2014

Multiparametric 3 Tesla magnetic resonance imaging as a clinical tool to characterize prostate cancer

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https://hdl.handle.net/2144/15343

Boston University
MULTIPARAMETRIC 3 TESLA MAGNETIC RESONANCE IMAGING
AS A CLINICAL TOOL TO CHARACTERIZE PROSTATE CANCER

by

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Submitted in partial fulfillment of the
requirements for the degree of
Master of Science
2014
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ACKNOWLEDGMENTS

I want to thank all those that have helped me on this journey in completing my thesis. Dr. Yanping Sun, for your guidance. Dr. Bloch, Dr. Andry, Dr. Killiany, and Dr. Jara, for your guidance and wisdom throughout the program and thesis ups and downs. Dr. Tempany, Dr. Rofsky, Dr. Babayan, Dr. Wang, Dr. Smith, Dr. Katz, and Dr. Kaplan, for taking the time out of your busy schedules to meet and contribute to this body of work. I will be forever grateful for the support of my fellow MBI program colleagues, we struggled and made it together. Lastly, but no less important, I would not be here today and have made it where I am without the constant support of my family and friends.
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MATTHEW CHRISTOPHER DUNN

ABSTRACT

Scientists have come a long way in understanding prostate cancer as a disease and how its progression affects the men who develop it. Prostate adenocarcinoma may be present without causing clinical symptoms. Prostate cancer may metastasize, which increases the likelihood of fatality. The cause of the disease is still not completely clear, but genetics, race, tissue damage, history of previous infections, diet, and environmental influences appear to play a role in its development. Magnetic resonance imaging (MRI) has become an excellent clinical tool to characterize prostate cancer without the use of ionizing radiation or surgery. It is concluded that MRI is the optimal imaging modality to achieve detection, characterization, and staging of intracapsular and extracapsular prostate disease. The advances in MRI technology, particularly 3 Tesla, allows for reduced surgical intervention thus improving quality of life for patients with the disease.
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LIST OF ABBREVIATIONS

ADC.................................................................apparent diffusion coefficient
AR .............................................................androgen receptor
BPH..........................................................benign prostatic hyperplasia/hypertrophy
BS..............................................................bone scintigraphy
BU .............................................................Boston University
CAD........................................................computer-assisted diagnosis
CE .............................................................contrast enhanced
CNR..........................................................contrast-to-noise ratio
CT..............................................................computed tomography
CZ..............................................................central zone
DCE..........................................................dynamic contrast enhanced
DNA..........................................................deoxyribonucleic acid
DRE...........................................................digital rectal exam
DWI ...........................................................diffusion weighted imaging
FA..............................................................flip angle
FDG..........................................................fluorodeoxyglucose
ISO ........................................................ International Standards Organization
MDP..........................................................methylene diphosphonate
mpMRI........................................................multiparametric magnetic resonance imaging
MRI..........................................................magnetic resonance imaging
MRS/MRSI........................................ magnetic resonance spectroscopy (imaging)
PCa .............................................................. Prostate cancer / prostate carcinoma
PET ............................................................. positron emission tomography
PLN .............................................................. pelvic lymph node
PSA ............................................................. prostatic specific antigen
PZ .............................................................. peripheral zone
SNR ............................................................. signal-to-noise ratio
SPECT ..................................................... single-photon emission computed tomography
SV ............................................................. seminal vesicles
T ................................................................. Tesla
T1-w ............................................................ T1-weighted imaging
T2-w ............................................................ T2-weighted imaging
Tc ............................................................ technetium
TNM .......................................................... primary tumor, lymph nodes, distant metastasis
TRUS .......................................................... transrectal ultrasound
TZ ............................................................. transition zone
US ............................................................. ultrasound
USA ........................................................... United States of America
INTRODUCTION

Prostate anatomy and the pelvic environment facilitate the development of multiple diseases. Carcinoma of the prostate is common in men in the developed world, with racial differences putting some populations at greater risk. Since the 1980s, the digital age has increased knowledge of the prostate environment. MRI of the prostate has slowly gained popularity, until now, where the modality has surpassed the other modalities in the clinical setting. This paper will paint illustrate the current environment of clinical prostate magnetic resonance imaging that is not just medical, but political, social, and economical.

The Prostate

The pelvic region of the human body is full of vital organs for the species to survive. The organs in this region are involved in reproduction, nutrient retention, blood supply to lower extremities, and excretion. One of these organs is only to be found in male pelvis, the prostate. The prostate is a part of the male reproductive system as an unpaired accessory structure. The prostate gland is located at the proximal end of the urethra after it has left the urinary bladder and anterior to the rectum.
The size of this organ varies over the age of a man and grows in volume over time. Prostate tissue consists of about thirty to fifty compound tubuloalveolar glands (epithelial elements), surrounded by and wrapped in a very thick layer of smooth muscle fibers (stromal elements). The gland primarily consists of cells that function to produce exocrine or endocrine secretions. Basal epithelial cells of the prostate tend to be the biggest source for the initiation of carcinoma of the prostate (PCa) tumors. Continuation or maintenance of the tumor is by luminal like epithelial cells (Stoyanova et al, 2013). The glands within the prostate serve an important function in the male reproductive system. They each produce an acidic solution that, when needed, is added to the semen flow during ejaculation. In fact, the liquid contributes between twenty and thirty percent of the total exiting semen volume. The secretions are passed through the prostatic urethra, where movement occurs due to the contractions of the
It is important to understand conventional medicine’s partitioning of the prostate into three zones, consisting of the peripheral zone (PZ), central zone (CZ), and transition zone (TZ) of the gland. The PZ is the outer region of the prostate, and is well known to be very sensitive to androgen levels. The zone is consistently has higher incidence of PCa than the other regions of the gland. Androgens are hormones that affect or stimulate the maintaining or developing of male attributes by coming together with androgen receptors (ARs). This contributes to PCa, which is substantiated by evidence that PCa is inhibited or does not develop when males undergo an orchiectomy or if they are castrated prior to puberty (Kumar et al, 2007). The CZ is the inner region of the prostate gland, which tends to be very sensitive to estrogen and have higher incidence of benign prostatic hyperplasia (BPH) relative to other regions of the gland. The TZ of the prostate gland is the area in direct proximity to the urethra (McPhee and Hammer, 2010). This zone contains ducts and stromal tissue that helps transport prostatic fluid. The TZ came about due to comprehension of BPH and was a term developed by John E. McNeal in 1978 (Selman, 2011).

Cancer and the Prostate

Diseases of the prostate are complex and require understanding the environment where the prostate tissue exists in order to have a complete comprehension of origination. The prostate gland has two major ducts that...
converge inside the organ to focus the outward flow of the fluids through one duct to exit through the penis. In addition, the prostate gland sometimes has added pressure from the bladder and the rectum, which are adjacent to the prostate, as they perform their bodily functions. This puts the prostate at risk from irritation internally and externally, and subsequently inflammation as a response to injury. Bacteria is another avenue for disease in the gland by traveling up or down the ducts into the prostate, for example chlamydia. Another intensely studied epidemiological aspect of disease in the organ is genetics, both inherited deoxyribonucleic acid (DNA) mutations and related DNA mutations. Genetic abnormalities can cause the various cell types in the prostate to replicate uncontrollably.

Diseases that are common to the prostate include various types of prostatitis, benign prostatic hyperplasia (BPH) and carcinoma. Prostatitis is swelling and inflammation of the prostate gland. The swelling or inflammation is a response to injury and sometimes occurs in conjunction with infections that can be a result of bacterial presence. This type of disease in the gland is characterized by several factors, which include but are not limited to: neutrophilic inflammatory infiltrate, stromal edema, glandular injury, lymphoid infiltrate, fibroblastic proliferation, foamy histiocytes, eosinophils, bacterial presence, microabscess formation, and leukocytic infiltration. On a larger scale, prostatitis can cause clinical symptoms, such as fever, pelvic pain, lower back pain, urination frequency changes, and even dysuria (Kumar et al, 2007). Onset of
prostatitis can also be caused by procedures on the prostate, such as biopsies, where the injury to the gland elicits a response of inflammation and swelling.

Another common disease is hyperplasia of the prostate gland, which is known as nodular hyperplasia of the prostate or benign prostatic hyperplasia (BPH), glandular hyperplasia, or stromal hyperplasia. Hyperplasia describes an increase in the number of cells in tissue and organs as a response to pathologic or physiologic alterations to the normal state. This disease is readily identifiable by utilizing the medical imaging modality, magnetic resonance imaging (MRI). Hyperplasia is found to be most prevalent in the transitional and central zones of the gland. Histologically, BPH is characterized by stromal and epithelial cells that have proliferated in the gland resulting in the enlargement of the gland and leading to possible obstruction of urinary flow. Other important morphology is that the disease forms nodules that are either solid or have cystic spaces (Kumar et al, 2007).

Unfortunately, BPH is not completely understood, but most theories point to the impact of hormonal influence. Research has shown androgens as the focus, citing that men with nodular hyperplasia have drastically increased stimulation of dihydrotestosterone, 3-alpha-androstandediol, and 5-alpha-reductase. Treatments have involved using inhibitors to prevent hormones from connecting with their receptors, such as the 5-alpha-reductase inhibitor. Males do not develop this condition when the testicles are removed prior to entering
puberty. This is informative because it verifies that hormones are involved, but it also suggests age as a factor (Kumar et al, 2007).

The most common cancer of the prostate is carcinoma of the prostate. Prostate cancers are mostly represented as prostate adenocarcinomas (about 95%), and about 5% of the carcinomas are squamous cell carcinoma, signet-ring carcinoma, transitional carcinoma, neuroendocrine carcinoma or sarcoma (Alivatos and Pavlos, 2014). Similar to BPH, this disease does not develop in males that have had their testicles removed (known as orchiectomy) prior to the initiation of puberty (Kumar et al, 2007). This links hormonal stimulation to the disease progression, more specifically androgens. Research has shown that there may be genetic and environmental links. The cancer develops primarily in the PZ of the prostate, but may develop in the CZ or TZ, especially in advanced stages of the disease (Kumar et al, 2007; McPhee and Hammer, 2010). The PZ tumors are palpable by digital rectal exam (DRE) because they tend to be hard nodules that are irregular in shape.

Early on, the disease tends to be of an ill-defined mass or masses, with margins that are difficult to differentiate. The carcinoma starts in the prostate gland, after which it spreads to the seminal vesicles (SV) and pelvic lymph nodes (PLNs). This is frequently followed by metastatic tumors in the urinary bladder wall and local pelvic bone structures. Clinically these are rare manifestations in the early stages of the disease. The disease tends to be discovered after a series of tests, such as the DRE, and the blood lab test measuring prostate
specific antigen (PSA). The disease can have high rates of entering remission, if the disease is caught early on, meaning prior to escaping the capsule of the prostate gland. The disease is generally characterized by a combination of test results that include the PSA blood test, biopsy, and imaging of the gland and surrounding tissues and structures. These tests provide information to guide clinicians in grading the tumor burden of the individual.

Socioeconomics

Carcinoma of the prostate is a social and an economic disease. This type of cancer appears primarily in developed countries of world. Not only that, but the most developed countries, such as the United States of America (USA) and countries in Europe, are where essentially the majority of the incidence are located on a yearly basis. The USA has the highest incidence of prostate carcinoma with hundreds of thousands of new prostate adenocarcinoma incidents each year and rising. This trend is substantiated in the literature. In 1999 there were 167,439 new cases of prostate adenocarcinoma (U.S. Cancer Statistics Working Group, 2013), and 189,000 new cases of prostate cancer and 30,200 prostate cancer related deaths in 2002 (National Cancer Institute, 2012). These rates rose to 192,280 new cases and 27,360 deaths related to prostate cancer in the USA in 2009 (American Cancer Society, 2009). Recently in 2013, the number of new cases reached 238,590 with 29,720 deaths related to the disease (Crawford et al, 2014).
Table 1: Center of Disease Control's US Cancer Statistics 1999 and 2010 for Prostate Cancer

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<td>130.1</td>
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<tr>
<td>Hispanic</td>
<td>54.6</td>
<td>6</td>
<td>49.6</td>
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Rates written as per 100,000 people compares incidences and mortality rates of prostate cancer by race in the United States of America (U.S. Cancer Statistics Working Group, 2013).

Looking at the statistics of a country’s trends and raw numbers, such as the USA, is a difficult task because of all the variations in data collection processes. The connection is possible when examining a particular state or city, for example Massachusetts and Boston. Boston serves as a model microcosm for the disease in the USA when looking at prostate cancer data. This is verified by the incidence rate of prostate cancer which closely matches the national incidence of recent prostate cancer trends (Boston Public Health Commission, 2011; American Cancer Society, 2014).

Figure 2: Prostate Cancer Incidence

The trends in the incidence rates when comparing races, are similar in that Black males tended to have the highest incidence of prostate adenocarcinoma, followed by Caucasian males, while Asian men tended to have the lowest incidence (Massachusetts Department of Public Health, 2012; Boston Public Health Commission, 2010; American Cancer Society, 2014; Siegel et al, 2014). Black residents of Boston have reported socioeconomic challenges that are shown to be disproportionately higher when compared to other Caucasian residents. They have significantly higher infant mortality rates, exposure to violence, higher rates of diabetes and higher hospitalization for heart disease (Boston Public Health Commission, 2010). Black men are disproportionately at a disadvantage in Boston, historically, from a social and economic perspective. This group of the population in Boston has high rates of poverty, underemployment, incarceration, lower amount of educational achievement, and higher rates of prostate cancer compared to other racial groups in Boston (Boston Public Health Commission, 2011; Boston Public Health Commission, 2013).

**Molecules, Genetics, Race**

Genetic testing at a genome wide level in each individual is providing a huge increase in understanding PCa and how it develops. Research has been focused on genetic susceptibility to PCa comparing various ethnicities, particularly men of European descent compared to men of African descent. The focus has been on androgen receptor activity, genes related to prostate cancer,
and methylation, which have been related to race, diet, age, and the environment (Farrell et al, 2013). Research has shown, based on primary tumor analysis, which metastatic promoting genes are found to be more highly expressed in African American samples compared to European American samples when using microarray technology (Powell et al, 2013).

The androgen receptor gene (AR gene) located on chromosome Xq11-12 is of particular interest as its first exon code has shown to be significantly different between African-Americans and Caucasian-Americans. This relates to the number of CAG repeats. The risk of developing and degree of aggressiveness of the prostate cancer is increased in populations with fewer CAG repeats, which African-American males tend to have significantly fewer of them compared to their Caucasian-American counterparts. This is supported by evidence demonstrating reduced CAG repeats allows for the increased likelihood of androgen-driven prostate adenocarcinoma. The genetic structure of the androgen receptor is of importance, but the overall genomic function of the androgen receptor is just as essential. Research has found that this particular genetic structure is significantly higher in African-Americans compared to other populations (Farrell et al, 2013).

Studies have reviewed inheritance and risk of PCa, especially since there appear to be racial differences in incidence. Epidemiology studies have found that a man’s risk of developing prostate cancer is 2.5 times as likely if they have a first-degree family member that has it, 3.37 times as likely if they have a
brother with it, 2.17 times as likely if they have an affected father, and 5 times as likely if they have two or more first-degree relatives with PCa. Over thirty-five alleles have been identified as inherited and associated with prostate cancer, and there are differences between African-Americans and Caucasian-Americans (Farrell et al, 2013).

Heritance and AR understanding in relation to prostate cancer allows for comprehending part of the puzzle that genetics of prostate cancer involves. The next piece of the puzzle is epigenetics, more specifically, methylation. Research compared prostate cancer tissue in African-Americans versus Caucasian-Americans in the amount of methylation of known genes. It was found that regulatory gene of prostate disease, including SPARC, TIMP3, AR, and NNX2-5 had greater levels of methylation in African American prostate cancer tissue compared to their Caucasian American counterparts (Farrell et al, 2013). Another study found in addition to AR, SPARC, and TIMP3 that RARbeta2 and GSTP1 have higher methylation prevalence in African Americans compared to Caucasian American males when analysis was done on normal prostate and PCa tissues samples. While methylation increases with age, the significance in the above findings is that it is above and beyond what is considered normal (Kwabi-Addo et al, 2010).  

**Categorizing the Malignancy**

The carcinoma of the prostate is typically a slow growing disease for most in whom the disease develops. The first step is determine who has the disease
through screening using the prostate specific antigen (PSA) test and digital rectal exam (DRE). It is important to determine what type of prostate cancer that patient has, level of progression and degree of aggressiveness. Prostate cancer is characterized by multiple tests and/or grading systems in what is called “staging”. These include Gleason scores based on biopsies and prostatectomy, TNM staging documentation and imaging results. Staging is defined as the “extent or severity of a person’s cancer” (National Cancer Institute, 2013). The previous mentioned are usually done in some combination to provide a multiple approach point of view to inform clinicians of the presenting patient’s prostate health or disease. The utilization of diagnostic tests prevents the need for exploratory surgery and improves standard of care for the patients involved.

The DRE is generally the first test men experience in regards to prostate health, which is the initial screening step. This exam has been important to finding the disease in men and considered part of primary care physicians’ annual physical exam for adult males by the age of 40 years old, but could be done earlier for men with relative(s) that have a history of prostate cancer. However, the doctors that use this technique are not guaranteed to find malignancies. The obstacles that are faced are the limited capability of the technique, finger sensitivity of the doctor performing the exam, doctors’ expertise with technique, and interobserver variability. New doctors are relying less and less on the DRE and focusing their base of information on imaging and other forms of technology.
The other test that may be performed separately or in conjunction with the DRE is a blood based laboratory test. The test is known as the prostate specific antigen (PSA) test, which is part of the screening process for prostate cancer. The blood test measures the antigen levels of PSA at nanogram per milliliter levels. The value is based on the premise that prostates produce prostate specific antigens. The levels vary dependent on the individual and age with respect to glandular health, but there are general guidelines what is considered healthy, abnormal or biochemical failure. The understanding is that a man’s PSA level will rise with age, but a certain increase from two consecutive blood tests or more would indicate various changes in health.
Male residents of Boston's prostate specific antigen testing rates for 2008 by various demographics. The asterisks are for demographics with insufficient data (Boston Public Health Commission, 2010).

Doctors consider a serum PSA value of 4.0 ng/mL or lower as in the normal range, but with a value that is above that range, doctors tend to recommend a biopsy to localize possible disease and extent of disease (National Cancer Institute, 2012; Barentsz et al, 2012).
A patient that has a positive DRE and an elevated PSA serum value will proceed to have a prostate biopsy. The histology of the prostate biopsy is evaluated using the Gleason grading system to assess prostate tissue pathology. The Gleason grading concept is based on the premise that it should be graded...
on the basis of just the architectural pattern of the tumor. The grading is given based on pattern categories of one (lowest grade) to five (highest grade). The score a patient receives is based on clinicians adding up the primary and secondary pattern category grades, which can be the same. The range of the scoring is two to ten, where two is the lowest score and may indicate that the sample is not cancer, while a ten is considered the most advanced stage of cancer. This scoring system is usually used in conjunction with other testing methods to discern health of the prostate tissues (Epstein et al, 2005).

The classification systems used in staging of carcinoma of the prostate are TNM and D'Amico. The TNM Classification of Malignant Tumours 7th edition went into effect in 2010 and has been the standard for staging PCa in patients. The system relies on physical exam, imaging, laboratory tests, pathology reports, and surgical reporting results. The analysis of data informs clinicians about the primary tumor in size and extent; nodular disease in the amount of spread to local lymph nodes; and metastatic disease spread to other body parts and possible secondary tumors. This system is used on an international scale and recently there has been a push for improved standardized grading to limit interobserver variability and incorrect grading (Alivatos and Pavlos, 2014; National Cancer Institute, 2013). The D'Amico Risk Classification is a method of arranging patients with prostate cancer that have had surgery into low, intermediate, and high risk groups for biochemical failure suggesting recurrence according to TNM staging at the clinical level, Gleason score from biopsy, and
pre-surgical PSA serum level. This model is used generally in conjunction with other tests. There is evidence that the relevance of this method may be becoming irrelevant based on shifting patient population (Hernandez et al, 2007).

Imaging is what holds the key in today’s world of clinical medicine to characterize prostate cancer in a more complete manner without necessarily needing surgery or biopsy. The modalities and their abilities have been tested with prostate cancer, some since before 1985. Clinical imaging of the prostate is constantly evolving over time as doctors learn new techniques and realize limits of other imaging modalities.

**Imaging Techniques**

Imaging has been at the center of the evolution in understanding of PCa. Imaging has come a long way from histology imaging to digital modalities, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), computed tomography (CT), ultrasound (US), bone scintigraphy (BS), and magnetic resonance imaging (MRI). These imaging modalities each have made contributions individually, in various combinations. Imaging has become standard to the clinical practice of diagnosing and staging of the disease. Imaging is complicated by trade-offs because some modalities provide fast imaging with poor resolution, while others take more time with better resolution. Some of the modalities emit ionizing radiation to patients, which adds to the risk a patient gains in order to be diagnosed, to localize treatment or to stage the disease.
The imaging modality that developed as a novelty to be the most preferred imaging technique by doctors the world is transrectal ultrasound (TRUS) technique. The typical image for the 2D gray scale TRUS is one that has the prostate in the field of view and a lesion that is hypoechoic. This image is in stark contrast to the sonograph of the normal prostate, which is one that has an echo pattern that is uniform. The 3D gray scale TRUS technique is one that is helpful for localizing extracapsular disease, but has similar sensitivity and specificity compared to the 2D gray scale TRUS. The Doppler US technique relies on blood flow rates in the case of imaging of the prostate and the possible
tumor will have different glow then the normal tissues it is surrounded by. Doppler is more time consuming and carries higher costs when compared to 2D or 3D gray scale TRUS options. Ultimately, this form of US is not suggested for prostate cancer as it has yet to be proven as a better option than the 2D TRUS.

Compression elastography, otherwise known as strain elastography, looks at the differentiation of tissue stiffness as it reacts to an applied force from US. This technique provides the 3D volume rendering with more details that help doctors understand the lesion(s) better, especially those located in the peripheral zone. These more detailed results allow for better staging and treatment planning. The other clinical elastographic technique is known as shear wave elastography. Shear wave is where a color coded image is superimposed on a B-mode image, and in the prostate that means the region(s) that are dark blue are possible lesion(s). When deciding which of the elastographic techniques to use, the shear wave method takes less time, but requires the tradeoff of needing more training to operate correctly.

The last US technique to be discussed is contrast enhanced ultrasound (CE-US). The CE-US technique utilizes highly echogenic microbubble contrast agents, where injectable gas is contained within a supporting shell. This allows for increased visibility of density vascular regions of the prostate, which is correlated with prostate adenocarcinoma lesions. If and when patients need a biopsy, it has become rather standard to use US to guide how and where the need to collect the biopsy is placed. US allows for more effective planning in
biopsy locations, which gives clinicians a higher rate of retrieving a sample of the tissue in question and not missing the tissue. This modality has seen many advances in machine finesse, pulse decisions, and refining of known methods, all while the digital world has evolved as well. US has been utilized most effectively in helping define possible malignancies in the prostate, where tissues are in contrast to one another. The following modalities will illustrate methods that help inform doctors of possible metastasis in the patients (Uchida et al, 2009; Seitz et al, 2011; Alivatos and Pavlos, 2014).

Nuclear medicine has developed several techniques, one is bone scintigraphy (BS). BS is sensitive to detecting bone and joint disease. The diseases it tends to illuminate are bone metastatic tumors, benign bone disease, and a whole list of degenerative joint disease. BS has become highly important in efficiently providing disease localization within a patient in one scan. There are a few issues that make this a less than absolute decision to use this modality. One is that ionizing radiation is administered, by way of tracers such as methylene diphosphonate (MDP) labeled with Technetium 99m (Tc-99m). This is a rather controversial issue, but usually when it comes to this modality it is a complete necessity. Another reason is that while BS is effective at localizing disease in the bone and joints, it is not specific. What appears suspicious on the images could be bone metastatic tumor(s) from prostate cancer, but it could be Paget’s disease among many possibilities (Alivatos and Pavlos, 2014). Suspicious uptake regions could be something else besides disease; it could be
bone scan “flare”. Correctly reading these exams is a difficult task for complex patient cases leading to interobserver variability. This can be limited by the use of manual or automated (use of computer-assisted diagnosis (CAD) software) (Tait et al, 2014). A weakness that is known, but not always thought of when analyzing BS is the images are of the secondary effects the tumor has on the skeleton, known as osteoblastic reaction, and not the tumor proliferation. This knowledge helps us make sense of the finding that micro-infiltrations by tumor lesions are not detectable (Crawford et al, 2014).

Bone scintigraphy lacks in providing planar diagnostic accuracy; the other modalities of nuclear medicine, which have the ability to be combined with x-ray technology have helped refine and improve scintigraphy. The options that are currently in use are single-photon emission computed tomography (SPECT) and positron emission tomography (PET) for prostate cancer. SPECT and PET may be stand along modalities, but can be combined with computed tomography (CT). From the point of view of radiotherapy, PET is part of a type of imaging coined as theragnostic imaging. In theragnostic imaging, molecular imaging is introduced to allow clinicians to draw and selectively treat each of the voxels of tumor volume with dose painting based on the biological and functional characterization (De Bari et al, 2014). PET and SPECT are valuable at providing 3D views of the patients with the use of radioactive isotope tracers that the human body is able to absorb (uptake), and exit the body through excretions.
after time passes. Both use sugar to see how the possible tumor(s) or lesion(s) metabolize it, typically fluorodeoxyglucose (FDG) is preferred carrier of the label.

If an institute has the ability to have a cyclotron on site, than the best tracer based on current publications is the carbon-11 (11 C) isotope because it has a blood clearance of five minutes and rapid uptake in prostatic tissue that is between three and five minutes. The isotope requires this because there is a 20 minute half-life. Unfortunately, many institutions can-not afford financially or physically to have such a device, so the isotope is usually fluorine-18 (18F) or technetium-99 (99Tc) that is attached to something such as choline (Cho), sodium fluoride (NaF), MDP (phosphonate), or FDG (glucose analog). These modalities struggle to provide high value information to clinicians as fluorodeoxyglucose (FDG) has a low uptake otherwise known as low avidity. Thus, these modalities combined with computed tomography provide accurate anatomical mapping. This allows for the regionalization of possible lesion(s).

The combined modalities allow for coregistration of imaging results. The fused images make possible the identification of nuances that would have a chance of being missed. The combination of the modalities does not change the fact that prostate cancer cells have low FDG uptake, which only further compounds the fact that doctors today are looking for small tumors. Published research only further complicates any stance on the use of 18F-FDG as there are varied results for clinical trials (Alivatos and Pavlos, 2014; De Bari et al, 2014). The focus and strength of combining modalities is that it provides molecular or
metabolic information, and morphological or anatomical information. This leads to sensitivity, specificity, and accuracy improvement.

**Figure 6: PET and CT Fusion**

Bone positron emission tomography imaging utilizing Flourine-18 sodium fluoride for patient with castrate resistant prostate cancer fused with computed tomography (Leung et al, 2014).

A primary example of this is when PET and CT are combined, sensitivity and accuracy reaches a diagnostic level locating lymph node metastatic tumor lesions (Kitajima, 2014). Choline PET/CT is considered by some as the optimal imaging modality for assessing the viable prostate cancer tumor lesion burden in the skeleton, but there is debate about its predictive value in early recurrence state. The contention is due to no clear guideline agreement on the correct serum PSA value for patients to be at biochemical failure, to decide to use choline PET/CT. Evidence is variable, with studies using different clinical and
pathological characteristics for their sample and different sample sizes. The other fact is that choline PET/CT sensitivity changes in relation to initial tumor burden, previous biochemical failure, and the patient’s age. There is some early evidence that choline PET/CT might appear to be acceptable in illuminating the local relapse of prostate cancer, if the patient has a serum PSA value great than 1.4 ng/mL.

When looking at lymph nodes, radiation oncologists struggle to determine treatments when they have elevated serum PSA value and there is choline PET uptake in some lymph nodes. They are left to make difficult decisions to treat just the positive nodes or to include the area of the nodes because micro metastatic infiltration is undetectable (De Bari et al, 2014). The other combination modality is SPECT/CT, which has improved lesion contrast and detection capability relative to bone scintigraphy (2014 & SMR & Ghosh).

**MRI of the Prostate**

Prostate cancer magnetic resonance imaging (PCa MRI) is and has been complex and multifaceted. Since the early testing in mid to late 1980s, MRI has developed in the way it is used, understood, utilized, and implemented. The imaging modality’s evolution has been one of science, financial gain, patient care, and politics. Prostate cancer multiparametric MRI (PCa mpMRI) has started to reach the world stage. Various organizations around the world are starting to form guidelines for scanning protocols, scanning equipment, among other aspects of prostate mpMRI.
METHODS

MRI Sequences

Prostate MRI sequences are constantly evolving and new sequences are being tested as they come into development. The first sequences utilized in the early days of prostate MRI, which would be early to late 1980s, were simple in sequence selection. There were just the T1-weighted (T1-w) and T2-weighted (T2-w) sequences. As time went on and innovations were made, other sequences came into the clinical setting. These sequences included dynamic contrast enhanced (DCE), diffusion weighted imaging (DWI), and magnetic resonance spectroscopy (MRS), among others. As research and clinical testing continued, and with the help of personal politics, some sequences have fallen out of favor. Today, sequences that are still in use in some form or another with variable popularity are the T1-w sequence, T2-w sequence, DCE, DWI, and MRS. There has been a movement in recent years in the development of terminology refinement for prostate MRI, one term that is quintessential is multiparametric. This is how prostate MRI is described, as multiparametric MRI because the sequence selection is imaging multiple parameters of the tissues.

The T1-weighted sequence provides clinicians with basic anatomy and morphology of the prostate and the surrounding tissues of the male pelvis. This sequence is traditionally acquired in the axial or transverse plane. Generally, the signal-to-noise ratio of the images for this sequence is good. Unfortunately, the contrast-to-noise ratio is low, especially within the prostate itself, as the tissues
are not differentiated as finely by internal tissue borders as is clearly visible on histology slides. However, if clinicians need to focus on the vasculature in the area, it is easily contrasted from surrounding tissues. A typical T1-w sequence will have flip angles (FA) are > 50° and a TR of > 300ms. Cancer of the prostate is not visible distinctly from the normal prostatic tissue, but after seeing another set of images for other sequences, it does become more readily apparent, for example T2-w imaging (Hedge et al, 2013).

**Figure 7: T2-weighted Imaging and Diffusion-weighted Imaging**

Image to the left is a T2-weighted image with the low signal or dark region is the area of prostate cancer. The diffusion weighted image to the right confirms this with a reduced or restricted diffusion region that also appears dark (Thompson et al, 2013).

T2-weighted imaging is used to provide detailed internal prostatic glandular structures, essentially assessing the anatomical zones and capsule that providing detection, localization, and staging. This sequence is acquired in all three planes (axial, sagittal, coronal). The parameters of this sequence varies, but traditionally the TR in the range of 2000 to 8000ms, TE in the range of 70 to 170 ms, slice thickness of 3 mm with no gap, and the in plane matrix of 256.
x 256. The structural components of the gland visible in the images from this sequence allow for clinicians to identify suspicious lesions and determine whether the tumor burden is intracapsular invasion or extracapsular extension and possible seminal vesicle invasion. This is possible due to high signal-to-noise ratio and spatial resolution. Prostate lesions will tend to appear as low signal intensities, which is juxtaposed to the surrounding normal high signal intensity of prostate’s peripheral zone. This sequence, in the axial plane, needs to cover the entire prostate and all of the seminal vesicles. It is important to understand that while this sequence is sensitive, it is not specific enough by itself to identify cancer lesions. The T2-w sequence is susceptible to motion and hemorrhagic artifact, so precautions should be taken to limit such artifacts (Hedge et al, 2013; Alivatos and Pavlos, 2014; Barentsz et al, 2012).

In the prostate, another important sequence is the diffusion-weighted imaging, which adds to the lesion characterization disambiguation. Tumors tend to be regions of restricted movement on DW images relative to the other areas of the prostate. The b-value selection is changed over time, but today there has been a move to higher b-values, so instead of using 0, 800, and 1000s/mm², using b-values such as 0, 1000, 2000s/mm². By utilizing a single shot spin echo EPI sequence clinicians are able to limit motion artifact in individual slices, but the signal-to-noise ratio is unfortunately not high. DWI sequences allow for apparent diffusion coefficient map (ADC map) to be computed, thus providing quantitative and qualitative analysis of prostate cancer aggressiveness. In fact,
ADC values that are lower are usually found to be cancerous tissues, and correlate to Gleason scores. In any great mpMRI protocol for the prostate, this sequence is considered standard and should always be part of the regular MRI work-up (Hedge et al, 2013; Bloch et al, 2004; Manenti et al, 2014; Barentsz et al, 2012).

The next sequence to be discussed is the dynamic contrast-enhanced imaging, which has high resolution (Barentsz et al, 2012). DCE, more specifically, is done using a 3D SPGR like sequence, which is a T1-w sequence that has high temporal resolution. In order to have clinical relevance, the sequence needs to be done in a timely manner and cannot consume a large amount of time. The length of each dynamic needs to be long enough to capture the in-flow and out-flow of contrast of the prostate and surrounding tissues. By allowing for the in-flow and out-flow to be charted, curves can be made to illustrate the various types of diffusion, otherwise known as the pharmacokinetics of the vasculature of the prostate. Institutions vary some in how they would like their curves to be done. Generally, the idea is to have one full dynamic without contrast, followed by a second dynamic where gadolinium contrast is injected during the dynamic, and as many dynamics after to the wash-in and wash-out of the contrast (Barentsz et al, 2012).

The magnetic resonance spectroscopy sequence is the least used clinical prostate MRI scan. MRS is able to look at metabolites in vivo by recording and analyzing their signal in the form of peaks caused by frequency shift, or
“chemical shift”, relative to the standard (Bushberg et al, 2012). The premise being that the spectra will display metabolite peaks, such as phosphocholine, involved in cell turnover and proliferation, and creatine, temporary storage of phosphates, will be different in tumor regions compared to healthy tissue region. The scanning time for just this sequence alone is close to 20 minutes, which further complicates the view of utility in the clinical setting.

**Figure 8: Magnetic Resonance Spectroscopy of the Prostate**

The above figure is a chart of the spectroscopic peaks of prostate cancer tissue in a patient’s prostate, which is evident by the increased choline to citrate ratio (Thompson et al, 2013).

The sequence design usually involves a STEAM, known as stimulated echo acquisition mode, and PRESS, known as point resolved spectroscopy, depending on preferences and experience of those employing the single voxel
technique (Bushberg et al, 2012). Using the single voxel technique allows us to see all the possible metabolites present in the MRI trace for the prostate tissue, while still achieving a high signal-to-noise ratio (SNR). The technique, whether single voxel or multivoxel, has higher SNR, scanning in less time, and higher spectral resolution when it is performed on the 3 Tesla scanners compared to the 1.5 Tesla scanners. The improvements come with the difficulties, such as what were once single peaks are now multiple peaks (Bushberg et al, 2012). Prostate MRS needs to be done with an endorectal coil and tends to focus on citrate and choline, especially their ratio when examining possible tumor tissues compared to normal prostate tissues (Barentsz et al, 2012).

**Coils**

Coil selection has changed over time as prostate imaging has progressed. The coils that have been used in prostate MRI have been the body coil, the pelvic phased array coil, and the endorectal surface coil. The body coil was initially the only coil for prostate MRI in the early to mid-1980s. As researchers and clinicians alike developed a better understanding of prostate MRI and continued to innovate, the pelvic phased array coil and endorectal surface coil came along. The pelvic phased array coil provided higher SNR, and maintained patient comfort, but did not allow clinicians to have the small FOV that they needed. Today, doctors have the endorectal surface coil. The coil allows for increased SNR and decreased motion artifact, this is essential for MRI sequences, such as DWI and MRS (Hedge et al, 2013).
Scanners

Prostate imaging has been done strictly on the 1.5T and 3.0T MRI scanners since its inception. The 1.5T scanner is useful because it has less magnetic field inhomogeneity, compared to the 3T scanner. By today’s standards and capabilities in prostate MRI, clinicians need the increased signal of the pelvic phased array coil combined with the endorectal surface coil. On the other hand, clinicians can choose to get the same signal as the 1.5T with endorectal coil, or may forego the endorectal coil with the 3T scanner. This definitely improves the experiences of the patient, but other ethical questions about clinical standards emerge (Hedge et al, 2013).

Reporting

Clinical reports of mpMRI findings of the prostate have traditionally varied in layout and terminology. The reports are further complicated by inter-observer variability in expertise and comprehension in prostate MRI. The complexities of this type of imaging can be read at the clinical level by just anyone, it requires considerable training, and learning combined with experience. As the number of clinicians proficient in prostate MRI has grown, so has the conscious understanding that there needs to be a unified layout or format to allow for other doctors to comprehend the findings of the imaging results. Recently clinicians have been gathering to discuss and produce standards in reporting of prostate cancer imaging results, more specifically clinical MRI.
In 2012, the European Society of Urogenital Radiology (ESUR) gathered experts on prostate MRI from all over Europe. They wanted to form guidelines for scanning and reporting of prostate cancer. They developed suggested minimum requirement protocols for “detection”, “staging”, and “node and bone” directing the use and parameters for T2-w, DWI, DCE, and MRS (Barentsz et al, 2012). There was conversation about the use of a standardized scoring system of prostate imaging, similar to what breast radiologists have employed called BI-RADS, which they decided to call PI-RADS. A revolutionary aspect of the scoring system is that there needs to be a clinical significance grade or score associated, which is valuable, as it provides other clinicians viewing the report an idea of the confidence the radiologist has in their findings (Barentsz et al, 2012).

**Learning from Others**

It is important to have the perspective of clinicians caring for patients by characterizing, staging, and treating the disease. This allows for a more complete understanding of the present state of prostate cancer and clinical imaging. Three urologists and three radiologists were contacted about interest in being interviewed regarding the value of MRI as a diagnostic tool. The premise of each meeting was to discuss prostate cancer and imaging from their point of view, both their experience and thoughts. The physicians were selected at Boston Medical Center, Beth Israel Deaconess Medical Center, and Brigham and Women’s Hospital based on the amount of experience they had in this area. The interviews were conducted at their convenience and ranged from 15 minutes to
90 minutes along. All interviews were recorded and summarized. The questions were all very similar, but curtailed to their particular interests and experience. The discussion section is a summation of those interviews.
Discussion

Upon review of the literature and interviews with health care professionals the following conclusions have been drawn.

**Current Opinion in the Department of Urology, Boston Medical Center**

Conclusions from interviews with several urologists at Boston Medical Center have led to the observations that follow. Urology today has undergone a deep revolution in clinical practices for prostate cancer and the use of MRI. Urologists are utilizing MRI with increased frequency for several reasons. Firstly, MRI provides improved sensitivity compared to US imaging. This allows for doctors to view prostate cancer metastasis involved in capsular penetration and seminal vesicle involvement, while providing a superior three dimensional global image of the prostate. Secondly, doctors have the ability to put patients in the early stages of disease for prostate into various programs for monitoring ("watchful waiting"), treating (radiation, surgery, etc), or staging in a logical evidence based manor. This reason is crucial to understand because it has led to the development and use of active surveillance. The third reason is prostate cancer patients are able to have their prostates imaged in areas of the prostate that random biopsy would traditionally miss, which ultimately allows for targeted biopsies. Urologists see that MRI allows them to treat prostate cancer like every other disease, by providing doctors with the ability to view the cancer through
imaging and focus on targeted areas. This new found capability doctors have, is seen as a major change, since traditionally the malignancy was treated and biopsied in a random and in a less targeted manner. The exam is long, about 30 to 45 minutes, which is not tolerable for all patients, according to urologists. Furthermore, in the USA, the Urology community understands in order to fully utilize MRI, there needs to be a radiologist who is an expert or has expertise in reading prostate MRI (R. Babayan and M. Katz, personal communication, May 27, 2014; D. Wang, personal communication, June 3, 2014).

Current Opinion of Radiologists in the Boston Area

The following observations have been drawn based on interviews to several seasoned radiologists in the Boston area. Radiology has constantly evolved in the clinical setting, especially in the imaging of prostate cancer. In particular, MRI has evolved from two sequence scanning protocol of T1-w and T2-w imaging in the early 1980s that did not utilize an endorectal coil, due to it not being developed at that time in MRI history, to today clinical imaging utilizes mpMRI with endorectal coil in a 3T scanner. A strong prostate MRI program at any clinical institution, today, just needs one sequence protocol with endorectal coil at a 3T scanner to efficiently image prostate cancer at a high volume. This requires DWI, T2-w, and DCE sequences to carry out the routine needs of the clinical setting, which are detection, characterization, and staging. MRI has become the best medical imaging modality for early detection and staging of prostate cancer. US or TRUS do not play a clinical role for radiologists today as
a diagnostic or staging tool. Computed tomography and nuclear medicine are not ideal for early detection of prostate cancer, but still remain effective at detecting advanced stage prostate cancer.

Regarding reports and notation for prostate cancer patients, European Radiologists, those associated with ESUR, have made strides in recent years to standardize them under PI-RADS. USA radiologists have not developed a standardization of reporting, such as PI-RADS, but a group in eastern USA has been working to publish a suggested standardized way of reporting and notation. In fact, radiologists in eastern USA are suggesting that prostate MRI could become part of the normal work-up for eligible men, which is already standard practice in Europe. On an international level, radiologists are increasingly agreeing about the value of MRI as a diagnostic tool to identify and monitor prostate cancer (C.M. Tempany, personal communication, May 28, 2014; N. Rofsky, personal communication, June 4, 2014; M. Smith, personal communication, June 4, 2014).
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Education
Boston University School of Medicine, Boston, MA
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Masters of Science – Bioimaging, August 2014
Thesis Title: Multiparametric 3T MRI as a Clinical Tool to Characterize Prostate Cancer

Boston College, Chestnut Hill, MA
College of Arts and Sciences
Bachelor of Arts in Biology, May 2011

Honors and Awards
Student of the Year Award – Latinos @ Boston College – 2011
Most Valuable Person – Boston College AHANA Caucus – 2010-2011
John A. Bosenquet Award – Scholar, Citizenship, Character – 2006-2007
Eagle Scout – 2006

Imaging Experience
Boston Medical Center, Boston, MA  January 2014 to August 2014
Clinical MRI Intern, Radiology Department (outpatient and inpatient)
• Positioning and scanning of adult and pediatric patients using 1.5T Phillips scanners and 3.0T GE scanner environment
• Communicating with culturally diverse patient populations in a comforting manor to maintain a positive environment
• Transporting patients to and from the MRI suites safely and efficiently
• Assisting in work flow of MRI operations
• Maintaining compliance with all MRI safety protocols and regulations
• Communicating with staff and radiologists to ensure proper patient care

Dana-Farber Cancer Institute, Boston, MA  April 2012 to September 2013
Pre-Clinical MRI Technologist, Center for Biomedical Imaging in Oncology – LFIC
• Executed pre-clinical MRI projects – scanning protocol, scheduling, reporting, post-processing, DICOM analysis
• Maintained 7.0T Bruker scanner – scanner, control area, chiller, scanner computing cabinets, ancillary supplies, weekly QA
- Ensured health of mice while in MRI suite
- Performed necropsies, smaller surgeries and sample collections of mice
- Developed scanning protocols for future studies
- Trained guest users to safely and efficiently operate scanner and local anesthesia independently for their studies
- Ordered parts and supplies to maintain the user needs and the scanner daily operations
- Performed IV, IP, and oral drug and fluid administration to mice

**Woods Hole Oceanographic Institution**, Woods Hole, MA May 2008 to January 2012

**Lab Assistant I, Ketten Lab**
- Assisted in necropsies of various species of dolphins, whales, seals, lobsters, squid
- Partnered with the Senior Scientist and lab technologist in CT scanning of various animals
- Digitized histology slides
- Created 3D models and videos with AMIRA software
- Research has been used in presentations for international conferences

**Technical Skills**
- Creating computerized 3D reconstructions, videos, and presentations of CT and MRI DICOMs
- Utilizing AMIRA, 3D Slicer, Image J, MRicro, MRicron, MATLAB software for image analysis of DICOMs
- Familiar with 1.5T Phillips scanners, 3.0T GE scanner, and 7.0T Bruker scanner
- Performing necropsies and sample collection of mice, whales, seals, dolphins, lobsters, squid