.
- 2.7.3** In one study, the prostate was examined histologically in 139 patients without known prostate cancer undergoing radical cystoprostatectomy for bladder cancer. Prostate cancer was found in 55 (40%) of the specimens, but only 8% of cases had a tumor volume of over 0.5 ml. The study concluded that only tumors greater than 0.5 ml are clinically important.
- 2.7.4** Stamey et al noted that the prevalence of extracapsular extension was only 18% in tumors with volume less than 3 cm<sup>3</sup> as compared with 79% in tumors with volume more than 3 cm<sup>3</sup>.
- 2.7.5** In a multivariate analysis of 379 men undergoing radical prostatectomy for peripheral zone tumors, cancer volume was independently predictive of disease-recurrence at a median follow-up of 5.7 years. The recurrence rate was 14% for a cancer volume of 0.5 to 2 ml, 39% for 2 to 6 ml, 67% for 6 to 12 ml, and 97% for over 12 ml. In this study the mean cancer volume was 4.7 ml. Capsular penetration and baseline PSA level were not independently predictive of recurrence.
- 2.7.6** The superiority of tumor volume over PSA as a predictor of pathologic stage was confirmed in another multivariate analysis of 104 prostatectomy specimens.
- 2.7.7** Such observations suggest radiological measurement of prostate cancer volume might contribute to the prediction of prognosis, and provide information on tumor extent that does not depend on the imaging detection of microscopic extracapsular extension. Previous attempts to estimate cancer volume preoperatively with sextant biopsy, transrectal ultrasound, or MR imaging have been disappointing.

## **2.8 Development of MRSI**

Over the last decade, in-vivo Magnetic Resonance Spectroscopy (MRS) has emerged as a valuable technique for evaluating tissue levels of various metabolites. This facilitates lesion characterization, such as the differentiation of benign and malignant tissue, and also helps in assessing disease progression and treatment response. MRS exploits differences in chemical shift between molecules. Chemical shift refers to the change in the Larmor frequency of a given nucleus when bound in different molecules due to the magnetic shielding effects of the orbiting electrons. In routine MRI, only protons from fat and water molecules contribute to tissue signal, because the contribution from nuclei in other molecules is so tiny. Using MRS, the signal from these other molecules can be detected, allowing non-invasive in-vivo assessment of the level of various metabolites. MRS may be performed with various nuclei including hydrogen (proton), phosphorus, and carbon. Proton spectroscopy ( $^1\text{H}$  MRS) is the most widely used technique because it can be implemented with standard MR systems and **coils**.

Clinically, this technique has been used most commonly in the brain.<sup>36</sup>

## **2.9 Technique of MRSI**

The two widely used techniques in localized  $^1\text{H}$  MRS are Single Voxel Spectroscopy (SVS) and MR spectroscopic imaging (MRSI). The SVS technique measures metabolites from a localized single volume that is typically  $5\text{ cm}^3$  or larger in about 5 minutes. Smaller volumes are difficult to measure with this technique because of signal-to-noise limitations. MRSI is a multi-volume technique that provides spectra from a 2D or 3D grid of contiguous volumes, allowing metabolic information to be obtained from a given voxel or anatomic area. The combination of MRSI and conventional MRI can therefore be used to perform a combined metabolic and morphologic evaluation as part of a single study. For evaluation of prostate cancer, MRSI requires good spatial resolution ( $1\text{ cm}^3$  or less), high S/N, efficient water and fat suppression techniques, and a short TE for optimum detection of short T2 metabolites.

## **2.10 MRSI Findings in Prostate Cancer**

Preliminary studies suggest that MRSI might provide information that could be used to increase staging accuracy for less experienced readers and thereby reduce inter-observer variability, improve the noninvasive assessment of tumor location, and provide guidance for biopsies and directed cancer therapies. Information obtained with MRSI may provide new insights into tumor aggressiveness, which may lead to improved risk assessment in patients with prostate cancer. In one study, MRSI was used to stratify the study group on the basis of relative tumor extent, and the risk of extracapsular extension in each group was determined. Patients with the least extensive tumor at MRSI ( $<1$  cancer voxel per section) were found to have only a 6% risk of extracapsular extension, whereas patients with the most extensive tumor ( $>4$  cancer voxels per section) had an 80% risk of non-organ confined disease.<sup>32</sup> These results support the use of 3D MRSI as a predictor of extracapsular extension and tumor aggressiveness.

## **2.11 Need for Multi-Institutional Studies of MRI/MRSI of Prostate Cancer**

As promising as this may seem, there are only a few academic medical centers worldwide that have any experience with the *in vivo* prostate MRSI. Only the groups working at the University of California, San Francisco, and Memorial Sloan-Kettering, New York, have performed diagnostic accuracy and preliminary treatment impact type studies that characterize the “discovery” and early “diffusion” stages in the emergence of an imaging method. In the next stage, the technique must be implemented and validated at multiple sites.

### **3.0 SPECIFIC AIMS OR OBJECTIVES**

#### **3.1 Main Objectives**

In this interdisciplinary ACRIN protocol, patients with documented prostate cancer who are planned for radical prostatectomy will undergo preoperative MRI and MRSI. Reference information will be derived from pathological examination of surgical specimens. The main objectives of the study are summarized in the following aims. The first objective is primary and the second and third objectives are secondary:

- 3.1.1** To evaluate the accuracy of MRSI performed at multiple institutions in the localization of prostate cancer and its incremental benefit on diagnostic accuracy when compared to MRI
- 3.1.2** To determine the incremental benefit for inter-observer agreement of MRSI when compared to MRI alone in the localization of prostate cancer.
- 3.1.3** To evaluate the accuracy of combined MRSI when compared to other available information on tumor extent derived from digital rectal examination, prostate specific antigen (PSA) level, Gleason score, and Partin nomogram.

#### **3.2 Hypotheses**

- 3.2.1** MRSI can be performed at multiple institutions and provide an accurate assessment of prostate cancer localization.
- 3.2.2** The addition of MRSI to MRI will result in improved tumor localization with greater interobserver agreement when compared to MRI alone.
- 3.2.3** MRSI will add clinically useful information to the current methods of preoperative assessment, including digital rectal examination, PSA level, Gleason score, and Partin nomogram.

### **4.0 STUDY OVERVIEW**

The study design is a prospective multi-institutional clinicopathologic study.

### **5.0 PATIENT SELECTION**

#### **5.1 Inclusion Criteria**

- 5.1.1** Biopsy-proven adenocarcinoma of the prostate. Biopsy may be performed outside of participating institution. Official report of biopsy from outside site. (Note: detailed results of transrectal ultrasound guided biopsy are not required since it is commonly performed at outside institutions with inconsistent techniques and protocols.)
- 5.1.2** Sites must submit written documentation that it is anticipated that the patient will undergo radical prostatectomy at the participating institution within six months of MRI/MRSI.
- 5.1.3** The interval between biopsy and protocol MRI/MRSI must not be less than 6 weeks.
- 5.1.4** Pathologic specimens from radical prostatectomy must be provided for central analysis.
- 5.1.5** Patients will sign a study-specific consent prior to study entry.

#### **5.2 Exclusion Criteria**

- 5.2.1** Patient who because of age, general medical or psychiatric condition, or physiologic status unrelated to the presence of prostate cancer cannot give valid informed consent.
- 5.2.2** Patient unwilling or unable to undergo MRI/MRSI, including patients with contra-indications to MRI such as the presence of cardiac pacemakers or non-compatible intracranial vascular clips.
- 5.2.3** Patients who cannot tolerate or have contra-indications to endorectal coil insertion; for example, patients who have had a prior abdominoperineal resection of the rectum or have Crohn's disease.
- 5.2.4** Patients with an allergic reaction to latex.
- 5.2.5** Cryosurgery, surgery for prostate cancer including TURP, prostatic radiotherapy, including

radiotherapy for rectal cancer, androgen deprivation therapy, rectal surgery, or complementary alternative medicine prior to radical prostatectomy.

- 5.2.6 Metallic hip implant or any other metallic implant or device that might distort local magnetic field and compromise quality of MRI/MRSI.
- 5.2.7 Radical prostatectomy not planned to be performed within six (6) months of protocol MRI/MRSI.
- 5.2.8 Patients who have undergone BCG for bladder cancer.

## **6.0 SITE SELECTION**

### **6.1 Institution Requirements**

- 6.1.1 Site must submit a protocol-specific application to ACRIN.
- 6.1.2 The site needs to have a proven record of 50 radical prostatectomies per year.
- 6.1.3 1.5T MRI scanner with hardware and software that can meet protocol requirements for MRI and 3D MRSI. In this first stage of what is anticipated to be a multi-stage study, only GE scanners will qualify since GE is the only vendor with the documented capability of performing protocol data acquisition and analysis at the time that the protocol was developed and initiated. In addition, in this early state of technology diffusion, it is desirable to limit the number of participating sites, to assure technical uniformity, and to complete the study expeditiously. These goals are best accomplished with a single vendor's equipment. If the hypothesis of this limited "proof of concept" study is proven, subsequent studies will be open to all sites and equipment vendors that meet participation criteria.
- 6.1.4 Demonstrated capability to perform protocol MRI and MRSI.
- 6.1.5 Written documentation of ability to provide appropriate pathological specimens for central analysis from the participating pathologist, including sectioning of the entire prostate and lower seminal vesicles.
- 6.1.6 Designated radiologist, urologic surgeon, and pathologist in the institution with signed documentation of willingness and commitment to participate.
- 6.1.7 Participation of a research associate (RA) and MRI technologist.
- 6.1.8 All participating sites must have Internet access.

### **6.2 IRB Approval and Informed Consent**

All institutions must have study-specific IRB approval. RAs must follow OHRP-approved consent procedures, as well as those set by the Institutional Review Board (IRB) at the institution. A copy of IRB approval and the sample institutional study-specific consent form must be on file at ACRIN Headquarters (fax 215-574-0300) prior to registering your first patient.

## **7.0 ONLINE REGISTRATION SYSTEM**

### **7.1 Using the Online Registration System**

- 7.1.1 Once the RA has completed the eligibility form and been found to be eligible, the patient may be consented. The RA will register the patient by logging onto the ACRIN web site ([www.acrin.org](http://www.acrin.org)) and selecting the link for data center login/ACRIN protocols. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist and the date the study-specific informed consent form was signed.
- 7.1.2 Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be

printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient specific-calendar. The system creates a case file in the study's database at the DMC and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

## **7.2 Unsuccessful Registrations**

**7.2.1** If either the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

**7.2.2** In the unlikely event that the ACR web registration site is not accessible, participating sites may still register a patient by faxing the completed eligibility checklist to the DMC at the ACR (215-574-0300, ATTN: PATIENT REGISTRATION). ACR staff will fax a response to the registering site with the confirmation of registration and patient case number as soon as possible.

## **8.0 DATA COLLECTION AND MANAGEMENT**

### **8.1 General**

**8.1.1** The ACRIN web address is [www.acrin.org](http://www.acrin.org).

**8.1.2** Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences in Providence, RI, and the Data Management Center (DMC) is located at the American College of Radiology's Data Management Department in Philadelphia.

**8.1.3** The BDMC uses screens on the ACRIN web site to register patients, collect patient data, and maintain calendars of data submissions for each patient. By using the World Wide Web, ACRIN has made patient registration, data entry, and updated calendar information available to clinical sites 24 hours a day.

### **8.2 Clinical Data Submission**

**8.2.1** As soon as a patient has been registered, the RA may download the patient's data submission calendar, which lists all forms and/or designated reports required by the protocol, along with the date that each form is due at the DMC. These calendars will be updated as the study proceeds to reflect data that has been received, reply to deadlines for queries about unclear data, generate deadlines for follow-up reports of adverse events or changes in the protocol which might change the data being collected or their timing. Updated calendars for each patient can be obtained 24 hours a day from the ACRIN website.

**8.2.2** An investigator is obliged to submit data according to protocol as detailed on each patient's calendar as long as the patient is alive and the case status is designated as open or until the study is terminated. The case is closed when all data have been received, reviewed and no outstanding query exists for the case.

**8.2.3** To submit data via the ACRIN website, the RA or investigator logs onto the web site and supplies the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the case report form, various logic checks will be performed. These logic checks look for missing data, data that is out of range, and data that is on the wrong form (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or to move to the next page. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the

DMC until all data entered passes these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The data is transferred to the DMC and held.

**8.2.4** Once a form is complete, the investigator presses the SUBMIT button on the patient calendar and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. An e-mail is generated and sent to the site listing all of the data completed and just submitted. Should a problem occur during transmission, this automated response supplies an explanation and instructions for resubmitting the data.

**8.2.5** If a temporary problem prevents access to the Internet, investigators should wait until access is restored to submit data. Investigators should notify the DMC of the problem and the DMC will give an estimated time when access is expected to be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACR can serve as an ISP.

### **8.3 Data Security**

The registration system has built-in security features which encrypt all data for transmission in both directions preventing unauthorized access to confidential patient information. Access to the system will be controlled by a sequence of identification codes and passwords.

### **8.4 Electronic Data Management**

**8.4.1** Data received from the web-based forms is electronically stamped with the date and time of receipt by the ACRIN server. The data is then entered into the database. A validation program is used to perform more extensive data checks such as for accuracy and completeness. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical based on data entered earlier in the current form and the more thorough checks. This validation program produces a log of errors which is sent to the research associate for resolution. This program is frequently updated to incorporate exceptions to rules so that subsequent, correctly entered data pass validity checks, minimizing the time the DMC research associate at the DMC needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC RA for resolution.

**8.4.2** If the program detects missing or problematic data, the DMC RA will send a Request for Information (query letter) to the investigator specifying the problem and requesting clarification. The DMC RA then updates the patient's data submission calendar with the due date for the investigator's response.

### **8.5 Missing and Delinquent Data Submission**

In addition to providing the investigator a data collection calendar for each case, institutions are periodically prompted for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the U.S. mail system directly to both the RA and the investigator at each site, this report lists data items that are delinquent and those that will come due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the investigator.

### **8.6 Data Quality Monitoring**

**8.6.1** The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing interim analyses. These data will be drawn directly from the

DMC's permanent database using a PowerBuilder utility that allows BC staff to log onto the DMC computer and select needed data. This analysis database will be maintained in permanent SAS (Statistical Analysis System software) format on the BC's ACRIN server and updated on a scheduled basis, usually monthly once the study is in its steady state. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

- 8.6.2** A major goal of the monitoring of data in the BC is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data, which appear to arise from causes specific to an institution, the BDMC will apprise the site of the problem and work with the site until the problem has been resolved. If the BDMC cannot find a solution, the problem will be brought to the Steering Committee for further discussion and resolution.
- 8.6.3** The BC, in conjunction with the DMC, will prepare frequent summaries of the accrued data to be presented to investigators. These summaries will report accrual rates (overall and by sub-groups of interest to the investigators), assess the completeness and accuracy of the data, and discuss any trends that may impact the outcomes of the trial. These intermittent summaries will not include analyses of the endpoints of the study. Only planned interim analyses will be performed.

## **9.0 DATA COLLECTION FORMS**

### **9.1 Data Collection Table**

<b><u>Form</u></b>		<b><u>Due Date</u></b>
A0	Registration Form	At time of registration
I1	Initial Clinical Evaluation Form	1 week post registration
M3	MRI Technical Form	1 week post imaging
PC	Pathology Transmittal Form for Pathology Slides (slides go to Path Core)	2 weeks post surgery
PI	Pathology Report (biopsy)	At time of registration
P4	Pathology Core Evaluation Form	4 weeks post specimen receipt
S5	Surgical-Pathology Report	2 weeks post surgery
MR	MRI Images	1 week post imaging
MS	MRSI Images	1 week post imaging
ME	MRI/MRSI Report	1 week post imaging
QA	MRSI Quality Assurance	1 week post imaging

## **10.0 PATHOLOGY AND IMAGE SUBMISSION**

### **10.1 Image Submission**

All images for this protocol are requested to be provided in digital format. ACRIN has developed software that allows for electronic transmission to the DMC image archive of images that have been scrubbed of all patient identifiers. Individual PC computers with this software installed will be supplied to each participating site. ACRIN will be contacting each site individually to determine their readiness and ability to work with this system. If you have preliminary questions, you may contact either Rex Welsh or Fraser Wilton (215-574-3215) for information about this system. Once readiness has been determined, imaging personnel from ACRIN will coordinate the shipment and installation of the PC computers and train all operating staff on use of the system.

**10.1.1** The GE prostate MRSI product (called PROSE) will output spectral arrays in DICOM format. The header recorded on DICOM formatted image data, which often contains information identifying the patient by name, will be scrubbed before the image is transferred. This involves replacing the *patient name* tag with the ACRIN Case#^Institution ID, the *patient ID* tag with the ACRIN case number again; the study number should be put on the *other patient ID* tag. This can be done using either software at the institution or software available from the ACRIN IMC (attention Rex Welsh, 215-574-3125).

**10.1.2** Images stored on the ACRIN IMC image archive will then be routed to other sites involved using FTP for purposes of secondary interpretation.

### **10.2 Pathology Submission**

**10.2.1** In order to allow accurate tumor localization, slides will be cut in one of two standardized methods:

#### Whole Mount Step-Sections

Axial step-sections through the entire gland will be obtained at 3 to 4 mm intervals in a plane perpendicular to the long axis of the prostate.

#### Standard Blocks

Because whole mount step sections are only performed routinely at a small number of institutions and require special equipment and expertise, participating institutions will be allowed to slice the prostate into standard numbered blocks, provided that the entire prostate and lower portions of the seminal vesicles are submitted for microscopic



examination, by a method which allows for precise reconstruction for mapping purposes.<sup>40</sup> In that way, these standard blocks will allow accurate tumor localization and measurement.

- 10.2.2** All pathology slides will be cut in duplicate. The specimens will be reviewed and signed out at the surgical institution. Following case sign-out, the duplicate set of all slides will be sent for a central review by ACRIN. Specimens should be prepared according to Section 11.5, Histopathological Standard of Reference. All slides should be sent to:

Thomas M. Wheeler, M.D.  
ACRIN Study 6659  
The Methodist Hospital  
Deputy Chief / Pathology Service  
6565 Fannin, MS 205  
Houston, TX 77030  
713-394-6475  
Fax # 713-793-1603  
[twheeler@bcm.tmc.edu](mailto:twheeler@bcm.tmc.edu)

- 10.2.3** All slides must be sent with the Pathology Transmittal Form (PC). At the time of shipment, a copy of the PC form and the pathology report (P1) should also be faxed to ACRIN Data Management at 215-717-0936. Pathology specimens can be labeled with the ACRIN study and case number of the participant. The pathology report can have the patient identifier replaced with the study and case number. Samples may be sent by regular first-class mail.
- 10.2.4** If the central pathologist substantially disagrees with the local pathologist so that the patient's diagnosis is changed in a clinically significant manner, then the pathologist at the local site where the patient is enrolled will be informed. The local pathologist should contact the patient's treating urologist about the discrepancy in opinion. In such cases, the central pathologist will send a letter of this notification to The Data Management Center, who will send a copy to the local pathologist and radiologist.

## **11.0 IMAGING MODALITIES**

### **11.1 MRI Technique**

All MR examinations will be performed on 1.5 Tesla whole body GE MR scanners utilizing Med Rad endorectal coils. Patients will be scanned in the supine position using a pelvic phased array coil and an endorectal coil. Both coils are receive-only devices. All images will be post-processed to reduce near-field artifact by automated correction for the reception profile of the endorectal and pelvic phased-array coils. The following sequences will be obtained:

- 11.1.1** Axial spin-echo or fast spin-echo T1-weighted images from the aortic bifurcation to the symphysis pubis. TR/TE = 600-700/-12 msec. Slice thickness 4-6 mm. Interslice gap 0-1 mm. Matrix 256 x 192. Frequency direction transverse (to prevent obscuration of pelvic nodes by endorectal coil motion artifact). Number of excitations = 1. Field of view = 20-32 cm.
- 11.1.2** Thin-section high-resolution axial and coronal T2-weighted fast spin-echo images of the prostate and seminal vesicles. TR/TE = 4000-6000/90-120 msec. Echo train length = 8 to 16. Slice thickness 3 mm. Interslice gap 0-1mm. Matrix 256 x 192. Frequency direction anteroposterior (to prevent obscuration of the prostate by endorectal coil motion artifact). Number of excitations = 3-4.
- 11.1.2.3** Subjects will be asked to administer a Fleet enema on the day of the study in order to reduce the potential for fecal residue to interfere with spectral acquisition and quality.

<b>MRI Technique (GE 1.5T)</b>				
Imaging Plane:	Axial	Axial	Coronal	
Coil(s):	Torso Phased Array Endo Rectal	Torso Phased Array Endo Rectal	Torso Phased Array Endo Rectal	Endo Rectal only
Sequence:	T1 (SE or FSE)	Thin Section Hi-Res FSE	Thin Section Hi-Res FSE	Spectro Spatial 3D
Anatomic Coverage:	Aortic Bifurcation to Symphysis Pubis	Prostate and seminal vesicles	Prostate and seminal vesicles	Determine coverage of prostate from Axial T2 images
TE (msec):	12	90-120	90-120	130
TR (msec):	600-700	4000-6000	4000-6000	1000
Slice Thickness /Spacing (Gap): (mm)	4-6/0-1	3/0-1	3/0-1	7/0
Field Of View (FOV):	20-32	10-14	10-14	55
Frequency Direction:	Transverse	AP	AP or SI	
Matrix:	256x192	256x192	256x192	16x8x8
NEX:	1	3-4	3-4	
Echo Train Length (ETL):		8-16	8-16	
Spectral Width:				1000 Hz
Points:				512
Signal(s) per phase encoding step:				1
Notes	Frequency: Transverse to prevent endorectal coil motion artifact from obscuring pelvic nodes	Frequency: AP to prevent endorectal coil motion artifact from obscuring the prostate gland		Shim water resonance to $\leq 12$ Hz, Spatial resolution= $.3\text{cm}^3$

## **11.2 MRSI Technique**

The 3D MRSI technique that will be employed will be based on the one that has been developed for prostate evaluation by the group at UCSF and produced as a commercial package by GE.<sup>32,37,38,39</sup> A spectroscopic imaging volume will be selected from the axial T2-weighted images to maximize coverage of the prostate, while minimizing inclusion of periprostatic fat. This will be accomplished by selecting a rectangular volume encompassing the prostate at the prostatic apex and base, the GE spectroscopy package will subsequently determine the position and dimensions of the volume including obliqueness. Magnetic field homogeneity will be optimized for the selected volume using an automated shimming algorithm provided as part of the GE package. Benefits of using spectral/spatial pulses include increased spectral bandwidths and therefore reduced chemical shift dependent localization errors, and reduced power requirements. To further improve spectral localization and reduce contamination from surrounding tissues, very selective outer voxel suppression (VSS) pulses will be utilized.<sup>50</sup> The selected volume will be over-prescribed by 10% (AP) and 30% (RL, SI). VSS pulses will be automatically placed at the original boundaries of the selected volume. Additionally, the technologist will have the ability to graphically place four more VSS pulses in order to better conform the rectangular selected volume to the shape of the prostate. PRESS excited MRSI data will be collected using the endorectal coil operating as part of a pelvic phased array in receive-only mode to provide a nominal spatial resolution of 0.3 cc. The MRSI parameters will be as follows: TR = 1 s; TE = 130 ms; NEX = 1; phase encoding steps = 16 x 8 x 8; FOV = 110 x 55 x 55 mm<sup>3</sup>; scan time = 17 min. The spectral data will be processed on the MR scanner similar to the MRI data. The GE spectroscopy package will also provide the tools for the MR technologist to align the spectral data with the MR images and archive the arrays of spectral data with the corresponding images in DICOM format. The software will also provide estimates of the areas of the metabolite peaks.

## **11.3 MRSI Quality Assurance**

MRSI quality will be assured in several ways.

Prior to the start of the trial: 1) All sites participating in the trial will receive a quality assurance prostate phantom with the GE prostate spectroscopy package. 2) Technologists at all participating sites will be trained in acquiring prostate spectral data from both the phantom and the patient. 3) Each site will have to prove that it can acquire good quality prostate spectral data. To accomplish this, all sites will acquire and submit one set of phantom data using the prostate phantom. Next, data sets from three test patients will be acquired and submitted. The MRI and MRSI data from the phantom and the 3 patients will be reviewed centrally, and each site will receive feedback regarding the test cases before randomizing the first study participant.

During the course of the trial: 1) All sites will perform QA phantom studies within one week of patient studies to assure the MR scanner is functioning properly for reproducible data acquisition. To accomplish this, PROBE single voxel spectroscopy package with body exit and 5-inch GE surface coil receive will be used to acquire spectra from the GE Brain spectroscopy phantom. 2) The technologists will run a simple protocol similar to the QA protocol used for MRI (see the QA protocol in Appendix VI) and will record a series of parameters including shim value, spectrometer gain, water line-width, and metabolite signal to noise ratios (see QA form).

## **11.4 MRI and MRSI Image Analysis**

**11.4.1** Images will be interpreted prospectively by one designated reader at each institution who will be aware that the patient has biopsy-proven prostate cancer. Each reader will analyze all accrued cases from their own institution as well as all cases from the other participating institutions. The readers will be unaware of pertinent clinical, laboratory, surgical, and histopathological data. (Note: the reading for the study will be performed separately from the clinical report, which will be issued by a different radiologist who will be aware of relevant clinical findings.) The readers will first interpret MRI alone by scoring each sextant on the degree of suspicion scale and will then interpret MRSI under the same scoring scheme. For each sextant, both the estimated probability of foci presence and the category of presence (defined on the standard 5-point scale) will be recorded. Note that both measures will be reported, first for the MRI alone and then for the MRI/MRSI combined. The quality of the MRI images will be graded as excellent, good, poor, or non-diagnostic. The degree of post-biopsy hemorrhage will be recorded as none, mild, moderate, or extensive. The location and size of areas of reduced T2 signal intensity in the peripheral zone of the prostate will be drawn on a sextant map. The degree of confidence in the presence of tumor within each sextant will be rated on a 5 point scale (5 = definitely present; 1 = definitely absent. Using an MRSI overlay sheet (see below) and pre-established criteria (see Section 2.9) for the probability of malignancy based on (choline + creatine)/citrate ratios, the location and size of areas suspicious for tumor in the peripheral zone of the prostate will be drawn. The total number and type of abnormal voxels will be recorded for each MRSI lesion. The degree of concordance between MRI and MRI/MRSI findings will be evaluated by noting the subset of abnormal MRSI voxels that have concordant MRI findings (defined as a voxel that demonstrates reduced T2 signal intensity in at least 50% of its extent).

## **11.5 Histopathological Standard of Reference**

Radical prostatectomy tissue specimens will be coated with standard marking ink and fixed in buffered formaldehyde. The specimen weight will be recorded after fixation, exclusive of seminal vesicles. The fixed specimen will be cut and two sets of slides cut from each block. One set will be retained at the local institution and used for routine pathologic analysis. The institutional pathology report will be issued in the usual fashion based on this set of slides. The second set of slides will be submitted to Dr. Thomas Wheeler for centralized ACRIN review. The latter will be the histopathological standard of reference for all data analysis in this study. The presence and grade of tumor *in each prostatic sextant* will be recorded on a standardized form, including schematic diagrams of the prostate that correspond to the MRI and MRSI diagrams ("tumor map")(see Appendix V). The presence or absence of extracapsular extension and seminal vesicle invasion will be noted, and a pathological T stage assigned.

## **11.6 Correlation of MRI and 3D-MRSI with Histopathological Findings**

Correlation between MRI, MRI/MRSI and histopathological specimens will be performed at a consensus conference with all readers and the project pathologist. Tumor sites on MRI and/or MRSI will be considered to match pathology if the tumor is present in the peripheral zone of the same sextant of the prostate (right or left base, right or left midgland, right or left apex) within the range of one MRI slice ( $\pm 3$ -4 mm cranio-caudal distance). However, such a per sextant correlation might result in misidentification of smaller tumors (occupying <25% of a sextant) as detected lesions (true positives) simply because a reader indicated the presence of tumor anywhere in the same sextant. To minimize the possibility of such "chance detection," smaller tumors (occupying <25% of a sextant) are required to be in the

same relative location within the sextant (i.e., medial, lateral, anterior, posterior) in order to be classified as detected lesions.

## **12.0 STATISTICAL CONSIDERATIONS**

REMOVED FROM WEB VERSION

## **13.0 ADVERSE EVENT REPORTING**

### **13.1 Definition of Adverse Event**

An **Adverse Event (AE)** is any untoward medical occurrence in a patient that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

### **13.2 Definition of Serious Adverse Effect**

**Serious Adverse Event (SAE)** is defined as any untoward medical occurrence that:

- Results in death or is life-threatening (at the time of the event) or
- Requires inpatient hospitalization or prolongation of an existing hospitalization or
- Results in persistent or significant disability or incapacity

### **13.3 Adverse Event Grading**

Grade is used to denote the severity of the adverse event. An AE is graded using the following categories (provided the term does NOT appear in the current version of the Common Toxicity Criteria [CTC]):

- 0 – Within normal limits
- 1 – Mild
- 2 – Moderate
- 3 – Severe
- 4 – Life-threatening or disabling
- 5 – Fatal

(For terms listed in the CTC, the grade is still recorded as 1, 2, 3, 4, or 5; however, the definition of the various grades will be specific to the term being used.)

### **13.4 Expected Adverse Events from MRI**

Claustrophobia in MRI magnet  
“Warming” sensation from endorectal coil  
Discomfort from rectal coil insertion

### **13.5 Reporting of Adverse Events**

Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate, and nurse engaged in clinical research. Please refer to the ACRIN Adverse Event Reporting Manual for specific details about what to report and when. Anyone uncertain about whether a particular adverse event should be reported should contact the ACRIN headquarters at 215-574-3150 for assistance. Any event that is judged to be NOT related to the treatment or procedure should NOT be reported as an adverse event. However, an adverse event report should be submitted if there is a reasonable suspicion of the medical treatment or imaging procedure effect.

### **13.6 When to Report**

**13.6.1** You must use expedited event reporting to within 10 working days for all Grade 5 events occurring within 30 days of the study intervention, regardless of attribution and regardless of

whether the event was expected or unexpected. You must use expedited event reporting within 10 working days for Grade 4 unexpected events occurring within 30 days of the study intervention, regardless of attribution. These reports should be sent to ACRIN, NCI's Cancer Imaging Program (CIP), and the local Institutional Review Board (IRB).

- 13.6.2** All fatal (Grade 5) adverse events should also be reported by telephone to NCI and ACRIN within 24 hours of the event.
- 13.6.3** Expedited adverse event reporting is NOT required for expected events of grades 1-4 or unexpected-indirect adverse events of any grade.
- 13.6.4** All expedited reports should be reported within ten (10) working days of knowledge of the event. All fatal adverse events should also be reported by telephone to the NCI and to ACRIN within 24 hours of knowledge of the event.

### **13.7 How to Report**

**13.7.1** An expedited adverse event report requires submission to the NCI-BIP and ACRIN using the paper templates "Adverse Event Expedited Report—Single Agent" or "Adverse Event Expedited Report—Multiple Agents," available on the CTEP home page, <http://ctep.info.nih.gov>. Protocols involving only imaging procedures must be submitted using a paper version. Investigators following those protocols should omit the Course Information section and the Protocol Agent section, even though the template indicates those as mandatory. (Do not try to send the form via the web site; it will not accept a form without those fields filled in.)

**13.7.2** Completed expedited reports should be sent to:

**NCI  
Program Director  
Re: Adverse Event Report  
Cancer Imaging Program  
6130 Executive Blvd., MSC 7412  
Bethesda, MD 20892-7412**

To make a telephone report, contact NCI at (301) 496-9531, available 24 hours a day (recorder after hours from 5 PM to 9 AM EST).

- 13.7.3** A copy of all expedited adverse event reports should be sent to ACRIN by fax at (215)-717-0936. All fatal adverse events should be reported by telephone within 24 hours of the event. To make a telephone report to ACRIN, call (215)-717-4763, available 24 hours a day (recorder after hours from 5 PM to 8 AM EST).
- 13.7.4** All expedited adverse event reports should be sent to your local Institutional Review Board (IRB). Adverse events not requiring expedited reporting are normally reported to your local IRB in an annual report.

## **14.0 INSTITUTIONAL AUDITS**

**14.1** Institutional on-site audits will be completed within 18 months of a site's enrolling its first ACRIN participant. Subsequent audits will be scheduled per the outcome of the initial audit. Auditors will follow procedures established by the Cancer Imaging Program (CIP) of the NCI. Instructions for preparing for the audit will be sent to sites in advance of the audit date. With these instructions, the auditors will specify which case records will be reviewed during the audit. Auditors will review on-site records against the reviewed data, and they will record their findings on specially prepared questionnaires. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and consent forms will be also reviewed at the audit.

- 14.2 To help sites prepare for audits and assure that clinical RAs maintain records appropriately, the BDMC will offer training. This training will cover all aspects of data collection, but will include special instructions for finding and filing the kinds of source documentation needed to verify the accuracy of submitted data for this trial.
- 14.3 **Source documentation:** Data elements that are expected to be extracted from the medical record (patient history, official clinical interpretations of images, pathology or surgery results) and recorded on the case report forms (CRFs) will be audited against the appropriate component of the medical record. Data elements gathered from signed patient questionnaires may be documented on the CRF. The image interpretation data beyond that documented in the radiology report may be recorded on the CRF and is accepted as source documentation if signed by the MD. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date on which the exam took place from the medical record. Any use of an approved CRF as source documentation requires that the CRF be signed and dated and refer to the source of the information (patient questionnaire, MR, etc.). Section 9.7 includes a listing of study-specific forms and the source documentation that will be accepted at the time of the audit. Any use of CRFs as source documentation where it is designated the information will be audited against the medical record will be considered a discrepancy.
- 14.4 **Institutional Review Board:** Sites must have on hand documentation of IRB approval prior to subject registration, including a copy of IRB approval of initial application, a copy of IRB approval of modifications, and copies of annual renewal(s).
- 14.5 **Equipment Safety or Service Reports:**  
**MRI Scanner:** Obtain copies of *MRI Preventive Maintenance Reports* for the previous 18 months or the duration of the study (whichever is less) for review at the time of the audit. Preventive maintenance is usually performed at least once every 3 months by the scanner manufacturer's service engineer, and reports may be maintained by the facility or the manufacturer. Sites must have MRI Preventive Maintenance Reports documenting quarterly service.
- 14.6 **Research Records:** Maintain *source documentation* for each case that substantiates the data reported to ACRIN.  
*Source documentation* includes the following:
- hospital chart or legible copies
  - clinic chart or legible copies
  - pathology reports or legible copies
  - MRI reports or legible copies
  - MRSI reports or legible copies
  - forms signed and dated by the subject
  - ACRIN case report forms signed by the physician
  - worksheets signed by the physician which are used by research staff to submit the data on case report form(s)
  - verification of receipt of submitted case report forms (mailed or emailed from ACRIN to site)

Source documentation must verify the eligibility criteria and data submitted on all case reporting forms. If an item is *not mentioned* (e.g., history and physical with no mention of a psychological condition) it will be assumed it is *not present*.

It is suggested that the research record for each case contain copies of the source documentation for the data reported to ACRIN. Copy the source documentation as you

abstract the data from the primary record. This will prevent a discrepancy and inability to document the data reported when reviewed by auditors.

**14.7 AUDIT 6659 Source Documentation**

AO-Case Registration Form	Printed copy, CRF signed and dated by RA*
I1-Initial Clinical Evaluation Form	Lab Report (PSA specifically) * History & Physical* Pathology Report* (biopsy)
M3-MRI/MRSI Imaging Technical Form	MRI Report* MRSI Report*
PC-Pathology Submission Form (slides)	Pathology Report* (surgical)
P4-Central Pathology Evaluation Form	Interpretation of Pathology Report from Central Reader*
QA-MRSI Quality Assurance Form	Printed copy, CRF signed and dated by person responsible for date*

\* Source documentation includes signature and date of appropriate persons.



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## **APPENDIX I**

**ACRIN # 6659**

### **SAMPLE CONSENT FOR RESEARCH STUDY**

#### **STUDY TITLE: MR IMAGING AND MR SPECTROSCOPIC IMAGING OF PROSTATE CANCER PRIOR TO RADICAL PROSTATECTOMY: A PROSPECTIVE MULTI- INSTITUTIONAL CLINICOPATHOLOGICAL STUDY**

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet "Taking Part in Clinical Trials: What Cancer Patients Need to Know" is available from your doctor.

You are being asked to be in this study because you have cancer of the prostate; we are going to evaluate the usefulness of MRI combined with MRSI (imaging studies) in determining the stage and location of your tumor.

#### **WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to determine if Magnetic Resonance Imaging (MRI) combined with Magnetic Resonance Spectroscopic Imaging (MRSI) is more accurate than MRI alone in determining the location and extent of your tumor. The accuracy of this imaging technique will be compared to information on your tumor that was derived from digital rectal examination, prostate specific antigen (PSA) level and biopsy before surgery, and to the pathology examination of your tissues after surgery.

Magnetic resonance techniques use magnetism and radio waves to non-invasively obtain pictures of body structure (MRI) and to measure concentrations of important chemicals within the body (MRSI).

This research is being done to determine the usefulness of combined MRI/MRSI in the diagnostic evaluation of prostate cancer. Hopefully, this modern imaging technique will enable physicians to use this technique before making treatment decisions in patients with newly diagnosed cancer of the prostate.

#### **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

About 134 men will take part in this study.

#### **WHAT IS INVOLVED IN THE STUDY?**

If you take part in this study, you will have the following tests and procedures:

You will have one MRI and one MRSI before your scheduled surgery to remove your prostate gland. The MRI and MRSI, combined, should take approximately one hour. You

will be administered a Fleet enema 1-3 hours before the MRI or MRSI. The enema is used to clear out your bowels in order to obtain the best quality image (scan).

### **MRI (Magnetic Resonance Imaging):**

Your MRI will be done at least six weeks following your biopsy. The MRI procedure will not require hospitalization or blood tests. You may be asked to eat a light diet one day prior to the study and to clear your bowels with a Fleet enema prior to the study. You will be placed in the center of the MRI machine, which is a large cylindrical magnet. The MRI machine produces a strong magnetic field that passes through your body. Pulses of radio frequency energy will be transmitted into your body. A surface coil encased in a plastic mold will be placed on your pelvis, and a coil encased in a plastic mold will be placed in your rectum so the tumor area can be magnified. The coil will remain in your rectum during the one hour of MRI and MRSI scans. There may be discomfort similar to that of an enema or digital rectal exam. A computer attached to the MRI machine will process the signals from the pelvic area into a picture. This procedure will take about 1 hour. You will have to lie still on your back during that time. A padded table will be provided for your comfort. Light sedation should be discussed with the physician prior to the MRI exam. If medication is currently prescribed, please bring it with you to the examination.

### **MRSI (Magnetic Resonance Spectroscopic Imaging):**

This part of the study will be done when you are finished with your MRI. This is done by computer, and involves a chemical analysis of the tumor area, similar to a chemical fingerprint. Prostate cancer is characterized by elevated and reduced levels of certain compounds, and the levels of these compounds will be determined in this portion of the study.

Additional studies may be done using the data and images we collect as part of this research project. The data and images will reside at the ACRIN data center as part of the overall ACRIN database and image archive.

### **PATHOLOGY**

Also, at the time of your surgery, prostate tissue and tumor will be removed and sent to the hospital's Pathology Department for routine testing and diagnosis. After that process is complete, the remaining tumor samples will be stored in the pathology department. You are being asked to use some of the tumor and tissue samples for tests related to this study. Since this tissue was removed at the time of surgery, your permission to use this tissue will not lead to any additional procedures or expense. This tissue will be sent to a central storage facility located at Methodist Hospital in Houston, Texas.

## **HOW LONG WILL I BE IN THE STUDY?**

You will be in the study from the time of your preoperative MRI/MRSI until you have your surgery. The researcher may decide to take you off this study if it is in your medical best interest, funding is stopped, your condition worsens, or new information becomes available.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

## **WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Many side effects go away shortly after the MRI is stopped, but in some cases side effects can be serious or long lasting or permanent.

### **Risks Associated with MRI (Magnetic Resonance Imaging)**

#### *Likely*

The MRI unit is noisy.

Some patients feel claustrophobic in the MRI magnet.

There is a possible “warming” sensation from the endorectal coil.

#### *Likely, but Not Serious*

There may be mild discomfort from insertion of the rectal coil similar to that of an enema or digital rectal exam.

#### *Unlikely, but Serious*

The probe could tear the rectum.

Because the MR instrument attracts iron, there is a possibility that an iron-containing object will accidentally fly into the magnet causing injury. Precautions have been made to prevent such an event from happening.

#### *Rare*

Another potential hazard of the exam is localized heating of the body due to the radio waves employed. Localized heating means elevation of skin temperature at the location of either the abdominal coil or endorectal coil. In the even of a heating sensation, you should notify the MR technologist immediately. However, the MR scanner and the MR coil have been designed to prevent this from happening, and there have been no reports local heating in patients scanned to date.

If you have some metallic surgical implants you will be excluded from the study. Most of these implants are compatible with MRI, but a small number are not. Please notify your physicians if you have any metallic surgical implants (for example cardiac pacemakers, heart valves, aneurysm clips, orthopedic prosthesis) prior to enrolling in the study. Other situations, which might exclude you from the imaging study, include metal fragments in your eye(s) or other parts of your body, having a pacemaker, or not being able to lie still or

on your stomach. Patients who cannot tolerate the placement of the coil within the rectum due to prior surgery on the rectum or other reasons will be excluded from the study.

### **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with prostate cancer in the future by allowing patients to be accurately diagnosed so that the appropriate therapy can be initiated in a timely manner.

### **WHAT OTHER OPTIONS ARE THERE?**

You may choose to not participate in this study. Your doctor can tell you more about the possible benefits of different available treatments.

### **WHAT ABOUT CONFIDENTIALITY?**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia and at the Center for Statistical Sciences at Brown University in Providence, Rhode Island. Your personal information may be disclosed if required by law.

Copies of your MRI films will be permanently kept on file at ACRIN. This information will be used for research purposes only. All identifying information will be taken off of the films to maintain confidentiality. Additional studies may be done using the data we collect as part of this research project.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as American College of Radiology Imaging Network (ACRIN), The Food and Drug Administration (FDA), the National Cancer Institute (NCI), and other groups or organizations that have a role in this study.

### **WHAT ARE THE COSTS?**

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. You will receive no payment for taking part in this study.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

*(This section must be completed)*

For additional information about your health, you may contact:

\_\_\_\_\_

Name

\_\_\_\_\_

Telephone Number

For information about this study, you may contact:

\_\_\_\_\_

Name

\_\_\_\_\_

Telephone Number

For information about your rights as a research subject, you may contact:

*(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)*

\_\_\_\_\_

Name

\_\_\_\_\_

Telephone Number

**WHERE CAN I GET MORE INFORMATION?**

You may call the NCI's Cancer Information Service at 1-800-4- CANCER (1-800-422-6237) or TTY:1-800-332-8615.

Visit the NCI's Web sites for comprehensive clinical trials information <http://cancertrials.nci.nih.gov> or the American College of Radiology Imaging Network's website [www.acrin.org](http://www.acrin.org).



**SIGNATURE**

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

\_\_\_\_\_  
Patient Signature (or Legal Representative)

\_\_\_\_\_  
Date

## APPENDIX II

### TISSUE BANKING CONSENT (ACRIN 6659)

#### CONSENT FORM FOR USE OF TISSUE FOR RESEARCH

##### ABOUT USING TISSUE FOR RESEARCH

You have had a surgery of your prostate to see if you had cancer. Your doctor removed some body tissue to do some tests. The results of these tests were given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept at a central storage facility at Methodist Hospital in Houston, Texas under the direction of Dr. Thomas Wheeler.

Your tissue may be helpful for cancer research. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

##### THINGS TO THINK ABOUT

The choice to let us keep the left over tissue for future research is up to you. **No matter what you decide to do, it will not affect your care.**

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and then any tissue that remains will no longer be used for research; or, you may request that your tissue be returned to you or your designee.

In the future, people who do research may need to know more about your health. While Methodist Hospital may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future. In the event that this



**APPENDIX III: Eligibility Checklist**

ACRIN      6659

Institution # \_\_\_\_\_

6659 Case # \_\_\_\_\_ (to be provided upon registration)

**ELIGIBILITY CHECKLIST**

**(page 1 of 3)**

- \_\_\_\_\_ (Y)      1. Biopsy proven adenocarcinoma of the prostate.
- \_\_\_\_/\_\_\_\_/\_\_\_\_      2. Date of prostate biopsy
- \_\_\_\_\_ (Y)      3. Written documentation from the Urologist confirming the scheduled date of the radical prostatectomy at the study site is within 6 months of MRI/MRSI.
- \_\_\_\_/\_\_\_\_/\_\_\_\_      4. Projected date of surgery (scheduled radical prostatectomy)
- \_\_\_\_\_ (Y)      5. The interval between the diagnostic biopsy and the MRI/MRSI is  $\geq$  6 weeks.
- \_\_\_\_/\_\_\_\_/\_\_\_\_      6. Projected date of MRI/MRSI
- \_\_\_\_\_ (N)      7. Known contraindications for patient to undergo MRI/MRSI? (*cardiac pacemakers, non-compatible intracranial vascular clips, metallic hip replacement, other metallic implants in the pelvic area or contraindications to endorectal coil insertion, allergic to latex, etc.*)
- \_\_\_\_\_ (N)      8. Prior cryosurgery, surgery for prostate cancer including TURP, prostatic radiotherapy, androgen deprivation therapy or complementary alternative medicine?
- \_\_\_\_\_ (Y)      9. Patient has agreed to undergo a Fleet's enema in preparation for the MRSI exam.
- \_\_\_\_\_ (Y)      10. Pathologic specimens from radical prostatectomy are available for central analysis
- \_\_\_\_\_ (Y/N)      11. Release for medical information consent signed by participant

**The following questions will be asked at Study Registration:**

- \_\_\_\_\_      1. Name of institutional person registering this case
- \_\_\_\_\_ (Y)      2. Has the Eligibility Checklist (above) been completed?
- \_\_\_\_\_ (Y)      3. Is the patient eligible for this study?
- \_\_\_\_\_      4. Date the study-specific Consent Form was signed (must be prior to study entry)

\_\_\_\_\_ 5. Participant Initials (last, first)

\_\_\_\_\_ 6. Verifying Physician (Site PI)

\_\_\_\_\_ 7. Patient's ID Number (optional; code 99999)

\_\_\_\_\_ 8. Date of Birth (mm-dd-yyyy)

\_\_\_\_\_ 9. Ethnic category  
1. Hispanic or Latino  
2. Not Hispanic or Latino  
9. Unknown

\_\_\_\_\_ 10. Race (check all that apply):  
 American Indian or Alaskan Native  
 Asian  
 Black or African American  
 Native Hawaiian or other Pacific Islander  
 White  
 Unknown

\_\_\_\_\_ (M/F) 11. Gender

\_\_\_\_\_ 12. Participant's country of Residence  
1. USA  
2. Canada  
3. Other

\_\_\_\_\_ 13. Zip Code (U.S. Residents)

\_\_\_\_\_ 14. Participant's Insurance Status  
0. Other  
1. Private Insurance  
2. Medicare  
3. Medicare and Private Insurance  
4. Medicaid  
5. Medicaid and Medicare  
6. Military or Veterans Administration  
7. Self pay  
8. No means of payment  
9. Unknown/Decline to answer

\_\_\_\_\_ (Y/N) 15. Will any component of the participant's care be given at a military or VA facility?

\_\_\_\_\_ 16. Calendar base date (mm-dd-yyyy)

\_\_\_\_\_ 17. Registration date (mm-dd-yyyy)

\_\_\_\_\_ 18. Other country of residence, specify (completed only if Q12 is coded *other*)

Completed by \_\_\_\_\_ Date \_\_\_\_\_

Name of person entering data onto the web \_\_\_\_\_

**APPENDIX IV**  
**ACRIN PROTOCOL-SPECIFIC APPLICATION**

**ACRIN 6659 – MR IMAGING AND MR SPECTROSCOPIC IMAGING OF PROSTATE CANCER PRIOR TO RADICAL PROSTATECTOMY: A PROSPECTIVE MULTI-INSTITUTIONAL CLINICOPATHOLOGICAL STUDY**

This application is in addition to the ACRIN General Qualifying Application that can be found on the ACRIN web page ([www.acrin.org](http://www.acrin.org)).

Name of Institution \_\_\_\_\_

ACRIN P.I. Name \_\_\_\_\_

Address \_\_\_\_\_

Address \_\_\_\_\_

Telephone \_\_\_\_\_

Fax \_\_\_\_\_

E-mail \_\_\_\_\_

Research Associate's Name \_\_\_\_\_

Name of Radiologist participating in this study at your site \_\_\_\_\_

Name of Urologic Surgeon participating in this study at your site \_\_\_\_\_

Name of Pathologist participating in this study at your site \_\_\_\_\_

Name of Spectroscopist participating in this study at your site \_\_\_\_\_

Does your institution have a 1.5 Tesla Whole Body GE MRI Scanner, with phased array torso coils, and endo-rectal MR coil, GE phantom, and PROSE package?                      Yes \_\_\_\_\_                      No \_\_\_\_\_

Do you have an MRI Technologist?                      Yes \_\_\_\_\_                      No \_\_\_\_\_

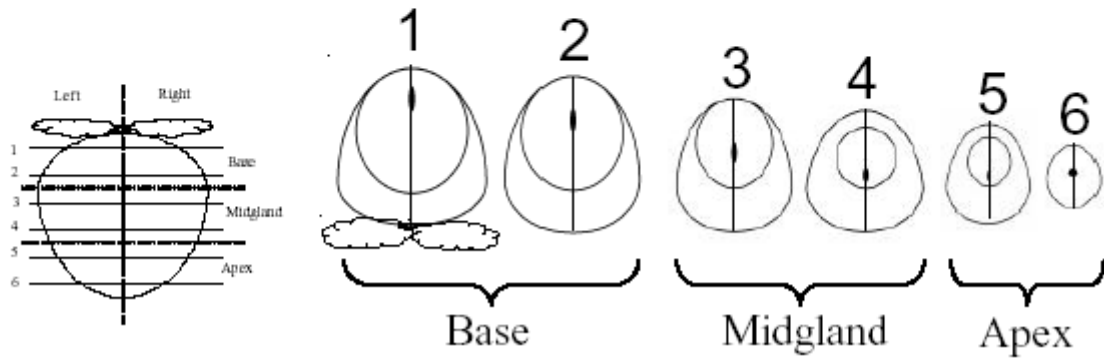
How many Radical Prostatectomies were performed at your institution in the past 12 months (must be >50) \_\_\_\_\_

Can you provide 3 qualifying MRSI image sets?                      Yes \_\_\_\_\_                      No \_\_\_\_\_

Do you have Internet Access?                      Yes \_\_\_\_\_                      No \_\_\_\_\_

**Please submit application to:**  
**ACRIN Administrator, Attn. 6659 PSA**  
**ACRIN**  
**1101 Market Street, Suite 1400**  
**Philadelphia, PA 19107**  
**Fax: 215-928-0153**

## APPENDIX V DIAGRAM OF THE PROSTATE





**APPENDIX VI**  
**QA SPECTROSCOPY SNR PROTOCOL**

Enter parameters for the QA protocol series I and II listed below and then save as “QA SPECTO”.

**SERIES I: Localizer Scan [landmark center of phantom]**

Patient Protocols: **site**

Scan Mode: **Research**

Protocol name and number: **QA SPECTRO** (number will be specific to site)

**Patient Information**

Patient ID: **geservice**

Patient Name: **Probe-p SNR**

Weight (LB): **111** (Important to enter this number)

Landmark: **Nasion** (Using the head coil cushion, center 5-inch surface coil on the pad and center the phantom atop the surface coil; then, landmark center strip of the phantom.) \*See set up illustrations on page 4.

**Patient Position**

Patient Position: **Supine**

Patient Entry: **Head First**

Coil Type: **5GP** (5-inch surface coil)

Series Description: **Localizer**

**Imaging Parameters**

Scan Plane: **3 Plane**

Monitor SAR: no entry /or **if entry is required, Y (for yes)**

Imaging Mode: **2D**

Pulse Sequence: **localizer**

Imaging options: **None**

PSD Filename: **None**

**Scan Timing**

Number of Echoes: **1** (default)

ETL: no entry

Flip Angle: no entry

Te: **1.8** (default)

Rep Time(TR): **25.8** (default)

T1 Time: no entry

**Scanning Range**

Field of View: **26**

Scan Thickness: **20**

Spacing: **0**

Center of FOV: **R/L= 0, A/P= 0, S/I= 0**

Number of scan locations: **3**

## Acquisition Timing

Acq. Matrix (freq): **256**

Axq. Matrix (phase): **256**

Frequency Direction: no entry

Phase FOV: **1.00**

Prescan Options: **Autoshim**

Auto CF: **Water**

Nex: **1**

**Imaging Time: 20 seconds**

## **SERIES II: Spectroscopy scan**

### Patient Position

Patient Position: **Supine**

Patient Entry: **Head First**

Coil: **5GP** (5-inch surface coil)

Series description: **Probe-p SNR**

### Imaging Parameters

Plane: **Axial**

Mode: **MRS**

Pulse Seq: **Probe-p**

Imaging Options: **Ext. Dyn. Range**

PSD Name: no entry

### Scan Timing

\*of Echoes: **1** (default)

TE: **37**

TR: **2000**

FOV: **24**

Voxel Thickness: **20**

Spacing: **20**

Locs per slab: **1**

### User CVs Screen

CV3 scan mode: **1.00**

CV4 total # of scans: **32.00**

CV17 AWS optimization: **0**

CV18 ROI Edge: **7**

## Scanning Range

FOV: 24

Start: S10

End: R10

Start: L10

End: I10

Start: A \*For A/P locations, move bottom of press box 1 cm anterior(up) from the bottom of the phantom.

End: P

Table Delta: 0.00 (default)

Select: Start

Select: End

Select: Accept

## Acquisition Timing

Freq: 1

Phase: 1

NEX: 2

Freq Dir: R/L

Auto Center Freq: Water

Select: Autoshim

Select: Save Series,

Select: Prepare to Scan

Select: Research Operations

Select: Display CVs

CV Value: tempC Enter: 24<sup>o</sup>

Select: Accept

Select: Research Operations

Select: Download

Select: Auto Prescan (Very important to do Auto Prescan first)

Record: Flip ang, SuppLvl, R1, R2, TG, and AX values on the **QA Dataform**. These values will appear at the bottom of the screen when the Auto Prescan is finished.

Select: Spectro Prescan

Record: the shim values on the **QA Dataform**.

Select: Done

Select: Scan

## Imaging Time: approximately 1:44

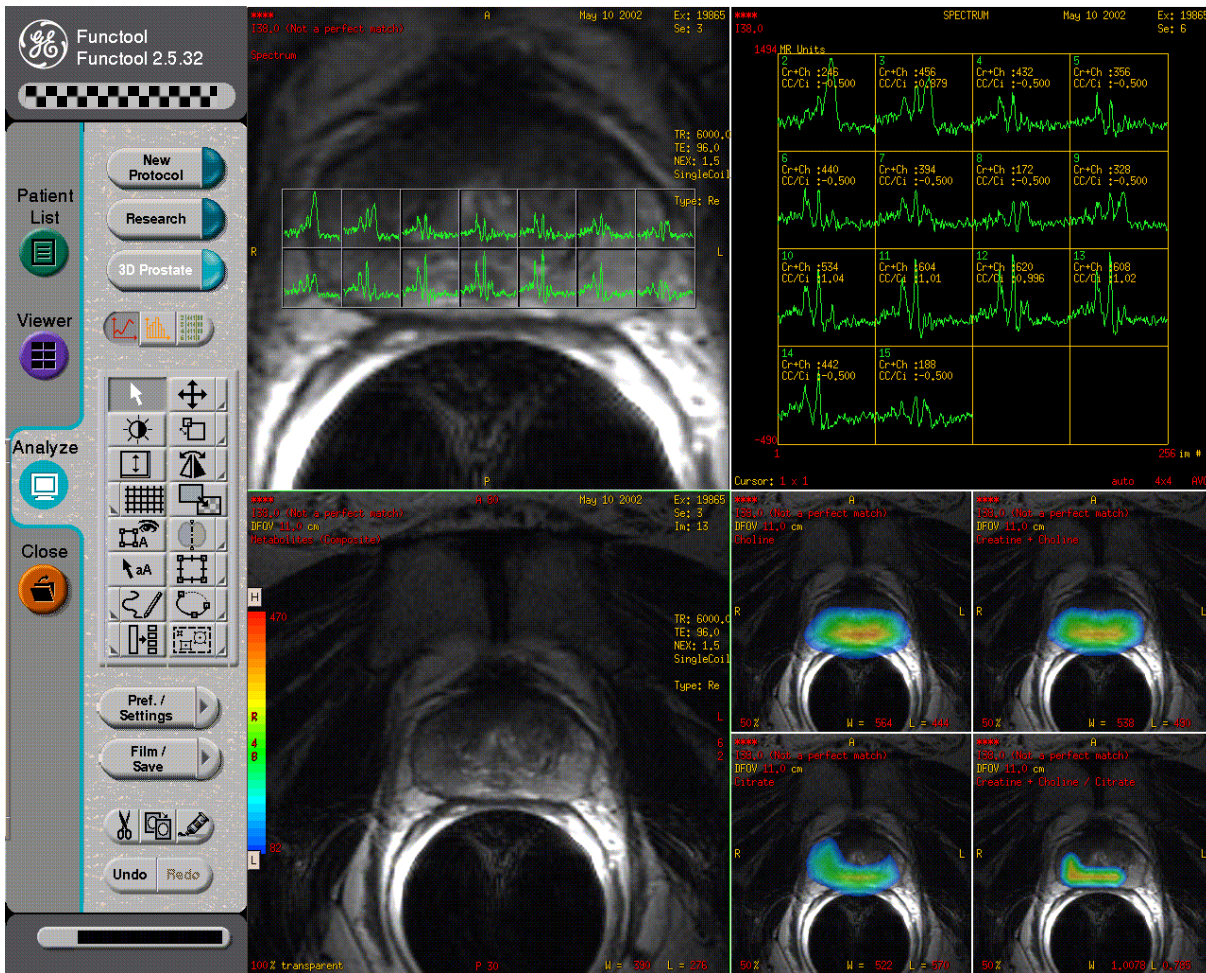
Record: **Sprectral dataset** values from Browser on **QA Dataform**.

**Illustrations of GE Brain phantom and 5-inch surface coil set up for Spectroscopy QA:**



## Appendix VII

### Procedure To Set Up the Prostate Exams Under Functool 2



#### Series selection under AW

- Click on **MR filter** to get only MR images.
- Select a patient by **left clicking** on the patient's name.
- Select the prostate spectroscopy (postage stamp) data by **left clicking** on the sequence.
- Select the appropriate localizer by pressing the **ctrl** key while **left clicking** the desired localizer image.  
At this point both the spectroscopy and image series should be highlighted in the browser.
- Click on Functool 2 button to load it.

#### If Functool 2 is not a button on the tool bar:

- Open the **Software Manager**: In the left menu select **More software/Software Manager**.
- Select the software to move.
- Middle click drag and drop** the software above the desired button to configure.

#### Functool 2

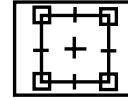
- Select **3D Prostate** protocol.

- Window and level the background image by moving the mouse in the top left view, while pressing the middle mouse button.
- Hide functional map in lower left view. To do this, **Middle click** on the red **50% transparent** active annotation and drag it to the right in order to hide the functional map (to reach **100% transparency**).
- Remove undesired voxels from the lower left view. To do this, either:

highlight the voxel to remove by selecting it with the mouse, then click on the **scissor** tool (or **Ctrl + x**). repeat for each voxel to eliminate.

or

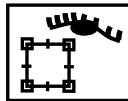
click on the **Create a Box ROI** icon, found on the left side toolbar.



Adjust the box size and position with the mouse to define the voxels to eliminate (voxels will turn green when selected for removal).

Additional voxels outside this rectangular box may be selected for removal by selecting them with the mouse. Once all voxels have been selected for removal, click on the scissors icon.

- To restore the ROIs in the top left view, click anywhere outside the box in that view.
- Press **Space bar** to autoscale the selected spectral ROIs in the upper views.
- Adjust the image fov in the lower left by holding the middle mouse button over the red **dfov** annotation and dragging to the desired fov.
- To voxel shift, click the show/hide grid icon on the left side toolbar. This will cause a red grid to be displayed on the top left view. Drag the grid to the desired location and the select **3D prostate** followed by the **compute** button.
- Remove the **PRESS Box** by **right clicking** on the view to open the contextual menu and select **Hide PRESS ROI**.



- To save DICOM screen shots, move the mouse over the image and type **shift + S**. This will create a new series called SCREENSAVE, within the current exam.
- To push these screen shots to PACS, drag them with the middle mouse button to the PACS icon at the bottom of the Advantage Windows patient list window. This requires that a PACS destination icon has been defined with the Network Manager tool (click on the **Tools**, then **Network Manager** button found on the AW patient list browser left side toolbar).

### **Display information:**

3. Click on the 3D Prostate button in order to call the protocol's wizard.
4. Click on **Advanced Settings** then the **Display** tab.
5. Select or deselect the value to display or hide (select Creatine + Choline, Creatine + Choline / Citrate).
6. **Save** button preserves preferences for future sessions.

## **APPENDIX VIII**

### **MRS/Imaging Test Case Submission and Approval Process**

Each participating site will be required to submit and have approved the 6659 study-specific MR Spectroscopy Imaging for three test participants prior to enrolling its first study participant. Notification of approval will be disseminated by ACRIN Headquarters upon completion of the case review. Your site will not be able to accrue to the 6659 protocol without this prior approval and notification.

Patients whose images will be sent as test cases do not need to sign the ACRIN 6659 study-specific consent form (Appendix I to the protocol) because they will not be participating in this study. Those patients will, however, need to sign a Health Insurance Portability and Accountability Act (HIPAA) authorization that gives permission for their images to be sent to ACRIN. ACRIN does not monitor HIPAA compliance; any HIPAA questions should be directed to the local Institutional Review Board (IRB).

The complete MRS/imaging studies will be transmitted to the ACRIN image server via the installed ACRIN transfer computer. (See Section 10.1 of the protocol for the image transmission procedure.) In the event the ACRIN transfer computer is not installed at your site, the MRS/I studies can be archived onto a CD that is PC readable. The images must be in valid DICOM 3.0 format. They should be sent to the following address:

**ACRIN Study 6659 Image Archive  
1101 Market Street, 14<sup>th</sup> Floor  
Philadelphia, PA 19107**

**URGENT: Image ACRIN study 6659 test cases enclosed**

It is required that the naming convention for each test study be consistent with the standard naming convention for actual study participants. (See Section 10.1.1.) In an effort to maintain consistency in naming the test MRS/imaging cases, the *patient name* tag will be replaced with the SITE Test#^Institution ID (ex: test1^4444, test2^4444 etc.) and the *patient ID* tag with the Site test number again (ex: test1^4444, test2^4444 etc.); the study number should be put on the *other patient ID* tag (6659). Once received at ACRIN, the imaging studies will be reviewed by the Spectroscopy Advisor, John Kurhanewicz, PhD ([john.kurhanewicz@mrsc.ucsf.edu](mailto:john.kurhanewicz@mrsc.ucsf.edu)). Any changes that may be required to the acquisition technical parameters or the anatomic coverage will be communicated by Dr. Kurhanewicz to each site via electronic mail. The anticipated turnaround time for approval of each case is 5-7 working days.

Please feel free to contact Anthony Levering ([alevering@phila.acr.org](mailto:alevering@phila.acr.org); 215-574-3244) or Sharlene Snowdon ([ssnowdon@phila.acr.org](mailto:ssnowdon@phila.acr.org); 215-717-2753) with questions you may have regarding the test case submission and approval process.

For questions regarding image transfer and ACRIN computer issues, contact either Rex Welsh ([rwelsh@phila.acr.org](mailto:rwelsh@phila.acr.org), 215-574-3215) or Fraser Wilton ([fwilton@phila.acr.org](mailto:fwilton@phila.acr.org)).