Health-related Quality of Life After Primary Treatment for Localized Prostate Cancer: A Systematic Review of the Literature

By

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ABSTRACT

Background
Prostate cancer is the most commonly diagnosed non-cutaneous cancer in American men. In 2007, approximately 218,890 men were diagnosed with and 27,050 men died from prostate cancer. With the advent of PSA screening, younger men are being diagnosed with prostate cancer at the earliest stages of disease. Over 90% of cancers are detected at the localized or regional stage, and early detection allows for a number of treatment options. Currently, there is no consensus on the best treatment for localized prostate cancer, but the most commonly utilized options are prostatectomy, radiation therapy and active surveillance. Without evidence from randomized controlled trials on the mortality benefits of these treatments, health-related quality of life (HRQOL) is becoming an increasingly important factor in treatment decision-making. The purpose of this paper is to systematically review the evidence regarding HRQOL after primary treatment for localized prostate cancer.

Methods
Inclusion criteria were English language articles published between 1995 and 2007. The studies must have focused on primary treatment of localized prostate cancer. Any study that addressed metastatic cancer or secondary treatment was excluded. Studies must use the SF-36 questionnaire for measuring general HRQOL. All study types were included in the review. The literature search was conducted using the PubMed MeSH terms “Prostatic Neoplasms/therapy” [MeSH] and keywords “localized or "early stage" AND (SF-36 OR short form 36).” An abstract review was then performed, followed by a full article review. At the end of the selection process, 14 articles met all the inclusion criteria and were considered in this review.

Results
The 14 studies varied widely in their study designs. The reporting of HRQOL within each study differed between studies, with some reporting only component scores, while others report each of the eight domains of the SF-36. Considering these differences, the review showed that there were some unique trends for recovery of HRQOL by treatment type. For those men undergoing prostatectomy, early decreases in specific domains of HRQOL (bodily pain, role physical, and role emotional) were seen at 3 to 6 months. These deficits usually returned to the patients’ baseline by 12 months after treatment. For men choosing radiation, fewer decreases were seen in the immediate post-treatment period. Long term decreases in role physical and role emotional were seen in those studies with follow-up periods longer than 1 to 2 years. The data regarding active surveillance was relatively sparse, with only three studies evaluating HRQOL for those men choosing active surveillance. There was some evidence for decreases in physical function, general health and role emotional.

Conclusions
Without convincing randomized controlled evidence showing a mortality benefit for any of the primary treatment options, HRQOL serves as a useful outcome for treatment decision-making. More studies, including upcoming randomized controlled trials, should include robust measures of HRQOL as primary outcomes in their study designs.
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INTRODUCTION

Epidemiology

Prostate cancer is the most commonly diagnosed non-cutaneous cancer in American men. In 2007, approximately 218,890 men were diagnosed with and 27,050 men died from prostate cancer. With the advent of prostate-specific antigen (PSA) testing in the 1980’s, the incidence of prostate cancer increased steadily over the years 1975-1988, with a subsequent decrease in incidence from 1992-1995.\textsuperscript{1} PSA testing has allowed for the early detection of cancers that are not yet clinically evident by digital rectal exam (DRE). Younger men are also being diagnosed with prostate cancer due to PSA screening. Localized prostate cancer is defined as cancer that has not extended beyond the capsule of the prostate. Over 90\% of cancers are detected at the localized or regional stage, indicating that the vast majority of cancers are found at a highly treatable stage.\textsuperscript{1} The 5-year survival rate for localized/regional prostate cancer is 100\%, but this rate drops to 31.9\% for distant prostate cancer.\textsuperscript{1}

Racial disparities

It is important to note that both the incidence and mortality rates of prostate cancer differ markedly by racial group. African-American men have the highest prostate cancer incidence and mortality rates of any subpopulation in the world.\textsuperscript{2} The prostate cancer incidence rates are 161.4/100,000 and 255.5/100,000 for whites and African-Americans, respectively.\textsuperscript{1} (See Table 1.) There is also a large disparity in mortality rates, with African-Americans over two times as likely to die from their cancer as whites. Overall 5-year survival rates for all races is 98.9\%, while in African-Americans this rate drops to 94.9\%.\textsuperscript{1}

Part of the explanation for the difference in mortality and survival rates between races is that African-Americans are more likely to first be diagnosed with higher PSA levels, higher
grade lesions, and at a higher clinical stage. 10% of prostate cancers detected in black men were classified as distant compared with 6% distant cancers in white males. Even when rates are adjusted by stage at diagnosis, African-Americans still experience a higher rate of mortality compared with whites. The cause of these differences is unknown at this time, but has been hypothesized to be associated with access to care, socioeconomic status, type of treatment, dietary differences, biological differences in the tumors, or patient-physician behaviors.

Table 1: Racial differences in cancer statistics

<table>
<thead>
<tr>
<th>Measure</th>
<th>African-Americans</th>
<th>Caucasians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>255.5 / 100,000 men</td>
<td>161.4 / 100,000 men</td>
</tr>
<tr>
<td>Prevalence</td>
<td>236,425</td>
<td>1,726,588</td>
</tr>
<tr>
<td>Mortality</td>
<td>62.3 / 100,000 men</td>
<td>25.6 / 100,000 men</td>
</tr>
<tr>
<td>Probability of Developing Cancer*</td>
<td>1.362%</td>
<td>0.700%</td>
</tr>
<tr>
<td>Probability of Dying of Cancer*</td>
<td>0.052%</td>
<td>0.015%</td>
</tr>
<tr>
<td>10-year survival, localized</td>
<td>89.7%</td>
<td>96.1%</td>
</tr>
</tbody>
</table>

*Developing or dying of cancer between the ages of 50-55

Another important difference between African-Americans and whites is choice of primary treatment. Blacks are less likely to choose definitive (or curative therapy), such as radical prostatectomy or radiation therapy, and also have lower rates of prostatectomy if they do choose to undergo definitive therapy. As a result, black men are more likely to receive conservative treatment, such as active surveillance. The rate of radical prostatectomy has been increasing for some ethnic groups, such as Hispanics, but the rate for African-Americans has not changed. While treatment choice does not explain the entirety of the outcomes disparity, it provides an interesting insight into differences in access and utilization of care, which may be systematic or culturally-based. In addition to understanding treatment outcomes, it is also important to understand the motivation for differences in treatment decision-making. The primary treatments have different side effect profiles that may contribute to these differences.
**Treatment Options**

Localized prostate cancer is defined as cancer that has not extended beyond the prostate gland. This early stage of cancer is a highly curable disease. Clinical staging is generally reported using the American Joint Committee on Cancer (AJCC) system, which groups cancers into Stage I – IV based on the Tumor, Node, and Metastasis (TNM) classification. Stage information is a key determinant of treatment options, with Stage I or II disease being the most curable, employing primary treatment modalities like surgery or radiation. The aggressiveness of prostate cancer is measured using a pathological grading system, known as the Gleason score. This score is calculated by adding the most dominant histological pattern seen to the second most dominant pattern. These scores can range from 2 – 10, with anything greater than 7 being considered high-grade or poorly differentiated. These cancers are more likely to behave in an aggressive manner and spread to surrounding lymph nodes and bones.

The most common treatment options for localized cancer are radical prostatectomy, radiotherapy and active surveillance (also referred to as watchful waiting or expectant management.) Radical prostatectomy (RP) involves the surgical removal of the prostate gland. One of the advantages to prostatectomy is that prostate and lymph node specimens can be examined by a pathologist to determine whether cancer-free margins have been achieved. Radical prostatectomy tends to be reserved for younger men who have less comorbidity and are therefore better surgical candidates. This trend is changing, however, and older men are choosing prostatectomy at an increasing rate.7

Radiotherapy can take two forms: brachytherapy (BT), which is the implantation of small seeds of radioactive material directly into the prostate, or external beam radiation (EBRT), which involves direct irradiation of the prostate gland from outside of the body. A combination of these
two modalities is also sometimes used. Radiotherapy is an option for men of any age, but is commonly used in men who are not healthy enough to undergo prostatectomy.

Active surveillance is a form of conservative therapy in which the cancer patient is monitored with regular PSA testing, DRE and prostate biopsy for evidence of disease progression. In the event of disease progression, curative therapy may be initiated at that time. This form of conservative management is often chosen when men are poor candidates for surgery or radiation, based on age or comorbidities, or are not willing to risk the side effects of more aggressive treatment. Active surveillance is an option for men with low grade disease, shorter life expectancy or preference for conservative management. While some of the treatment-related effects are avoided with active surveillance, progression of disease can still cause urinary and sexual symptoms.

A less common form of treatment is cryotherapy, which is the use of thin needles to infuse argon gas or liquid nitrogen into the prostate, thus destroying the tissue. Androgen deprivation therapy is more commonly used for advanced disease, but is also an option alone or in combination with one of the other primary treatments.

Clinical guidelines

A search of the National Guidelines Clearinghouse for “localized prostate cancer” gives 10 results, none of which are recommendations for primary treatment. Browsing the results in the 14 guidelines under the heading “prostate cancer,” most of them focus on prevention, locally advanced or metastatic cancer and adjuvant therapies, but there are no primary treatment guidelines.

The most current recommendation from the American Urological Association (AUA) is now 12 years old and is limited to an assessment of patient characteristics and discussion of the
benefits and harms of each treatment. In the absence of randomized controlled trials, which constitutes Level 1 evidence, the recommendations for prostate cancer treatment remain vague and based on discussions between the physician and patient. Prior to making a decision regarding treatment, the AUA standard involves an assessment of patient characteristics, tumor characteristics, and overall health status. The patient should then be informed of their treatment options, including radical prostatectomy, radiation, or surveillance, along with a discussion of the benefits and harms of each treatment. The AUA also states that the patient’s preference should be considered when deciding on treatment.

The AUA guidelines then go on to discuss the three treatments separately, indicating which patients are most likely to benefit from each treatment. Radical prostatectomy is recommended for patients with a “relatively long life expectancy,” no contraindications for surgery and a preference for surgery. Radiation is recommended for patients with a relatively long life expectancy, no risk factors for radiation toxicity and a preference for this treatment. Watchful waiting is recommended for men with a shorter life expectancy and/or a low-grade tumor. While these recommendations are helpful in discussing treatment with a patient, they still leave a great deal of uncertainty regarding what is considered a “relatively long life expectancy” and the relative importance of life expectancy versus patient preference versus risk of harms.

The European Association of Urology (EAU) issued guidelines on treatment of prostate cancer in 2001, which were regularly updated through the year 2005. These guidelines present similar options for treatment of localized cancer as those suggested by the AUA, including watchful waiting, radical prostatectomy or radiation. For localized regional cancer, the EAU has made a Grade A recommendation for radical prostatectomy for healthy men with a life expectancy greater than 10 years. They do issue a caveat that men must “accept treatment related
complications.” The guidelines go on to state that it is not possible to state that one therapy is superior to another because of the lack of randomized controlled trials addressing this question.

The National Comprehensive Cancer Network (NCCN) has developed a more extensive algorithm for treatment decisions, recommending expectant management, radiation or surgery for men with life expectancy greater than 10 years. This approach is not unlike the AUA and EAU recommendations, focusing on overall life expectancy as the most important factor for recommending surgery versus radiation or active surveillance. It also makes distinctions based on stage and Gleason score, suggesting radical prostatectomy as a choice for men with stage T2b-2c or Gleason score >7, independent of life expectancy.

In fact, the AUA recommends further research into not only the effectiveness of the various prostate cancer treatments, but also how those treatments affect patients’ quality of life. Without high-quality evidence of survival advantage of one treatment modality, HRQOL becomes an increasingly important factor in treatment decision making. Early studies by Litwin et al showed that general health related quality of life did not differ according to treatment type. However, this study was a retrospective cross-sectional design, and only measured HRQOL once after about 5 years of follow-up. This study may not have captured the many changes that occur in the first months or year after treatment. Since that time, investigators have continued to look at both general and disease-specific quality of life as an important health outcome.

**Past and Ongoing Research on Primary Treatment Efficacy**

With the increasing early detection of localized disease, more men are increasingly faced with the decision of how to manage their cancer among several options. At this time, the only Level 1 evidence from a randomized controlled trial comparing survival after surgery or active surveillance shows a modest mortality benefit for men undergoing surgery. Bill-Axelson and
colleagues randomized 695 men to either radical prostatectomy or watchful waiting. After a median 8.2 years of follow-up, they reported a significant reduction in both overall and disease-specific mortality for radical prostatectomy. These mortality differences were small, but there was a large decrease in risk of progression to advanced or metastatic disease. Decreasing the risk of progression may be as important as survival, due to the considerable burden of suffering caused by advanced disease and the costs of caring for those patients.

Another American randomized trial comparing prostatectomy and active surveillance is currently underway, the Prostate Cancer Intervention Versus Observation Trial, (PIVOT). This trial aims to randomize over 1000 men to prostatectomy or active surveillance and the primary outcome is overall mortality. It will also report on disease-specific and treatment-specific morbidity and mortality, important outcomes that have not been previously investigated. At this time, over 400 men have been enrolled in the trial. Results are not expected until at least 2010.

There are no randomized trials comparing prostatectomy with radiotherapy, or radiotherapy with active surveillance. Most studies are observational in nature, with very few gathering prospective, longitudinal data, subjecting these studies to significant recall bias. Observational studies are often confounded by the differences in clinical indications for prostatectomy versus radiotherapy, and the initial groups are significantly different in terms of age, comorbid status and tumor characteristics. As such, it is difficult to draw conclusions from this body of evidence.

Health-related Quality of Life

Although there is no universally accepted definition of health-related quality of life (HRQOL), one attempt to define it is “patients' appraisal of their current level of functioning and satisfaction with it compared to what they perceive to be ideal.” The term encompasses a
patient’s physical, psychological and social functioning and well-being. In the past, prostate cancer treatment success was generally based on measures of overall and disease-specific survival rates and PSA recurrence, but HRQOL has become increasingly important as an outcome in the study of cancer treatment.

For prostate cancer, with an already high survival rate that continues to increase with earlier detection and better treatment, there has been greater focus on HRQOL as a more pertinent measure of treatment outcomes. This is particularly important given that more men are being diagnosed with localized disease and undergoing curative therapy. It is unknown at this time whether or not there is any increased mortality benefit for a particular treatment modality. Once curative treatment is undertaken, these men are likely to live for many years, making HRQOL an important measure. Additionally, the side effects of primary treatment are severe enough that even in the case of a complete cure of the disease men are faced with serious harms over time, including incontinence and impotence. These symptoms can be measured by disease specific QOL instruments, but they also appear to interact with and influence general HRQOL as measured by the SF-36. As such, HRQOL becomes a critical marker of the success of treatment encompassing the patient’s perception of their overall physical and mental well-being. It is also important for guiding the discussion regarding the expected outcomes of the various treatment with patients in the decision making process.

The development of validated survey instruments has been critical to the expansion of this area of study, as HRQOL was previously ascertained by physician’s subjective assessment. After the advent of the Medical Outcomes Survey Short Form 36 (SF-36), Litwin et al used the survey to compare urologists’ assessment of patients’ HRQOL with their own self-report. He found that physician assessment of HRQOL was not highly correlated with self reported SF-36
scores and in all cases physicians underestimated the patients' symptoms. With objective measures of HRQOL, physicians can now give their patients a relatively accurate depiction of the likely functional outcomes of their treatment. Litwin was also involved in the development of the prostate cancer-specific instrument known as the UCLA Prostate Cancer Index (PCI).

The HRQOL outcomes after treatment for prostate cancer vary by treatment type and often change for years after the initial treatment. Radical prostatectomy is associated predominantly with urinary and sexual side effects, while radiation is associated with bowel and sexual side effects. In terms of HRQOL, as measured by the SF-36, many studies have shown long-term variation in the different realms of well-being by treatment type and time after treatment. For example, most of the negative physical side effects of prostatectomy are realized within 6 months of surgery, while side effects continue to develop for up to 3-6 years after radiation. There is also a difference in the time to recovery of some realms of the HRQOL, meaning that men can expect to reach their maximal functioning earlier in some domains than others.

HRQOL can be discussed in terms of general QOL or disease-specific domains of QOL. There are many validated questionnaires that measure both types of QOL. The most commonly used instruments for studying prostate cancer outcomes are the SF-36 for general HRQOL and the PCI for disease-specific QOL. Both of these survey instruments have been validated internationally and are available in numerous foreign languages.

General well-being is commonly measured after primary treatment using the SF-36, which consists of 36 multiple choice questions addressing 8 realms of well-being:

1. limitations in physical activities because of health problems
2. limitations in social activities because of physical or emotional problems
(3) limitations in usual role activities because of physical health problems
(4) bodily pain
(5) general mental health (psychological distress and well-being)
(6) limitations in usual role activities because of emotional problems
(7) vitality (energy and fatigue)
(8) general health perceptions

The SF-36 is scored on a 100 point scale, with 100 being the highest HRQOL and 0 being the lowest. The SF-36 can also be used to generate two component scores, one of physical functioning and one of mental functioning. Clinically significant differences in these scales are 5-10 points for the individual scales and 3 points for the component scores. 

Disease specific QOL is also commonly measured after primary therapy. A number of instruments have been developed that are specific for prostate cancer, including the PCI and the International Prostate Symptom Score (IPSS). These instruments focus on symptoms that are specific to prostate cancer, such as urinary, bowel and sexual function. The use of disease specific measures, derived from PCI or IPSS, is useful for explaining the course of side effects after treatment, as different treatments tend to have varying time courses for resolution (or decline) of each of these domains. This knowledge would be important for many men, in order to prepare them for the changes that are likely to occur over time and what they can expect 6 months or 1 year after surgery. It is important to note that different men will value these domains of side effects in varying manners. For example, sexual dysfunction might be intolerable for one person, and unimportant for another.

Not surprisingly, disease specific symptoms often overlap with overall HRQOL. It is not difficult to imagine that urinary incontinence and the necessity of wearing a pad would affect
one’s overall well-being. Bacon et al examined the association of prostate cancer treatment side effects, such as urinary and bowel dysfunction, with specific domains of the SF-36 HRQOL.\textsuperscript{19} They found a strong inverse association between bowel function and HRQOL, with men reporting bowel dysfunction having lower HRQOL. A significant, but less powerful, correlation was seen with urinary and sexual function. These results are particularly important because surgery has been shown to have a greater negative impact on urinary and sexual function, while radiation is more likely to cause bowel dysfunction.\textsuperscript{19}

Eton et al also analyzed correlations between prostate-specific QOL and general HRQOL.\textsuperscript{23} They found that better urinary function, sexual function and bowel function were associated with better general physical functioning. These prostate-specific measures were also correlated with better general mental functioning. With more data on these correlations, one could potentially make some general predictions about HRQOL based on treatment type. It appears that these three prostate-specific symptoms are very influential on general HRQOL and alerting men to the differences in side effect profiles of the treatments might be helpful in decision-making.

In a time when mortality data is very limited to guide clinical practice, HRQOL must be a significant component of the discussion about treatment of localized cancer. Shared decision making is becoming increasingly important for these choices, and data on both disease-specific and general QOL can inform that discussion. Capturing the long-term experiences of men who have undergone treatment will contribute greatly to this effort. Prospective trials that use HRQOL as a primary outcome are needed, and future randomized trials should also include these measures as part of the study.
Goals of Review

The purpose of this paper is to systematically review the evidence regarding health related quality of life after primary treatment for localized prostate cancer. The goal is not to determine which treatment is “best,” rather, it is to accurately describe the most likely HRQOL outcomes following each treatment type. This will allow patients and clinicians alike to make better-informed decisions about treatment, with an understanding of the most common changes in general HRQOL as measured by the SF-36 over time. Until clear and consistent evidence of mortality benefit is produced, differences in quality of life following treatment will be most useful for men deciding what treatment to choose for localized treatment. Highlighting any racial differences in treatment outcomes in HRQOL will also be an important contribution of this review.

METHODS

This systematic review was initiated to inform an analysis of secondary observational data on men newly diagnosed with prostate cancer, including their health related quality of life, as measured by the SF-36 questionnaire. Disease specific quality of life has been considered in numerous studies and this review focuses on the SF-36 measure of general health related quality of life as a proxy for a more subjective, patient-centered measure of overall health. It will also focus on any evidence addressing racial disparities in quality of life outcomes.

Key questions

The following questions were specifically addressed in this review:

1. How is the type of primary treatment for localized prostate cancer related to health related quality of life, as measured by the SF-36?
2. Does general health related quality of life differ between racial groups undergoing similar treatment?

**Inclusion and Exclusion Criteria**

Inclusion criteria were English language articles published between 1995 and 2007. The studies must have focused on primary treatment of localized prostate cancer. Any study that addressed metastatic cancer or secondary treatment was excluded. Only studies that measured health related quality of life by the SF-36 questionnaire were sought, as this is the instrument that will be used in a subsequent secondary data analysis. Only studies that focused on the following treatment types were included: radical prostatectomy, radiotherapy (brachytherapy or external beam radiation, but not a combination of both), and active surveillance. Because of the observational nature of this question and lack of randomized controlled trials, we did not limit the search by study type and observational studies were included. Studies that focused on the development or validation of measurement tools were not included in the review. The inclusion and exclusion criteria are summarized in Table 2.
Table 2: Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>English Language</td>
</tr>
<tr>
<td>1995-2007</td>
</tr>
<tr>
<td>SF-36 measurement</td>
</tr>
<tr>
<td>Localized prostate cancer</td>
</tr>
<tr>
<td>Primary treatment</td>
</tr>
<tr>
<td>Radical Prostatectomy</td>
</tr>
<tr>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Brachytherapy</td>
</tr>
<tr>
<td>External Beam Radiation</td>
</tr>
<tr>
<td>Watchful Waiting/Active Surveillance</td>
</tr>
<tr>
<td>All study types</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
</tr>
<tr>
<td>Cryosurgery</td>
</tr>
<tr>
<td>Treatment subtype</td>
</tr>
<tr>
<td>Advanced/metastatic prostate cancer</td>
</tr>
</tbody>
</table>

Literature Search and Retrieval Process

Databases and Search Terms: PubMed was searched using a combination of MeSH terms “Prostatic Neoplasms/therapy”[MeSH] and keywords “localized or "early stage" AND (SF-36 OR short form 36).” PsychInfo was searched using a similar strategy, using “localized prostate cancer” and “quality of life.” Web of Science was then used to conduct a citation analysis using one of the most frequently cited articles on the topic (Litwin 1995).

Article Selection and Review: One person was responsible for the review of articles based on the above inclusion and exclusion criteria by reviewing abstracts. A total of 27 articles were retrieved using the initial search strategy referenced above. Of those 27 articles, 14 were deemed to meet all of the inclusion criteria. Reasons for exclusion included not being published in English, methods papers, secondary treatment, and intervention trials. Figure 1 outlines the process of article selection and exclusion.
Figure 1: Selection of studies

MEDLINE search, Web of Science, PsychInfo (n = 27)

1 article not published in English (n = 1)

Full abstract review (n = 26)

Studies excluded after abstract review (n = 12)
1 - intervention to improve QOL
1 - advanced prostate cancer
2 - no focus on treatment type
2 - secondary treatment
3 - treatment subtypes
3 - methods

Studies included in systematic review (n = 14)

Evaluation of Quality and Strength of Evidence

Using the Centre for Reviews and Dissemination (CRD) monograph’s quality criteria for observational studies, the studies were ranked from highest to lowest quality. Prospective cohort studies were considered the strongest, followed by retrospective cohorts and cross-sectional studies. The CRD report provides a checklist for quality criteria for assessment of observational studies. We used this checklist to determine the overall quality of each study, assigning the following grades to each study:

A - Prospective cohort study that meets the majority of items on the checklist
B – Prospective cohort study that meets less than the majority of items on the checklist
- Retrospective cohort study that meets the majority of items on the checklist
- Case-control study that meets the majority of items on the checklist

C – Retrospective cohort study that meets less than the majority of items on the checklist
- Case-control study that meets less than the majority of items on the checklist
- Cross-sectional study

Details of Excluded Studies

The initial literature search resulted in 27 studies to be considered for the review. A preliminary review of titles found one study that was published in German,\textsuperscript{25} which did not meet the eligibility requirement of publication in English. From there, I performed a full abstract review of the remaining 26 articles. Of these articles, 12 were deemed not to meet eligibility requirements for various reasons. One study was a randomized controlled trial investigating an educational intervention to improve HRQOL following treatment for prostate cancer.\textsuperscript{26} This study was excluded because the HRQOL data would potentially be altered by the intervention, and therefore not be representative of the general experience of men following treatment. There was one study excluded because it did not focus on a specific treatment type, instead focusing on the experience of “regret” following treatment decisions.\textsuperscript{27} Another study did not focus on treatment type, but rather the HRQOL outcomes of men with and without erectile dysfunction.\textsuperscript{28}

A study of HRQOL after treatment for metastatic cancer was excluded based on the previously stated exclusion criteria.\textsuperscript{29} Five articles were excluded because they focused on either secondary treatment or a combination of treatments, such as brachytherapy plus external beam radiation.\textsuperscript{30-34} Three of the excluded articles were methodological papers concerned with the development and validation of HRQOL instruments.\textsuperscript{35-37}
<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>Treatment*</th>
<th>Sample size</th>
<th>Population</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namiki</td>
<td>Prospective longitudinal cohort</td>
<td>BT</td>
<td>n = 70</td>
<td>Japanese</td>
<td>Pre-treatment, 1, 3, 6, 12 months post-treatment</td>
</tr>
<tr>
<td>Arredondo</td>
<td>Retrospective observational</td>
<td>RP</td>
<td>N = 856</td>
<td>American</td>
<td>Pre-treatment, 1 and 2 years post-treatment</td>
</tr>
<tr>
<td>Ficarra</td>
<td>Prospective longitudinal cohort</td>
<td>RP</td>
<td>N = 75</td>
<td>Italian</td>
<td>Pre-treatment, 3, 6, 12 months post-treatment</td>
</tr>
<tr>
<td>Dalkin</td>
<td>Prospective longitudinal cohort</td>
<td>RP</td>
<td>N = 105</td>
<td>American</td>
<td>Pre-treatment, 1 and 2 year post-treatment</td>
</tr>
<tr>
<td>Namiki</td>
<td>Prospective longitudinal cohort</td>
<td>RP</td>
<td>N = 112</td>
<td>Japanese</td>
<td>Pre-treatment, 3, 6, 12, 18 and 24 months post-treatment</td>
</tr>
<tr>
<td>Korfage</td>
<td>Prospective longitudinal cohort</td>
<td>EBRT, RP</td>
<td>n = 127, n = 97</td>
<td>Dutch</td>
<td>Pre-treatment, 6, 12, and 52 months post-treatment</td>
</tr>
<tr>
<td>Namiki</td>
<td>Retrospective observational</td>
<td>RP</td>
<td>N = 280</td>
<td>Japanese</td>
<td>Baseline (&lt;1 month pre-treatment), 1-3, 4-6, 7-12, 13-24, 25-36, and &gt;36 months after treatment</td>
</tr>
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<td>Litwin</td>
<td>Prospective longitudinal cohort</td>
<td>RP</td>
<td>N = 247</td>
<td>American</td>
<td>Pre-treatment, 3, 6, 9, 12, 18, 24, 30, 36, 42 and 48 months</td>
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<tr>
<td>Eton</td>
<td>Cross-sectional</td>
<td>BT, EBRT, RP</td>
<td>n = 51, n = 49, n = 156</td>
<td>American</td>
<td>Within 3 months of treatment</td>
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</table>
Table 3: Included articles, continued

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<th>Follow-up</th>
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<td></td>
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<td></td>
<td>AS</td>
<td>n = 31</td>
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<td></td>
<td>RP</td>
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<td>Prospective longitudinal cohort</td>
<td>EBRT</td>
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<td>Dutch</td>
<td>Pre-treatment, 6 and 12 months</td>
</tr>
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<td></td>
<td>RP</td>
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<td>Schapira</td>
<td>Prospective longitudinal cohort</td>
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<td>AS</td>
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* Treatment abbreviations: AS = active surveillance, BT = brachytherapy, EBRT = external beam radiotherapy, RP = radical prostatectomy, RT = radiotherapy (not specified)
RESULTS

Critical Appraisal of the Literature

In 2006, Namiki et al\textsuperscript{15} published a prospective longitudinal cohort study of 70 and 67 Japanese men who underwent brachytherapy or who had radical prostatectomy. They collected pre-treatment baseline measures of HRQOL using the SF-36 instrument and did repeated measures of HRQOL at 1, 3, 6 and 12 months following treatment. The pre-treatment baseline is critical to the comparison of post-treatment HRQOL because it allows each man to serve as his own control.

This study showed that there were significant decreases (as defined by the SF-36 criteria of 5-10 point change, but not always reported as statistically significant) in role physical from a baseline mean of 88.5 to 64.9 at 1 month in the radical prostatectomy group (-23.6 points). In the same group, the bodily pain mean score also decreased by 18.6 points at 1 month, indicating more pain. The role emotional mean score went from 86.7 at baseline to 68.4 at 1 month, another significant decrease of 18.3 points. A mean decrease of 20.6 from baseline was observed in this group after one month. There was also an observed increase in mental health/emotional well-being, with an increase of 6.3 points from baseline to the 1 year follow-up. In the brachytherapy group, the only clinically significant difference observed was a decrease in social function from 90.4 at baseline to 79.3 at 1 month (-11.1). Despite these short term differences, there were no significant differences remaining by 6 months after treatment. The only exception was the increase in the mental health/emotional well-being score at 12 months in the radical prostatectomy group.

The strengths of this study included the exclusion of any men who underwent neoadjuvant or adjuvant therapy, meaning that changes in HRQOL were related only to primary
treatment. There were no baseline differences in HRQOL between the groups. The two groups were similar in terms of PSA and clinical stage of cancer, but differed in terms of age and Gleason score. This difference is to be expected based on the clinical indications for prostatectomy versus radiotherapy. Limits of this study include a relatively small sample of 137 men and the non-randomized allocation of treatment.

Arredondo et al\textsuperscript{8} conducted a retrospective observational study analyzing the pre-treatment HRQOL and the same measure at 1 and 2 years post-radical prostatectomy. The study included 856 American men who underwent prostatectomy at one major academic medical center and were enrolled in the longitudinal CaPSURE study. In this analysis, the authors specifically examined the effect of comorbidities on HRQOL outcomes, but presented the data stratified by the number of comorbidities.

At 1 year, the investigators report a statistically significant decrease in the physical component score in those with no comorbidities, but this difference was only 1.4 points which would not be considered clinically significant. There were other domains in which there appear to be clinically significant changes that were not statistically significant. Looking only at the group with no comorbidities at 1 year post-treatment, there was a 5.0 (± 1.2) point increase in mental health scores and a 3.8 (± 2.8) increase in role emotional. The role emotional mean is not clinically significant, but the standard error overlaps significance. There was also a 2.5 (± 0.7) point increase in mental component summary score at 1 year which was reported as statistically significant and overlaps with clinical significance of a change of 3 points.

Two-years after treatment, they observed a clinically significant decrease in bodily pain score (-6.1 ± 2.2) from the before treatment baseline, indicating more pain. Other borderline clinically significant changes were seen in role physical (-2.6 ± 3.2), mental health/emotional
well-being (4.6 ± 1.6), role emotional (+3.2 ± 3.7), and social function (+3.3 ± 2.2). The mental health component score was borderline significant at 2 years, with an increase of 2.6 (± 0.9). The physical component score was also borderline significant, with a decrease of 2.7 (± 0.7). Both of the component score differences were reported as statistically significant (p < 0.05).

The men who responded to this survey tended to be of higher SES, with 50% of the sample having a college education and 44% with income >$75,000. The sample was also 92% white, which severely limits the generalizability of the results. Another limitation of this study is its retrospective design. This limitation is balanced somewhat by the availability of pre-treatment baseline data. One strength of this study is the exclusion of men who underwent adjuvant or neoadjuvant therapy, thus limiting the confounding effect of additional treatment. It also sampled a relatively large number of men. The overall conclusion that comorbidities have an effect on longitudinal HRQOL is probably valid, but the degree to which it influences outcomes is unknown.

Ficarra et al. performed a prospective longitudinal cohort study in which they followed 75 Italian men who underwent radical prostatectomy. They collected pre-treatment baseline data along with follow-up at 3, 6 and 12 months. This study found that by 12 months after surgery, 80-90% of patient reported SF-36 scores overlapped with baseline. This finding indicates that the vast majority of men will recover to their baseline status by 1 year following surgery. However, there were many clinically significant changes in individual domains. The physical function score decreased by 10.51 at 3 months and 5.51 at 6 months compared with baseline. By 12 months, it was within the mean ± standard deviation of baseline. For role physical, there was a decrease of 39.21 at 3 months and 24.03 at 6 months compared to baseline. Again, this had recovered by 12 months post-treatment. There was a clinically significant decrease in role
emotional at 3 months, with a decrease of 21 from baseline. This difference was only 8.5 at 6 months. By 12 months, the score for role emotional had actually increased by 5.31 points over baseline. For energy/fatigue at 3 months, there was a 9.12 point decrease from baseline, which improved to only 7.86 points by 6 months. The difference had resolved by 12 months. For social function, the only clinically significant difference was seen at 3 months, with a decrease of 6.22 points. The authors report only the changes in physical function, role physical, role emotional and energy/fatigue as statistically significant.

This study was limited by very small sample size, with only a 50% response rate to the initial survey. The investigators did not present demographic data on the non-responders, which means there is likely a high degree of selection bias due to the low response rate. The combination of small sample size and high bias lowers the power of the study to detect differences in SF-36 measures and the ability to apply the results. Additionally, every one of the patients was Caucasian and 89% were married, severely limiting the generalizability of the results. It may be more generalizable to Italian men, but would not compare well with the American population. The overall results indicate that short-term changes (3 to 6 months) in many domains are of clinical significance, but most of these differences resolve by 12 months.

A single-surgeon series of cases was presented by Dalkin et al. They conducted a prospective longitudinal cohort study of 158 patients undergoing radical prostatectomy with 1 year of follow-up and 105 with 2 years of follow-up. Pre-treatment baseline HRQOL was measured, along with 1 and 2 year measures. The authors conclude that prostatectomy had little adverse effect on SF-36 at 1 and 2 years. They report a non-statistically significant change in mean role physical scores from baseline to 2 years post-treatment of 5 points, which would be
clinically significant. The only other clinically significant change is an 8 point increase in role emotional at 1 year post-treatment, indicating fewer limitations due to emotional problems.

One strength of this study is that it eliminates the variation caused when multiple surgeons perform surgery, which may have different techniques or levels of experience. However, with the follow-up at only 1 and 2 years and no interim data means that early changes in SF-36 were likely missed. Considering it was a single-surgeon series, the sample size is fairly large, but may still lack some power to detect small differences. The results show that in this population undergoing radical prostatectomy, there were very few changes in HRQOL over the 2 year follow-up period.

Namiki et al. performed a 2 year prospective longitudinal study following 112 Japanese men undergoing radical prostatectomy. They collected pre-treatment baseline data, as well as 3, 6, 12, 18 and 24 month post-treatment SF-36 scores. The findings were that general HRQOL was mostly unaffected 6 months after surgery and there was a favorable impact on mental health. The time course of HRQOL changes was similar to that reported in other studies; at 3 months there was a decrease in role limitations due to physical problems (87.7 to 77.1) and bodily pain scores (84.4 to 78.2). When you include the very large standard deviations associated with these means, all of these means overlap baseline, however. These scores had returned to within 5 points of baseline by 6 months.

This study was limited by a relatively small sample size and lack of matched controls for comparison. While it is useful to have the pre-treatment baseline to use as a control for the men undergoing surgery, it is difficult to know how that baseline compares to other men in the population. There may be significant differences in those men who chose to enroll in the study, based on age, current QOL and disease status. The results of this study show that men who
undergo radical prostatectomy experience the greatest decreases in HRQOL at 3 months, with rapid recovery by 6 to 12 months.

Korfage et al\textsuperscript{42} conducted a prospective longitudinal cohort study that followed 127 Dutch men undergoing prostatectomy and 187 men undergoing external beam radiation. They followed these men for up to 5 years, but the response rate by that time had decreased their sample to 97 and 127 for prostatectomy and EBRT, respectively. This would lead to some degree of selection bias, and it would be helpful to know the characteristics of those men who did not respond. The investigators collected pre-treatment HRQOL scores with follow-up at 6, 12, and 52 months. This study concluded that prostatectomy patients reported better functioning before and after treatment compared to EBRT patients. There was also a significant trend towards improvement in functioning over time with prostatectomy, while it decreased in those undergoing EBRT.

For those men undergoing radical prostatectomy, the domains showing clinically significant differences at 6 months include a 5 point increase in general health perception, a 10 point increase in mental health, and a 3 point increase in the mental health component score. At 12 months, there was a 6 point increase in role emotional, a 9 point increase in mental health, and a 4 point increase in mental component score when compared to pre-treatment means. By 52 months post-treatment, there was a 7 point increase in role physical, a 10 point increase in mental health and a 3 point increase in the mental component score. In the numbers reported by the authors, there were no significant decreases – statistical or clinical – in any of the SF-36 domains or component scores when compared to the general population.

For the brachytherapy group, at 6 months there was a 5 point increase in general health perception, a 7 point increase in role emotion, a 12 point increase in mental health and a 4 point
increase in the mental component score compared with the general population. At 12 months, there was a 6 point increase in role emotional, an 11 point increase in mental health, and a 4 point increase in the mental component score. The final measure conducted at 52 months showed a 12 point increase in mental health and 4 point increase in mental component score. At 52 months there was a 9 point decrease in physical functioning and a 3 point decrease in the physical component score, the only significant decreases in either the brachytherapy or prostatectomy group.

Interestingly, this study used Dutch general population SF-36 scores as a comparison to the treatment groups and found that the prostatectomy patients had higher baseline SF-36 scores, with the exception of mental health scores. This would support the hypothesis that healthier men are differentially selected for prostatectomy. By 52 months post-treatment, the prostatectomy group's SF-36 scores were significantly better than the general population in all SF-36 realms. The radiotherapy group had lower scores compared to the Dutch general population in mental health and general health perceptions and similar scores for vitality and social functioning. After 52 months of follow-up, the radiotherapy group had equal or significantly improved (role-physical, bodily pain, and role-emotional) scores compared to Dutch general population.

The two groups were dissimilar in terms of age, comorbidities and average PSA levels between the two groups, with prostatectomy having a generally healthier baseline. There was a higher rate of recurrence in the radiotherapy arm, which may have accounted for some of the decrease seen in general physical function. However, this association is complicated by the fact that men in the EBRT group were also older and may have had some age-related declines in general quality of life.
Namiki et al. performed a retrospective cross-sectional analysis of 280 Japanese men who underwent radical prostatectomy. Outcomes after treatment were assessed by dividing the men into 7 time periods during which the SF-36 questionnaire was administered. These groups included baseline, 1-3 months, 4-6 months, 7-12 months, 13-24 months, 25-36 months and greater than 36 months after treatment. This design is complicated by the fact that these groups are not a longitudinal cohort, but groups of different men who are within the same time window after treatment. The conclusion of this study is that SF-36 scores did not vary significantly between the groups over time. It appeared that most of the SF-36 recovery occurred by the 6 month time period.

For this study, in order to calculate changes in HRQOL from baseline, the mean at T0 (pre-treatment) was compared with T3 (7-12 months). Using this comparison is limited by the sample included men who answered the survey anywhere from 7 to 12 months after treatment, as well as the lack of a pre-treatment control for the individual. However, this study did show a 6.6 point decrease in physical function compared to the pre-treatment mean, which is clinically significant. There were also clinically significant increases in mental health (+9.2) and social function (+8.3). Using a p-value of 0.05, the only statistically significant difference was the 9.2 point increase in mental health score.

This study did not control for the use of adjuvant or neoadjuvant therapy, so the effect of additional treatment may have biased the final results. Two-thirds of the men followed at 24-36 or >36 months had received androgen deprivation therapy (ADT). It would be likely that ADT would be associated with a decrease in HRQOL, so this addition may have biased the results towards the null. The retrospective nature of this study and the lack of pre-treatment controls for
individuals make the results less meaningful than a prospective longitudinal study with pre-treatment baselines.

This study had an extremely high response rate, in the mid-90%. The authors do acknowledge that there may have been some inherent differences in the group that did not return the surveys, leading to selection bias. The investigators state that the survey instrument was self-report to exclude observer bias. While this does circumvent the role of physicians in estimating QOL, it does not mean that the self-report instrument is free from bias. The investigators also did not distinguish between the types of surgical procedure performed, nor did they exclude men who may have had neoadjuvant or adjuvant therapy.

Eton et al.\(^2^3\) presented a retrospective analysis of 256 men undergoing radical prostatectomy or radiation therapy, surveying them within 7 weeks of their treatment. Their sample was largely Caucasian (229 Caucasian vs. 27 African-American), married and skewed strongly towards RP over RT. The investigators concluded that men who undergo prostatectomy are at an increased risk of general deficits in HRQOL compared with those undergoing radiotherapy. The authors of this paper did not report raw SF-36 scores, so no differences can be calculated.

They did make an effort to discuss racial differences in their sample, however, and reported that African-Americans reported more physical problems. This led them to conclude that African-Americans were at increased risk of experiencing general deficits in HRQOL. They also state that African-Americans reported more symptom-specific deficits in urinary and sexual function. In the context of huge differences in the sample, it is difficult to accept that conclusion.

This study had many weaknesses, most notably that the follow-up was only 7 weeks. Comparing differences between treatment types over this period of time is severely limited by
the fact that the side effect profiles vary greatly over time. Surgery has very short-term side effects as a result of the invasive nature of the procedure and anesthesia, whereas radiation has almost no short-term effects. To make meaningful conclusions about differences in QOL at 7 weeks would be very difficult. Additionally, the study design of this paper seems to be somewhat explanatory in nature, with no preformed hypothesis stated. They did consider racial differences, but the sample was not adequate to allow for much interpretation of those results.

Bacon et al\textsuperscript{19} combined a retrospective cross-sectional study with a prospective longitudinal study aimed at evaluating differences in QOL after radical prostatectomy or radiation therapy. The cross-sectional portion of the study had a sample of 842 men, while the prospective study followed 146 men using the SF-36 instrument which included a baseline measurement. Unfortunately, the authors do not report the mean follow-up time of that prospective cohort, making it difficult to interpret their conclusions regarding differences over time. They report that RT patients had greater decreases in vitality and role limitations due to physical problems; however, they do not report raw SF-36 scores. The $\beta$ coefficients or odds ratios are presented for each of the SF-36 domains, derived from a multivariable model adjusted for a number of covariates. This model used the radical prostatectomy group as the referent, so the $\beta$ coefficients and odds ratios for that group are 0 and 1.0, respectively.

Without raw scores, differences in SF-36 changes from baseline to post-treatment cannot be calculated. Based on their regression model, the authors report a significant decrease in physical function (-8.7) and general health perception (-8.4) for men undergoing watchful waiting. For external beam radiation, there was a significant decrease in physical component score (-3.1), mental component score (-1.6), physical function (-5.6), bodily pain (-5.8), general
health perception (-4.9), and vitality (-5.8). There were no significant differences reported for men undergoing brachytherapy.

There were important demographic differences between the treatment groups, congruent with the standard differences in surgical versus non-surgical patients. RP patients were younger, with mid-grade cancers and had less comorbidity. The strengths of this study include the multi-institutional national scale, which makes the results more generalizable. They also had a high response rate of 94%, limiting the role of selection bias. They also correlated the self-reported instruments with medical record abstractions to ensure that men were actually receiving the treatment that they indicated on their surveys.

In another retrospective, cross-sectional study, Davis et al. compared HRQOL in men undergoing RP and brachytherapy with an age-matched sample of men without prostate cancer. They used this age-matched sample as a baseline for comparison, which may not be adequate given that men without prostate cancer may not have similar QOL to those with prostate cancer. The sample was largely Caucasian and the RP group had slightly more favorable cancer characteristics than the brachytherapy group. This study found that general HRQOL was similar in the surgery and radiation groups, but those men undergoing brachytherapy had lower scores in physical function and role physical than those who chose surgery. The cross-sectional design of this study does not allow for a comparison of baseline to post-treatment scores.

The measurement of HRQOL occurred around 5 years after treatment, and was then compared to the age-matched controls without prostate cancer. This design does not allow for the detection of any QOL differences that occur before 5 years, but does give enough time for the natural history of both surgery and radiation effects to become evident. It is also somewhat limited in that the participants came from a single-institution, but the age-matched controls came
from a previously published national sample. It may not be appropriate to compare these two groups.

Litwin et al\textsuperscript{45} reported a prospective cohort of 247 American men who underwent RP. The investigators included pre-treatment baseline along with follow-up of 48 months. The study was designed to detect trends in HRQOL changes, by including frequent interval measurements. There was also discussion of racial differences in time to recovery of baseline scores for QOL. In this sample, at 6 to 9 months 90\% of men had regained their baseline general HRQOL. There was a rapid recovery in many of the domains, as soon as 3 months after surgery. Compared to pre-treatment baseline, there were clinically significant increases seen at 12 months in role physical (+5.6), role emotional (+7.4), and social function (+6.8).

However, the sample was once again skewed with Caucasians (89\%) outnumbering the African-Americans greatly. The sample was also skewed in terms of income (56\% having income >$75,000), education (46\% with graduate or professional degree), and marital status (90\% were married or living with spouse or partner.) These differences limit the generalizability of the results.

In a prospective longitudinal study, Madalinska et al\textsuperscript{46} reported on 278 Dutch men undergoing either RP or XRT for prostate cancer. This study was undertaken as a nested observational study within the European Study of Screening for Prostate Cancer (ERSPC) screening trial.\textsuperscript{47} They collected pre-treatment baseline data and had follow-up at 6 and 12 months after treatment. The men included in the study were largely married, with an intermediate education level. There is no report of racial demographics of the participants. There are some differences in cancer characteristics, with the RP group having slightly more favorable tumors. The results of this study showed that men undergoing radiation had more bodily pain and lower
general health perception at 12 months following treatment. There was also a significant decrease in role emotional in those men undergoing radiation at 6 to 12 months.

For men undergoing radical prostatectomy, the SF-36 differences at 12 months were clinically significant in the domains of general health perception (+6), role emotional (+7), mental health (+9) and mental component score (+3). For those men undergoing radiation therapy, there was a significant increase in role emotional (+5), mental health (+9), and mental component score (+3) at 12 months.

This study is well-designed for detecting shorter-term changes in HRQOL. The investigators were also able to comment on the effect of having your cancer screen-detected versus not screen-detected on QOL, in the context of the larger screening trial. However, it is limited by a relatively small sample size, with baseline data for 278 men and 12 month follow-up data for only 261 men. As with the other studies, it is likely that not all of the side effects of XRT were realized at the end of 12 months.

Schapira et al\textsuperscript{48} undertook a prospective observational cohort study comparing HRQOL after radical prostatectomy, radiotherapy and active surveillance. They collected baseline data with 3- and 12-month follow-up. The investigators had 2 explicitly stated hypotheses; 1) patients who elected expectant management would demonstrate a greater decline in role-emotional compared with other treatment groups and 2) patients who underwent RP or XRT would demonstrate a greater decline in role-physical due to the aggressive nature of the treatment. They found that after adjustment for baseline demographic and clinical variables, treatment was not predictive of any of the general HRQOL domains.

The authors reported change in generic HRQOL domains for RP, RT and active surveillance at 12 months in one table. For prostatectomy, there were clinically significant
decreases in bodily pain (-10.8) and general health perception (-9.7). When a multivariable analysis was performed comparing across treatment groups, these decreases were not significant. For radiation therapy, there were clinically significant decreases in physical function (-5.4), role physical (-15), and social function (-19.1). Only social function was reported as statistically significant. For the active surveillance group, the only significant difference was an 8.4 point decrease in physical function. This was not statistically significant.

This study was severely limited by its sample size of 122 men, which represented only a 45% participation rate. Additionally, the study was powered to detect greater than 20 point differences in HRQOL domains. (For the SF-36, meaningful differences are 3 points for the component summary scales and 5-10 points for the other scales.) As a result, the study may have missed smaller, but significant, differences in HRQOL. This appears likely given that the conclusions were almost exclusively no difference across the various domains. The authors state that this may be due to the fact that general HRQOL is not as sensitive to treatment choice as the disease-targeted domains. The study was not powered to detect smaller differences that may have been clinically significant.

In the seminal paper in the literature, Litwin et al performed a cross-sectional analysis of HRQOL after radical prostatectomy, radiotherapy or active surveillance. This study included only men with localized cancer, and used age-matched, zip-code matched patients to serve as a baseline for comparison. There were 214 cancer patients, and 273 age-matched controls included in the sample. The men were mostly white, and there were differences between the treatment groups as expected by the indications for surgery versus radiation. The response rate was 79% for this study, which is adequate. Due to the cross-sectional design, it is not possible to derive a change from baseline score, but they report no differences in general HRQOL. The authors argue
that this means that general HRQOL is not a sensitive enough instrument, compared to the disease-specific scales. It is important to note that in 1995, nerve-sparing surgery was not yet commonly used and the symptoms following radical prostatectomy would be expected to be much worse than with present techniques.

The cross-sectional data was collected approximately 5 years after primary treatment, but they did not report how long after treatment the surveys were administered. The authors did report that the time since treatment was “roughly equivalent” between the different treatment groups. As with any cross-sectional study, there was no way to control for different forms of bias, particularly selection and recall bias. Also, a cross-sectional approach after 5 years may lack the ability to detect true changes in general HRQOL, as men may have completely adjusted to their current status and report it as normal.

Summary of Literature Analysis

After critically appraising the 14 articles that addressed my specific question, there are a number of issues that make drawing conclusions quite difficult. Firstly, the studies vary widely in their design. Even excluding the retrospective studies leaves prospective studies with very different follow-up criteria and reporting of the results. Some studies report only component scores, while others report each of the eight domains of the SF-36.

Secondly, there are marked differences in the studies’ criteria about what is a significant change in SF-36 scores. One study may report “no significant difference” for a change of 5 points, because they powered the study to detect changes of 10 points or more. One would expect this to be less of a problem given that the methods paper for the development of the SF-36 explicitly states what should be considered a significant change in the domain or component scores. Another study may report that as a significant difference, which would make the studies
appear discordant. These inconsistencies make it impossible to quantitatively express the
changes in health-related quality of life over time.

**Table 4: Quality assessment of studies**

<table>
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<th>Grade</th>
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<tbody>
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<td>Namiki 2006</td>
<td>A</td>
<td>n = 137, multiple intervals, 12 month total follow-up</td>
</tr>
<tr>
<td>Dalkin 2006</td>
<td>A</td>
<td>n = 105 for 2 year data, single-surgeon case series</td>
</tr>
<tr>
<td>Namiki 2005</td>
<td>A</td>
<td>n = 112, multiple intervals, 24 month total follow-up</td>
</tr>
<tr>
<td>Korfage 2005</td>
<td>A</td>
<td>n = 224, multiple intervals, 52 month total follow-up</td>
</tr>
<tr>
<td>Litwin 2002</td>
<td>A</td>
<td>n = 247, 24 month follow-up</td>
</tr>
<tr>
<td>Madalinska 2001</td>
<td>A</td>
<td>n = 278, 6 and 12 month follow-up</td>
</tr>
<tr>
<td>Schapira 2001</td>
<td>A</td>
<td>n = 122, 3 and 12 month follow-up</td>
</tr>
<tr>
<td>Arredondo 2006</td>
<td>B</td>
<td>n = 856, only 1 and 2 year follow-up</td>
</tr>
<tr>
<td>Namiki 2003</td>
<td>B</td>
<td>n = 850, attempted to illustrate trends by using cross-sectional data at different time periods</td>
</tr>
<tr>
<td>Ficarra 2005</td>
<td>B</td>
<td>n = 75, very low response rate, all Caucasian</td>
</tr>
<tr>
<td>Eton 2001</td>
<td>C</td>
<td>n = 256, cross-sectional, average 7 week post-treatment</td>
</tr>
<tr>
<td>Bacon 2001</td>
<td>C</td>
<td>Combination of retrospective and prospective design, prospective n = 146</td>
</tr>
<tr>
<td>Davis 2001</td>
<td>C</td>
<td>n = 511, retrospective, age-matched comparison group</td>
</tr>
<tr>
<td>Litwin 1995</td>
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<td>“case-control” used to establish a comparison group</td>
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</table>

Interpreting these results requires some understanding of the natural course of side effects
of the two treatments. After prostatectomy, symptoms tend to be worse very early on and
improve for up to 2-3 years after surgery. In the case of radiation therapy, there tend to be very
few symptoms initially and they increase over time as tissues in the pelvic area begin to scar
down and fibrose, or scar down, for up to 3-6 years. Studies with shorter follow-up periods may
not have allowed sufficient time for the full effects of radiation to be realized.

In the included studies, the evidence regarding quality of life after prostatectomy was
relatively homogeneous. The greatest declines in HRQOL were seen in the 3 to 6 month period
following surgery. These studies reliably showed that SF-36 scores returned to baseline in most
domains within 6 to 12 months following surgery. The domains that showed the greatest declines
to the physical component scores.
In a number of the studies, men showed an actual increase in the mental component scores after prostatectomy, as compared to those undergoing radiation or watchful waiting.

The evidence regarding radiation treatment was more heterogeneous. Depending on the study follow-up period, there were vast differences in the results of SF-36 over time. Typically, the longer the follow-up, the more decreases seen in those patients undergoing radiation. These differences were particularly seen in the domains of role physical and role emotional. These decreases were noted primarily in the early period following treatment, but many persisted throughout the 1 to 2 year follow-up period. The study with the longest follow-up, 52 months, was able to show a trend for EBRT that showed decreased physical function in the 2 to 3 year range, with a return to baseline by 52 months. Eton, on the other hand, showed that men undergoing prostatectomy are more likely to experience deficits in general functioning than those undergoing radiation.

The three studies that examined HRQOL with active surveillance had very disparate results. Bacon showed that men choosing active surveillance had lower physical function and general health compared with those men that chose radical prostatectomy. Another study by Schapira showed there was no worsening of role emotional or mental health in those men choosing active surveillance. However, in Litwin’s 1995 study, the only difference he found in general measures of HRQOL was a decrease in role emotional in those men choosing observation over curative treatment.
DISCUSSION

Implications of Results

This systematic review was an attempt to begin to assimilate the current evidence about HRQOL after treatment for prostate cancer, focusing on the general measure using the SF-36 instrument. Because of differences in HRQOL that result from different treatment modalities, understanding trends in HRQOL after treatment will remain useful for physicians and patients when making decisions regarding treatment. This is amplified by the fact that there is very little randomized controlled trial evidence showing mortality benefit of any of the primary treatment. This strengthens the argument for the use of HRQOL as an important outcome measure. However, this review was limited by a lack of consistency in the study design, and a body of evidence dominated by retrospective studies. A lack of good prospective studies makes it difficult to reliably apply results to clinical practice.

Limitations of Review

The most important discussion regarding this review is the utility of the SF-36 as a measure for HRQOL. Many of the authors argued that it is not a sensitive enough instrument to detect differences in HRQOL, compared with disease-specific instruments such as the PCI. I think this notion is based on past research showing no differences in SF-36 over time, particularly Litwin’s first article which used both the SF-36 and PCI. As the study methods are developing into more prospective longitudinal designs, with measurements at frequent intervals, it is becoming more obvious that there are significant changes after treatment. These changes do appear to be different between treatment groups.

It is incorrect to discount these trends in general HRQOL, even if the resounding conclusion is that after a year or two, there are no differences between treatments. It is important
for men facing decisions regarding their treatment to understand what kind of changes to expect as they recover from their cancer. The specific symptoms are important and will likely affect the choices a man will make, but there are also the physical and mental changes that will occur that cannot be pinpointed so directly. The SF-36 instrument more accurately, albeit more generally, depicts those sorts of changes.

The review was also limited by the preponderance of articles that evaluated HRQOL after treatment with radical prostatectomy. All of the 14 articles reviewed addressed HRQOL after surgery, whereas only eight evaluated it after radiation therapy and only three evaluated it following watchful waiting. This may explain why the results from the radical prostatectomy evidence appear more homogeneous than the other modalities. Ideally, each study would compare all three modalities using the same study design, but this review found that many studies only examined RP alone, or compared RP to radiation without considering active surveillance.

One of the goals of this systematic review was to examine racial differences in health-related quality of life after prostate cancer treatment. The body of evidence is almost completely devoid of studies that examined this question explicitly. Most of the studies that were reviewed for this article sampled largely white populations, making the results more difficult to generalize to African-Americans. In fact, there were only two studies that stated racial differences as a primary outcome. There was more discussion of racial differences in symptom-specific measures of quality of life, and this generally showed that African-American men typically report greater dissatisfaction with their quality of life.

Another difficulty in interpreting these results is the selection bias inherent in this field of study. There are baseline differences in the type of person that is recommended for each type of
treatment, meaning that there will be differences between treatment groups based on comorbidities, age and tumor characteristics. Without randomization to treatment, these differences will almost certainly affect the measurement of HRQOL in various ways. For example, men undergoing RP tend to be healthier and younger and are likely to begin with a higher baseline HRQOL. Unless the investigators explicitly state there are no differences in the baseline HRQOL, comparing prostatectomy, radiotherapy and active surveillance may not be valid.

Accepting the limitations of this review, there are some generalizable results that may serve to inform physicians and patients involved in the decisions surrounding prostate cancer treatment. It appears that men who undergo prostatectomy are generally at their baseline health-related quality of life within 6 to 12 months following surgery. Additionally, an actual increase in mental component scores and emotional well-being is sometimes seen in these men. This has a number of implications: 1) more invasive procedures do not necessarily equate with physical limitations, 2) men may derive a mental or emotional benefit from the knowledge that their tumor has been completely removed and 3) when compared to radiation or watchful waiting, prostatectomy has a similar, if not favorable, quality of life profile.

**Future Research**

This review suggests the importance of future research in this area including HRQOL measures, especially randomized controlled trials of prostate cancer treatment. Without randomization, it will be impossible to completely eliminate the selection bias between treatment groups. It also suggests that investigators who wish to research this question without an RCT could design prospective longitudinal trials that take into account the natural history of the trends in HRQOL. This would require longer follow-up times and measuring at time intervals that are
sensitive enough to detect early changes as well as the long-term conclusions. Continuing to investigate this question with retrospective studies is unlikely to contribute significantly to the current body of evidence.

This review found that very few investigators looked at this question explicitly, and those who did drew conclusions from samples that were predominantly Caucasian. In order to answer this question appropriately, studies need to be designed to include more African-Americans and powered in a way that will make the results more valid. Given that there already appears to be weak evidence for racial differences, with African-Americans at greater risk for negative effects from treatment, a more robust study addressing this particular question seems warranted. It would require enrolling more African-Americans in research trials, particularly the ongoing randomized controlled trials, or designing new prospective studies to look at HRQOL in African-Americans and Caucasians.

Another interesting approach to future research would be further investigation of the relationship between disease-specific measures of HRQOL and general health related quality of life. There is some evidence that certain symptoms significantly correlate with general HRQOL. Eton showed that urinary, bowel and sexual function correlate with better general physical and mental functioning. Combining the evidence for what treatments are associated with what symptoms and which symptoms correspond to deficits in general function, physicians may be able to guide patients to understand how their chosen treatment may affect their future quality of life. This could be helpful in future decision making, particularly if the treatments continue to be equivocal in terms of mortality benefits.
Works Cited


Appendix I. Abbreviation List

AJCC – American Joint Committee on Cancer
AS – Active Surveillance
BT – Brachytherapy
CRD – Centre for Reviews and Dissemination
DRE – Digital Rectal Exam
EBRT – External Beam Radiation Therapy
ERSPC – European Study of Screening for Prostate Cancer
HRQOL – Health-related Quality of Life
IPSS – International Prostate Symptom Score
PCI – Prostate Cancer Index
PSA – Prostate Screening Antigen
RP – Radical Prostatectomy
RRP – Retropubic Radical Prostatectomy
RT – Radiation Therapy
TNM – Tumor, Node, Metastasis