3D modelling system for diagnosis and treatment planning of prostate cancer

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3D MODELLING SYSTEM FOR DIAGNOSIS AND TREATMENT PLANNING OF PROSTATE CANCER

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**SCHOOL OF MECHANICAL AND AEROSPACE
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Abstract

An apparently rising incidence of and mortality from prostate cancer coupled with an increasing life expectancy and an expanding population at risk have made this neoplasm a major medical and socioeconomic problem. Adenocarcinoma of the prostate is estimated to be among the most common malignancies diagnosed in men all over the world. It is the second cause of male cancer death in USA and fifth in Singapore. For this reason, the study of prostate cancer and development of improved treatment methods takes on an almost urgent significance.

Currently, both diagnostic and therapy procedures require x-ray fluoroscopy, trans-rectal ultrasound (TRUS), CT and/or MRI for assessing the condition of the prostate and the success of the procedure. Modeling of multidimensional volume image data and accurate instrument tracking, are significantly advancing our capabilities for improved and minimally invasive diagnosis and treatment, obviating the need for exploratory surgery, physical dissection, blind biopsies, and mental reconstruction of anatomy.

The author presents an approach to anatomical surface segmentation, reconstruction of medical images of prostate, especially Magnetic Resonance (MR) images. This dissertation focuses on the methods of MR prostate image segmentation and the reconstruction of prostate volume and its surrounding pelvic area, and visualization. The software tool is used to extract information on axial, coronal and sagittal orientation from MR diffusion data using reconstruction methods. Methodology of reformatting the images into 3d imaging and reconstruction was also discussed.

Such visualization technology can be readily applied to diagnosis and treatment of prostate cancer, and deployed in the operating or procedure room to provide the surgeon with on-line, intra-operative access to 3D volume images of the pelvic anatomy and associated pathology, all translated faithfully to the patient on the procedure table.

Key words: Medical image analysis, Reconstruction, Image segmentation, Visualization, Image guided Surgery, Prostate Cancer

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CHAPTER ONE

INTRODUCTION

1.1.BACKGROUND

We have been exploring anatomy and function through time, beyond the 3rd dimensions, for almost three decades. We have developed efficient methods for the production of accurate patient-specific models of anatomy from volumetric image data acquired from CT, MRI, PET, SPECT and ultrasound scanning systems. The anatomic models can include dynamic changes through time and can be enhanced with various functions, such as regional tissue elasticity and vascular flow, mapped onto the anatomy. Interactive visualization of these functional models opens new realms in the practice of medicine by permitting the images obtained from modern medical imaging systems to be directly displayed and manipulated with intuitive immediacy and with sufficient detail and speed so as to evoke sensorial experience similar to that of real experience. This allows physicians and surgeons to “enter” the visualizations on-line, to take up any viewpoint, to see dynamic functional processes as well as detailed anatomy and pathology, to make accurate measurements, and to manipulate and control interventional processes. The ultimate value of such visualization technology will derive more from the sensory enhancement of real experience than from the simulation of normally sensed reality.

Imaging prostate carcinoma is a subject of controversy. The recommendations range from denial to strong advocacy for imaging prior to any therapy decision. Considering the disagreements about prostate cancer detection and choice of treatment, the debate concerning imaging is not surprising. The incidence of Prostate Cancer is increasing even when adjusted for the aging population. In 1989, the incidence of Prostate Cancer was 99,000 and rose to an estimated 244,000 in the year 1995. [1]. While this increased incidence, in part, may be attributed to earlier detection, there is also an increase in the mortality rate from Prostate Cancer. Based on estimates by the American Cancer Society, there has been a 21% increase in the mortality from Prostate Cancer between the years 1959 and 1991. [1]. If at the time of diagnosis the cancer is confined to the prostate gland, the

five-year cancer-free survival rate is 91%. This is why earlier detection for cancer has been endorsed, and the American Cancer Society recommends that men after the age of 50 years should undergo a yearly digital rectal examination (DRE) and has the prostate specific antigen (PSA) assay. If either of one is abnormal, transrectal ultrasound (TRUS) should be performed. Biopsy is recommended if the lesion is either palpable or detectable on TRUS, or the PSA density (PSA divided by the gland volume) is greater than 0.15. Once the diagnosis has been established, the choice of treatment is often empirical, and physician and patient preference are the determining factors. A number of treatment options are available including watchful waiting, radical prostatectomy, cryosurgical ablation, radiation therapy, hormonal therapy, chemotherapy, or a combination of the above. The disarray in choice of therapy stems, in part, from the lack of reliable non-invasive methods of assessing the tumor's locoregional extent as well as documenting the presence of metastases. Clinical staging is inaccurate, and understaging occurs in as many as 72% of patients thought to have localized disease by digital rectal examination. Radiologic staging by either TRUS (accuracy 58%; sensitivity for extracapsular extension [EC] 49%; seminal vesicle invasion [SVI] 25%); CT (accuracy 61-65%); or body coil MR imaging (accuracy 69%; sensitivity for ECE 22%) is unreliable [2]. The use of endorectal, phased array (multicoil), and combined endorectal and phased-array imaging improves staging accuracy, but the exact role of MR imaging is yet to be defined.

Medical imaging is largely dedicated to oncological (cancer) imaging. However, 85% of all cancers are not adequately addressed by conventional imaging modalities due largely to their lack of sensitivity to small density changes in soft tissue. Medical imaging of early stage tumors – e.g. skin, breast, prostate, or lung cancer - thus represents a tremendous opportunity for new technologies to make a significant impact on health care, as well as a significant commercial opportunity.

The compelling clinical requirement for a new technology to image epithelial and other early stage tumors has been designated a priority area by both the US and EU health authorities. The detection of epithelial cancer at early stages when it can be effectively treated or surgically removed represents enormous potential savings to surgeons and health providers and has the potential to reduce patient morbidity.

1.2.OBJECTIVE

The main objective of this study is to analyze and support diagnosis and surgical planning of prostate cancer and its existing imaging technologies and evaluate its merits and demerits.

The crux of the practice dilemma is the need for improved non- invasive pre-operative techniques that can more accurately visualize and measure tumor volume and extent, and thereby more clearly indicate the need for surgery or alternative therapy, such as brachytherapy. Several measures of the pathologic state of prostate cancer have been proposed to allow stratification of patients into either treatment or "watchful waiting". These measures include prostate tumor size and microvessel density, which have been shown to be useful indicators of the metastatic potential of the tumor. However, currently there is no reliable technique, imaging or otherwise, to measure these factors in vivo. If such measures were available, patients who have cancer with a low possibility of metastasis may be able to forgo aggressive treatment and associated morbidities. To address this dilemma, Literature review on the existing technologies of medical imaging and their critical assessment was done. In this report, we have developed advanced 3D interactive and immersive visualization capabilities to analyze the prostate and its anatomic/functional environment.

1.3.SCOPE

Because of the shortcoming of the conventional techniques used for the detection and surgery of prostate cancer, improvement in both accuracy and objectivity of present imaging systems is of major clinical importance and greater impact on general health care.

The author used a software package, which uniquely integrates several facets of image-guided medicine into a single portable, extendable environment. It provides capabilities for automatic registration, semiautomatic segmentation, 3D surface model generation, 3D visualization, and quantitative analysis of various medical data of the region of our interest.

1.4.ORGONIZATION OF THE REPORT

Table 1

This report, intended to serve as a system for the prostate cancer diagnosis and treatment planning. Chapter one is introductory and it discussed about the background, objective and scope of the dissertation. Second chapter expressed in detail about the literature of prostate cancer. Preliminary diagnosis was carried out in chapter three which explains about MR imaging and Dicom viewing and analysis. Chapter four covered 3d modeling of the prostate itself. It has two primary objectives: to present a clear, consistent picture of image analysis and to teach the reader how to carry out 3d modeling using 3d Slicer itself. Considerable thought is given to the conclusions and recommendations to this subject since it is a critical assessment of this study and is stated in Chapter five.

CHAPTER TWO

LITERATURE REVIEW

2.1. Cancer-An overview

More than 10 million people are diagnosed with cancer every year. It is estimated that there will be 15 million new cases every year by 2020. Cancer causes 6 million deaths every year—or 12% of deaths worldwide. Cancer-A chaotic Process within the rational order of biology.

Cancer is a disease process in which healthy cells stop functioning and maturing improperly. A mishap occurs inside these cells. Perhaps it begins with a change (mutation) in the genetic blue print, its DNA. The altered DNA makes copies of it and passes its information and gene sequencing on other cells, which then become cancer prone. As the normal cycle of cell creation and death is interrupted, the newly mutated cancer cells begin multiplying uncontrollably, no longer operating as an integrated and harmonious part of the body.

In its simplest terms, cancer represents an accelerating process of inappropriate, uncontrolled cell growth—a chaotic within the order of biology. Cancer cells, when examined under a microscope, are abnormally shaped, inconsistently formed, and disorganized and contain misshapen internal structures—the essence of biological disorder. Cancer, despite its horror for the individual, is a natural phenomenon; it represents the body's response to a continuous attack on its balancing and regulatory mechanisms by numerous factors.

Cancer may seem to us modern epidemic, but traces of cancer have been detected in the bones and skulls of mummies from Egypt and Peru embalmed 5000 years ago. Hippo crates (circa 400 B.C.), the renowned Greek physician, first coined the term "carcinoma" to indicate skin cancer, to him, this Greek word (karkinoma, which means "crab") is like a crab because of the way a spreading cancer extends claw like extensions across the cell, tissue, or skin. What is different today is the incidence of cancer; it is steadily

affecting more people each year, specifically 1 out of 3. It is no longer one serious disease among many, but the disease of our time.

The development and growth of a cancer is called carcinogenesis. Physicians now understand that it involves many steps, beginning with specific, undesirable changes in the nucleus of the cell, specifically in its genetic components, the DNA. What distinguishes a cancer process from life-as-usual in the cell is that normally –in a state of health– DNA mutations are repaired and rendered harmless by the immune system, an intricate, multifaceted biochemical defense system. When undesirable genetic alterations remain uncorrected, then a cancer process can potentially escalate to its next stage of uncontrolled rapid growth.

It does this by making copies of itself. This replication, again, is a normal function of DNA, but the trouble here is that it is altered, mutated, and undesirable DNA that is copying itself. As more cancer cells are generated, the process continues to expand and form a tumor. The normal mechanisms of cell growth, replication, differentiation, and maturation then become unregulated, leading to chaos in the body. [3]

2.1.1. Prostate Anatomy

The prostate makes some of the milky fluid (semen) that carries sperm. The gland is the size of a walnut and is found just below the bladder, which stores urine. The prostate wraps around a tube (the urethra) that carries urine from the bladder out through the tip of the penis.

During a man's orgasm (sexual climax), muscles squeeze the prostate's fluid into the urethra. Sperm, which are made in the testicles, also go into the urethra during orgasm. The milky fluid carries the sperm through the penis during orgasm.

Figure.1– Anatomy of the male reproductive system (left) (Courtesy, Merck Human Health Division), Cross section of prostate showing the central and peripheral Zones. (Right)

The **prostate** is a firm, partly glandular and partly muscular body, which is placed immediately below the internal urethral orifice and around the commencement of the urethra. It is situated in the pelvic cavity, below the lower part of the symphysis pubis, above the superior fascia of the urogenital diaphragm, and in front of the rectum, through which it may be distinctly felt, especially when enlarged. It is about the size of a chestnut and somewhat conical in shape, and presents for examination a **base**, an **apex**, an **anterior**, a **posterior** and two **lateral surfaces**.

The **base** (*basis prostatæ*) is directed upward, and is applied to the inferior surface of the bladder, The greater part of this surface is directly continuous with the bladder wall; the urethra penetrates it nearer its anterior than its posterior border.

The **apex** (*apex prostatæ*) is directed downward, and is in contact with the superior fascia of the urogenital diaphragm.

Figure 2.The prostate and surrounding structures (courtesy, Merck Human health Division)

2.1.2 Surfaces

Figure 3.The prostate Zones, coronal view (courtesy, Devaki MRI/CT scan, Madurai, India)

The **posterior surface** (*facies posterior*) is flattened from side to side and slightly convex from above downward; it is separated from the rectum by its sheath and some loose connective tissue, and is distant about 4 cm. from the anus. Near its upper border there is a depression through which the two ejaculatory ducts enter the prostate. This depression serves to divide the posterior surface into a lower larger and an upper smaller part. The upper smaller part constitutes the **middle lobe** of the prostate and intervenes between the ejaculatory ducts and the urethra; it varies greatly in size, and in some cases is destitute of glandular tissue. The lower larger portion

sometimes presents a shallow median furrow, which imperfectly separates it into a **right** and a **left lateral lobe**: these form the main mass of the gland and are directly continuous with each other behind the urethra. In front of the urethra a band, which is named the isthmus, connects them: this consists of the same tissues as the capsule and is devoid of glandular substance.

Figure 4. The prostate Zones , Axial view (courtesy, Devaki MRI/CT scan, Madurai, India)

The **anterior surface** (*facies anterior*) measures about 2.5 cm. from above downward but is narrow and convex from side to side. It is placed about 2 cm. behind the pubic symphysis, from which it is separated by a plexus of veins and a quantity of loose fat. It is connected to the pubic bone on either side by the puboprostatic ligaments. The urethra emerges from this surface a little above and in front of the apex of the gland.

The **lateral surfaces** are prominent, and are covered by the anterior portions of the Levatores ani, which are, however, separated from the gland by a plexus of veins.

The prostate measures about 4 cm. transversely at the base, 2 cm. in its antero-posterior diameter, and 3 cm. in its vertical diameter. Its weight is about 8 gm. It is held in its position by the puboprostatic ligaments; by the superior fascia of the urogenital diaphragm, which invests the prostate and the commencement of the membranous portion of the urethra; and by the anterior portions of the Levatores ani, which pass backward from the pubis and embrace the sides of the prostate. These portions of the Levatores ani,

from the support they afford to the prostate, are named the **Levatores prostate**.

The urethra and the ejaculatory ducts perforate the prostate. The urethra usually lies along the junction of its anterior with its middle third. The ejaculatory ducts pass obliquely downward and forward through the posterior part of the prostate, and open into the prostatic portion of the urethra.

2.1.3 Structure

The prostate is immediately enveloped by a thin but firm fibrous capsule, distinct from that derived from the fascia endopelvina, and separated from it by a plexus of veins. This capsule is firmly adherent to the prostate and is structurally continuous with the stroma of the gland, being composed of the same tissues, viz.: non-striped muscle and fibrous tissue. The substance of the prostate is of a pale reddish-gray color, of great density, and not easily torn. It consists of glandular substance and muscular tissue.

The **muscular tissue** according to Kölliker, constitutes the proper **stroma** of the prostate; the connective tissue being very scanty, and simply forming between the muscular fibers, thin trabeculæ, in which the vessels and nerves of the gland ramify. The muscular tissue is arranged as follows: immediately beneath the fibrous capsule is a dense layer, which forms an investing sheath for the gland; secondly, around the urethra, as it lies in the prostate, is another dense layer of circular fibers, continuous above with the internal layer of the muscular coat of the bladder, and blending below with the fibers surrounding the membranous portion of the urethra. Between these two layers strong bands of muscular tissue, which decussate freely, form meshes in which the glandular structure of the organ is imbedded. In that part of the gland which is situated in front of the urethra the muscular tissue is especially dense, and there is here little or no gland tissue; while in that part which is behind the urethra the muscular tissue presents a wide-meshed structure, which is densest at the base of the gland—that is, near the bladder—becoming looser and more sponge-like toward the apex of the organ.

The **glandular substance** is composed of numerous follicular pouches the lining of which frequently shows papillary elevations. The follicles open into elongated canals, which join to form from twelve to twenty small excretory ducts. They are connected together by areolar tissue, supported by prolongations from the fibrous capsule and muscular stroma, and enclosed in a delicate capillary plexus. The **epithelium** which lines the canals and the terminal vesicles is of the columnar variety. The prostatic ducts open into the floor of the prostatic portion of the urethra, and are lined by two layers of epithelium, the inner layer consisting of columnar and the outer of small cubical cells. Small colloid masses, known as **amyloid bodies** are often found in the gland tubes.

Vessels and Nerves.—The **arteries** supplying the prostate are derived from the internal pudendal, inferior vesical, and middle hemorrhoidal. Its veins form a plexus around the sides and base of the gland; they receive in front the dorsal vein of the penis, and end in the hypogastric veins. The **nerves** are derived from the pelvic plexus.

2.2 Prostate Cancer

2.2.1. History of Prostate Cancer

There are specific types of DNA mutations that we call the initiators of cancer. Our current understanding of the cancer process suggests that mutations in the genetic code at the important places on the “supercoiled” DNA molecule that will set the stage for the eventual uncontrolled malignant replication of that cell. Once the initiator events have the damaged DNA in a certain way, other factors come into play—This is called the promotion phase. During promotion, further mutation may or may not occur. A cell that is primed for cancerous overgrowth will do so at some point during or after the initiating DNA-damaging events have taken place.

All cancer shares the carcinogenesis process. After initiation has occurred and the promotion phase is operative, cancer varies markedly both in their

growth rates and in their ability to invade its surrounding structures and spread through metastasis. This is an important issue and pertains to the natural history, or variable behavior, of prostate cancer.

With the powerful techniques of molecular biology, we can recognize a cell as being cancerous by detecting certain significant gene alterations, some times long before the cell would have begun the typical uncontrolled growth of malignancy.

Prostate cancer is one of a variety of different types of human carcinomas. There are malignant growths that arise in epithelial tissues: the skin, the lining of the digestive tract and blood vessels, and the internal organs, such as pancreas, liver, ovaries, and the prostate gland. An important subcategory of carcinomas into which prostate cancer falls is adenocarcinomas, “adeno” meaning gland like. These malignant tumors grow in the glandular tissue of organs. (the portion of the organ’s structure that produces secretions). Some adenocarcinomas such as cancers of the pancreas and lung are usually dangerously aggressive. Prostate cancer, though heterogeneous in its natural history, tends to be less aggressive than these other types of adenocarcinomas.

2.2.2. Benign prostatic hyperplasia

During puberty, increasing levels of male hormones promote the development of the prostate’s glandular component. The prostate continues to grow throughout a man’s life. At the onset of middle age, the rate of growth in prostate tissue-notably the stromal component-almost always increases. By age 70, the weight of the prostate can average between 30 to 60 grams, compared to 20 grams at age 25.

Figure 5. Showing hyperplastic nodule with pseudocapsule(left) and microscopic view of the BPH cells(right).

This enlargement is called benign prostatic hyperplasia (BPH)/Due to BPH, the prostate may eventually expand to several times its normal adult volume. The increase in the volume of prostate tissue most frequently involves the stomal tissue, but epithelial tissue can also be involved. The prostate tissue overgrowth does not necessarily result in prostate cancer. BPH and prostate cancer are common and are most likely unrelated.

2.2.3 Examination of prostate cancer

The most reliable standard for determining a growth as being cancerous is through pathology: the examination (most often microscopic) of a biopsy sample by a trained pathologist. A diagnosis of cancer can be made in certain cases in the level of molecular biology by identifying specific changes in the DNA of a cell's genes. Such genetic analyses are being used more frequently these days and will undoubtedly be employed more widely in the future. This means that much earlier diagnosis of cancer in growths we now call precancerous will be possible. Examination will be discussed in detail in fore coming chapters.

2.2.4 Symptoms of Prostate Cancer

Inability to urinate, Weak urinary system, Urinating small amounts frequently, Urinating more frequently during night, Painful urination and Bone pain.

However, there may not be any symptoms in its early stages, which is why testing is so important.

Figure 6. Real cross section of a prostate showing left, right, anterior and posterior (left), microscopic structure the cell's nuclei (right)

2.3 Treatment Methods

Prostate cancer can be treated in many ways. Each of the specific treatment methods is described below.

PROSTATECTOMY

Removal of the prostate by surgery

Surgery can be used to remove cancer from the prostate and from nearby areas to which the cancer has spread. It is most often used during the cancer's early stages (Stages T1 and T2), when prostate cancer is located only within the prostate. Surgery may help prevent further spread of the cancer. If the cancer is small and located exclusively within the prostate, the surgery may cure the disease.

One surgical procedure is called perineal prostatectomy. It involves removing the cancer through the perineum, the area between the scrotum and the anus. The entire prostate is removed, together with any nearby cancer.

Another procedure is called retro pubic prostatectomy. It consists of removing the cancer through the lower abdomen. The entire prostates are removed, and if necessary, nearby pelvic lymph nodes are removed as well.

A transurethral resection of the prostate, or TURP, involves removing benign tissue from the prostate by inserting an instrument through the urethra in the penis. Only part of the prostate is removed by this technique. This is usually done to relieve symptoms and make urinating easier. It does not cure prostate cancer.

Advantages

Prostatectomy is a one-time procedure that may cure prostate cancer in its early stages and may help extend life in the later stages. Surgery avoids the problems seen with radiation therapy. These problems are discussed in the next section.

Disadvantages

Prostatectomy is a major operation that requires hospitalization and can produce side effects, including impotence, incontinence (loss of urinary control), and narrowing of the urethra, which can make urination difficult. Impotence occurs in a high percentage of patients. In recent years, however, the percentage of men with impotence following surgery has decreased because of a new nerve sparing surgical technique. Incontinence occurs in only a small percentage of patients.

RADIATION THERAPY

Radiation therapy uses high-energy rays to kill prostate cancer cells, shrink tumors, or prevent cancer cells from dividing and spreading. Because the rays cannot be directed perfectly, they may damage both cancer cells and

healthy cells nearby. If the dose of radiation is small and spread out over time, however, the healthy cells are able to recover and survive, and the cancer cells eventually die.

Radiation therapy is usually used when prostate cancer has not spread beyond the prostate (Stages T1-T2). It can help prevent the cancer from spreading further. Like surgery, radiation therapy works best when the cancer is located in a small area. In early stages of prostate cancer, radiation therapy may cure the disease. Radiation therapy may also be used alone or in combination with hormone therapy when cancer cells have spread beyond the prostate to the pelvic area (Stages T3-T4) and for pain relief in prostate cancer that is no longer responding to hormone therapy and has spread to the bones (Stage M+). The high-energy rays can be delivered in numerous ways. Three of those are discussed below.

EXTERNAL BEAM

External beam refers to the fact that the radiation therapy is generated and administered by a machine outside of the patient's body, as opposed to implants, which temporarily or permanently place radioactive sources within the body. The radiation is typically given in brief sessions, usually one session each weekday for several weeks. External beam therapy includes x-ray therapy and Cobalt 60 gamma ray therapy.

CONFORMAL / PROTON BEAM

Conformal / Proton Beam therapy is a form of external beam radiation treatment. Other forms of external beam radiotherapy Conformal means that it is possible to shape the beam in three dimensions to the shape of a tumor so that the majority of radiation is given to the tumor and not to the surrounding normal tissue. It is this unique ability to conform a proton beam

to a specific tumor or target, which sets it apart from other forms of external beam radiotherapy.

IMPLANTS / INTERNAL BEAM / BRACHYTHERAPY (SEEDS)

In internal radiation therapy (brachytherapy), the rays come from tiny radioactive seeds inserted directly into the prostate. The seeds are inserted while the patient is under anesthesia; they are too small to cause discomfort. They give off rays continually for about a year and remain safely in place for the rest of a person's life. Internal radiation therapy does not make the patient radioactive.

Another form of internal radiation is delivered by injection and is used to control bone pain in patients with metastasized (Stage M+) prostate cancer that no longer responds to hormone therapy. Radioactive compounds have been found that go directly to the bone and may give dramatic pain relief to many patients with discomfort.

Advantages

It avoids major surgery. Radiation therapy may cure prostate cancer in its early stages and may help extend life in later stages. It rarely causes loss of urinary control, and it leads to impotence less frequently than does surgery. New injectable radioactive compounds, such as those containing radioactive strontium, can provide pain relief from cancer that has spread to the bone. These new compounds have fewer side effects than do the radioactive phosphorous compounds that have been available for many years.

Disadvantages

Radiation therapy can cause a variety of side effects. Most of these are minor and disappear after therapy stops. These side effects include tiredness, skin

reactions in the treated areas, frequent and painful urination, upset stomach, diarrhea, and rectal irritation or bleeding. When a radiation therapy provided by an external machine, it can cause later development of impotence in some patients. Internal radiation therapy causes impotence less often, but may be associated with decreased white blood cell and platelet counts.

CRYOTHERAPY / CRYOABLATION

Freezing of prostate cancer tissue

Targeted cryoablation of the prostate (TCAP, cryosurgery) is a minimally invasive therapy involving ultrasound-guided placement of several probes into the prostate. Rapid cooling at the probe tips (using Argon gas) results in immediate cancer cell death with pinpoint accuracy. Recent advances make it safe and effective, especially for men who don't want or can't have surgery or radiation. It may also be very effective for men who are at high risk of having small amounts of cancer just outside the prostate or who have an aggressive tumor (Gleason grade 7). It is FDA-cleared and fully Medicare-approved for primary and salvage treatment of localized prostate cancer with an 89-92% success rate in 7-8 year studies.

The procedure is performed under either a spinal (epidural) or a general anesthesia. Under ultrasound guidance, slender probes about the size of small knitting needles enter the prostate through tiny holes in the perineum (the skin between the scrotum and the rectum). The probes deliver lethally cold temperatures to cancer cells in two or more freeze-thaw cycles. Thermocouples and a urethral warming device protect healthy tissue from damage. The procedure usually takes an hour and a half or less. Patients go home the day of or morning after.

Cryosurgery is most often suggested for localized or locally advanced disease (T1-T3) or as salvage therapy after any type of failed radiation

treatment (recurrence.) It can be combined with hormonal therapy to downsize the gland prior to freezing. When cancer is confined to the prostate or just outside of it, cryo has the potential to cure the disease. With promising improvements in potency rates, cryoablation may be a desirable alternative to major surgery, or to radiation treatments that may diminish potency over time.

Advantages

It avoids major surgery. Less likely to cause urinary tract damage, obstructions, or bowel difficulties than radiation. Patients often fully recover within days. Highest negative biopsy rate at 1, 5 and 7 years of all prostate cancer treatments. Repeatable if necessary.

Disadvantages

Side effects similar to surgery and radiation historically include impotence (22-85%), incontinence (1-5%), and fistula (< 1%). Recent technology advances and the development of nerve sparing cryo promise significant improvements in potency results.

HORMONE THERAPY

Hormone therapy is most commonly used to treat cancer that has spread (metastasized) outside the pelvic area (Stages N+ and M+). Two types of hormone therapy can be used: 1) surgical removal of the testicles, which produce male hormones, or 2) drugs that prevent the production or block the action of testosterone and other male hormones. Hormone therapy cannot cure prostate cancer. Instead, it slows the cancer's growth and reduces the size of the tumor or tumors.

Hormone therapy in combination with radiation therapy or surgery is also used in advanced stages of cancer when the disease has spread locally beyond the prostate (Stages T3-T4). This therapy helps extend life and relieve symptoms. When the cancer has spread beyond the prostate, complete surgical removal of the prostate is not common. In patients with early-stage cancer (Stage T2), hormone therapy may be used in combination with radiation therapy. A short course of hormone therapy can also be used prior to surgery to reduce the size of the prostate and make it easier to remove.

The primary strategy of hormone therapy is to decrease the production of testosterone by the testicles. Regardless of the method of hormone therapy, however, the decrease in testosterone can result in certain side effects. These commonly include hot flashes, a loss of sexual desire, and impotence.

The specific methods used to reduce testosterone production or block the actions of testosterone and other male hormones are described below:

ORCHIECTOMY

Surgical removal of the testicles

An operation called Orchiectomy removes the testicles, which produce 95% of the body's testosterone.

Advantages

Orchiectomy is an effective procedure that is relatively simple and performed only once. Often, the patient is given a local anesthetic and is allowed to go home the same day as surgery.

Disadvantages

Orchiectomy is a surgical procedure, and many patients prefer a nonsurgical option if it will work as well. Many men also find it difficult to accept this type of surgery. Depending on the kind of anesthesia used, there may be special risks in certain types of patients. Orchiectomy may in some cases require hospitalization, and it is not reversible.

ESTROGEN THERAPY

Another method, although not used much anymore, is to administer a female hormone such as estrogen. Female hormones reduce the production of testosterone by the testicles. The most commonly used estrogen in prostate cancer is diethylstilbestrol, or DES.

Advantages

Estrogen therapy is simple and involves taking a pill. Unlike Orchiectomy, estrogen therapy does not involve removal of the testicles, and its effects can be reversed.

Disadvantages

Estrogen therapy produces various side effects of its own. Estrogens can cause water retention, embarrassing breast growth and tenderness, and symptoms such as stomach upset, nausea, and vomiting. In addition, even low doses of estrogen may significantly increase the risk of heart and blood vessel problems.

LHRH THERAPY

Another method of treatment consists of administering a drug called a luteinizing hormone-releasing hormone analogue (or an LHRH analogue); this leads to a drop in testosterone. Taking an LHRH analogue works just as well as removal of the testicles but does not involve surgery. Currently available LHRH analogues are ZOLADEX (goserelin acetate) and Lupron (leuprolide acetate).

Advantages

Administering LHRH analogue therapy is simple; it involves an injection every 28 days or every 12 weeks. Treatment with LHRH analogues is as effective as Orchiectomy, but it does not require surgical removal of the testicles. It also avoids the side effects of estrogen therapy.

Disadvantages

In a small percentage of patients, LHRH analogue therapy may cause a brief rise in cancer symptoms, such as bone pain, before the testosterone level begins to fall. This pain may be eased by the use of a pain reliever (such as aspirin or acetaminophen) or an antiandrogen drug, which is discussed next.

ANTIANDROGEN THERAPY

This therapy involves the use of a drug that blocks the action of male hormones. Such a drug is called an Antiandrogen. Antiandrogen drugs are used in combination with LHRH analogue therapy. This combination therapy is commonly known as maximal androgen blockade (MAB) or combined androgen blockade (CAB). The currently available Antiandrogen includes CASODEX (bicalutamide), Eulexin (flutamide) and VIADUR (leuprolide acetate implant) a unique once yearly implant.

Advantages

Ongoing clinical trials suggest that men treated with MAB therapy live longer than men treated with LHRH analogue therapy alone. The combined use of an LHRH analogue and an Antiandrogen can also be of benefit before or after prostate surgery or radiation therapy.

Disadvantages

Antiandrogen may cause gynecomastia (breast enlargement), breast tenderness, hot flushes/hot flashes and loss of libido. Other possible side effects may also include diarrhea, nausea, vomiting, and liver injury.

CHEMOTHERAPY

Chemotherapy is the use of powerful toxic drugs to attack cancer cells. The drugs circulate throughout the body in the bloodstream and kill any rapidly growing cells, including healthy ones. To destroy cancer cells while minimizing the harm to healthy ones, the drugs are carefully controlled in dosage and frequency.

Chemotherapy is generally reserved for patients with advanced stage cancer (Stage M+) that no longer responds to hormonal therapy. Chemotherapy drugs do not work well in many men with prostate cancer.

There are many different chemotherapy drugs, each with its own strengths and weaknesses. Often the drugs are used in combination with one another. EmCyt (estramustine phosphate) is a frequently used chemotherapy drug in prostate cancer.

Advantages

Chemotherapy drugs provide an additional means of relieving the symptoms of advanced prostate cancer.

Disadvantages

Because the drugs circulate widely throughout the body and affect healthy as well as cancerous cells, they produce many side effects. These include hair loss, nausea, vomiting, diarrhea, lowered blood counts, reduced ability of the blood to clot, and an increased risk of infection. Most of the side effects disappear when the drugs are stopped. (Hair grows back when chemotherapy is stopped.)

WATCHFUL WAITING (Expectant Therapy)

For some patients and certain stages of prostate cancer, the recommended treatment may simply be to "watch and wait," at least in the short term. This means that you won't receive any immediate therapy. Instead, your doctor will monitor the cancer by performing routine DRE and PSA tests. Watchful waiting may be used when prostate cancer is diagnosed at a very early stage or is not expected to progress quickly enough to begin using therapy. Watchful waiting may also be used if a patient is not expected to tolerate other therapy due to other adverse health conditions.

CHAPTER THREE

PRELIMINARY DIAGNOSIS

3.1.Diagnosis

Screening for prostate cancer is crucial, since the disease often exhibits no symptoms, and is most effectively treated when caught early. Caucasian men are advised to visit their doctors for screening beginning at age 50, and African American men and men with a family history of prostate cancer, at age 40. However, once man turns 40, the prostate starts to grow-and when it grows, there is a possibility it can become cancerous.

Digital Rectal Exam (DRE)

The prostate is located just in front of the rectum. As a rectal exam is done, a gloved, lubricated finger is inserted into the rectum, and the surface of the prostate is easily felt with the examiner's finger. It is always the surgeon looking for during the examination is both a rough estimate of the size of the prostate, but more importantly, any abnormal nodules or masses in the prostate.

Figure 7. Digital Rectal Examination by Surgeon.

With the index finger, the examiner palpates the anal canal to determine sphincter tone, tenderness, and the presence of abnormalities. The examiner then slides the index finger further into the rectum to examine the prostate gland.

The normal firmness of the prostate is duplicated by the tightness of the thenar compartment when the hand is flexed as in the picture. Nodules, lumps, or hardness within the boundaries of the prostate must draw the examiners attention for these are signs of prostate cancer.

PSA blood test

The PSA blood test is a measure of a chemical that is produced by prostate tissue: both normal prostate tissue and abnormal prostate tissue. Prostate cancers tend to produce a higher level of PSA than does normal prostate tissue. As the prostate grows, the PSA level may raise a little, but if there's a prostate cancer in that gland, very often the PSA rises to a higher level than what is considered normal.

Every lab has different ranges of normal versus abnormal. For the most part around the United States, most laboratories have 0 to 4.0 as the normal range of PSA. What are important about PSA are not only the magnitude of the number, but also how it might have changed. So for example, if a 53-year-old man had a PSA of 2.5 two years ago and now comes in and has 3.8, even though that 3.8 is still in the "normal" range, it's a marked elevation from where it was previously. That change would make a physician more suspicious that there may be something abnormal going on.

Well, a number of countries, institutions and organizations have looked at the PSA test as a screening tool. We know a few things about it. We know that it is by far the most sensitive means of detecting prostate cancer, although it is by no means a substitute for the digital rectal exam. The test really is a

complement. There are prostate cancers that will be diagnosed based on an abnormal digital rectal examination, but will have a normal PSA. Moreover, the reverse is true. Everybody would agree that the PSA test enables us to diagnose cancers in younger men.

Biopsy

A biopsy is a test that's generally done at the discretion of the urologist. It may be ordered after an abnormal digital rectal examination or an elevation in PSA. The way the biopsies are done really depend upon the clinical situation. For example, if a nodule is felt on digital rectal examination, a thin needle is inserted into the prostate, and a small core of tissue is removed—less than a millimeter in width, and perhaps an inch in length. However, in men who have a normal-feeling prostate and have an elevated PSA, we use a prostate sonogram as a guide. We actually obtain several biopsy specimens from the prostate to get a fair representation of the entire volume of the prostate.

The average standard is to obtain six cores of tissue. It probably does about 90 to 95 percent. There has been a trend towards doing more biopsies, 10, 12, and sometimes—even 14 to increase your yield. Nevertheless, even that is not a hundred percent. It does a very good job, but it's not perfect.

There are probably many men walking around with a completely normal digital rectal examination and a normal PSA, who do have small areas of prostate cancer within their glands. Many of these men won't be diagnosed, and many of these men won't die from prostate cancer. However, that does not mean that men should not be concerned about prostate cancer, and be screened.

3.2. Establishing treatment Specifications

Introduction

Prostate cancer is the most commonly diagnosed cancer in men, making this disease a significant public health issue. Unfortunately, the anatomic location of the prostate does not lend itself to straightforward examination. Historically, digital rectal examination has been the principal method of examination of the prostate. However, this technique has its own inherent limitations. The advent and refinement of ultrasound technology have provided a new, important method to examine the prostate. Transrectal ultrasound with prostate biopsy, a generally well-tolerated outpatient procedure, in conjunction with the development of serum assays for prostate-specific antigen (PSA), has resulted in an impressive change in the manner of diagnosis and stage presentation of men with prostate cancer.

Before Ultrasound: Digital Rectal Examination

Digital rectal examination (DRE) is the primary method of examination of the prostate. This technique allows the examiner to appreciate the gland's morphology, including any irregular, nodular, or indurated areas, that may be suspicious for malignancy. In 1971, Gilbertson published a series of 5,856 men who underwent annual DRE as a screening for prostate cancer from 1948 through 1964. This study was the first of its type to document a survival advantage to DRE screening.

As a subjective examination, however, DRE has limitations. Not all prostatic malignancies are palpable on DRE. When DRE findings are correlated to pathologic evaluation, understaging and overstaging are often found. Ultimately, DRE fails to detect a significant number of malignancies, and of those that it does detect, a significant number are at an advanced stage.

History of Transrectal Ultrasound

Transrectal ultrasound (TRUS) was initially described as a technique to evaluate rectal pathology. In 1963, Takahashi and Ouchi were the first to describe the use of TRUS to evaluate the prostate. However, medical ultrasound was rather primitive at this time, so the images created with this array were of such poor quality that they carried little medical utility. The first clinically applicable images of the prostate obtained with TRUS were described in 1967 by Watanabe et al. They used a 3.5 MHz transducer, which at that time was considered state of the art, to obtain images that were clinically meaningful. As ultrasound technology has become more refined, the use of TRUS in the evaluation of prostatic disease has increased. By the mid 1980s, the 7 MHz ultrasound probe, which more clearly delineated the architecture of the prostate, had become a standard diagnostic instrument of the urologist.

History of TRUS-Guided Prostate Biopsy

Ferguson performed the first prostate needle biopsy in 1930. He described a transperineal approach with an 18-gauge needle in which he aspirated a sample of prostate tissue. Astraldi performed the first transrectal biopsy in 1937. In the mid 1980s, a transperineal ultra-sound array was fitted with biopsy apparatus to allow direct correlation of the sonographic appearance of focal prostatic lesions with the histology of these lesions. Several years later, a spring-loaded core biopsy device was developed that operated via a TRUS probe.

In 1987, the first literature appeared describing the use of TRUS with transrectal biopsy. Since then, as ultrasound technology has become more refined, this technique has been described as a superior method of performing a core biopsy of the prostate.

Since the initial reports of TRUS of the prostate by Wild and Reid, substantial technological advances have improved the diagnostic capabilities of this modality. The current state-of-the-art TRUS probe is a 5-8 MHz hand-held, high-resolution probe with multiaxial planar imaging capabilities, which has the capacity for both transverse and sagittal imaging of the prostate in real time. This probe can be fitted with an adapter that accepts the needle of a spring-loaded biopsy gun, thus allowing multiple cores of tissue to be easily obtained. The visualization provided by the new higher resolution transducers, coupled with the ability to direct the biopsy needle into various regions of interest and to provide uniform spatial separation of the areas to be sampled, has helped to make TRUS-guided prostate biopsy a standard technique in the diagnosis of prostate cancer.

Other Modalities: Transperineal and Transabdominal Prostatic Ultrasound

Although TRUS is the current standard for ultra-sound imaging of the prostate, other modalities are available. Transabdominal ultrasound can image the prostate, as well as other abdominal organs. The primary advantage of this technique is that it is noninvasive and thus does not require special patient preparation. Similarly, transperineal ultrasound can image the prostate, is noninvasive, and does not require any special patient preparation. Despite their advantages, these techniques have fallen out of favor as tools with which to image the prostate, except in unusual cases (e.g., a patient without a rectum after an abdominoperineal resection). These techniques provide images inferior to TRUS, primarily because of the anatomic consideration that the prostate is physically closer to the TRUS probe than it is to the probe in either of these other two methods.

New Technology: Doppler Ultrasound and Intravenous Contrast Agents

TRUS technology has limits in specificity and sensitivity, which has led investigators to explore the potential use of color Doppler imaging with and without intravenous contrast administration. Doppler Sonography is based on the principle that the frequency of a sound beam changes when that beam is reflected by a moving target. In the case of Doppler Sonography of the prostate, the transducer generates the sound beam, and the moving target is blood. This technique allows real-time visualization of blood flow. The utility of color Doppler ultrasound rests on the theory that tumors in general, and prostate tumors in particular, have different blood flow characteristics from the surrounding normal tissue. Recent literature, however, fails to support this technique as being superior to traditional gray-scale imaging in the diagnosis of prostate cancer.

Recognizing that traditional Doppler ultrasound is limited in its ability to display small, deep, and low-volume-flow blood vessels, such as those of the prostate, the addition of intravenous contrast agents have been used to promote vascular visualization. Ultrasound scanning using contrast agents has been performed extensively in the heart, liver, and kidney, with good results. ^[13] Preliminary studies suggest that employing sonographic contrast agents enhances the visualization of neovascularity associated with prostatic cancer.

Indications for Prostate Biopsy

Elevated Serum PSA

The most common indication for prostate biopsy is an elevated serum PSA. Although a level greater than 4 ng/mL is considered elevated, age-adjusted normal PSA values have been established. Oesterling et al demonstrated an 8% increase in the number of biopsies and organ-confined cancers detected

in men with a normal DRE aged 50 years or less when these age-specific reference ranges were used. A rising PSA over time, though still less than 4 ng/mL, may also be an indication for biopsy, especially in high-risk groups. Carter et al demonstrated that a change in PSA, or PSA velocity, of more than 0.75 ng/mL per year was a specific marker for the presence of prostate cancer. Furthermore, in their study, men diagnosed with cancer had significantly more rapid rates of a rise in PSA than men without prostate cancer when the PSA levels were normal.

Abnormal DRE

An abnormal finding on DRE is an indication for prostate biopsy regardless of the patient's PSA value. Abnormalities include a discrete nodule, focal induration, a diffusely hard prostate and, in some cases, asymmetry.

TRUS in Practice-Patient Preparation

Full informed consent that outlines alternatives, consequences, and complications of biopsy is obtained prior to the procedure. Patients routinely receive either preprocedural enemas or a formal polyethylene glycol bowel preparation. Administration of prophylactic antibiotics around the time of biopsy has become standard of care. At our institution, we routinely use a 3-day course of a quinolone antibiotic beginning the day before biopsy. Patients with valvular heart disease are administered parenteral antibiotics as outlined by the American Heart Association.^[17] Furthermore, patients are taken off anticoagulants and antiplatelet drugs for an appropriate time period.

There has been recent interest in techniques to reduce the morbidity associated with TRUS and prostate biopsy. A recent trial from Emory University concluded that the use of intrarectal lidocaine gel is simple, safe, and efficacious in providing satisfactory anesthesia in men undergoing transrectal prostate biopsy. At our institution, patient comfort is provided by

injecting a solution of 1% lidocaine (Xylocaine) along the neurovascular bundles of the prostate, beginning at the seminal vesicles and moving outward to the apex. This is accomplished with a 20-gauge spinal needle, and the injection is performed under TRUS guidance. This procedure is simple and inexpensive, and patients describe good anesthetic results.

Imaging Techniques

A DRE is performed prior to insertion of the probe. The reason for this is 2-fold: It rules out any rectal pathology that would contraindicate insertion of the probe, and it allows the identification of any palpable prostatic abnormalities to which special attention could be paid during ultrasound examination.

The probe is introduced and the contrast of the console is adjusted to provide a uniform mid-gray image of the normal peripheral zone. The shading of the peripheral zone should be the homogenous gray standard by which other areas of the prostate are classified as hyperechoic, hypoechoic, or isoechoic. Imaging of the gland is then carried out, first in a transverse fashion. The right and left seminal vesicles are viewed, followed by the bladder neck, mid gland, and apex. After complete transverse imaging, the transducer is configured to provide for sagittal imaging, and the right, mid, and left aspects of the prostate are visualized. During this part of the examination, particular attention is paid to any regions that are hypo and hyper-echoic when compared to the peripheral zone of the prostate.

The console is reconfigured for volume measurement of the prostate. First, in the transverse view, an image of the prostate at its largest diameter is obtained, and this diameter is recorded. Then, in the sagittal view, the greatest cephalocaudal and anterior-posterior dimensions of the prostate are recorded. These measurements are used to calculate the volume of the

prostate. The volume of the prostate is based on the assumption that the gland is an ellipsoid.

Thus, the formula for the prostate's volume =

(Transverse diameter) X (cephalo-caudal diameter) X (anterior-posterior diameter) /6).

With the volume of the gland and the patient's PSA level, PSA density (PSAD) can be calculated (PSA divided by gland volume). PSAD recognizes that PSA originates not only from prostate cancer cells, but also from normal prostate epithelial cells, so it is not specific to prostate cancer. The concept of PSAD assumes that for any prostate volume, there is a finite number of normal prostate epithelial cells that can occupy that volume and thus an upper limit to PSA of benign origin. Once the critical PSA level has been passed, nonbenign epithelial cells must occupy the prostate gland; this is prostate cancer. A PSAD of 0.15 has been proposed as a threshold for recommending prostate biopsy in men with mildly elevated PSA (4-10 ng/mL) and no suspicion of cancer on DRE or TRUS.

Sonographic Findings

The normal prostate gland has a homogenous, uniform echo pattern. The seminal vesicles are visualized at the base of the bladder and are hypoechoic compared with the remainder of the prostate. In contrast to the homogenous appearance of the normal prostate, a prostatic malignancy may take on unique ultrasound findings. Most ultrasound-detected lesions found to be carcinoma are described as hypoechoic regions with irregular borders. However, this is not a rule, and the appearance of carcinoma on ultrasound is variable.

Evaluation of the prostate by TRUS requires a comprehensive knowledge of the anatomy of the prostate, as the current PSA-era phenomenon of stage migration has made most tumors nonpalpable at diagnosis. In 1968, McNeal proposed that the prostate is composed of three distinct glandular zones (Figure 8). The transition zone surrounds the urethra and extends from the ejaculatory ducts proximally. The transition zone is surrounded by a discrete fibromuscular band of tissue, and it is the site of origin of benign prostatic hyperplasia. The peripheral zone encompasses the posterolateral aspect of the prostate from the base (superior) to the apex (inferior), and it accounts for the majority of the volume of the prostate. The majority (70%-80%) of prostate cancers arise from the peripheral zone. The central zone is composed of tissue immediately surrounding the ejaculatory ducts, and it expands inferiorly.

Figure 8. Schematic depiction of the transition zone (TZ), peripheral zone (PZ), and central zone (CZ) in transverse (A) and sagittal (B) planes. The arrows represent the path of sextant biopsy needles. From Terris MK, McNeal JE, Stamey TA. Detection of clinically significant prostate cancer by transrectal ultrasound-guided systematic biopsies.

The anatomic distinction between the central and peripheral zones is generally not appreciated by ultra-sound. In a normal man, these two zones are seen as a homogenous, isoechoic area in the posterior section of the prostate. Their normal echo pattern is used as a reference for defining other structures as hypoechoic or hyperechoic. The normal transition zone in a young man comprises only a small percentage of the gland and thus is difficult to image. In an older man with benign prostatic hyperplasia, the transition zone expands, compressing its surrounding fibromuscular band of tissue. This compressed tissue gives rise to the "surgical capsule" of the prostate, which is a sono-graphic landmark of zonal demarcation. The transition zone itself is moderately hypoechoic when compared to the central and peripheral zones.

Cancer of the prostate was initially thought to have a hyperechoic appearance on ultrasound. However, recent literature confirms that modern ultrasound technique displays prostate cancer as generally a hypoechoic area. Lee et al reported that the most common sonographic appearance of prostate cancer was a hypoechoic peripheral-zone lesion. The highest predictive values for prostate cancer are seen in hypoechoic lesions that are well defined and are larger than 1 cm. The etiology of this hypoechogenicity is currently believed to be due to the replacement of the prostatic stroma with infiltrating glandular elements. However, not all hypoechoic regions in the peripheral zone are prostate cancer. Potential hypoechoic lesions also include prostatitis, prostatic infarction, dilated glands, smooth muscle bundles, scarring, and prostatic intraepithelial neoplasia. Studies following Lee's work reported that a significant number of prostate carcinomas are isoechoic. The average yield of a biopsy of a peripheral-zone hypoechoic lesion has been 30%-50%. With these limitations, the sonographer should be able to recognize more subtle findings such as irregularity or asymmetry, extension of hypoechoic areas from the central zone into the seminal vesicle, or any area corresponding to an abnormality on DRE.

TRUS evaluation of the prostate is not without its weaknesses. Carter et al were the first to suggest a relative lack of sensitivity with TRUS when they observed that only 54% of carcinomas identified on the nonclinically suspicious side of the prostate could be visualized with ultrasound. Another study found that in radical prostatectomy specimens, only 36% of nonpalpable tumors were visualized on ultrasound.^[29] Others have also reported that up to 40% of prostate cancers are isoechoic on ultrasound and therefore "invisible" to TRUS. This number is probably much higher today with the stage-migration seen at presentation of prostate cancer. The specificity of the classic hypoechoic ultrasound finding of prostate cancer is low; a hypoechoic lesion can reflect anything along the continuum from normal prostate to prostatitis to infarct to prostatic intraepithelial neoplasia.

TRUS-Guided Prostate Biopsy Techniques

Systematic Sextant Prostatic Biopsy

The limitations in cancer detection based on sono-graphic appearance and the stage migration during the PSA era have been driving forces in the evolution of TRUS and prostate biopsy. Patients are presenting earlier in the disease process, when tumors are more likely to be nonpalpable and isoechoic. The true utility of ultrasound in the modern era, therefore, is to enable sampling of all relevant areas of the prostate, including those that appear normal on Sonography.

Hodge et al published the landmark paper demonstrating the efficacy of systematic sampling of the prostate during TRUS-guided biopsy. They were the first to report that systematic sampling of the prostate guided by TRUS improved the detection rate of prostate cancer over merely sampling hypoechoic or other lesions. By taking sextant biopsies from the mid lobe (parasagittal) of each side of the prostate at the apex, middle, and base, the cancer detection rate was superior to lesion-directed biopsies in 136 men

with palpable abnormalities. This technique was accepted at the time as the standard of care and helped to emphasize that TRUS was more useful for biopsy than for imaging.

Recent evidence, however, demonstrates that this technique may no longer be the standard of care. The sextant technique was recommended based on biopsies of men with palpable abnormalities. In the current PSA era, though, most men who are undergoing prostate biopsy do not have palpable abnormalities or hypoechoic lesions. Furthermore, mapping of radical prostatectomy specimens has shown that the majority of nonpalpable lesions lie in the far lateral peripheral zone of the prostate, which is not routinely sampled by the sextant technique. Literature has demonstrated under sampling by the sextant technique, notably in a study by Levine et al in which 137 men underwent two consecutive sets of parasagittal sextant biopsies in a single setting. The initial biopsy revealed cancer in 30 men (22%), while 13 (10%) had cancer diagnosed only on the second set of biopsies.

Figure 9. Transrectal ultrasound in sagittal plane demonstrating hyperechoic biopsy tracts (arrows) evenly spaced throughout the gland. From Eskew LA, Bare RL, McCullough DL. Systematic 5 region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate. J Urol. 1997; 157:199-203.

Optimizing Biopsy Methods

Increasing numbers of investigators are modifying the number and the areas of the prostate sampled. Based on cancer mapping of radical prostatectomy specimens, Stamey suggested that biopsies near the middle or the base should be directed laterally into the anterior lateral crescent of the peripheral zone. Around 75% of all prostate cancer originates from the peripheral zone. However, the standard sextant technique samples a limited portion of the peripheral zone and does not take advantage of the common extension of peripheral-zone cancers into the anterior lateral aspect of the peripheral zone.

A prospective study from the same institution assessed the yield of a 5-region biopsy method in which cores are obtained by ultrasound guidance from the far lateral peripheral zone and midline in addition to the standard sextant biopsies (Figure 9). By obtaining at least 13 cores (18 cores in glands greater than 50 g by ultrasound), the authors demonstrated a significant increase in prostate cancer detection over sextant biopsies. The overall cancer detection rate was 40%, with 35% of the cancers diagnosed by the additional regions only. The benefit of this technique was most notably seen in patients with a PSA <10 ng/mL where 54% of the cancers diagnosed were found in the additional regions only. In a subsequent study, the authors demonstrated no statistically significant difference in the tumor volume, Gleason's score, or pathologic stage between tumors diagnosed by the 5-region technique or those diagnosed by standard sextant biopsies. Ongoing data accrual has demonstrated this technique to be durable after 256 biopsy sessions. Furthermore, other authors using clinical studies as well as computer-generated models have demonstrated results consistent with the increased yield of the 5-region technique. Chang et al prospectively evaluated the usefulness of adding four lateral biopsies of the peripheral zone to the routine sextant biopsy regimen for prostate cancer. Lateral biopsies of the peripheral zone were obtained just medial to the lateral border

of the prostate, in addition to the routine lesion-directed and systematic sextant regimen in 273 patients. Forty-four percent of patients had cancer on biopsy. Routine sextant biopsies detected 82% of cancers, while the combination of sextant and lateral biopsies detected 96% of the cancers diagnosed. They concluded that the addition of lateral peripheral-zone biopsies increases the sensitivity for cancer detection while virtually eliminating the need for lesion-directed biopsies. Looking specifically at 6-core biopsy combinations, the regimen with greatest sensitivity was the combination of the two apical biopsies of routine sextant and four additional lateral cores. Their findings emphasized the importance of not only increasing the number of biopsies, but also specifying location.

Figure 10. Transverse and posterior views of the prostate showing the peripheral zone (PZ) and lateral areas of biopsy. Shaded areas represent the additional regions of the 5-region biopsy technique. From Eskew LA, Woodruff RD, Bare RL, et al. Prostate cancer diagnosed by the 5-region biopsy method is significant disease. J Urol. 1998; 160:794-796. Reprinted with permission.

In 2000, these same authors examined their 10-core biopsy regimen more closely as they performed a prospective trial of 483 consecutive patients in an attempt to identify the optimum systematic biopsy regimen to detect carcinoma of the prostate. They believed that the biopsies of the base in the standard sextant regimen could be dropped without adversely affecting sensitivity. Eliminating these two cores would have decreased the cancer detection rates by only 1%-2%. Variations in cancer detection rates were

most pronounced in patients with a PSA less than 10-ng/mL or prostate volume greater than 50 cc. The low yield from the mid lobar base may be because this samples largely the central zone, where the incidence of cancer is low.

Chen et al [10] sought to determine the optimum biopsy strategy based on a stochastic computer simulation model of ultrasound-guided biopsies using mathematically reconstructed radical prostatectomy specimens. Sextant biopsies reliably detected cancer in only 107 (73%) of 147 patients in whom the total cancer volume was greater than 0.5 cc. The authors demonstrated that a 10-core biopsy regimen that included the parasagittal base and apex, the inferior anterior horn (far lateral peripheral zone), the midline peripheral zone, and the anterior transition zone reliably detected 96% of cancers. They suggested that sampling of these additional areas be incorporated into an initial or repeat biopsy regimen. They emphasized that biopsy localization must be described in a highly specific way to facilitate further clinical study and confirmation, and this is heavily reliant on TRUS guidance for standardization.

In a subsequent paper, these authors used the same computer simulation to compare the ability of different biopsy regimens published in the literature to detect prostate cancer. The cancer detection rate for cancers greater than 0.5 cc in volume was highest for an 11-core multisite-directed scheme (94%) followed by the 5-region peripheral zone (18 cores, 87%) and 5-region peripheral zone (13 cores, 86%). The 11-core multisitedirected scheme consists of sextant, one posterior mid-line, two-transition zone, and two inferior anterior horn biopsies. This is similar to the above-mentioned 10-core scheme and has similar detection rates. Again, cancer yield was not related solely to the number of cores; strategic sampling of multiple regions of the prostate under ultrasound guidance is also important.

Babaian et al [10] tested the 11-core multisite-directed prostate biopsy strategy of Chen and colleagues. Over all, a 33% increase in cancer detection over sextant in 362 patients was observed when this biopsy technique was utilized. The anterior horn was the most frequently positive biopsy site. This technique was significantly better in men whose DRE and TRUS were normal and in those with PSA between 4 and 10.

Another computer simulation by Bauer et al [10] comparing various published prostate biopsy regimens suggests that all the biopsy protocols using laterally placed biopsies based on the 5-region anatomic model are superior to the routinely used sextant prostate biopsy pattern. Of the lateral biopsy regimens, the authors suggest that the 10-core pattern that includes sextant plus far lateral mid and apical biopsies is the optimum. Lateral biopsies in the mid and apical aspects of the gland had higher yields than any other cores and, similar to reports by Chen and colleagues, sextant biopsies detected only 73% of cancers. Transition-zone biopsies added little to the detection rate, and the authors suggested that these biopsies are rarely required to detect cancer if lateral biopsies are used.

Interestingly, Naughton et al [10] recently reported a prospective, randomized trial to compare 6-core and 12-core biopsy protocols. Prostate cancer was found in 27% and 26% of patients after 6-core and 12-core biopsies, respectively. They concluded that the overall cancer detection was not improved by the addition of six additional laterally placed cores. However, 21% of men in the 12-core biopsy group would not have been detected without the addition of lateral biopsies. Furthermore, the authors acknowledge that there may have been a tendency to obtain the sextant biopsies alone a little more laterally, thus partially obscuring significant differences.

The Role of Transition-Zone Biopsies

Although approximately 20% of prostate cancers originate in the transition zone, isolated transition-zone tumors detected on prostate biopsy are uncommon. The addition of transition-zone biopsies to the initial biopsy strategy increases detection rates by only 1.8%-4.3 %, and there is little evidence to support the recommendation for routine transition-zone sampling. In men undergoing repeat biopsies, though, the yield of malignancy from the transition zone is 10%-13%.

Thus, transition-zone biopsies may be indicated for patients in whom prior negative systematic sextant biopsies failed to reveal cancer but whose PSA is markedly elevated or rapidly increasing.

In men with previously negative biopsies, the important question is whether the undiagnosed cancer is in the transition zone. In their study of patients undergoing repeat biopsy, Keetch and Catalona found a yield of only 10% from transition-zone biopsies. However, certain subsets of patients may have a much higher incidence of transition-zone carcinoma. In repeat biopsies in men with a mean PSA of 32, a normal DRE, and a clinical picture suspicious for carcinoma, Lui et al found that 53% of cancers were detected in the transition zone only.

TRUS is critical to ensure proper needle placement during biopsy of the transition zone. Imaging of the transition zone is not as reliable because the echo patterns are much more hypoechoic and heterogeneous, especially in the setting of benign prostatic hyperplasia. Fortunately, the posterior and posterolateral border of the transition zone is usually well seen on ultrasound and serves as an excellent marker for these biopsies. Chen et al found that the highest detection rate for transition-zone biopsies in a computer-generated model was observed when the biopsies were initiated near the prostatic apex and the needles were inserted to a depth of 3 cm before firing.

Lower rates of detection were noted when the needles were inserted to a depth of 1-2 cm and as they were moved more toward the base of the gland.

The Impact of Prostatic Volume on Prostate Biopsy Technique

The most objective TRUS finding is prostatic volume. Calculating gland volume should be a routine part of every prostate biopsy session. Not only does prostatic volume have implications in future treatment planning in the setting of a positive biopsy and risk stratification using PSA density, but also an indirect relationship has been demonstrated between prostate size and the likelihood of finding prostate cancer. Recent studies have questioned the ability of the standard 6-core biopsy to provide optimal sampling in larger glands. The relative amount of gland that is sampled relies directly on the size of the gland, and thus the ideal number of cores to take may be dependent on the size of the gland calculated by TRUS.

Uzzo et al [10] reported on cancer detection rates and their variation with prostate size using a systematic sextant core biopsy regimen. Using a sextant regimen, the cancer detection in glands greater than 50 g was 23% vs 38% in glands less than 50 g. Their data suggest that significant sampling error may occur in men with large glands, and more biopsies may be needed under these circumstances.

Karakiewicz et al [10] also evaluated the positive rate of sextant biopsy according to gland size. The positive biopsy rate for glands less than 20 cc was 40% vs 10% for glands 80-90 cc. Their findings suggest that gland size represents an important determinant contributing to the yield of sextant biopsy in men at risk of harboring a nonpalpable, isoechoic cancer. They recommend an individualized approach to TRUS-guided biopsy based on prostate volume.

Levine et al also contributed to the evidence of increased sampling error in larger glands. In their study population, cancer was detected in 43%, 27%, and 24% of men with prostate volumes of <30 cc, 30-50 cc, and >50 cc, respectively. Furthermore, data from our own institution on the 5-region prostate biopsy method has also demonstrated a decreasing yield with increasing gland size. The cancer detection rate for glands <30 cc, 30-50 cc, and >50 cc was 49%, 42%, and 32%, respectively.

Vashi et al [10] created a mathematical model to determine the minimum number of cores necessary to detect clinically significant cancers in prostate glands 10-80 cc. Their data suggests that the sextant biopsy regimen optimally samples only a minority of prostate glands, and an approach to biopsy based on patient age and gland volume maximizes the detection of clinically significant cancer. They provided a table that indicates the number of cores to obtain based on patient age and gland volume. Their findings indicate that sextant biopsy does not provide adequate sampling of large prostate glands or the prostates of younger men who have normal or minimally elevated PSA.

Chen et al used a computer-simulated model to compare the yield of the sextant technique in glands ≤ 50 g and >50 g. The yield was 67% and 48%, respectively. However, they also found that smaller volume cancers were more prevalent in the larger glands. They concluded that the lower biopsy rates in larger glands might be driven by elevations in PSA from benign prostatic tissue. Contrary to other studies, they felt that increasing the number of cores solely to compensate for an increase in prostate size risks a disproportionate increase in the detection of small-volume tumors with a low clinical likelihood of progression. However, most of the cancers detected in the large glands were still >0.5 cc and thus clinically significant.

Prostate cancer is diagnosed currently by transrectal ultrasound- (TRUS-) guided needle biopsy prompted by either an elevated prostate-specific serum

antigen (PSA) level or a palpable nodule. Guidance is limited by low sensitivity of 60% with only 25% positive predictive value. These studies have shown that more than 20% of cancers required more than one biopsy session to diagnose. A randomized study of the efficacy of 6 versus 12 biopsy samples showed no difference in cancer detection; this suggests that the sensitivity of prostate biopsy is affected more by targets rather than number of samples. As it is a transrectal procedure, there is a risk of infection, which ranges from 4-11%, depending on the antibiotic regime used. It is higher in patients with indwelling catheters, diabetes, and prior histories of urinary or prostatic infections. The study group, it might be as high as 17%. Magnetic resonance imaging (MRI) can clearly depict not only the prostate itself but also its substructure including the peripheral zone (PZ) and on T2 weighted images identify nodules in PZ, though the specificity for diagnosis of cancer is limited. Since PZ is the most common site of origin of prostate cancer, among the three prostate zones (PZ, central zone (CZ) and transitional zone), localizing and targeting PZ and tumor foci in prostate biopsy may increase the cancer detection rate. For these reasons and those related to the problems of TRUS, Perotti et al. have used the endorectal MRI findings of suspected tumor foci to guiding the placement of needles during TRUS-guided biopsy. They localized suspicious tumor lesions/targets (based only on signal and not size) on the endorectal MRI and visually correlated the locations to ultrasound images, during TRUS guided biopsy. They found in a study of 33 patients that the accuracy of the TRUS guided biopsies aided by MRI was 67%. [10].

In this paper, we propose a method to use MRI for prostate biopsy, not only to localize tumors and PZ, but also to guide the needles into focal lesions. This MRI-guided prostate biopsy is possible by advancing the technical capabilities of the MR-guided prostate brachytherapy in an open-configuration MRI scanner and implementing surgical navigation software originally developed for neurosurgeries. The MRI guided prostate brachytherapy system, in the open-configuration MRI scanner, has

demonstrated the ability to place needles through the perineum into specific targets under the guidance of real-time fast gradient recalled (FGR) images. Since it was possible to insert the needles through perineum as opposed to transrectal approach, the newly proposed biopsy method can be applicable to the patient with prior abdominoperineal resection (APR) of the rectum. It will also allow direct sampling of the peripheral zone in a cranio-caudal direction, as opposed to transaxial, as in the TRUS approach. The surgical navigation software, referred, as the 3D Slicer hereafter, is in-house software originally developed to navigate neurosurgeries by generating simulated real-time images from pre-loaded MRI. In MR-guided biopsy, it simulates real-time T2- weighted images that are impractical due to the long scanning time (18 seconds/scan) and poor delineation of PZ and tumor. [10]

Figure 11. Diagram showing nerve and veins around prostate
(Courtesy: Medline plus)

TRUS maintains a critical role in the early diagnosis of prostate cancer. With the stage migration seen in the current PSA era, directed biopsies at lesions detected on ultrasound and DRE are becoming less common. However, ultrasound is essential in ensuring accurate sampling of the gland and can be

helpful in tailoring the number of cores and their distribution based on the size of the gland and patient risk stratification. Although the ideal number of cores is not clear, TRUS is an integral facet of prostate biopsy and will continue to contribute to our understanding of the optimum regimen for the diagnosis of prostate cancer. With more patients presenting earlier for biopsy as a result of PSA screening, together with potentially earlier diagnosis resulting from increased gland sampling, prostate cancer may be diagnosed at an earlier and more treatable point in the disease process.

Serum PSA (ng/mL)	Age (Years)
0.0-2.5	40-49
0.0-3.5	50-59
0.0-4.5	60-69
0.0-6.5	70-79

Table. Age-Specific Reference Ranges for Serum PSA

3.3 DICOM VIEWING

INTRODUCTION

HISTORY

With the introduction of computed tomography (CT) followed by other digital diagnostic imaging modalities in the 1970's, and the increasing use of computers in clinical applications, the American College of Radiology (ACR) and the National Electrical Manufacturers Association (NEMA) recognized the emerging need for a standard method for transferring images and associated information between devices manufactured by various vendors. These devices produce a variety of digital image formats. The American College of Radiology (ACR) and the National Electrical Manufacturers Association (NEMA) formed a joint committee in 1983 to develop a standard to: Promote communication of digital image information, regardless of device manufacturer Facilitate the development and expansion of picture archiving and communication systems (PACS) that can also interface with other systems of hospital information — Allow the creation of diagnostic information data bases that can be interrogated by a wide variety of devices distributed geographically. ACR-NEMA Standards Publication No. 300-1985, published in 1985 was designated version 1.0. The Standard was followed by two revisions: No. 1, dated October 1986 and No. 2, dated January 1988. ACR-NEMA Standards Publication No. 300-1988, published in 1988 was designated version 2.0. It included version 1.0, the published revisions, and additional revisions. It also included new material to provide command support for display devices, to introduce a new hierarchy scheme to identify an image, and to add data elements for increased specificity when describing an image. These Standards Publications specified a hardware interface, a minimum set of software commands, and a consistent set of data formats.

THE DICOM STANDARD

This Standard, which is currently, designated Digital Imaging and Communications in Medicine (DICOM), embodies a number of major enhancements to previous versions of the ACR-NEMA Standard:[14]

- a. It is applicable to a networked environment. The ACR-NEMA Standard was applicable in a point-to-point environment only; for operation in a networked environment, a Network Interface Unit (NIU) was required. DICOM supports operation in a networked environment using the industry standard networking protocol TCP/IP.
- b. It is applicable to an off-line media environment. The ACR-NEMA Standard did not specify a file format or choice of physical media or logical file system. DICOM supports operation in an offline media environment using industry standard media such as CD-R and MOD and logical file systems such as ISO 9660 and PC File System (FAT16).
- c. It specifies how devices claiming conformance to the Standard react to commands and data being exchanged. The ACR-NEMA Standard was confined to the transfer of data, but DICOM specifies, through the concept of Service Classes, the semantics of commands and associated data.
- d. It specifies levels of conformance. The ACR-NEMA Standard specified a minimum level of conformance. DICOM explicitly describes how an implementer must structure a Conformance Statement to select specific options.

PS 3.1-2004

- e. It is structured as a multi-part document. This facilitates evolution of the Standard in a rapidly evolving environment by simplifying the addition of new features. ISO directives which define how to structure multi-part documents have been followed in the construction of the DICOM Standard.
- f. It introduces explicit Information Objects not only for images and graphics but also for waveforms, reports, printing, etc.
- g. It specifies an established technique for uniquely identifying any Information Object. This facilitates unambiguous definitions of relationships between Information Objects as they are acted upon across the network.

3.4 Image Analysis

Imaging Planes

Figure.12.Orientation of axial, coronal and sagittal planes with respect to the human body.

Axial

Extending in a direction essentially perpendicular to the plane of a cyclic structure

Coronal

An imaging plane bisecting the body into top and bottom parts perpendicular (rotated 90°) to the long axis of the human body

Sagittal

A plane, slice or section of the body cutting from front to back through the sagittal suture of the skull, and continued down through the body in the same direction, dividing it into two parts

Oblique

A plane or section not perpendicular to the xyz coordinate system, such as long and short axis views of the heart

Axial plane

Figure 13. Axial plane MRI view of the human hip showing prostate.

Zonal anatomy of the prostate can be seen easily. Relation with seminal vesicles, levator ani, obturator internus and rectum can be studied.

Sagittal plane

Figure 14. Sagittal plane MRI view of the human hip showing prostate.

It is very useful to know the prostate in relation with bladder base, seminal vesicle and rectum

Coronal Plane

Figure.15. Coronal plane MRI view of the human hip showing prostate

It is useful to identify Seminal vesicle evaluation. Symmetry of levator ani muscles can be seen. Difference between CZ and TZ can be best seen.

Figure.16. Schematic views showing zones of prostate and its cancer.

Figure.17.schematic views showing cross sections of prostate, ejaculatory ducts and its capsule.

Figure 18.T1W and T2W image of prostate

T1W image

Homogenous intermediate signal intensity. Zones cannot be differentiated
Helpful in tissue characterization (Figure 18 Top left and right)

T2W image

Zonal anatomy well demonstrated. PZ isointense to fat. CZ Hypointense to PZ. TZ Hypointense to PZ—Helpful in detection of intraprostatic disease.
(Figure 18.Bottom left and right)

The techniques behind T₁, T₂ and FSE Images of MRI

T₁, T₂, & ρ Images

The spin-lattice relaxation time (T_1), spin-spin relaxation time (T_2), and the spin density (ρ) are properties of the spins in tissues. The value of these quantities changes from one normal tissue to the next and from one diseased tissue to the next. They are therefore responsible for contrast between tissues in the various image types.

There are several methods of calculating T_1 , T_2 , and ρ values. These methods are applied to individual pixels to produce a calculated T_1 , T_2 , or ρ image. The smaller the voxel corresponding to a pixel, the more likely the T_1 , T_2 , and ρ values are to represent values for a single tissue. The larger the voxel, the more likely the calculated values are to represent that of a combination of tissue components.

The calculation of T_1 , T_2 , or ρ starts with the collection of a series of images. For example, if you wish to produce a T_2 image, a spin-echo pulse sequence is used and a series of images are recorded with varying TE. The signal for a given pixel can be plotted for each TE value and the best fit line from the spin-echo equation drawn through the data to find T_2 .

A T_1 image can be created from the same pulse sequence using a series of images with varying TR. The signal for a given pixel can be plotted for each TR value and the best fit line from the spin-echo equation drawn through the data to find T_1 . The spin density can be calculated once T_1 and T_2 are found using the spin echo signal equation and any spin echo signal.

The procedures just outlined will produce T_1 , T_2 , or ρ images, but are not the most efficient or accurate. The reader is directed to the scientific literature for more appropriate methods.

Fast Spin-Echo (FSE) Imaging

A fast spin echo imaging sequence is a multi-echo spin-echo sequence where different parts of k-space are recorded by different spin-echoes. For example, we might have a four-echo spin-echo sequence with a TE of 15 ms. The k-space will be divided into four sections. The first echo is used to fill the central part, lines 96-160, of k-space. The second echo is used for lines 64-96 and 160-192. The third echo fills lines 32-64 and 192-224. The last echo fills lines 1-32 and 224-256 of k-space. There are some problems with the steps between the parts of k-space, but since there is little data in these regions the steps can be corrected for. The benefit of the technique is that a complete image can now be recorded in one fourth of the time.

3.5 Results

MR scan of five healthy men were studied identifying normal prostate volumes. The scanner manufacturer was SIEMENS, Model Name “Concerto” and the scanning was all done at DEVAKI MRICT SCAN, Madurai, Tamilnadu, India.

Varying slice thickness and different MRI sequence were studied using the same scanner and model of different age groups, which ranges between 27 to 70 years.

The entire MRI scan was viewed and analyzed by the author using DICOM viewing software called Acculite DICOM viewer.

DICOM Information of patient Number 1

Figure 19. DICOM Viewer showing MRI slide having a thickness 6mm thickness of the hip (left) and MRI slide of 4x4 frame view of 6mm thickness slides of the hip (right)

Sample Acquisition Data

Scanning sequence	SE
Sequence Variant	SK\SP\OSP
MR Acquisition Type	2D
Sequence Name	tse2d1_17
Angio flag	N
Slice Thickness	6
Repetition Time	4370
Echo Time	130
Number Of Averages	2
Imaging Frequency	8.280322
Image Nucleus	1H
Magnetic Field strength	0.19374
Spacing Between Slices	9
Number of Space Encoding Step	204
Echo Train length	17
Parent Sampling	70
Parent Phase Field of View	82.8125
Pixel Band Width	90
Device Serial Number	17397
Software Version	Syngo MR 2002B 4VA21A
Protocol Name	t2_tse_cor
Date of Last Calibration	20030705
Time of Last Calibration	183506.000000
Transmitting Coil	TxCoil
Acquisition Matrix	0 256 148 0
Phase Encoding Direction	ROW
Flip Angle	180
Variable Flip Angle Flag	N
SAR	0
dBdt	0
Patient Position	HLS

Figure 20. Coronal view of T2 TSE MRI scan. (Arrow indicating the prostate)

Patient Number One

Patient age	60
Series Description	t2_tse_cor
Slice thickness	6
Spacing Between Slices	9
Patient Position	HLS

Figure 21.4x4 frame view showing the entire image sequence in DICOM viewer.

Figure 22. Transverse view of T2 MRI scan of patient one.

Patient Number One	
Patient age	60
Series Description	t1_tirm_fs_tra
Slice thickness	5
Spacing Between Slices	7.5
Patient Position	HLS

Figure 23. Coronal View of T1 TSE MRI of patient one. (Arrow showing prostate)

Patient Number One	
Patient age	60
Series Description	t1_tse_cor
Slice thickness	6
Spacing Between Slices	9
Patient Position	HLS

Figure.24. Coronal view of T1 TSE MRI image of patient two.

Patient Number two	
Patient age	28
Series Description	t1_tse_cor
Slice thickness	6
Spacing Between Slices	6.6
Patient Position	HLS

Figure 25.4x4 frame view showing the entire image sequence in DICOM viewer (patient no two).

An full frame view a better understanding of overall structure of the prostate and it's surrounding area for diagnosis and aids in planning the treatment options. It also gives a clear anatomical structure of the patient to determine how to plan the biopsy in that region without affecting the surrounding region.

Figure .26. Coronal view of T1 SE of patient three

Patient Number three

Patient age	73
Series Description	t1_se_cor
Slice thickness	6
Spacing Between Slices	9
Patient Position	HLS

T1 weighted image has homogeneous intermediate signal density. The zones can be well differentiated. It is very helpful in tissue characterization. The figure 26 shows that it is spin echo type MR image and the spacing between slices were 9mm having an slice thickness of 6mm clearly depicting the capsule of the prostate. This is very important to identify whether the cancer has spread out of the capsule or not.

Figure.27. Transverse view of T2 TSE MRI of patient number four.

Patient Number four	
Patient age	27
Series Description	t2_tse_tra_cv_1
Slice thickness	6
Spacing Between Slices	7.2
Patient Position	HLS

Figure.28. Coronal and sagittal view of T2 TSE MRI of patient number four of same slice thickness of 6mm and gap between slices were 7.2

Figure.29.7x4 frame showing the entire slices in DICOM viewer.(Patient Number four)

Figure.30.Axial view of T1 TSE MRI showing the prostate (patient number four)

Figure 31. Coronal view of T2 TSE MRI of prostate (patient number five)

Patient Number five	
Patient age	37
Series Description	t2_tse_tra
Slice thickness	5
Spacing Between Slices	6
Patient Position	HLS

In T2 weighted image, zonal anatomy was well differentiated. It is very helpful in identifying intraprostatic disease. The slice thickness was 5mm and the spacing between slices was 6mm as shown in the figure.

Figure 32. Axial view of T1 TSE MRI of prostate (top)
Axial view of T2 FSE MRI of prostate (bottom)

CHAPTER FOUR

3D MODELING

4.1. Overview of Proposed Concept

Systems for surgical guidance additionally provide a means of establishing a correspondence between the fused, pre-operative data and the patient as positioned on the operating table. The author utilized a software package called **3D slicer** which was jointly developed by **MIT AI Laboratory**, Cambridge MA, USA and Brigham and Women's Hospital, **Harvard Medical School**, Boston, MA, USA. The system has been applied in over 20 neurosurgical cases at Brigham and Women's Hospital, and continues to be routinely used for 1-3 cases per week. [41].

The software provides capabilities for automatic registration, semiautomatic segmentation, 3D surface model generation, 3D visualization, and quantitative analysis of various medical scans. In this dissertation, real time scans were visualized as slices in the same 3D view along with the pre-operative slices and surface models. The detailed instruction on how to use the 3D slicer can be found at www.slicer.org in a detailed tutorial format.

This chapter will discuss about the visualization and 3D modeling of the region of interest (ROI), which is the prostate gland itself and its surrounding pelvic area.

The following are the steps to accomplish the process.

- 1) Loading Data-loading the DICOM volume.
- 2) Viewing Data-Viewing volumes.
- 3) Modifying data-Editing data.
- 4) Saving data-Saving Models.

4.2 Loading the DICOM volume

A volume is a collection of volume elements (voxels) of an image. A slice is a portion of a volume. DICOM is a complicated standard. Slicer is not capable of reading all flavors of it. Slicer assumes that the slices of the volume are

stored in separate files and that they are not compressed, and that the header data is correct (contains the correct values of the study and the series UIDs). Slicer uses the following method to determine the correct slicer order. First, it tries to find the image number (0x0020, 0x0013) data element. If that is not present, it tries the slice location (0x0020, 0x1041) data element. If neither data element is available, the files will be ordered, as they were found, possibly not in the correct order. Slicer has a restriction that the slice thickness and spacing must be the same for every slice.

When loading DICOM images, the dialogue box appears as figure 33, showing the patient, studies, series, and files (indicated by arrows). Then the header data will be extracted once said ok. After which the volume was read finally.

Figure 33.3D slicer loading the DICOM images taken from MR scanner (patient number two).

4.3 REFORMATTING THE SLICES

Viewing volume is nothing but reformatting the slices. The volume data was visualized (3D array of voxels) through Multi Plane Reformating (MPR) as shown in figure 34. A reformatted image is derived by arbitrarily orienting a plane in 3D space, and assigning values to each 2D pixel of the plane by interpolating the 3D voxels of the volume data intersected by the plane. It was reformatted up to three slices (as shown fig 34) at once with independent orientations, in real time. Slices can be arbitrarily oblique, or orthogonal and oriented relative to either the coordinate frame of the scanner or the tracked pointing device. Some radiological applications insist on minimum interpolation, and so it provided additional orientation options that generate orthogonal slices relative to the data itself rather than the coordinate frame it has been registered. [41]

Figure 34. Reformatting of transverse, sagittal and coronal planes in 3D space viewed using rainbow color setting.

Multiple Volumes on the Same Slice

Each reformatted slice may be generated from any of the available data sets. For example, one slice could be reformatted from preoperative SPGR, a second slice could be reformatted from preoperative T2-weighted MRI, and a third slice could display the images that are being scanned in real time. We extended reformatting to slice through both anatomical and functional volumes of data simultaneously. Each slice is the composite of a background layer, foreground layer, and label layer. The background image is typically gray-scaled anatomical data, and the optional foreground can be colored, functional information. The foreground layer is overlaid on the background layer with an adjustable opacity to form the image that is displayed on the slice. As for the third layer, the output of image segmentation is a label map where each voxel is assigned an integer label according to the segmented structure it belongs to. The boundaries of each of these structures can optionally be drawn in color on the image.

Figure 35. Thresholding the bladder area to distinguish the prostate

Display Windows

There is an image-processing pipeline for each slice that takes 3D volume data as input, computes a fast reformat using integer math to create 2D data, converts from scalar values to screen colors, overlays the foreground layer on the background layer, and draws cursors and annotation. The output images are displayed in 2D image windows (one for each slice) and texture-mapped onto graphics planes that are correctly positioned in 3D space and rendered in a 3D view. Focus can be varied between the 2D images and the 3D rendering. It provided three different methods in attempting to create a convenient interface for all users. First, there is a foveal view in the form of a 2D window that provides a magnified version of the area around the cursor. Second, each 2D image can be zoomed independently. Third, the display mode may be set to show a huge 3D view, a large 3D view and the three 256x256 2D images, or all 4 windows set to size 512x512.

4.4 SURFACE MODEL GENERATION

Surface models (see figure 36) of key anatomical structures can be visualized in the 3D view along with the reformatted slices. Using the endoscopic module, detailed part of the model can be zoomed for clarity. The endoscopic view (see figure 37) can be switched on or off for simplicity. A camera is used to in all three axes and it could move all three directions. It is useful in guiding biopsies and other operating procedures in operating room. It can be adapted to track instruments in surgery. The surface model was done using linear interpolation methods (shown in figure 37), which is a built in function of the software.

The volume rendering was done using the MIP (Maximum Intensity Projection) option in the software. The Scalar Opacity Box defined the function that assigned the color value for a given voxel value. A voxel is nothing but a 3-dimensional pixel.

Figure 36. 2d texture mapping creates an surface model of the hip using 3d slicer.

Figure 37. 2d texture mapping and an endoscopic view

Figure 38. Axial and coronal plane of the MR Image viewed in 3d slicer.

Trajectory Assistance

In addition to slices and models, the locator (a tracked wand or surgical instrument) is also rendered as a cylinder in 3D space at its correct location and orientation which can be seen in figure 40. The software can also provide means for assisted trajectory planning and guidance. Once a low-contrast target is identified using near real-time imaging, it is sometimes difficult to quickly get it again. This can be simply avoided by marking the probe's position with a bright red sphere on the 3D display, so the location can be easily returned to. Trajectory assistance is achieved through marking the point of entry with one sphere, and the target tissue with another sphere, and rendering a cylinder between the two points. Thus, it was necessary to align the rendered locator with the target in a video-game-like exercise to and the planned approach.

Figure.39.1.5 T T2 weighted image (left), 0.5-T real time FGR Image (middle), and 0.5 T real time T2 weighted image (right) of the prostate gland. Courtesy: Department of radiology, Brigham and Women’s hospital.

1.5-T weighted T2 weighted images are used to identify PZ and tumor foci in the PZ, while 0.5-T images are mainly used for guiding the needle to the pre identified lesion and targets.

Figure.40.Left: 1.5 T T2 weighted FSE for identifying the tumor foci prospectively (arrows). Middle: Real time FGR to guiding needle appearing as shadow artifact (arrow head). Left: T2 weighted image to visualize the suspicious tumor lesion processed by the 3d slicer. Courtesy: Department of radiology, Brigham and Women’s hospital.

Note that the tumor foci is well visualized both in 1.5-T and 0.5-T T2-weighted images,while T1 weighted image does not show the PZ, tumor or a

distinctive boundary of the gland. Pathology result of the sample taken from the lesion was prostatic Adenocarcinoma (Gleason score 3+3).

Multi-Modal Registration

The 3D Slicer supports rigid, manual registration by allowing the user to specify which volume to move, and then intuitively translate and rotate that data set by clicking and dragging on the images in the 2D windows. The reference volume can be displayed as the background layer of the slices, and the registered volume can be displayed translucently as the foreground layer. Furthermore, with one button click, the result of manual registration can be used as an initial pose for automatic registration by maximization of mutual information.

Figure 41. 3d slicer view of showing the reference volume viewed as background layer of the slices.

Volume Editing

Volumetric data can be semi-automatically segmented using the 3D Slicer's suite of editing tools. Effects such as thresholding, morphological operations, island removal (erasing small groupings of similar pixels), measuring the size of islands, cropping, and free-hand drawing of polygons (as shown in figure 42), lines, or points can be applied to the data on a 3D or slice-by-slice basis. It allowed the slice-by-slice editing to be administered on axial, coronal, or sagittal slices merely by clicking on the appropriate slice. Each effect may be applied to either the *original* volume, or a *working* volume. Multiple editing effects may be applied to the working volume, and when finished, the working volume may be merged with a *composite* volume to overlay smaller structures onto larger ones. For example, the author used the draw option to define the boundary of the prostate and created the working volume of the prostate.

Figure 42.Clip showing the draw panel of 3d slicer’s modification tools.

Figure.43.Prostate working volume is created using the draw and save island effect.

output is the working volume. Then remove islands in the working volume, and finish with erosion and dilation to smooth the edges, as was performed in the making of Figure 42. This working volume is then copied to the composite volume. Next, segmentation of the prostate can be performed in the working volume, and all non-zero voxels of the working volume can overwrite the composite volume to form a combination of both working and composite volume. Strength of the system is that effects can be visualized by overlaying the working volume translucently on the original volume and explored in the 3D view.

Figure.44. Thresholding effect on the working volume.

Figure.45.Volume measuring of the whole model.

The measure volume module measures the geometric volume, in millimeters, of each label within an image volume. This is useful for making measurements. The measure tab lets you specify the volume to measure and an output file for the results. Figure 45 shows the volume measurement done on the image volume of the region of interest.

4.5 3D MODEL GENERATION

The output of the segmentation process is a set of label maps, where pixels take on values corresponding to tissue type. The bounding surfaces of the label maps are extracted and represented as a collection of triangles using marching cubes. Decimation reduces the number of triangles to a quantity that can be more quickly rendered with little observable loss in detail. It is helpful to have the 3D Slicer call a separate process to generate the models so that sets of many models could be performed as a batch job in the

background while the user continues to use the 3D Slicer for other tasks. Model generation can be run on another machine with more memory and the user is emailed when the job is complete so the models can be viewed in the 3D Slicer.

Figure 46. Showing 3D model of volume clipped by two planes.

Using clipping option, an image volume can be clipped or sliced at any direction and view the resultant. This enables an deeper understanding of the every structure of the model in detail and it is possible to view all the inner parts of the body by slicing anywhere inside the region just by selecting planes for clipping as indicated in the figure 46.

Figure.47.3d model of the image volume before clipping.

4.6 VOLUMETRIC ANALYSIS

The 3D Slicer facilitates several types of quantitative measurements that may be made in 3D space. One can click on a particular surface model to measure its surface area or volume. Markers can be positioned on the surface models and slice planes by clicking on the 3D view, and then the distances or angles between markers can be measured.

MRI-based segmentation is highly accurate in assessing prostate volume. Diameter-based measurements are closely correlated to the segmented prostate volume and are feasible to monitor therapy. [40].

Figure.48. Working volume of the prostate together with the slices.

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

5.1.CONCLUSION

Analysis previously reserved for pre-operative data can now be applied to exploring the anatomical changes as the surgery progresses. Real-time scans are visualized as slices in the same 3D view along with the pre-operative slices and surface models. The 3d Slicer software has been applied in over 20 neurosurgical cases at Brigham and Women's Hospital, and continues to be routinely used for 1-3 cases per week. [39]

The author strived to achieve one or more of the following:

1. Data analysis
2. Surgical planning
3. Surgical guidance
4. Surgical guidance with intra-operative updates

The present system important ongoing needs and developments include

1. Increased multidimensional resolution through space and time of images, procedures and devices
2. Automatic accurate anatomic and functional segmentation from image data produced by medical volume Scanners of the human body-design automation.
3. Fast and robust multi-dimensional registration and data fusion
4. Faithful tissue feature and property classification-software development
5. Realistic, real-time volume rendering and visualization-high graphics support.

Limitations of the present system.

1. Proposed new methods should be based on real clinical needs and align with the expectations of physicians and surgeons.
2. The new method(s) should be relevant to problems, which currently have no satisfactory solutions.

3. The new approach should demonstrate distinct promise in improving outcomes, which is not clearly known.
4. Safety of the equipment and procedures needs to be documented and demonstrated.
5. Reliability, accuracy, ease of use, modularity, and versatility of the method or procedure are all-important factors to consider and document which can be only obtained if the system could be directly tested on real clinical needs.

5.2.RECOMMENDATIONS

3D Visualization

Interventional images are presently two-dimensional requiring the surgeon to mentally map the 2D images seen on a computer screen to the 3D operating field. The 3D Slicer is a software package that addresses the aforementioned areas. Image resolution, imaging time, and localization are improved by performing real-time re-slicing of both pre-operative and intra-operative data sets, and displaying them for simultaneous review. Multi-modal information is incorporated through automatic registration. The 3D Slicer features a computer graphics display that offers the flexibility to see the situation from viewpoints not physically possible. It has the ability to fly through virtual data to facilitate the understanding of complex situations, and aids in avoiding damage to healthy tissue. The important achievements reported here are the lessons learned in evaluating the system. This is an effective and frequently used surgical tool, and the author recommends the reader to use the system in a variety of applications.

Many projects that have been initiated in the last decade will continue into the next decade, especially image-guided diagnosis and treatment. These are predicted to have an ever-increasing positive impact on medicine and healthcare. Medical Imaging will move toward the future successfully the same as we have done in the past, through a synergistic combination of

ideas and tools. Ideas alone are not worth much. Tools that have not been based on good ideas are not implemented effectively. Together they become the basis for worthwhile change and sustained progress. The author strongly believes that design automation can significantly increase the efficiency and reliability of the system and it could well be implemented to any such software and systems.

Current and future medical imaging research will continue to focus in four main areas:

1. Devices and instrumentation
2. Algorithm development,
3. Modeling and simulation-wherein the contributions are made.
4. Application prototyping.

The author felt the lack of comprehensive software toolkits and customized software for rapid prototyping and testing of new methods, procedures and devices has impeded progress. Conversely, recent availability of such resources has significantly empowered the field and moved it forward. One must also consider several practical issues commonly associated with new methodology, including the training of new users and the maintenance of new systems and/or devices. Conformance to existing standards or development of new standards is often crucial to success. Standards in imaging and image-guided procedures have been slow to develop, but some emerging conventions are promising. Validation and evaluation are critical, as is careful assessment of cost versus benefit.

As such, design automation is not available in any of the software in the biomedical imaging. Design automation could be very useful as it can dramatically reduce the burden of surgeon relying upon an engineer to the laborious process of 3d modeling.

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APPENDIX I

3D Slicer System Architecture

Coordinate Systems and Transforms

This section describes the various coordinate systems used by the 3D Slicer and the coordinate system transformations used to drive reformatting.

The RAS Coordinate System

The RAS coordinate system defines a right-handed, three-dimensional space with millimeter units and orthogonal axes relative to the patient. The *R* axis extends from the patient's left to Right side, the *A* axis runs from the posterior to the Anterior, and the *S* axis runs from the inferior to the Superior (feet to head). Every scanner has its own coordinate system, and patients can assume different positions within the same scanner. By working in RAS space, the 3D Slicer becomes scanner independent, and automatic registration has an immediate head start because the patient's nose will always roughly point in the direction of the *A* axis.

The IJK Coordinate System

The IJK coordinate system refers to a framework for accessing the 3D array of voxels in a volume scan. The axes extend in the order that the voxels are stored on disk. Typically, this implies that the *I* axis runs across an image from left to right, the *J* axis runs down an image from top to bottom, and the *K* axis extends from the first slice acquired to the last. The coordinates of a particular voxel equal the indices into a 3D array that a computer would use to access the voxel.

The XYZ Coordinate System

The position of the tracked locating device is reported with respect to a calibration point in the center of the open MR imaging volume. These XYZ coordinates are in millimeter units, and conversion to RAS is merely a matter of permuting the axes. The permutation is a function of the patient entry (feet-first or head-first), patient position (supine, prone, left-decubitus, or right-decubitus), and the docking position of the table (front or side). RAS

coordinates equal the scanner's XYZ coordinates when the patient is lying head-first, supine on a table docked at the front of the magnet.

Converting from RAS to IJK

Reformatting is the process of identifying, which RAS points lie on the desired image plane, and then transforming those points to IJK space to obtain indices into the array of voxels stored in computer memory. This conversion from RAS to IJK space is stored in a RAS-to-IJK matrix in the MRML file. The matrix can be computed from the corner points of the volume, when available, or from the voxel size, scan orientation (axial, sagittal, or coronal), and slice order (such as left-to-right, or right to-left for sagittal scans).

Handling Rigid Registration

Rigid registrations that allow 6 degrees of freedom (3 translation, 3 rotation) can be represented by a 4x4 transformation matrix. Registrations between volumes are stored as hierarchies of transform nodes in the MRML file. These transforms are concatenated when the MRML file is read to form a REF-to-RAS transform, where *REF* refers to the *reference* volume that the data was registered to. If the 3D Slicer is used to perform registration, it computes a WLD- to-REF transform which relates the 3D Slicer's view of the world (the RAS coordinate system for its 3D view window) to the reference volume. At bootup, the WLD-to-REF transform for each volume is initialized to the identity matrix. For the purpose of reformatting, points in the 3D Slicer's RAS world space are converted to the IJK space of the specific volume being reformatted. This is achieved by multiplying the points by a transformation matrix, M , that is generated by concatenating the RAS-to-IJK, REF-to-RAS and WLD-to-REF transforms. In the equation below, WLD is a point from world space, and IJK is a point from IJK space.

$$\underline{M} = RAS\ to\ IJK .\ REF\ to\ RAS.\ WLD\ to\ REF \tag{5.1}$$

$$\underline{M}.WLD = IJK \tag{5.2}$$

Figure 49: The location of a reformatted plane is expressed as a matrix that transforms the base coordinate system, u , to the coordinate system, r , of the reformatted plane.

Computing the Reformat Matrix

The orientation and position of a reformatted plane are specified by what we call the reformat matrix. This is the matrix that would transform a plane initially centered at the origin, and lying in the RA-plane, to the desired location of the reformatted slice. Figure 48 shows the coordinate system of the desired reformatted slice (defined by the axes $r^{\wedge}x$, $r^{\wedge}y$, and $r^{\wedge}z$) has been rotated and translated with respect to the base coordinate system defined by the axes $u^{\wedge}x$, $u^{\wedge}y$, and $u^{\wedge}z$. The 4x4 matrix R that rotates the r coordinates system to the u system will take the form of equation 5.3.

$$\begin{pmatrix} r_{11} & r_{12} & r_{13} & 0 \\ r_{21} & r_{22} & r_{23} & 0 \\ r_{31} & r_{32} & r_{33} & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \quad (5.3)$$

The upper left 3x3 submatrix of R is orthogonal, which means that the rows form a set of orthogonal unit vectors. When R is multiplied by $U^{\wedge}x$, it forms the $r^{\wedge}x$ axis of the reformatted system as shown below. (See [Hearn and Baker 1997] for more details)

$$\underline{R} \cdot u^{\wedge}x = r^{\wedge}x \quad (5.4)$$

$$\begin{pmatrix} 1 \\ 0 \\ 0 \\ 1 \end{pmatrix} = \begin{pmatrix} r_{11} \\ r_{21} \\ r_{31} \\ 1 \end{pmatrix} \quad (5.5)$$

If the reformatted system is translated from the original system by a translation $\underline{r_o}=(t_x, t_y, t_z)$, then the translational component of the offset may be specified as:

$$\underline{T} \cdot \underline{u_o} = \underline{r_o} \quad (5.6)$$

$$\underline{I} = \begin{pmatrix} 1 & 0 & 0 & tx \\ 0 & 1 & 0 & ty \\ 0 & 0 & 1 & tz \\ 0 & 0 & 0 & 1 \end{pmatrix} \quad (5.7)$$

The complete reformat matrix, $\underline{M}$, that transforms any points between the two systems is the concatenation of the $\underline{R}$ and $\underline{I}$ transforms:

$$\underline{M} = \underline{R} \cdot \underline{I} \quad (5.8)$$

$$\underline{I} = \begin{pmatrix} r_{11} & r_{12} & r_{13} & tx \\ r_{21} & r_{22} & r_{23} & ty \\ r_{31} & r_{32} & r_{33} & tz \\ 0 & 0 & 0 & 1 \end{pmatrix} \quad (5.9)$$

This reformat matrix, M , is computed by the 3D Slicer in one of two different ways. When the tracked locator device is driving the location of the reformatted slices, then the elements of M are filled in by using the position of the locator's tip as (tx, ty, tz) , and the normal direction of the locator (from handle to needle tip) is used as $r^{\wedge}z$, and the transverse axis (from handle to cord) is used as $r^{\wedge}y$, and $r^{\wedge}x$ can be computed by their cross product. When the user, rather than the locator, is driving the location of the reformatted planes, and the slices are oblique, then they may be generated relative to the viewing direction instead of the locator. Here, the focal point (center of rotation of the 3D display) is used as the translation, the view direction is used as $r^{\wedge}z$, and the "up" direction is used as $r^{\wedge}y$.

(Courtesy: MASSACHUSETTS INSTITUTE OF TECHNOLOGY)

APPENDIX II

Glossary of prostate cancer related terms & abbreviations

Adenocarcinoma

A cancer that develops in the lining or inner surface of an organ. More than 95% of prostate cancers are adenocarcinomas.

Adjuvant Treatment

Treatment that is added to increase the effectiveness of a primary therapy i.e., radiation, to radical prostatectomy (RP) or chemotherapy after surgery.

Adrenal Glands

Two glands located above the kidneys that produce small amounts of the male hormone testosterone as well as other hormones.

Alkaline Phosphatase

An enzyme active in an alkaline medium such as blood plasma or serum, bone, kidney, spleen, lungs, etc. which can be used to detect bone or liver metastasis.

Analog

A man-made compound similar to the one manufactured by the body. Examples are LH-RH analogues lupron depot, luproline acetate and zoladex; examples of antiandrogen analogues are flutamide and its Canadian version, euflex.

Androgen Hormone

Any hormone that produces male physical characteristics. In men the main hormone is testosterone.

Antiandrogen Drug

A drug that blocks the activity of an androgen hormone (testosterone from the adrenal glands) by blocking the androgen receptor sites in target organ cells.

Antibody

A protein substance in the body produced in response to an antigen to provide immunity.

Antigen

A biological substance, such as a vaccine or foreign protein, that produces an immunological response by producing antibodies.

Artificial Urinary Sphincter

A prosthetic device inserted in the body to remedy incontinence by constricting the urethra.

Asymptomatic

Without obvious signs or symptoms of disease. When cancer is in its early stages it may develop and grow without symptoms.

Autologous Transfusion

When one donates blood for himself prior to an operation in case he will need it during his operation.

Benign Prostatic Hyperplasia (BPH)

A non-cancerous condition in which the prostate grows and pushes against the urethra and the bladder blocking the flow of urine. There is an abnormal multiplication of the non-malignant prostate cells.

Benign Prostatic Hypertrophy (BPH)

A non-cancerous condition in which the prostate swells because of an increase in the size of the constituent cells and causes the same symptoms. In both BPH's there may be an above normal PSA reading as with individuals with prostatitis and prostatic infarction (a sudden blockage of the blood supply to a portion of the prostate gland).

Benign Tumors

Non-cancerous tumors that do not spread to other areas of the body.

Biological Therapy

Also known as biotherapy or immunotherapy, is a new form of cancer treatment based on the knowledge and tools of modern molecular biology, immunology, and genetics.

Biopsy

The removal and microscopic examination of a sample of tissue to ascertain if cancer is present. It is the most important procedure in diagnosing cancer. In the tradition "true cut" biopsy or spring loaded biopsy gun, a large hollow needle removes a core or plug of the

tissue. In a fine needle aspiration, the tissue is aspirated, or sucked out, of the suspected area.

Bladder Catheterization

Passage of a catheter into the urinary bladder through the urethra.

Blastic Lesions

Refers to the increased density of bone seen on x-rays when there is extensive new bone formation due to cancerous destruction of the bone. It appears cloudy on x-rays with an added layer look when compared to unaffected bone.

Blood Chemistry

Analysis of multiple components in the blood serum including tests to evaluate function of the liver and kidneys, minerals, cholesterol, etc.; important because abnormal values can indicate spread of cancer or side effects of any treatments.

Blood Count

Examination of a blood specimen in which the number of white blood cells (which protect against infection), red blood cells (which transports oxygen) and platelets (necessary for clotting blood) are determined.

Blood Urea Nitrogen (BUN)

A blood test that helps measure kidney function.

Bone Marrow

Soft tissue in bone cavities; produces blood cells.

Capsule

The layer of cells around an organ such as the prostate.

Carcinoma

Cancer that begins in the tissues that line or cover an organ.

Cell Saver Blood

Blood recovered during an operation and transfused back into the patient.

Chemotherapy

Treatment of cancer with certain chemicals that interfere with cell division not only of cancer cells, but all young and dividing cells of the body, such as blood cells. Chemotherapy alone may destroy immunity if given too long and too intensely. It is not usually curative for prostate cancer patients except in rare instances.

Clinical Trial

A study conducted using patients, usually to evaluate a new treatment.

Combinational Hormonal Therapy (CHT)

The blocking in manufacturing of testosterone through surgical or chemical castration plus an antiandrogen to inhibit the prostate cancer receptor cells from utilizing dihydrotestosterone converted from the testosterone of the adrenal glands.

Computed Tomography (CAT or CT Scan)

An x-ray procedure that uses a computer to produce a detailed picture or cross section of the body. Useful in evaluating soft tissue organs.

Creatinine

A blood test involving normal metabolic waste in the body to indicate kidney function.

Cryosurgery or Cryoablation

Minimally invasive computer-guided lethal freeze of all or part of the prostate using argon gas. Medicare-approved for primary and salvage treatment of localized prostate cancer. 89-92% success in 7-8 year studies.

Cystoscopic Examination

An examination of the urethra and urinary bladder with a cystoscope. A cystoscope is an instrument having a narrow tube with light at one end of an opening so the physician can observe what the light reveals.

Digital Rectal Examination (DRE)

A procedure in which a physician inserts a finger in the rectum to examine the area as well as the prostate gland for signs of cancer.

DNA

A nucleic acid found in cell nucleus that is the carrier of genetic information.

DNA Ploidy Analysis through Flow Cytometry

An objective analysis of prostate cancer cells from a biopsy that enables a more accurate determination of cellular characteristics. You should request this from your doctor before the biopsy to insure sufficient tissue sample. This test compares the number of chromosomes and the DNA in a normal cell. If the cell has two sets of chromosomes and the DNA is normal the cells is called diploid and is normally slower growing. If the cell has more DNA than a normal cell, it is classified aneuploid and has a potential for faster growth. Other combinations that require immediate attention are any combination of aneuploid and/or tetraploid (polyploid), which have the potential to become fast growing. This test is often referred to as the ploidy test and may be valuable because it may assist in determining treatment options.

DNA Ploidy Analysis Through Static Cytometry

A recent pathological development that may determine the ploidy patterns from a much smaller sample of tissue as obtained from a fine needle aspiration biopsy.

Double - Blind Study

A controlled experiment in which neither the patient nor the attending physician knows whether the patient is getting one or another drug or dose. In a single - blind study only the patient doesn't know which of the several treatments he is receiving.

Drug "Interaction"

Any mechanism by which one drug may interact with the action(s) of another drug.

Edema

The swelling or accumulation of fluid in a part of the body.

Efficacious (Efficacy)

The capability of producing the desired effect i.e. hormonal therapy reducing the PSA of an individual.

Endocrinologist

A specialist of the endocrine glands and hormone systems of the body. i.e. pituitary gland, adrenal gland, testes.

Enzyme

A protein that acts as a catalyst, increasing the rate at which chemical change occurs in the body.

External Urethral Sphincter Muscle

A voluntary and involuntary ring-like band of muscle fibers that you voluntarily contract when you want to stop urinating. This sphincter acts as an involuntary mechanism of continence following a radial prostatectomy. The prostatic urethra ends at the external urethral sphincter muscle.

False Negative Report

A negative result when in reality it is positive in nature.

False Positive Report

A positive result when in reality it is negative in nature.

Fine Needle Aspiration

The use of a thin needle to withdraw tissue from the body. In the case of suspected prostate cancer used in conjunction with transrectal ultrasound of the prostate (TRUS/P).

Fistula

An epithelial lined passage or tunnel formed in the body congenitally, by disease, injury, or occasionally by surgery or radiation; and leading from one internal organ to another or from an internal organ to the body's exterior. Anal fistula is the most common.

Flutamide (Eulexin)

An anti-androgen medication that may be prescribed with an LHRH analog or an orchiectomy in combination hormonal therapy.

Foley Catheter

A self-retaining tube placed through the urethra into the bladder for continuous urinary drainage.

Frozen Section

A technique in which tissue is removed by biopsy, then frozen, cut into thin slices, stained and examined under a microscope. A pathologist can usually rapidly examine a frozen section for immediate diagnosis. This procedure is often done during surgery to help the surgeon decide the most appropriate course of action.

Gleason Score

A subjective method of measuring the differentiation of cells to classify tumors by their microscopic appearance and how aggressively cancer cells may multiply. This system divides prostate cancer into five histologic patterns ranging from 1-5. Patterns 1 and 2 represent well-differentiated tumors and are dealt with more easily; Gleason patterns 3 represents moderately well-differentiated tumor cells beginning to scatter; Gleason patterns 4 and 5 indicate poorly differentiated cells with the potential for fast growth. The total Gleason score is determined by adding a primary and secondary score pattern for each prostatic lesion i.e. $3+4=7$. The most well-differentiated cancer cells would consist entirely of Gleason pattern 1 (primary +secondary + $1+1$ or Gleason 2) and the most poorly differentiated cancer cells would have a $5+5$ or total Gleason score of 10.

Gynecomastia

A tender enlargement of the breasts.

Hematuria

Blood in the urine.

Hormonally Independent Cells

Cancer cells that are not affected by hormones.

Hormone Therapy (HT)

The use of medication or surgery to prevent cancer cells from getting the hormones needed to grow. In prostate cancer this means the hormone testosterone.

Hyperthermia of the Prostate

The use of heat, generally microwave, to shrink the prostate and shrink BPH without damaging the surrounding tissue. This protocol has been extensively used in England and France with a machine named The Prostatron. Hyperthermia of the prostate gland is not presently FDA approved in the United States although it is being investigated.

Immunotherapy

Treatment by stimulation of the body's immune system.

Impotence

Inability to have an erection suitable for intercourse. May be a result of an injury secondary to radiation therapy, surgical resection of the prostate, hormonal deprivation therapy, or other aspects of neurological, vascular or disease processes.

Incontinence

Inability to hold urine in the bladder. May be a result of radiation therapy, surgical resection of the prostate, or other disease process.

Informed Consent

Consent given by a patient after learning about and understanding fully the purpose and other aspects of a clinical trial or any medical procedure.

Interferon

A body protein capable of affecting antibody production in the body and can be a modulator of the immune system of an individual.

Interleukin

A protein substance in the blood that helps the body's immune system fight infection and cancer.

Investigational New Drug

A drug allowed by the Food and Drug Administration (FDA) to be used in clinical trials, but not approved for sale to the general public.

Laparoscopic Lymphadenectomy

The removal of pelvic lymph nodes with a laparoscope done through four (4) small incisions in the lower abdominal region.

LHRH Agonists

Compounds that are similar to LHRH that suppress the testes production of testosterone i.e., lupron and zoladex.

Lupron Depot (Leuprolide)

Monthly injection of a long-acting LHRH analog used in chemical castration and combination hormonal therapy. A three month longer acting depot injection is under investigation for FDA approval.

Luteinizing Hormone - Releasing Hormone (LH-RH or LHRH)

A hormone that controls sex hormones in men and women.

Lymphadenectomy

A procedure in which lymph nodes are taken from your body for purposes of diagnosing or staging cancer.

Lymphangiogram

An x-ray that makes use of special dye to determine whether cancer has spread to the lymph nodes.

Lymph Nodes

Small bean-shaped structures scattered along the vessels of the lymphatic system. The nodes filter bacteria and cancer cells that may travel through the system.

Lytic Lesions

As seen on x-rays, rarefied areas of bone that have been the site of destruction by cancer cells. It appears black on affected bones.

Magnetic Resonance Imaging (MRI)

A picture produced by a computer and a high powered magnet that shows a detailed x-ray type image of a particular body part or region that can detect if the tumor has penetrated the prostate gland and/or invaded the seminal vesicles. It can also be used to evaluate whether lymph nodes are enlarged.

Malignant Tumors

Cancerous tumors.

Metastasis

The spread of cancer cells from one part of the body to another by way of the lymph system, blood stream or direct extension.

Metastatic Work Up

Includes bone scans, bone x-rays, chest x-rays, blood PSA tests and probably blood acid phosphatase and alkaline phosphatase.

Metastron (Strontium 89 Chloride)

A recently FDA approved non-narcotic radiopharmaceutical medication designed for the relief of bone pain associated with metastatic cancer.

Morbidity

Relates to becoming less healthy or sick resulting from a treatment protocol i.e. incontinent or impotent from radical prostatectomy.

Nerve Sparing Technique

A surgical technique during a radical prostatectomy where one or both of the neurovascular bundles controlling erections are spared. The utilization of this procedure is governed by the extent of the cancer.

Nocturia

A condition where an individual must get up several times during the night to urinate.

Nucleic Acids

Large molecules made up of chemical building blocks of nucleotides. The two nucleic acids are DNA and RNA (Deoxyribonucleic Acid and Ribonucleic Acid).

Nuclear Scan

A procedure in which a weak radioactive material called a radioactive tracer is injected in the blood stream. The material is taken up by the body and a machine that looks like an x-ray machine moves over the area being tested and takes pictures.

Oncologist

A medical doctor specializing in cancer.

Oncology

The branch of medical science dealing with tumors.

Orchiectomy (Castration)

The surgical removal of the testicles (see hormone therapy). Patient will be sterile and 50- 60% will become impotent.

Palliative Treatment

Therapy that relieves symptoms, such as pain, but does not alter the course of the disease. Its primary purpose is to improve the quality of life.

Pancytopenia

Decreased platelet, white cell and red blood count.

Pathologist

A doctor who specializes in the diagnosis of disease by studying cells and tissues removed from the body.

PDQ

A database available to physicians supported by NCI on the latest information on standard treatments and ongoing clinical trials for each type and stage of cancer.

Pelvic Node Dissection

Removal of possible cancer carrying lymph nodes near the prostate for their evaluation just prior to a radical prostatectomy. If the lymph nodes are involved, the patient usually has an orchiectomy or hormonal therapy or both (see lymphadenectomy).

Penile Prosthetic Implant

A prosthetic device inserted into the penis that allows for an erection. There are over fifteen different varieties from one piece rigid structures to self contained unit implants.

Perineal Prostatectomy

An operation to remove the prostate gland from an opening between the anus and scrotum. The advantage is shorter hospital stay and less bleeding. The disadvantage is that the lymph nodes cannot be examined simultaneously. A separate lymphadenectomy is required to examine the lymph nodes. This approach can also be used for the treatment of BPH and cryoprostatectomy.

Placebo

A substance that has no real therapeutic pharmacological value i.e., sugar pill instead of an actual medicine. Placebos are often given to patients who require a pill for psychological reasons, but mostly as part of clinical trials to test the effectiveness of new drugs. The placebo effect is a classic example of the mind-body relationship.

Prognosis

A prediction of the course of the disease; the future prospects for the patient.

Proscar (Finasteride)

A recently approved FDA drug that shrinks the prostate gland in the treatment of early BPH. Long term effects are unknown at this time.

Prostate Acid Phosphatase (PAP)

an enzyme produced by the prostate that is elevated in some patients when prostate cancer has spread beyond the prostate. This is useful in staging the disease.

Prostate Gland

A walnut-size gland that surrounds the neck of the bladder and approximately the first inch of the urethra. Its main function is to supply fluid for the sperm during ejaculation.

Prostate Specific Antigen (PSA)

A blood test for the measurement of a substance produced by prostate gland cells. An elevated reading indicates an abnormal condition of the prostate gland, either benign or malignant requiring further investigation. The PSA is the most sensitive "marker" of the prostate cancer currently available and is used to monitor the progress of a patient undergoing treatment as well as after surgery or radiation therapy.

There are two PSA assays: The more commonly used is the Hybritech where a score of 0-4 is generally considered within the normal range. The other is called the Yang Pros - Check where a score of 0-2.5 is generally considered within the normal range. To convert from Hybritech to Yang Pros-Check you multiply your assay by .625. To convert from Yang Pros - Check to Hybritech you multiply your assay by 1.625.

Protocol

The term used to describe an individual's treatment program.

Radiation Therapy (RT)

Uses high energy rays to kill prostate cancer cells. Usually healthy cells are also affected. Like surgery, radiation therapy works best when the tumor is small and localized. There are two ways in which high frequency rays can be delivered: one by External Beam Radiation four or five times a week over six or seven weeks; the other by Interstitial Radiation Therapy also referred to as Brachytherapy, receiving rays from tiny radioactive seeds inserted directly into the prostate tumor. Most men are able to have sexual intercourse after interstitial radiation. Other forms of radiation are Proton Beam Irradiation which has high selectivity without damage to surrounding tissue and negligible morbidity; 3-D Directed Radiation which utilizes computer generated scans that provide the ability to confine the radiation selectively to the targeted area without peripheral

involvement; and Neutron Therapy which is specialized radio therapy using atomic particles.

Radical Retropubic Prostatectomy

An operation to remove the entire prostate gland and seminal vesicles through the lower abdomen.

Refractory

A term commonly used to describe a situation where the disease is no longer controlled by current therapy. It amounts to disease progression.

Remission

Complete or partial disappearance of the signs and symptoms of disease in response to treatment. The period during which a disease is under control. A remission does not necessarily mean a cure.

Retrograde Ejaculation

Semen going backwards into the bladder instead of through the urethra during a male orgasm. This is most often the case following a transurethral resection of the prostate gland (TURP) in the treatment of BPH.

Staging

A medical term for the process of determining if a known cancer is still confined within the prostate where it is curable, or if it has spread outside of the prostate gland where it is probably not curable, but treatable. It is a system for classifying patients with malignant disease according to the extent and severity of disease, and thereby helping to determine the appropriate therapy.

There are 2 systems for staging Prostate Cancer. The Whitmore-Jewett ranges from A to D with substages for more precise definition. The Tumor Nodes Metastasis (TNM) staging system offers greater precision and ranges from T1 through the T's and M's.

Testosterone

A male sex hormone produced by the testicles with a small amount produced by adrenal glands. It is associated with the activity and growth of the prostate gland and other sex organs.

Transrectal Ultrasound Of The Prostate (TRUS/P)

A test using sound wave echoes to create an image of an organ or gland to visually inspect for abnormal conditions like gland enlargement, nodules, penetration of tumor through capsule of the gland and/or invasion of seminal vesicles. It is also extremely useful for guidance of needle biopsies of the prostate gland and guiding the nitrogen probes in cryosurgery.

Transurethral Incision Of The Prostate (TUIP)

A surgical technique for treating BPH on individuals with small prostates. It is a simple operation which is less likely to cause a significant loss of blood. The instrument is passed into the neck of the bladder where one or two incisions are made through the wall to open the prostatic urethra.

Transurethral Laser Incision Of The Prostate (TULIP)

the use of laser through the urethra which melts the tissue with minimal bleeding and no need for a postoperative catheter.

Transurethral Resection Of The Prostate (TUR/P)

also known as Roto-Rooter Procedure A surgical procedure by which portions of the prostate gland are removed through the penis. The technique is used to relieve obstruction of urine flow due to the enlargement of prostate. Many times unsuspected cancer cells are discovered during this procedure when removed tissue is examined by a pathologist. After this operation, semen released during sexual activity usually flows into the bladder rather than out the penis (retrograde ejaculation).

"Tumor Flare"

When LHRH agonists may temporarily stimulate tumor growth and symptoms. To prevent this, doctors usually recommend taking the

antiandrogen flutamide (eulexin) every eight hours beginning at least two days before the first lupron or zoladex injection.

Ultrasound (Ultrasonography)

A non-invasive imaging modality utilizing high frequency sound waves for visualizing tissue. Transrectal Ultrasound is becoming a more prevalent tool in the diagnosis and treatment of prostate cancer.

Ureter

The tube that carries urine from each kidney to the bladder.

Urethra

The tube that carries urine from the bladder and fluid from the prostate through the penis to the outside of the body. It is the first part of the urethra leading from the neck of the bladder, surrounded by the prostate gland and ends at the external sphincter muscle.

Urologist

A doctor who specializes in diseases of the urinary and sex organs of humans.

Vacuum-Tumescent-Enhancement Therapy

A mechanical non-surgical method of producing penile engorgement and rigidity sufficient for intercourse in most impotent patients.

"Watchful Waiting" (No Treatment)

A term used when a patient and/or physician monitors a potentially dangerous condition. A good example would be PSA monitoring of early stage A or B organ confined prostate cancer.

Whitmore-Jewett Staging

Classifications of extent of prostate cancer disease are normally designated by the Whitmore Staging scale composed of alphabetical classifications a-d, followed by numerical prefixes 1-3. Examples would be A1, A2, B1, B2, B3, etc. to D1, D2, D3.

Zoladex (Goserelin Acetate)

A monthly injection of an LHRH analog administered sub-cutaneously and used in chemical castration and in combination hormonal therapy.