Role of Magnetic resonance spectroscopy as a noninvasive diagnostic investigation in carcinoma prostate

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M.Ch (UROLOGY)

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FORWARDING CERTIFICATE

This is to certify that the dissertation titled "**Role of Magnetic resenonce spectroscopy as a noninvasive diagnostic investigation in carcinoma prosatate**" submitted by Dr.P.V.Srinivasan appearing for M.Ch. (Urology) degree examination in August 2011, is a bonafide record of work done by him under my guidance and supervision in partial fulfillment of requirement of the Tamil Nadu Dr.M.G.R.Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R.Medical University, Chennai.

Prof.R.Jeyaraman, M.S., M.Ch.,
Professor & Head of the Department,
Department of Urology,
Government General Hospital,
Madras Medical College,
Chennai – 600 003.

The Dean,
Madras Medical College,
Chennai – 600 003.

DECLARATION

I solemnly declare that this dissertation titled **“ MAGNETIC RESONANCE SPECTROSCOPY AS A NONINVASIVE DIAGNOSTIC INVESTIGATION IN CARCINOMA PROSTATE**” was prepared by me in the Department of Urology, Government General Hospital, Chennai under the guidance and supervision of Prof. R. Jeyaraman,M.S,M.Ch., Professor & Head of the Department, Department of urology, Government General Hospital, Chennai between 2008 and 2011.

This dissertation is submitted to the Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of M.Ch. Urology.

Dr.P.V.SRINIVASAN

Place : Chennai

Date :

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CONTENTS

INTRODUCTION

Prostate cancer is common and remains the second leading cause of cancer death among elderly men. Current methods for its detection, like Digital rectal examination, Transrectal ultrasound, Prostate Specific Antigen assay and even sextant biopsy have limited accuracy for most early prostate cancers. Moreover diagnosing carcinoma prostate in patients in grey zone of PSA [4 to 10 ng/ml] and patients with normal Digital rectal examination is still difficult.

There is much overlap between Benign prostatic hyperplasia[BPH] and carcinoma prostate in this diagnostic grey zone of Prostate specific antigen. The histologic diagnosis of prostate cancer is made, in the majority of cases, by prostate needle biopsy.

Prostate cancer rarely causes symptoms until it is advanced. Thus, suspicion of prostate cancer resulting in a recommendation for prostatic biopsy is most often raised by

abnormalities found on digital rectal examination [DRE] or by serum prostate-specific antigen (PSA) elevations. Although there is controversy regarding the benefits of early diagnosis, it has been demonstrated that an early diagnosis of prostate cancer is best achieved using a combination of DRE and PSA.

Transrectal ultrasound (TRUS)-guided, systematic needle biopsy is the most reliable method, at present, to ensure accurate sampling of prostatic tissue in men considered at high risk for harboring prostatic cancer on the basis of DRE and PSA findings.

This challenge in diagnosis, localization and staging of potentially curable early disease has prompted further research into radiological imaging which could be more specific and sensitive, and also noninvasive that provides good positive and negative predictive value(PPV and NPV).

Magnetic Resonance Imaging [MRI] is well known for its diagnostic potential, primarily due to its capability to

noninvasively generate high-resolution anatomical images based on various inherent tissue characteristics.[1] With ongoing research on ways of data acquisition during MRI and their analysis, newer sequences and strategies have been developed that provide more specific information like diffusion imaging, functional imaging, metabolic imaging, etc., faster image generation and higher resolution.

With these newer technologies, the diagnostic potential of MR techniques is improving further, and its indications are also developing. Magnetic Resonance spectroscopic imaging (MRSI) is one of these new promising techniques, and uses the regular MRI machine, requiring only software upgrades as an additional cost factor.

It is not only useful in diagnosing the disease but also useful in assessing the local extant of disease which is also important in cure of the disease.

So this study is intented to assess the role of MR spectroscopy in diagnosing carcinoma prostate in patients with grey zone PSA with normal DRE.

AIM & OBJECTIVES

The aim of this study is to

- To find out the "**Role of Magnetic resenonce spectroscopy as a noninvasive diagnostic investigation in carcinoma prostate**" in patients with PSA between 4 and 10ng/ml [Diagnostic grey zone] and normal DRE.

REVIEW OF LITERATURE

According to the American Cancer Society [ACS], the incidence of carcinoma prostate is ever increasing and African American men are twice as vulnerable to prostate cancer compared to white men. Although the death rate has dropped over the last few years, it still remains the second leading cause of cancer deaths among men after lung cancer in the United States.

The ACS recommends that the PSA test and the digital rectal examination should be offered annually, beginning at age 50, to men who have a life expectancy of at least 10 years and those men that are at higher risk like African American men and those men with a strong family history of one or more first-degree relatives diagnosed with prostate cancer at an early age.

The survival and successful treatment of Prostatic Carcinoma patients is dependent upon the early diagnosis of Prostatic Carcinoma.

Further, the ability to monitor the progression and regression of malignancy is critical in the management of the disease.

Currently the combination of digital rectal examination [DRE] and prostate-specific antigen [PSA] testing is the primary diagnostic procedure. Typically, an elevated PSA or a nodule detected on physical examination prompts an evaluation and an eventual transrectal ultrasound-guided (TRUS) biopsy may reveal cancer.

However in most cases, positive identification of Prostatic Carcinoma only becomes evident when malignancy has been established and the cancer has metastasized beyond the capsular region of the prostate.

Hence detection of prostatic carcinoma within grey zone of PSA [4-10 ng/ml] with normal DRE is critical. Here, MRI in conjunction with endorectal / pelvic surface coil provides superior visualization of zonal prostate anatomy compared to

TRUS[2]. MRI by itself can however be limited, as various pathologies can mimic cancer thus compromising the diagnosis.

In recent years, magnetic resonance spectroscopy of the prostate has shown to provide very useful metabolic information of the prostate. The combined used of MRI and MRSI has shown to increase the sensitivity and specificity in the detection of prostate cancer[3].

Citrate Metabolism

The metabolism of normal mammalian cells involves the complete oxidation of glucose and fat through the intermediary steps involving the synthesis and oxidation of citrate via the Krebs cycle[4]. Coupled with phosphorylation, this intermediary synthesis and oxidation of citrate is essential for the cells to generate their major supply of cellular energy through the production of ATP.

The citrate synthesized during this process in the Krebs cycle forms the source for acetyl-CoA required for lipogenesis.

The Krebs cycle and the recycling of its intermediates are essential for the various reactions of amino acid metabolism. These established pathways are essential to normal mammalian aerobic cell metabolism, cellular function, survival, growth, and reproduction[5].

The normal human prostate on the other hand does not go through the process of citrate oxidation thus accumulating large amounts of citrate which essentially is the end product of the intermediary metabolism. Cooper and Imfeld were the first to report that citrate levels were significantly decreased in prostate cancer tissue compared to the normal prostate or BPH[6]. Shortly thereafter the same group suggested that the biochemical alterations seen through altered citrate metabolism may well occur before any malignant changes are histologically obvious[7]. While these observations were made over four decades ago, it is only in the last decade that scientists have been paying attention to the measurement of citrate levels within the prostate.

The altered citrate metabolism has now been further studied by Costello, Franklin and their colleagues who have shed some light on the role of zinc in the production of citrate[8, 9].

In addition to citrate, the normal and BPH prostate also accumulates high levels of zinc. The level of zinc in the normal prostate is about 150μg/g of tissue wet weight. However, the levels of zinc and citrate are not uniformly distributed throughout the prostate gland. For example in the normal peripheral zone there is high level of zinc concomitant with high levels of citrate.

In the normal central gland, the levels of zinc and citrate are at a lower concentration[10]. It is thought that in the presence of zinc, the mitochondrial aconitase activity that is responsible for citrate oxidation is severely limited in the normal prostate epithelial cells, which ultimately leads to the accumulation of citrate. The accumulation of citrate comes at the cost of ATP production which is reduced by about 65% in the normal prostate epithelial cells (14 moles of ATP) compared to other

normal mammalian cells (38 moles of ATP) that completely oxidize glucose.

In prostate cancer however, the ability of intramitochondrial accumulation of zinc diminishes. It is thought that such a decrease in the zinc level restores the m-aconitase activity that leads to increased citrate oxidation. This is coupled with ATP production essential for progression towards malignancy[9, 11, 12].

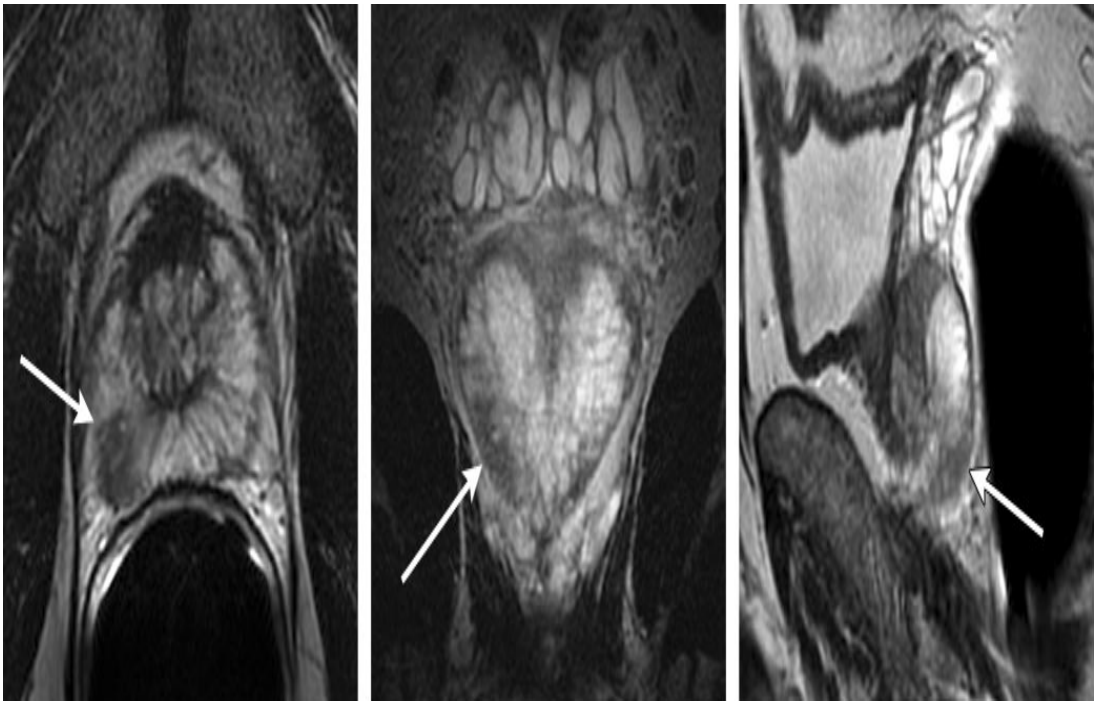
While many aspects of the zinc-citrate relationship are still under investigation, there is ample evidence suggesting that zinc-citrate interactions play an important role in the pathogenesis and progression of prostate malignancy.

Magnetic Resonance Imaging

Recent studies show that the combined use of an endorectal and phased-array coil and a high field strength MR imaging system provides the highest image resolution possible

(2). MR imaging accurately depicts internal prostatic zonal anatomy and displays the physiologic complexity of the gland.

Over the past several years, the superiority of MRI in the staging accuracy of cancer involving the peripheral zone has been consistently reported between 75% and 90%[3].



MRI showing malignant focus in peripheral zone

Most prostate cancer involves the peripheral zone of the gland, where cancer is identified as low signal abnormality on

T2-weighted imaging. Although MRI has allowed intra-prostatic evaluation of tumor location, results are often non-specific[13]. Torricelli et al showed that cancer could mimic post-biopsy hemorrhage, scar, prostatitis, or interglandular dysplasia on MR imaging of the prostate with specificity in the order of 50% [14].

Magnetic Resonance Spectroscopy

MRSI is a powerful tool that can provide useful biological information associated with many different metabolites[15]. Proton (1H) spectroscopy is attractive in terms of sensitivity, spatial resolution, signal to noise, and acquisition time. It has been widely used in the brain and its application and availability for imaging various anatomical regions of body has been increasing.

MRS can provide a description of the chemical makeup of an imaged area in order to determine the presence of cancer[16]. Molecules that can be studied with MRS include water,

lipids, choline, citrate, lactate, creatine, and amino acids[15]. Based on the initial work by Costello and Franklin at the University of Maryland, the prostate gland is unique in the body by the fact that it contains high levels of citrate[17].

As the normal glandular epithelial cells are replaced by cancer, the concentration of citrate and choline change in the transformation to a malignant state. Choline levels increase and citrate levels decrease in the presence of active cancer[4].

As mentioned above, the reason for the decline in the levels of citrate is the altered intermediate metabolism in the Krebs cycle[5]. Although the mechanism for the elevation of the choline peaks is less understood, just as in the case of brain spectroscopy, its elevation is thought to be associated with changes in cell membrane synthesis and degradation that is normally associated with cancer.

The choline resonance observed in-vivo at 3.22 ppm, sometimes referred to as total choline arises from the methyl

hydrogens of trimethylamines and is comprised of choline, phosphocholine (PC),glycerophosphocholine (GPC), phosphoethanolamine (PE), glycero-phosphoethanolamine (GPE), and ethanolamine[18-22]. These compounds are essential in the synthesis and hydrolysis of phosphatidylcholine and phosphatidylethanolamines that are an integral part of the characteristic bilayer structure of cells and regulate membrane integrity and function.

Polyamines such as spermine can be visualized in prostate MRSI[23]. Polyamines are involved in many cellular processes such as maintenance of DNA structure, RNA processing, translation and protein activation[24,25]. Disruption to the synthesis of polyamines is known to modulate the genetic effects of these genes. Polyamines can be visualized in proton MRSI as a broad peak between choline and creatine.

Normal prostate epithelial cells will demonstrate large amounts of citrate and polyamines. The malignant cells on the other hand exhibit low levels of citrate and polyamines to the

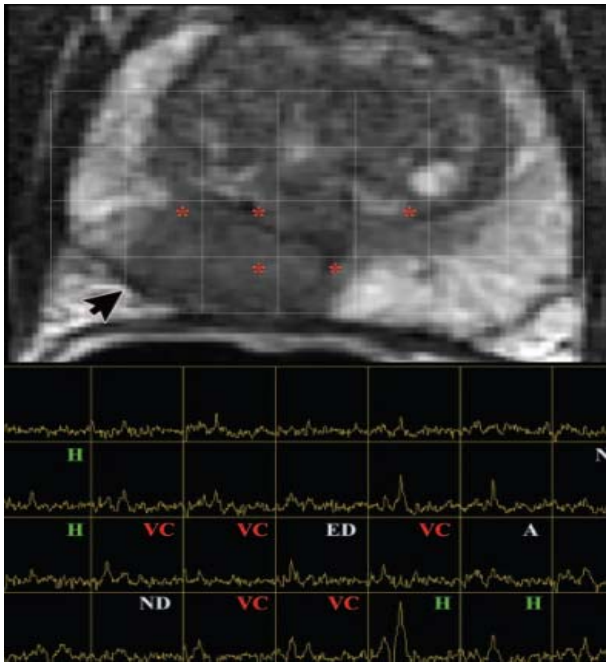
extent that the choline and creatine resonances are resolved to the baseline.

One unfortunate consequence of prostate MRSI is the inability to monitor metabolites such as lactate and lipids in vivo due to the necessity for suppressing lipids to minimize contamination from the lipids surrounding the prostate gland. It has been shown in vitro that the citrate to lactate ratio can be used to discriminate prostate cancer from BPH and that the ratio can be used as an indicator of cancer aggressiveness[7]. It is hoped that future MRSI improvements will allow for the interrogation of these metabolites.

MRSI Techniques

Although significant developments have been made with MRSI of the brain, the translation of this technology to other body parts including the prostate gland has proven to be far from trivial.

In the case of the prostate gland, the deep location of the prostate, the possible movement of the prostate gland during the MRSI acquisition, and the dominating triglyceride signals from the surrounding adipose tissues often pose a challenge in obtaining reliable quality spectra. Initial studies employing prostate spectroscopy used single voxel techniques such as STEAM (Stimulated Echo Acquisition Method) and PRESS (Point Resolved Spectroscopy) using the body coil[26-29].



MRSI showing voxels

Usually the voxel size was large and encompassed both the peripheral zone and the central gland. Although these techniques showed the feasibility for performing proton spectroscopy, their use in the clinical setting was limited due to long scan times and the poor signal to noise of the spectra. **[fig-1].**

However, with the arrival of 2D and 3D MRSI techniques the interest in prostate spectroscopy has increased[30-33]. Several technical hurdles had to be overcome to reliably detect the resonances from the biological relevant compounds in the prostate including accurate localization and the suppression of large signals from both water and lipids[34-37].

3D-MRSI technique appears to be the most suitable for the prostate gland as it is able to provide the prostate metabolite level information with high spatial resolution for the entire gland. Typically PRESS localization and band selective

excitation with gradient dephasing (BASING) for water and lipid suppression is used[34].

3D-MRSI provides an array of spectra from contiguous voxels from the entire prostate gland. The contiguous array of spectra that map the entire prostate are in alignment with the anatomical T1- and T2-weighted images allowing for a comparative interpretation between the anatomical images and the metabolic information.

Investigators at the University of California San Francisco (UCSF) showed that 3D-MRSI can be used to differentiate and localize the tumor foci to a volume as small as 0.24cc[38-42]. Similar results have been reported by the group in the University of Nijmegen, Netherlands who further refined the 3DMRSI technique by using elliptical encoding to further reduce the scan time[43-45].

Interpretation resulting from a combined evaluation of the MR images and by metabolic changes observed through MRSI

leads to the most confident identification of cancer with a specificity of up to 98% (43). Decreased signal intensity on T2-weighted images in conjunction with decreasing levels of citrate and polyamines and a concomitant increase in the levels of choline increases the specificity in the diagnosis of prostate cancer. Hence an increased choline to citrate ratio is usually used as a method for depicting prostate cancer. Since the choline and creatine resonances are inseparable for quantification purposes, most investigators use [Choline+Creatine]/Citrate (CC/C) for spectral analysis.

A standardized scoring method was developed by Jung et al which is based on the deviation of the CC/C ratio from its normal value of 0.22±0.013. A voxel CC/C value within one standard deviation of this normal value was given a score of 1, a value between 1 and 2 standard deviations was given a score of 2, a value between 2 and 3 standard deviations was given a score of 3, a value between 3 and 4 standard deviations was given a score of 4, and a value greater than 4 standard deviations was assigned a score of 5.

Additional adjustments were made to the score to account for the elevation of choline over creatine, reduced polyamines, and poor signal to noise rations. In these way each voxel obtained a score between 1 and 5 which was designated to an interpretative scale of likely benign, probably benign, equivocal, probably malignant and likely malignant corresponding to a voxel score from 1-5 respectively. Using this standardized five-point scale they were able to show good accuracy and excellent interobserver agreement.

It should be noted that 3D-MRSI produces vast amounts of spectroscopic data and a standardized scale such as the one developed by Jung et al is likely to make the task of spectral interpretation less formidable[46]. Such standardized scales will allow one to easily characterize the tumors aggressiveness and spatial extent.

The combination of MRI and MRSI in conjunction with the endorectal and phased-array body coil is emerging as the most sensitive tool for anatomic and metabolic evaluation of the prostate gland[3,47,48].

Improvements in pulse sequences and MR technology have enabled the acquisition of the metabolic information from the entire prostate at high resolution within a reasonable time of ten minutes or less.

Proton MRI/MRSI may be of great value for patients who are at increased risk for prostate cancer, for patients who have chosen watchful waiting, for longitudinal follow up from therapy, and in guiding various localized therapeutic treatments [49-51].

MRI/MRSI of the prostate gland is likely to benefit from the recent trend towards ultra-high field magnet systems and emergence of multi-channel parallel imaging[52-54].

Further newer techniques such as diffusion and perfusion are likely to increase the sensitivity and specificity of prostate cancer detection and characterization[55-63].

PROSTATE IMAGING

TRUS of the prostate, first described by Wantanabe and colleagues[64], expanded to routine clinical use with improvements in ultrasound technology and the introduction of the TRUS-guided systematic sextant biopsy protocol by Hodge and associates[65,66].

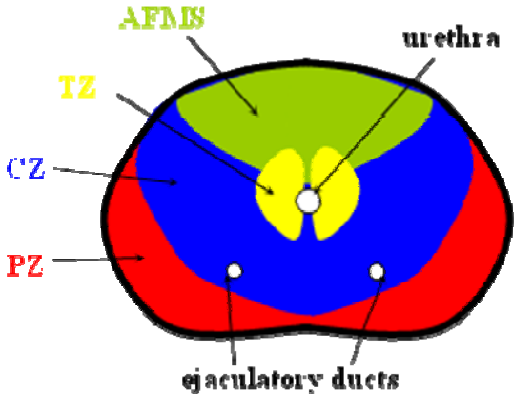
Concurrent with improved biopsy techniques, the use of PSA screening increased the number of men undergoing early prostate cancer screening and prostate biopsy, with estimates as high as 800,000 biopsies annually in the United States alone[67].

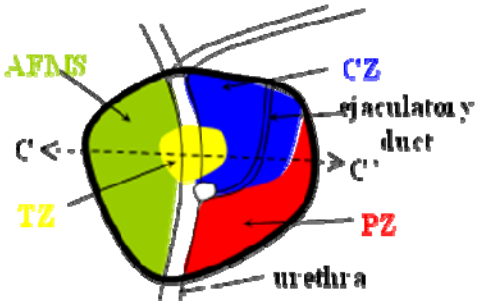
Given the prevalence of prostate cancer and the frequency with which TRUS-guided prostate biopsies are performed, significant efforts have been focused on determining the appropriate indications for biopsy and the ideal technique by which to image and biopsy the prostate.

TRUS technology has become a mainstay of many image-guided prostate interventions, including prostate biopsy, brachytherapy, cryotherapy, and high-intensity focused ultrasound (HIFU), as well as being used in the evaluation of appropriate patients for treatment of benign prostatic hyperplasia (BPH)[68].

ULTRASONOGRAPHIC ANATOMY OF THE PROSTATE

The prostate lies between the bladder neck and the urogenital diaphragm, just anterior to the rectum, an ideal position to be imaged via TRUS. The prostate gland is traditionally described based on a pathologic zonal architecture. These divisions consist of the anterior fibromuscular stroma (AFS) that is devoid of glandular tissue, transition zone (TZ), central zone (CZ), periurethral zone, and peripheral zone (PZ). Unfortunately, these regions are not visible sonographically as distinct entities.**fig-2.**





However, the TZ may often be discernible from the PZ and CZ, particularly in glands with significant BPH. Located posteriorly, the normal CZ and PZ, from which a majority of adenocarcinomas arise, have a homogeneous echogenic

appearance whereas the anteriorly situated TZ is more heterogeneous.

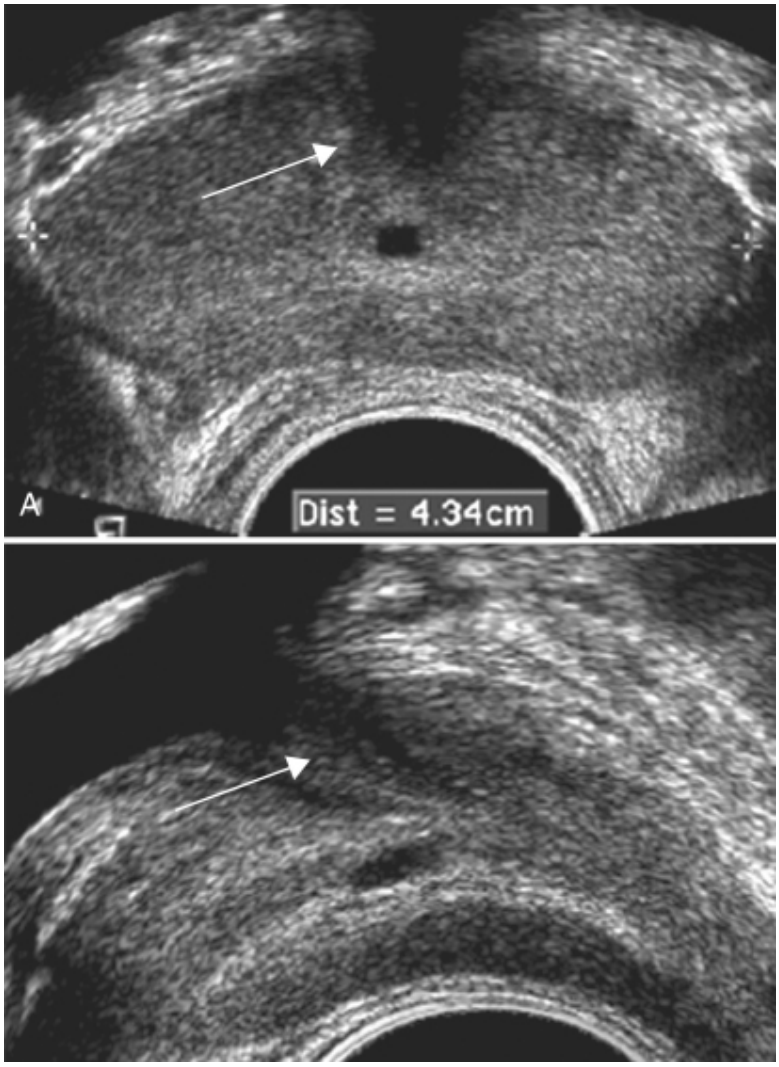


Fig-2. Normal appearance of prostate in TRUS

Prostate Cancer Imaging on TRUS

All hypoechoic lesions within the PZ should by noted and included in the biopsy material. The lack of a distinct hypoechoic focus does not preclude proceeding with biopsy because 39% of all cancers are isoechoic and up to 1% of tumors may be hyperechoic on conventional gray-scale TRUS[69]. Despite the higher prevalence of cancers discovered in prostates with hypoechoic areas, the hypoechoic lesion itself was not associated with increased cancer prevalence compared with biopsy cores from isoechoic areas in a contemporary series of almost 4000 patients[70]. **fig-3**

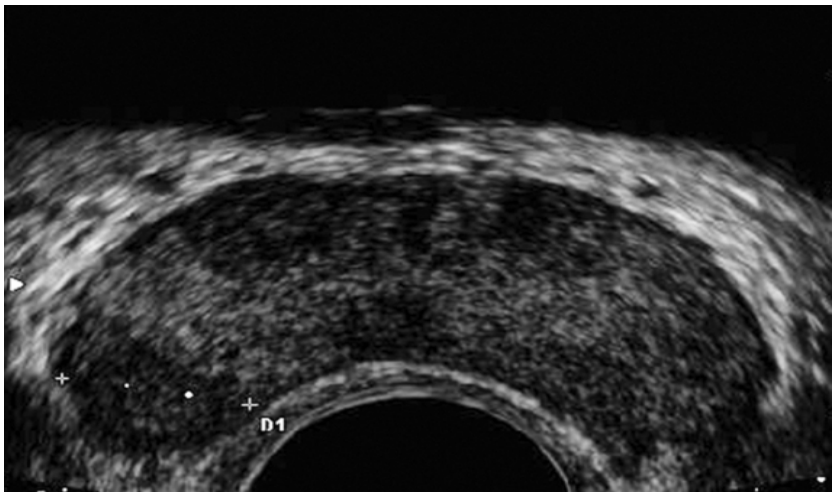


Fig-3. TRUS image of prostatic carcinoma.

Color and Power Doppler TRUS

Color Doppler imaging is based on the frequency shift in the reflected sound waves from the frequency of insonation and thus depicts the velocity of blood flow in a directionally dependent manner .

Color assignment is based on the direction of blood flow related to the orientation of the transducer receiving the signal; flow toward the transducer is depicted in shades of red and flow away in shades of blue; the color is not specific for arterial or venous flow.

Power Doppler utilizes amplitude shift to detect flow in a velocity and directionally independent manner[71]. The advantages of power Doppler imaging are its ability to detect slower flow and to have less reliance on the Doppler angle, making it more suitable for detection of prostate cancer neovascularity.

Although power Doppler imaging offers improved sensitivity to small amounts of flow, neither modality has yet proved itself superior to the other for cancer detection. Enhancements in the technical aspects of color Doppler TRUS, including the use of contrast agents , may provide the necessary improvements to specifically identify cancer sites in the future.**fig-4**.

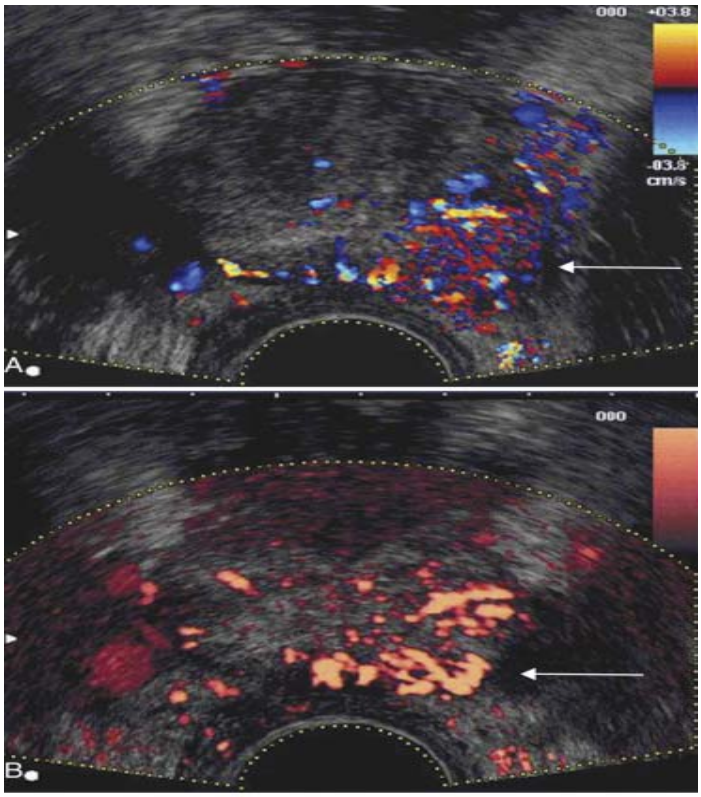


Fig-4. TRUS with color and power Doppler.

A new sonographic technique known as elastography may prove to be superior to color Doppler imaging in identification of malignant areas in the prostate[72,73]. This technique employs real-time sonographic imaging of the prostate at baseline and under varying degrees of compression. Through computerized calculations, differences in displacement between ultrasonic images from baseline and during compression may be visualized and regions with decreased tissue elasticity may be tagged as suggestive of malignancy. **fig-5.**

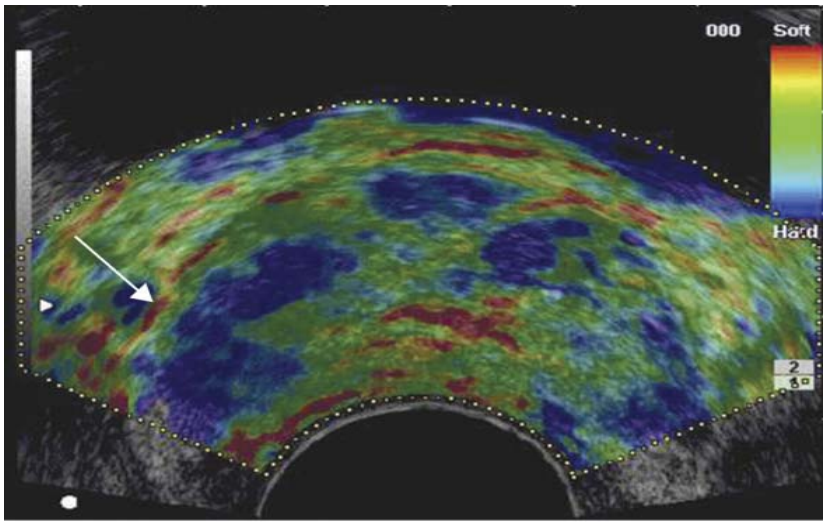


Fig-5. Elastography of prostatic carcinoma

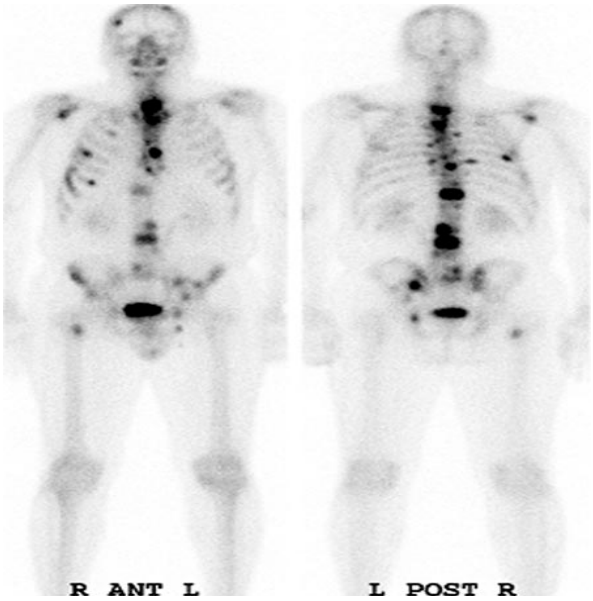
New Doppler, contrast medium–enhanced, and other developing techniques have the potential to allow accurate localization and diagnosis of prostate cancer and minimize or eliminate the need for multiple biopsy sites to diagnose prostate cancer in the future. However, until these techniques are proved superior in the localization of prostate cancer, systemic TRUS gray-scale core needle biopsy will continue to be regarded as the "gold standard" for the diagnosis of prostate cancer.

A variety of imaging modalities have been evaluated for staging prostate cancer. None of these techniques are sensitive enough to detect reliably the extraprostatic spread of prostate cancer. The inability to image microscopic disease limits the accuracy of current imaging modalities.

Radionuclide bone scan (bone scintigraphy) is the most sensitive modality for the detection of skeletal metastases. This is in contrast to bone survey films (skeletal radiography), which

require more than 50% of the bone density to be replaced with tumor before they can identify distant spread.

Today, skeletal radiography is obtained only to confirm a positive bone scan in men at low risk for bone metastases. Radionuclide bone scan can also screen for upper urinary tract obstruction and thus can obviate the need for further evaluation of the urinary tract in men with prostate cancer.



Because bone metastases at diagnosis are rare in men without bone pain in the PSA screening era, the routine use of bone scans in this population may not be useful and can create

needless stress by detecting benign conditions that require further tests to rule out occult malignant disease.

In addition, a strategy of using bone scintigraphy in the staging evaluation of all PSA-screened men may not be cost-effective. Bone scans are not routinely obtained for patients with PSA levels less than 10 ng/mL and no bone pain. When a bone scan is performed, however, it provides a baseline evaluation for comparison in men who later may complain of bone pain.

The use of computed tomography (CT) and MRI to evaluate the local extent of disease and the possibility of nodal involvement is not routinely recommended because of the low sensitivity of these modalities.

Such tests may be appropriately reserved for high-risk patients such as those with locally advanced disease by DRE, a PSA greater than 20 ng/mL, or men with poorly differentiated cancer on needle biopsy.

Furthermore, the cost effectiveness of these tests in populations with probabilities of lymph node involvement less than 30% has been questioned. Given the rarity of lymph node involvement in screened populations, it appears that these imaging modalities are being overused in the staging of prostate cancer.

Combined MRI and MRI spectroscopy (MRIS) are being evaluated for staging prostate cancer, but there is no evidence that these methods will overcome the current limitation of the inability to image microscopic disease.

Specialized techniques such as high-resolution MRI used in tandem with the intravenous administration of lymphotropic superparamagnetic nanoparticles may allow the detection of small and otherwise undetectable lymph node metastases in patients with prostate cancer. These techniques, however, require further clinical evaluation before widespread use.

MATERIALS AND METHODS

Title of study

"**Role of Magnetic resenonce spectroscopy as a noninvasive diagnostic investigation in carcinoma prostate**" in patients with PSA between 4 and 10ng/ml. [Diagnostic grey zone] and normal DRE.

- Period of Study

September 2008 - April 2011

Type of Study

Prospective Study

Ethical committee approval obtained

Source of patients

Patients with obstructive lower urinary tract symptoms who presented to the Department of Urology,

Madras Medical College, Government General Hospital, Chennai.

PATIENT SELECTION

Inclusion Criteria

- 20 males with age between 50 - 78 yrs
- PSA between 4 and 10 ng/ml
- Normal DRE
- Proper consent obtained
- No other co morbidities

Exclusion criteria

Patients with

- UTI
- Bleeding disorder
- Claustrophobia

- Nodular DRE
- Patients with AUR
- Patients with prostatitis
- Patients with implants

Patient preparation

Pre procedural antibiotics tab.ciprofloxacin-500mg half an hour prior to procedure and rectal enema were given.

Viral serology done. All the patients are explained about the procedure.

Patient position

Supine position for MRSI and left lateral position for TRUS and Biopsy.

IMAGING EXAMINATION

MR Spectroscopy

All the twenty patients were subjected to undergo MRS. The machine used in this study is siemens 1.5 tesla surface coil machine. MRI study of prostate with 3DCSI MR Spectroscopy done.**fig-6**.

High resolution Axial, Sagittal and coronal T2WI, T1 Axial and 3D CSI MRS technique was used.

The signal intensities of prostate gland involving lateral lobes, median lobe and periurethral glandular region were analyzed.

The prostatic volume is measured. The appearance of prostatic capsule, bladder wall appearance any thickening, irregularity were noted. The seminal vesicle appearance noted.

3D MV MRS of prostate was analyzed. The choline integral values and citrate integral values were analyzed. Any significant increase or decrease in each voxel were noted. The choline/citrate ratio is calculated.

Any increase in choline/citrate ratio more than 2SD is considered as abnormal and indicative of malignancy in each voxel. In our study this ratio more than or equal to 1.2 is considered as malignancy.**fig-7.**

Retro peritoneal lympyadinopathy if present was noted.

TRUS scan and TRUS guided biopsy

All the twenty patients were subjected for TRUS scan with 7 Mhz Aloka machine with rectal probe in left lateral position. Complete zonal anatomy of prostate was studied. Systematic sextant biopsies of 13 core were taken. Each biopsy specimen is specifically labeled according to the

orientation of biopsy site and sent for histopathological examination.

All the patients were given one dose of ciprofloxacin 500 mg half an hour prior to TRUS biopsy. All were given low rectal enema prior to biopsy.

No patient developed any untoward complication following the procedure.

Statistical Analysis:

Statistical analysis was done with **SPSS software.**

OBSERVATION AND RESULT

Total No of patients studied: 20.

The patients ranged in age from 50 to 75 years, with a mean age of 31.21 years.

The prostate volume ranged from 40 to 60 ml.

The gleason sum was between 4 and 7.

	Positive for malignancy	**Negative for malignancy**
MRS	8/20	12/20
TRUS Bx	6/20	14/20

		TRUS Biopsy		Total
		+ ve	– ve	
MRS	+ ve	6	2	8
	– ve	0	12	12
Total		6	14	20

	Value	(95% CI)
Sensitivity	100%	51.7 – 100.0
Specificity	87%	56.2 – 97.5
Positive Predictive value	75%	35.6 – 95.5
Negative Predictive value	100%	69.9 – 100.0
Accuracy	90%	76.9 – 100.0

Correlation co-efficient

	N	Corr Co-eff	P – value
Age Vs MR score	20	0.420	0.065
Prostate Volume Vs MR Score	20	– 0.459	0.042*
PSA Vs MR Score	20	0.461	0.041*
Gleason sum Vs MR Score	6	0.571	0.237

* Statistically significant ant 5% level.

DISCUSSION

The triad of DRE, serum PSA, and TRUS-directed prostatic biopsy is used in the early detection of prostate cancer. The combination of DRE and serum PSA is the most useful first-line test for assessing the risk of prostate cancer being present in an individual[74-78.]

TRUS is not recommended as a first-line screening test because of its low predictive value for early prostate cancer[78-81] and high cost of examination.

The effectiveness of PSA as a screening method for prostate cancer is debated. However, it has been proved that use of PSA increases detection rates of prostate cancer and leads to the detection of prostate cancers that are more likely to be confined when compared with detection without the use of PSA.

This has been documented in population-based data, observational studies, and randomized screening trials.

An increase in detection lead time for a disease with a long natural history can increase the probability of detecting cancers with more favorable biology and those that are unlikely to pose a threat during the host's remaining life[82].

The choice of a PSA threshold or cut point above which one would recommend further evaluation to rule out prostate cancer (prostate biopsy) is controversial[83-85].

The PSA threshold that most efficiently leads to the detection of life-threatening cancers while avoiding unnecessary testings like PSA measurements and biopsies and overdiagnosis is not known.

The controversy stems from the following the use of higher PSA thresholds risks missing an important cancer until it is too late for a cure, whereas the use of lower PSA thresholds increases not only unnecessary biopsies but also the proportion of biopsies that identify clinically insignificant disease like

disease that would not have been detected in the absence of screening. The use of a PSA threshold of 4.0 ng/mL for men older than 50 years has been accepted by most clinicians as striking a reasonable balance between these tradeoffs.

Morgan and colleagues[86] have shown that the PSA cutoff value that results in 95% sensitivity with the detection of 95% of cancers is close to 4.0 ng/mL for men between the ages of 50 and 70 years the target population for screening at present and 2.5 ng/mL for men age 40 to 50 years.

Improvements in test sensitivity are associated with the tradeoff of reduced specificity [correct exclusion of cancer in men who do not have the disease] and lead to an increase in the numbers of unnecessary biopsies.

PSA elevations below 10 ng/mL in men with a DRE that is not suspicious for prostate cancer are more likely the result of Benign prostatic enlargement (BPH) and represent “false” elevations. Distinguishing between men who have PSA

elevations driven by BPH or cancer is difficult because PSA is not specific for cancer and the prevalence of BPH in the population is high compared with prostate cancer.

Volume-based PSA parameters [with prostate volume determined by ultrasonography] including PSA density [PSA divided by prostate volume], complexed PSA density [complexed PSA divided by prostate volume], and PSA transition zone [PSA divided by transition zone volume] have been evaluated as methods for excluding men with PSA elevations related to BPH.

Specificity of PSA velocity using a cut point of 0.75 ng/mL per year remained high (over 90%) when PSA levels were between 4 and 10 ng/mL or below 4 ng/mL, but sensitivity for cancer detection was 11% at levels below 4 ng/mL, compared with 79% for levels between 4 and 10 ng/mL.

The cutoff for percentage of free PSA that optimizes sensitivity and specificity for cancer detection depends on prostate size because overlap in the percentage of free PSA is greatest among men without cancer who have enlarged prostates and men with cancer in the setting of prostate enlargement[87].

Maintaining a sensitivity for cancer detection of 90% among men with PSA levels between 4 and 10 ng/mL and nonsuspicious DREs, Catalona and associates[87] found that a free PSA cutoff of 23% [biopsy only if 23% or less] would have eliminated 31% of unnecessary biopsies in men with prostate glands larger than 40 cm^3, whereas a free PSA cutoff of 14% would have eliminated 76% of unnecessary biopsies in men with prostate glands smaller than 40 cm^3.

Enthusiasm for using TRUS to identify early prostate cancers by detection of hypoechoic lesions has not been justified with longer follow-up .

A number of studies have confirmed the inability of TRUS to localize early prostate cancer[80,81,88], So to avoid unnecessary TRUS biopsies at the same time detecting carcinoma in patients with grey zone PSA is a challenging task.

TRUS biopsies are limited by a low sensitivity of 60%, a PPV of only 25% and false-negative rate estimated to be as high as 15–34%[89,90]. Combining MRSI with TRUS-guided biopsy could help in (i) directing biopsy to the suspicious area and therefore improve its detection rate, and (ii) avoiding the biopsy in those who have no suspicious lesions and therefore avoiding all risks associated with an invasive biopsy.

3D MRSI data can be overlaid on corresponding T2-weighted MRI images to identify the anatomical and pathological location of spectroscopic voxels. Tri-planar coordinates of the suspicious area can thus be obtained and used to take a biopsy from the suspicious area under TRUS guidance[91].

The addition of MRSI to MRI has been shown to improve the localization of cancer to a sextant of the prostate, with a sensitivity of up to 95% and a specificity of 91% when compared with MRI alone ($P< 0.05$)[92,93].

Prospectively evaluated the role of MRI/MRSI in men with a PSA level of < 10 ng/mL, who have poorest cancer detection rate and the highest false-negative rate on TRUS biopsy, and found a cancer detection rate about three times better, and a NPV approaching 100%[91,94].

In our study we have investigated 20 patients, out of which 8 patients were MRS positive for malignancy and all the 20 patients were subjected to under go TRUS biopsy 0f targeted and extended core biopsy which 6 out of 8 who were positive for malignancy by MRS were positive for malignancy.

The results were analysed by SSPS software and the following statistical reports were arrived.

In our study the sensitivity of MRS is 100% with a confident interval of 95%.

The specificity of MRS is 87% with confident interval of 95% [56.2-97.5].

The positive predictive value is 75% with confident interval of 95% [35.6-95.5].

The negative predictive value is 100% with confident interval of 95% [69.9-100.0].

The correlation of co-efficients showed that, Age vs MRS score is 0.420 and the P value is 0.065, statistically insignificant.

Prostate volume vs MRS score is 0.459 and the P value is 0.042 and statistically significant. [$P<0.05$]

PSA vs MRS score is 0.461 and the P value is 0.041 and statistically significant. [$P<0.05$]

Gleason sum vs MRS score out of 6 MRS and TRUS Bx proven malignant patients is 0.057 and P value is 0.237.

In other studies done by Sheidler et al, Kumar et al, Coakley et al [92-94] showed sensitivity of 95%, and specificity of 91% with negative predictive value approaching to 100%.

CONCLUSION

MR spectroscopy of prostate for patients with grey zone PSA and normal DRE is a non invasive and feasible option to detect carcinoma prostate with a Positive predictive value of 75% and Negative predictive value of 100%.

Fig-1

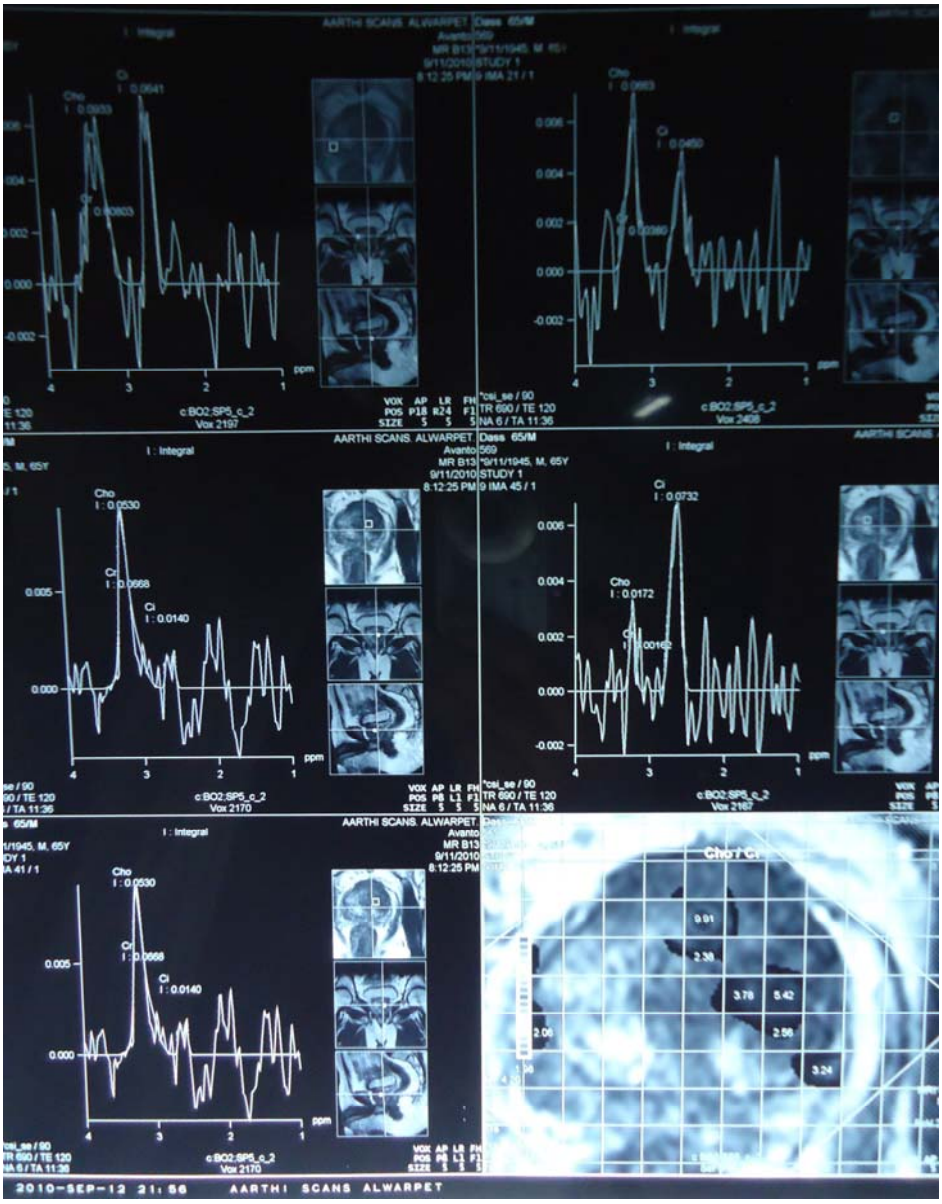
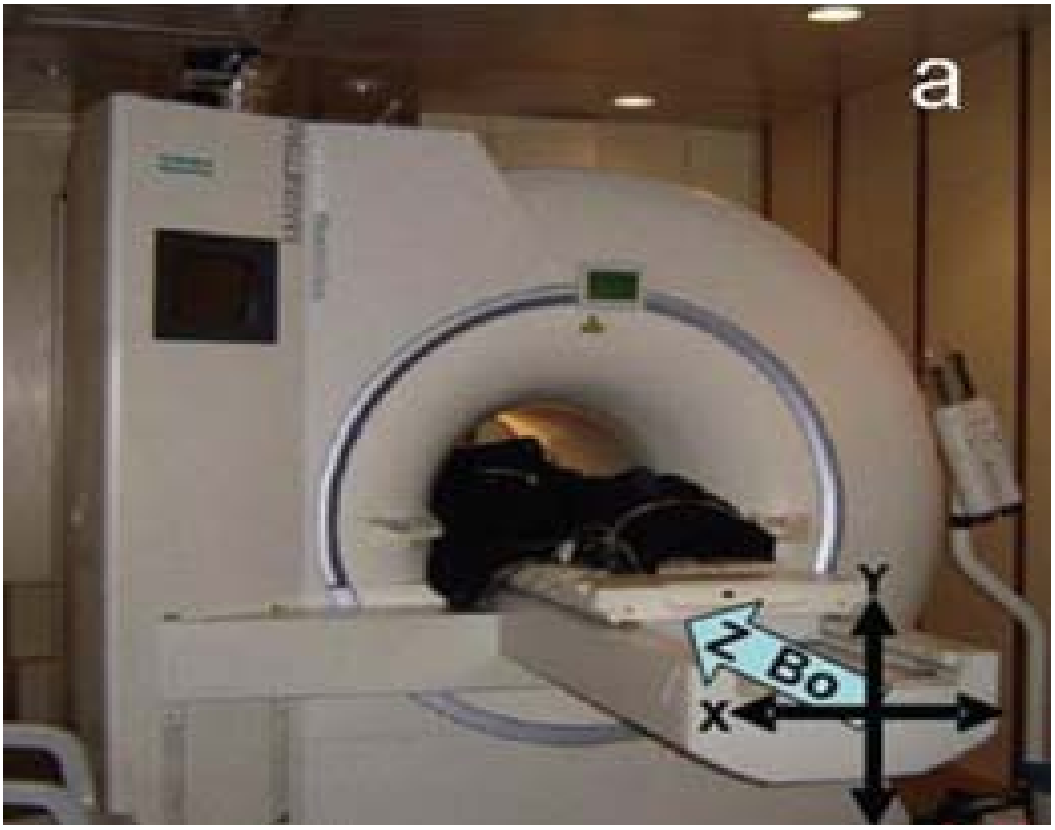
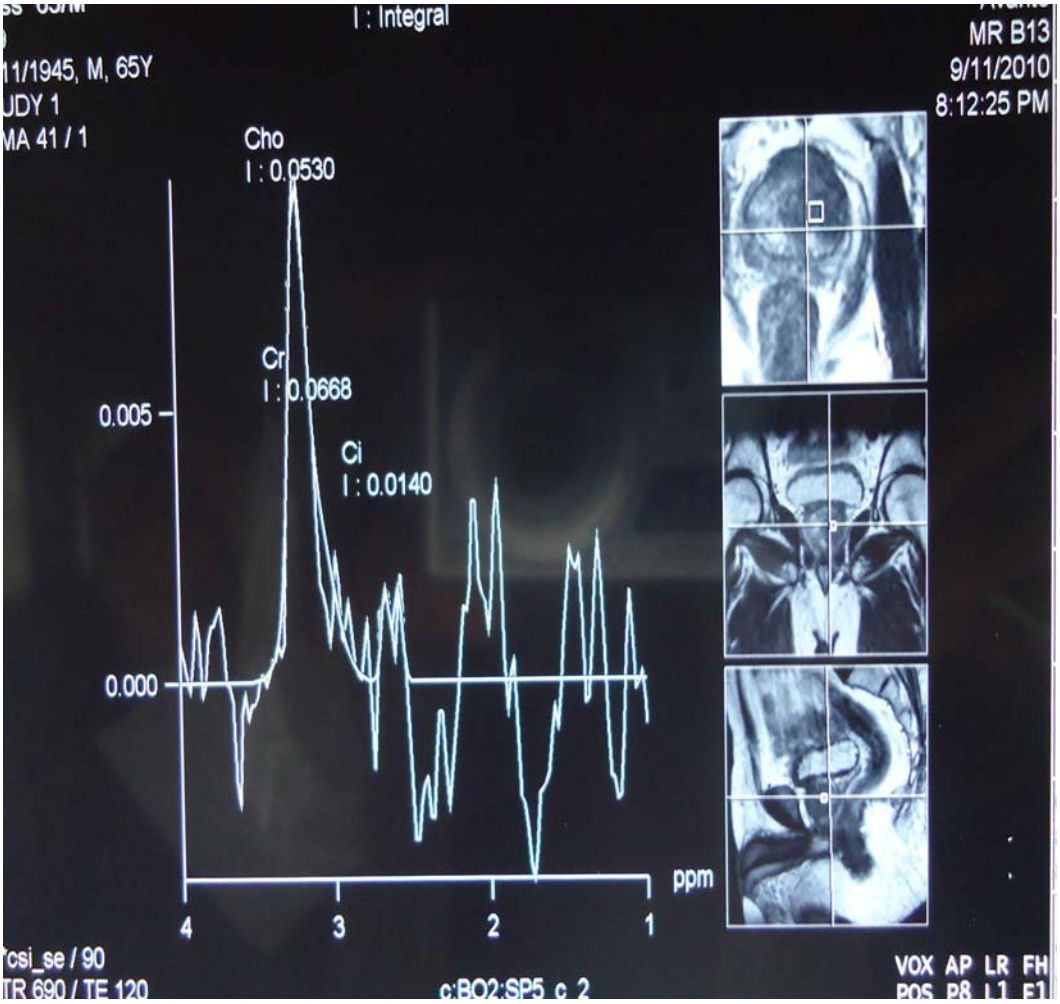

AARTHI SCANS. ALWARPET.
Cho
I : 0.0530
Ci
I : 0.0668
Ci
I : 0.0140
Cho
I : 0.0172
Ci
I : 0.0732
Cho/Cr
2010-SEP-12 21:56
AARTHI SCANS ALWARPET

Fig-6



1.5. T MRI Machine

Fig – 7



Voxel showing malignant lesion

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

"MR SPECTROSCOPY IN DIAGNOSING CA PROSTATE"

ஆராய்ச்சி நிலையம் : சிறுநீரியல் துறை,
அரசு பொது மருத்துவமனை,
சென்னை மருத்துவக்கல்லூரி,
சென்னை - 3.

பங்கு பெறுபவரின் பெயர் :
பங்குபெறுபவரின் எண் :

பங்கு பெறுவர் இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தகமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டஏாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-600 003

Telephone 25363970
Fax 044 2535115
Dated : 07.04.2010

L.Dis No.14597/ME5/Ethics Dean/MMC/2010

Title of the work : "Magnetic Resonance Spectroscopy As a non invasive Diagnostic investigation in Carcinoma Prostate !"

Principal Investigator : Dr. P.V. Srinivasan
Designation : PG in MCh. Urology
Department : Dept. of Urology
Madras Medical College, Ch-3.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 7th April 2010 at 2.p.m in Pharmacology Seminar Hall, Madras Medical College, Chennai -3

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
4. You should not deviate form the area of the work for which you applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulation of the institution(s).
7. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, MMC,CHENNAI

CHAIRMAN
IEC,MMC, CHENNAI

DEAN
MADRAS MEDICAL COLLEGE,
CHENNAI -3

“MAGNETIC RESONANCE SPECTROSCOPY AS A NONINVASIVE DIAGNOSTIC INVESTIGATION IN CARCINOMA PROSTATE”

PROFORMA

NAME: AGE & SEX

ADDRESS:

PHONE NO: URO NO:

HISTORY:

LUTS;

DM/HT/PT H/O DRUG INTAKE

PREVIOUS INTERVENTION/ SURGERY

G/E:

GENITALIA:

P.R:

INVESTIGATIONS:

Basic blood investigations ,Urine routine and C/S, RFT

Coagulation profile

USG-KUB

PSA

MRI MR spectroscopy

TRUS scan & Biopsy

MASTER CHART

s.no	Name	age	symptom	RFT	PSA	Pr.volume	DRE	Cho/cit	TRUS-Bx	gleason sum
1	subramani	64	Obst	N	8.6	28cc	gr-1	1.6	Adeno ca	2+2
2	Palani	62	Asympt	N	4.3	35cc	gr-2	0.4	BPH	
3	Ganesan	74	Obst	N	8	32cc	gr-2	1.5	Adeno ca	3+2
4	Krishnamoorhy	70	Obst	N	8.2	32cc	gr-2	1.5	Adeno ca	3+2
5	Narayanan	50	Obst	N	8.04	30cc	gr-2	0.8	BPH	
6	Doss	65	Obst	N	4.8	37cc	gr-2	0.6	BPH	
7	Dasan	70	Obst	N	6.2	30cc	gr-2	1.6	Adeno ca	3+3
8	Raman	72	Obst	N	8.06	32cc	gr-2	1.8	Adeno ca	3+4
9	Avinasi	70	Obst	N	9.6	36cc	gr-2	0.6	BPH	
10	Moorthy	56	Obst	N	4.8	30cc	gr-1	0.8	BPH	
11	Rajaram	62	Obst	N	4.6	32cc	gr-2	0.4	BPH	
12	Ramsing	68	Obst	N	4.6	30cc	gr-1	0.5	BPH	
13	Joseph	65	Obst	N	6.2	30cc	gr-1	1.5	Adeno ca	3+3
14	Subramani	70	Obst	N	9.2	32cc	gr-2	0.6	BPH	
15	Rangan	68	Obst	N	4.2	30cc	gr-1	1.2	BPH	
16	Muthu	62	Obst	N	6.2	38cc	gr-2	0.6	BPH	
17	Singaram	60	Obst	N	4.8	30cc	gr-2	0.5	BPH	
18	Philip	64	Obst	N	8.2	30cc	gr-1	1.2	BPH	
19	Kesavan	68	Obst	N	4.8	32cc	gr-2	0.5	BPH	
20	Murugan	60	Obst	N	4.2	36cc	gr-2	0.6	BPH	

BIBLIOGRAPHY

1. Rishi N, Rajeev K, Virendra K, et al. Magnetic Resonance Spectroscopic imaging in cancer prostate.BJU I 103:1614-1620, 2009.

2. Hricak H, White S, Vigneron D, et al. Carcinoma of the prostate gland: MR imaging with pelvic phased-array coils versus integrated endorectal-pelvic phased-array coils. Radiology 193:703-709, 1991.

3. Kurhanewicz J, Vigneron DB, Males RG, Swanson MG, Yu K, Hricak H. The prostate: MR imaging and spectroscopy. Present and Future. Radiol Clin North Am 38:115-138, viii-ix, 2000.

4. Costello LC, Franklin RB, and Narayan P. Citrate in the diagnosis of Prostate Cancer. The Prostate 38:237-245, 1999.

5. Costello LC, and Franklin RB. The intermediary metabolism of the prostate: A key to understanding the pathogenesis and progression of prostate malignancy. Oncology 59:269- 282, 2000.

6. Cooper JF, and Imfeld H. The role of citric acid in the physiology of the prostate: A preliminary report. J Urol 81:157-163, 1959.

7. Cooper JF, and Farid I. The role of citric acid I the physiology of the prostate: Lactic/citrate rations in benign and malignant prostatic homogenates as an index of prostatic malignancy. J Urol 92:533-536, 1964.

8. Costello LC, Liu Y, Franklin RB, Kennedy MC. Zinc inhibition of mitochondrial aconitase and its importance in citrate metabolism of prostate epithelial cells. J Biol Chem 46(14):28875-81, 1997.

9. Costello LC and Franklin RB. Novel role of zinc in the regulation of prostate citrate metabolism and its implications in prostate cancer. The Prostate 35:285-296, 1998.

10. Zaichick VY, Sviridova TV, Zaichick SV. Zinc concentration in human prostatic fluid: Normal, chronic prostatitis, adenoma and cancer. Int Urol Nephrol 28:687-694, 1996.

11. Zaichick VY, Sviridova TV, Zaichick SV. Zinc in the human prostate gland: Normal hyperplasia, cancerous. Int Urol Nephrol 29:565-574, 1997.

12. Costello LC, Franklin RB, Liu Y, Kennedy MC. Zinc causes a shift toward citrate at equilibrium of the m-

aconitase reaction of prostate mitochondria. Inorg Biochem 78:161-165, 2000.

13. Perrotti M, Han KR, Epstein RE, Kennedy EC, Rabbani F, Badani K, Pantuck AJ, Weiss RE, Cummings KB. Prospective evaluation of endorectal magnetic resonance imaging to detect tumor foci in men with prior negative prostatic biopsy: a pilot study. J Urol 162(4) 1314-7, 1999.

14. Torricelli P, Iadanza M, De Santis M, Pollastri CA, Cesinaro AM, Trentini G, Romagnoli R. Magnetic resonance with endorectal coil in the local staging of prostatic carcinoma. Comparison with histologic macrosectionis in 40 cases. Radiol Med (Torino) 97(6):491-498, 1999.

15. Negendank W. Studies of human tumors by MRS: a review. NMR Biomed 5(5):303-324, 1992.

16. Gillies RJ, Morse DL. In vivo magnetic resonance spectroscopy in cancer. Annu Rev Biomed Eng, 7:287-326, 2005.

17. Costello LC and Franklin RB. Bioenergetic theory of prostate malignancy. Prostate 25(3):162- 166, 1994.

18. Cornel EB, Smuts GA, Oosterhof GO, et al. Characterization of human prostate cancer, benign

prostatic hyperplasia and normal prostate by in vitro 1H and 31P magnetic resonance spectroscopy. J Urol 150:2019-24, 1993.

19. Kurhanewicz J, Thomas A, Jajodia P. et al., 31P spectroscopy of the human prostate gland in vivo using a transrectal probe. Magn Reson Med 22:404-413, 1991.

20. Kurhanewicz J, Dahiya R, Macdonald JM et al. Phosphorus metabolite characterization of human prostatic adenocarcinoma in a nude mouse model by 31P magnetic resonance spectroscopy and high pressure liquid chromatography. NMR Biomed 5:185-192, 1992.

21. Schiebler M, Miyamoto KK, White M, Maygarden SJ, Mohler JL. In vitro high resolution 1Hspectroscopy of the human prostate: benign prostatic hyperplasia, normal peripheral zone and adenocarcinoma. Magn Reson Med 29:285-291, 1993.

22. Kurhanewicz J, Dahiya R, Macdonald JM, Chang LH, James TL, Narayan P. Citrate alterations in primary and metastasis human prostatic Aden carcinomas: 1H magnetic resonance spectroscopy and biochemical study. Magn Reson Med 29:149-157, 1993.

23. Van der Graaf M, Schipper RG, Oosterhof GO, Schalken JA, Verhofstad AA, Heerschap A. Proton MR spectroscopy of prostatic tissue focused on the detection of spermine, a possible biomarker of malignant behavior in prostate cancer. Magma 10:153-159, 2000.

24. Childs AC, Mehta DJ, Gerner EW. Polyamine-dependent gene expression. Cell Mol Life Sci 60:1394-406, 2003.

25. Babban N and Gerner EW. Polyamines as modifiers of genetic risk factors in human intestinal cancers. Biochem. Soc Trans. 31:388-392, 2003.

26. Frahm J, Bruhn H, Gyngell ML, Merbolt KD, Hanicke W, Sauter R. Localized high-resolution proton NMR spectroscopy using echoes: initial applications to human brain in vivo. Magn Reson Med 9:79-93, 1989.

27. Bottomley PA. Spatial localization in NMR spectroscopy in vivo. Ann N Y Acad Sci, 508:333-348, 1987.

28. Heerschap A, Jager G, de Koster A, Barentsz J, de la Rosette J, Debruyne F and Ruijs J. 1H MRS of prostate pathology, in Proceedings of Soc of Magn Reson Med , 12th annual meeting, New York, 1993, p213.

29. Kurhanewicz J, Vigneron DB, Nelson SJ, Hricak HJ, McDonald JM, Konety B, Narayana P. Citrate as an in

vivo marker to discriminate prostate cancer from benign hyperplasia and normal prostate peripheral zone: detection via localized proton spectroscopy. Urology 45:459-66, 1995.

30. Brown TR. Practical applications of chemical shift imaging. NMR Biomed. 5:238-243, 1992.

31. Brown TR, Kincaid BM, and Ugurbil K. NMR chemical shift in three dimensions. Proc Natl Acad Sci USA, 79:3523-26, 1982.

32. Maudsley AA, Hilal SK, Simon HE, Wittekoek S. In vivo MR spectroscopic imaging .

31. Work in progress. Radiology 153:745-750m 1984.

33. Luyten PR, Marien AJ, den HJ. Acquisition and quantitation in proton spectroscopy. NMR Biomed 4:64-69, 1991.

34. Star-Lack J, Nelson SJ, Kurhanewicz J, Huang LR, Vigneron DB. Improved water and lipid suppression for 3D PRESS CSI using RF Band selective inversion with gradient dephasing (BASING). Magn Reson Med 38:311-321, 1997.

35. Tran T-KC, Vigneron DB, Sailasuta N, Tropp J, Le Roux P, Kurhanewicz J, Nelson S, Hurd R. Very selective

suppression pulses for clinical MRSI studies of brain and prostate cancer. Magn Reson Medi 43:23-33, 2000.

36. Star-Lack J, Vigneron DB, Pauly J, Kurhanewicz J, Nelson SJ. Improved solvent suppression and increased spatial excitation bandwidths for three-dimensional PRESS CSI using phasecompensating spectral/spatial spin-echo pulses. J Magn Reson Imaging 7:745-757,1997.

37. Males RG, Vigneron DB, Star-Lack J, Falbo SC, Nelson SJ, Hricak H, Kurhanewicz J. Clincal application of BASING and Spectral/Spatial Water and Lipid Suppression Pulses for Prostate Cancer Staging and Localization by In Vivo 3D 1H Magnetic Resonance Spectroscopic Imaging. Magn Reson Med 43:17-22, 2000.

38. Kurhanewicz J, Vigneron DB, Hricak H, Narayan P, Carroll P, Nelson SJ. Three-dimensional H-1 MR spectroscopic imaging of the in Situ human prostate with high (0.24-0.7 cm3) spatial resolution. Radiology 198:795-805, 1996.

39. Yu KK, Scheidler J, Hricak H, Vigneron DB, Zaloudek CJ, Males RG, Nelson SJ, Carroll PR, Kurhanewicz J. Prostate Cancer: Prediction of extracapsular extension with

endorectal MR imaging and three-dimensional proton MR spectroscopic imaging. Radiology 213:481-88, 1999.

40. Coakley FV, Kurhanewicz J, Liu Y et al. Prostate cancer tumor volume: Measurement by endorectal MR imaging and MR spectroscopic imaging. Radiology 223:91-97, 2002.

41. Wefer AE, Hricak H, Vigneron DB, et al. Sextant localization of prostate cancer: comparison of sextant biopsy, magnetic resonance imaging and magnetic resonance spectroscopic imaging with step section histology. J Urol 164:400-404, 2000.

42. Kurhanewicz J, Vigneron DB, Nelson SJ. Three-dimensional magnetic resonance spectroscopic imaging of brain and prostate cancer. Neoplasia 2:166-189, 2000.

43. Scheenen TWJ, Klomp DWJ, Roll SA, Futterer JJ, Barentsz JO, Heerschap A. Fast acquisitionweighted three-dimensional proton MR spectroscopic imaging of the human prostate. Magn Reson Med 52:80-88, 2004.

44. Scheenen TWJ, Gambarota G, Weiland E, Klomp DWJ, Futterer JJ, Barentsz, Heerschap A. Optimal timing for in vivo 1H-MR Spectroscopic imaging of the human prostate at 3T. MagnReson Med 53:1268-74, 2005.

45. Scheenen T, Weiland E, Futterer J, van Hecke P, Bachert P, Villeirs G, Lu J, Lichy M, Holshouser B, Roell S, Barentsz J, Heerschap A. Preliminary results of IMAPS: An International Multi-Centre Assessment of Prostate MR Spectroscopy. Proceedings of the Thirteenth Int Soc Mag Reson Med., Miami Beach, 2005, p 260.

46. Jung JA, Coakley FV, Vigneron DB, Swanson MG, Qayyum A, Weinberg V, Jones KD, Carroll PR, Kurhanewicz J. Prostate depiction at endorectal MR spectroscopic imaging: Investigation of a standardized evaluation system. Radiology 233:701-708, 2004.

47. Swanson MG, Vigneron DB, Tran T-K C, Kurhanewicz J. Magnetic resonance imaging and spectroscopic imaging of prostate cancer. Cancer Investigation 19(5):510-523, 2001.

48. Hricak H. MR imaging and MR spectroscopic imaging in the pre-treatment evaluation of prostate cancer. Br J Radiol 78:S103-S111, 2005.

49. D'Amico AV, Whittington R, Malkowicz B, et al. Endorectal magnetic resonance imaging as a predictor of biochemical outcome after radical prostatectomy in men with clinically localized prostate cancer. J Urol 164:759-763, 2000.

50. DiBiase SJ, Hosseinzadeh K, Gullapalli RP, et al. Magnetic resonance spectroscopic imagingguided brachytherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 52L429-8, 2002.

51. Mizowaki T, Cohen GN, Fung AY, Zaider M. Towards integrating functional imaging in the treatment of prostate cancer with radiation: the registration of the MR spectroscopy to ultrasound/CT images and its implementation in treatment planning. Int J Radiat Oncol Biol Phys 54:1558-64, 2002.

52. Sosna J, Rofsky NM, Gaston SM, DeWolf WC, Lenkinski RE. Determinations of prostate volume at 3-Tesla using an external phased array coil: Comparison to pathologic specimens. Acad Radiol 10:846-853, 2003.

53. Sosna J, Pedrosa I, Dewolf WC, Mahallati H, Lenkinski RE, Rofsky NM. MR imaging of the prostate at 3 Tesla: Comparison of an external phased-array coil to imaging with an endorectal coil at 1.5 Tesla. Acad Radiol 11:857-862, 2004.

54. Bloch BN, Rofsky NM, Baroni RH, Marquis RP, Pedrosa I, Lenkinski RE. 3 Tesla magnetic resonance imaging of the prostate with combined pelvic phased-array and

endorectal coils: Initial experience. Acad Radiol 11:863-867, 2004.

55. Gibbs P, Pickles MD, Turnbull LW. Diffusion imaging of the prostate at 3.0 Tesla. Invest Radiol 41(2):185-188, 2006.

56. Pickles MD, Gibbs P, Sreenivas M, Turnbull LW. Diffusion-weighted imaging of normal and malignant prostate tissue at 3.0T. J Magn Reson Imaging 23(2):130-134, 2006.

57. Shimofusa R, Fujimoto H, Akamata H, Motoori K, Yamamoto S, Ueda T, Ito H. Diffusionweighted imaging of prostate cancer. J Comput Assist Tomogr 29(2):149-153, 2005.

58. Padhani AR, Gapinski CJ, Macvicar DA, Parker GJ, Suckling J, Revell PB, Leach MO, Dearnaley DP, Husband JE. Dynamic contrast enhanced MRI of prostate cancer: Correlation with morphology and tumor stage, histological grade and PSA. Clinical Radiology 55:99-109,2000.

59. Hara N, Okuizumi M, Koiki H, Kawaguchi M, and Bali V. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a useful modality for the precise detection

and staging of early prostate cancer. The Prostate 62(2):140-147, 2004.

60. Huisman HJ, Engelbrecht MR, Barentsz JO. Accurate estimation of pharmacokinetic contrast enhanced dynamic MRI parameters of the prostate. J Magn Reson Imaging 13:607-14, 2001.

61. Engebrecht MR, Huisman HJ, Laheij RJF, Jager GJ, van Leenders GJLH, Hulsbergenvan de Kaa CA, de la Rosette JJMCH, Blickman JG. Discrimination of prostate cancer from normal peripheral zone and central gland tissue by using contrast-enhanced MR imaging. Radiology 229:248-254, 2003.

62. Buckley D, Roberts C, Parker GJM, Hutchinson CE. Prostate Cancer:Evaluation of vascular characteristics with dynamic contrast-enhanced T1-weighted MR imaging – Initial experience. Radiology 233:709-15, 2004.

63. van Dorsten FA, van der Graaf M, Engelbrecht MR, van Leenders GJLH, Verhofstad A, Rjpkema M, de la Rosette JJMCH, Barentsz JO, Heerschap A. Combined quantitative dynamic contrast enhanced MR imaging and 1H MR spectroscopic imaging of human prostate cancer. J Magn Reson Imaging 20:279-287, 2004

64. Wantanabe et al.,1968.Wantanabe H, Kato H, Kato T, Masayoshi M: Diagnostic applications of the ultrosonotomography for the prostate. Jpn J Urol 1968; 59:273-279.

65. Hodge et al., 1989a. Hodge KK, Mc Neal JE, Stamey TA: Ultrasound guided transrectal core biopsies of the palpably abnormal prostate. J Urol 1989; 142:66-70.

66. Hodge et al., 1989b. Hodge KK, Mc Neal JE, Terris MK, Stamey TA: Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol 1989;142:71-75.

67. Halpern and strup.2000. Halpern EJ, Strup SE: Using grey scale and color and power Doppler sonography to detect prostatic cancer. AJR 2000; 174:623-627.

68. Beerlage, 2003. Beerlage HP: Alternative therapies for localized prostate cancer. Curr Urol Rep 2003; 4: 216-220.

69. Shinohara et al.,1989. Shinohara K, Wheeler TM, Scardino PT: The appearance of prostate cancer on transrectal ultrasonography: Correlation of imaging and pathological examinations. J Urol 1989; 142:76-82.

70. Onur et al.,2004. Onur R, Littrup PJ, Pontes JE, Biancojr FJ: Contemporary impact of trans rectal ultrasound lesion for prostate cancer detection. J Urol 2004; 172: 512-514.

71. Bude and Rubin, 1996. Bude RO, Rubin JM: Power Doppler sonography. Radiology 1996; 200: 21-23.

72. Klauser et al., 2003. KLAUSER a, Koppel staetter F, Horninger W, et al: Real-time elastography for prostate cancer detection: Preliminary experience [abstract] Radio Soc North Am 2003; 89-665-666.

73. Ives et al.,2005. Ives EP, Waldman L, Gomella LG, Halpern EJ: Proceeding of the 105 th Annual meeting of the American Roentgen Ray Socity. AJR Am J Roentgenol 2005;[4 suppl]: 61.

74. Catalona et al., 1994b. Catalona WJ, Richie JP, Ahmann, et al; Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: Results of a multicenter clinical trial of 6, 630 men. J Urol 1994: 151: 1283

75. Littrup et al., 1994. Littrup PJ, Kane RA, Mettlin CJ, et al: Cost effective prostate cancer detection. Cancer 1994; 74: 3146.

76. Stone et al., 1994. Stone NN, De Antoni EP, Crawford ED: Screening of prostate cancer by digital rectal examination and prostate specific antigen: Results of prostate cancer awareness week, 1982-1992. Urology 1994; 44: 18.

77. Bangma et al., 1995. Bangma CH, Kranse R, Blijenberg BG, Schoeder FH: The value of screening tests in the detection of prostate cancer, Part 1: Results of a retrospective evaluation of 1726 men. Urology 1995; 46: 773.

78. Vander cruijsen-Koeter et al., 2001. Vander cruijsen-Koeter IW, Wildhagen MF, Dekoneis HJ, Schroder FH: The value of current diagnostic tests in prostate cancer screening. BJU int 2001; 88: 458.

79. Carter et al., 1989. Carter HB, Hamper UM, Sheth S, et al: Evaluation of transrectal ultrasound in the diagnosis of prostate cancer. J Urol 1989: 142: 1008.

80. Ellis et al., 1994. Ellis WJ, Chetner MP, Preston SD, Brawer MK: Diagnosis of prostatic carcinoma: The

yield of serum prostate specific antigen, digital rectal examination and transrectal ultrasonography. J Urol 1994; 52: 1520

81. Flanigan et al., 1994. Flanigan RC, Catalona WJ, Richie JP, et al: Accuracy of digital rectal examination and transrectal ultrasonography in localizing prostate cancer. J Urol 1994; 152: 1506

82. Gosselaar et al., 2005. Gosselaar C, Roobol MJ, Schroder FH: Prevalence and charecteristics of screen detected prostatic carcinoma at low prostate-specific antigen level: Aggressive or insignificant ? BJU int 2005; 95: 231

83. Carter, 2000. Carter HB, A PSA threshold of 4ng/ml for early detection of prostate cancer. The only rational approach for men 50 years old and older. Urology 2000: 55: 796

84. Carter, 2004. Carter HB; Prostate cancer in men with low PSA levels- Must we find them ? N Engl J Med 2004; 350: 2292

85. Catalona et al., 2000a. Catalona WJ, Ramos CG, Carvalhal GF, Yan Y: Lowering PSA cutoffs to

enhance detection of curable prostate cancer. Urology 2000; 55: 791

86. Morgan et al., 1996. Morgan TO, Jacobsen SJ, Mc carthy WF, et al: Age specific reference ranges for prostate specific antigen in black men. N Engl Med 1996; 335:304

87. Catalona et al., 1995. Catalona WJ, Smith DS, Wolfert RL, et al: Evaluation of percentage of free serum prostate specific antigen to improve specificity of prostate cancer screening. JAMA 1995; 274:1214

88. Rifkin et al., 1990. Rifkin MD, Zerhowni EA, Gatsonis CA, et al: Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. Results of a multi institutional co operative trial. N Engl J Med 1990; 323: 621

89. Naughton CK, Smith DS, Humphrey PA, Catalona WJ, Keetch DW. Clinical and pathological tumour charactericstics of prostate cancer as a function of number of biopsy cores: A retrospective study. Urology 1998; 52: 808-13

90. Rabbani F, Stroumbakis N, Kava BR, Cookson MS, Fair WR. Incidence and clinical significance of false

negative sectant prostate biopsies. J Urol 1998; 159: 1247-50

91. Kumar V, Jagannathan NR, Kumar R, et al. Transrectal ultrasound guided biopsy of prostate voxels identified as suspicious of malignancy on three dimensional 1H MR Spectroscopic imaging in patients with abnormal digital rectal examination or raised prostate specific antigen level of 4-10ng/ml. NMR Biomed 2007; 20: 11-20

92. Sheidler J, Hricak H, Vigneron DB, et al.,Prostate cancer: Localization with three dimentional proton MR Spectroscopic imaging- clicico pathologic study. Radiology 1999: 213:473-80

93. Cockley FV, Kurhanewicz J, Luy, et al. Prostate cancer tumour volume measurement with endorectal MR Spectroscopic imaging. Radiology 2002; 223: 91-7.

94. Kumar V, Jagannathan NR, Kumar R et al., 3D 1H MRI based TRUS guided biopsies in men with suspected prostate cancer. Proc inti soc Mag Reson Med 2006: 14: 1790.

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FORWARDING CERTIFICATE

This is to certify that the dissertation titled "**Role of Magnetic resenonce spectroscopy as a noninvasive diagnostic investigation in carcinoma prosatate**" submitted by Dr.P.V.Srinivasan appearing for M.Ch. (Urology) degree examination in August 2011, is a bonafide record of work done by him under my guidance and supervision in partial fulfillment of requirement of the Tamil Nadu Dr.M.G.R.Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R.Medical University, Chennai.

Prof.R.Jeyaraman, M.S., M.Ch.,
Professor & Head of the Department,
Department of Urology,
Government General Hospital,
Madras Medical College,
Chennai – 600 003.

The Dean,
Madras Medical College,
Chennai – 600 003.

DECLARATION

I solemnly declare that this dissertation titled **“ MAGNETIC RESONANCE SPECTROSCOPY AS A NONINVASIVE DIAGNOSTIC INVESTIGATION IN CARCINOMA PROSTATE**” was prepared by me in the Department of Urology, Government General Hospital, Chennai under the guidance and supervision of Prof. R. Jeyaraman,M.S,M.Ch., Professor & Head of the Department, Department of urology, Government General Hospital, Chennai between 2008 and 2011.

This dissertation is submitted to the Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of M.Ch. Urology.

Dr.P.V.SRINIVASAN

Place : Chennai

Date :

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