BURDEN OF PROSTATE CANCER: ADDRESSING ISSUES OF DIAGNOSIS AND OVERTREATMENT

by

PALAK KRUNAL KUMAR PATEL

(Under the Direction of Randall L. Tackett)

ABSTRACT

Objective: Increased detection of clinically insignificant prostate cancer with routinely used diagnostic tests, as well as uncertainties in the available treatments to manage the low risk disease, are expected to increase the future burden of the prostate cancer substantially. This study aims to address three major areas in the field of prostate cancer including economic burden, diagnostics, and treatment for low risk disease.

Methods: The economic burden of prostate cancer was assessed retrospectively using a population based database. A novel imaging technique such as multiparametric magnetic resonance imaging (MP-MRI) assisted transrectal ultrasound (TRUS) guided biopsy in prostate cancer diagnosis was assessed and compared with the conventional 12-core TRUS guided biopsy by performing a cost-effectiveness analysis. The Surveillance Epidemiology and End Results-Medicare database was used to compare toxicity profiles among localized prostate cancer patients who receive either conservative management or immediate treatment.

Results: An annual average total of $5.6 billion was spent on prostate cancer related conditions in 2010 in the United States. Use of chemotherapy and ultrasound increased the expenditure related to outpatient visits significantly; whereas use of ultrasound and x-ray increased office-

based visit costs significantly. The MP-MRI strategy was found to be cost-effective compared to conventional TRUS guided biopsy assuming a threshold to pay for is $1781.60. Conservative management was found to have lower odds of urinary, rectal, and erectile complications without compromising the survival within a 5 year time period than the immediate treatment.

Conclusion: Routinely used TRUS guided biopsy is associated with a higher economic burden on society. There is a need for tests that can diagnose prostate cancer accurately. MP-MRI/TRUS fusion guided biopsy can characterize prostate cancer accurately and was found to be cost-effective compared to TRUS guided biopsy provided the threshold to pay for this technology is at least $1781.60. To avoid overtreatment among low risk prostate cancer patients, a conservative management approach was found to be a better option because patients can delay or avoid treatment related side effects without compromising prostate cancer specific survival within a 5 year time period.

Keywords: Prostate cancer, economic burden, cost-effectiveness, multiparametric magnetic resonance imaging, conservative management, comparative effectiveness analysis

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DEDICATION

I dedicate this dissertation to my husband, Krunal, my two kids Milit and Shanaya, and my parents. Without your support, guidance, sacrifice, and blessings, I wouldn't have accomplished my dreams.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Prostate Cancer

Prostate cancer is the second leading cause of cancer deaths among men in the United States.[1] Statistics related to prostate cancer diagnosis and death suggest that prostate cancer is the most frequently diagnosed non-cutaneous cancer affecting one in every six men.[2] The American Cancer Society estimated that there were approximately 238,590 new cases and 29,720 deaths due to prostate cancer in 2013.[1] Annual expenditures associated with prostate cancer in 2006 was $9.862 billion in the U.S.[3] Costs associated with prostate cancer are expected to rise due to increased diagnosis, diagnosis at an earlier stage and increased survival.[3]

Prostate cancer is considered a disease of aging.[4] Men under 50 years have a low risk of being diagnosed with prostate cancer. The probability of developing prostate cancer rises from one in 14 in those aged 60-69 to one in seven above the age of 70 years.[4] The majority of men diagnosed with localized prostate cancer are older than 65 years. The median age at diagnosis is 72 years and many patients, especially those with localized tumors, may die of other illnesses without ever having suffered significant disability from the cancer.[5] The approach to treatment is influenced by age and coexisting medical problems. The risk of prostate cancer increases in black Caribbean and black African men in comparison with Caucasians.[6]

Prostate Cancer Screening

Currently, prostate cancer screening is based on the assessment of the serum level of prostate specific antigen (PSA) and digital rectal examination (DRE). Both tests are limited in accurately diagnosing prostate cancer.[7] The PSA test has been widely criticized due to its low specificity. A PSA level of 4 ng/mL is used as the cut off value.[8] If PSA values rise above 4 ng/mL, patients are considered to have a higher risk of prostate cancer. However, a PSA elevation above the threshold of 4 ng/mL has a low specificity for prostate cancer.[7] Mild elevations above 4 ng/mL may be caused by benign conditions such as benign prostatic hyperplasia (BPH) or prostatitis. This may result in a false-positive PSA test and subsequently an unnecessary biopsy.

At least 15% of biopsy-proven prostate cancers occur in patients with PSA levels below 4 ng/mL.[8] However, only 33% of patients with PSA values between 4 and 10 ng/ml actually have cancer.[8] In addition to the total PSA level, several additional PSA variant tests have been used clinically to stratify patients. PSA velocity is the increase in the total PSA level over time. A PSA velocity greater than 0.35 to 0.75 ng/mL/year is commonly considered suspicious for the presence of prostate cancer.[7] For men with PSA values less than 4 ng/mL, the threshold value of PSA velocity is 0.35 ng/mL/year. In men with a PSA greater than 4 ng/ML, a PSA velocity of 0.75 ng/mL/year is reported to be suspicious for the presence of cancer.[9,10]

The ratio of free to total PSA has been found to improve the specificity of an elevated total PSA level. In benign processes of the prostate, the percentage of free PSA tends to be higher in comparison to the total PSA. If a ratio is below 10%, there is a 30% chance of being diagnosed with prostate cancer.[7] Another PSA variant test is the PSA density, which is defined as the total PSA level divided by the prostate volume. Prostate volume is assessed by TRUS guided biopsy by measuring three gland dimensions: the maximum length, the maximum height

orthogonal to the length, and the maximum width. Generally, a PSA density greater than or equal to 0.15 has been proposed as the threshold for biopsy in men with PSA levels of 4 to 10 ng/mL. With this cut off value, approximately 40% of prostate cancers were missed.[7]

Transrectal Ultrasound (TRUS) Guided Biopsy

TRUS guided biopsy is considered the gold standard technique for diagnosing prostate cancer with more than 1.2 million biopsies performed annually in the US.[11] Ultrasound cannot differentiate normal prostate gland from cancerous tissue.[11] As a result, biopsies are not target specific. Instead, a nontargeted, systematic, sextant biopsy schemata is used for cancer detection and characterization (Figure 1.1).[11] Taking cores in an organized way is referred to as a systematic biopsy.

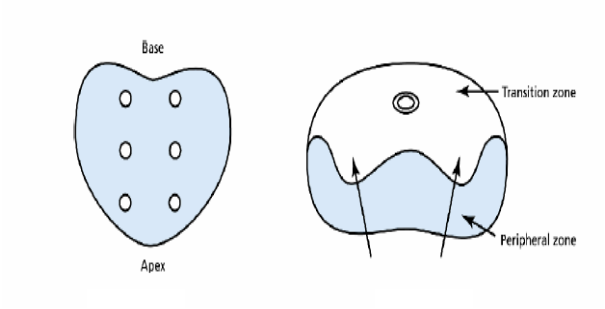

Figure 1.1: Sextant biopsy scheme. A: site of biopsy cores on base, midline, and apex of each lobe of the prostate. B: Transverse view of the prostate. Figure is adapted from Mian, 2004.[12]

TRUS is the most commonly utilized guiding tool for insertion of a biopsy needle into the correct anatomical or topographical region of the prostate. This exact schema is not always possible to follow and certain regions of the prostate (i.e., apex, anterior and lateral regions) cannot be sampled even with the extended systematic plan such as with 8-12 cores (Figure 1.2). This can result in the overdiagnosis of clinically insignificant cancer and under diagnosis of potentially lethal cancer.[13] TRUS guided biopsy is also referred to as 'blind' biopsy. The systematic sextant technique is associated with an estimated false negative rate as high as 15 to

34%.[14] Thus, it requires numerous repeat biopsies, which has a cancer detection rate between 20 and 35%.[15]

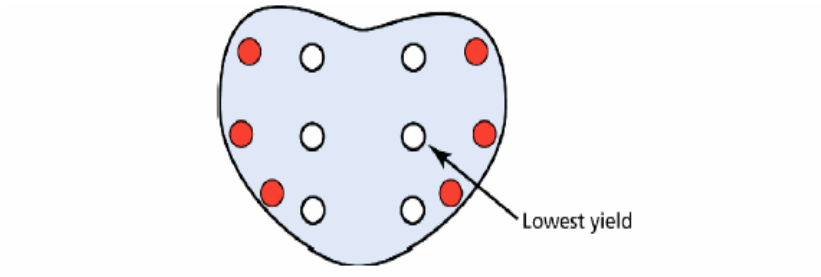

Figure 1.2: Twelve core biopsy scheme. Figure is adapted from Mian, 2014.

To improve diagnostic performance, various biopsy strategies have been proposed in prostate cancer detection. This includes sampling of visually abnormal areas, more lateral placement of biopsies, anterior biopsies, and obtaining an increased number of cores, with up to 45 biopsy cores.[16] Loch reported that there are centers where up to 143 biopsy specimens are taken in one session.[17] However, the efficiency of this practice is debated because of its invasiveness and patient morbidity. Further, it leads to overdiagnosis of insignificant prostate cancer. Alternatively, several studies have shown that systematic biopsy still misses a considerable number of prostate cancers.[18-21] Therefore, a diagnostic strategy that can improve the quality of the investigation instead of raising the quantity of biopsies is clearly needed.

Current Trend of Repeat Biopsy

For patients with the suspicion of having prostate cancer but with more than one negative biopsy, a repeat biopsy has been shown to be positive 10 to 35% of the time.[19] When considering a repeat biopsy, the adequacy of the initial biopsy should be considered. After an initial extended biopsy, prostate cancer has been detected in 18%, 17% and 14% of second, third and fourth saturation biopsies, respectively.[19] If a patient has a precancerous condition, e.g.,

having atypical small acinar proliferation, repeat biopsy should be considered.[22] A repeat biopsy can create significant anxiety for the patient and his family because of fear of the procedure, positive diagnosis of prostate cancer and also the risk of biopsy induced complications.[19,22,23] A large proportion of patients refuse a repeat biopsy because of fear of complications and/or discomfort.[19]

Multiparametric Magnetic Resonance Imaging (MP-MRI)

In recent years, there has been considerable interest in the use of functional MRI in prostate cancer diagnosis. Functional imaging or MP-MRI uses at least one of the following: dynamic contrast enhancement, diffusion weighted imaging and magnetic resonance spectroscopy together with T2-weighted imaging (T2-WI).[16] On T2-WI (based on the transverse relaxation time of tissue content upon magnetization), the peripheral zone of the normal prostate shows high signal intensity due to high water content whereas central and transitional zones show lower signal intensity.[24] If prostate cancer is present, it shows lower signal intensity on T2-WI. MRI technology has undergone a significant advancement and more consistent and accurate results have been reported with its use.[7,13,21,25-29] The capability of combining MRI with techniques to simultaneously perform a targeted biopsy of the prostate is of particular interest to urologists. MP-MRI used in conjunction with a MRI-ultrasound fusion guided biopsy platform has demonstrated improved prostate cancer detection and localization.[14,30]

Conventional MRI at 1.5 or 3.0 Tesla (T) provides morphological information such as the prostate's zonal anatomy, seminal vesicles and the prostatic capsule using T2-WI.[22,31,32] T1 weighted imaging (T1-WI) has been used to detect post-biopsy hemorrhage, lymph nodes, and bone metastasis.[16] T1-WI is based on longitudinal relaxation time of tissues upon magnetization. Conventionally, MRI has been used in clinical practice for determining prostate cancer stage[16]

and has emerged as a promising tool in diagnosing prostate cancer. MRI detects the location of more aggressive lesions on imaging that cannot be accessed even with extended biopsy schemes.[13] MP-MRI is capable of detecting metabolic, diffusion and perfusion abnormalities associated with the cancer.[13,33-37] Proton MRS imaging provides metabolic information, DWI shows Brownian motion of extracellular water molecules, and DCE-MRI visualizes tissue vascularity, especially neoangiogenesis. Thus, efficient cancer identification with high sensitivity and specificity can be made by combining morphologic and functional imaging.[7]

Recently, the U.S. Preventive Services Task Force (USPSTF) attributed a grade of D to PSA screening indicating that there is moderate or high certainty of no net benefit of PSA screening.[27] Application of verification tests such as an imaging test earlier in the diagnostic pathway has the potential of improving the diagnosis of prostate cancer. This practice is already adopted by clinicians for treating other solid organ cancers such as breast cancer.[38]

MP-MRI cannot detect clinically insignificant or low-risk localized disease because of its low sensitivity for low grade, low-volume disease.[27] However, it has a greater sensitivity for detecting clinically significant disease. Thus, it has the potential to address the problem of overdiagnosis and overtreatment of clinically insignificant disease if used as a triage test before TRUS guided biopsy. Over diagnosis and overtreatment of clinically insignificant disease is the main reason that the USPSTF recommended against the use of PSA screening.[27] Kasivisvanathan et al. found that MP-MRI detects clinically significant cancer at an encouraging rate while also reducing the detection rates of clinically insignificant cancer.[22] They further reported that the MP-MRI requires fewer biopsy specimens than systematic template guided biopsy. MP-MRI also has the potential to address the problem of under diagnosis of clinically significant disease with the current diagnostic practice when cancer is located in the transition zone or in the anterior or

peripheral zone, which are parts of the prostate that are not easily palpable by DRE and are not routinely sampled during biopsy.[13,18,20,27,32,38-40]

There are various techniques used to target biopsies on lesions identified with MP-MRI.[27,33,40] These include (i) 'cognitive' registration of the results of the MP-MRI to target biopsies on TRUS, (ii) targeting within the magnet or 'in-bore' targeting, and (iii) registration of magnetic resonance images onto an ultrasound platform to allow real-time targeting of lesions in the out-patient setting. 'Cognitive' registration suffers from poor interpretation of imaging because the physician first reviews the lesion seen on MRI and then uses this knowledge to select the appropriate area for targeting the biopsy. 'In- bore' targeting within the MRI scanner is a time consuming and expensive approach as it is performed in an inpatient setting. The MRI based image fused onto an ultrasound platform is a promising approach because of real-time targeting of lesions.

With the image guided approach, it is expected that (i) fewer men will undergo biopsy overall, (ii) a greater proportion of patients with clinically significant cancer will undergo biopsy and (iii) fewer men will have a diagnosis of clinically insignificant cancer. However, radiologists with significant training are needed to perform this image guided approach for diagnosing prostate cancer. Thus, prebiopsy MP-MRI requires an initial investment in equipment as well as staff.

Localized Prostate Cancer (Low-risk or intermediate-risk)

a. Low-risk prostate cancer and associated treatments

Fifty percent of patients diagnosed with prostate cancer have low-risk localized one.[10,41,42] Low-risk prostate cancers are also labeled as clinically insignificant or indolent disease. Clinical stages of cancer are presented in Table 1.1. T indicates clinical stage of the tumor.

Table 1.1: Tumor staging system[41]

T Categories	Description
T1	Non-palpable tumor
T1a	Cancer found incidentally during transurethral resection of the prostate (TURP) and less than 5% of the tissue removed is cancer and more than 95% benign. Cancers found during TURP and more than 5% of the removed tissue has cancer.
T1b	
T1c	Cancer found by biopsy upon abnormal PSA blood test result.
T2	Palpable tumor confined to the prostate
T2a	Cancer is in only one side and covers half or less of the side of the prostate.
T2b	Cancer is in only one side of the prostate, but is in more than half of that side.
T2c	Cancers are found in both sides of the prostate.
T3	Cancer has spread beyond the capsule of the prostate into the connective tissue next to the prostate and/or the seminal vesicles and/or the bladder neck
T3a	Cancer is growing outside the prostate but has not spread to the seminal vesicles.
T3b	Cancer has spread to the seminal vesicles.
T4	Metastasis

As per National Comprehensive Cancer Network guidelines, clinically localized low-risk prostate cancer can be defined as[10]:

Low-risk prostate cancer	Very low-risk prostate cancer
• T1-T2a • Gleason score ≤ 6 • PSA <10 ng/mL	• T1c • Gleason score ≤6 • PSA <10 ng/mL • Fewer than 3 prostate biopsy cores positive, ≤50% cancer in any core • PSA density <0.15 ng/mL/g

Note: Gleason score indicates tumor aggressiveness. Gleason score of ≤ 6 indicates that tumor is well differentiated.

The category of very low-risk prostate cancer differs from low-risk cancer and includes criteria suggested by Epstein et al. among patients with stage T1c disease.[43] Stage T1c includes patients with impalpable tumors found by biopsy after abnormal PSA test results.[44] PSA density is included in very low-risk disease which has been confirmed to be a significant predictor of higher risk disease.[43]

Early low-risk prostate cancer is usually asymptomatic.[45] However, advanced prostate cancer can cause symptoms such as slow or weak urinary stream, nocturia, hematuria, impotence, pain in the hips, back, chest or other areas where the cancer has spread to bones, and weakness or numbness in the legs or feet.[45] Appropriate management of screen-detected, early stage low-risk prostate cancer is an important public health issue. Treatment depends on the patient's age, life expectancy, tumor stage, tumor grade, existing co-morbidities and other patient specific risk factors. A tumor stage of T1 (impalpable) and stage T2 (palpable but limited to the prostate) are considered to have localized disease with no lymph node involvement and

no distant metastasis. Tumor grade is also referred to as the Gleason grade, which is a histological assessment of the prostate's glandular pattern and measures the aggressiveness of the tumor.[46] Glandular pattern is graded from 1 to 5 (Figure 1.3) where 1 indicates normal, 2 indicates minimal abnormality, 3 indicates variable shapes and spacing of glands, 4 indicates glandular fusion and 5 shows solid sheets of the cells.[46] The two most predominant patterns are identified and their scores are added to determine the Gleason score.

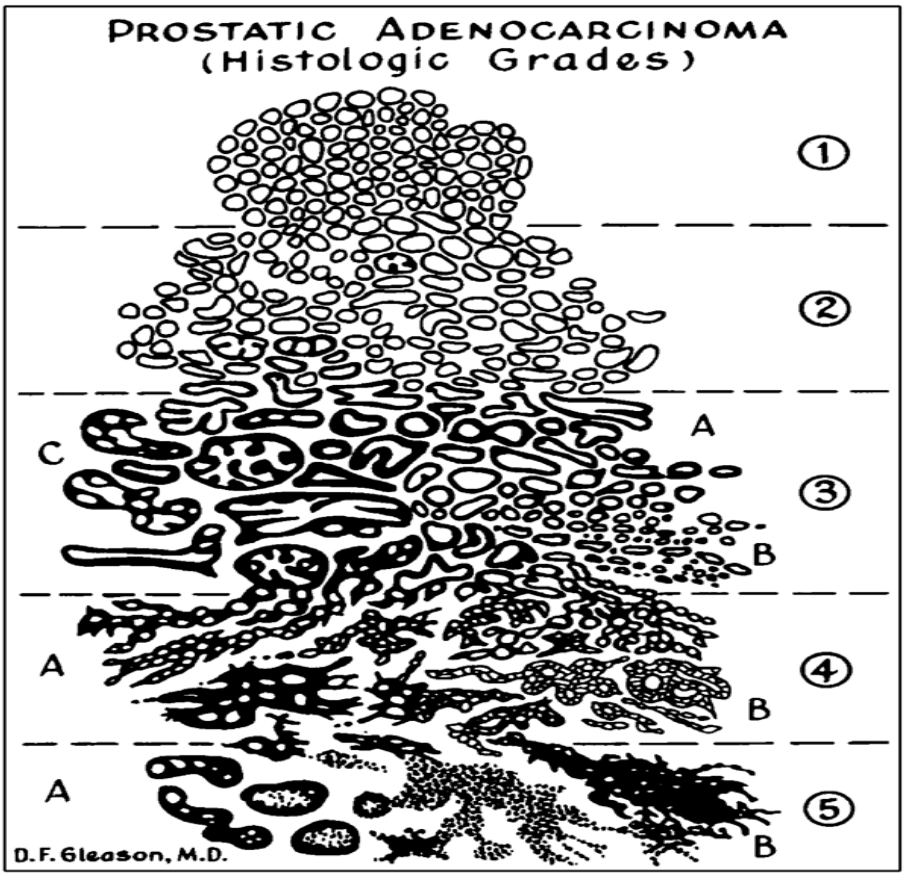

Figure 1.3: Gleason grading of prostate carcinoma. Figure is adapted from Hymphrey 2004.[44]

As per the American Urological Association (AUA), life expectancy rather than age is the major factor to consider regarding treatment for a patient.[47] When a patient has a relatively short life expectancy and when other comorbidities are present, the hazard of dying due to

prostate cancer is reduced. However, if the patient has a relatively longer life expectancy, localized prostate cancer can lead to morbidity or even mortality.

Conventional treatment options for localized early stage prostate cancer include: radical prostatectomy, cryosurgery, radiation therapy, or conservative management. Currently there are a lot of uncertainties regarding the relative efficacies of these treatments and there is no consensus regarding which treatment to choose under what circumstances among providers. As a result, this has led to marked variation in practice patterns.[43]

(i) Radical Prostatectomy

Radical prostatectomy has been the standard treatment for localized prostate cancer for more than 25 years because of two common assumptions: (i) cure is achieved upon organ removal, and (ii) the patient is fully recovered after organ removal.[4,48] However, there is evidence of PSA progression due to tumor recurrence after prostatectomy.[48] Prostatectomy may involve removal of the prostate with or without the neurovascular bundles running alongside of the prostate. These surgeries are associated with urinary, rectal, and erectile complications.[49] Modern applications of prostatectomy such as laparoscopic radical prostatectomy or robot-assisted laparoscopic prostatectomy involve nerve sparing techniques to preserve post-surgical erectile function.[50]

(ii) Radiation Therapy

Radiation therapy consists of administration of ionizing radiation by means of various techniques such as external beam radiation, intensity modulated radiation therapy, proton therapy, and brachytherapy. Radiation therapy is less invasive than prostatectomy and has outcomes comparable to those of prostatectomy.[4] Common side effects associated with

radiation therapy include nocturia, urinary frequency, impotence, and radiation proctitis.[4,49] Intensity modulated radiation therapy and proton therapy are relatively advanced techniques of administering radiation into the body and are expected to reduce urinary and rectal toxicity.[51] Both of these techniques provide comparable outcomes.[51] Brachytherapy involves radioactive seed implantation such as iodine-125 or palladium-103 and is recommended as a monotherapy.[52] However, radiation therapy is combined with neoadjuvant and adjuvant androgen deprivation treatment in many cases.

(iii) Cryosurgery

Cryosurgery uses liquid nitrogen to freeze and destroy abnormal tissue.[53] Long-term outcomes of cryosurgery are not known and this technique is relatively less well established.

(iv) Hormone ablation therapy

Hormonal therapy such as androgen deprivation treatment can be used along with radiation therapy or prostatectomy as the initial treatment for patients who have a high risk of cancer recurrence.[1] Most of the time, hormonal therapy is reserved for those whose cancer has already spread beyond the prostate gland or in men with limited life expectancy who are not candidates for surgery or radiation. Possible side effects associated with hormone therapy include reduced or absent libido, impotence, hot flashes, breast tenderness, osteoporosis, anemia, decreased mental sharpness, loss of muscle mass, weight gain, fatigue, and depression.[1]

Both prostatectomy and radiation therapy are reported to reduce mortality among men with high risk tumors.[54] However, it is reported that prostatectomy among younger patients with relatively low-risk prostate cancer is associated with moderate overtreatment (the number

needed to treat to prevent one prostate cancer death ranges from 7 to 15) and prolonged side effects.[55] In one trial performed in US Department of Veterans Affairs hospitals, radical prostatectomy did not show any mortality benefit over conservative management.[56] Despite these results, the majority of patients diagnosed with low-risk prostate cancer receive immediate aggressive treatment.

(v) Conservative management

Conservative management of early stage low-risk prostate cancer includes two observational strategies: (i) watchful waiting, and (ii) active surveillance. Watchful waiting involves relatively passive patient follow-up and is palliative.[57] It is reserved for relatively older patients who cannot tolerate the aggressive treatments. Upon cancer progression, androgen deprivation treatment is initiated. Active surveillance has emerged as a treatment option for relatively younger individuals who are closely monitored by frequent PSA testing and imaging.[57] However, there is no strict criterion regarding the patient's age as older men may also opt for surveillance despite some high risk features.[58] The NCCN favors active surveillance in patients with very low risk disease and a life expectancy of less than 20 years or in those with low-risk disease and less than 10 years of life expectancy.[10] Patients with very low risk disease who are in active surveillance are less likely to have adverse pathology at the time of radical prostatectomy during the course of progression compared to those who have low risk disease.[43] Also patients with very low risk disease are less likely to experience biochemical recurrence upon switching to curative treatment.[43]

Different institutions have suggested different inclusion criteria for active surveillance. These criteria mainly include identifying clinically insignificant, low-risk tumors based on biopsy and other clinical data (Table 1.2).

Table 1.2: Institution based inclusion criteria for active surveillance

Institution	Clinical stage	PSA	Gleason grade	Total positive cores	Single core positivity	Other
Johns Hopkins	≤T2a	-	≤3 + 3	≤2	≤50%	PSA DT ≤0.15
University of Toronto	NS	≤10	≤3 + 3	NR	NR	-
UCSF	≤T2a	≤10	≤3 + 3	≤33%	≤50%	-
ERSPC (PRIAS criteria)	≤T2a	≤10	≤3 + 3	≤2	NR	PSA DT ≤0.2
Royal Marsden Hospital	≤T2a	≤15	≤3 + 4	≤50%	NR	-
MSKCC	≤T2a	≤10	≤3 + 3	≤3	≤50%	-
University of Miami	≤T2a	≤10	≤3 + 3	≤2	≤20%	-

Note: PSA DT = PSA doubling time; NS = Not stated; NR = Not recorded; UCSF = University of California, San Francisco; MSKCC = Memorial Sloan-Kettering Cancer Center; ERSPC = European Randomized Study of Screening for Prostate Cancer; PRIAS = Prostate Cancer Research International Active Surveillance. Table is adapted from Dall'Era et al., 2012[58]

The threshold to trigger treatment in patients who are on active surveillance are not standardized.[59] Some institutions use PSA velocity as an indicator to measure disease progression whereas some use PSA doubling time within 3-4 years.[59] Some institutions rely only on the results of repeat biopsy.[59] The NCCN guidelines have recommended that patients in an active surveillance program should have PSA measurement as often as every 3 months but at least every 6 months, DRE performed as often as every 6 months but at least every 12 months, and a needle biopsy may be repeated within 6 months of diagnosis if the initial biopsy included fewer than 10 cores.[10]

As prostate cancer is a slowly growing tumor, it makes observational strategies more appealing to patients who have low-risk localized disease. Further, there is a high level of evidence that older men with low risk disease are over treated and observational strategies are underutilized in this group of patients.[43] However, patients who undergo observational strategy

have anxiety of tumor progression and not being treated. Additional barriers to the adoption of active surveillance include potential disease misclassification issues due to inaccurate diagnoses described earlier.[60] As a result, both clinicians and patients lack confidence in prostate biopsy results. Further, there remain uncertainties regarding the long-term all-cause or disease-specific mortality, optimal patient selection, surveillance strategies, and triggers for intervention.

b. Intermediate risk prostate cancer and associated treatment

The NCCN guideline has defined intermediate risk prostate cancer as one with T2b-T2c disease, a Gleason score of 7 or PSA of 10-20 ng/mL.[10] T2b indicates that the cancer covers more than half of only one side of the prostate whereas T2c indicates that the cancer is present in both sides of the prostate.[44] Treatment for localized intermediate risk can be categorized based on life expectancy. If the patient has a life expectancy lower than 10 years, then treatment options include[10]: (1) Conservative management: Watchful waiting or active surveillance; (2) Radiation therapy alone or in combination with androgen deprivation or brachytherapy; or (3) Brachytherapy as a monotherapy.

If the patient has a life expectancy greater than 10 years then treatment options include[10]: (1) Radical prostatectomy; or (2) Radiation therapy alone or in combination with androgen deprivation or brachytherapy.

Evidence on Comparative Clinical Effectiveness of Conservative Management vs Immediate Treatment

Two large randomized controlled trials, the Prostate Testing for Cancer and Treatment (ProtectT) trial in the United Kingdom and the Surveillance Therapy Against Radical Treatment (START) trial in North America, are currently ongoing to compare active surveillance versus

treatment with radiation or surgery. Results of these trials will not be available in the near future.

A study was performed using the Surveillance Epidemiology End Results (SEER)-Medicare database to measure survival among patients diagnosed with localized prostate cancer who did not receive initial definitive treatment within 6 months of diagnosis.[61] Low-risk patients aged 66 to 74 years with comorbidity scores of 0,1, and 2+ had 10- year overall and prostate cancer specific mortality rates of 29% and 4.8%, 51% and 2%, and 83% and 5.3% respectively. This study indicates that fewer men older than 65 years of age die due to prostate cancer within 10 years of diagnosis.[61] Abdollah et al compared radiotherapy with observation within the SEER database.[62] They found radiotherapy provided a 10-year cancer-specific mortality benefit among elderly men (75-80 years) compared with observation.[62] However, the benefit of radiation therapy was not seen in men with low to intermediate risk disease.[62]

The greatest advantage of active surveillance is to maximize and maintain quality of life since all immediate treatment strategies have risk of urinary, bowel, and sexual side effects. As active surveillance is a relatively new management strategy, studies comparing the quality of life by measuring long term urinary, bowel and erectile toxicity among patients receiving active surveillance versus immediate treatment are very few. Recently, Hayes et al performed a decision analysis that compared active surveillance with brachytherapy, intensity-modulated radiation therapy, and radical prostatectomy in terms of quality adjusted life expectancy among 65-year old men with low-risk prostate cancer.[42] Active surveillance had the longest quality-adjusted life expectancy compared with the rest. However, it is important to note that this study was limited to those 65-year olds and cannot be generalized to other age categories. Liu et al compared active surveillance with radical prostatectomy among low-risk prostate cancer

patients and found that older men in worse health have better quality adjusted life expectancy in active surveillance than radical prostatectomy.[63] Fujita et al studied approximately 150 patients on active surveillance who underwent a mean of 2.3 biopsies and reported that patients' urinary complications such as lower urinary tract symptoms in active surveillance did not decrease over a period of approximately 3 years.[64]

Patients who are on active surveillance have to undergo frequent repeat biopsies. Frequent biopsy associated long-term adverse outcomes among active surveillance patients are not known. Biopsies frequently lead to bleeding and lower urinary tract infections. Both of these side effects are transient. Recent evidence suggests there is an increased risk of erectile dysfunction among patients who undergo serial prostate biopsies.[64] Clinical guidelines have suggested some key recommendations to healthcare professionals regarding patient counseling and choosing treatment options or observation.[52] Table 1.3 depicts these recommendations.

Table 1.3: Recommendation to healthcare professionals regarding patient counseling

Clinical recommendation	Evidence rating
Immediate curative treatment should be recommended for patients having localized higher risk tumor. Risk can be estimated based on cancer stage and grade, PSA level, and comorbidity adjusted life expectancy	B
Counseling that surgery and external beam radiation therapy are almost equal should be provided to patients.	B
Brachytherapy can be recommended as a monotherapy in low-risk patients.	B
Active surveillance is a reasonable approach for low risk and very low risk patients.	B

Note: Evidence A = consistent, good-quality patient-oriented evidence; B= inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. This Table is adapted from Mohan et al., 2011.[52]

There is a need for research that can identify the long-term side effects of the active surveillance protocol. Patients diagnosed with low-risk localized disease need to know treatment effects so that they can make an informed decision regarding what treatment strategy to pursue. Multiple factors influence a patient's treatment decisions; however, perceptions of treatment efficacy and side effects (either from the physician's description or from experience of family and friends) have been reported to be the most influential.[65]

Economic Burden

The five year survival rate for patients diagnosed with localized prostate cancer is 100% irrespective of the type of treatment received.[1] Health care costs have been rising for several years and represent a significant national issue in health care reform. Increased detection of clinically insignificant prostate cancer due to PSA testing, frequent repeat biopsies to rule out the possibility of the presence of lethal prostate cancer, and uncertainties in the available treatments to manage the low-risk disease are expected to substantially increase the future fiscal burden of the disease.

In the United States, the prevalence based total costs of prostate cancer were estimated to be almost $10 billion in 2006.[66] Stokes et al estimated the average per person prostate cancer specific life-time cost to be approximately $34,000 for patients diagnosed between 1991 and 2002.[66] However, it is important to note that these costs vary by cancer stage and its estimates were shown to vary from $26, 078 (stage III) to $39, 182 (stage I).[66] There is a report of racial and ethnic disparities in health care utilization and associated costs of prostate cancer but these studies are dated.[67]

In health care cost analysis, costs are generally divided into three categories: direct, indirect, and intangible costs.[68] Direct health care costs include all costs related to drugs, tests,

health care professionals, and medical facilities. Direct non-health care costs include cost related to transportation to medical facilities, child care cost or cost resulting due to accommodation at home or home care givers. Indirect costs include costs due to productivity loss. This may include costs due to loss or impaired ability to work due to the disease condition or morbidity. Intangible costs cannot be measured directly and may include costs due to limitation in leisure activities. Previous studies have reported treatment specific short-term and long-term costs. Hormonal therapy has been reported to cost the highest ($26,896) within 5 years of cancer diagnosis followed by hormonal + radiation treatment ($25,097), surgery ($19,214), radiation therapy only ($15,589) and watchful waiting ($9130) among the older population.[69] However, these estimates are found to vary widely among the relatively younger population. Watchful waiting strategy is found to cost approximately $24, 809 per patient for a period of 2 years due to multiple follow-ups and close monitoring.[2]

Recently, Cooperberg et al. conducted a comprehensive lifetime cost-utility analysis among hypothetical men with clinically localized prostate cancer having low, intermediate or high risk of disease.[70] In this hypothetical scenario, patients received relatively advanced and conventional treatments such as open radical prostatectomy, laparoscopic-assisted radical prostatectomy, robot-assisted radical prostatectomy, three-dimensional conformal radiation therapy, intensity modulated radiation therapy, brachytherapy, or a combination of intensity modulated radiation therapy and brachytherapy in 2009.[70] Further, they assumed that low, intermediate, and high risk patients are 75%, 50%, and 25% likely to receive salvage radiation therapy respectively. The remainder receives androgen deprivation treatment. Surgical methods such as open radical prostatectomy, laparoscopic-assisted radical prostatectomy, or robot-assisted radical prostatectomy were found to cost around $20,000, $28,500, and $35,500

respectively, for low, intermediate, and high risk patients.[70] Brachytherapy was found to cost around $25,066, $32,553 and $43, 952 for low, intermediate, and high risk patients.[70]

In each risk stratum, all advanced radiation therapies were found more costly while less effective. On the other hand, surgeries were less costly and more effective compared to all radiation therapies. This study did not include active surveillance in modeling.[70] In view of the new and emerging diagnostic technologies and increasing aging population, there is a need for more recent overall national estimate of the economic burden associated with prostate cancer.

REFERENCES

1. American Cancer Society. Prostate cancer. 2013; Retrieved in 2014 from http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics.

2. Crawford ED, Black L, Eaddy M, Kruep EJ. A retrospective analysis illustrating the substantial clinical and economic burden of prostate cancer. *Prostate Cancer and Prostatic Diseases.* Jun 2010;13(2):162-167.

3. Roehrborn CG, Black LK. The economic burden of prostate cancer. *BJU International.* Sep 2011;108(6):806-813.

4. Mohile SG, Lachs M, Dale W. Management of prostate cancer in the older man. *Seminars in Oncology.* Dec 2008;35(6):597-617.

5. National Cancer Institute. General information about prostate cancer. 2014. Retrieved in 2014 from http://www.cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional/page1

6. Pal RP, Maitra NU, Mellon JK, Khan MA. Defining prostate cancer risk before prostate biopsy. *Urologic Oncology.* Nov 2013;31(8):1408-1418.

7. Bonekamp D, Jacobs MA, El-Khouli R, Stoianovici D, Macura KJ. Advancements in MR imaging of the prostate: From diagnosis to interventions. *Radiographics.* 2011;31(3):677-703.

8. Umbehr M, Bachmann LM, Held U, et al. Combined magnetic resonance imaging and magnetic resonance spectroscopy imaging in the diagnosis of prostate cancer: A systematic review and meta-analysis. *European Urology.* 2009;55(3):575-590.

9. American Urological Association. *Prostate cancer: Screening and management.* etrieved in 2014 from http://www.auanet.org/education/prostate-cancer-psa.cfm.

10. National Comprehensive Cancer Network. *The NCCN guidelines for prostate cancer early detection.* 2013; Retrieved in 2014 from http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

11. Stoianovici D. Technology advances for prostate biopsy and needle therapies*. The Journal of Urology*. 2012 Oct;188(4):1074-5. doi: 10.1016/j.juro.2012.06.127. Epub 2012 Aug 15.

12. Mian BM. Prostate biopsy strategies: Current state of the art. *Journal of the National Comprehensive Cancer Network : JNCCN.* May 2004;2(3):213-222.

13. Dianat SS, Carter HB, Macura KJ. Performance of multiparametric magnetic resonance imaging in the evaluation and management of clinically low-risk prostate cancer. *Urologic Oncology.* 2013;17(13):002.

14. Rais-Bahrami S, Siddiqui MM, Turkbey B, et al. Utility of Multiparametric MRI Suspicion Levels in Detecting Prostate Cancer. *The Journal of Urology.* 2013;29(13):04417-04410.

15. Engehausen DG, Engelhard K, Schwab SA, et al. Magnetic resonance image-guided biopsies with a high detection rate of prostate cancer. *Scientific World Journal.* 2012;975971(10):12.

16. Pinto F, Totaro A, Calarco A, et al. Imaging in prostate cancer diagnosis: Present role and future perspectives. *Urologia Internationalis.* 2011;86(4):373-382.

17. Loch T. Urologic imaging for localized prostate cancer in 2007. *World Journal of Urology.* 2007;25(2):121-129.

18. Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. *BJU International.* 2011;108(8 Pt 2):22.

19. Kirby R, Fitzpatrick JM. Optimising repeat prostate biopsy decisions and procedures. *BJU International.* 2012;109(12):1750-1754.

20. Komai Y, Numao N, Yoshida S, et al. High Diagnostic Ability of Multiparametric Magnetic Resonance Imaging to Detect Anterior Prostate Cancer Missed by Transrectal 12-Core Biopsy. *The Journal of Urology.* 2013;28(13):03871-03878.

21. Nix JW, Turkbey B, Hoang A, et al. Very distal apical prostate tumours: Identification on multiparametric MRI at 3 Tesla. *BJU International.* 2012;110(11 Pt B):4.

22. Mowatt G, Scotland G, Boachie C, et al. The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: Asystematic review and economic evaluation. *Health Technology Assessment.* 2013;17(20):1-281.

23. Stravodimos KG, Haritopoulos KN, Alamanis C, Anastasiou I, Constantinides C. Local anesthesia during transrectal ultrasonography-guided prostate biopsy: Does it have any effect on sexual function? *International Urology and Nephrology.* 2007;39(3):893-896.

24. Abdellaoui A, Iyengar S, Freeman S. Imaging in prostate cancer. *Future Oncology (London, England).* May 2011;7(5):679-691.

25. Perdona S, Di Lorenzo G, Autorino R, et al. Combined magnetic resonance spectroscopy and dynamic contrast-enhanced imaging for prostate cancer detection. *Urologic Oncology.* 2013;31(6):761-765.

26. Carey BM. Imaging for prostate cancer. *Clinical Oncology.* 2005;17(7):553-559.

27. Dickinson L, Ahmed HU, Allen C, et al. Clinical applications of multiparametric MRI within the prostate cancer diagnostic pathway. *Urologic Oncology.* 2013;31(3):281-284.

28. Goris Gbenou MC, Peltier A, Addla SK, et al. Localising prostate cancer: comparison of endorectal magnetic resonance (MR) imaging and 3D-MR spectroscopic imaging with transrectal ultrasound-guided biopsy. *Urologia Internationalis.* 2012;88(1):12-17.

29. Hambrock T, Hoeks C, Hulsbergen-van de Kaa C, et al. Prospective assessment of prostate cancer aggressiveness using 3-T diffusion-weighted magnetic resonance imaging-guided biopsies versus a systematic 10-core transrectal ultrasound prostate biopsy cohort. *European Urology.* 2012;61(1):177-184.

30. Fiard G, Hohn N, Descotes JL, Rambeaud JJ, Troccaz J, Long JA. Targeted MRI-guided prostate biopsies for the detection of prostate cancer: Initial clinical experience with real-time 3-dimensional transrectal ultrasound guidance and magnetic resonance/transrectal ultrasound image fusion. *Urology.* 2013;81(6):1372-1378.

31. Kaplan I, Oldenburg NE, Meskell P, Blake M, Church P, Holupka EJ. Real time MRI-ultrasound image guided stereotactic prostate biopsy. *Magnetic Resonance Imaging.* 2002;20(3):295-299.

32. Puech P, Sufana Iancu A, Renard B, Villers A, Lemaitre L. Detecting prostate cancer with MRI - why and how. *Diagnostic and Interventional Imaging.* 2012;93(4):268-278.

33. Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: A systematic review. *European Urology.* 2013;63(1):125-140.

34. Park BK, Lee HM, Kim CK, Choi HY, Park JW. Lesion localization in patients with a previous negative transrectal ultrasound biopsy and persistently elevated prostate

specific antigen level using diffusion-weighted imaging at three Tesla before rebiopsy. *Investigative Radiology.* 2008;43(11):789-793.

35. Hara N, Okuizumi M, Koike H, Kawaguchi M, Bilim V. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a useful modality for the precise detection and staging of early prostate cancer. *Prostate.* 2005;62(2):140-147.

36. Nagarajan R, Margolis D, Raman S, et al. MR spectroscopic imaging and diffusion-weighted imaging of prostate cancer with Gleason scores. *Journal of Magnetic Resonance Imaging.* 2012;36(3):697-703.

37. Sciarra A, Panebianco V, Ciccariello M, et al. Value of magnetic resonance spectroscopy imaging and dynamic contrast-enhanced imaging for detecting prostate cancer foci in men with prior negative biopsy. *Clinical Cancer Research.* 2010;16(6):1875-1883.

38. Villers A, Marliere F, Ouzzane A, Puech P, Lemaitre L. MRI in addition to or as a substitute for prostate biopsy: The clinician's point of view. *Diagnostic and Interventional Imaging.* 2012;93(4):262-267.

39. Sciarra A, Barentsz J, Bjartell A, et al. Advances in magnetic resonance imaging: How they are changing the management of prostate cancer. *European Urology.* 2011;59(6):962-977.

40. Ouzzane A, Puech P, Lemaitre L, et al. Combined multiparametric MRI and targeted biopsies improve anterior prostate cancer detection, staging, and grading. *Urology.* 2011;78(6):1356-1362.

41. Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. *JAMA : the Journal of the American Medical Association.* Sep 16 2009;302(11):1202-1209.

42. Hayes JH, Ollendorf DA, Pearson SD, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: A decision analysis. *JAMA : the Journal of the American Medical Association.* Dec 1 2010;304(21):2373-2380.

43. Carter HB. Management of low (favourable)-risk prostate cancer. *BJU International.* Dec 2011;108(11):1684-1695.

44. Roswell Park Cancer Institute. Prostate Cancer Staging. https://www.roswellpark.org/cancer/prostate/diagnosis/staging.

45. Mayo Clinic. Prostate Cancer Symtoms. http://www.mayoclinic.org/diseases-conditions/prostate-cancer/basics/symptoms/con-20029597.

46. Humphrey PA. Gleason grading and prognostic factors in carcinoma of the prostate. *Mod Pathol.* 02/13/online 2004;17(3):292-306.

47. American Urological Association. The Management of Localized prostate cancer Patient guide. 2008. https://www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Cancer-PatientGuide.pdf.

48. Weissbach L, Altwein J. Active surveillance or active treatment in localized prostate cancer? *Deutsches Arzteblatt International.* May 2009;106(22):371-376.

49. Michaelson MD, Cotter SE, Gargollo PC, Zietman AL, Dahl DM, Smith MR. Management of complications of prostate cancer treatment. *CA: A Cancer Journal for Clinicians.* Jul-Aug 2008;58(4):196-213.

50. American Cancer Society. Surgery for prostate cancer. 2013. http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-surgery.

51. Hoppe BS, Michalski JM, Mendenhall NP, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. *Cancer.* Apr 1 2014;120(7):1076-1082.

52. Mohan R, Schellhammer PF. Treatment options for localized prostate cancer. *American Family Physician.* Aug 15 2011;84(4):413-420.

53. National Cancer Institute. Cryosurgery in cancer treatment: Questions and answers. 2003.

54. Thompson IM, Tangen CM. Prostate Cancer — Uncertainty and a Way Forward. *New England Journal of Medicine.* 2012;367(3):270-271.

55. Sandhu GS, Andriole GL. Active surveillance for prostate cancer: Barriers to widespread adoption. *European Urology.* Dec 2012;62(6):984-985.

56. Wilt TJ, Brawer MK, Jones KM, et al. Radical Prostatectomy versus Observation for Localized Prostate Cancer. *New England Journal of Medicine.* 2012;367(3):203-213.

57. Klotz L. Active surveillance for prostate cancer: patient selection and management. *Current Oncology (Toronto, Ont.).* Sep 2010;17 Suppl 2:S11-17.

58. Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. *European Urology.* Dec 2012;62(6):976-983.

59. Whitson JM, Carroll PR. Active surveillance for early-stage prostate cancer: defining the triggers for intervention. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology.* Jun 10 2010;28(17):2807-2809.

60. Singer EA, Kaushal A, Turkbey B, Couvillon A, Pinto PA, Parnes HL. Active surveillance for prostate cancer: Past, present and future. *Current Opinion in Oncology.* May 2012;24(3):243-250.

61. Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of comorbidity on survival among men with localized prostate cancer. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology.* Apr 1 2011;29(10):1335-1341.

62. Abdollah F, Sun M, Schmitges J, et al. Competing-risks mortality after radiotherapy vs. observation for localized prostate cancer: A population-based study. *International Journal of Radiation Oncology, Biology, Physics.* Sep 1 2012;84(1):95-103.

63. Liu D, Lehmann HP, Frick KD, Carter HB. Active surveillance versus surgery for low risk prostate cancer: a clinical decision analysis. *The Journal of Urology.* Apr 2012;187(4):1241-1246.

64. Fujita K, Landis P, McNeil BK, Pavlovich CP. Serial prostate biopsies are associated with an increased risk of erectile dysfunction in men with prostate cancer on active surveillance. *The Journal of urology.* Dec 2009;182(6):2664-2669.

65. Xu J, Dailey RK, Eggly S, Neale AV, Schwartz KL. Men's perspectives on selecting their prostate cancer treatment. *Journal of the National Medical Association.* Jun 2011;103(6):468-478.

66. Stokes ME, Ishak J, Proskorovsky I, Black LK, Huang Y. Lifetime economic burden of prostate cancer. *BMC Health Services Research.* 2011;11:349.

67. Jayadevappa R, Malkowicz SB, Chhatre S, Gallo J, Schwartz JS. Racial and ethnic variation in health resource use and cost for prostate cancer. *BJU International.* Sep 2010;106(6):801-808.

68. Gold MR. *Cost-effectiveness in health and medicine.* New York: Oxford University Press; 1996.

69. Snyder CF, Frick KD, Blackford AL, et al. How does initial treatment choice affect short-term and long-term costs for clinically localized prostate cancer? *Cancer.* 2010;116(23):5391-5399.

70. Cooperberg MR, Ramakrishna NR, Duff SB, et al. Primary treatments for clinically localised prostate cancer: A comprehensive lifetime cost-utility analysis. *BJU International.* Mar 2013;111(3):437-450.

CHAPTER 2

RATIONALE AND HYPOTHESIS

This work focuses on three broad areas in the realm of prostate cancer outcomes research. The first part of the dissertation focuses on assessing healthcare utilization and associated expenditures among prostate cancer patients. The economic burden of the disease is commonly estimated using cost of illness studies.[1] Most cost of illness studies associated with prostate cancer are dated.[2-4] As overdiagnosis of prostate cancer has imposed a greater burden on the healthcare system, there is a need for more recent cost studies that determine the average cost per patient as well as provide estimates on utilization of different health services in different delivery settings. This study is important for policy makers and health researchers to determine how healthcare resources are expended on prostate cancer and the magnitude of the impact of prostate cancer on society.

The second part of the dissertation focuses on determining cost-effectiveness of multiparametric magnetic resonance imaging (MP-MRI) followed by fusion guided biopsy in prostate cancer diagnosis. Accurate prostate cancer diagnosis is limited by poor specificity and the sensitivity of PSA and TRUS guided biopsy. Further, to rule out the presence of prostate cancer, many patients undergo additional biopsies and are diagnosed with clinically insignificant cancers.[5] These biopsies are not without complications and are associated with hematuria, hematospermia, rectal bleeding and urinary retention.[6] To avoid these repeated biopsies, new diagnostic strategies are needed that can identify patients with clinically significant cancer only.

MP-MRI is one of the promising modalities for prostate imaging. MP-MRI involves the use of different MRI based techniques such as T1-weighted, T2-weighted, diffusion weighted imaging, dynamic contrast enhanced imaging, and/or magnetic resonance spectroscopy in one or more combinations.[7] MRI/TRUS fusion guided biopsy is an outpatient procedure, in which prebiopsy MRI of the prostate is fused with real-time TRUS.[8] Currently, a clinical trial is being conducted to determine whether MRI/TRUS fusion guided biopsy is superior to conventional biopsy alone in diagnosing subjects with prostate cancer.[9] However, the results of this study will not be available until April 2015. Economic modelling would be an appropriate approach to compare the relative performance of these diagnostic technologies.

The third part of the dissertation focuses on the comparative analysis of harms associated with conservative management and immediate treatment among low-risk prostate cancer patients. Conservative management, especially watchful waiting of low-risk prostate cancer, is not new. However, active surveillance is a new emerging term that focuses on individuals who are relatively healthy and have longer life expectancies rather than the sicker older population. Active surveillance has been recommended as a treatment option in many guidelines but is not practiced clinically because of uncertainties associated with clinical outcomes.[10] The Institute of Medicine's Committee on Comparative Effectiveness Research has identified treatment for localized prostate cancer as a high-priority research area.[11] This study focuses on the urinary, rectal, and erectile complications, and survival associated with conservative management and immediate treatment approach within 5 years of diagnosis.

This part of the study aims to reduce uncertainties such as the probability of developing adverse effects associated with two broad treatment regimens. The relative effectiveness of treatment alternatives for localized prostate cancer is uncertain and costs are variable. More

specifically, patients need predictions of not only effectiveness but also the various long-term outcomes such as survival, impotence, incontinence, and bowel problems associated with treatment choice. Clinical decision regarding which treatment to choose is a multidimensional and complex process in which patients consider their personal preferences and the advice of their health care practitioners. In this decision process, patients give subsequent emphasis of treatment related side effects. Our study makes this decision process easier for patients by providing long-term outcomes associated with a conservative management option.

Specific Aims

The three specific aims of this project are to:

Aim 1: Estimate the annual average prostate cancer cost in different health delivery settings in the United States and to determine the predictors of higher annual costs of prostate cancer.

We hypothesized that higher expenditures may be associated with chemotherapy, advanced diagnostic strategies such as magnetic resonance imaging, radiation treatment, and surgery.

Aim 2: Determine the cost-effectiveness of MP-MRI followed by MRI/TRUS fusion guided biopsy compared with the conventional TRUS guided biopsy among biopsy naïve patients in prostate cancer diagnosis.

We hypothesized that the MP-MRI approach is more cost-effective than the conventional TRUS guided biopsy because MP-MRI may reduce the number of many false positive and false negative cases and thus avoid costs related to unncecessary repeated biopsies and overdiagnosis.

Aim 3: Compare side effect profile and survival among patients diagnosed with low to intermediate risk prostate cancer undergoing either conservative management or immediate treatments.

We hypothesized that patients who undergo conservative management options such as watchful waiting or active surveillance may delay or avoid toxicities associated with immediate treatment as prostate cancer is a slowly growing tumor and many patients diagnosed with low-risk prostate cancer may not require treatment for long time.

REFERENCES

1. Segel J.E. Cost-of-Illness Studies - A primer. RTI International; 2006.
2. Roehrborn CG, Black LK. The economic burden of prostate cancer. BJU International 2011;108:806-13.
3. Stokes ME, Ishak J, Proskorovsky I, Black LK, Huang Y. Lifetime economic burden of prostate cancer. BMC Health Services Eesearch 2011;11:349.
4. Stokes ME, Black L, Benedict A, Roehrborn CG, Albertsen P. Long-term medical-care costs related to prostate cancer: Estimates from linked SEER-Medicare data. Prostate cancer and Prostatic Diseases 2010;13:278-84.
5. Shariat SF, Roehrborn CG. Using biopsy to detect prostate cancer. Reviews in Urology 2008;10:262-80.
6. Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. European Urology 2013;64:876-92.
7. Pinto F, Totaro A, Calarco A, et al. Imaging in prostate cancer diagnosis: Present role and future perspectives. Urologia Internationalis 2011;86:373-82.
8. Penzkofer T, Tempany-Afdhal CM. Prostate cancer detection and diagnosis: the role of MR and its comparison with other diagnostic modalities - A radiologist's perspective. NMR in Biomedicine 2014;27:3-15.
9. ClinicalTrials. MRI/TRUS Fusion Guided Prostate Biopsy- An Improved Way to Detect and Quantify Prostate Cancer. 2013.
10. Weissbach L, Altwein J. Active surveillance or active treatment in localized prostate cancer? Deutsches Arzteblatt International 2009;106:371-6.

11. Perlroth DJ, Bhattacharya J, Goldman DP, Garber AM. An economic analysis of conservative management versus active treatment for men with localized prostate cancer. Journal of the National Cancer Institute Monographs 2012;2012:250-7.

CHAPTER 3

DIRECT MEDICAL EXPENDITURE AND PREDICTORS ASSOCIATED WITH PROSTATE CANCER FOR THE U.S. ADULT POPULATION: ESTIMATES FROM MEDICAL EXPENDITURE PANEL SURVEY (2010)

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[1]Patel P, Perri M, Tackett R. To be submitted to Journal of Pharmacy and Pharmacology.

Purpose: The purpose of this study was to explore the annual average prostate cancer cost in different health delivery settings in 2010 and to determine significant predictors of the annual cost of prostate cancer. **Methods:** Using the Medical Expenditure Panel Survey (MEPS), a retrospective study was conducted assessing healthcare utilization and associated expenditures among patients having prostate cancer. Information on patient demographics, health care service utilization and cost estimates were derived from the database representing 1,422,218 patients with prostate cancer and related conditions. To predict the effects of demographics, testing procedures, and types of services used on annual prostate cancer related costs, an ordinary least squares model with logarithmic form of expenditure was used. **Results:** An annual average total of $5.6 billion was spent on the treatment of prostate cancer related conditions in 2010 in the United States. Outpatient and inpatient visits were found to contribute significantly to the increased total prostate cancer related expenditure. Weighted multiple linear regression analyses revealed that the use of chemotherapy (p value=0.0004) and ultrasound (p value<0.0001) were found to increase the expenditures related to outpatient visits significantly. Use of ultrasound (p value<0.0001) and x-ray (p value <0.0001) were found to increase office-based visit costs significantly. **Conclusion:** Results of our study indicate that the expenditure related to prostate cancer absorbs a significant portion of healthcare resources. Ultrasound, the most commonly used diagnostic technique to guide biopsy, was found to be associated with higher prostate cancer expenditure. Lately, there is advancement in chemotherapy drugs that have improved cancer care but these modern medicines are expensive. The current study found chemotherapy to be associated with higher prostate cancer expenditure. Cost estimates derived from this study may be used by healthcare decision makers in developing disease management strategies with efficient allocation of resources.

Keywords: Prostate cancer expenditure, service utilization, Medical Expenditure Panel Survey

Introduction

Prostate cancer is the second leading cause of non-cutaneous cancer deaths among men in the United States.[1] Statistics related to prostate cancer diagnosis and death suggest that prostate cancer is one of the most frequently diagnosed cancers affecting one in every six men.[2] The American Cancer Society estimated that there were approximately 238,590 new cases and 29,720 deaths due to prostate cancer in 2013.[1] Annual expenditures associated with prostate cancer in 2006 was $9.862 billion in the U.S.[3] Costs associated with prostate cancer are expected to rise due to increased diagnosis, diagnosis at an earlier stage and increased survival.[3] With the advent of Prostate Specific Antigen (PSA) screening as the most common method of detection in the United States, the ability to diagnose nonlethal prostate cancers has further increased.[4] Thus, increased detection combined with increased survival has imposed a greater burden from prostate cancer on the healthcare system.

Most cost of illness studies associated with prostate cancer are dated.[3,5,6] Thus, there is a need for more recent cost studies that determine the average cost per patient. In addition, we need more current information on the utilization of different health services in different delivery settings associated with prostate cancer. The incidence of prostate cancer has been reported to vary according to race with black men experiencing a higher incidence and more advanced anatomic stage of disease.[7] Additionally, current diagnostic procedures associated with prostate cancer result in frequent unnecessary biopsy procedures and cause a financial burden.[8] Few studies in the literature have determined the factors that document the high costs associated with prostate cancer. It is important for policy makers and health researchers to determine how resources are expended for prostate cancer. Increased attention must be paid to the patient's average cost of care and to the factors that predict those costs.

The purpose of this study was to explore the annual average prostate cancer cost in different health delivery settings in 2010 and to determine the significant predictors of the annual cost of prostate cancer. From the perspective of policymakers and researchers, this study is important as it will provide reliable estimates of prostate cancer-specific medical care costs. These estimates can be used to help describe the overall economic burden associated with cancer morbidity and mortality and to understand the magnitude of financial resources that must be mobilized to effectively care for cancer patients.

Methods

Data source: Using the Medical Expenditure Panel Survey (MEPS), a retrospective study was conducted assessing healthcare utilization and associated expenditures among patients having prostate cancer. Administered by the Agency for Healthcare Research and Quality, the MEPS is a nationally representative survey of health care use, expenditures, sources of payment, and insurance coverage for the US civilian, non-institutionalized population.[9] The Health Component is the core survey and collects detailed data at both the personal and house-hold levels, using an overlapping panel design with 5 rounds of computer-assisted personal interviews over a 2.5-year period.[9] In the MEPS database, one respondent per household is interviewed about the medical events of household members, including health status, health care utilization, and health insurance. Surveys of the household's medical providers, employers, and health insurers verify and supplement the interview data.[9] In particular, medical providers, such as office based physicians, hospital, home health agencies, and pharmacies, serve as the primary source for expenditure information, including out-of-pocket payments by the family.

Subjects: The subjects for this study were identified using the clinical classification system code of 29, which indicates that the patient has prostate cancer related conditions. Patients of all ages and ethnicities were included in this study.

Measures: The primary outcome measures were prostate cancer related health care services use and associated costs. Services included outpatient visits, emergency department visits, inpatient visits, office-based visits, prescriptions, and home health visit days. Costs consisted of total as well as component costs, such as outpatient, emergency department, home health, inpatient, and prescriptions. Health care service utilization and cost estimates were derived from the 2010 MEPS Full Year Consolidated File, Medical Conditions File, Office-Based Medical Provider Visit File, Outpatient Visits File, Emergency Room Visit File, Hospital Inpatient Stays File, Home Health File, and Prescribed Medicine File.

The effect of various demographic characteristics, comorbidities, types of diagnostic services, chemotherapy, radiation, and laboratory tests performed on prostate cancer related expenditures was evaluated. Demographic characteristics such as age, race/ethnicity and insurance status were determined through the full year consolidated data file. Comorbidity was measured using the Charlson comorbidity index.[10] The Charlson comorbidity index assigns weights ranging from 0 to 6 based on the severity of a number of major conditions. The index severity score was calculated for each patient by adding the assigned weight for each patient's comorbid conditions, with higher scores representing greater severity of comorbidity. Patients were categorized based on the comorbidity level. A Charlson score of 0 indicates no comorbidity; a score of 1 to 2 indicates moderate comorbidity; and a score greater than or equal to 3 indicates severe comorbidity. Total expenses for an "event" were defined as the sum of

direct payments by households, private insurance, Medicare, Medicaid, and other sources to providers of the care.

Statistical analysis: Estimates presented in the tables and texts were statistically weighted to reflect national population totals. The weights, which were provided by the data collection agency, are equal to the inverse of the sampling probability for each case, adjusted for nonresponse. As medical expenditure data are not normally distributed, an ordinary least squares model with logarithmic form of expenditure was used to predict the effects of demographics, testing procedures, and types of services used on annual prostate cancer related costs.[11] All analyses were conducted using SAS (version 9.3, SAS Institute, Carey NC).

Results

Sample characteristics:

Data for 1,422,218 patients with prostate cancer (weighted sample size) were analyzed from the 2010 MEPS dataset. Demographic characteristics of the study population (Table 3.1) show that the mean age of the patients with prostate cancer was approximately 70 years and the majority of patients were between 65 and 75 years old. The majority of patients were white (≈85%) with moderate comorbid conditions (Charlson comorbidity index of ≈ 2) and had some form of private insurance (≈69%).

Patterns of Health care use and expenditure associated with prostate cancer:

Results related to health care services used and the associated expenditures are presented in Table 3.2. As a group, patients with prostate cancer related conditions had a total of 5.2 million office-based visits, 1.1 million outpatient visits, and 0.2 million in-patient visits. Patients with prostate cancer received a total of 2.5 million prescriptions in 2010.

An annual average total of $5.6 billion was spent on treatment of prostate cancer related conditions in 2010 in the US. Almost half of the expenditure was spent on office based and outpatient visits. Approximately $1.7 billion was spent on inpatient services such as surgery or diagnostic testing. Due to the smaller number of patients who visited hospitals and stayed overnight in our sample, the expenditure related to inpatient services should be interpreted with caution. There were no patients in the study sample who visited the emergency department due to prostate cancer. Prescription expenditures for treatment of prostate cancer amounted to $0.3 billion.

Among persons with any expense for prostate cancer, the average annual expenditure was $3,977.78 in 2010. The mean expense per adult for office-based visits was $410.68, $1272.3 for outpatient visits, and $110.67 for prescriptions. The average per person amount spent on hospital stays was $10,502. The frequency distribution of prostate cancer related direct medical costs is presented in Figure 3.1.

Predictors of Health care expenditure related to prostate cancer:

We examined the influences of demographic characteristics and types of health service utilization on annual per capital health care expenditures associated with prostate cancer. An ordinary least squares model with logarithmic form of expenditure was employed incorporating survey design strategies such as stratum, primary sampling unit, and sampling weight information. The results of the multivariate analysis for predictors of prostate cancer specific healthcare costs are presented in Table 3.3.

The overall model with log transformed cost data was found to be statistically significant (Table 3.3). After controlling for other variables, outpatient and inpatient visits were found to be statistically significant predictors for the expenditure related to prostate cancer. In order to

eliminate bias associated with retransformation of log transformed cost data back into natural form, a smearing estimator was calculated. This estimator is the mean of the antilog of the residuals and represents the estimate of the untransformed scale free from the distribution assumptions on the error distribution. Compared to office based visits, patients with outpatient visits increased the prostate cancer expenditure annually on average by 18.62 fold (antilog of estimate*smearing estimator). Similarly inpatient visits were found to increase expenditures by 20.5 fold on average compared to office based visits. Age or prescriptions were not statistically significantly associated with prostate cancer related expenditures.

Predictors of outpatient visit costs associated with prostate cancer:

As outpatient visits were found to be statistically significant predictors of prostate cancer expenditure, a separate regression analysis was performed to assess the predictors of total annual expenditures associated with prostate cancer related outpatient visits (Table 3.4). We also analyzed office based visit data to estimate the influence of various predictors on office based visit expenditures (Table 3.5). We could not analyze predictors of inpatient costs because of the limited number of patients who had inpatient visits in our sample.

Multiple linear regression analysis of outpatient visit costs revealed chemotherapy, ultrasound, and x-ray as the statistical significant predictors of the cost. Chemotherapy and ultrasound were found to increase the expenditures related to outpatient visits whereas x-ray cost was found to decrease it while holding other variables constant.

Predictors of office-based visit costs associated with prostate cancer:

Multiple regression analysis examining predictors of office-based visit explained approximately 25% of the variance in the model (Table 3.5). Ultrasound and x-ray were

associated with the higher office-based visit costs, whereas age was found to be associated with lower office-based visit costs.

Discussion

This study used a nationally representative database and provides the most comprehensive and recent estimates of direct medical costs of prostate cancer related conditions among adults in the US. Using estimates from this study, the annual direct medical expenditures associated with prostate cancer was found to be $5.6 billion in 2010 US dollars. A recent study by Roehrborn et al. estimated the cost of prostate cancer to be $9.862 billion for 2006 using published data and internet sources.[3] There are only a few recent studies in the literature that provide estimates on different health service utilization and expenditure associated with prostate cancer. Our study is comprehensive in terms of providing estimates of total expenditure, expenditure related to specific health service used, and predictors of expenditures.

With respect to cost categories, outpatient and inpatient visits were found to be the major driver of healthcare costs related to prostate cancer. Inpatient and outpatient visits accounted for approximately 30% and 25% of the overall costs, respectively. Our findings are consistent with the known healthcare utilization patterns and treatment seeking behaviors of individuals with prostate cancer.[12] Higher costs found with the inpatient visits can be explained by the fact that the majority of patients diagnosed with localized prostate cancer undergo surgery in an inpatient setting. Most of the treatments other than surgery occur in the outpatient setting explaining higher costs associated with the outpatient setting.

This study found strong associations that are of great interest to policy makers. Individual regression analysis for outpatient visit cost found chemotherapy and ultrasound as

the major source of higher expenditure related to outpatient expenditure. As ultrasound is cheaper than some advanced imaging technologies, it is the most commonly preferred technique to guide biopsy for the diagnostic confirmation of prostate cancer.[13] Although ultrasound is cheaper, it is not as reliable a technique and leads to many false negative test results.[14] As a result, patients undergo repeated biopsy techniques for further confirmation leading to increased costs due to additional ultrasound biopsy techniques performed as well as treatment of biopsy induced complications. There is a need for imaging technologies that can diagnose prostate cancer accurately and avoid repeated testing resulting in cost saving. Ultrasound guided biopsy is usually performed either in the medical provider's office or in outpatient settings. However, it's a fact that if the biopsy is performed in an outpatient setting, it is more expensive due to overhead costs.

Chemotherapy is administered at late or an advanced stage of prostate cancer mainly in a hospital setting.[15] Chemotherapy use has increased markedly for almost all cancers.[16] The most commonly used chemo drug for prostate cancer is docetaxel, combined with prednisone.[17] Cabazitaxel was approved as a second line choice in June 2010 for patients among whom docetaxel does not work.[18] Both treatments have been reported to have improved survival outcomes among patients with metastatic prostate cancer and thus, are the preferred choice. Prescription drugs in this study were not found to be statistical significant predictors of higher expenditure associated with prostate cancer in 2010. However, it is important to note that the prescription drug file in MEPS data does not collect information on prescription drugs obtained during hospital visits. Advanced treatments for castrate resistant prostate cancer such as sipuleucel-t vaccination and abiraterone acetate were approved in April 2010 and April 2011, respectively.[19] These recently approved treatment options are very expensive and are expected to increase prostate cancer expenditure with improved survival benefits in the near future.

X-ray imaging and computed tomography (CT) scans that use x-ray for prostate cancer stage diagnoses are found to be the significant predictor of higher expenditure in the office setting. X-ray is generally used for bone scanning to check for bone metastases. Falchook et al. recently evaluated Surveillance, Epidemiology, and End Results (SEER)-Medicare data from 2004 to 2007 to quantify the use of bone scans during the prostate cancer work up and associated costs.[20] They found that almost one third to one-half of low- and intermediate-risk prostate cancer patients who have almost 0% chance of metastatic disease undergo bone scans and of those patients, 21% undergo subsequent x-rays. Thus, there is overutilization of bone scans in patients with low- and intermediate-risk prostate cancer. However, they also concluded that there is underuse of bone scans among high risk patients for whom metastatic disease is highly likely.

The Affordable Care Act, signed into law on March 2010, aims to expand coverage for all Americans, enhance the quality of care, and lower healthcare costs.[21] In this regard, economic evaluations, such as cost of illness studies, provide valuable information in creating a healthcare system with lower costs and higher quality of care.[22] Policy makers can quantify both the prevalence and cost associated with the disease using cost of illness studies and as a result, can prioritize funding.[22] By identifying present spending patterns and resource allocation, cost of illness studies can highlight possible areas of cost savings.[22]

If different data sources are used to obtain healthcare costs, it may lead to data inconsistency and unreliability of results. Therefore, obtaining data from only one database is the preferred method. As MEPS contains comprehensive information regarding the healthcare utilization cost for participants in the survey to estimate direct cost attributed to disease, we used MEPS as the only data source for analyses.[9]

The confidence in the current findings is also derived from the adaptation of a robust statistical analysis technique. In modeling healthcare cost data, bias was reduced in estimates by employing statistical techniques that considered the skewed nature of such data.

Limitations

This study has several limitations. Most importantly, our findings might have under-estimated the direct medical expenditures associated with prostate cancer. Patients with prostate cancer conditions were identified as those who reported being diagnosed with these conditions. So prevalence of prostate cancer might have been under-reported in MEPS. As such, our findings should be interpreted with caution. Results from this study, due to potential under-representation of prostate cancer in MEPS, should be interpreted as a conservative estimate of the total direct medical costs of prostate cancer related conditions. Some covariates such as history and severity of illness were not included in the analysis, due to unavailability of this information in MEPS. We have studied the direct medical costs of prostate cancer related conditions. A more comprehensive study capturing indirect costs such as morbidity and mortality costs, as well as direct medical costs, would provide a more precise estimate of the economic burden of these conditions. We could not study the predictors of inpatient service cost due to the limited number of patients in our sample who had overnight hospitalization. The household component of MEPS consists of non-institutionalized, community-dwelling residents. Prostate cancer patients living in supported living facilities, nursing homes, institutions, and prisons were not included. Homeless people and undocumented immigrants were also not included. Thus, the studied population is not representative of all prostate cancer patients in the U.S. We accounted for prostate-related costs only but it is sometimes difficult to separate

prostate-related and unrelated costs, especially at later time periods in the disease and in those patients with multiple comorbidities.

Conclusion

The current study demonstrates conclusively that prostate cancer conditions, cost around $ 5.6 billion annually in 2010 US dollars. In effectively reducing the economic burden of a disease, one needs to know the overall cost of illness, as well as the distribution of costs in different health delivery settings. The latter provides more insight as to which category of healthcare services requires more costs, and therefore would benefit the most from disease management programs. Our results revealed that office-based visits account for the highest proportion of the overall cost of prostate cancer followed by outpatient costs. Further, chemotherapy and ultrasound are the main drivers of increased outpatient setting costs, whereas ultrasound and x-ray are responsible for increased office based costs. Our cost estimates may also be used by healthcare decision makers in developing disease management strategies.

TABLES

Table 3.1: Descriptive statistics of weighted sample of patients with prostate cancer

Variable	Mean (SE)*
Age (years)	69.9 (±0.82)
45-65 (%)	29.3 (±5.16)
65-75 (%)	40.1 (±5.17)
75-90 (%)	30.6 (±4.79)
Sample with private insurance (%)	68.7 (±4.54)
Race	
White (%)	84.5 (±2.85)
Black (%)	13.3 (±2.65)
Others (%)	2.20 (±0.99)
Charlson comorbidity index score	1.99 (±0.01)

Table 3.2: Health care use and costs among patients with prostate cancer

Health care use and costs	Mean (SEM)	Weighted Total (Std)
Service use		
Office-based visits	57.83 (%) (±2.19)	5,179,228 (±211,478)
Outpatient visits	12.7 (%) (±1.62)	1,137,294 (± 151,501)
Inpatient visits	1.86 (%) (±0.72)	166,262 (± 64,857)
Prescription	27.62 (%) (±1.94)	2,473,224 (± 179,131)
Expenditure, $		
Office-based visits	410.68 (± 73.92)	2,127,010,643 (± 412,287,455)
Outpatient visits	1272.30 (±147.62)	1,446,979,485 (±30,756,549)
Inpatient visits	10502	1,746,053,092
Prescription	110.67 (±20.49)	273,723,923 (± 97,234,123)
Total	3,977.78 (± 1,004.81)	5,657,264,402 (± 1,598,361,118)

Table 3.3: Predictors of prostate cancer related total health care costs (R^2=0.1233, F=49.22, p value <0.001)

Parameters	Estimate	Antilog(estimate)	Standard error	T statistics	P value
Intercept	8.751	6317	1.65	5.32	< 0.0001*
Age	-0.037	0.96	0.02	-1.62	0.1101
Type of service					
Prescription	0.965	2.62	0.5	1.92	0.0582
Outpatient	1.511	4.53	0.51	2.96	0.0042*
Inpatient	1.607	4.99	0.55	2.91	0.0047*
Office visit					
* indicates significant at alpha of 0.05; smearing factor=4.11; Cost data converted to log(cost); office visit was used as a reference for type of services.					

Table 3.4: Predictors of outpatient visit costs associated with prostate cancer (R^2=0.2424, F=58.60, p value <0.0001)

Parameters	Estimate	Antilog(estimate)	Standard error	T statistics	P value
Intercept	5.7	298.87	0.33	17.3	< 0.0001*
Chemotherapy	1.12	3.06	0.27	4.12	0.0004*
Ultrasound	2.84	17.11	0.38	7.47	<0.0001*
Xray	-1.73	-0.177	0.48	-3.56	0.0016*
Labtests	-0.98	-0.375	0.64	-1.54	0.1375
* indicates significant at alpha of 0.05; smearing estimator=3.92; cost is in log(cost) form					

Table 3.5: Predictors of office-based visit costs associated with prostate cancer (R^2=0.1208, F=39.37, p value <0.0001)

Parameters	Estimate	Antilog(estimate)	Standard error	T statistics	P value
Intercept	7.78	2392.27	1.3	6	< 0.0001*
Age	-0.04	0.96	0.02	-2.2	0.03*
Ultrasound	2.02	7.54	0.48	4.22	<0.0001*
Xray	1.31	3.71	0.23	5.77	<0.0001*
* indicates significant at alpha of 0.05; smearing estimator=3.05; cost is in log(cost) form					

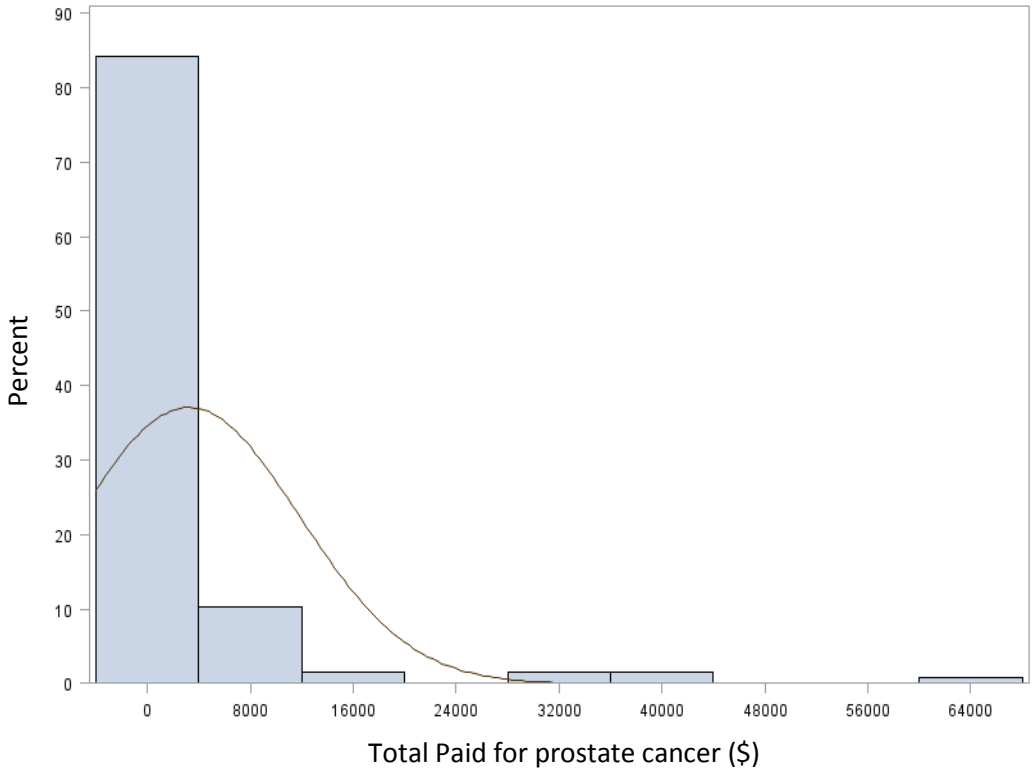

Figure 3.1: Distribution of annual prostate cancer related direct medical costs

REFERENCES

1. Prostate cancer. 2013. 2014, at http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics.)
2. Crawford ED, Black L, Eaddy M, Kruep EJ. A retrospective analysis illustrating the substantial clinical and economic burden of prostate cancer. Prostate Cancer and Prostatic Diseases 2010;13:162-7.
3. Roehrborn CG, Black LK. The economic burden of prostate cancer. BJU International 2011;108:806-13.
4. National Cancer Institute. (Accessed December, 4th, 2013, at http://www.cancer.gov/cancertopics/pdq/treatment/prostate/healthprofessional.)
5. Stokes ME, Black L, Benedict A, Roehrborn CG, Albertsen P. Long-term medical-care costs related to prostate cancer: Estimates from linked SEER-Medicare data. Prostate Cancer and Prostatic Diseases 2010;13:278-84.
6. Stokes ME, Ishak J, Proskorovsky I, Black LK, Huang Y. Lifetime economic burden of prostate cancer. BMC Health Services Research 2011;11:349.
7. National Cancer Institute. SEER Stat Fact Sheets: Prostate Cancer.Retrieved in 2014 from http://seer.cancer.gov/statfacts/html/prost.html
8. Voigt JD, Zappala SM, Vaughan ED, Wein AJ. The Kallikrein Panel for prostate cancer screening: Its economic impact. The Prostate 2014;74:250-9.
9. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey. 2009.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases 1987;40:373-83.

11. Trogdon JG, Finkelstein EA, Hoerger TJ. Use of econometric models to estimate expenditure shares. Health Services Research 2008;43:1442-52.
12. Wilson LS, Tesoro R, Elkin EP, et al. Cumulative cost pattern comparison of prostate cancer treatments. Cancer 2007;109:518-27.
13. Shariat SF, Roehrborn CG. Using biopsy to detect prostate cancer. Review of Urology 2008;10:262-80.
14. Rais-Bahrami S, Siddiqui MM, Turkbey B, et al. Utility of multiparametric magnetic resonance imaging suspicion levels for detecting prostate cancer. The Journal of Urology 2013;190:1721-7.
15. Krahn MD, Zagorski B, Laporte A, et al. Healthcare costs associated with prostate cancer: Estimates from a population-based study. BJU International 2010;105:338-46.
16. Warren JL, Yabroff KR, Meekins A, Topor M, Lamont EB, Brown ML. Evaluation of trends in the cost of initial cancer treatment. Journal of National Cancer Institute 2008;100:888-97.
17. Chemotherapy for prostate cancer. 2014. at http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-chemotherapy.)
18. Paller CJ, Antonarakis ES. Cabazitaxel: A novel second-line treatment for metastatic castration-resistant prostate cancer. Drug Design, Development and Therapy 2011;5:117-24.
19. FDA News & Events. U.S. Food and Drug Administration. Retrieved in 2014 from http://www.fda.gov/NewsEvents/.
20. Falchook AD, Salloum RG, Hendrix LH, Chen RC. Use of bone scan during initial prostate cancer workup, downstream procedures, and associated medicare costs. International Journal of Radiation Oncology,Biology,Physics 2013; 89:243-48

21. Affordable Care Act. Medicaid. Retrieved in 2014 from http://www.medicaid.gov/AffordableCareAct/Affordable-Care-Act.html.

22. Cost-of-Illness Studies: A Primer. RTI International, 2006. 2014, at http://www.rti.org/publications/abstract.cfm?pubid=6042.)

CHAPTER 4

SYSTERMATIC REVIEW ON ROLE OF MAGNETIC RESONANCE IMAGING IN PROSTATE CANCER DIAGNOSIS

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[1]Patel P**,** Perri M, Griffin S, Tackett R. To be submitted to *Magnetic Resonance Imaging*.

Prostate cancer is the most frequently diagnosed and the second leading cause of non-cutaneous cancer related deaths among men in the US. Routinely used prostate cancer screening and diagnostic tests are associated with low sensitivity and specificity. As a result, these tests are more likely to identify smaller and more indolent tumors compared to larger and more aggressive ones among patients having localized disease. An imaging technology is needed that can accurately detect and differentiate clinical significant tumors from nonsignificant tumors. Multiparametric magnetic resonance imaging (MP-MRI), a promising technology has been proposed to be used before biopsy to make an accurate diagnosis. This article reviews the current clinical role of MP-MRI and its potential role in the detection of prostate cancer using a systematic literature research. Results of this study suggest that MP-MRI has the potential to detect clinically significant disease while avoiding detection of clinically insignificant disease. In prebiopsy settings, MP-MRI is expected to cause financial and physical burdens. However, prebiopsy MRI is also reported to yield possible savings from fewer biopsies, the avoidance of unnecessary biopsies and treatment, and better risk stratification. Performance of cost-effectiveness analysis of prebiopsy use of MP-MRI is absolutely needed.

Key words: Multiparametric magnetic resonance imaging, Prostate specific antigen, Digital rectal examination, Transrectal ultrasound guided biopsy, Prostate cancer, magnetic resonance spectroscopy, dynamic contrast enhanced imaging, diffusion weighted imaging, MRI-TRUS fusion, cost-effectiveness

Introduction

Prostate cancer, a major public health issue, is the most common solid-organ malignancy in men in the US and a leading cause of cancer related deaths.[1] In 2013, approximately 238,590 new cases of prostate cancer were diagnosed, and 29,720 men died due to it in the US.[1] Accurate pretreatment diagnosis is absolutely essential for the implementation of the appropriate treatment. Detection of prostate cancer is based on digital rectal examination (DRE), serum prostate-specific antigen (PSA) levels, and transrectal ultrasound (TRUS) guided random biopsy. Systematic TRUS guided biopsy is performed following either an abnormal DRE or an elevated serum PSA level. However, none of these tests can accurately detect the presence of cancer.

Since the beginning of PSA based screening, the majority of patients are diagnosed with low risk clinically indolent organ confined prostate cancer. As a result, it is suggested that a significant proportion of men diagnosed with prostate cancer are overtreated.[1] This reflects the limited sensitivity and specificity of PSA, DRE, and TRUS guided biopsy that can identify smaller, more indolent, lower risk cancers compared to larger, more aggressive and higher risk ones among patients having localized disease. TRUS guided biopsy misses cancer in up to 35% of cases.[2] Men with a first negative biopsy but a persistently elevated PSA level represent a great diagnostic challenge for urologists. In order to reduce false-negative rates associated with the biopsy, further biopsy with an increased number of cores (saturation biopsy) has been proposed.[3] However, such saturation biopsies are associated with significant patient morbidity. Therefore, a new imaging technology is clearly needed that can accurately detect and differentiate prostate cancer in a clinically significant manner.

Many emerging imaging technologies are under investigation to either substitute the standard biopsy technique or to supplement it to address the above limitations.[4] One promising technology is multiparametric magnetic resonance imaging (MP-MRI). MP-MRI, such as dynamic contrast material-enhanced (DCE) imaging, diffusion weighted imaging (DWI), and magnetic resonance spectroscopy (MRS) imaging used alone or in combination with standard T2-weighted imaging (T2-WI) has the potential to dramatically change the role of imaging for prostate cancer diagnosis.[4] Currently, MRI has been used to diagnose cancer in patients with persistent elevation of serum PSA and previous negative TRUS-guided biopsies. However, the MP-MRI technique is now proposed for patients before performance of any biopsy so that an accurate diagnosis can be made and unnecessary biopsies avoided.[5] The main concerns with the use of prebiopsy MRI are its expense and the complexity of actually performing the procedure. The aim of this article is to review the current clinical role of MP-MRI and its potential role in the detection of prostate cancer. This article also focuses on the economic feasibility of this emerging diagnostic tool.

Methods

A systematic literature review was performed in Medline, Elsevier, Cochrane Library databases, and Biosis databases using the key words as “prostate cancer”, “multiparametric MRI”, “magnetic resonance imaging”, “MR*”, “biopsy”, “guided biopsy”, “cost-effectiveness”, “cost*”, “TRUS”, and “economic evaluation” alone or in combination. All reviews and original articles were included in this study.

Multiparametric Magnetic Resonance Imaging (MP-MRI)

Use of functional MRI is gaining considerable interest in recent years. Functional imaging or MP-MRI uses dynamic contrast enhancement (DCE), diffusion weighted imaging

(DWI) or magnetic resonance spectroscopy (MRS) together with T2-weighted imaging (T2-WI) in one or more combinations.[4] MRI technology has undergone a significant advancement and more consistent and accurate results have been reported with its use.[6-13] The capability of combining MRI with techniques to simultaneously perform a targeted biopsy of the prostate is of particular interest to urologists. MP-MRI used in conjunction with a MRI-ultrasound fusion guided biopsy platform has demonstrated improved prostate cancer detection and localization.[1,14]

MRI has an unparalleled ability to provide detailed information about the prostate due to excellent soft tissue contrast.[8] Conventional MRI at 1.5 or 3.0 Tesla (T) provides morphological information such as the prostate's zonal anatomy, seminal vesicles and the prostatic capsule using T2-WI.[15-17] T1-weighted imaging (T1-WI) has been used to detect post-biopsy hemorrhage, lymph nodes, and bone metastasis.[4] Conventionally, MRI has been used in clinical practice for determining prostate cancer stage[4] and has emerged as a promising tool in diagnosing prostate cancer. MRI detects the location of more aggressive lesions on imaging that cannot be accessed through even with extended biopsy schemes.[8] MP-MRI is capable of detecting metabolic, diffusion and perfusion abnormalities associated with the cancer.[8,18-22] Proton MRS imaging provides metabolic information, DWI shows Brownian motion of extracellular water molecules, and DCE-MRI visualizes tissue vascularity, especially neoangiogenesis. Thus, efficient cancer identification with high sensitivity and specificity can be made by combining morphologic and functional imaging.[7]

Magnetic Resonance Spectroscopy (MRS) based Imaging

MRS imaging also known as chemical shift imaging assesses the level of metabolites in tissue.[1,4] The metabolites measured by MRS include citrate (reflecting glandular composition) [8], creatine and choline (a composite of phospholipid membranes).[17] Generally, prostate cancer

shows a high level of choline and a low level of citrate relative to the normal peripheral zone. An increase in the choline-to-citrate ratio is used as a marker in prostate cancer and increases the specificity of diagnosis. Scheidler et al. showed a sensitivity and specificity for prostate cancer detection of 95% and 91%, respectively, for combined MRS and MRI, but 61% to 77% and 46% to 81% for MRI alone and 75% and 63% for MRS alone.[4] MRS together with MRI has been found to significantly improve localization of prostate cancer.[4]

MRS suffers from long acquisition time, possible variability in results dependent on post-processing or shimming, no direct visualization of the periprostatic anatomy and its expense.[4] Some of these limitations of MRSI might be improved by new technical developments and the use of higher magnetic fields (3.0 T).

Dynamic Contrast Material-Enhanced (DCE) based Imaging

Cancerous tissue is generally marked by an increased number of vessels as well as greater vascular permeability. DCE MRI measures the passing of an intravenously administered contrast agent through prostate on T1-weighted imaging.[4,7,8] Cancerous tissues show higher contrast enhancement parameters, such as mean transit time, blood flow, permeability surface area and interstitial volume compared to normal tissue, and therefore allow differentiation between benign and malignant tissue.

Several studies comparing the results of DCE-MRI with surgical pathology as the reference standard have reported sensitivity, specificity, and accuracy levels ranging from 69% to 95%, from 80% to 96.2%, and from 77.5% to 92%, respectively.[4] Addition of DCE-MRI in conjunction with T2-WI of MRI has been shown to increase sensitivity from 69% to 95% and specificity from 80% to 93%.[4] Moreover, combined DCE-MRI and MRSI significantly improve the

accuracy in prostate cancer localization. The limitation of DCE MRI is primarily an unsatisfactory depiction of transitional zone cancer in patients with hypervascular BPH.[4]

Diffusion-Weighted Imaging (DWI)

The amount of interstitial free water and permeability determines the diffusion properties of the tissues. DWI provides information on the functional environment of water in tissue by measuring the Brownian motion or diffusion coefficient of water molecules.[7,8] Thus, based on the motion of water molecules, differentiation between malignant and normal tissues can be made. Cancer tissues have higher cell densities and extracellular disorganization. Therefore, cancer tissues tend to have more restricted water diffusion than normal tissue. Without administration of any exogenous contrast material, these images can be acquired quickly.[4]

Addition of DWI to conventional T2-WI imaging significantly improves tumor detection compared to conventional MRI alone. Combined DWI with MRI has been shown to have sensitivity, specificity, positive predictive value, and negative predictive value of 86%, 84%, 90% and 79%, respectively.[4] In addition to detection of cancer, DWI has also been shown to provide information about tumor aggressiveness with good correlation between diffusion coefficient values and the Gleason score.[17] The main strengths of DWI are shorter acquisition time and high contrast resolution between tumors and normal tissue.[4] However, this technique suffers from poor spatial resolution and susceptibility-induced distortions.[4]

Imaging algorithm suggested in patients:

If hemorrhage is present in the patient, DWI should be included in the MR diagnosis.[7] With post hemorrhage detection of prostate cancer, MRS together with DCE is recommended.

Use of 3.0 T strength and an endorectal coil is preferred in general but use of 3.0 T without a endorectal coil is an option among patients who do not prefer to use a endorectal coil.[7] For patients with a low glomerular filtration rate, DCE should be avoided. For assessment of transition zone cancer in patients with advanced age, DWI is recommended.[7]

Prebiopsy MRI for Men at Risk

Application of verification tests such as an imaging test earlier in the diagnostic pathway has the potential of improving the diagnosis of prostate cancer diagnosis. This practice is already adopted by clinicians for treating other solid organ cancers such as breast cancer.[5] MP-MRI cannot detect clinically insignificant disease because of its low sensitivity for low grade, low-volume disease.[10] However, it has a greater sensitivity for detecting clinically significant disease. Thus, it has the potential to address the problem of overdiagnosis and overtreatment of clinically insignificant disease if used as a triage test before TRUS guided biopsy.

Overdiagnosis and overtreatment of clinically insignificant disease is the main reason that the United States Preventive Services Task Force (USPSTF) recommended against the use of PSA screening.[10] Kasivisvanathan et al. found that multiparametric MRI detects clinically significant cancer at an encouraging rate while also reduces the detection rates of clinically insignificant cancer.[17] They further reported that the MP-MRI requires fewer biopsy specimens than systematic template guided biopsy. MP-MRI also has the potential to address the problem of underdiagnosis of clinically significant disease with the current diagnostic practice when cancer is located in the transition zone or in the anterior or peripheral zone, which are parts of the prostate that are not easily palpable by DRE and are not routinely targeted during biopsy.[3,5,8,10,16,23-25]

Pinto et al reported MP-MRI outcomes on patients with low, moderate or high suspicion lesions that were subsequently targeted via an MRI/ultrasound fusion biopsy platform.[4] They found prostate cancer detection rates to be 27%, 66% and 89% for low, moderate and high suspicion lesions, respectively. With MP-MRI, more accurate classification of patients into observational strategies such as active surveillance can be made with greater confidence.[5,8,10,16,21,26,27] Further, if upgrading of disease occurs in patients undergoing active surveillance, MP-MRI can accurately detect, localize and characterize tumors. Thus, MP-MRI can act as an accurate monitoring tool for prostate cancer progression in those undergoing active surveillance.

Techniques used to target biopsies on lesions identified with MP-MRI include[10,18,25]: (i) 'cognitive' registration of the results of the MP-MRI to target biopsies on TRUS, (ii) targeting within the magnet or 'in-bore' targeting, and (iii) registration of magnetic resonance images onto an ultrasound platform to allow real-time targeting of lesion in out-patient setting. 'Cognitive' registration suffers from poor interpretation of imaging because the physician first reviews the lesion seen on MRI and then uses this knowledge to select the appropriate area for targeting biopsy. 'In- bore' targeting within the MRI scanner is a time consuming and expensive approach as it is performed in an inpatient setting. The MRI based image fused onto an ultrasound platform is a promising approach because of real-time targeting of lesions.

Cost-Effectiveness Analysis of Prebiopsy MRI Use

Cost-effectiveness analysis allows one to understand the probable health outcomes and fiscal expenditures associated with a particular health policy or program.[28] Jager et al. performed a cost effectiveness study to determine role of preoperative MRI staging.[29] They

concluded that MR staging was cost-effective for men with moderate or high prior probability of extracapsular disease.

Recently, Mowatt et al. carried out a systematic review of the literature to assess the diagnostic accuracy of MP-MRI techniques and the clinical effectiveness and cost-effectiveness of these techniques in the localization of prostate abnormalities for biopsy in patients with a prior negative biopsy.[17] In their study, they included costs associated with the final diagnosis, management of biopsy complications, cancer staging, cancer treatment, and management of complications resulting from cancer treatment. They concluded that T2-MRI may be cost-effective compared to systematic TRUS under certain circumstances. They further reported that MRS and DWI could be cost-effective if they can be shown to have a high sensitivity for detecting moderate to high risk cancer while ignoring disease in patients with no cancer or low risk disease. They recognized that there were not enough reliable studies so further studies were recommended. Their main approach focused on those patients having prior negative biopsy. Further, they did not report any results using the MRI-TRUS fusion platform.

Use of MRI before performing any biopsy can reduce unnecessary biopsies as well as treatments. The MRI-TRUS fusion approach to guide biopsies is an attractive alternative to MRI guided biopsy because it significantly reduces the procedure time as well as cost and can be performed in an outpatient setting.[30] A cost-effectiveness study of prebiopsy use of MP-MRI as a screening test is needed. There is concern about its financial and physical burdens, at the initial biopsy setting. However, it is expected that the initial biopsy cost of prebiopsy MP-MRI will be compensated by the possible savings that would result from fewer biopsies, the avoidance of unnecessary biopsies and treatment, and better risk stratification. Unnecessary biopsies cost much more than MRI.[31] Performance of a cost-effectiveness analysis of prebiopsy use of MP-

MRI is absolutely needed in order to relieve concerns of clinicians adopting it as a routine practice.

Conclusion

Urologists and other physicians who manage patients who may have prostate cancer are frustrated with the current standards of care, due to their limitations, especially in patients for whom a first set of biopsies was negative. It is possible to miss cancer because of the limitation of biopsy schemes, volume of biopsy specimen sampled and the multifocal nature of prostate cancer. Extended biopsy schemes (8-12 cores) or saturation biopsy schemes (greater than12 cores) have been proposed to solve this problem. This trend has led to performance of many unnecessary biopsies and treatments as well as a financial burden on patients. It also creates emotional stress for patients who may be facing a series of repeat biopsies. There is a risk of the diagnosis being delayed, possibly leading to disease progression, and increased morbidity due to the biopsy as well as the disease itself.[17] Many older men who present for biopsy are taking anticoagulants or antiplatelet drugs.[32] In this group of patients, biopsy complications could become life threatening. The number of prostate biopsies should be limited to reduce potential and serious complications. A promising imaging technology is needed that can detect prostate cancer accurately at a lower cost. MP-MRI used in conjunction with a MR/US fusion guided biopsy platform has demonstrated improved prostate cancer detection and localization. MP-MRI has a negative predictive value ranging from 90 to 100% in identifying significant cancer. Thus, it can be used as a screening tool to avoid biopsy if it does not reveal any abnormalities on MR images. Its cost-effectiveness in prebiopsy setting has not been evaluated yet.

In the prebiopsy setting, MP-MRI can diagnose lesions that cannot be diagnosed with even an extended systematic biopsy scheme. Additionally, it can improve targeting of biopsy for

more precise tumor characterization such as size and histological grade of the cancer. MP-MRI represents a reasonable approach alternative to extended systematic biopsies to relieve tremendous psychological stresses in a group of patients by improving the accuracy in diagnosing significant prostate cancer.

REFERENCES

1. Rais-Bahrami S, Siddiqui MM, Turkbey B, et al. Utility of Multiparametric MRI Suspicion Levels in detecting prostate cancer. The Journal of Urology 2013;29:04417-0.
2. Roethke M, Anastasiadis AG, Lichy M, et al. MRI-guided prostate biopsy detects clinically significant cancer: Analysis of a cohort of 100 patients after previous negative TRUS biopsy. World Journal of Urology 2012;30:213-8.
3. Sciarra A, Barentsz J, Bjartell A, et al. Advances in magnetic resonance imaging: How they are changing the management of prostate cancer. European Urology 2011;59:962-77.
4. Pinto F, Totaro A, Calarco A, et al. Imaging in prostate cancer diagnosis: Present role and future perspectives. Urologia Internationalis 2011;86:373-82.
5. Villers A, Marliere F, Ouzzane A, Puech P, Lemaitre L. MRI in addition to or as a substitute for prostate biopsy: The clinician's point of view. Diagnostic and Interventional Imaging 2012;93:262-7.
6. Perdona S, Di Lorenzo G, Autorino R, et al. Combined magnetic resonance spectroscopy and dynamic contrast-enhanced imaging for prostate cancer detection. Urologic Oncology 2013;31:761-5.
7. Bonekamp D, Jacobs MA, El-Khouli R, Stoianovici D, Macura KJ. Advancements in MR imaging of the prostate: From diagnosis to interventions. Radiographics 2011;31:677-703.
8. Dianat SS, Carter HB, Macura KJ. Performance of multiparametric magnetic resonance imaging in the evaluation and management of clinically low-risk prostate cancer. Urologic Oncology 2013;17:002.
9. Carey BM. Imaging for prostate cancer. Clinical Oncology 2005;17:553-9.

10. Dickinson L, Ahmed HU, Allen C, et al. Clinical applications of multiparametric MRI within the prostate cancer diagnostic pathway. Urologic Oncology 2013;31:281-4.

11. Goris Gbenou MC, Peltier A, Addla SK, et al. Localising prostate cancer: Comparison of endorectal magnetic resonance (MR) imaging and 3D-MR spectroscopic imaging with transrectal ultrasound-guided biopsy. Urologia Internationalis 2012;88:12-7.

12. Hambrock T, Hoeks C, Hulsbergen-van de Kaa C, et al. Prospective assessment of prostate cancer aggressiveness using 3-T diffusion-weighted magnetic resonance imaging-guided biopsies versus a systematic 10-core transrectal ultrasound prostate biopsy cohort. European Urology 2012;61:177-84.

13. Nix JW, Turkbey B, Hoang A, et al. Very distal apical prostate tumours: Identification on multiparametric MRI at 3 Tesla. BJU International 2012;110:4.

14. Fiard G, Hohn N, Descotes JL, Rambeaud JJ, Troccaz J, Long JA. Targeted MRI-guided prostate biopsies for the detection of prostate cancer: Initial clinical experience with real-time 3-dimensional transrectal ultrasound guidance and magnetic resonance/transrectal ultrasound image fusion. Urology 2013;81:1372-8.

15. Kaplan I, Oldenburg NE, Meskell P, Blake M, Church P, Holupka EJ. Real time MRI-ultrasound image guided stereotactic prostate biopsy. Magnetic Resonance Imaging 2002;20:295-9.

16. Puech P, Sufana Iancu A, Renard B, Villers A, Lemaitre L. Detecting prostate cancer with MRI - why and how. Diagnostic and Interventional Imaging 2012;93:268-78.

17. Mowatt G, Scotland G, Boachie C, et al. The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: A systematic review and economic evaluation. Health Technology Assessment 2013;17:1-281.

18. Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: A systematic review. European Urology 2013;63:125-40.

19. Park BK, Lee HM, Kim CK, Choi HY, Park JW. Lesion localization in patients with a previous negative transrectal ultrasound biopsy and persistently elevated prostate specific antigen level using diffusion-weighted imaging at three Tesla before rebiopsy. Investigative Radiology 2008;43:789-93.

20. Hara N, Okuizumi M, Koike H, Kawaguchi M, Bilim V. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a useful modality for the precise detection and staging of early prostate cancer. Prostate 2005;62:140-7.

21. Nagarajan R, Margolis D, Raman S, et al. MR spectroscopic imaging and diffusion-weighted imaging of prostate cancer with Gleason scores. Journal of Magnetic Resonance Imaging 2012;36:697-703.

22. Sciarra A, Panebianco V, Ciccariello M, et al. Value of magnetic resonance spectroscopy imaging and dynamic contrast-enhanced imaging for detecting prostate cancer foci in men with prior negative biopsy. Clinical Cancer Research 2010;16:1875-83.

23. Komai Y, Numao N, Yoshida S, et al. High diagnostic ability of multiparametric magnetic resonance imaging to detect anterior prostate cancer missed by transrectal 12-Core biopsy. The Journal of Urology 2013;28:03871-

24. Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial biopsy: Comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. BJU International 2011;108:22.

25. Ouzzane A, Puech P, Lemaitre L, et al. Combined multiparametric MRI and targeted biopsies improve anterior prostate cancer detection, staging, and grading. Urology 2011;78:1356-62.

26. Kuru TH, Roethke MC, Seidenader J, et al. Critical evaluation of magnetic resonance imaging targeted, transrectal ultrasound guided transperineal fusion biopsy for detection of prostate cancer. The Journal of Urology 2013;19:04093-7.

27. Kirkham AP, Emberton M, Allen C. How good is MRI at detecting and characterising cancer within the prostate? European Urology 2006;50:1163-74.

28. Saigal CS, Litwin MS. The economic costs of early stage prostate cancer. Pharmacoeconomics 2002;20:869-78.

29. Jager GJ, Severens JL, Thornbury JR, de la Rosette JJMCH, Ruijs SHJ, Barentsz JO. Prostate cancer staging: Should MR imaging be used?—A Decision analytic approach. Radiology 2000;215:445-51.

30. Sonn GA, Natarajan S, Margolis DJA, et al. Targeted biopsy in the detection of prostate cancer using an office based magnetic resonance ultrasound fusion device. The Journal of Urology 2013;189:86-92.

31. Park BK, Park JW, Park SY, et al. Prospective evaluation of 3-T MRI performed before initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-specific antigen and no previous biopsy. American Journal of Roentgenology 2011;197.

32. Philip J, Manikandan R, Javle P, Foster CS. Prostate cancer diagnosis: Should patients with prostate specific antigen >10ng/mL have stratified prostate biopsy protocols? Cancer Detection and Prevention 2009;32:314-8.

CHAPTER 5

COST-EFFECTIVENESS OF MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING FOLLOWED BY FUSION GUIDED BIOPSY IN PROSTATE CANCER DIAGNOSIS: AN ECONOMIC ANALYSIS

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[1]Patel P**,** Perri M, Griffin S, Tackett R. To be submitted to *Journal of the National Comprehensive Cancer Network.*

Purpose: The purpose of this study was to determine the cost-effectiveness of multiparametric magnetic resonance imaging (MP-MRI) followed by MRI/Transrectal ultrasound (TRUS) fusion guided biopsy compared with the standard TRUS guided biopsy among biopsy naïve men in diagnosing prostate cancer. **Methods:** A decision analytic model was developed to evaluate the costs and outcomes for conventional TRUS guided biopsy and experimental MP-MRI followed by MRI/TRUS guided biopsy. Input data for the model such as sensitivity, specificity, and risks of complications associated with diagnostic strategies were derived through a systematic literature search. Costs associated with diagnostic strategies were based on 2013 Medicare reimbursement rates. To test the robustness of the results in model parameters, n-way sensitivity analyses were conducted by varying values of different parameters such as the cost of MP-MRI and MRI/TRUS fusion guided biopsy, positive predictive value of TRUS guided biopsy, positive and negative predictive values of MRI/TRUS fusion guided biopsy. **Results:** Use of MP-MRI strategy was found to be more costly than TRUS guided biopsy ($1249.65 vs $860.05); however, it was more effective (no. of correct diagnoses 0.90 vs 0.68). The MP-MRI strategy was found to be cost-effective even at a threshold of $10,000. **Conclusion:** MRI assisted TRUS fusion guided biopsy was found to be cost-effective compared with conventional 12-core TRUS guided biopsy in symptomatic patients with suspected prostate cancer. As MRI/TRUS fusion is a new strategy, there is little data on its effectiveness. Further studies demonstrating the effectiveness of MRI/TRUS fusion are required.

Keywords: Multiparametric magnetic resonance imaging, Transrectal ultrasound, biopsy, cost-effectiveness

Introduction

Prostate cancer is a commonly diagnosed malignancy in men in the United States.[1] Despite its very high incidence, a small percentage of men will die from the disease.[2] Six to 12-core transrectal ultrasound (TRUS) guided biopsy has been the standard technique for diagnosing prostate cancer followed by elevated prostate specific antigen (PSA) and/or digital rectal examination (DRE).[3] Although TRUS biopsy is simple, relatively easy, and cheaper, it is limited by its poor sensitivity.[4,5] As a result, many patients undergo additional biopsies. Most of the biopsies are well tolerated but some may experience complications such as hematuria, hematospermia, rectal bleeding and urinary retention.[6] Rarely, infectious complications can also result.[6] Further, TRUS guided biopsy detects many clinically insignificant cancers.[7] With the increased recognition of over-diagnosis and overtreatment, prostate cancer has substantial psychological and economic impacts on society.[8] There is a need for new diagnostic strategies that can identify patients with clinically significant cancer.

Multiparametric magnetic resonance imaging (MP-MRI) is one of the promising modalities for prostate imaging. MP-MRI involves the use of different MRI based techniques such as T1-weighted, T2-weighted, diffusion weighted imaging, dynamic contrast enhanced imaging, and/or magnetic resonance spectroscopy in one or more combinations.[2] MP-MRI can easily detect lesions in areas that are poorly sampled by the TRUS biopsy.[9] Targeted biopsy of suspicious areas identified through MP-MRI has the potential to improve diagnosis. MRI guided biopsy can be performed either 'in-bore' or 'out-of-bore'.[2] The 'in-bore' or direct MRI guided biopsy is time consuming and expensive.[2] The 'out-of-bore' procedure involves MRI/TRUS fusion guided biopsy where patients first undergo prebiopsy MP-MRI and then images obtained are fused with real-time TRUS to guide biopsy.[2] As MRI/TRUS fusion guided biopsy is performed in an outpatient setting, it is expected to cost less compared to the direct MRI guided biopsy.

One concern regarding MP-MRI followed by MRI/TRUS fusion guided biopsy in biopsy naïve patients is the cost effectiveness compared to the conventional less expensive TRUS guided biopsy. There is a clinical trial in progress to determine whether MRI/TRUS fusion guided biopsy is superior to conventional biopsy alone in diagnosing subjects with prostate cancer.[10] However, the results of this study will not be available until April 2015. Further, this trial does not mention that whether it aims to determine the cost-effectiveness of MRI/TRUS fusion guided biopsy or not. The objective of this study is to determine the cost-effectiveness of the MP-MRI followed by MRI/TRUS fusion guided biopsy compared with the standard TRUS guided biopsy among biopsy naïve men in diagnosing prostate cancer.

Methods

We developed a decision analytic model to evaluate the costs and outcomes for conventional TRUS guided biopsy and experimental MP-MRI followed by MRI/TRUS guided biopsy. Strategies were compared based on costs and number of correct diagnoses, false-positive results avoided, and false-negative results avoided among patients with an elevated PSA (>4 ng/mL) and/or abnormal DRE. The model was a decision tree. Based on clinical guidelines, a typical clinical setting was created. The first strategy evaluated the current standard of care, where an elevated serum PSA is followed by systematic 12-core TRUS guided biopsy. The second strategy was the experimental strategy in which an elevated serum PSA is followed by MP-MRI including T2-weighted, dynamic contrast-enhanced, diffusion weighted imaging, and magnetic resonance spectroscopy sequences performed on a 3.0 T MRI scanner. The second strategy assumed that patients underwent a 5-core targeted biopsy only when a tumor suspicious area was identified on MP-MRI. The decision tree was not extrapolated to future outcomes as there is not enough information on the long term outcomes associated with

MP-MRI guided biopsy (Figure 5.1) in the literature. Further, it was assumed that if differences in the initial outcomes between two diagnostic strategies are observed, their future outcomes can be predicted.

Clinical Model Input Parameters: A systematic literature search was performed in PubMed, Elsevier, Cochrane Library databases, and Biosis to obtain sensitivity, specificity, and risks of complications associated with 12-core TRUS guided biopsy, MP-MRI, and MRI/TRUS fusion guided biopsy (Table 5.1 & Table 5.2).

Cost information: We used a payer's perspective. Costs associated with diagnostic strategies were based on 2013 Medicare reimbursement rates. Costs of hospitalization due to biopsy induced complications were obtained from a study conducted by Adibi et al.[11] Table 5.3 outlines the resources and costs used in the economic model.

The total direct cost per patient for the conventional 12-core TRUS biopsy was estimated using the following formula:

Cost of TRUS biopsy + cost of histopathological analysis of 12-core + (probability of moderate or severe post biopsy complications * probability of hospitalization * total cost of hospital admission). The total direct cost per patient for the MRI/TRUS fusion guided biopsy was estimated using the following formula:

Cost of MP-MRI + cost of MRI/TRUS fusion + cost of histopathological analysis of 5 cores obtained through targeted biopsy + (probability of moderate or severe post biopsy complications * probability of hospitalization * total cost of hospital admission).

Cost-effectiveness analyses were performed using TreeAge Pro Suite 2014. Three different incremental cost-effectiveness ratios (ICERs) were calculated by dividing the estimated

difference in costs by three different outcome measures which include the difference in the number of false positives avoided, number of false negatives avoided, or number of correct diagnoses.

Sensitivity Analysis: To test the robustness of the results in model parameters, n-way sensitivity analyses were conducted. The following model parameters were varied: the cost of MP-MRI and the MR/TRUS fusion guided biopsy, positive predictive value (PPV) of TRUS guided biopsy, PPV and negative predictive value (NPV) of MRI/TRUS fusion guided biopsy.

Results

Cost-effectiveness of MP-MRI followed by MR/TRUS fusion guided biopsy compared with TRUS guided biopsy:

Expected costs and the number of correct diagnoses made using two diagnostic strategies are presented in Table 5.4. Use of MP-MRI strategy was found to be more costly than TRUS guided biopsy ($1249.65 vs $860.05); however, it was more effective (number of correct diagnoses 0.90 vs 0.68). The MP-MRI strategy was found to cost approximately $1781.60 per one additional correct diagnosis compared to 12-core TRUS guided biopsy.

Table 5.5 shows the number of misdiagnoses such as false positive and false negative tests avoided for each diagnostic strategy. MRI strategy was found to cost around $2238.69 per additional false positive case avoided compared to the 12-core TRUS biopsy. The numbers of false negative cases avoided did not differ much between the two strategies. MRI strategy was found to cost around $8725.74 per additional false negative case avoided compared to the 12-core TRUS biopsy.

Sensitivity analysis:

A one-way sensitivity analysis was conducted on key model parameters (Figure 5.2 – Figure 5.5). The sensitivity analysis revealed that the model results were sensitive to the PPVs of the 12-core TRUS guided biopsy and MRI/TRUS fusion guided biopsy respectively. If the PPV of 12-core TRUS guided biopsy is as high as 0.99, ICER is approximately $18,000 per one correct diagnosis for the MRI strategy compared with 12-core TRUS guided biopsy (Figure 5.2).

Similarly, if the PPV of MRI/TRUS fusion guided biopsy is as low as 0.53 or below, ICER per one correct diagnosis is around $13,000 for the MRI strategy compared to the 12-core TRUS guided biopsy (Figure 5.5). As there are uncertainties regarding cost of MP-MRI and MRI/TRUS fusion guided biopsy, two way sensitivity analysis was performed varying the cost of MP-MRI (from $200 to $900) and the cost of MRI/TRUS fusion guided biopsy (from $200 to $700), MRI strategy was found to be cost-effective at a threshold value of $4,000.

A three-way sensitivity analysis was carried out in which all three parameters were varied: PPV of 12-core TRUS biopsy, NPV of MP-MRI, and PPV of MRI/TRUS fusion guided biopsy. Figure 5.6 shows that result with varying values of PPV of 12-core TRUS guided biopsy and NPV of MP-MRI while holding positive predictive value of MRI/TRUS fusion constant at 0.875. This result indicates that 12-core TRUS guided biopsy is favored when NPV of MP-MRI is very low whereas, PPV of 12-core is very high considering PPV of MRI/TRUS fusion guided biopsy is 0.875. However, the literature suggests that the NPV of MP-MRI is quite high (0.91) and PPV of 12-core TRUS is not so high (0.59).

Discussion

The results of our model suggest that the MRI strategy is cost-effective in diagnosing prostate cancer compared with the TRUS guided biopsy assuming a threshold to pay per correct diagnosis is at least $1781.60. In our study, decision analysis was used to compare the cost-effectiveness of MP-MRI followed by MRI/TRUS fusion guided biopsy with the conventional 12-core TRUS guided biopsy. As health care expenses are rapidly rising, cost-effectiveness analyses are increasingly being advocated as techniques to compare alternative strategies to optimize delivery of healthcare. Due to several limitations associated with these techniques, they should not be used as the only basis for a decision. In spite of the limitations, they can aid in making decisions, give structure to the problem, allow consideration of relevant effects of a decision and also identify key assumptions. Limitations associated with decision tree analysis are presented in a separate section. Thus, one can use decision-analytic methods and sensitivity analysis to address issues for which randomized controlled trials have not been performed or are not feasible.

Approximately 1.3 million prostate biopsies are performed each year in the United States.[12] It has been estimated that only 25% of men who undergo a prostate biopsy due to elevated PSA actually have prostate cancer indicating that many unnecessary biopsies are performed.[12] Unnecessary biopsies are estimated to cost around $2 billion per year.[13] In our baseline model, assuming MP-MRI to have a sensitivity and specificity of 94% and 28% respectively[14], it can avoid biopsy in 17% of patients who enter the current diagnostic pathway. Further, MP-MRI followed by MRI/TRUS fusion guided biopsy can avoid 17% of more false positive cases compared to conventional 12-core TRUS guided biopsy. The cost of unnecessary treatment among those who have indolent or insignificant disease is estimated to be around

$1.6 billion.[13] Thus, use of MP-MRI is expected to save costs by avoiding unnecessary biopsies and reducing treatment costs resulting from fewer false positives and a better estimation of tumor aggressiveness.

Sensitivity analysis found that our model was sensitive to the PPVs of 12-core TRUS and MRI/TRUS fusion guided biopsy. With the extended biopsy scheme such as 12-core TRUS guided biopsy, there is an increased chance of detecting smaller-volume tumors of little clinical relevance.[15] Some studies have reported that a higher number of biopsy cores are associated with smaller tumor volumes at radical prostatectomy.[15] Thus, the risks of detecting insignificant tumors and missing significant ones should be balanced with the extended biopsy scheme. The current study used a PPV of 0.59 for 12-core TRUS guided biopsy.[16] In order to make 12-core TRUS guided biopsy more cost-effective at threshold of $4,000, it has to have a PPV higher than approximately 0.8. Advancement in imaging technology such as MP-MRI has improved the diagnosis of significant cancer. Fusion of MR images of suspicious lesions with real-time TRUS biopsy techniques in an office/outpatient setting can guide biopsy needles to be inserted into suspicious areas. Targeted biopsy using MRI/TRUS fusion has greater ability to detect intermediate and high risk prostate cancer with greater than 85% positive predictive value.[16] Our model suggests that the positive predictive value of MRI/TRUS should be greater than 0.53 to make it cost-effective.

To our knowledge, this is the first study comparing the cost-effectiveness of the MRI/TRUS fusion strategy with the TRUS guided biopsy in United States. Recently, de Rooji et al. published a paper on the cost-effectiveness of MRI and MR-guided targeted biopsy versus systematic TRUS-guided biopsy in diagnosing prostate cancer.[17] Their results show that a MRI strategy leads to the reduction of overdiagnosis and overtreatment due to reduced false

positives with improvements in quality of life at almost equal cost to the conventional care.[17] Although the conclusions are in line with this paper, their study was conducted in the Netherlands.[17] Further, they used MRI guided biopsy but did not clarify whether they used a MRI/TRUS fusion approach, which is cheaper and a more convenient option than the MRI in-gantry biopsy.[17]

We acknowledge several limitations of the present study. First, we could not find current procedural terminology (CPT) codes to estimate the reimbursement rates of MP-MRI and MRI/TRUS fusion guided biopsy. Therefore, we used other relevant codes. For example, the CPT code associated with MRI guidance for needle placement was used to estimate the reimbursement rate of MRI assisted TRUS fusion guided biopsy. Similarly, cost associated with MP-MRI was estimated using a CPT code which determines the reimbursement rate of MRI of the pelvis with and without contrast material followed by further sequences. However, we varied costs of both MP-MRI and MRI/TRUS fusion in sensitivity analyses to see their influence on incremental cost-effectiveness ratio. Our model was found to be robust and did not change our conclusion of MRI strategy being more cost-effective at threshold of $10,000. Our model used cost associated with hospital admission due to biopsy induced complications from a study previously done in one institution.[15] This analysis was performed from the perspective of the payer and considered only direct costs, without including other economic healthcare concerns such as costs due to productivity loss and reduced quality of life due to hospital admissions. Decision tree analysis simplifies the real life situation and thus ignores the complexity. Finally, this study did not construct a long term Markov model and results of this model are based on intermediate patient outcomes.

Conclusion

MRI assisted TRUS fusion guided biopsy was found to be cost-effective compared with conventional 12-core TRUS guided biopsy in symptomatic patients with suspected prostate cancer provided threshold to pay for MRI/TRUS fusion biopsy is at least $1781.60. As MRI/TRUS fusion guided biopsy represents targeted biopsy, it is less invasive due to the reduced number of cores required to diagnose compared to conventional 12-core TRUS guided biopsy. However, due to the paucity of data on effectiveness of MRI/TRUS fusion guided biopsy, further studies demonstrating their effectiveness are required.

TABLES

Table 5.1: Probabilities used in the decision analytic model (test accuracy input data)

Transition probabilities	Probability value	Source
Mp-MRI sensitivity	0.94	Rais-Bahrami et al., 2013[84]
Mp-MRI specificity	0.28	Rais-Bahrami et al., 2013[84]
Mp-MRI PPV	0.38	Rais-Bahrami et al., 2013[84]
Mp-MRI NPV	0.91	Rais-Bahrami et al., 2013[84]
12-core TRUS biopsy sensitivity	0.70	Rastinehad et al., 2013[111]
12-core TRUS biopsy specificity	0.66	Rastinehad et al., 2013[111]
12-core TRUS biopsy PPV	0.59	Rastinehad et al., 2013[111]
12-core TRUS biopsy NPV	0.76	Rastinehad et al., 2013[111]
MRI/TRUS fusion sensitivity	0.92	Rastinehad et al., 2013[111]
MRI/TRUS fusion specificity	0.85	Rastinehad et al., 2013[111]
MRI/TRUS fusion PPV	0.9	Rastinehad et al., 2013[111]
MRI/TRUS fusion NPV	0.88	Rastinehad et al., 2013[111]

Note: Mp-MRI = Multiparametric magnetic resonance imaging; PPV = Positive predictive value; NPV= Negative predictive value; TRUS= Transrectal ultrasonography

Table 5.2: Risks of biopsy complication

Transition probabilities	Probability value	Source
Minor complications	0.646	Rosario et al., 2012[113]
No complications	0.021	Rosario et al., 2012[113]
Moderate or severe complications	0.333	Rosario et al., 2012[113]
Hospitalizations	0.113	Rosario et al., 2012[113]

Note: Risks of complications after 6 core or 12-core biopsies are the same.[114] Therefore, complications following 12-core biopsy and up to 5-core MRI assisted TRUS fusion biopsy are assumed to be the same.

Table 5.3: Resources and cost input

Procedure	Cost	Source
TRUSBx	$216.73	Medicare Reimbursement, CPT code:55700
Histopathological analysis (1-20) cores	$670.93	Medicare Reimbursement, CPT code: G0416
Histopathological analysis 12-core	$402.56	Medicare Reimbursement, cost of 1-core histopathological analysis assumed to be $33.55 based on CPT code of G0416
Histopathological analysis Upto 5-core (for targeted biopsy)	$167.73	Medicare Reimbursement, cost of 1-core histopathological analysis assumed to be $33.55 based on CPT code of G0416
Mp-MRI	$585.88	Assumption based on CPT code of 72197
MRI/US fusion	$391.26	Assumption based on CPT code of 77021
Hospital admission	$6335.91	Adibi et al., 2011[108]**

*As most of the TRUS biopsies are performed in an office based settings, non-facility charges were used from Medicare website. **2011 costs were converted into 2013 costs using Medical care service index. Medical care services index in 2011: $161.38; Medical care services index in 2013: $173.301; Costs of hospital admission in 2011: $5900. CPT codes: Current Procedural Terminology codes.

Table 5.4: Economic model base case, number of correct diagnoses

Strategy	Mean cost per strategy ($)	Incremental costs ($)	Effectiveness # of correct diagnoses	Incremental effectiveness	ICER ($/correct diagnosis)
TRUSgb	860.05		0.68		
MRI	1249.65	389.62	0.90	0.22	1781.60

Note: ICER = Incremental cost-effectiveness ratio

Table 5.5: Number of false positive and false negative cases avoided and associated costs

Strategy	Effectiveness # of false positives avoided	Effectiveness # of false negatives avoided	ICER (Incremental cost ($) per false positive case avoided)	ICER (Incremental cost ($) per false negative case avoided)
TRUSgb	0.29	0.39		
MRI	0.46	0.43	2238.69	8725.74

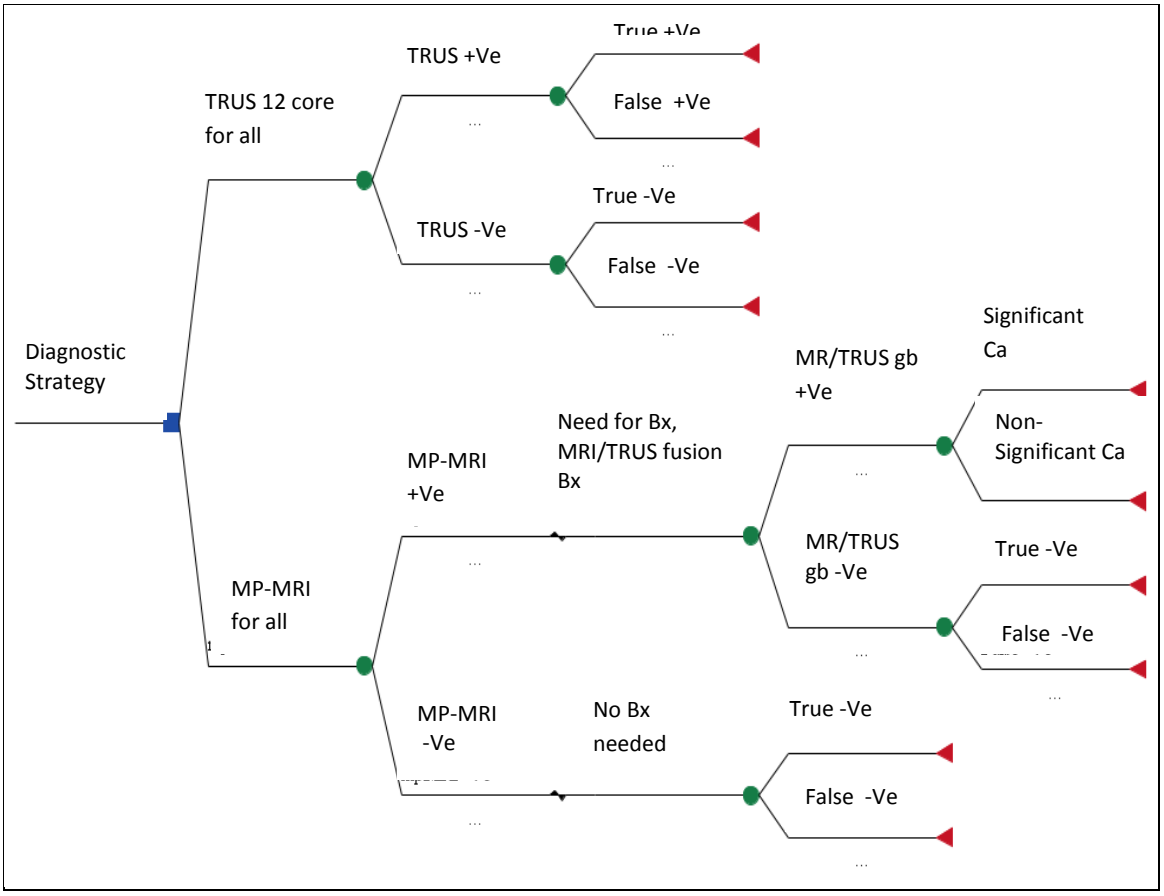

Figure 5.1: Decision analytical model comparing conventional 12-core TRUS guided biopsy with MP-MRI followed by MRI/TRUS fusion guided biopsy

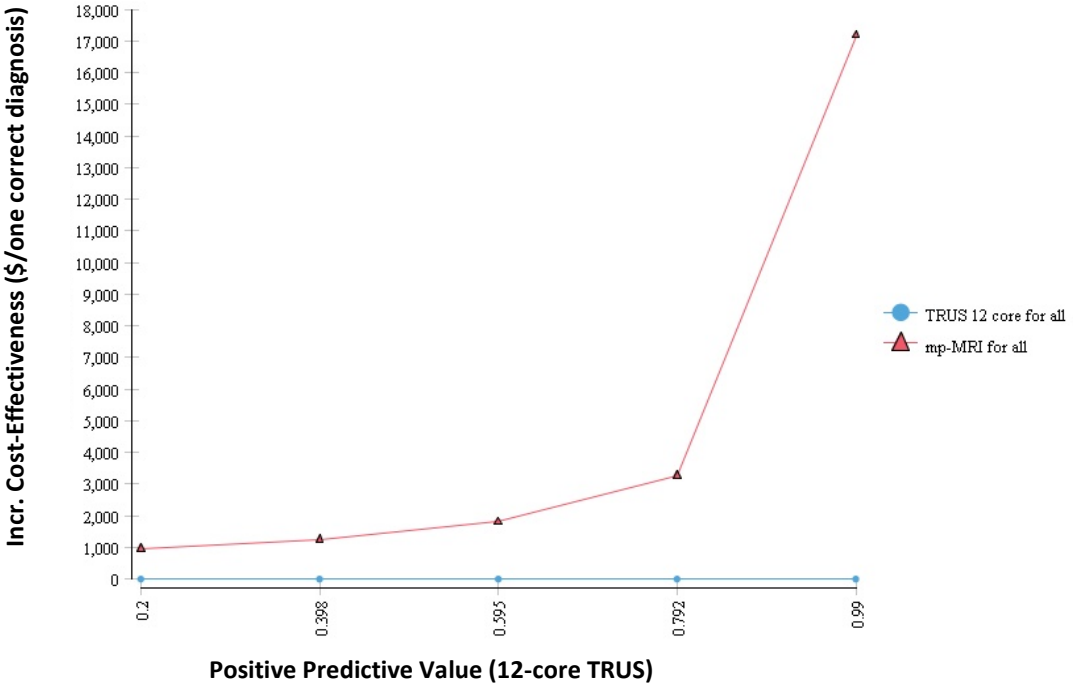

Figure 5.2: One-way sensitivity analysis varying positive predictive value of 12-core TRUS biopsy

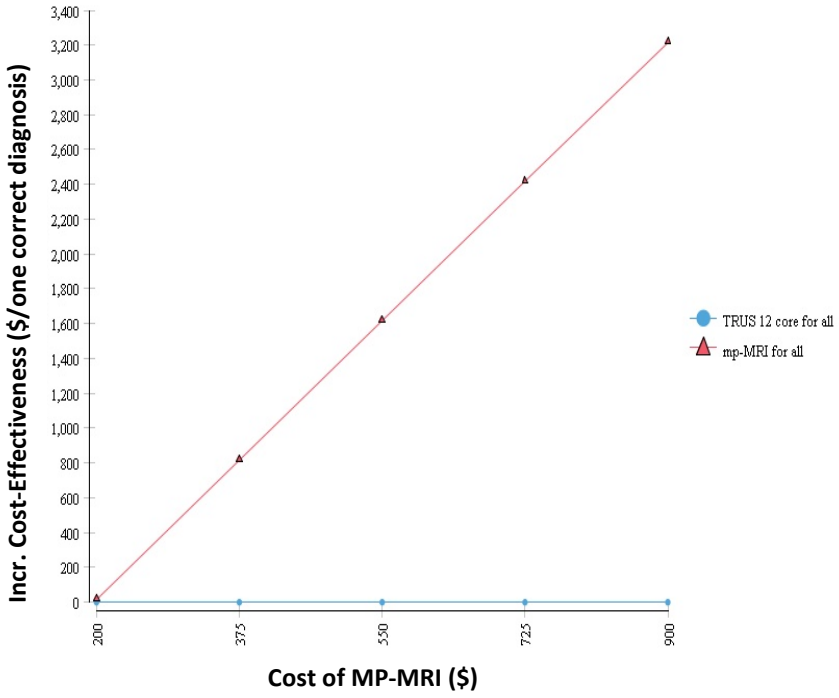

Figure 5.3: One-way sensitivity analysis varying cost of MP-MRI

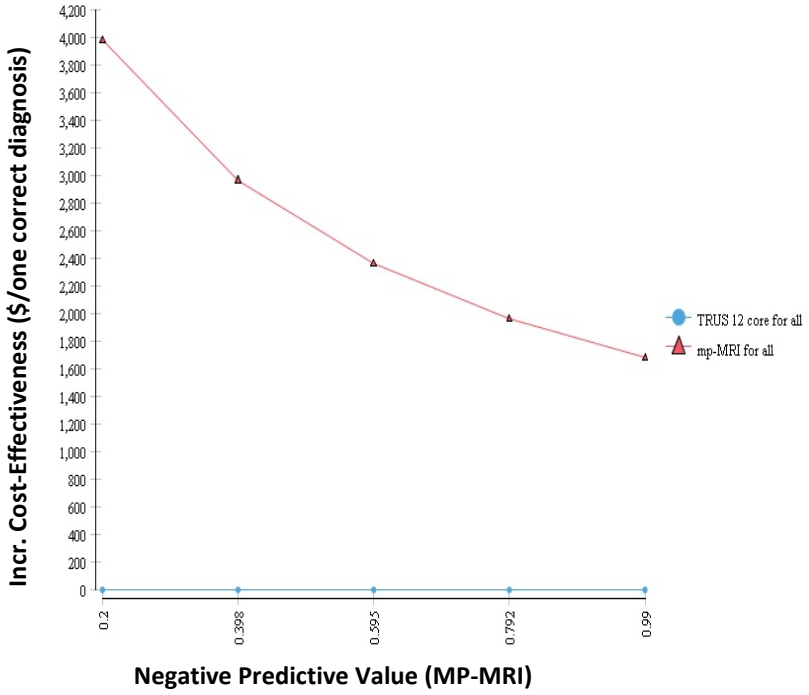

Figure 5.4: One-way sensitivity analysis varying negative predictive value of MP-MRI

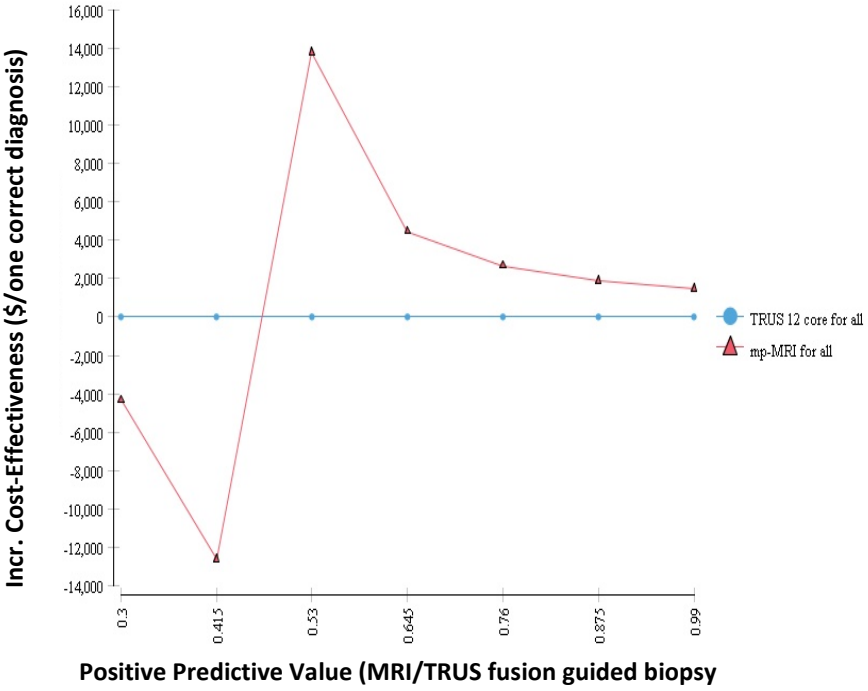

Figure 5.5: One-way sensitivity analysis varying positive predictive value of MRI/TRUS fusion guided biopsy

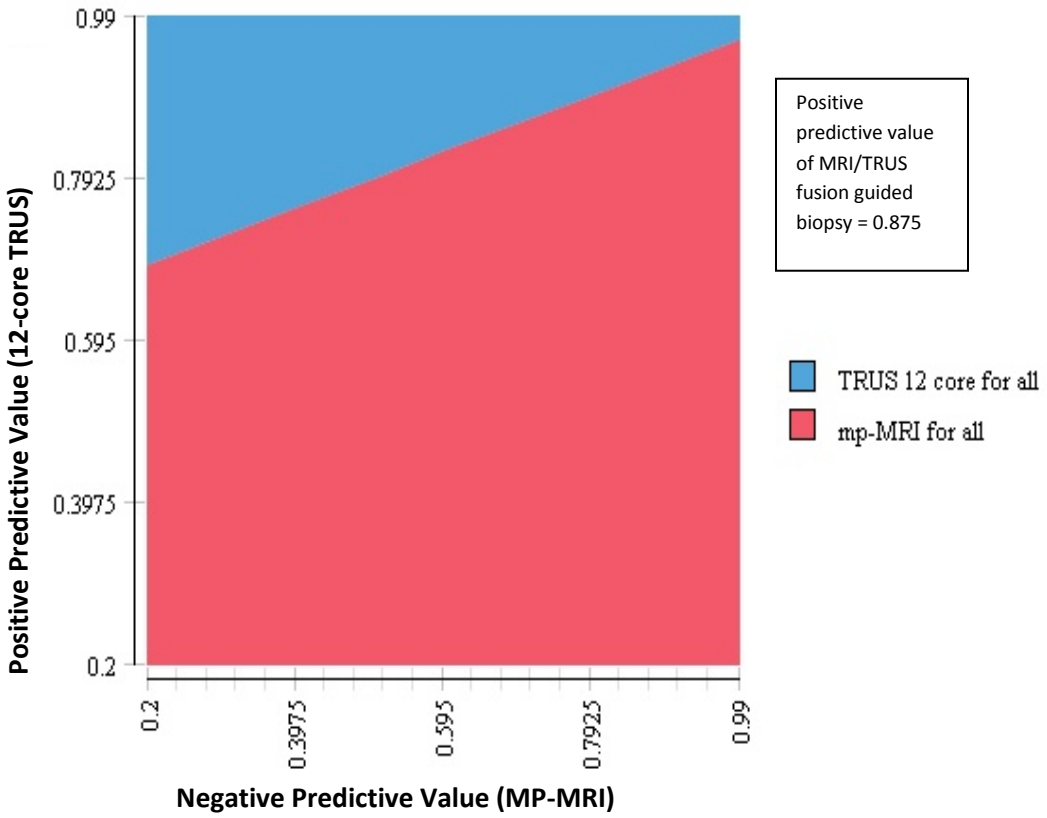

Figure 5.6: Three-way sensitivity analysis evaluating the impact of varying positive predictive value of 12-core TRUS guided biopsy, negative predictive value of MP-MRI and positive predictive value of MRI/TRUS fusion guided biopsy. Note: Blue area indicates 12-core TRUS is preferred and red area indicates MP-MRI assisted TRUS fusion guided biopsy is favored.

REFERENCES

1. Prostate Cancer 2014. (Accessed 2013, at http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-diagnosis.)

2. Penzkofer T, Tempany-Afdhal CM. Prostate cancer detection and diagnosis: The role of MR and its comparison with other diagnostic modalities – a radiologist's perspective. NMR in Biomedicine 2014;27:3-15.

3. AUA/Optimal techniques of prostate biopsy & specimen handling. (Accessed 2014, at https://www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Biopsy-WhitePaper.pdf.)

4. Xu S, Kruecker J, Turkbey B, et al. Real-time MRI-TRUS fusion for guidance of targeted prostate biopsies. Computer Aided Surgery 2008;13:255-64.

5. Fiard G, Hohn N, Descotes JL, Rambeaud JJ, Troccaz J, Long JA. Targeted MRI-guided prostate biopsies for the detection of prostate cancer: Initial clinical experience with real-time 3-dimensional transrectal ultrasound guidance and magnetic resonance/transrectal ultrasound image fusion. Urology 2013;81:1372-8.

6. Satyanarayana R, Parekh D. Prevention and treatment of biopsy-related complications. Current Urology Reports 2014;15:013-0381.

7. Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. European Urology 2013;64:713-9.

8. Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. BJU International 2011;108:22.

9. Puech P, Sufana Iancu A, Renard B, Villers A, Lemaitre L. Detecting prostate cancer with MRI - why and how. Diagnostic and Interventional Imaging 2012;93:268-78.

10. ClinicalTrials. MRI/TRUS Fusion Guided Prostate Biopsy- An Improved Way to Detect and Quantify Prostate Cancer. 2013.

11. Rais-Bahrami S, Siddiqui MM, Turkbey B, et al. Utility of multiparametric magnetic resonance imaging suspicion levels for detecting prostate cancer. The Journal of Urology 2013;190:1721-7.

12. Rastinehad AR, Turkbey B, Salami SS, et al. Improving detection of clinically significant prostate cancer: Magnetic resonance imaging/transrectal ultrasound fusion guided prostate biopsy. The Journal of Urology 2013;12:06089-8.

13. Rosario DJ, Lane JA, Metcalfe C, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. British Medical Journal 2012; 344:d7894.

14. Naughton CK, Ornstein DK, Smith DS, Catalona WJ. Pain and morbidity of transrectal ultrasound guided prostate biopsy: A prospective randomized trial of 6 versus 12 cores. The Journal of Urology 2000;163:168-71.

15. Adibi M, Pearle MS, Lotan Y. Cost-effectiveness of standard vs intensive antibiotic regimens for transrectal ultrasonography (TRUS)-guided prostate biopsy prophylaxis. BJU International 2011;110:E86-91.

16. Crawford ED, Ventii K, Shore ND. New biomarkers in prostate cancer. Oncology 2014;28:135-42.

17. Ahmed HU, Kirkham A, Arya M, et al. Is it time to consider a role for MRI before prostate biopsy? Nature Reviews Clinical Oncology 2009;6:197-206.

18. Shariat SF, Roehrborn CG. Using biopsy to detect prostate cancer. Reviews in Urology 2008;10:262-80.

19. de Rooij M, Crienen S, Witjes JA, Barentsz JO, Rovers MM, Grutters JP. Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy versus systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: A modelling study from a health care perspective. European Urology 2013;21:012.

CHAPTER 6

COMPARATIVE ANALYSIS OF HARMS ASSOCIATED WITH CONSERVATIVE MANAGEMENT AND IMMEDIATE TREATMENT AMONG LOW RISK LOCALIZED PROSTATE CANCER PATIENTS: A POPULATION BASED STUDY

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[1]Patel P**,** Perri M, Griffin S, Tackett R. To be submitted to *Journal of the National Comprehensive Cancer Network.*

Purpose: The purpose of this study was to examine urinary, rectal, erectile side effects, and cancer specific survival in localized prostate cancer patients who were treated with immediate treatment or conservative management. **Methods:** Using the Surveillance Epidemiology and End Results Medicare-linked database, a total of 6,868 patients ≥ 66 years of age with localized low risk prostate cancer were identified (2004 and 2005). Patients who received either immediate treatment or delayed treatment (> 6 months after diagnosis) were followed for a period of 5 years to determine toxicities and survival. Propensity score matching was used to adjust for selection bias associated with treatment type received. The presence of toxicity in each cohort was determined using logistic regression. The Cox proportional hazard model was used to estimate prostate cancer specific survival rates. **Results:** Overall, 735 patients received delayed treatment and 6,133 patients received immediate treatment. Multivariate logistic regression analysis showed that the conservative management group was found to have lower odds for urinary complications (odds ratio: 0.824, p value<0.0001), rectal complications (odds ratio: 0.770, p value<0.0001) and erectile toxicities (odds ratio: 0.636, p value < 0.0001) compared to the immediate treatment group within 5 years of diagnosis. The results of survival analysis showed that there was no additional hazard of dying due to prostate cancer in conservative management within a 5 year time period among studied patients than those in the immediate treatment group (Hazard ratio: 0.736, p value: 0.2696). **Conclusion:** Patients ≥ 66 years of age diagnosed with low risk prostate cancer are not at additional risk of dying due to prostate cancer within a 5 year time period if kept on conservative management or delayed treatment. The results of this study should be interpreted with caution because we could not differentiate active surveillance from watchful waiting group from the database.

Keywords: Prostate cancer, treatment strategies, survival analysis, comparative effectiveness

Introduction

Prostate cancer is the second leading cause of non-cutaneous cancer related deaths among men in the United States.[1] The National Cancer Institute has estimated that there will be approximately 233,000 new cases of prostate cancer and approximately 29,480 will die of it in 2014.[2] Prostate cancer leads in terms of costs as well. The overall direct cost of prostate cancer in the United States in 2010 was estimated to be more than $12 billion in annual costs.[3] In 2020, the direct cost of prostate cancer is projected to be $19 billion.[3] Currently, most prostate cancers are detected by a blood test that measures prostate specific antigen (PSA), and digital rectal examination.[4] More than half of cancers detected with PSA screening are localized, not aggressive at diagnosis, and unlikely to become life threatening.[5] However, 90% of patients receive immediate treatment for prostate cancer such as surgery or radiation therapy resulting into tremendous overtreatments.[5,6] In many patients, these overtreatments have substantial short- and long-term effects without any clinical benefit.

Appropriate management of screen detected, early-stage, low to intermediate risk prostate cancer is an important public health issue given the number of men affected and the risk for adverse outcomes, such as diminished sexual function and loss of urinary control. Potential strategies to eliminate overtreatment include more widespread implementation of observational therapies. Currently, clinicians rely on two observational strategies as alternative to immediate treatment of early-stage prostate cancer: watchful waiting and active surveillance. Watchful waiting involves relatively passive patient follow-up, with palliative interventions when any symptoms develop. Active surveillance typically involves proactive patient follow-up in which PSA levels are closely monitored, prostate biopsies may be repeated, and eventual treatment is anticipated.

As prostate cancer often has an indolent natural history, it makes observational management strategies more appealing.[7] The life time risk of being diagnosed with prostate cancer is about 17%, while the corresponding risk of dying of this disease is 3%.[8,9] This evidence suggests that conservative management may be an important treatment consideration of the sizable majority of men diagnosed with localized prostate cancer.

Watchful waiting in low-risk prostate cancer is not new to the field. However, active surveillance is a new emerging strategy that focuses on relatively young individuals rather than the sicker older population. Despite its potential as a reasonable treatment choice active surveillance has been used in only about 10% of the patients, perhaps because of a limited understanding of and contemporary data on the anticipated course and outcomes of this approach. Long term outcomes and effects on quality of life have not been well characterized.[8,10] The Institute of Medicine's Committee on Comparative Effectiveness Research has identified treatment for localized prostate cancer as a high-priority research area.[11]

The objective of the current study was to compare conservative management with the immediate treatment based on long term clinical outcomes mainly disease and treatment related toxicities. The central hypothesis of the study is that conservative management has a better toxicity profile compared to the group of immediate treatment. The rationale behind this study is that it may provide substantial evidence to choose an appropriate regime that may reduce the patient burden and healthcare costs associated with prostate cancer.

Methods

Data Sources: Data for this study was obtained from the National Cancer Institute's Surveillance Epidemiology Ends Results (SEER) program database linked to Medicare administrative claims from 2003 to 2009. The SEER program captures clinical, demographic and survival information of

approximately 28% of the US population and is 98% complete for case ascertainment.[12] The Medicare program covers approximately 97% of the persons aged 65 years and older.[13] This study was approved by the University of Georgia's Institutional Review Board as well as by the SEER-Medicare for Data Use Agreement with National Cancer Institute. As the data did not contain personal identifiers, informed consent was not requested by the Institutional Review Board.

Cancer related information such as cancer stage, grade, tumor extension, and tumor size was obtained from the SEER's Patient Entitlement and Diagnosis Summary File (PEDSF). Well differentiated cancers were characterized by a Gleason score of 2 to 4; moderately differentiated, 5 to 6, and poorly differentiated, 7 to 10. Treatment related information was obtained from both SEER and Medicare files. A Charlson comorbidity score was derived from Medicare claims during the year prior to prostate cancer diagnosis using a validated algorithm. Race was self-determined by the patients.

Study Participants: Study participants were men that were mainly 66 years or older SEER residents and diagnosed with stage T1 or T2a between 2004 and 2005 (ICD-O-3 site code C619) and followed for 5 years. The current study utilized only newly diagnosed cases to understand the outcomes of the treatment strategies from the identification of the disease. Patients were excluded from the study if they (i) did not survive the first 6 months after the diagnosis, (ii) had a personal history of malignant neoplasm of prostate, (iii) were enrolled in HMO, (iv) did not have both Medicare Part A and Part B, and (v) had end-stage renal disease. Eligible identified patients were categorized into two cohorts: 1) conservative management and 2) immediate treatment. Patients who were in the immediate treatment group were identified as patients undergoing radical prostatectomy, radiation, or brachytherapy immediately after diagnosis. ICD-9 codes and

Healthcare Common Procedure Coding System (HCPCS) codes used in identifying patients are presented in Table 6.1. Patients who were in the conservative management group were identified as those who did not receive any immediate treatment within 6 months of diagnosis of localized prostate cancer.

Outcomes Assessment: Both incident and prevalent cases of urinary, rectal, and erectile complications were assessed separately in both cohorts. Urinary complications were defined as having incontinence, obstruction, irradiation cystitis, bladder hemorrhage, urinary fistulas, or urinary tract infections. Rectal complications were defined as having rectal hemorrhage, ulcers, fistulas or bowel incontinence. Erectile complications were defined as having impotence. These complications were identified using appropriate ICD-9 diagnoses codes as well as based on Common Procedure Terminology (CPT) /HCPCS codes of invasive procedures performed to repair these complications. The medical codes for diagnoses and procedures performed for the complications are provided in Table 6.2. Patient's dates of diagnosis and death were obtained from the SEER's PEDSF file.

Statistical Analyses: Demographic and clinical variables across study cohorts were compared. A chi-square test was used to compare categorical variables and a t-test was used to compare continuous variables. As the aim of this study was to compare treatment outcomes, propensity score matching was used to address the issue of selection bias and generate comparable study arms. In this two-step procedure, the probability of receiving treatment (conservative management vs. immediate treatment) was first calculated based on multivariate logistic regression that included the patient's demographic information such as age, race, income, and tumor related information (e.g., grade, tumor extension and tumor size) as predictors of receiving treatment. The obtained probability scores were then used in analyzing outcomes. Risk

of complications such as urinary, rectal, and sexual dysfunction was estimated using logistic regression. A Cox proportional hazard model was used to estimate the prostate cancer specific survival rate in both the cohorts. All analyses were performed using SAS statistical software (version 9.3, SAS Institute, Cary, NC).

Results

The study population included 6,868 patients who were diagnosed with incident prostate cancer between 2004 and 2005, and fit into the eligibility criteria. Conservative management and immediate treatment cohorts consisted of 735 and 6,133 patients respectively. Table 6.3 describes the baseline characteristics of the study cohorts. The majority of eligible patients were aged 66 to 74 years and white in both the cohorts. Approximately 97% of the patients in both cohorts had either a moderately or intermediately differentiated tumor grade. All patients had localized prostate cancer. Tumor size was not recorded in more than 85% of patients in both cohorts. There was no nodal involvement in all the eligible patients. In terms of comorbidity burden, the majority of patients had either 0 or 1 comorbid condition. There were more married individuals in the immediate treatment group than the conservative management cohort. There was no significant difference in the proportion of patients who had T1 or T2a staging in both the treatment arms.

Risk of adverse outcomes:

Patients diagnosed with prostate cancer were followed for a 5 year time period to measure adverse events in both cohorts. Adverse events studied included urinary, rectal and erectile complications. Rates of urinary, rectal and erectile complications were 55.51%, 20.27% and 6.12%, respectively, for conservative management patients. Immediate treatment patients were found to have urinary, rectal and erectile rates of 57.26%, 25.04% and 10.75%

respectively. Table 6.4 presents crude rates of complication diagnoses and invasive procedures performed for both cohorts.

Table 6.5 shows the results of the logistic regression predicting urinary complications based on the treatment arm, demographic, and tumor related variables adjusted with propensity scores. Odds of urinary complications were statistically significantly lower in the conservative management than the immediate treatment group (odds ratio: 0.824, $p< 0.0001$).

Patients aged from 66 to 79 years were found to have significantly lower odds of urinary complications than those above 80 years old. Patients with null or moderate comorbidity were found to have reduced odds of urinary complications than those with more than one comorbidity. Black patients compared to whites had reduced odds of urinary complications. Single patients were found to have higher odds of having urinary complications than married patients. Results related to rectal complications are presented in Table 6.6. Conservative management was found to have a lower odds of rectal complications compared to the immediate treatment group (odds ratio: 0.770, $p<0.0001$). Compared to whites, black and patients with other ethnicities were found to have reduced odds of rectal complications. Those with null or moderate comorbidity were found to have lower odds of getting rectal complications than those with higher comorbidity.

Factors associated with rates of erectile complications are presented in Table 6.7. Conservative management was found to be less likely to have erectile complications than the immediate treatment group (odds ratio: 0.636, $p<0.0001$). There was not a statistically significant difference between blacks and whites regarding erectile complications. However, patients with other ethnicities (other than black) were found to have reduced odds of having erectile complications than whites. Patients aged from 66 to 79 years were found to have higher

odds of erectile complications than those above 79 years of age. Patients with null or one comorbidity had higher odds of having erectile complications than those with higher comorbidity.

Survival analysis:

Data for survival analysis are presented in Table 6.8. These data represent up to a 5-year follow up period from time of diagnosis. Patients who were in the conservative management group did not differ significantly from those in the immediate treatment group in terms of prostate cancer specific mortality at any point in time (Hazard ratio: 0.736, p value: 0.2696) within the 5 year time period. However, our study found that black patients compared to whites had higher hazard of dying due to prostate cancer within 5 year time period (Hazard ratio: 2.537, p value: 0.0112). Patients aged from 66 to 79 years were found to have better survival experience than those aged above 79 years within the study time period. We also found that patients with null or one comorbidity had a reduced hazard of dying due to prostate cancer than those with greater than one comorbidity.

Discussion

Our study of prostate cancer patients diagnosed between 2004 and 2005, with a 5-year follow up, has focused on whether urinary, rectal, or erectile complication rates differ between conservative management and immediate treatment groups. Further, this study assessed the survival experiences of both treatment groups. Prostate cancer is considered a disease of older men and the median age at diagnosis reported is 72 years.[14] Thus, the SEER-Medicare population is representative of the population of interest. Results of the current study suggest that urinary, rectal and erectile complications are more likely to be present in the immediate treatment group than in the conservative management group within a 5 year time period

among patients aged above 65 years. Results of survival analysis indicate that patients who opt for conservative management have no additional higher hazard of dying due to prostate cancer within 5 years than those who undergo immediate treatment.

Results of this study are important to patients as well as health care practitioners. Patients who are in the conservative group can delay or avoid urinary, rectal, and erectile complications by delaying immediate treatment strategies such as radical prostatectomy or radiation therapy. Radical prostatectomy and radiation therapy affect a patient's bowel, urinary and sexual function tremendously and thereby affect the patient's quality of life.[15] Men in the intermediate risk category face the most challenging decisions regarding treatment and physicians recommend working backward from the known side effects associated with each treatment option.[15] Prostate cancer itself can affect bladder and sexual function.[16] Urinary incontinence is the most common symptom of prostate cancer and its severity depends on the type of the disease. Tumor growth can also damage the nerves that control the erection and thus leave a patient unable to engage in sexual activity.

As patients live longer with low-risk localized prostate cancer, they live with sequalae of the treatments they receive. Thus, it is important that both patients and clinicians understand the long-term consequences of various treatments. Demographic characteristics and tumor grades also were found to affect the complication rates in the current study. Relatively younger individuals, healthy, or black patients were less likely to experience urinary complications. On the other hand, younger individuals were more likely to experience erectile dysfunction than older people. We found this difference because younger individuals were more likely to receive both non-surgical and surgical treatments to repair erectile dysfunction.[17] Older individuals may not seek surgical treatments but prefer to take medication.[18] As we did not study Medicare part

D data, we could not find any claims related to drugs such as sildenafil citrate, tadalafil citrate or vardenafil to treat erectile dysfunction. Patient preferences for outcomes among competing treatment strategies may be an important factor that drives treatment decisions.

There are patients who want to avoid therapy induced distressful symptoms even when faced with a reduced prospect of survival. Some men give full priority to survival even though the survival gain may be very small. Our study found no significant difference in hazards of dying due to prostate cancer between the conservative management group and the immediate treatment. This result is consistent with the literature. Recently, Bill-Axelson et al. presented extended follow up results of the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4).[19] This trial randomized patients to watchful waiting or radical prostatectomy between 1989 and 1999. They found a substantial reduction in mortality after the radical prostatectomy group was followed for up to 23.2 years among men younger than 65 years of age. They did not find a significant difference in mortality rate between radical prostatectomy and watchful waiting among low risk localized prostate cancer patients. However, our study is different than SPCG-4 trial or other studies that have compared immediate treatment options with watchful waiting program.[9,20] We combined different immediate treatment options into one category. Further, we had a conservative management group that included both watchful waiting and active surveillance options. Acceptance of active surveillance or watchful waiting depends on a patient's physical and psychological well-being. Both strategies offer the opportunity to delay treatment. However, watchful waiting is reserved for those who cannot tolerate aggressive treatment and are offered hormonal therapy upon cancer progression. On the other hand, active surveillance involves curative treatment upon cancer progression. It is difficult to separate patients who received watchful waiting versus active surveillance from the claims database as

both groups receive frequent PSA screening. As a result, both treatment options in this study are combined as a conservative management approach.

Several potential limitations of this study should be considered when interpreting these results. Large administrative data sets such as Medicare data contain data originally intended for billing purposes. Procedures or treatments that do not incur any costs are not reported as there is no financial incentive to document them. Further, complication rates obtained using these data represent underestimates as not all patients are likely to receive treatments for complications. The treatment modalities were not randomized in the study. However, the issue of selection bias was addressed using propensity score matching. We could not differentiate patients who had watchful waiting or active surveillance as an observational strategy. This may bias the results because patients in watchful waiting are more likely to receive hormonal treatment and are at higher risk of having serious side effects or even death. Finally, the study was limited to Medicare eligible patients aged 66 years or older and those receiving care through the traditional, fee-for-service system, limiting the utility of the finding to older patients not enrolled in managed care programs.

Conclusion

Treatment options for patients diagnosed with low to intermediate risk prostate cancer include i) immediate treatment with either radical prostatectomy or radiation therapy and ii) observational strategies such as active surveillance or watchful waiting. In summary, our study suggests that the conservative management approach is associated with lower urinary, rectal, and erectile complications than immediate treatment within 5 years of diagnosis. Prostate cancer specific mortality does not differ significantly among patients who receive either immediate treatment or observation treatment. Choosing the appropriate treatment regimen

for disease management is critical and should account for (i) the patient's tumor characteristics such as its grade or aggressiveness, (ii) patient age, overall health, and remaining life expectancy, and (iii) patient preferences for the potential side effects of treatment options.

TABLES

Table 6.1: ICD-9 and CPT/HCPCS codes used to identify treatment modality

Treatment	**ICD-9 codes**	**HCPCS**
Immediate Radiation treatment	V58.0, V66.1, V67.1, 92.21-92.29	77401-77499, 77750-77799, 77014, 77334, 77336, 77520, 77522-77525
Prostatectomy	60.5, 60.2, 60.21-60.29, 60.3-60.6, 60.61, 60.62, 60.69, 60.9	55812-55845, 55866, 55810, 55899, 55867-55880
Chemotherapy	V58.1, V66.2, V67.2, 99.25	96401-96549

Table 6.2: ICD-9 and CPT/HCPCS codes used to identify complications

Complications	**Diagnoses** **ICD-9**	**CPT/HCPCS**
Urinary	788.3X, 595.85, 596.7, 599.0, 596.0, 598.X, 599.6, 788.2X, 596.1, 596.2, 599.1	52275, 52276, 52281, 52510, 53010, 53400, 53405, 53410, 52415, 53420, 53425, 53600, 53601, 53605, 53620, 53621, 52252, 53440, 51840, 51841, 53442, 53443
Rectal	558.0, 558.1-558.4, 558.9, 569.0-569.4, 569.41-569.44, 569.49, 569.81, 565.0, 562.10-562.12, 578.1, 787.6, 787.60-787.63, 455.7, 455.8	45800, 45805, 45820, 45825
Erectile	607.84	54400-54402, 54405, 54407-54411, 54415,-54417, C1007, C1813, C2622, C3500 C8514, C8516, L7900, 54231, 54235, J0270, J0275, J2440, J2760

Table 6.3: Clinical and demographic characteristics of patients with clinically localized Prostate cancer

Characteristics	Conservative Management (n=735)	Immediate treatment (n=6,133)	p value	P value after PS matching
Age group (yr)				
66-69	196 (26.67%)	2611 (42.57%)	<0.0001	0.9842
70-74	224 (30.48%)	1971 (32.14%)		
75-79	191 (25.99%)	1159 (18.90%)		
80-84	124 (16.87%)	392 (6.39%)		
Race				
White	640 (87.07%)	5236 (85.37%)	0.4023	-
Black	60 (8.16%)	540 (8.80%)		
Other	35 (4.76%)	357 (5.82%)		
Tumor grade				
Well-differentiated	17 (2.31%)	162(2.64%)	0.5973	-
Moderately differentiated	718 (97.69%)	5971 (97.36%)		
Tumor extension				
T1	675 (91.84%)	5567 (90.77%)	0.3429	-
T2a	60 (8.16%)	566 (9.23%)		
Tumor Size				
<888 mm	15 (2.04%)	561 (9.15%)	<0.0001	-
Microscopic foci	14(1.90%)	116 (1.89%)		
< 1 cm	0 (0.00%)	7 (0.11%)		
< 2 cm	0 (0.00%)	1 (0.02%)		
Size not stated	706 (96.05%)	5448 (88.83%)		
Stage				
In-situ	1 (0.14%)	0 (0.00%)	0.1070	-
Localized	734 (99.86%)	6133 (100.00%)		
Lymph nodes status				
No nodes involvement	735 (100.00%)	6133 (100.00%)		-
Charlson comorbidity index				
0	447 (60.82%)	3860 (62.94%)	0.4482	-
1	178 (24.22%)	1444 (23.54%)		
2 +	110 (14.97%)	829 (13.52%)		
Marital status				
Single	67 (9.12%)	491 (8.01%)	0.2980	-
Married	668 (90.88%)	5642 (91.99%)		

Table 6.4: Crude rates for complication diagnoses and invasive procedures

Complications	Conservative management	Immediate treatment	P value
Urinary	55.51%	57.26%	0.3640
Rectal	20.27%	25.04%	0.0045
Erectile	6.12%	10.75%	<0.0001

Table 6.5: Logistic regression analysis of urinary complications and predictors using propensity score

Parameter	Estimate	Odds ratio (95% CI)	P value
Treatment			
Conservative Management	-0.1941	0.824 (0.769, 0.882)	<0.0001
Race			
Black	-0.2512	0.778 (0.690, 0.878)	<0.0001
Others	-0.0082	0.992 (0.857, 1.148)	0.9126
Marital status			
Single	0.3679	1.445 (1.270, 1.644)	<0.0001
Age			
66-69	-0.5685	0.566 (0.492,0.652)	<0.0001
70-74	-0.3062	0.736 (0.638,0.850)	<0.0001
75-79	-0.1647	0.848 (0.729, 0.987)	0.0333
Grade			
Well-differentiated	-0.3074	0.735 (0.596, 0.908)	0.0042
Comorbidity			
Null	-0.5763	0.562 (0.505, 0.625)	<0.0001
One	-0.2433	0.784 (0.696, 0.883)	<0.0001

Note: Model was found to be statistically significant. Result of likelihood ratio test: χ^2 value – 404.668 and p value <0.0001. CI indicates confidence interval. Base case includes patients who were in immediate treatment group, with race white, married, aged 80 or above, with moderately differentiated tumors, and with greater than 1 comorbidities.

Table 6.6: Logistic regression analysis of rectal complications and predictors using propensity score

Parameter	Estimate	Odds ratio (95% CI)	P value
Treatment			
Conservative Management	-0.2620	0.770 (0.710, 0.834)	<0.0001
Race			
Black	-0.1925	0.825 (0.712, 0.956)	0.0104
Others	-0.5486	0.578 (0.474, 0.705)	<0.0001
Marital status			
Single	-0.3301	0.719 (0.612, 0.845)	<0.0001
Age			
66-69	0.1219	1.130 (0.959, 1.331)	0.1453
70-74	0.0902	1.094 (0.927, 1.292)	0.2861
75-79	0.1218	1.130 (0.949, 1.345)	0.1704
Grade			
Well-differentiated	-0.1525	0.859 (0.664, 1.111)	0.2459
Comorbidity			
Null	-0.4056	0.667 (0.594, 0.748)	<0.0001
One	-0.1563	0.855 (0.752, 0.973)	0.0172

Note: Model was found to be statistically significant. Result of likelihood ratio test: χ^2 value – 156.787 and p value <0.0001. CI indicates confidence interval. Base case includes patients who were in immediate treatment group, with race white, married, aged 80 or above, with moderately differentiated tumors, and with greater than 1 comorbidities.

Table 6.7: Logistic regression analysis of erectile complications and predictors using propensity score

Parameter	Estimate	Odds ratio (95% CI)	P value
Treatment			
Conservative Management	-0.4524	0.636 (0.564, 0.718)	<0.0001
Race			
Black	-0.0691	0.933 (0.758, 1.149)	0.5142
Others	-0.7625	0.467 (0.330, 0.660)	<0.0001
Marital status			
Single	-0.1877	0.829 (0.656, 1.048)	0.1168
Age			
66-69	1.6555	5.236 (3.521, 7.785)	<0.0001
70-74	1.1695	3.220 (2.154, 4.816)	<0.0001
75-79	0.8049	2.236 (1.469, 3.404)	0.0002
Grade			
Well-differentiated	0.2031	1.225 (0.857, 1.751)	0.2652
Comorbidity			
Null	0.2799	1.323 (1.074, 1.630)	0.0085
One	0.4896	1.632 (1.302, 2.045)	<0.0001

Note: Model was found to be statistically significant. Result of likelihood ratio test: χ^2 value – 281.549 and p value <0.0001. CI indicates confidence interval. Base case includes patients who were in immediate treatment group, with race white, married, aged 80 or above, with moderately differentiated tumors, and with greater than 1 comorbidities.

Table 6.8: Cox proportional hazard model to assess hazard of dying due to prostate cancer adjusted with propensity scores

Parameter	Estimate	Hazard ratio (95% CI)	P value
Treatment			
Conservative Management	-0.3062	0.736 (0.427, 1.268)	0.2696
Race			
Black	0.9310	2.537 (1.235, 5.211)	0.0112
Others	-1.1677	0.311 (0.046, 2.094)	0.2301
Marital status			
Single	-1.4567	0.233 (0.038, 1.415)	0.1135
Age			
66-69	-3.1571	0.043 (0.016, 0.112)	<0.0001
70-74	-1.7305	0.177 (0.094, 0.334)	<0.0001
75-79	-1.8661	0.155 (0.072, 0.334)	<0.0001
Grade			
Well-differentiated	-0.9618	0.382 (0.057, 2.582)	0.3237
Comorbidity			
Null	-1.0699	0.343 (0.189, 0.623)	0.0004
One	-1.3512	0.259 (0.119, 0.566)	0.0007

Note: Model was found to be statistically significant. Result of likelihood ratio test: χ^2 value – 840.389 and p value <0.0001. CI indicates confidence interval. Base case includes patients who were in immediate treatment group, with race white, married, aged 80 or above, with moderately differentiated tumors, and with greater than 1 comorbidities.

REFERENCES

1. Wilt TJ, Brawer MK, Barry MJ, et al. The Prostate cancer Intervention Versus Observation Trial:VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy to watchful waiting for men with clinically localized prostate cancer. *Contemporary Clinical Trials.* 2009;30(1):81-87.

2. National Cancer Institute. Prostate Cancer. 2014.

3. Hodges JC, Lotan Y, Boike TP, Benton R, Barrier A, Timmerman RD. Cost-effectiveness analysis of stereotactic body radiation therapy versus intensity-modulated radiation therapy: An emerging initial radiation treatment option for organ-confined prostate cancer. *Journal of Oncology Practice.* May 1, 2012 2012;8(3S):e31s-e37s.

4. American Urological association. www.auanet.org.

5. Wong YN, Mitra N, Hudes G, et al. Survival associated with treatment vs observation of localized prostate cancer in elderly men. *The Journal of Medical Association.* 2006;296(22):2683-2693.

6. van den Bergh RC, Steyerberg EW, Khatami A, et al. Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer.* 2010;116(5):1281-1290.

7. Klotz L. Active surveillance for prostate cancer: Patient selection and management. *Current Oncology.* 2010;17(2):S11-17.

8. Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. *The Journal of Medical Association.* Sep 16 2009;302(11):1202-1209.

9. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *New England Journal of Medicine.* 2012;367(3):203-213.

10. Hayes JH, Ollendorf DA, Pearson SD, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: A decision analysis. *The Journal of Medical Association.* Dec 1 2010;304(21):2373-2380.

11. Institute of Medicine. Initial National Priorities for Comparative Effectiveness Research. 2009; http://www.iom.edu/reports/2009/comparativeeffectivenessresearchpriorities.aspx.

12. Surveillance E, and End Results: Program Turning Cancer Data Into Discovery,. Overview of the SEER program. In: Institute NC, ed 2014.

13. Engels EA, Pfeiffer RM, Ricker W, Wheeler W, Parsons R, Warren JL. Use of surveillance, epidemiology, and end results-medicare data to conduct case-control studies of cancer among the US elderly. *American Journal of Epidemiology.* 2011;174(7):860-870.

14. National Cancer Institute. General information about prostate cancer. 2014.

15. Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: The Prostate Cancer Outcomes Study. *Journal of the National Cancer Institute.* September 15, 2004 2004;96(18):1358-1367.

16. Mayo Clinic. Prostate Cancer. 2013; http://www.mayoclinic.org/diseases-conditions/prostate-cancer/basics/symptoms/con-20029597, 2014.

17. Tal R, Jacks LM, Elkin E, Mulhall JP. Penile implant utilization following treatment for prostate cancer: Analysis of the SEER-Medicare database. *Journal of Sex Medicine.* 2011;8(6):1797-1804.

18. Prasad MM, Prasad SM, Hevelone ND, et al. Utilization of pharmacotherapy for erectile dysfunction following treatment for prostate cancer. *Journal of Sex Medicine.* 2010;7(3):1062-1073.

19. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *New England Journal of Medicine.* 2014;370(10):932-942.

20. Hoffman RM, Barry MJ, Stanford JL, Hamilton AS, Hunt WC, Collins MM. Health outcomes in older men with localized prostate cancer: Results from the Prostate Cancer Outcomes Study. *American Journal of Medicine.* 2006;119(5):418-425.

CHAPTER 7

CONCLUSIONS

The current study has addressed three major areas in the field of prostate cancer outcomes research. The first part of the study addressed the issue of healthcare utilization and associated expenditures among prostate cancer patients in United States. This study provides the most recent cost estimate as well as associated predictors of higher costs among patients with prostate cancer compared to other previously conducted studies. Using a nationally representative database, the annual direct medical expenditures associated with prostate cancer was found to be $5.6 billion in 2010 US dollars. Both outpatient and inpatient settings are associated with greater costs as the majority of prostate cancer related treatments are performed in those settings.

Our study found chemotherapy and ultrasound as the significant predictors of higher outpatient expenditure. This result requires further attention from policymakers. Ultrasound is the most commonly preferred technique to guide biopsy for diagnostic confirmation of prostate cancer. However, ultrasound is not a reliable technique and physicians and patients lack confidence in ultrasound guided biopsy results. Frequent repetitive biopsies are performed in many patients to rule out the possibility of false results. As a result, ultrasound is associated with increased costs. X-ray imaging and computed tomography (CT) scans were found to be the significant predictors of higher expenditure in office-based visits. X-rays and CT scans are generally used to check for bony metastases and expenditure related to x-ray imaging and CT scans may be avoided in certain cases that are at very low risk of having metastases but routinely undergo bone scans.

The second part of the study addressed the issue of diagnosis especially that of transrectal ultrasound (TRUS) guided biopsy in prostate cancer diagnosis. Conventional TRUS guided biopsy has been reported to miss 30-40% of cancers. Likewise, conventional biopsy may detect clinically insignificant tumors as well. MRI/TRUS fusion guided biopsy is performed out-of-bore where tumor vascularity and anatomical data provided by multiparametric MRI is electronically delivered to a fusion device that allows urologists to use the detail provided during MRI to guide live, real-time ultrasound scanning. This study performed cost-effectiveness analysis of relatively advanced and more accurate MRI/TRUS fusion guided biopsy compared with 12-core TRUS guided biopsy. Our study found MRI assisted TRUS fusion guided biopsy to be cost-effective compared with 12-core TRUS guided biopsy. MRI/TRUS fusion guided biopsy has better ability to identify and characterize prostate cancer. However, further studies demonstrating the effectiveness of MRI/TRUS fusion approach are required.

The third part of the study addressed the issue of overtreatment especially among low- to intermediate-risk prostate cancer patients who have very low risk of having metastasis. This study focused on incidence as well as prevalence based urinary, rectal, and erectile complications, and survival associated with conservative management and immediate treatment approach within 5 years of diagnosis. Results of our study indicate that patients in conservative management can delay or avoid urinary, rectal, and erectile dysfunction significantly compared to the immediate treatment with radical prostatectomy or radiation therapy. Patients older than 65 years in conservative management do not have a higher risk of mortality due to prostate cancer within a 5 year time period. Results of our study indicate that patients with conservative management can have a better quality of life without compromising survival in 5 year time frame. Younger individuals are more likely to have better survival compared to older individuals irrespective of the treatment received. Similarly, patients with

one or no comorbidity have better survival experience than those with more than one comorbidity irrespective of the treatment received. Treatment selection for patients diagnosed with low to intermediate risk is very crucial and should account for the patient's tumor characteristics, age, life-expectancy, comorbidities, and patient's preference for treatment side effects.

The results of this study indicate that there is a need for more accurate cost-effective technology in prostate cancer diagnoses. Routinely used TRUS guided biopsy is associated with higher economic and psychological burden on society due to numerous inaccurate diagnoses associated with it. Mp-MRI/TRUS fusion guided biopsy which can characterize prostate cancer accurately is found to be cost-effective compared to TRUS guided biopsy at a threshold to pay minimum of $1781.60. Observational strategies among low risk localized prostate cancer can avoid treatment related side effects especially rectal and erectile complications significantly within 5 years of diagnosis without compromising with survival. Thus, observational strategies represent one of the best approaches in reducing over treatment among patients diagnosed with low risk localized prostate cancer.