Prostate biopsy upgrading and its implications on treatment modality and outcomes in men treated with radical prostatectomy or permanent seed implantation at UT M.D. Anderson Cancer Center, 2000-2001

By

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ABSTRACT

Introduction: Radical prostatectomy and permanent seed implantation are among the standard of care treatment options for men with low or intermediate risk prostate cancer. Pathologic upgrading of Gleason score from biopsy to radical prostatectomy specimen has been previously described, but the meaning for men undergoing permanent seed implantation is unclear. The purpose of this study is to compare the biochemical recurrence-free survival and prostate cancer specific survival outcomes of a cohort of patients whose disease was upgraded between outside institution biopsy to UT MD Anderson Cancer Center biopsy, or between biopsy to radical prostatectomy Gleason score, to those patients who were not upgraded.

Methods: A retrospective cohort was assembled using data from 387 men with clinical T1-T2b, prostate-specific antigen (PSA) level < 20 ng/mL, and Gleason score (GS) 6-7 disease on biopsy treated with either radical prostatectomy (n=294) or permanent seed implantation (n=93) at the UT MD Anderson Cancer Center during 2000-2001. No patient in the radical prostatectomy or permanent seed implantation group received adjuvant external beam radiation therapy. We compared the 5-year biochemical recurrence-free survival between the upgraded and non-upgraded patients using the outside biopsy Gleason score, UT MD Anderson Cancer Center centrally reviewed Gleason score, and radical prostatectomy Gleason score using Kaplan-Meier estimates. The prostate cancer specific survival was compared between men who had full pathologic evaluation for upgrading (radical prostatectomy) versus those who only had a biopsy.

Results: The median follow-up time was 7.2 years for the radical prostatectomy group and 7.6 years for the permanent seed implantation group. There was no statistically significant difference in mean PSA level between men treated with radical prostatectomy (6.2 ng/mL) and permanent seed implantation (6.6 ng/mL), and the most common clinical stage was T1c for both groups. For patients presenting with outside pathologic review, upgrading from Gleason 6 to Gleason 7 occurred in 43 men treated with radical prostatectomy (14.6%) and 16 men treated with permanent seed implantation (17.2%). For men treated with radical prostatectomy, 132 men had subsequent upgrading from MD Anderson biopsy Gleason score to radical prostatectomy Gleason score (44.9%). In the radical prostatectomy group, the biochemical recurrence-free survival at 5 years was 93.2% in men with concordance between the outside Gleason score and MD Anderson central review Gleason score, and 95.3% for men with an upgrading from Gleason 6 to 7 (p=0.60). In the permanent seed implantation monotherapy group, the 5 year biochemical recurrence-free survival rate was 91.6% in men with concordant Gleason score, and 100% in men with upgrading from Gleason 6 to Gleason 7 (P=0.40).

Conclusions: In this retrospective cohort analysis with central pathology review at a tertiary cancer center, we found no differences in biochemical recurrence-free survival rates or prostate cancer specific survival for men who are upgraded versus not upgraded. We are currently evaluating these findings in a prospective cohort of permanent seed implantation monotherapy in men with intermediate risk localized disease.

INTRODUCTION

Burden of Suffering

Prostate cancer is the most common cancer diagnosis among men in the United States, comprising one quarter of all cancer cases in males. In 2009, an estimated 192,280 men were diagnosed with prostate cancer. Prostate cancer is the second leading cause of cancer death in men, following lung and bronchus cancer. An estimated 27,360 men died of prostate cancer in 2009.[1]

Prostate Cancer Screening and Diagnosis

Prostate cancer screening remains a contentious issue in the United States. The American Cancer Society's 2010 recommendations are for men to talk to their doctor about the pros and cons of testing starting at age 50. For men who are African American or who have a first-degree relative diagnosed with prostate cancer before age 65, the American Cancer Society recommends initiating a conversation about prostate cancer at age 45.[2] The United States Preventive Services Task Force (USPSTF) recommendations state are that there is insufficient evidence to assess the balance of benefits and harms for prostate cancer screening in men under 75 years of age (Grade I statement). For men over 75 years of age, the USPSTF recommends against prostate cancer screening (Grade D Statement).[3]

Prostate cancer screening is accomplished through the use of a blood test to detect PSA, with the accepted cutoff at 4.0 ng/mL. A digital rectal examination is performed to palpate any prostate abnormalities and assign a clinical stage to any prostate cancer present. Typical screening in the United State for prostate cancer relies upon both the

PSA test and the digital rectal examination, but the current trend in prostate cancer screening is to emphasize shared decision making before any screening is performed.[4]

In the PSA era, prostate cancer in most men is diagnosed as clinical T1c, meaning that there is no palpable disease on digital rectal examination. From 1999 to 2006, 80% of all newly diagnosed prostate cancer cases were classified as localized disease, meaning that disease was limited to the prostate with no lymphatic or distant involvement. The relative survival, looking at the population with localized disease compared to the general population without prostate cancer, was 100% over the seven years from 1999 to 2006.[5]

Prostate Cancer Risk Stratification

Men presenting with prostate cancer are classified into different risk groups to help determine an appropriate treatment strategy. The National Comprehensive Cancer Network (NCCN) publishes a widely-used set of guidelines for oncologists in the United States that lays out the steps to determine the management strategy for individual patients. Initially, the NCCN recommended that men who are asymptomatic with a life expectancy of less than five years undergo no further workup or treatment unless symptoms develop. The exception to this is men with high risk disease features, who can have a life expectancy of less than five years and are still recommended to pursue workup and treatment.[6]

For the rest of the men with a life expectancy of greater than five years, the NCCN recommends that the PSA, clinical stage, and Gleason score be evaluated to assign each patient to a risk group. The NCCN recognizes six risk categories: very low risk, low risk, intermediate risk, high risk, very high risk, and metastatic disease.[6] Very low risk is defined by the Epstein criteria as a clinical stage T1 (non-palpable disease),

Gleason score of six or less, PSA < 10 ng/mL, and fewer than three biopsy cores positive with less than 50% cancer in each core.[7] This new category of very low risk was created in the NCCN guidelines for 2010 to reflect their low risk of progression.

Low risk disease is defined as clinical stage T1c (non-palpable) to T2a (nodule palpated on less than 50% of one lobe of the prostate), Gleason score of no more than 6, and PSA < 10 ng/mL. Intermediate risk disease, as defined by the NCCN, is clinical stage T2b (involving one lobe of the prostate) to T2c (involving both lobes of the prostate) or Gleason score of seven or PSA 10 -20 ng/mL. High risk disease is clinical T3 (extraprostatic extension) or a Gleason score of 8-10 or a PSA > 20 ng/mL. Having any one of these features is sufficient to classify disease as high risk prostate cancer.[6]

Prostate Cancer Treatment Options: Very Low Risk and Low Risk Prostate Cancer

Men who meet the Epstein criteria for very low risk prostate cancer as defined above are encouraged to go on active surveillance. Active surveillance allows delay, or potentially avoidance, of treatment while monitoring the disease to ensure that no progression is occurring. It entails a PSA test as often as every 6 months and a DRE as often as every 12 months in the NCCN guidelines. The NCCN cites data from a European randomized trial of prostate screening to emphasize the problem of over-treatment related to the increased diagnosis of early-stage prostate cancer from PSA testing.[8] Active surveillance is the preferred mode of therapy for this patient subgroup as of 2010.[6]

Men who fall in the low risk group (clinical T1-T2a, PSA < 10 ng/mL, and Gleason score of 6 or less) have several treatment options. For men whose life expectancy is less than 10 years, the NCCN recommends that they enter active

surveillance. For those whose life expectancy is longer than 10 years, they can chose from active surveillance, external beam radiation therapy with 3D conformal radiation therapy or intensity-modulated radiation therapy (IMRT), brachytherapy with permanent seed implantation or with a combination high dose rate (HDR) approach, or radical prostatectomy with or without lymph node dissection.[6] This cutoff of a 10-year life expectancy arose from data looking at men with low-risk disease after 20 years of follow-up. By 20 years after diagnosis, less than 10% of patients had had a cancer-specific death. No standard metric exists for quantifying life expectancy.

The standard of care for external beam radiation therapy is a dose of at least 78 Gy as established by a randomized controlled trial of 70 Gy versus 78 Gy at UT MD Anderson Cancer Center.[9, 10] Image-guided radiation therapy is the standard of care for doses of 78 Gy or more to ensure that toxicity to the bladder and rectum is minimized based on appropriately targeted therapy. Patients with low risk prostate cancer should not receive adjuvant hormone therapy or treatment of the pelvic lymph nodes in conjunction with their external beam radiation therapy.

Prostate Cancer Treatment Options: Intermediate Risk Prostate Cancer

Men with intermediate risk prostate cancer face a different set of choices for their treatment. Treatment options listed by the NCCN for intermediate risk patients are again split by life expectancy: for patients with a life expectancy of less than 10 years, options include active surveillance, radical prostatectomy with a lymph node dissection if risk of lymph node metastases is >2%, or radiation therapy with 3D conformal radiation therapy or IMRT with or without androgen deprivation therapy and with or without brachytherapy.

For patients with a life expectancy of more than 10 years, options include radical prostatectomy with a lymph node dissection if risk of lymph node metastases is >2%, or radiation therapy with 3D conformal radiation therapy or IMRT with or without androgen deprivation therapy and with or without brachytherapy. Surgical guidelines for intermediate risk disease are clear and similar to the treatment guidelines for low risk prostate cancer patients. However, the radiation therapy guidelines for intermediate risk prostate cancer are less precise in that the addition or exclusion of brachytherapy and/or androgen deprivation therapy are options for those undergoing external beam radiation therapy.[6]

A randomized controlled trial demonstrated a benefit from the addition of six months of androgen deprivation therapy to external beam radiation to 70 Gy.[11] Unfortunately, 70 Gy was shown to be an inadequate dose in a separate randomized trial,[9, 10] so it is still uncertain whether the addition of androgen deprivation therapy will add any benefit to patients treated optimally with radiation therapy to at least 78 Gy with external beam radiation. That is, the trial in which androgen deprivation therapy was added to external beam radiation to 70 Gy showed that androgen deprivation therapy can make up for inadequate radiation, but the benefit is unclear and unproven in men treated with the standard of care radiation dose of 78 Gy.

Treating intermediate risk prostate cancer with one modality confers one set of potential side effects. When brachytherapy is added to external beam radiation, the risk of side effects goes up, since each treatment brings its own set of risks and side effects. The risk of local side effects from overdosing critical structures, such as the small bowel, bladder, and rectum, goes up when two modalities are combined.

While combining two radiation modalities can increase the risk of a local side effects, the use of androgen deprivation therapy for 6 months as an adjuvant therapy poses its own risks. Men who were enrolled in three separate clinical trials were combined into a meta-analysis to examine the impact of androgen deprivation therapy on cardiovascular health. Men who had 6 months of androgen deprivation therapy had an increased risk of dying from myocardial infarction compared with men who were treated with radiation therapy alone ($p=0.017$).[12] Further study revealed that men with moderate to severe co-morbidities were more likely to experience death from a cardiovascular event on androgen deprivation therapy than those with minimal or no co-morbidities.[13]

For men presenting with clinically localized prostate cancer, radical prostatectomy and permanent seed implantation have been previously reported to show equivalent biochemical recurrence-free survival outcomes with long-term follow-up.[14] In particular, men with low-risk prostate cancer have been shown to do as well with permanent seed implantation as they do with radical prostatectomy or external beam radiation therapy.[15, 16] Reports of biochemical recurrence-free survival are more mixed among men with intermediate-risk prostate cancer treated by permanent seed implantation. D'Amico and colleagues reported an inferior survival with permanent seed implantation in intermediate-risk men.[17] Other reports find that men with intermediate risk disease have equivalent outcomes when treated with permanent seed implantation or with other modalities.[18, 19]

No randomized data directly comparing radical prostatectomy to permanent seed implantation in terms of overall survival or biochemical recurrence-free survival are available for men with intermediate risk disease. The SPIRIT trial was initiated to

compare these two modalities in treating low and intermediate risk disease, but accrued slowly and has not produced mature data.[20] A survey of practice patterns among physicians treating intermediate risk prostate cancer with permanent seed implantation revealed that most are treating with implants alone in the absence of perineural invasion.[21]

The side effect profiles and quality of life differ between patients treated with permanent seed implantation or radical prostatectomy.[22] One potential advantage of surgery is the consequent ability to analyze the prostate specimen to determine pathologic features that may influence the use of adjuvant therapy. Bostwick and colleagues noted that the accuracy of biopsy Gleason grade compared to radical prostatectomy pathologic evaluation is decreased in low grade cancer or tumors with small volumes, which constitute a significant percentage of cases in the PSA era.[23] The rate of pathologic upgrading has been reported by single institutions, with the percentage varying up to 70%.[24]

Since patients treated with permanent seed implantation undergo the same biopsy procedure and staging as those who undergo radical prostatectomy, it follows that they may have a similar degree of pathologic upgrading were their prostates to be removed. Men treated with permanent seed implantation do not have their prostate removed, but perhaps the data obtained from radical prostatectomy specimens can be used as a surrogate. By looking at the outcomes of men based on both their biopsy grade and the radical prostatectomy grade, the impact of upgrading on outcome can be assessed.

Some have tried to predict which men will have disease that is upgraded at radical prostatectomy. Factors that are reported as associated with upgrading include number of

biopsy cores (men undergoing extended core biopsies much less likely to be upgraded). Also, treatment at low volume centers, long intervals between biopsy and radical prostatectomy, and increasing PSA levels are associated with increased probability of upgrading. Even with the best nomograms, there is a significant risk of occult higher grade disease in patients treated with radiation therapy.[26] A higher percentage of positive biopsy cores has also been shown to be associated with upgrading.[27] In a cohort study, D'Amico and colleagues found predictors of upgrading include low prostate volume (<75 cm3) and PSA >20.[28]

The purpose of this study was to examine the outcomes of men treated with permanent seed implantation versus radical prostatectomy at MD Anderson Cancer Center during 2000-2001. We also looked at the rate of pathological upgrading between outside biopsy and MD Anderson biopsy, and the final upgrading on radical prostatectomy specimen. Finally, we investigated the potential impact of upgrading on disease outcome. We wanted to answer the question of whether the extra information obtained from a radical prostatectomy specimen would put the radical prostatectomy patients at an advantage over the permanent seed implantation patients in terms of clinical outcome.

METHODS:

Patient Selection

From January 1, 2000 to December 31, 2001, 387 consecutive men with Gleason 6 - 7, PSA <20, and clinical stage T1 – T2b underwent radical prostatectomy or permanent seed implantation for adenocarcinoma of the prostate at MD Anderson Cancer

Center. Of this group, 294 men received radical prostatectomy and 93 men received permanent seed implantation. The choice of treatment was chosen made jointly by the patient and their clinicians. A protocol to retrospectively review these patient records was approved by the appropriate UT M.D. Anderson Cancer Center Institutional Review Board.

Staging

All of the men in the study underwent a history and physical, including clinical staging by a digital rectal examination. All patients underwent prostate biopsy at M.D. Anderson. Patients diagnosed at outside facilities provided available pathology slides from outside biopsies for comparison. Prior to any therapy, UT MD Anderson Cancer Center required pathologic confirmation of prostate cancer by a transrectal ultrasound guided prostate in all patients. Some men had more than one transrectal ultrasound guided prostate biopsy, either at an outside hospital or to guide treatment recommendations. Exclusion criteria for the study were PSA >20, biopsy Gleason score 8 – 10, and clinical stage T2c or above.

Treatment

Iodine-125 permanent seed implantation was performed under general anesthesia using ultrasound guidance for prostate localization and treatment planning. The prescribed dose to the planning treatment volume (PTV) for the BT patients was 145 Gy, and no patient in the permanent seed implantation group received external beam radiation therapy. Post-implant CT based dosimetry was performed at Day 0 and Day 30, with the plan evaluated at the genitourinary radiation oncology quality assurance meeting.

Surgical therapy consisted of a radical retropubic prostatectomy with bilateral pelvic lymph node dissection.

Follow-up

The median follow-up was 7.6 years for permanent seed implantation and 7.2 years for radical prostatectomy. Follow-up consisted of history and physical including DRE, as well as serum PSA measurement. Data was recorded on cause of death, biochemical recurrence, salvage treatment, and outcome.

Statistical Methods

We employed the product limit estimator of Kaplan and Meier to estimate the median and 5 year recurrence free survival. Considering radical prostatectomy and permanent seed implantation separately, the 5 year BRFS was estimated using Kaplan-Meier curves. We used the log rank test to test for the presence of a significant difference between the Kaplan Meier curves. We used SAS 9.1 for Windows (2003, SAS Institute, Cary NC) for all statistical analyses.

Systematic Review of the Literature

I performed a systematic review of the literature using multiple sources to ensure that the most up to date information was included in this manuscript. I did the majority of the literature review, with significant help and guidance from Lara Handler, a research librarian at the University of North Carolina, Chapel Hill Health Science Library.

The initial search terms on PUBMED were broad to determine the amount of literature available. A search of the terms, "prostate cancer", revealed 84, 909 sources on PUBMED. A search of the terms, "prostatic neoplasm", revealed 70, 993 sources on PUBMED, indicating that the search had to be narrowed substantially. Since prostate

cancer collected a broader representation of papers, this was used as an anchor MESH term for future searches.

I employed the MESH terms feature on PUBMED to narrow the literature to the low-risk and intermediate-risk prostate cancer patient population. Unfortunately, no such MESH terms existed. Further, prostate cancer was not broken down into local versus systemic disease or subgroups that allow for simple narrowing. This was confirmed in a search session with Lara Handler, the research librarian.

To isolate the population of men with prostate cancer treated with radical prostatectomy, I combined MESH terms prostate cancer AND prostatectomy, resulting in a reduction to 12, 830 papers. This was further limited by adding the term AND upgrading, leading to just 67 papers. By expanding the search to prostate cancer AND upgrading, 80 papers were found using the MESH terms approach.

I conducted a separate search on PUBMED for systematic reviews on prostate cancer. This yielded a valuable publication by Wilt et al in 2008 that utilized the Cochrane Library, Cochrane Review Group in Prostate Diseases and Urologic Malignancies, and Medline to pull out relevant papers on the effectiveness and harms of treating localized prostate cancer. This publication yielded 18 randomized controlled trials and 473 observational studies that were analyzed and included in the systematic review. The bibliography from this labor-intense publication was utilized in order to further gather papers for review in this project.

Given the limitation that MESH terms are not up to date with the current literature, and may take months to implement for a new publication, I reviewed the recent annals of Urology, New England Journal of Medicine, International Journal of Radiation

Oncology, Biology, and Physics for any recent publications of relevance to this topic. Table of contents were reviewed for 2009-2010 in order to pick up articles that may not yet have MESH terms available on PUBMED.

My thesis advisor, Dr. Steven Frank at UT MD Anderson Cancer Center, gave further literature recommendations and guidance. He suggested a number of papers that proved of value to include in the literature review. Importantly, he also assisted in excluding papers that were not highly relevant to this topic.

RESULTS:

Descriptive Statistics

Table 1 indicates the mean PSA was 6.2 for radical prostatectomy patients and 6.6 for permanent seed implantation patients. The median clinical stage was T1c for both groups. 61.6% of radical prostatectomy patients and 69.9% of permanent seed implantation patients were clinical stage T1c (non-palpable disease). 28.9% of radical prostatectomy patients and 26.9% of permanent seed implantation patients were clinical stage T2a (palpable disease in less than 50% of one lobe of the prostate). 7.8% of radical prostatectomy patients and 3.2% of permanent seed implantation patients were clinical stage T2b (palpable disease in greater than 50% of one lobe of the prostate).

Regarding Gleason score, 64.6% of radical prostatectomy patients and 88.2% of permanent seed implantation patients were Gleason 6 on UT MD Anderson Cancer Center biopsy interpretation. 35.4% of radical prostatectomy patients and 11.8% of permanent seed implantation patients were Gleason 7 on UT MD Anderson Cancer Center biopsy interpretation. There was a statistically significant difference in mean age

between radical prostatectomy patients (60.1 years) and permanent seed implantation patients (65.5 years) ($p<0.0001$).

The median follow-up was 7.2 years for radical prostatectomy and 7.6 years for permanent seed implantation. Patients treated with permanent seed implantation were 89.9% white, 3.2% African American, 3.2% Hispanic, and 4.3% Asian. Patients treated with radical prostatectomy were 81.6% white, 9.5% African American, 6.1% Hispanic, 1.7% Asian, and 1% other race or ethnicity.

Pathology Changes from outside institution to UT MD Anderson Cancer Center

For patients presenting with outside biopsy pathologic review, a UT MD Anderson Cancer Center pathologist read the slides obtained and prepared at an outside institution. Most of the patients did not have a change from their outside institution Gleason score to the UT MD Anderson pathologist Gleason scoring of the same slide, with 77.4% of permanent seed implant patients and 83.3% of radical prostatectomy having no change. Upgrading from the outside institution to UT MD Anderson Cancer Center occurred in 43 men treated with radical prostatectomy (14.6%) and 16 men treated with permanent seed implantation (17.2%). Downgrading of the slides occurred in 5.4% of permanent seed implant patients and 2.0% of radical prostatectomy patients. The proportion of men undergoing a pathology change was not different between permanent seed implantation patients and radical prostatectomy patients ($p=0.16$).

Pathology Changes from UT MD Anderson Cancer Center biopsy to radical prostatectomy

All men had UT MD Anderson Cancer Center biopsies, with biopsy slides interpreted at UT MD Anderson Cancer Center. For men treated definitively with

surgery, their radical prostatectomy slides were also assigned a Gleason score by a UT MD Anderson Cancer Center pathologist. The pathologist had all relevant biopsy information when evaluating the radical prostatectomy evaluation, with no blinding performed. Following radical prostatectomy, 132 men had subsequent upgrading from UT MD Anderson Cancer Center biopsy Gleason score to radical prostatectomy Gleason score (44.9%). 155 men (52.7%) had no change between their UT MD Anderson Cancer Center biopsy Gleason score and radical prostatectomy Gleason score. 7 men (2.4%) were downgraded from their UT MD Anderson Cancer Center biopsy Gleason score to their radical prostatectomy Gleason score.

Pathology Changes from outside institution biopsy to UT MD Anderson Cancer Center radical prostatectomy

For men with outside institution biopsy, their outside biopsy Gleason score was compared to their radical prostatectomy Gleason score. These were read by different pathologists, and reflect both the difference between institutions and the difference between a biopsy and a radical prostatectomy Gleason score. The UT MD Anderson Cancer Center radical prostatectomy Gleason score was higher than the outside biopsy in 159 men (54.1%). The Gleason score was the same in 127 men (43.2%). 8 men (2.7%) had a downgrading of their Gleason score from outside institution biopsy to UT MD Anderson Cancer Center radical prostatectomy Gleason score.

Biochemical Recurrence-Free Survival

The Kaplan-Meier estimates of BRFS are illustrated in Figures 1 and 2. In the radical prostatectomy group, the BRFS at 5 years was 93.2% in men with concordance between the outside GS and MDACC central review GS, and 95.3% for men with an

upgrading from Gleason 6 to 7. The log rank test between the curves is not statistically significant (p=0.603). In the permanent seed implantation monotherapy group, the 5-yr BRFS was 91.6% in men with concordant Gleason score, and 100% in men with upgrading from Gleason 6 to Gleason 7. The log rank test between the curves is not statistically significant (P=0.564).

Prostate Cancer Specific Survival

We also used prostate cancer specific survival as a clinical outcomes measure for men treated with permanent seed implantation or radical prostatectomy. There was one prostate cancer related death in the permanent seed implantation cohort and two prostate cancer related deaths in the radical prostatectomy cohort. Using permanent seed implantation as the baseline with a hazard ratio of 1.00, radical prostatectomy patients had a hazard ratio of death from prostate cancer of 1.01 which was not statistically significant [95% CI 0.08-13.33]. No difference was seen between men who underwent radical prostatectomy and had a full pathological examination of the prostate for upgrading versus men treated with permanent seed implantation who did not have a pathological examination of the prostate.

DISCUSSION:

This retrospective cohort study of men with low and intermediate risk prostate cancer treated at UT MD Anderson Cancer Center from 2000-2001 shows that there is a predominance of upgrading, rather than downgrading, from biopsy to radical prostatectomy. We found that nearly half of the men had an upgrade, even when read by the same pathologist. Statistical analysis using Kaplan Meier estimates and the log rank

test showed no differences in the biochemical recurrence-free survival between those who were upgraded versus those who were not upgraded. We found no difference in prostate cancer specific survival between the upgraded and non-upgraded men.

Our results are in concordance with numerous studies that cite a significant rate of pathological upgrading between biopsy Gleason score and radical prostatectomy Gleason score.[29] Earlier studies show an even higher rate of upgrading (>70%).[30] Karakiewicz found that upgrading in Gleason score from biopsy to radical prostatectomy is greater in centers with lower volume than tertiary centers.[31] Performing a repeat biopsy within three months has been shown to yield a statistically significant rate of upgrading on rebiopsy.[32]

This paper emphasizes the previously reported phenomenon of pathological upgrading that occurs among patients with a biopsy and radical prostatectomy at MDACC. In this case, the slides were read by the same dedicated prostate pathologist, eliminating inter-physician variability. This still does not address intra-physician variability, which would require blinding of the biopsy information and patient information from the pathologist. This is not practical or ethical in the scope of clinical practice, but could be incorporated into a future study design.

Using the same pathology processing lab and pathologist, 44.9% of men were upgraded from MDACC biopsy to MDACC radical prostatectomy. This information is not available for men treated primarily with permanent seed implantation or external beam therapy, but a significant rate of occult higher GS is likely present. There is no reason why men treated primarily with radiation therapy should have a lower rate of pathologic upgrading than is observed in the radical prostatectomy population.

This implies that a number of men who have low risk disease on biopsy actually have occult intermediate risk disease. Most of the men who had a pathologic upgrade went from low risk to intermediate risk disease, with a minority moving to high risk disease on radical prostatectomy. Importantly, we found that men with pathologic upgrading did no worse than their counterparts who were not upgraded.

Additionally, a number of men who had an outside biopsy GS available underwent an upgrading of those same slides when interpreted by an MDACC pathologist. This suggests the importance of a dedicated prostate pathologist with high volume to guide clinicians to the most appropriate treatment. More than half of the men were upgraded from outside biopsy GS to radical prostatectomy GS, indicating that some undergrading may be present. This is consistent with literature from other institutions. On the other hand, perhaps academic pathologists have a bias towards upgrading compared to community pathologists, since there appears to be no clinical difference between the upgraded and non –upgraded men in our cohort.

Men treated with permanent seed implantation, including those who are initially classified in the intermediate risk category, did not have worse outcomes than their counterparts treated with radical prostatectomy. The men who were upgraded by biopsy or radical prostatectomy did no worse than the cohort that was not upgraded, suggesting that the extra information obtained in radical prostatectomy may not be crucial for radiation therapy patients. While the data continues to mature, this suggests that selected men with intermediate risk prostate cancer may be appropriate candidates for monotherapy, including with permanent seed implantation.

Limitations of this Study

Several potential types of bias are faced when considering the results of this study, including selection bias, migration bias, measurement bias, and confounding.[33] Selection bias occurs at the level of the study population. In this case, the study population consisted of men who presented to UT MD Anderson Cancer Center for treatment of their prostate cancer. UT MD Anderson Cancer Center is a major referral center for the Houston area. Some of the men from Houston and the surrounding area may represent a cross-section of the local population, though there are other centers in Houston that treat prostate cancer. This population in the study would likely have reasonable external validity for men with prostate cancer around Houston.

However, many of the patients seen and treated at UT MD Anderson Cancer Center are self-selected patients from other parts of the country. They may have a higher socioeconomic status if they have the resources to take time off of work, fly to Houston, and live in a hotel for their consultation and treatment. Seeking a second opinion at a respected cancer center may be associated with a higher education level. It is difficult to tell what effect this migration to UT MD Anderson Cancer Center may have on our study population. From a source population level, this may limit the external validity of our study, to some extent.

Not all men have equal access to screening for prostate cancer in the United States. Men who present with localized disease in the PSA era of prostate cancer would be more likely to have a regular health care and a primary care provider. They would also be selected for those men that have health insurance, and those that undergo expensive local therapy for prostate cancer would be even more likely to have health insurance. Men who do not speak English as a first language may be underrepresented

among men who receive prostate cancer screening and treatment. Again, these represent potential bias that may be inherent in our source population for this study.

The type of treatment each man received was based on personal preference and physician preference. It was not randomized in this study. Therefore, imbalances between the two groups may be expected. This allows the possibility of introducing a systematic bias, such as men with worse disease choosing to have surgery, or men with urinary dysfunction prior to intervention choosing permanent seed implantation. Given the non-randomized design, it is impossible to completely control for what may be a systematic difference between the two arms.

The method of sampling men for this study was not likely to introduce bias. Our list of men treated with each modality was provided by the department of pathology at UT MD Anderson Cancer Center based on pre-designed inclusion criteria. Since the pathology department has a complete list of the prostate biopsies and radical prostatectomy specimens reviewed in 2000-2001, no selection bias should have occurred at this step in the source population identification. Men signed consent for potential participation in chart reviews when initially treated at UT MD Anderson Cancer Center and were not contacted for this study. Thus, we should have a complete representation of men with localized prostate cancer treated during this time period at UT MD Anderson Cancer Center.

As with any retrospective study, measurement bias can be a major source for the introduction of bias in generation and interpretation of results. We attempted to control measurement bias by choosing the same measures for each group, biochemical-

recurrence free survival and prostate cancer specific survival. These were measured at the same time point for each group and the same measure over time was maintained.

One point of introduction for measurement bias is what is chosen as a definition of failure for permanent seed implantation and radical prostatectomy. Due to inherent differences between the PSA responses following radical prostatectomy or permanent seed implantation, the NCCN recommends using differing definitions.[34] What definition is most appropriate has been a moving target in the literature of both specialties over the years. Papers continue to be published using different definitions of failure which can affect the timing and quantity of failures reported in both surgery and permanent seed implantation patients.

For permanent seed implantation, we debated using the American Society of Therapeutic Radiation Oncology (ASTRO) definition of failure versus the Phoenix definition of failure. The ASTRO definition stems from a 1997 consensus statement that defines biochemical failure as three consecutive rises of the PSA.[35] One disadvantage of the ASTRO definition is that biochemical failures are backdated, causing an early underestimation of recurrences and a late flattening of the curves. The ASTRO definition was developed based on external beam radiation patient data alone, and this may ignore the well-described phenomenon of the PSA bounce in patients treated with permanent seed implantation.

The Phoenix definition was developed in response to the concerns about the ASTRO definition by a consensus panel of radiation oncologists in 2006. The Phoenix definition of biochemical recurrence is the PSA nadir, or lowest point, plus 2 ng/mL.[36] The definition we chose for the permanent seed implantation patients is the Phoenix

definition, since it introduces less bias than the ASTRO definition. Additionally, this definition of PSA nadir plus 2 ng/mL has been shown to predict for overall survival in patients with prostate cancer.[37] The Phoenix definition has been applied to the permanent seed implantation patient population and was found to be the best surrogate for biochemical failure.[38]

For the patients treated with radical prostatectomy, the definition must be different since the prostate has been surgically removed. Following radical prostatectomy, there should be no source of PSA except prostate cancer cells. Freedland and colleagues examined cut points of 0.1 ng/mL to 0.5 ng/mL to determine the point associated with the highest risk of PSA progression within one year. They found that using a cutoff of up to 0.1 ng/mL in the postoperative setting was associated with a 36% of progression in one year and 67% risk of progression in three years. Increasing the cut point to 0.2 ng/mL led to a one and three year risk of progression of 86% and 100%, respectively. This was determined by the authors to be the most appropriate cut point since all of the patients they followed progressed within three years [39]

The question of what PSA cut point should be used was also addressed by Amling and colleagues, who found that a PSA cutoff of 0.4 ng/mL was better correlated with PSA progression in their cohort.[40] Given these differing findings, a multivariate regression analysis was done by Stephenson and colleagues on ten different definitions of PSA failure after radical prostatectomy, including 0.2 ng/mL and 0.4 ng/mL. They chose distant metastatic disease as the outcome of interest and looked at which PSA value best predicted distant metastatic disease. They found that a definition of biochemical recurrence as 0.4 ng/mL followed by another progression was the best surrogate for

predicting distant metastatic disease and suggested the use of 0.4 ng/mL as the most appropriate cutoff for PSA values. We chose to use 0.4 ng/mL as the value for defining biochemical failure in radical prostatectomy patients following surgery.

Once the definition of failure was set for each group, the clinical outcome measures were chosen for our cohort. Many measures are available, including biochemical recurrence-free survival, overall survival, prostate cancer specific survival, distant metastases-free survival, and time to recurrence. Biochemical recurrence-free survival is the outcome that offers the earliest glimpse at differences that may exist between different groups of prostate cancer patients.

While studies have correlated biochemical recurrence-free survival to distant metastases and overall survival, I thought adding another measure looking at clinical outcomes, rather than just biochemical outcomes, would provide more information. While overall survival is ultimately the outcome of greatest interest, it would be hard to see any differences in overall survival for this cohort with seven years of follow-up. Prostate cancer specific survival was chosen as the measure that would be a representation of the clinical outcome of these prostate cancer patients.

When applying clinical outcome measures to a group of patients, the issue of power must be considered. In this cohort, we had less than 400 men with a favorable category of prostate cancer, an indolent cancer in many cases. Our power to detect a difference between the upgraded and non-upgraded men is limited by all of these factors. A larger patient number would allow us to increase our confidence level in the findings. Longer follow-up in prostate cancer studies is always helpful, since some men may not have a biochemical recurrence, or a prostate cancer related death, for many years.

Future Directions

While this hypothesis-generating study has raised the interesting question of whether additional pathology information in the form of pathological upgrading affects outcome, further studies are needed to clarify the issue of what treatments are appropriate for what patients. Ideally, a randomized controlled trial would be designed comparing all of the treatment modalities directly to one another. Randomizing patients to possibly get a surgery or a radiation treatment is not easy, since some patients may have already made up their mind that they do not want surgery or radiation in any case. However, many men would likely be amenable were it to be presented in the right light by their physician. In these favorable risk men, much data exists to suggest that they will do very well in terms of biochemical recurrence-free survival and prostate cancer specific survival, with any of the selected modalities.

The failure of large randomized cooperative group studies to accrue may partially lie with the physicians. In this case, if a patient sees a urologist and is randomized to radiation, the urologist will not participate in the care of this patient anymore. The inverse is also true for a radiation oncologist whose patient is randomized to surgery. This makes the engagement of specialists in a trial that may deprive them of patients somewhat harder to accomplish. That said, a large academic center like UT MD Anderson Cancer Center where the patients are seen in a multidisciplinary clinic should be able to accomplish such a randomization.

Outcomes for a clinical trial include many of those discussed for this study, such as overall survival, prostate cancer specific survival, time to recurrence, biochemical recurrence-free survival, and salvage therapy-free survival. The best measure would

likely be overall survival, though the time to reach a potential difference in this group would likely be at least ten years. All patients would have to be cleared for surgery, since they might be randomized to surgery. Unfortunately, this would exclude some of the patients who tend to get external beam radiation therapy, which is often used in patients who may not be able to tolerate anesthesia or a surgical procedure.

Secondary outcomes in a randomized trial of intermediate risk patients could include biochemical recurrence-free survival and measures of quality of life to quantify side effects of each procedure. Salvage therapy-free survival could also be examined to determine if one treatment in associated with the need for additional therapies. The idea that this would compound side effects and potentially diminish quality of life could be looked at using these outcome measures.

Ultimately, the detection of biomarkers that are prognostic of future disease behavior would prove the most helpful. As suggested by this and other studies, the incorporation of clinical factors in a nomogram does not necessarily correlate to the an individual patient's outcome. Prognostic factors could help us decide who to enroll on active surveillance protocols, avoiding side effects like urinary incontinence and erectile dysfunction for some time, or potentially forever if treatment is never used.

For patients whose prognostic markers indicate the disease is more aggressive, predictive biomarkers could be used to guide treatment. Perhaps a protein will be found that is associated with relative radioresistance, and these patients can be guided towards surgery. As we gain more information about cardiac markers that may be prognostic for cardiovascular disease, the balance of risk versus benefit of using androgen deprivation therapy can also be improved.

Ideally, we can obtain tissue through a prostate biopsy that will lead us to predict whether treatment may be needed at all, and what treatments may prove most beneficial, or detrimental to an individual patient. Until that time, continued studies that attempt to maximize the utility of our current pathological information will be necessary to offer the least treatment for the best outcome in an individual patient.

Table 1. Descriptive statistics for the cohort

	Radical Prostatectomy (n=294)	Permanent seed implantation (n=93)
Mean Age	**60.1**	**65**
Mean PSA	**6.2**	**6.6**
Clinical Stage: T1c	**181 (61.6%)**	**65 (69.9%)**
Clinical Stage: T2a	**85 (28.9%)**	**25 (26.9%)**
Biopsy Upgrading	**43 (14.6%)**	**16 (17.2%)**
Radical Prostatectomy Upgrading	**132 (44.9%)**	**N/A**
Median Follow-up	**7.2 years**	**7.6 years**

Figure 1. Kaplan-Meier Estimate of Biochemical Recurrence Free Survival for men treated with permanent seed implantation.

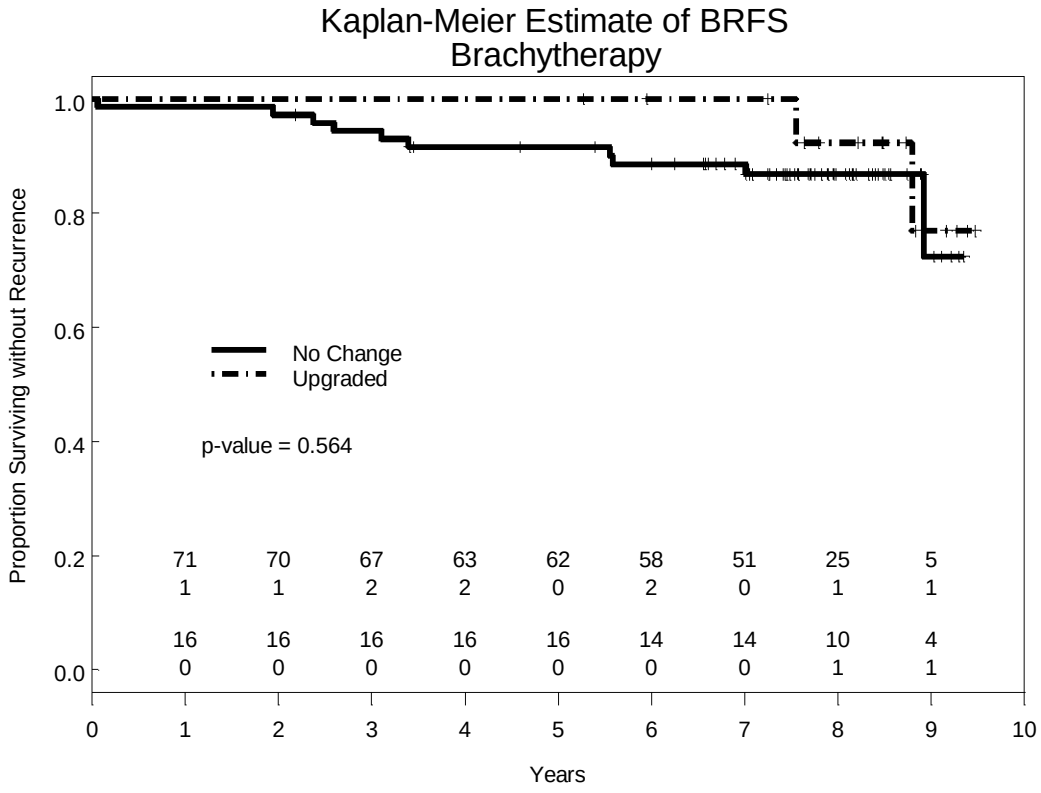
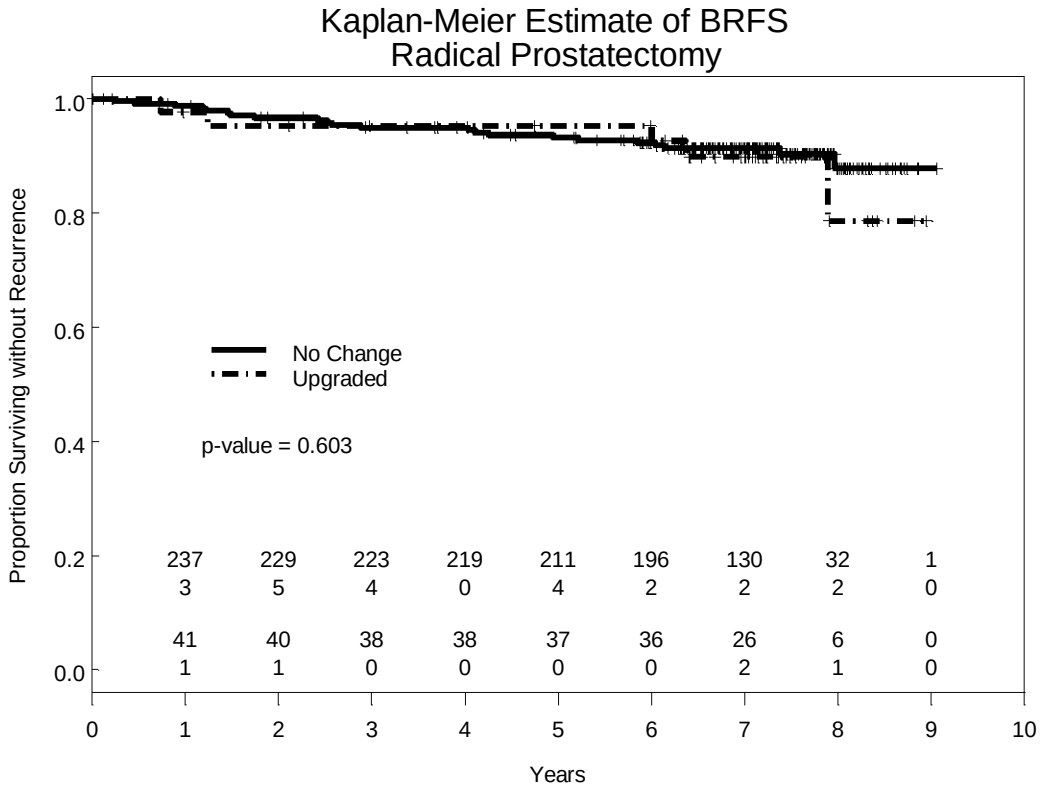


Figure 2. Kaplan-Meier Estimate of Biochemical Recurrence Free Survival for men treated with radical prostatectomy.



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