# COMPARATIVE EFFECTIVENESS AND COSTS OF CONSERVATIVE MANAGEMENT AND CRYOTHERAPY IN PATIENTS WITH LOCALIZED PROSTATE CANCER

by

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(Under the Direction of Henry N. Young and Ewan K. Cobran)

## ABSTRACT

Prostate cancer is the second leading cause of death in American Men. Nearly, 4 out of 5 cases are diagnosed with localized prostate cancer. Although, several treatment options are available to treat localized prostate cancer, there is insufficient evidence on long term outcomes associated with these treatments. Therefore, the purpose of this study was to assess treatment related side-effects, cancer specific survival, rates of mental health issues including depression and anxiety disorder, and costs associated with conservative management and cryotherapy in patients with localized prostate cancer.

This retrospective longitudinal study design utilized Surveillance, Epidemiology, and Ends Results (SEER)-Medicare linked data set from 2000 -2013. Patients' aged 66 years or older with stage I and stage II cancer diagnosis were included in the study. Patients in the CM cohort were identified as those who did not receive any immediate treatment within 6 months of diagnosis of localized prostate cancer. Patients in the cryotherapy cohort were identified using ICD-9 procedure code, Healthcare Common Procedure Coding System (HCPCS) code/Current Procedural Terminology (CPT) code.

The ICD-9 diagnosis and procedure codes were used to identify treatment related side-effects (Erectile dysfunction, lower urinary tract obstruction, bowel fistula, urinary fistula, urinary incontinence, bleeding and hydronephrosis), and mental health issues (major depressive disorder, depressive disorder NOS, neurotic depression, adjustment disorder with depressed mood, and anxiety disorder). Medicare claims information was utilized to evaluate costs. The date of diagnosis and date of death was used to assess cancer specific survival.

There were 7,998 and 3,051 patients identified in the conservative management and cryotherapy cohorts, respectively. Findings suggest that the rates of side-effects, and depression and anxiety disorders were lower in patients who choose conservative management over cryotherapy. Cancer specific survival rates were also found to be higher in patients in the conservative management cohort compared to cryotherapy. The total mean cost, mean annual cost and phase specific costs were found to be lower in the conservative management cohort. Overall, conservative management was found to be a better treatment strategy in older patients with localized prostate cancer.

INDEX WORDS: Prostate cancer, conservative management, cryotherapy, comparative effectiveness, economic evaluation, mental health issues

# IMPACT OF CONSERVATIVE MANAGEMENT AND CRYOTHERAPY ON COST AND OUTCOMES IN PATIENTS WITH LOCALIZED PROSTATE CANCER

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# DEDICATION

I dedicate this thesis to god for bestowing his kind blessings onto me at every stage of my life, to my husband (Yogesh), my parents, sister and parents-in-laws who have been a constant support for me throughout my life's odyssey. This would not have been possible without you all.

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# CHAPTER 1

# INTRODUCTION AND LITERATURE REVIEW

## *Prostate cancer incidence and economic burden*

Prostate cancer is the most common cancer, and a second leading cause of death in American men.[1,2] There were approximately 220,800 new cases and an estimated 27,540 deaths from prostate cancer in 2015.[1,3] Recent statistics suggests that about 1 man in every 7 men is diagnosed with prostate cancer during his lifetime.[1] The lifetime risk of being detected with prostate cancer in the United States has nearly doubled to 20 percent with the increase in Prostate Specific Antigen (PSA) testing.[4] Men aged 65 years or older are more often diagnosed with prostate cancer. The average age of men at the time of prostate cancer diagnosis is suggested to be 66 years. Approximately, 6 out of 10 cases are being diagnosed in older men.[1,2] It has been reported that nearly 4 out of 5 cases are diagnosed with localized prostate cancer (also known as early stage prostate cancer).[5] The localized stage means that there is no sign that the cancer has spread outside of the prostate, which is referred to cancer stage I and II.[5] The treatment for localized prostate cancer has been promising, and has shown 10-year survival rates of nearly 97% in patients with localized prostate cancer.[5] However, the treatment and subsequent monitoring of prostate cancer imposes a high economic burden in the US.[6-8] The total cost of care was estimated to be about US $12 billion in 2010.[8,9] This cost is projected to

rise to US $16 billion in 2020 due to the increasing prevalence of prostate cancer, and emerging new treatments and technologies.[6,8,9]

***Treatment for prostate cancer***

Several treatment options such as conservative management, intensity-modulated radiation therapy (IMRT), brachytherapy, cryotherapy, and radical prostatectomy are available to treat localized prostate cancer.[2,10] These treatment options are common, however side-effects and risks associated with them vary widely.[2] All these treatment options could result in side effects that are primarily urinary, bowel or sexual, but differ in the frequency and severity of these adverse effects.[4] Urinary and bowel dysfunction appeared to be more common with radiation therapy and surgery.[4] These side effects along with their associated pain and inconvenience are one of the important factors in choosing treatments, along with the treatment cost and effectiveness.[4] Patients with indolent tumors usually have higher survival rates,[11] hence consideration of side-effects may become critical for older patients. As a result, patients with localized prostate cancer tend to choose minimally invasive options (i.e., options with fewer side effects than surgery and radiation).[12] Conservative management and cryotherapy are two such treatments with minimal invasion. These treatment options are common in older patients because of their intolerance to more aggressive treatments such as radiation therapy or surgery.[12]

***Conservative management and cryotherapy***

Conservative management is an observational treatment strategy, which is commonly used for localized prostate cancer, which allows patients to avoid aggressive treatment. In this strategy, no treatment is given to the patients until cancer progresses to advanced or metastatic stage.[13] Patients, who are on conservative management, need to be followed by digital rectal examinations (DRE) and prostate-specific antigen (PSA) level tests at regular intervals.[2] Conservative management involves two approaches: watchful waiting and active surveillance.[14] These two terms are used interchangeably by some providers.[14] In general, watchful waiting refers to delaying immediate treatment (i.e., surgery and radiation therapy), in those patients who have low probability of significant cancer progression.[2] This process allows patients time to consider possible treatment options.[12] Active surveillance is another approach in conservative management, which involves repetitive intense monitoring of patients with PSA, digital rectal exams and biopsies.[12] The goal of this approach is to keep the cancer under close watch to assess its progression and need for curative treatment.[12] This approach has been suggested to be effective in improving clinical outcomes such as survival and reducing side-effects while lowering initial cost.[2,15]

Cryotherapy is another effective, and minimally invasive treatment option for patients with localized prostate cancer.[12] Cryotherapy involves the use of trans rectal guided probe placement and injection of very cold gases (liquid nitrogen) to destroy cancer cells through rapid freezing and thawing, while avoiding lethal freezing to the surrounding healthy tissues.[2,16] This procedure is usually performed in an outpatient setting, and typically requires only one treatment.[12]

The goal of conservative management and cryotherapy is curative, which could possibly reduce healthcare cost, and treatment related side-effects. The choice of these treatment depends on their survival benefits, side-effects, their long-term impact on the development of mental health issues (MHI), and cost associated with them over time.[2]

***Impact of conservative management and cryotherapy on survival***

The Agency for Healthcare Research and Quality (AHRQ) conducted a review on comparative effectiveness of treatments used in localized prostate cancer. It was concluded that there are uncertainties about the comparative effectiveness and harms of these treatments due to inadequate evidence on long term survival outcomes.[4] There are no completed randomized clinical trials available that compared conservative management with immediate treatments.[17] However, literature suggests that the rates of survival are higher in patients who choose conservative management.[11,18,19] A prospective, single-arm study conducted by Klotz et al. evaluated long term outcomes of active surveillance. The overall survival in the cohort was found to be 78%.[20] However, 10-year cancer specific survival was found to be 92% in the cohort.[20] A systematic review conducted on active surveillance in 2012 also demonstrated low disease specific mortality associated with it.[21] Overall, conservative management has been found to be a feasible option for patients with localized prostate cancer.[20,22-24]

There is lack of adequate evidence regarding the long-term efficacy of cryotherapy and prostate cancer-specific survival in comparison to other more established forms of therapy such as surgery, radiation therapy and radical prostatectomy.[25-27] A study conducted by Rodriguez et al in 2014 showed that the cancer specific survival was

98% while the overall survival rate was 94% with a median follow-up of 5 years. A pilot study conducted by Cohen et al. showed survival rates of nearly 80% in low-risk patients who underwent cryotherapy between 1991-1996.[28] Similarly, another study found a 5-year survival rate to be 82% in patients aged 75 years and above.[29] However, these studies conducted in the past are either outdated, conducted outside the US, or had shorter follow-ups.

***Impact of conservative management and cryotherapy on side-effects***

Although research suggests that conservative management approaches are promising and beneficial due to avoidance of treatment related side-effects, various factors could influence the effectiveness of these approaches.[2,30] Repeated biopsies performed in conservative management approach may increase the chances of sampling errors in biopsy, costs, morbidities and anxiety in patients.[2] Furthermore, this approach may also reduce the compliance with repeat biopsy protocols.[2,30] Evidence suggests that there is an increased risk of erectile dysfunction among patients who undergo repeated prostate biopsies.[31,32] Biopsies are also found to be associated with bleeding, infections, pain and low risk of urinary track symptoms.[33] A large proportion of patients refuse repeated biopsies due to the fear of complications and/or discomfort.[32]

Cryotherapy involves lesser pain, faster recovery with least side-effects compared to active treatments such as radical prostatectomy and surgery.[16] Some of the most common side-effects associated with cryotherapy are due to freezing of the prostate, which may damages the nerves near the prostate. Erectile dysfunction is a very common side-effect after cryotherapy.[34] Rates of incontinence are usually low in patients who

undergo cryotherapy in comparison to other treatments due to constant monitoring of the temperature during cryotherapy.[34,35] Some other less commonly reported side-effects include bleeding, urinary and bowel fistulas, lower urinary tract obstruction, and hydronephrosis.[36,37] A prospective study conducted in a single institution of Spain evaluated side-effects associated with cryotherapy.[27] Rates of incontinence, urinary tract obstruction, bleeding and fistula were found to be 5.6%, 1.9%, 1.9%, and 0.9%, respectively.[27] Erectile dysfunction was found in 98.1% of the patients. Higher rates of erectile dysfunction was found due to the presence of these symptoms before treatment initiation.[27] Another study conducted on patients above 75 years of age found rates of fistula, urinary obstruction, and incontinence to be 0.1%, 6% and 0.9%, respectively.[29]

***Impact of conservative management and cryotherapy on mental health***

Rising healthcare costs along with evolving treatments have also resulted in greater interest in measuring other patient related outcomes.[2] As patients are living longer with cancer, other outcomes are becoming more relevant, such as the pervasive impact of treatment choices on mental health.[38,39] Studies have shown the rates of psychological distress, such as depression and anxiety disorders in cancer patients to be in the range of 0% to 44%. In fact, it has been shown that nearly 60 % of the localized prostate cancer patients encounter psychological distress.[40] Nearly 20% of the patients showed clinically significant levels of depressive symptoms.[41] Prevalence of MHI such as anxiety and depressive disorders are common in older men with localized prostate cancer.[42] Further, MHI such as depression and anxiety are common in patients with prostate cancer, but often remain undiagnosed and untreated.[41]

Development of MHI including depression and anxiety disorders are common during the treatment phase of the prostate cancer, and is associated with significant health resource utilization, costs and mortality among men with prostate cancer.[38] These MHI including depressive and anxiety disorders in patients with prostate cancer results in nearly fivefold increase in the risk of emergency room visits, nearly threefold increase in the risk of hospitalization, and a threefold increase in the risk of excess death compared to those without MHI.[38] Another systematic review and meta-analysis conducted by Watts et al. concluded that the prevalence of depression and anxiety in men with prostate cancer, across the treatment spectrum, is relatively high.[43] Post-treatment prevalence of depression and anxiety disorders were found to be 18.44% and 18.59%, respectively.[43] Various factors such as cancer diagnosis and repeated screenings, uncertainties about treatment decisions, side-effects associated with the treatments, and increasing healthcare costs could contribute to these MHI.[38,42]

The entire course of screening and diagnosis leads to anxiety in patients. It can be psychologically challenging for patients to choose conservative management as a treatment strategy for cancer.[42] Opting for conservative management could lead to anxiety and psychological stress in patients due to the fear of not receiving any active treatment for such a life threatening condition.[39,42] The risk of side effects associated with biopsies in conservative management aggravates the stress, anxiety and could lead to depressive disorders.[39,42,44] A study conducted by Ravi et al to assess burden of MHI among patients with localized prostate cancer found that patients who were treated with radical prostatectomy or radiotherapy were at a lower risk of developing mental health issues as compared to those patients who were on conservative management.[42] The time

to develop these MHI among patients undergoing radical prostatectomy was also found to be significantly greater than conservative management.[42] However, another study conducted by Burnet et al found that conservative management was not associated with greater psychological distress than more immediate treatment for prostate cancer.[45] Similarly, no significant differences in psychological distress were found between conservative management and immediate treatment in other studies.[20,45-47] Hence, there are uncertainties associated with these MHI in men undergoing conservative management.

Lower rates of any MHI found in the conservative management cohort could be due to lower rates of side-effects such as erectile dysfunction, urinary incontinence or obstructions, pain and fatigue in the cohort.[48] Side-effects such as sexual, urinary, and bowel dysfunction could be associated with lower levels of mental and social functioning in men with prostate cancer.[49,50] A study conducted to assess quality of life among men undergoing cryotherapy has shown that despite the reported side effects, the overall quality of life was comparable to other prostate cancer therapies.[51] There could be a possibility of fewer rates of depressive and anxiety disorders with cryotherapy, as this treatment is minimally invasive with lesser pain, costs, lower side-effects; compared to other immediate treatments, such as brachytherapy, radiation therapy and surgery. However, scant research has been conducted on cryotherapy. There are gaps in the knowledge on the prevalence of these MHI among men undergoing conservative management or cryotherapy. Such evidence is needed to make informed decisions for older patients, who tend to choose treatment options that leads to lower MHI and improves quality of life, rather than those options that maximize survival.[52,53] Careful

consideration of these outcomes is crucial when choosing treatments for localized prostate cancer.

***Economic impact of conservative management and cryotherapy***

The economic burden of prostate cancer is high; however the burden varies widely by the choice of the treatment.[54,55] In addition, the treatment options for localized prostate cancer pose significant potential risks to quality of life in older patients, which further increases the cost of care.[56] These costs rapidly change over time i.e. with different phases of care. The phase of care approach divides care into clinically relevant periods: the initial phase after diagnosis, the last year of life, which is the terminal phase, and the continuing period. Literature suggests that treatment costs for prostate cancer are highest in the initial phase of care i.e. within the first year of prostate cancer treatment, and in the terminal phase i.e. the last 12 months of treatment before death.[57] Contrarily, cost projections from 2010 – 2020 showed that prostate cancer had the lowest cost in the initial phase, and highest cost in the continuing phase i.e. the period between initial phase and the terminal phase.[9] A study conducted by Warren et al. showed that the average Medicare cost in the initial phase of treatment for prostate cancer was $18,261 in 2002.[58] Another study conducted by Yabroff et al. using SEER-Medicare data from 1999 – 2003 showed that the mean annual cost was $10,612 for the initial phase of prostate cancer treatment; $2,134 for continuing phase of care and $33,691in the end-of-life or terminal phase.[59]

Compared to other treatment options for localized prostate cancer, conservative management and cryotherapy are less expensive, and are minimally invasive

options.[12,55,56,60] Crawford et al. found that the 2-year cost of care related to watchful waiting (i.e., conservative management) was $24,809 per patient, which was mainly due to multiple follow-ups and close monitoring.[6] Snyder et al. showed that conservative management was associated with the lowest initial short-term cost (treatment cost within 1 year of diagnosis) of US $4,270, and 5-year total costs of US $9,130.[61] However, a cost-effectiveness analysis conducted by Hayes et al., which compared conservative management and active treatment (brachytherapy, intensity-modulated radiation therapy, or radical prostatectomy), showed that the cost was higher in patients who were on conservative management.[62] The initial treatment of brachytherapy was found to be more effective and less expensive than active surveillance by US $1238.[62] The highest costs in patients on conservative management were associated with treating underlying erectile dysfunction and urinary symptoms along with repeated biopsies.[62] Similarly, another study showed that the average initial 6 months costs and annual costs were low for those choosing conservative management ($2,586 and $5843, respectively), however the cumulative costs demonstrated that these patients require more prostate-related expenses over time.[55]

An average initial 6 months costs and annual cost for the men who chose cryotherapy were found to be $7,574 and $7,838, respectively.[55] However, cryotherapy has been found to be least expensive with the localized prostate cancer.[55] Other economic analyses also revealed significantly lower costs with cryotherapy compared to radiation therapy or surgery.[37,63] In 2012, a cost-effectiveness study was conducted to compare brachytherapy with cryotherapy.[37] The authors found that healthcare expenditures were higher for brachytherapy as compared to cryotherapy by nearly $4000.[37] A study

conducted in a single tertiary-care institution in 2016 assessed costs among different treatments used in localized prostate cancer, and found that the average 5 year cost for the conservative management and cryotherapy were $7,298 and $11,215, respectively.[64] Overall, very few studies have been conducted in the past on conservative management and cryotherapy. With many treatment options, and a paucity of comparative effectiveness data on cryotherapy and conservative management, treatment for clinically localized prostate cancer remains controversial.[65]

Most of the studies conducted in the past are either dated, had shorter follow up periods, or were unable to evaluate costs across initial, continuous and terminal phases of care. Because of the high survival rates, the long-term follow-up care for these men is critical. As the number of elderly population has been increasing with improvement in survival rates, much of the cost of treating cancer has been borne by Medicare, and these trends will continue in the future.[58] This makes it critical to understand cost from the Medicare perspective, and the cost distribution across different phases of care.

***Demographic and clinical factors influencing outcomes in prostate cancer***

Various patient related factors including age, race, comorbidities, year of diagnosis, education, region, and population density could impact the outcomes associated with these treatment options in localized prostate cancer.[66-68] The incidence and morbidity of prostate cancer could differ based on patient age, and there are differences in the treatments offered to men at different age ranges.[4,66] Men with multiple comorbidities also derive little survival benefit.[69] Clinical factors such as tumor stage (T1 or T2), and histologic grade could influence prognosis and treatment outcomes.[2,67,68]

Histologic grade is associated with overall and prostate-cancer-specific survival.[4] Histologic grades are determined by Gleason score, and is classified as well differentiated (Gleason scores of 2–4), moderately differentiated (Gleason scores of 5 - 7), and poorly differentiated (Gleason score of 8 and above).[70,71] Men with well differentiated tumors have minimal risk of dying (7%) from prostate cancer, while men with poorly differentiated tumors have a high risk of dying (53%) from their disease within 10 years of diagnosis.[4]

***Problem statement and need for the study***

Uncertainty about the comparative effectiveness and harms of the primary treatments for localized prostate cancer is the major gap in knowledge.[4] Emerging treatments such as conservative management and cryotherapy are increasingly being used; however there are neither head to head randomized controlled trials, nor adequate evidence on long-term outcomes. More comparative effectiveness research using observational data is needed to assess the relative benefits and risks of localized prostate cancer treatments. Additional studies are needed to evaluate clinical and economic benefits, and to demonstrate improvement in patient outcomes associated with prostate cancer therapies.[2]

Scant research has been conducted to assess the outcomes associated with conservative management, and studies conducted in the past are dated. Cryotherapy is a relatively newer treatment option and long terms outcomes are not adequately known.[16,72] Trends in the management of patients with localized prostate cancer suggests that the rates of conservative management increased sharply in 2010 through 2013.[73] This

suggests that with an increase in utilization of conservative management approach in recent years, newer evidence is needed to assess long term outcomes. Since, localized prostate cancer typically is a slow growing tumor, observational and less invasive strategies are more appealing to patients.

Conservative management and cryotherapy could have significant impact on clinical and economic outcomes in patient with prostate cancer. These treatments for prostate cancer have the potential to improve outcomes by prolonging survival and reducing symptoms. Hence, such treatments could be associated with significant costs, causing payers to closely scrutinize clinical and economic data before approving reimbursement. Adequate knowledge about the impact of these treatments on the prevalence of other outcomes including depression and anxiety disorders is lacking. Such evidence is needed to make informed decisions for older patients, who tend to choose treatment options that leads to lower MHI and improves quality of life, rather than those options that maximize survival.[52,53]

The clinical decision making is a multidimensional and complex process.[74] Optimal treatment decision making should involve the consideration of various outcomes including side-effects, survival, mental health issues and cost associated with treatments over time.[72] Evidence of long term comparative effectiveness of these treatment strategies is needed. Comparative effectiveness research of localized prostate cancer treatments has also been identified as a top priority by the Institute of Medicine in 2009.[75] The evidence generated through this research could provide reliable costs estimates, which are needed to describe the overall economic burden associated with these two treatments. Further, comparative effectiveness research might reduce expenditures by identifying care that is

either ineffective or no more effective than lower cost alternatives in our patient populations.[75] This could help policy makers in understanding and justifying resource allocation. The evidence generated could also guide physicians and patients in choosing appropriate treatment based on their preferences for better survival or better quality of life. This comparative effectiveness study could provide possibility to outweigh these clinical outcomes based on patients preferences. The American Urological Association (AUA) guidelines emphasize that patients' preferences regarding treatment options are important.[72]

Therefore, the purpose of this study is to provide evidence on comparative effectiveness of conservative management and cryotherapy based on treatment related side-effects, cancer specific survival, healthcare costs and prevalence of depressive and anxiety disorders in men with localized prostate cancer.

### *Specific Aims*

The following are the three specific aims of this study:

**Specific Aim 1:** To assess the comparative effectiveness of conservative management and cryotherapy based on treatment related side-effects, and cancer specific survival in men with localized prostate cancer.

*Hypotheses: We hypothesized that men on conservative management may experience lower treatment related-side effects, and higher survival rates as compared to men on cryotherapy.*

**Specific Aim 2:** To compare rates of subsequently diagnosed mental health issue (MHI), and time to develop any MHI in men with localized prostate cancer undergoing conservative management or cryotherapy.

*Hypotheses: We hypothesized that men on conservative management may have lower rates of MHI as compared to men on cryotherapy. We also hypothesized that men on conservative management may develop MHI earlier than men on cryotherapy.*

**Specific Aim 3:** To estimate the total direct medical costs and phase of care costs associated with cryotherapy and conservative management in men with localized prostate cancer.

*Hypotheses: We hypothesized that men on conservative management may have lower direct medical costs, and phase of care costs as compared to men on cryotherapy.*

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# CHAPTER 2

# COMPARATIVE EFFECTIVENESS OF CONSERVATIVE MANAGEMENT VERSUS CRYOTHERAPY IN LOCALIZED PROSTATE CANCER PATIENTS: AN ANALYSIS OF TREATMENT RELATED SIDE-EFFECTS AND SURVIVAL[†]

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**Abstract**

**Background:** There are uncertainties on comparative effectiveness of conservative management and cryotherapy in patients with localized prostate cancer due to insufficient evidence. Therefore, this study aims to compare treatment related side-effects and cancer specific survival associated with conservative management and cryotherapy in patients with localized prostate cancer.

**Methods:** Patients with localized prostate cancer diagnosed between 2000 and 2013 and their Medicare claims information from 2000-2014 were obtained from the Surveillance, Epidemiology, and Ends Results (SEER)-Medicare linked data. Rates of erectile dysfunction, lower urinary tract obstruction, bowel fistula, urinary fistula, urinary incontinence, bleeding and hydronephrosis; and cancer specific survival were assessed. The multivariate logistic regression analyses and cox proportional hazard regression were performed.

**Results:** There were 7,998 and 3,051 patients in the conservative management and cryotherapy cohort, respectively. The likelihood of erectile dysfunction, lower urinary tract obstruction, urinary fistula, urinary incontinence and hydronephrosis were found to be significantly lower (53%, 35%, 69%, 65% and 36%, respectively) in the conservative management cohort. The cancer specific survival rates in the conservative management and cryotherapy cohort were found to be 95.79 % and 93.59%, respectively. Patients in the conservative management cohort also had significantly 12% lower hazards of dying as compared to patients in the cryotherapy cohort.

**Conclusion:** Conservative management seems to be a better treatment option over cryotherapy in terms of treatment related side-effects and survival. Further research is

needed to compare other significant long-term outcomes such as costs associated with these treatment choices and quality of life.

**Keys words:** Prostate Cancer; Conservative Management; Cryotherapy; Side-effects; Survival, SEER-Medicare

## Introduction

Prostate cancer is the most prevalent cancer and a second leading cause of death in American men.[1,2] There were approximately 220,800 new cases of prostate cancer and approximately 27,540 deaths from prostate cancer as estimated in 2015.[1,3] Men aged 65 years or older are more often diagnosed with prostate cancer.[1] It has been reported that nearly 4 out of 5 cases are diagnosed with localized prostate cancer (early stage prostate cancer).[4] Several treatment options are available for localized prostate cancer. However, the impact of these treatment options on survival and patients' quality of life may vary due to different side-effects. Minimally invasive treatment options with fewer side effects than surgery and radiation, such as conservative management and cryotherapy, may be more preferable among patients with localized prostate cancer.[5]

Conservative management is an observational treatment strategy, in which no treatment is given to patients until cancer progresses to advanced or metastatic stage.[6] Conservative management is commonly used for localized prostate cancer. Patients on conservative management were found to have higher survival rates than active treatment strategies.[7] A study conducted in 2010 found an overall survival for the cohort on conservative management to be 78% while 10-years cancer specific survival was found to

be 92%.[8] Contrarily, few studies have shown lower rates of survival with conservative management as compared to active treatment.[9,10] Patients who are on conservative management are often followed by repeated biopsies, digital rectal examinations (DRE), and prostate specific antigen (PSA) testing. However, evidence suggests that there is an increased risk of erectile dysfunction among patients who undergo repeated prostate biopsies.[11,12] Biopsies are associated with bleeding, infections, pain and low risk of urinary track symptoms.[13]

Cryotherapy involves destruction of cancer cells through rapid freezing and thawing, and injection of very cold gases, while avoiding lethal freezing to the surrounding healthy tissues.[2,14] This procedure is usually performed on an outpatient basis and typically only requires one treatment.[5] The frequency of side-effects associated with cryotherapy are fewer than other treatments, however erectile dysfunction is very common after cryotherapy.[15] Some other less commonly reported side-effects of cryotherapy are bleeding, urinary and bowel fistulas, lower urinary tract obstruction, hydronephrosis, and incontinence.[16,17 15,18] Compared with other treatment modalities such as surgery and radical prostatectomy, long term outcomes of cryotherapy are not known because cryotherapy is relatively newer technique.[2,19]

Previous research examining the clinical outcomes associated with conservative management has focused on shorter follow-up periods which may not capture important events. Also, long term outcomes of cryotherapy are not known, which may contribute to uncertainties that hinder treatment decision making. The Agency for Healthcare Research and Quality (AHRQ) conducted a review on comparative effectiveness of treatments used in localized prostate cancer.[20] It was concluded that there are

uncertainties about the comparative effectiveness and harms of these treatments due to inadequate evidence on long term outcomes.[20] Insufficient evidence and uncertainties associated with conservative management and cryotherapy highlight the need for further evaluation of these two treatments. Evidence is needed regarding the long term outcomes of these treatment options for localized prostate cancer to guide patients, their families and health care providers in choosing optimal treatment. Thus, the purpose of this study was to assess the comparative effectiveness of conservative management and cryotherapy based on treatment related side-effects, and cancer specific survival in patients with localized prostate cancer.

## Methods

*Study design and data source*

This retrospective longitudinal cohort study utilized the Surveillance, Epidemiology, and Ends Results (SEER)-Medicare linked data set. This data included patients diagnosed from 2000 through year 2013, and their claims information available from 2000 through 2014. The linkage of the SEER and Medicare data is the result of the collaborative effort of the National Cancer Institute, the SEER registries, and the Center for Medicare and Medicaid Services (CMS).[21] The SEER program captures clinical, demographic and survival information for approximately 28% of the US population and is 98% complete for case ascertainment. The Medicare program covers approximately 97% of persons aged 65 years and older.[21] Several data files were utilized for this study. The Patient Entitlement and Diagnosis Summary File (PEDSF) was used to obtain clinical information regarding cancer, patients' demographics and Medicare status. The

Carrier file (NCH) was used to capture information on physician and non-institutional provider services (Part B) provided to the inpatient and outpatient study population. The Medicare Provider Analysis and Review file (MEDPAR) and the Outpatient files were utilized to extract information regarding inpatient cancer care and hospital outpatient services respectively. Additional Medicare claims files including Home Health Agency (HHA), Durable Medical Equipment (DME) and Hospice were also reviewed to capture claims information of the study cohorts. This study was approved by the University of Georgia's Institutional Review Board.

*Study cohorts*

Patients with localized prostate cancer were identified as those with stage I or stage II cancer diagnosis.[22,23] Patients in the conservative management group were identified as those who did not receive any immediate treatment within the first 6 months of diagnosis of localized prostate cancer.[24,25] Patients in the cryotherapy cohort were identified using either the International Classification of Diseases, ninth revision, (ICD-9) procedural code (60.62), Healthcare Common Procedure Coding System (HCPCS) codes (G0160 or G0161) or Current Procedural Terminology (CPT) code (55873). Patients were excluded from the study if they were (i) first diagnosed at autopsy or by death certificate, (ii) had other types of cancer, (iii) enrolled in HMO, (iv) at other stages of cancer, or (v) were below 66 years of age (restricting the cohort to patients aged 66 years old allowed at least 12 months of Medicare claims data).

*Outcomes*

Seven treatment related side-effects were identified in these patients: erectile dysfunction, lower urinary tract obstruction, bowel fistula, urinary fistula, urinary incontinence, bleeding and hydronephrosis.[15-18,26] These side-effects were identified by relevant diagnostic and procedural codes, which are presented in Table 2.1. Cancer specific survival was measured as the time from prostate cancer diagnosis until death as a result of prostate cancer. Information on cancer specific survival such as date of diagnosis, and death along with cause of death were obtained from the SEER's PEDSF file.

*Covariates*

Demographic information included patients' age (66-69 years, 70-74 years, 75-79 years, and 80 and above), race (Caucasians, African American, and others), marital status (married, unmarried/single and unknown), year of diagnosis (2000-2004, 2005-2009, and 2010-2013), geographic location (Northeast, South, Central, West), and urban residency (yes/no). Information about education (i.e., the proportion of population with less than a high school degree) was obtained from the census tract file of the SEER. The education variable was categorized into quartiles. The categories for the proportion of population with less than a high school degree were: 0% to 7.13% (representing high educational level), 7.14% to 11.91% (medium), 11.92% to 20.46% (lower), 20.47% to 100% (lowest), and unknown.[27] The Charlson Comorbidity Index (CCI) was derived from the Medicare claims during the year prior to prostate cancer diagnosis using a validated algorithm.[28,29] The CCI was categorized as 0, 1, and 2 and above.

Cancer related information including tumor stage and grade were also extracted. Tumor grades were determined by Gleason score, and is classified as well differentiated

(Gleason scores of 2–4), moderately differentiated (Gleason scores of 5 - 7), and poorly differentiated (Gleason score of 8 and above).[30,31] Tumor stage was also classified as T1 and T2.

*Statistical analysis*

Descriptive statistics were performed to characterize the conservative management and cryotherapy cohorts. Chi-square tests were conducted to examine the differences in characteristics between the study cohorts. Differences in treatment related side effects between the cohorts were compared using chi-square tests. Multivariate logistic regression was utilized to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between each side-effects and the treatment selection, after controlling for other covariates. The Kaplan-Meier survival method was used to test for the crude differences among the 2 cohorts using a log-rank test. A multivariate cox proportional hazard model was used to estimate the cancer specific survival rates, controlling for all the covariates. All analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary, NC).

## Results

### *Characteristics of the study cohorts*

The final analytical cohort included 11,049 eligible patients, diagnosed with localized prostate cancer between 2000 and 2013. Figure 2.1 shows the derivation of the final analytical cohort based on the inclusion and exclusion criteria. There were 7,998 patients in the conservative management cohort and 3,051 patients in the cryotherapy cohort. Table 2.2 describes the baseline characteristics of the study cohorts. Overall, the

conservative management and cryotherapy cohorts were found to be statistically different in terms of age, race, education, geographic location, marital status, urban residency, year of diagnosis, tumor grade, and stage ($p < 0.05$). Compared to the cryotherapy cohort, patients in the conservative management cohort were more likely to be aged 66-69 years (36.30% vs 24.98%), while patients in the cryotherapy cohorts were more likely to be aged between 70 to 74 years (36.18%). Patients in the conservative management and cryotherapy cohort were less likely to be above 80 years (10.44% and 12.13%, respectively).

A majority of patients in the conservative management and cryotherapy cohort were Caucasians, married, had a comorbidity score of 0, residing in urban areas and were at T2 stage. Compared to the cryotherapy cohort, patients in the conservative management group were less likely to be Caucasians (77.41% vs 80.40%), less likely to be married (65.19% vs 67.94%), less likely to have a comorbidity score of 0 (74.92% vs 75.06%), more likely to be residing in urban areas (92.71% vs 86.04%), and were more likely to be at T2 stage (57.31% vs 53.29%). Similarly, compared to the patients in the cryotherapy cohort, patients in the conservative management cohort were less likely to belong to the West (46.25% vs 53.82%), were more likely to have more than high school education (33.95% vs 26.75%), were less likely to be diagnosed between 2005 and 2009 (41.61% vs 53.72%) and were more likely to have moderately differentiated tumors (56.39% vs 43.17%).

***Treatment related side-effects***

Side-effects assessed in this study included erectile dysfunction, lower urinary tract obstruction, bowel fistula, urinary fistula, urinary incontinence, bleeding and hydronephrosis. The crude rates of treatment related side-effects in both the cohorts are presented in Table 2.3. Overall, patients in the cryotherapy cohort experienced significantly higher rates of any side-effects compared to patients in the conservative management cohort (29.29% vs 42.61%, $p < 0.0001$). Compared to conservative management cohort, patients in the cryotherapy experienced significantly higher rates of erectile dysfunction (12.02% vs 20.65%, $p < 0.0001$), lower urinary tract obstruction (9.06% vs 13.63%, $p < 0.0001$), urinary fistula (<0.14% vs 0.39%, $p < 0.05$), and hydronephrosis (1.74% vs 2.79%, $p < 0.05$). There were no statistically significant differences observed in the rates of urinary incontinence, bleeding and bowel fistula between the two cohorts.

Controlling for all the covariates, it was found that patients in the conservative management cohort were nearly 50% less likely to experience any side-effects compared to patients in the cryotherapy cohort (Table 2.4). Compared to patients in the cryotherapy cohort, patients in the conservative management cohort were 53% less likely to experience erectile dysfunction (Odds Ratio (OR): 0.47; 95% Confidence Interval (CI) [0.41, 0.53]). Similarly, patients in the conservative management had lower odds of experiencing lower urinary tract obstruction (OR: 0.65; 95%CI [0.57, 0.75]), urinary fistula (OR: 0.31; 95%CI [0.13, 0.74]), hydronephrosis (OR: 0.64; 95%CI [0.48, 0.86]), and urinary incontinence (OR: 0.35; 95%CI [0.13, 0.93]).

***Cancer specific survival***

Overall, cancer specific survival rates in the conservative management and cryotherapy cohort were found to be 95.79 % and 93.59%, respectively at the end of the study period. Figure 2.2 shows the cancer specific Kaplan-Meier survival curves across the treatment groups. Survival rates were found to be significantly different between the patients receiving conservative management and cryotherapy (log-rank p-value <0.05). Results from the multivariate cox model are presented in Table 2.5. Patients in the conservative management cohort had significantly 12% lower hazards of dying as compared to patients in the cryotherapy cohort (HR: 0.78, 95% CI [0.56 - 0.98]), after controlling for all the covariates.

Demographic characteristics such as age, race, tumor grade, comorbidities and year of diagnosis were found to be significantly associated with cancer specific survival. Patients in the age group of 70-74 yrs.(HR: 1.44; 95% CI [1.12,1.86]), 75-79 yrs.(HR: 1.47; 95% CI [1.12,1.93]), and 80+ yrs.(HR: 2.70; 95% CI [2.10,3.61]) had significantly higher hazards of dying as compared to those in the age group of 66-69 yrs. African American patients had 30% higher hazards of dying as compared to Caucasian patients (HR: 1.30; 95% CI [1.01, 1.68]). Compared to patients with poorly differentiated tumors, patients with well-differentiated (HR: 0.40; 95% CI [0.16, 0.97]) and moderately differentiated tumors (HR: 0.38; 95% CI [0.31, 0.46]) had significantly lower hazards of dying. The hazards of dying in patients with a comorbidity score of one (HR: 1.82; 95% CI [1.65, 1.92]) and 2 and above (HR: 1.87; 95% CI [1.68, 1.98]) was significantly higher as compared to those with no comorbidities. The hazards of dying were also found to be significantly higher in patients diagnosed between 2005 and 2009 (HR: 1.43; 95% CI

[1.13, 1.82]), and 2010-2013 (HR: 5.94; 95% CI [3.45, 10.21]) as compared to those diagnosed between 2000 and 2004.

**Discussion**

Treatment choices for localized prostate cancer are overwhelming; however there is limited evidence to support one choice over the other.[20] This study addresses a significant gap in the literature by providing evidence about the side effects and long term outcomes associated with two treatment choices for localized prostate cancer. Findings suggest that the rates of side-effects are lower in patients who choose conservative management over cryotherapy. Cancer specific survival rates were also found to be higher in patients in the conservative management cohort compared to cryotherapy.

Study findings indicate that the crude rates of erectile dysfunction, lower urinary tract obstruction, urinary fistula, and hydronephrosis were significantly lower in patients who chose conservative management as compared to those who chose cryotherapy. In fact, after controlling for all the covariates, patients in the conservative management cohort had significantly lower odds of erectile dysfunction, lower urinary tract obstruction, urinary fistula, hydronephrosis, and urinary incontinence. Lower rates of side-effects associated with conservative management found in this study are similar to previous research that compared conservative management approaches with other active treatments.[32,33] Wilt et al. compared radical prostatectomy with conservative management and found that radical prostatectomy was associated with a significant increase in urinary incontinence and erectile dysfunction.[32] Acar et al. conducted a study that compared brachytherapy, robot-assisted laparoscopic prostatectomy and conservative management,

and found that rates of erectile dysfunction were lower with conservative management.[33] Side effects associated with cryotherapy are also found to be low, with lower urinary tract obstruction and erectile dysfunction being the most common side-effects.[26] In a cost-effectiveness analysis of cryotherapy and brachytherapy, rates of erectile dysfunction and urinary complications were found to be higher with cryotherapy as compared to brachytherapy.[17] However, the rates of bowel complications were found to be lower in the cryotherapy cohort.[17]

Although non-significant, our findings also showed that the rates of bowel fistula and bleeding were slightly higher in the conservative management cohort compared to the cryotherapy cohort. Conservative management involves periodic monitoring which involves procedures such as biopsy.[34] Evidence suggests that biopsies in prostate cancer are associated with various complications such as bleeding and fistulas.[13,35] The higher rates of bleeding and bowel fistula in the conservative management cohort in our study may be associated with frequent biopsies. These treatments related side-effects could significantly impact patients' quality of life, and therefore it is important to take them into consideration when making treatment choices.

The 13 years survival rates associated with conservative management and cryotherapy were found to be 95.79 % and 93.59%, respectively. Although, the rates of survival are comparable to those in the literature, there is inconclusive evidence on the treatment option with higher survival rates. A prospective, single arm study conducted by Klotz et al on a conservative management cohort found the 10-year cancer specific survival rate to be 97.2% with conservative management.[8] Similarly, a prospective study conducted by Rodriguez et al. on a cryotherapy cohort in Spain found the cancer specific

survival rates of 98.1%.[36] However, this study lacked the comparison group. A recent review conducted on cryotherapy concluded comparable survival benefits of cryotherapy over other treatments such as radiation therapy.[37] However, due to the limitations in available evidence in literature, assessment of comparative benefits and harms of these treatments have been difficult. Although, our findings align with the available literature showing high survival rates with both conservative management and cryotherapy, choosing conservative management provides slightly higher survival benefit over cryotherapy.

Additionally, increasing age, patients belonging to African American racial group, having poorly differentiated tumors and higher comorbidities were found to have significantly higher likelihood of dying. Similar to the available evidence in the literature, our findings shows considerable factors that could influence survival.[20,38] Significant racial disparities exists in survival rates among patients with prostate cancer. African American patients are approximately twice as likely than Caucasian patients to die from prostate cancer.[39,40] Literature also suggests that patients with well differentiated tumors have minimal risk of dying from prostate cancer, while men with poorly differentiated tumors have a high risk of dying from their disease within 10 years of diagnosis.[20] When choosing treatments, these factors play an important role, and hence should be carefully considered.

These outcomes are extremely relevant for the treatment decision making process. Evidence on the long term outcomes generated from this study could be helpful and convincing in preferring conservative management over cryotherapy in elderly patients with localized prostate cancers, thus avoiding the associated risks and its impact on

survival. A study examining literature on patient preferences indicated that patients with prostate cancer are not well informed.[41] In this era of shared decision making, it is increasingly important for healthcare providers to provide better quality of life with minimal post-treatment decision regrets among patients. Therefore, healthcare providers should actively engage in translating the available evidence to practice, not only through communication with their patients but also by practicing evidence-based decision making.

This study has several limitations that warrant mentioning. The study cohorts were restricted to only Medicare beneficiaries who were aged 66 years and above. Therefore, study findings may not be generalizable to other patient populations such as Medicaid, Health Maintenance Organizations, other insurance plans, or to those younger than 65 years of age. There might be a possibility of selection bias due to non-randomized nature of the study. The use of Medicare administrative claims data to estimate treatment-related side-effects may be underestimated. Finally, this study did not account for other factors that may influence treatment choices such as physicians or patient preferences, or self-management strategies, which may have influenced our results.

Despite these limitations, findings from this study are important for patients, healthcare providers and policy makers. Better quality of care can be provided to patients suffering from prostate cancer with careful consideration of these outcomes. Findings from this comparative effectiveness research can assist policy makers, healthcare providers, and patients in making informed treatment decisions to optimize care. In addition, evidence from this study could guide policy makers in changing reimbursement

by justifying resource allocations. Conservative management seems to be a better treatment option over cryotherapy in terms of treatment related side-effects and survival. Further research is needed to compare other significant long-term outcomes such as costs associated with these treatment choices and quality of life.

**Tables**

Table 2.1: ICD-9 and CPT/HCPCS codes for treatment related side-effects

| Side-effects | ICD-9 diagnoses codes | ICD-9 procedure codes | CPT/HCPCS code |
|---|---|---|---|
| **Erectile dysfunction** | 607.84 | 64.94, 64.95, 64.96, 64.97 | 54400, 54401, 54402, 54405, 54407, 54408, 54409, 54410, 54411, 54415, 54416, 54417, C1007, C1813, C2622, C3500, C8514, C8516, C8534, L7900, 54231, 54235, J0270, J0275, J2440, J2760 |
| **Lower urinary tract obstruction** | 596.0, 598.x, 599.6, 788.2x | 57.85, 57.91, 57.92, 58.0, 58.1, 58.3x, 58.44, 58.46, 58.47, 58.5, 58.6, 58.99, 60.95, 60.2x | 52275, 52276, 52281,52510, 53010, 53400, 53405,53410, 53415, 53420, 53425, 53600, 53601, 53605, 53620, 53621, 52601, 52612, 52614, 52620, 52630, 53850, 53852, 2282, 52283 |
| **Bowel fistula** | 569.41, 569.81 | 48.73, 48.93, 46.1x, 48.31, 48.32, 48.33 | 45800, 45805, 45820, 45825, 45562, 45563 |
| **Urinary fistula** | 596.1, 596.2, 599.1 | 57.83, 57.84, 58.43 | 44660, 44661, 53520 |
| **Urinary incontinence** | 788.3x, 599.82 | 59.72, 58.93, 59.3, 59.4, 59.5, 59.6, 59.71, 59.79 | 51715, 53445, 53447, 53440, 51840, 51841, 53442, 53443 |
| **Bowel bleeding** | 569.41, 569.81 | | |
| **Hydronephrosis** | 591 | | |

Abbreviations: ICD-9, International classification of diseases, ninth revision; CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System

Table 2.2: Baseline characteristics of the study cohorts

| Baseline Characteristics | Conservative management (n=7,998) | Cryotherapy (n=3,051) | P-value |
|---|---|---|---|
| **Age group, n (%)** | | | |
| 66-69 | 2,903 (36.30 %) | 762 (24.98%) | <0.0001 |
| 70-74 | 2,661 (33.27%) | 1,104 (36.18%) | |
| 75-79 | 1,599 (19.99%) | 815 (26.71%) | |
| 80+ | 835 (10.44 %) | 370 (12.13%) | |
| **Race, n (%)** | | | |
| Caucasians | 6,191 (77.41%) | 2,453 (80.40%) | 0.0029 |
| African Americans | 1,136 (14.20%) | 372 (12.19%) | |
| Others | 671 (8.39%) | 226 (7.41%) | |
| **Tumor grade, n (%)** | | | |
| Well-differentiated | 123 (1.54%) | 18 (0.59%) | <0.0001 |
| Moderately differentiated | 4,510 (56.39%) | 1,317 (43.17%) | |
| Poorly differentiated | 3,140 (39.26%) | 1,584 (51.92%) | |
| Unknown | 225 (2.81%) | 132 (4.33%) | |
| **Tumor stage, n (%)** | | | |
| T1 | 3,414 (42.69%) | 1,425 (46.71%) | 0.0001 |
| T2 | 4,584 (57.31%) | 1,626 (53.29%) | |
| **Charlson comorbidity index, n (%)** | | | |
| 0 | 5,992 (74.92%) | 2,290 (75.06%) | 0.3600 |
| 1 | 1,833 (22.92%) | 708 (23.21%) | |
| 2+ | 173 (2.16%) | 53 (1.74%) | |
| **Marital Status, n (%)** | | | |
| Married | 5,214 (65.19%) | 2,073 (67.94%) | 0.0019 |
| Unmarried/Single | 1,758 (21.98%) | 577 (18.91%) | |
| Unknown/missing | 1,026 (12.83%) | 401 (13.14%) | |
| **Education, n (%)** | | | |
| First quartile (highest) | 2,715 (33.95%) | 816 (26.75%) | <0.0001 |

| | | | |
|---|---|---|---|
| Second quartile | 1,526 (19.08%) | 599 (19.63%) | |
| Third quartile | 1,372 (17.15%) | 558 (18.29%) | |
| Fourth quartile (lowest) | 1,986 (24.83%) | 942 (30.88%) | |
| Unknown | 399 (4.99%) | 136 (4.46%) | |
| **Geographic location, n (%)** | | | |
| Northeast | 2,074 (25.93%) | 277 (9.08%) | <0.0001 |
| South | 905 (11.32%) | 540 (17.70%) | |
| Central | 1,320 (16.50%) | 592 (19.40%) | |
| West | 3,699 (46.25%) | 1,642 (53.82%) | |
| **Urban residency, n (%)** | | | |
| Yes | 7,415 (92.71%) | 2,625 (86.04%) | <0.0001 |
| No | 583 (7.29%) | 426 (13.96%) | |
| **Year of diagnosis, n (%)** | | | |
| 2000 -2004 | 2,597 (32.47%) | 713 (23.37%) | <0.0001 |
| 2005-2009 | 3,328 (41.61%) | 1,639 (53.72%) | |
| 2010-2013 | 2,073 (25.92%) | 699 (22.91%) | |

Table 2.3: Rates of side-effects in the Conservative management and Cryotherapy cohort

| **Side-effects** | **Conservative Management, ( n =7,998)** | **Cryotherapy, (n = 3,051)** | **P-value** |
|---|---|---|---|
| Overall side-effects, n (%) | 2343 (29.29 %) | 1300 (42.61 %) | <0.0001 |
| **Side-effects by categories** | | | |
| Erectile dysfunction, n (%) | 961 (12.02 %) | 630 (20.65 %) | <0.0001 |
| Lower Urinary tract obstruction, n (%) | 725 (9.06 %) | 416 (13.63 %) | <0.0001 |
| Urinary Fistula, n (%) | <11 (<0.14 %) | 12 (0.39 %) | 0.0047 |
| Hydronephrosis, n (%) | 139 (1.74 %) | 85 (2.79 %) | 0.0005 |
| Urinary Incontinence, n (%) | <11 (<0.14 %) | <11 (0.36 %) | 0.1573 |
| Bleeding, n (%) | 547 (6.84 %) | 187(6.13 %) | 0.1803 |
| Bowel Fistula, n (%) | 43 (0.54 %) | 13 (0.43 %) | 0.4604 |

Notes: Cell size less than 11 are not shown in accordance with SEER-Medicare data use agreement

Table 2.4: Likelihood of treatment related side-effects in patients receiving Conservative Management vs Cryotherapy

| **Side-effects (Conservative management vs Cryotherapy)** | **Adjusted Odds Ratio (95% CI)** | **P-value** |
|---|---|---|
| Overall side-effects, n (%) | 0.54 (0.49, 0.59) | <0.0001 |
| **Side-effects by categories** | | |
| Erectile dysfunction, n (%) | 0.47 (0.41, 0.53) | <0.0001 |
| Lower Urinary tract obstruction, n (%) | 0.65 (0.57, 0.75) | <0.0001 |
| Urinary Fistula, n (%) | 0.31 (0.13, 0.74) | 0.0085 |
| Hydronephrosis, n (%) | 0.64 (0.48, 0.86) | <0.0001 |
| Urinary Incontinence, n (%) | 0.35 (0.13, 0.93) | 0.0344 |
| Bleeding, n (%) | 1.18 (0.98, 1.41) | 0.0763 |
| Bowel Fistula, n (%) | 1.42 (0.75, 2.70) | 0.2865 |

Notes: Odds ratio adjusted for age, race, tumor grade, tumor stage, Charlson comorbidity index, geographic location, urban density, year of diagnosis, marital status, and education

Abbreviations: CI, Confidence Intervals

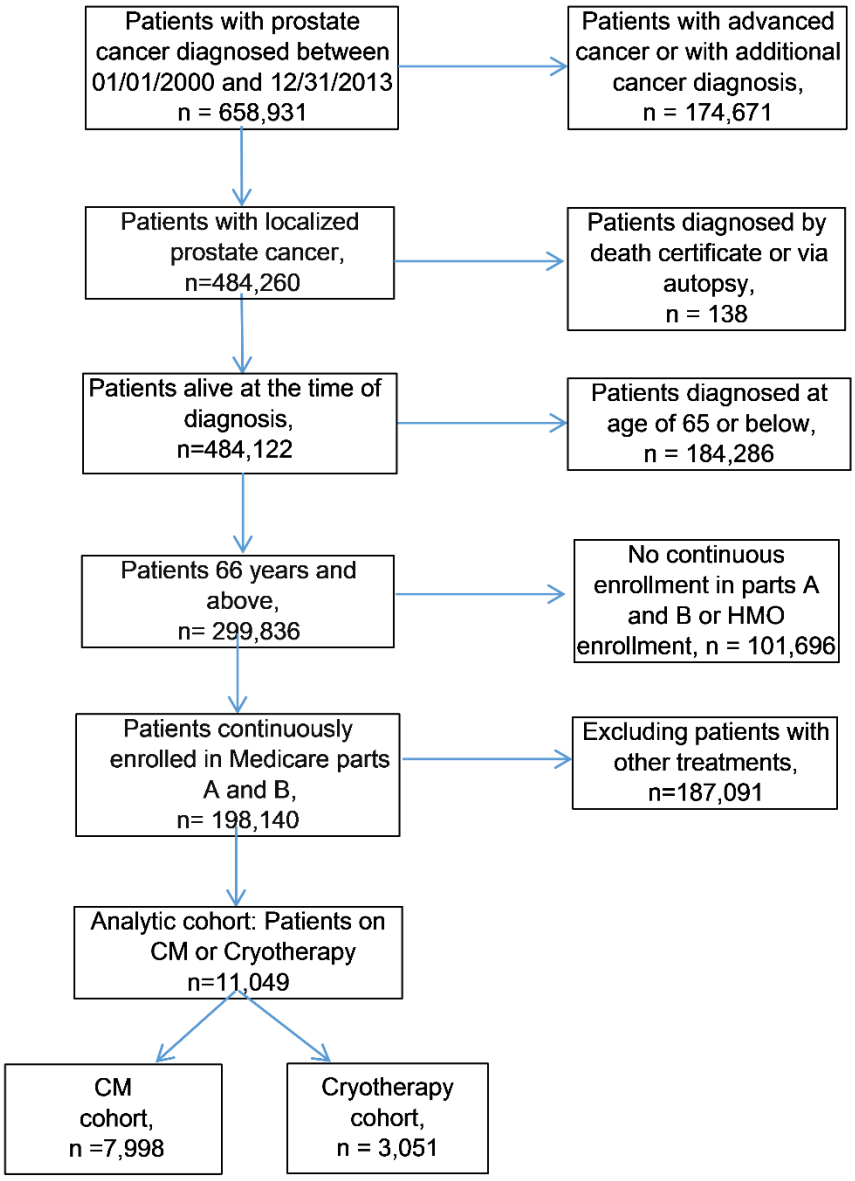
Table 2.5: Multivariate cox proportional hazards model of cancer specific survival

| | **Cancer specific survival** | |
|---|---|---|
| **Variable** | **Hazards Ratio (95% CI)** | **P-value** |
| **Treatment group** | | |
| Conservative Management | 0.78 (0.56 – 0.98) | 0.031 |
| Cryotherapy | 1 | |
| **Age** | | |
| 66-69 | 1 | |
| 70-74 | 1.44 (1.12 - 1.86) | 0.005 |
| 75-79 | 1.47 (1.12 – 1.93) | 0.006 |
| 80-84 | 2.70 (2.10 – 3.61) | <0.0001 |
| **Race** | | |
| Caucasians | 1 | |
| African Americans | 1.30 (1.01 – 1.68) | 0.044 |
| Others | 1.20 (0.86 – 1.66) | 0.283 |
| **Tumor grade** | | |
| Unknown | 0.58 (0.36 – 0.94) | 0.026 |
| Well-differentiated | 0.40 (0.16 – 0.97) | 0.042 |
| Moderately differentiated | 0.38 (0.31 – 0.46) | <0.0001 |
| Poorly differentiated | 1 | |
| **Tumor Stage** | | |
| T1 | 0.88 (0.71 -1.10) | 0.229 |
| T2 | 1 | |
| **Charlson comorbidity Index** | | |
| 0 | 1 | |
| 1 | 1.82 (1.65 – 1.92) | 0.0002 |
| 2+ | 1.87 (1.68 – 1.98) | 0.026 |
| **Marital status** | | |
| Married | 1 | |

| | | |
|---|---|---|
| Unmarried | 1.08 (0.82 – 1.43) | 0.576 |
| Unknown | 1.24 (1.01 – 1.54) | 0.050 |
| **Education** | | |
| First quartile (highest) | 1.16 (0.92 – 1.47) | 0.216 |
| Second quartile | 1.14 (0.87 – 1.49) | 0.344 |
| Third quartile | 1.18 (0.92 – 1.53) | 0.197 |
| Fourth quartile (lowest) | 1 | |
| **Geographic location** | | |
| West | 1 | |
| South | 1.28 (0.97 – 1.70) | 0.079 |
| Central | 1.25 (0.97– 1.59) | 0.080 |
| Northeast | 0.93 (0.72 – 1.19) | 0.549 |
| **Urban residency** | | |
| Yes | 1 | |
| No | 1.05 (0.75 – 1.48) | 0.762 |
| **Year of diagnosis** | | |
| 2000 - 2004 | 1 | |
| 2005 - 2009 | 1.43 (1.13 – 1.82) | 0.003 |
| 2010 - 2013 | 5.94 (3.45 – 10.21) | <.0001 |

Abbreviations: CI, Confidence Intervals

## Figures




Abbreviations: CM, Conservative management;

HMO, Health Maintenance Organizations

Figure 2.1: Procedure to generate the study sample of the analytic cohort

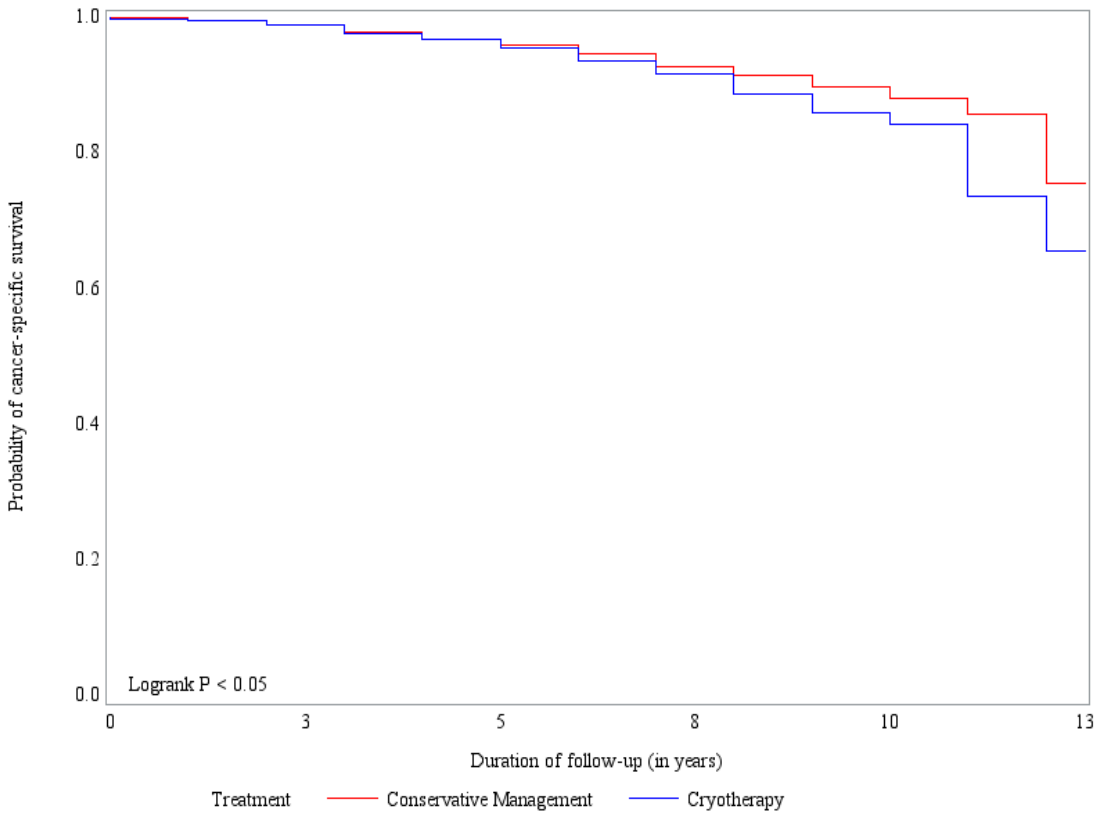



Figure 2.2: Kaplan Meier Plot of Cancer Specific Survival

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# CHAPTER 3

# IMPACT OF CONSERVATIVE MANAGEMENT AND CRYOTHERAPY ON DEPRESSION AND ANXIETY DISORDERS DIAGNOSES IN MEN WITH LOCALISED PROSTATE CANCER[†]

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**Abstract**

**Objectives:** To examine the rates of diagnosed mental health issues (MHI), and time to develop MHI in patients with localized prostate cancer undergoing conservative management or cryotherapy.

**Methods:** The Surveillance, Epidemiology and End Results (SEER)-Medicare linked data from 2000-2014 was used to identify the study cohorts. The diagnoses of any MHI (major depressive disorder, anxiety, depression-not otherwise specified (NOS), neurotic depression, and adjustment disorder with depressed mood) were identified using the ICD-9 codes. Rates of each of the MHI were assessed. The multivariate logistic regression analyses and cox proportional hazard regression were performed.

**Results:** There were 7,998 and 3,051 patients in the conservative management and cryotherapy cohort, respectively. Patients in the conservative management cohort also had significantly lower rates of depressive disorder (4.46% vs 5.64%, $p < 0.05$) and anxiety disorders (3.46% vs 4.33%, $p < 0.05$) in comparison to the cryotherapy cohort. After controlling for the covariates, patients in the conservative management cohort were 18% less likely to develop anxiety disorders. Findings from the Kaplan Meier plot also show a divergence in time to develop MHI between the conservative management and cryotherapy cohort; the time free from the development of any MHI was much longer in the conservative management cohort.

**Conclusions:** The burden of MHI is greater with cryotherapy. Healthcare providers could use this evidence in providing evidence based optimized care, and in providing need based interventions to alleviate anxiety and depression.

**Keywords:** Prostate Cancer; Conservative Management; Cryotherapy; depression; anxiety disorders, SEER-Medicare

## Introduction

According to the American Cancer Society, prostate cancer is the most common cancer and second leading cause of death in men.[1,2] About one out of seven men are diagnosed with prostate cancer during their lifetime.[1] The average age of men at the time of prostate cancer diagnosis is approximately 66 years.[1,2] Nearly four out of five cases are diagnosed with localized prostate cancer.[3] Localized prostate cancers are usually indolent with higher survival rates.[4,5] As patients are living longer with prostate cancer, other outcomes become increasingly relevant such as mental health issues.[6,7] Nearly 60% of localized prostate cancer patients encounter psychological distress,[8] and nearly 20% show clinically significant levels of depressive symptoms.[9]

Depressive and anxiety disorders are considered to be the most important mental health issues (MHI) in patients with prostate cancer, and are common during the treatment phase.[10] The presence of MHI during the treatment phase of prostate cancer are associated with significant healthcare resource utilization, costs and mortality.[6] Researchers have found that comorbid MHI in patients with prostate cancer result in nearly a fivefold increase in the risk of emergency room visits, a threefold increase in the risk of hospitalization, and a threefold increase in the risk of death compared to those without MHI.[6]

Although several treatment options are available for prostate cancer, the impact of these treatment options on mental health may vary due to differences in side effects and

effectiveness.[11] Minimally invasive options such as conservative management and cryotherapy are the two common choices among older patients due to increasing intolerance to aggressive treatments.[12] Conservative management and cryotherapy are effective in localized prostate cancer and cause less side effects, however they may also have a pervasive impact on mental health.[7]

Opting for conservative management can be mentally challenging for patients because it involves a watch and wait strategy; active therapy only begins when symptoms from locally advanced disease become apparent.[13,14] Conservative management also involves repeated biopsies to track cancer progression, which also may increase stress due to waiting for results from such tests. In addition, the risks of side effects associated with biopsies further aggravates this anxiety and fear.[7] However, previous studies have found inconsistent evidence regarding the impact of conservative management on MHI.[13,15-17] One study found that conservative management was associated with a higher risk of developing MHI in comparison to other treatment options such as radical prostatectomy and radiotherapy.[13] On the contrary, a few other studies failed to find any significant differences in MHI or psychological distress when comparing conservative management and active treatment.[15-18]

The use of cryotherapy has increased over the last 10 years due to technological advances that led to reduced side effects and mortality rates.[19] The lower side effect profile and better mortality rates could reduce patients' anxiety regarding cryotherapy treatment. However, scant research has examined cryotherapy and its long term outcomes are not completely known.[20,21] To our knowledge, MHI has not been studied in patients undergoing cryotherapy. However, a study conducted to assess quality of life among men

undergoing cryotherapy showed that overall quality of life was comparable to other prostate cancer therapies; mental health was a component of quality of life in this study.[22]

Insufficient evidence and uncertainties regarding the associations between minimally invasive prostate cancer treatment options (i.e., conservative management, cryotherapy) and MHI highlight the need for further evaluation. Such evidence is essential to help patients and providers make informed decisions regarding treatment options that align with patients' preferences and overall healthcare goals (e.g., better quality of life).[23,24] Thus, the primary objectives of this study are to examine the rates of diagnosed MHI, and time to develop MHI in patients with localized prostate cancer who underwent conservative management or cryotherapy. The secondary purpose of this study is to compare the differences in the rates of mental health issues among conservative management and cryotherapy cohorts.

## Methods

*Study design and data source*

The Surveillance, Epidemiology, and Ends Results (SEER)-Medicare linked data set was used for this retrospective longitudinal cohort study. The linkage of the SEER and Medicare data is the combined effort of the National Cancer Institute, the SEER registries, and the Center for Medicare and Medicaid Services.[25] The clinical, demographic and survival information of the cancer cases are captured by the SEER program for approximately 28% of the US population.[26] The Medicare program covers approximately 97% of the US population aged 65 years and older.[27] Several data files were utilized for this study including the Patient Entitlement and Diagnosis Summary

File (PEDSF), Carrier file (NCH), Medicare Provider Analysis and Review file (MEDPAR), Outpatient file, Home Health Agency (HHA), Durable Medical Equipment (DME) and Hospice file to capture claims information of the study cohorts. Information was extracted regarding clinical and demographic characteristics; physician and non-institutional provider services (Part B) provided to the inpatient and outpatient study population, inpatient cancer care and hospital outpatient services. The data used for this study included patients diagnosed from 2000 to 2013, with claims data through the year 2014.The University of Georgia's Institutional Review Board approved this study.

*Study cohorts and inclusion criteria*

Patients were identified as those who were aged 66 years and above, with stage I and stage II cancer diagnosis.[28,29] Patients in the conservative management cohort were identified as those who did not receive any immediate treatment within the first 6 months of diagnosis of localized prostate cancer.[30-32] Patients in the cryosurgery cohort were identified using ICD-9 procedure code (60.62), Healthcare Common Procedure Coding System (HCPCS) code (G0160 and G0161) and Current Procedural Terminology (CPT) code (55873). Patients were excluded from the study if they were: (i) first diagnosed at autopsy or by death certificate, (ii) had other types of cancer, (iii) enrolled in HMO, (iv) at other stages of cancer, or (v) were below 66 years of age (restricting the cohort to patients aged 66 years old allowed at least 12 months of Medicare claims data).

*Outcomes*

The primary outcome of interest was the presence of MHI (not previously diagnosed), specifically depression and anxiety disorders among the cohorts. The Medicare claims files and International Classification of Diseases, ninth revision (ICD-9)

codes were used to identify patients who had any of the following MHI: major depressive disorder, depressive disorder not otherwise specified (NOS), neurotic depression, adjustment disorder with depressed mood, and anxiety disorder. The ICD-9 codes for these disorders are provided in Table 3.1. The time to develop any MHI was defined as the time between the treatment initiation and diagnosis of any MHI. The date of diagnosis of these MHI and dates of treatment initiation were obtained from the SEER and Medicare claim files.

*Covariates*

The following demographic information was assessed: patients' age (66-69 years, 70-74 years, 75-79 years, and 80 and above), race (Caucasians, African American, and others), marital status (married, unmarried/single and unknown), years of diagnosis (2000-2004, 2005-2009, and 2010-2013), geographic location (Northeast, South, Central, West), and urban residency (yes/no). Information about education (i.e., the proportion of population with less than a high school degree) was obtained from the census tract file of the SEER. The education variable was categorized into quartiles. The categories for the proportion of population with less than a high school degree were: 0% to 7.13% (representing high educational level), 7.14% to 11.91% (medium), 11.92% to 20.46% (lower), 20.47% to 100% (lowest), and unknown.[33] The Charlson Comorbidity Index (CCI) was derived from the Medicare claims during the year prior to prostate cancer diagnosis using a validated algorithm.[34,35] The CCI was categorized as 0, 1, and 2 and above. Cancer related information including tumor stage and grade was also extracted. Tumor grades were determined by Gleason score, and is classified as well differentiated (Gleason scores of 2–4), moderately differentiated (Gleason scores of 5 - 7), and poorly

differentiated (Gleason score of 8 and above).[36,37] Tumor stage was also classified as T1 (i.e. the tumor cannot be felt with a DRE or seen with imaging) and T2 (i.e. the tumor is confined to the prostate and can be either felt with a DRE or seen with imaging) stage.

*Statistical analyses*

Descriptive statistics were performed to characterize the conservative management and cryotherapy cohorts, and rates of MHI. Chi-square tests were conducted to examine the differences in characteristics between the study cohorts, and differences in the rates of each of the MHI. Multivariate logistic regression was utilized to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between each MHI and the treatment selection, after controlling for other covariates. The Kaplan-Meier survival method was used to test for the crude differences in the time to develop MHI among the study cohorts using a log-rank test. A multivariate cox proportional hazard model was used to estimate the time to develop MHI, controlling for all the covariates. All analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary, NC).

## Results

There were 11,049 eligible patients diagnosed with localized prostate cancer between 2000 and 2013. The derivation of the eligible final analytical cohort is presented in Figure 3.1. There were 7,998 and 3,051 patients identified in the conservative management and cryotherapy cohorts, respectively. The baseline characteristics of the study cohorts are presented in Table 3.2. Overall, the conservative management and cryotherapy cohorts were significantly different in terms of age, race, education,

geographic location, marital status, urban residency, year of diagnosis, tumor grade, and stage ($p < 0.05$). Patients in the conservative management cohort were more likely to be younger than the patients in the cryotherapy cohort. A majority of patients in both the cohorts were Caucasians, married, had a comorbidity score of 0, residing in urban areas and were at T2 stage.

*Rates of MHI*

Table 3.3 presents the rates of depressive and anxiety disorders for the study cohorts. Compared to the cryotherapy cohort, the rates of any MHI were lower in the conservative management cohort (8.74% vs 10.32%, $p < 0.05$). Patients in the conservative management cohort also had significantly lower rates of depressive disorder (4.46% vs 5.64%, $p < 0.05$) and anxiety disorders (3.46% vs 4.33%, $p < 0.05$) in comparison to the cryotherapy cohort. After controlling for the covariates, patients in the conservative management cohort were 18% less likely to develop anxiety disorders (Odds Ratio (OR): 0.82; 95% Confidence Interval (CI) [0.65, 0.98]) in comparison to patients in the cryotherapy cohort (Table 3.4).

*Time to the development of MHI*

The unadjusted Kaplan Meier survival curves illustrating the risk of being diagnosed with MHI and stratified by treatment received are shown in the Figure 3.2. The median time to receiving a diagnosis of any mental health issue in the conservative management and cryotherapy cohort were 67.5 months and 46.7 months, respectively. The curves depicting the time to develop any MHI were significantly different between

the study cohorts (log-rank p-value <0.05). Results from the multivariate cox proportional hazards model are presented in Table 3.5. There was no statistically significant difference between the CM and cryotherapy groups in time to developing MHI after controlling for the covariates. The time to develop any MHI was found to be significantly associated with comorbidities, marital status, education and years of diagnosis. Patients with 2 or more comorbidities had 46% higher chances of early diagnosis of any MHI (Hazard Ratio (HR): 1.46; 95%CI [1.16- 2.03]) compared to those with no comorbidities. Patients with highest education were 16% less likely to develop MHI early (HR: 0.84; 95%CI [0.63- 0.98]) compared to those with lowest education. Single or unmarried patients were 26% more likely to develop MHI earlier (HR: 1.26; 95%CI [1.07- 1.48]) than married patients. Patients diagnosed from 2005-2009 (HR: 1.23; 95%CI [1.07- 1.53]) and from 2010-2013 (HR: 1.53; 95%CI [1.15-2.04]) were more likely to develop any MHI earlier in comparison to patients diagnosed between 2000 and 2004.

**Discussion**

Understanding the associations between treatment options and MHI is extremely important for older patients with prostate cancer.[23,24] The purpose of this study was to examine MHI associated with two minimally invasive treatment options in patients with localized prostate cancer. This study addresses a gap in the literature regarding the associations between MHI, conservative management, and cryotherapy. Findings suggest that the rates of MHI are low for conservative management. Study findings also indicate that other factors may play a significant role in the development of MHI among prostate

cancer patients undergoing minimally invasive treatments. These findings indicate the possibility that choosing conservative management over cryotherapy could prove beneficial for older patients in terms of MHI.

Although none of the studies in the past compared conservative management and cryotherapy, studies that compared conservative management with other active treatments such as radical prostatectomy found inconsistent results.[15-18,38,39] A prospective study conducted by Burnet et al compared conservative management and active treatment to assess the prevalence of anxiety and depression in patients with localized prostate cancer.[15] The researchers found that conservative management was not associated with greater psychological distress than active treatments.[15] Similarly, no significant psychological differences were found between conservative management and active treatment in other studies.[15-18] On the contrary, Ravi et al found that patients who were treated with radical prostatectomy or radiotherapy were at a lower risk of developing MHI as compared to those patients who were on conservative management.[13] The time to develop these MHI among patients undergoing radical prostatectomy was also found to be significantly greater than conservative management.[13] There is scant literature on the impact of cryotherapy on MHI in localized prostate cancer. Therefore, our findings provide the necessary evidence on cryotherapy and conservative management in terms of their comparative effectiveness. Since, anxiety is more common in older patients suffering from cancer, opting for conservative management might prevent older patients from developing anxiety disorders.

This study showed overall lower rates of MHI in patients who chose conservative management in comparison to patients who underwent cryotherapy. Specifically,

conservative management patients may experience less depressive disorder NOS and anxiety disorders than cryotherapy. Findings from the Kaplan Meier plot also show a divergence in time to develop MHI between the conservative management and cryotherapy cohort; the time free from the development of any MHI was much longer in the conservative management cohort. A possible explanation for lower rates of MHI and time free from MHI in the conservative management cohort could be the lower rates of side effects associated with this strategy.[11] Depression and anxiety are associated with various treatment related sexual and urinary outcomes, which could influence quality of life in prostate cancer.[40] Conservative management allows patients to avoid side effects associated with various active treatments that may lead to depression and anxiety.[7] Another plausible explanation for better outcomes associated with conservative management strategy in patients could be their increasing confidence in the strategy with no evidence of the disease progression over time.[7]

The presence of MHI among patients who choose minimally invasive treatment options warrant early monitoring and screening of depressive and anxiety disorders. MHI such as depression and anxiety are common in patients with prostate cancer, but often remain undiagnosed and untreated.[9] Periodic screening for MHI among prostate cancer patients who choose minimally invasive treatments may help detect such problems. Early psychotherapy, various stress coping strategies such as meditation, obtaining social and emotional support, self- distraction,[41] and counseling by healthcare providers could possibly reduce the level of stress and anxiety among prostate cancer patients. Efforts may also be needed to address treatment related side effects such as erectile dysfunction, and pain which could potentially influence patients' quality of life.

Result from this study also suggests that several biopsychosocial factors including comorbidities, marital status, and education also may play a role in the development of MHI among patients with prostate cancer. Previous studies have also shown the influence of such factors on depression or psychological distress.[10,42,43] Researchers have found a positive relationship between the number of comorbidities and levels of anxiety and depression in older adults with cancer.[44] The impact of prostate cancer treatments on mental health could be exacerbated by the presence of comorbidities. A greater number of comorbidities could interfere with treatment and associated side-effects, and thus influence the levels of anxiety and depression.[45] The role of social support such as partners or spouses has been found to be critical in reducing psychological distress.[46] Partners can help patients manage prostate cancer by providing emotional support (coping and adapting), and assisting with interpreting treatment related information provided by healthcare providers.[46]

Researchers also have found that education levels are associated with anxiety and depression disorders.[47] Findings from this study showed that a higher level of education was a protective factor against the development of MHI. Patients with less education may not fully comprehend treatment strategies which resulted in anxiety for the fear of unknown. In addition, physicians more often discuss conservative management strategies with patients who have attained higher levels of education in comparison to those with lower educational attainment.[48] It is important to educate patients and help them understand prostate cancer treatment options, and their long term impact regardless of education level. Decision support interventions based on health literacy principles may

improve patients' knowledge about prostate cancer treatment options, and reduce decision and cancer-related distress.[49]

This study has several limitations that warrant mentioning. The study cohorts were restricted to only Medicare beneficiaries who were aged 66 years and above. Therefore, study findings may not be generalizable to other patient populations such as Medicaid, Health Maintenance Organizations, other insurance plans, or to those younger than 66 years of age. There also may be a possibility of selection bias due to non-randomized nature of the study. The use of Medicare administrative claims data to estimate MHI may be underestimated. Finally, this study did not account for other factors such as physicians or patient preferences in choosing treatments, or self-management strategies, which may have influenced our results.

This study aimed to address a significant gap in literature by providing evidence regarding MHI among patients who underwent conservative management and cryotherapy to treat prostate cancer. Overall, results from this study suggest that patients who chose conservative management experienced fewer MHI in comparison to cryotherapy. As older patients' tend to choose treatment options that reduce psychological issues and improve quality of life rather than those options that maximize survival,[23,24] careful consideration of MHI becomes extremely important when choosing treatments for localized prostate cancer. Study findings could further help healthcare providers in providing evidence based optimized care, and in providing need based interventions to alleviate anxiety and depression. Policy makers could use this information to judge merits of the two treatment strategies in order to change reimbursement policies. Providing tailored psychological interventions to patients along

with the initiation of treatments could prove helpful in reducing MHI, particularly in cryotherapy. Further research is needed to investigate impact of patients' preferences on effectiveness of these two treatment options. This study could also be replicated to study non-Medicare patient population.

## Tables

Table 3.1: List of ICD-9 codes for identification of mental health issues

| Mental health issues | ICD-9 diagnoses codes |
|---|---|
| Major depressive disorder | 296.2, 296.3 |
| Depressive disorder NOS | 311 |
| Neurotic depression | 300.4 |
| Adjustment disorder with depressed mood | 309.0 |
| Anxiety disorder | 300.0, 300.01, 300.02, 300.09 |

Abbreviations: ICD-9, International classification of diseases, ninth revision; NOS, Not otherwise specified

Table 3.2: Baseline characteristics of the study cohorts

| Baseline Characteristics | Conservative management (n=7,998) | Cryotherapy (n=3,051) | P value |
|---|---|---|---|
| **Age group, n (%)** | | | |
| 66-69 | 2,903 (36.30 %) | 762 (24.98%) | <0.0001 |
| 70-74 | 2,661 (33.27%) | 1,104 (36.18%) | |
| 75-79 | 1,599 (19.99%) | 815 (26.71%) | |
| 80+ | 835 (10.44 %) | 370 (12.13%) | |
| **Race, n (%)** | | | |
| Caucasians | 6,191 (77.41%) | 2,453 (80.40%) | 0.0029 |
| African Americans | 1,136 (14.20%) | 372 (12.19%) | |
| Others | 671 (8.39%) | 226 (7.41%) | |
| **Tumor grade, n (%)** | | | |
| Well-differentiated | 123 (1.54%) | 18 (0.59%) | <0.0001 |
| Moderately differentiated | 4,510 (56.39%) | 1,317 (43.17%) | |
| Poorly differentiated | 3,140 (39.26%) | 1,584 (51.92%) | |
| Unknown | 225 (2.81%) | 132 (4.33%) | |
| **Tumor stage, n (%)** | | | |
| T1 | 3,414 (42.69%) | 1,425 (46.71%) | 0.0001 |
| T2 | 4,584 (57.31%) | 1,626 (53.29%) | |
| **Charlson comorbidity index, n (%)** | | | |
| 0 | 5,992 (74.92%) | 2,290 (75.06%) | 0.3600 |
| 1 | 1,833 (22.92%) | 708 (23.21%) | |
| 2+ | 173 (2.16%) | 53 (1.74%) | |
| **Marital Status, n (%)** | | | |
| Married | 5,214 (65.19%) | 2,073 (67.94%) | 0.0019 |
| Unmarried/Single | 1,758 (21.98%) | 577 (18.91%) | |
| Unknown/missing | 1,026 (12.83%) | 401 (13.14%) | |
| **Education, n (%)** | | | |

| | | | |
|---|---|---|---|
| First quartile (highest) | 2,715 (33.95%) | 816 (26.75%) | <0.0001 |
| Second quartile | 1,526 (19.08%) | 599 (19.63%) | |
| Third quartile | 1,372 (17.15%) | 558 (18.29%) | |
| Fourth quartile (lowest) | 1,986 (24.83%) | 942 (30.88%) | |
| Data missing | 399 (4.99%) | 136 (4.46%) | |
| **Geographic location, n (%)** | | | |
| Northeast | 2,074 (25.93%) | 277 (9.08%) | <0.0001 |
| South | 905 (11.32%) | 540 (17.70%) | |
| Central | 1,320 (16.50%) | 592 (19.40%) | |
| West | 3,699 (46.25%) | 1,642 (53.82%) | |
| **Urban residency, n (%)** | | | |
| Yes | 7,415 (92.71%) | 2,625 (86.04%) | <0.0001 |
| No | 583 (7.29%) | 426 (13.96%) | |
| **Year of diagnosis, n (%)** | | | |
| 2000 -2004 | 2,597 (32.47%) | 713 (23.37%) | <0.0001 |
| 2005-2009 | 3,328 (41.61%) | 1,639 (53.72%) | |
| 2010-2013 | 2,073 (25.92%) | 699 (22.91%) | |

Table 3.3: Rates of mental health issues in conservative management and cryotherapy cohort

| Mental Health Issues | Conservative management (n=7,998) | Cryotherapy (n=3,051) | P-value |
|---|---|---|---|
| Any mental health issue, n (%) | 699 (8.74%) | 315 (10.32%) | 0.009 |
| **Mental health issues by category** | | | |
| Major depressive disorder, n (%) | 77 (0.96 %) | 25 (0.82 %) | 0.481 |
| Depressive disorder NOS (not otherwise specified), n (%) | 357 (4.46 %) | 172 (5.64 %) | 0.0286 |
| Neurotic depression, n (%) | 27 (0.34 %) | 15 (0.49 %) | 0.239 |
| Adjustment disorder with depressed mood, n (%) | 16 (0.20 %) | <11 (0.36 %) | 0.249 |
| Anxiety disorder, n (%) | 277 (3.46 %) | 132 (4.33 %) | 0.032 |

Notes: Cell size less than 11 are not shown in accordance with SEER-Medicare data use agreement

Table 3.4: Likelihood of mental health issues in patients receiving Conservative Management vs Cryotherapy

| **Mental Health Issues (Conservative management vs Cryotherapy)** | **Adjusted Odds Ratio (95% CI)** | **P-value** |
|---|---|---|
| Any mental health issue, n (%) | 0.88 (0.76, 1.03) | 0.103 |
| **Mental health issues by category** | | |
| Major depressive disorder, n (%) | 1.28 (0.80, 2.04) | 0.309 |
| Depressive disorder NOS (not otherwise specified), n (%) | 0.83 (0.68, 1.01) | 0.056 |
| Neurotic depression, n (%) | 0.82 (0.42, 1.60) | 0.562 |
| Adjustment disorder with depressed mood, n (%) | 1.31 (0.75, 1.89) | 0.195 |
| Anxiety disorder, n (%) | 0.82 (0.65, 0.98) | 0.0344 |

Notes: Odds ratio adjusted for age, race, tumor grade, tumor stage, Charlson comorbidity index, geographic location, urban density, year of diagnosis, marital status, and education

Abbreviations: CI, Confidence Intervals

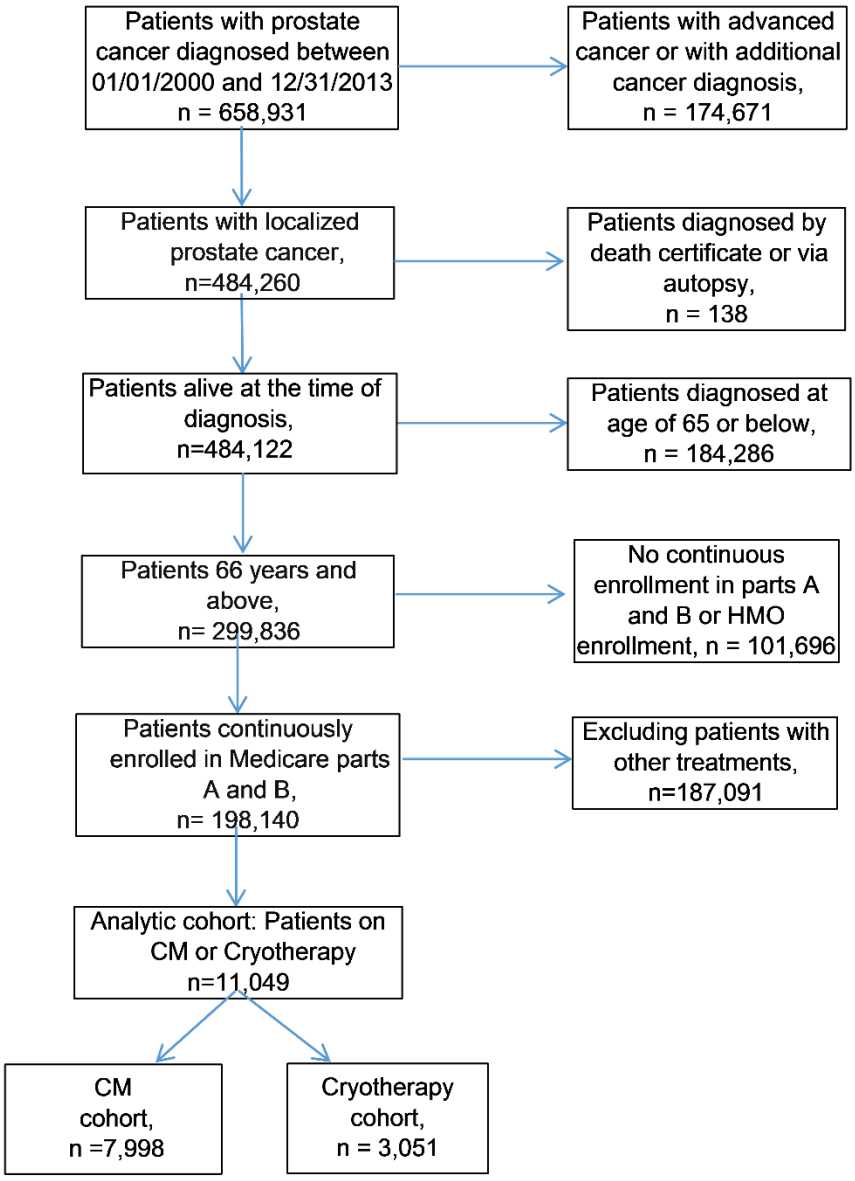
Table 3.5: Multivariate cox proportional hazards model testing time to develop mental health issues

| Variables | Cancer specific survival | |
|---|---|---|
| | **Hazards Ratio (95% CI)** | **P-value** |
| **Treatment group** | | |
| Conservative Management | 0.96 (0.82 – 1.14) | 0.690 |
| Cryotherapy | 1 | |
| **Age** | | |
| 66-69 | 1 | |
| 70-74 | 1.04 (0.87 - 1.25) | 0.676 |
| 75-79 | 1.04 (0.85 – 1.27) | 0.721 |
| 80 and above | 1.03 (0.79 – 1.34) | 0.847 |
| **Race** | | |
| Caucasian | 1 | |
| African Americans | 0.94 (0.70 – 1.25) | 0.651 |
| Others | 0.95 (0.69 – 1.30) | 0.733 |
| **Tumor grade** | | |
| Well-differentiated | 1 | |
| Moderately differentiated | 0.62 (0.38 – 1.02) | 0.059 |
| Poorly differentiated | 0.69 (0.42 – 1.13) | 0.139 |
| Unknown | 0.49 (0.26 – 0.91) | 0.024 |
| **Tumor stage** | | |
| T1 | 1 | |
| T2a | 1.09 (0.92 -1.29) | 0.309 |
| **Charlson comorbidity Index** | | |
| 0 | 1 | |
| 1 | 1.12 (0.73 – 1.31) | 0.328 |
| 2 or more | 1.46 (1.16 – 2.03) | 0.025 |

| | | |
|---|---|---|
| **Marital status** | | |
| Married | 1 | |
| Single | 1.26 (1.07 – 1.48) | 0.005 |
| Unknown | 1.18 (0.93 – 1.49) | 0.172 |
| **Education** | | |
| First quartile (highest education) | 0.84 (0.63-0.98) | 0.033 |
| Second quartile | 0.89 (0.68-1.06) | 0.159 |
| Third quartile | 0.96 (0.77 – 1.19) | 0.712 |
| Fourth quartile (lowest education) | 1 | |
| **Geographic location** | | |
| Northeast | 0.86 (0.71– 1.06) | 0.159 |
| South | 1.13 (0.91 – 1.41) | 0.278 |
| Central | 1.07 (0.87 – 1.33) | 0.514 |
| West | 1 | |
| **Urban residency** | | |
| Yes | 1 | |
| No | 1.01 (0.78 – 1.29) | 0.993 |
| **Years of diagnosis** | | |
| 2000 -2004 | 1 | |
| 2005-2009 | 1.23 (1.07 – 1.53) | 0.014 |
| 2010-2013 | 1.53 (1.15 – 2.04) | 0.003 |

Abbreviations: CI, Confidence Intervals

## Figures




Abbreviations: CM, Conservative management;

HMO, Health Maintenance Organizations

Figure 3.1: Procedure to generate the study sample of the analytic cohort

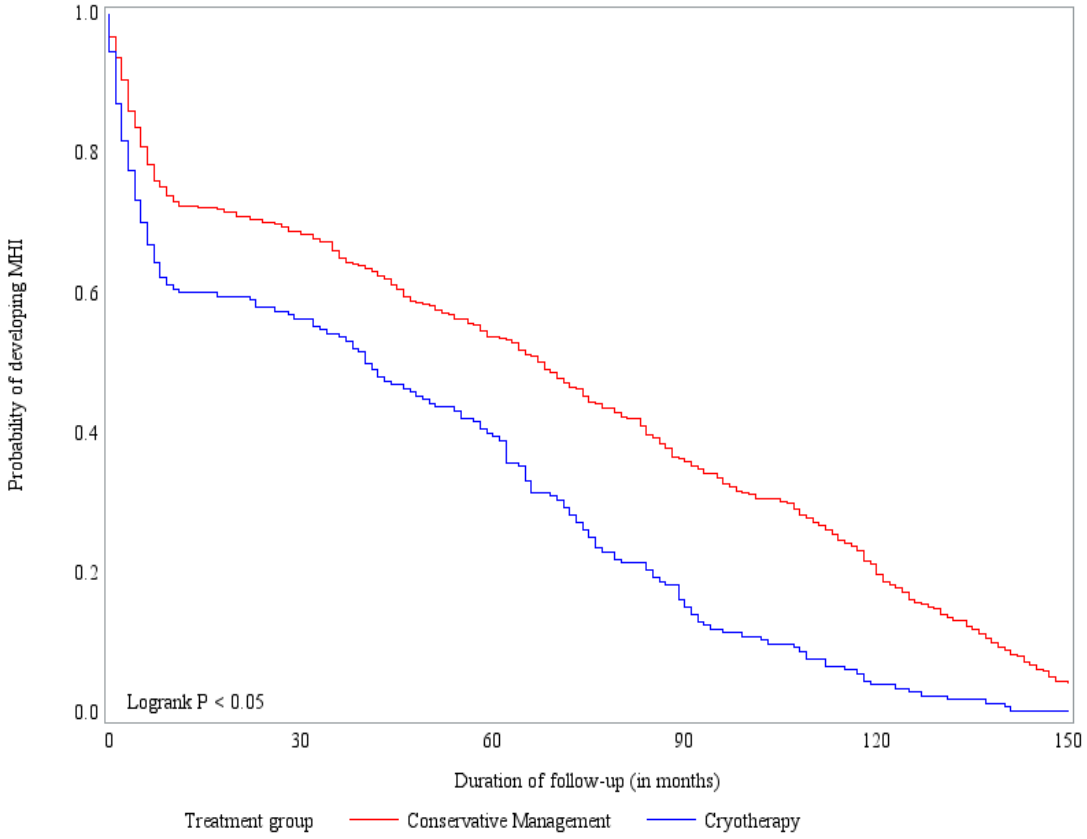



Figure 3.2: Kaplan-Meier plot illustrating time to develop any mental health issues in the conservative management and cryotherapy cohort

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# CHAPTER 4

# AN ECONOMIC EVALUATION OF CONSERVATIVE MANAGEMENT AND CRYOTHERAPY IN MEN WITH LOCALIZED PROSTATE CANCER[†]

[†] Shah, S., Young, H.N., Perri, M., Jayawardhana, J., Cobran, E.K. To be submitted to *Cancer*

**Abstract**

**Objectives:** To estimate the total direct medical costs and the specific costs associated with the phases of care associated with conservative management and cryotherapy from Medicare perspective in patients with localized prostate cancer.

**Methods:** Patients aged 66 years or old and diagnosed with localized prostate cancer between 2000 and 2013 were selected from the SEER-Medicare database. An average total direct cost and phase specific costs were calculated from the Medicare claims. Summary statistics were reported for the costs, and validated using nonparametric bootstrapping method. A gamma distributed generalized linear model with a log link function was used to assess variations in costs for each phase of care.

**Results:** There were 11,049 eligible patients diagnosed from 2000 to 2013, of which 7,998 patients underwent conservative management and 3,051 patients underwent cryotherapy. The average total direct cost of cancer care in the conservative management and cryotherapy cohort were approximately $13,664 and $14,312, respectively. Compared to the cryotherapy cohort, the average cost in the conservative management cohort in the initial phase ($ 3,708 vs $ 4,780), continuing phase ($1,504 vs $2,253), and the terminal phase ($13,387 vs $ 15,532) were low. The costs incurred by conservative management cohort were lower across all the phases even after controlling for the covariates.

**Conclusions:** This study highlights the importance of conservative management as a cost saving strategy for patients with prostate cancer. The economic burden across all the phases of care was higher with cryotherapy in comparison to conservative management in patients with localized prostate cancer.

**Keywords:** Prostate Cancer; Conservative Management; Cryotherapy; costs; phases of care approach, SEER-Medicare

## Introduction

The incidence of the prostate cancer is increasing in the United States.[1] Nearly, 1 in every 7 men are diagnosed with prostate cancer during his lifetime.[1,2] The treatment and subsequent monitoring of prostate cancer imposes a high economic burden in the United States.[3-5] In 2010, the total cost of prostate cancer care was estimated to be about $12 billion in 2010 , and the cost of initial treatment was estimated to be around $4.5 billion.[6] This cost is projected to rise to $16 billion in 2020 due to the increasing incidence of prostate cancer, and emerging new treatments and technologies.[3,5,6] Although the cost of prostate cancer is substantial, the economic burden varies widely by the choice of the treatment.[7,8]

Conservative management and cryotherapy are two minimally invasive treatment options for localized prostate cancer which are less expensive in comparison to some other treatment options such as radiation therapy and surgery.[8-11] Corcoran et al reported an average 15 year cost of conservative management to be in the range of $6,558 to $11,992.[10] Costs associated with conservative management are usually due to repeated biopsies and associated side-effects such as erectile dysfunction and urinary symptoms.[12] Perloth et al found that active treatments had higher long term costs in comparison to conservative management.[13] The cost associated with cryotherapy could be due to the procedure and its associated side-effects. A comparative effectiveness study of cryotherapy and brachytherapy found the cost to be $12,626 with cryotherapy.[14] Previous

studies also revealed significantly lower costs associated with cryotherapy when compared to brachytherapy or surgery.[14,15]

The cost of treatment also varies across different phases of cancer care. The literature suggests that treatment costs for prostate cancer are higher in the initial (i.e., within the first year of prostate cancer treatment) and terminal phases (i.e., the last 12 months of treatment before death), and lower in the continuing phase (period between the initial and terminal phase) of cancer care.[16] For example, de Oliveira et al found costs in the initial, continuing and terminal phases of prostate cancer treatments to be $8,394, $5,017 and $17,391, respectively.[17] Snyder et al. showed that the cost of conservative management was $3,936 during the initial phase of cancer care.[18] Researchers also have found that the cost of cryotherapy was $7,838 during the initial phase.[8] However, studies assessing the specific costs of conservative management and cryotherapy across all phases of care for patients with localized prostate cancer are scarce.

Many of the studies evaluating the costs associated with conservative management and cryotherapy had shorter follow up periods and did not examine costs across initial, continuous, and terminal phases of care. The evaluation of costs across the continuum of care is important because of the high survival rates in prostate cancer. Furthermore, the number of older adults is increasing, and coupled with the improvement in prostate cancer survival rates, much of the economic burden of prostate cancer treatment will fall on Medicare.[19] This makes it critical to understand the economic burden of prostate cancer from Medicare's perspective. The assessment of phase-specific costs of care could provide evidence regarding the efficiency and cost-effectiveness of less invasive treatments such as conservative management and cryotherapy, and provide a

rationale for resource allocation and guide optimal decision making. In addition, phase specific cost estimates may also be beneficial in planning prevention (e.g., screening), intervention, and cost controlling strategies. Therefore, the purpose of this study was to estimate the total direct medical costs and the specific costs associated with the phases of care associated with conservative management and cryotherapy from Medicare perspective in patients with localized prostate cancer.

## Methods

### *Study design and data source*

The Surveillance, Epidemiology, and Ends Results (SEER) program linked to the Medicare data from 2000-2014 was utilized for this longitudinal retrospective study. The National Cancer Institute, the SEER registries, and the Center for Medicare and Medicaid Services (CMS) collaboratively link the SEER and Medicare data.[20] The SEER program captures clinical, demographic and survival information for approximately 28% of the US population and is 98% complete for case ascertainment. The Medicare program covers approximately 97% of persons aged 65 years and older.[20] Several data files were utilized for this study. The Patient Entitlement and Diagnosis Summary File (PEDSF) was used to obtain clinical information regarding cancer, patients' demographics and Medicare status. The Carrier file (NCH) was used to capture information on physician and non-institutional provider services (Part B) provided to the inpatient and outpatient study population. The Medicare Provider Analysis and Review file (MEDPAR) and the Outpatient files were utilized to extract information regarding inpatient cancer care and hospital outpatient services respectively. Additional Medicare claims files including

Home Health Agency (HHA), Durable Medical Equipment (DME) and Hospice were also reviewed to capture claims information of the study cohorts. This study was approved by the University of Georgia's Institutional Review Board.

*Study cohorts*

Patients with localized prostate cancer were identified as those with stage I or stage II cancer diagnosis.[21,22] Patients in the conservative management cohort were identified as those who did not receive any immediate treatment within the first 6 months of diagnosis of localized prostate cancer.[23,24] Patients in the cryotherapy cohort were identified using either the International Classification of Diseases, ninth revision, (ICD-9) procedural code (60.62), Healthcare Common Procedure Coding System (HCPCS) codes (G0160 or G0161) or Current Procedural Terminology (CPT) code (55873). Patients were excluded from the study if they were (i) first diagnosed at autopsy or by death certificate, (ii) had other types of cancer, (iii) enrolled in HMO, (iv) at other stages of cancer, or (v) were below 66 years of age (restricting the cohort to patients aged 66 years old allowed at least 12 months of Medicare claims data).

*Outcomes*

The following types of costs were evaluated in this study: total direct cost, and phase-specific cost. The total direct cost was defined as the Medicare reimbursement amount, which is the payment from Medicare to the service providers on behalf of the beneficiary. It was calculated as the average costs from all Medicare claims between time of diagnosis and time of death or end of follow-up in the two cohorts. The cost estimates were also derived based on the phases of care approach. The period of time from diagnosis until death (or date of censoring) was divided into distinct phases of cancer

care: initial phase, continuing phase and terminal phase.[25,26] The costs in the initial phase was defined as the costs in the initial first year after diagnosis while the costs in the terminal phase was defined as the costs in the last year before death. The cost in the continuing phase was defined as the costs between the initial and the terminal phases. If a patient survived no longer than 12 months, all costs were allocated to the terminal phase. If a patient was alive as of December 2014 (i.e. the last date of follow-up), the continuing phase costs was utilized only through December 2013 because of our inability to determine if these costs during 2014 should be assigned to the continuing or terminal phase.[27]

All the costs were reported in 2014 United States dollars. Similar to other studies,[19,28-30] costs were adjusted for inflation using the Hospital Wage Index and the Medicare Economic Index for inpatient and outpatient services, respectively. Adjustments were also made for geographic variability in costs across SEER registry sites by using the Medicare Wage Index and Capital Geographic Adjustment Factor for Part A and the Medicare Geographic Practice Cost Index for Part B.

*Covariates*

Demographic information included patients' age (66-69 years, 70-74 years, 75-79 years, and 80 and above), race (Caucasians, African American, and others), marital status (married, unmarried/single and unknown), year of diagnosis (2000-2004, 2005-2009, and 2010-2013), geographic location (Northeast, South, Central, West), and urban residency (yes/no). Information about education (i.e., the proportion of population with less than a high school degree) was obtained from the census tract file of the SEER. The education variable was categorized into quartiles. The categories for the proportion of population

with less than a high school degree were: 0% to 7.13% (representing high educational level), 7.14% to 11.91% (medium), 11.92% to 20.46% (lower), 20.47% to 100% (lowest), and unknown.[31] The Charlson Comorbidity Index (CCI) was derived from the Medicare claims during the year prior to prostate cancer diagnosis using a validated algorithm.[32,33] The CCI was categorized as 0, 1, and 2 and above. Cancer related information including tumor stage and grade were also extracted. Tumor grades were determined by Gleason score, and is classified as well differentiated (Gleason scores of 2–4), moderately differentiated (Gleason scores of 5 - 7), and poorly differentiated (Gleason score of 8 and above).[34,35] Tumor stage was also classified as T1 and T2.

*Statistical analysis*

Descriptive statistics were conducted to describe the baseline characteristics of the two cohorts. Differences in the baseline characteristics were assessed using Chi-square tests for the categorical variables. The average of total direct costs and phase specific costs were summarized for the conservative management and cryotherapy cohorts. Average costs were compared between the study cohorts using a Wilcoxon rank sum test. To assess the robustness or validity of the cost estimates, nonparametric bootstrapping method was utilized.[36] This method involves re-sampling with replacement from the study population to create 1,000 random samples.[37] All estimates of phase specific costs were repeated for each sample. Confidence Intervals (CIs) were derived from the sample distribution of costs from the 1,000 study replicates at the 2.5% and 97.5% quantiles.[37] Summary statistics, including means and standard deviations, were also obtained accordingly. Since cost data is highly skewed, differences in the phase specific costs between the cohorts were assessed using a gamma distributed generalized linear model

with a log link function for each phase.[38] All analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary, NC).

## Results

### *Baseline characteristics of the cohorts*

There were 11,049 eligible patients diagnosed from 2000 to 2013, of which 7,998 patients underwent conservative management and 3,051 patients underwent cryotherapy. Figure 4.1 presents the procedure to generate the final analytical cohort. The baseline characteristics of the study cohorts are presented in Table 4.1. Patients in both the conservative management and cryotherapy cohorts differed significantly in terms of age, race, education, geographic location, marital status, urban residency, year of diagnosis, tumor grade, and stage ($p < 0.05$). Patients in the conservative management cohort were more likely to be younger than the patients in the cryotherapy cohort. A majority of patients in the conservative management and cryotherapy cohort were Caucasians, married, had a comorbidity score of 0, residing in urban areas and were at T2 stage.

### *Total average cost and phases of care cost*

The total direct cost was found to be lower in the conservative management cohort. The average total direct cost of cancer care in the conservative management and cryotherapy cohort were approximately $13,664 (95%CI: $13,566; $13,761) and $14,312 (95%CI: $14,107; $14,516), respectively. The differences between conservative management and cryotherapy cohorts in the total direct costs across the two cohorts were statistically significant ($p < 0.05$).

Table 4.2 presents the summary statistics of costs across all the phases in both the cohorts. The average cost in the initial phase was approximately $ 3,708 and $ 4,780 in the conservative management and cryotherapy cohort, respectively. The average costs per year in the continuing phase of treatment were $1,504 in the conservative management cohort and $2,253 in the cryotherapy cohort. The average costs in the terminal phase of care were approximately $13,387 in the conservative management cohort and $ 15,532 in the cryotherapy cohort. Results from the nonparametric bootstrapping showed similar cost estimates. The average cost in the initial treatment phase was approximately $3,715 (95%CI: $3,708; $3,721) and $4,805 (95%CI: $4,797; $4,815) in the conservative management and cryotherapy cohorts, respectively. The average cost in the continuing phase was approximately $1,503 (95%CI: $1,497; $1,511) and $2,259 (95%CI: $2,238; $2,280) in the conservative management and cryotherapy cohorts, respectively. The average cost in the terminal phase was approximately $13,369 (95%CI: $3,341; $13396) and $15,532 (95%CI: $15,475; $15,590) in the conservative management and cryotherapy cohorts, respectively. The differences across all phase-specific cost estimates for the conservative management and cryotherapy cohorts were statistically significant ($p < 0.05$).

Results from the generalized linear models for the initial phase of care are presented in Tables 4.3. In the initial phase of care, the conservative management cohort had significantly lower treatment costs (cost ratio: 0.86; 95% CI: 0.79 - 0.93) than the cryotherapy cohort after adjusting for all the covariates. Patients in the age group of 80+ years had significantly lower treatment costs (cost ratio: 0.79; 95% CI: 0.70 - 0.90) than the patients in the age group of 66-69 years in the initial phase. Compared to the

comorbidity score of 0, patients with a comorbidity score of 1 (cost ratio: 1.80; 95% CI: 1.43 - 2.25) had significantly higher treatment costs in the initial phase of care. Patients who were single (cost ratio: 0.88; 95% CI: 0.80 - 0.96) or residing in rural areas (cost ratio: 0.73; 95% CI: 0.64 -0.83) had significantly lower treatment costs. Patients with the lowest education (cost ratio: 1.17; 95% CI: 1.10 - 1.29) or those diagnosed between 2005 and 2009 (cost ratio: 1.20; 95% CI: 1.10 - 1.30) had significantly higher treatment costs in the initial phase of care.

Table 4.4 presents the results from the generalized linear models for the continuing phase of care**.** In the continuing phase of care, the conservative management cohort had significantly lower treatment costs (cost ratio: 0.81; 95% CI: 0.70 - 0.94) than the cryotherapy cohort after adjusting for all the covariates. Patients diagnosed between 2010 and 2013 (cost ratio: 0.61; 95% CI: 0.40 – 0.93), or with T1 stage of tumor (cost ratio: 0.80; 95% CI: 0.69 - 0.93) had significantly lower cost in the continuing phase of care. However, patients who were in the age group of 70-74 years (cost ratio: 1.23; 95% CI: 1.03 - 1.47) or in other racial groups (cost ratio: 1.35; 95% CI: 1.02 – 1.80) had significantly higher costs in the continuing phase.

Results from the generalized linear models for the terminal phase of care are presented in Tables 4.5. Similar to the other phases of care, the conservative management cohort had significantly lower terminal phase costs (cost ratio: 0.89; 95% CI: 0.81 - 0.99) than the cryotherapy cohort. Patients in the age group of 80+ years (cost ratio: 0.83; 95% CI: 0.73 - 0.95), southern (cost ratio: 0.76; 95% CI: 0.67 – 0.86) or central region (cost ratio: 0.75; 95% CI: 0.67 – 0.84), or those diagnosed between 2010 and 2013 (cost ratio: 0.80; 95% CI: 0.65 – 0.99) had significantly lower terminal phase costs. Patients with a

comorbidity score of 1 (cost ratio: 1.13; 95% CI: 1.02 – 1.26) or with lowest education (cost ratio: 1.13; 95% CI: 1.01 – 1.26) had significantly higher terminal phase costs.

**Discussion**

This study evaluated long term direct medical costs and phase specific costs associated with conservative management and cryotherapy in patients with localized prostate cancer. Long-term economic evaluations of treatments for prostate cancer are important due to the longer course of the disease and continuous treatment over time. To our knowledge, this study is the first study to compare phase specific costs associated with conservative management and cryotherapy. The study findings showed that conservative management had significantly lower direct medical cost and phase specific cost as compared to the cryotherapy cohort.

Overall, the average total direct cost of cancer care in the conservative management was lower than cryotherapy ($13,664 vs $14,312). Similar results were reported in other studies that evaluated costs associated with conservative management or cryotherapy.[14,39] A study comparing conservative management with active treatments found the ten year cost of conservative management to be $13,116 in 2013.[39] Williams et al to compared cryotherapy with brachytherapy and found that the cost of cryotherapy was $12,629 (reported in 2008 dollar value).[14] The literature also suggests that conservative management is the least expensive option when compared to the other active treatments.[39-41] The lower cost estimates for conservative management may be due to lower rates of side-effects or no involvement of surgical techniques as in cryotherapy. These findings could guide patients and healthcare providers in choosing treatment

options based on their economic status; and could guide policymakers in allocating resources more efficiently to cover additional care associated with conservative management such as covering treatment for side-effects associated with biopsies.

The phase specific cost estimates also showed conservative management to be more economical than cryotherapy. Compared to the cryotherapy cohort, patients in the conservative management cohort had significantly lower cost in the initial ($ 3,708 vs $ 4,780), continuing ($1,504 vs $2,253) and the terminal phases of care ($13,387 vs $ 15,532). These phase specific cost estimates for conservative management and cryotherapy cohorts followed a similar pattern to the phase of care costs across prostate cancer treatments for all stages.[17] In addition, the cost estimates regarding the initial phase of treatment found in this study were similar to previous studies. Previous research that showed the initial cost of $3,936 for conservative management, and $7,838 for cryotherapy.[8,18] The specific costs estimates for the continuing and terminal phases associated with conservative management and cryotherapy remained unexplored due to shorter follow up study periods. However, similar to the available literature on cost estimates for all cancers, our cost estimates in both the cohorts followed a typical 'U' shaped cost curve.[30] This 'U' shaped curve reflects a higher cost in the initial and terminal phase, while lower costs in the continuing phase. The evaluation of overall mean costs and phase specific costs in our study suggest that choosing conservative management might be more economical than cryotherapy in older patients from the Medicare perspective.

The costs associated with terminal phases of care were the highest in both cohorts. The costs of treatment in cancer are projected to rise with increasing number of cases

among older adults, higher survival rates and increasing costs of therapies.[42] A recent international commission suggested that one of the ways to reduce cancer care costs is to improve end-of-life care or terminal care.[42] Care in the terminal phases of cancer is expensive and sometimes ineffective; therefore providing palliative care could be particularly beneficial in reducing costs and improving quality of life. This study significantly highlights the need to critically evaluate the reasons associated with such high costs in the terminal phases. Understanding these factors could potentially provide guidelines on developing efficient targeted strategies to provide optimal care at a lower cost.

In this study, we found similar results even after adjusting for all the covariates. Conservative management was found to incur significantly lower costs across all phases of care compared to cryotherapy after adjusting for the covariates. Although the purpose of our study was not to assess the impact of patients' clinical and demographic characteristics on costs, of particular note, comorbidities, age, education and year of diagnoses were significantly associated with costs. Patients with a comorbidity score of 1 incurred higher costs in the initial and terminal phase in comparison to patients with a comorbidity score of 0. Previous research showed that increasing comorbidities is a significant predictor of high costs.[43] In the course of cancer diagnosis and treatment, patients and healthcare providers may give less attention to chronic disease management. For example, there may be less emphasis on routine diabetes management which could have a negative impact on health outcomes and costs. Findings from this study suggest that more emphasis may need to be placed on managing comorbidities.

Patients in the age group of 80 years and above incurred significantly lower costs in the initial and terminal phases after controlling for other factors. These findings suggest higher utilization of palliative care as opposed to receiving more expensive healthcare services among patients above 80 years. Our study also found a significant impact of education on costs. Compared to the patients with highest level of education, patients with lowest educational level incurred higher costs in both initial and terminal phases. The level of education has also been found to be an independent predictor of cancer morbidity and mortality.[44] Lower educational attainment could contribute to poor understanding of cancer management and a lack of awareness about cancer or other comorbidities. Tailored educational programs may help improve patients' knowledge and awareness of cancer treatment and management, and perhaps lead to lower costs. Interestingly, our findings also indicated that patients diagnosed in the years of 2010-2013 incurred lower costs in the continuing and terminal phases. These findings may be due to increasing utilization of conservative management and cryotherapy in our study sample.[45] Trends in the management of patients with localized prostate cancer suggests that the rates of conservative management increased sharply in 2010 through 2013.[46]

There are some limitations to this study that warrants mentioning. The study cohorts were restricted to only Medicare beneficiaries who were aged 66 years and above. Therefore, study findings may not be generalizable to other patient populations such as Medicaid, Health Maintenance Organizations, other insurance plans, or to those younger than 66 years of age. There might be a possibility of selection bias due to non-randomized nature of the study. We could only assess the direct medical costs from the Medicare perspective due to lack of appropriate information on other types of costs such

as indirect costs (e.g. productivity loss). The use of the Medicare claims to estimate medical costs are limited to the services used by patients, which Medicare covers. Finally, our study did not assess out-of-pocket costs or copayments. Although information on out of pocket expenses or copayments is available in SEER-Medicare, this information might not reflect the actual amount paid by patients. Many patients may have supplementary insurance that covers a part of their out-of-pocket expenses or copayments which may not be captured in SEER-Medicare data. Future research should assess costs from the patient's perspective to give a full account of all costs associated with cancer care.

In summary, this study highlights the importance of conservative management as a cost saving strategy for patients with prostate cancer. The economic burden across all the phases of care was higher with cryotherapy in comparison to conservative management in patients with localized prostate cancer. Tailored interventions and policy changes may address the issues of high costs in the terminal phase of cancer care, and to incentivize healthcare providers based on practicing value based care.

**Tables**

Table 4.1: Baseline demographic characteristics

| Baseline Characteristics | Conservative management (n=7,998) | Cryotherapy (n=3,051) | P value |
|---|---|---|---|
| **Age group, n (%)** | | | |
| 66-69 | 2,903 (36.30 %) | 762 (24.98%) | <0.0001 |
| 70-74 | 2,661 (33.27%) | 1,104 (36.18%) | |
| 75-79 | 1,599 (19.99%) | 815 (26.71%) | |
| 80+ | 835 (10.44 %) | 370 (12.13%) | |
| **Race, n (%)** | | | |
| Caucasians | 6,191 (77.41%) | 2,453 (80.40%) | 0.0029 |
| African Americans | 1,136 (14.20%) | 372 (12.19%) | |
| Others | 671 (8.39%) | 226 (7.41%) | |
| **Tumor grade, n (%)** | | | |
| Well-differentiated | 123 (1.54%) | 18 (0.59%) | <0.0001 |
| Moderately differentiated | 4,510 (56.39%) | 1,317 (43.17%) | |
| Poorly differentiated | 3,140 (39.26%) | 1,584 (51.92%) | |
| Unknown | 225 (2.81%) | 132 (4.33%) | |
| **Tumor stage, n (%)** | | | |
| T1 | 3,414 (42.69%) | 1,425 (46.71%) | 0.0001 |
| T2 | 4,584 (57.31%) | 1,626 (53.29%) | |
| **Charlson comorbidity index, n (%)** | | | |
| 0 | 5,992 (74.92%) | 2,290 (75.06%) | 0.3600 |
| 1 | 1,833 (22.92%) | 708 (23.21%) | |
| 2+ | 173 (2.16%) | 53 (1.74%) | |
| **Marital Status, n (%)** | | | |
| Married | 5,214 (65.19%) | 2,073 (67.94%) | 0.0019 |
| Unmarried/Single | 1,758 (21.98%) | 577 (18.91%) | |

| | | | |
|---|---|---|---|
| Unknown/missing | 1,026 (12.83%) | 401 (13.14%) | |
| **Education, n (%)** | | | |
| First quartile (highest) | 2,715 (33.95%) | 816 (26.75%) | <0.0001 |
| Second quartile | 1,526 (19.08%) | 599 (19.63%) | |
| Third quartile | 1,372 (17.15%) | 558 (18.29%) | |
| Fourth quartile (lowest) | 1,986 (24.83%) | 942 (30.88%) | |
| Data missing | 399 (4.99%) | 136 (4.46%) | |
| **Geographic location, n (%)** | | | |
| Northeast | 2,074 (25.93%) | 277 (9.08%) | <0.0001 |
| South | 905 (11.32%) | 540 (17.70%) | |
| Central | 1,320 (16.50%) | 592 (19.40%) | |
| West | 3,699 (46.25%) | 1,642 (53.82%) | |
| **Urban residency, n (%)** | | | |
| Yes | 7,415 (92.71%) | 2,625 (86.04%) | <0.0001 |
| No | 583 (7.29%) | 426 (13.96%) | |
| **Year of diagnosis, n (%)** | | | |
| 2000 -2004 | 2,597 (32.47%) | 713 (23.37%) | <0.0001 |
| 2005-2009 | 3,328 (41.61%) | 1,639 (53.72%) | |
| 2010-2013 | 2,073 (25.92%) | 699 (22.91%) | |

Table 4.2: Summary statistics for costs across the phases of care

| | Conservative management | Cryotherapy | p- value |
|---|---|---|---|
| Initial phase of care | | | |
| N | 4871 | 2190 | < 0.0001 |
| Mean (95% CI) | $3708.3 ( $3509.3, $3907.4) | $4799.6 ($4515.1, $5084.1) | |
| Standard deviation | $7085.1 | $6788.7 | |
| Continuing phase of care | | | |
| N | 6536 | 2760 | 0.0072 |
| Mean (95% CI) | $1503.9 ($1280.1, $1727.6) | $2252.9 ($1583.9, $2921.8) | |
| Standard deviation | $2346.4 | $3944.5 | |
| Terminal phase of care | | | |
| N | 1,822 | 727 | 0.020 |
| Mean (95% CI) | $13387.1 ($12508.5, $14265.7) | $15532.8 ($13696.2, $17369.5) | |
| Standard deviation | $19120.9 | $25224.3 | |

Table 4.3: Generalized linear regression model for cost across initial phase of care

| Variables | Estimate | Standard error | Cost Ratio | 95% Confidence Limits | p-value |
|---|---|---|---|---|---|
| **Treatment group** | | | | | |
| Conservative management | -0.1546 | 0.041 | 0.86 | 0.79 - 0.93 | 0.0002 |
| Cryotherapy (reference) | - | - | - | - | - |
| **Age groups** | | | | | |
| 66-69 years (reference) | - | - | - | - | - |
| 70-74 years | -0.0276 | 0.048 | 0.97 | 0.89 - 1.07 | 0.5648 |
| 75-79 years | -0.0601 | 0.057 | 0.94 | 0.85 - 1.04 | 0.2528 |
| 80+ years | -0.2302 | 0.065 | 0.79 | 0.70 - 0.90 | 0.0004 |
| **Race** | | | | | |
| Caucasians (reference) | - | - | - | - | - |
| African Americans | -0.0784 | 0.061 | 0.92 | 0.82 - 1.04 | 0.1937 |
| Others | -0.0809 | 0.072 | 0.92 | 0.80 - 1.06 | 0.2611 |
| **Tumor grade** | | | | | |
| Well-differentiated (reference) | - | - | - | - | - |
| Moderately differentiated | -0.1156 | 0.189 | 0.89 | 0.61 - 1.29 | 0.5418 |
| Poorly differentiated | -0.1152 | 0.191 | 0.89 | 0.61 - 1.29 | 0.5467 |
| Unknown | -0.1083 | 0.218 | 0.90 | 0.59 - 1.38 | 0.6195 |
| **Tumor stage** | | | | | |
| T1 | -0.0567 | 0.040 | 0.94 | 0.87 - 1.02 | 0.1599 |
| T2 (reference) | - | - | - | - | - |
| **Charlson comorbidity index** | | | | | |
| 0 (reference) | - | - | - | - | - |
| 1 | 0.5859 | 0.116 | 1.80 | 1.43 - 2.25 | <.0001 |
| 2+ | 1.0215 | 0.547 | 2.78 | 0.95 - 8.12 | 0.062 |
| **Marital Status** | | | | | |
| Married | - | - | - | - | - |
| Unmarried/Single | -0.1288 | 0.047 | 0.88 | 0.80 - 0.96 | 0.0066 |
| **Education** | | | | | |
| First quartile (highest) (reference) | - | - | - | - | - |
| Second quartile | -0.0227 | 0.054 | 0.98 | 0.88 - 1.09 | 0.673 |
| Third quartile | 0.0189 | 0.054 | 1.02 | 0.92 - 1.13 | 0.7263 |
| Fourth quartile (lowest) | 0.1547 | 0.051 | 1.17 | 1.10 - 1.29 | 0.0026 |
| **Geographic location** | | | | | |
| Northeast | -0.0004 | 0.051 | 1.01 | 0.90 - 1.10 | 0.9937 |
| South | -0.0907 | 0.061 | 0.91 | 0.81 - 1.03 | 0.137 |

| | | | | | |
|---|---|---|---|---|---|
| Central | -0.0409 | 0.053 | 0.96 | 0.86 - 1.07 | 0.4425 |
| West | - | - | - | - | - |
| **Urban residency** | | | | | |
| Yes | - | - | - | - | - |
| No | -0.3194 | 0.068 | 0.73 | 0.64 - 0.83 | <.0001 |
| **Year of diagnosis** | | | | | |
| 2000 -2004 | - | - | - | - | - |
| 2005-2009 | 0.1822 | 0.042 | 1.20 | 1.10 - 1.30 | <.0001 |
| 2010-2013 | 0.1303 | 0.178 | 1.14 | 0.80 - 1.62 | 0.4647 |

Table 4.4: Generalized linear regression model for cost across continuous phase of care

| Variables | Estimate | Standard error | Cost Ratio | 95% Confidence Limits | p-value |
|---|---|---|---|---|---|
| **Treatment group** | | | | | |
| Conservative management | -0.2092 | 0.077 | 0.81 | 0.70 - 0.94 | 0.0067 |
| Cryotherapy (reference) | - | - | - | - | - |
| **Age groups** | | | | | |
| 66-69 years (reference) | - | - | - | - | - |
| 70-74 years | 0.2069 | 0.092 | 1.23 | 1.03 - 1.47 | 0.024 |
| 75-79 years | -0.1007 | 0.093 | 0.9 | 0.75 - 1.09 | 0.279 |
| 80+ years | 0.0245 | 0.105 | 1.02 | 0.83 – 1.26 | 0.816 |
| **Race** | | | | | |
| Caucasians (reference) | - | - | - | - | - |
| African Americans | -0.0263 | 0.097 | 0.97 | 0.81 – 1.18 | 0.785 |
| Others | 0.3038 | 0.145 | 1.35 | 1.02 – 1.80 | 0.036 |
| **Tumor grade** | | | | | |
| Well-differentiated (reference) | - | - | - | - | - |
| Moderately differentiated | -0.0558 | 0.248 | 0.95 | 0.58 - 1.54 | 0.8221 |
| Poorly differentiated | -0.1788 | 0.252 | 0.84 | 0.51 - 1.37 | 0.4776 |
| Unknown | -0.1274 | 0.304 | 0.88 | 0.48 - 1.60 | 0.6755 |
| **Tumor stage** | | | | | |
| T1 | -0.2191 | 0.074 | 0.80 | 0.69 – 0.93 | 0.0031 |
| T2 (reference) | - | - | - | - | - |
| **Charlson comorbidity index** | | | | | |
| 0 (reference) | - | - | - | - | - |
| 1 | 0.0999 | 0.084 | 1.11 | 0.94 – 1.30 | 0.232 |
| 2+ | 0.0028 | 0.304 | 1.01 | 0.55 – 1.82 | 0.998 |
| **Marital Status** | | | | | |
| Married | - | - | - | - | - |
| Unmarried/Single | 0.0908 | 0.080 | 1.10 | 0.94 – 1.28 | 0.257 |
| **Education** | | | | | |
| First quartile (highest) (reference) | - | - | - | - | - |
| Second quartile | 0.0349 | 0.089 | 1.04 | 0.87 - 1.23 | 0.696 |
| Third quartile | -0.0381 | 0.092 | 0.96 | 0.80 - 1.15 | 0.677 |
| Fourth quartile (lowest) | 0.1166 | 0.091 | 1.12 | 0.94 - 1.34 | 0.202 |
| **Geographic location** | | | | | |

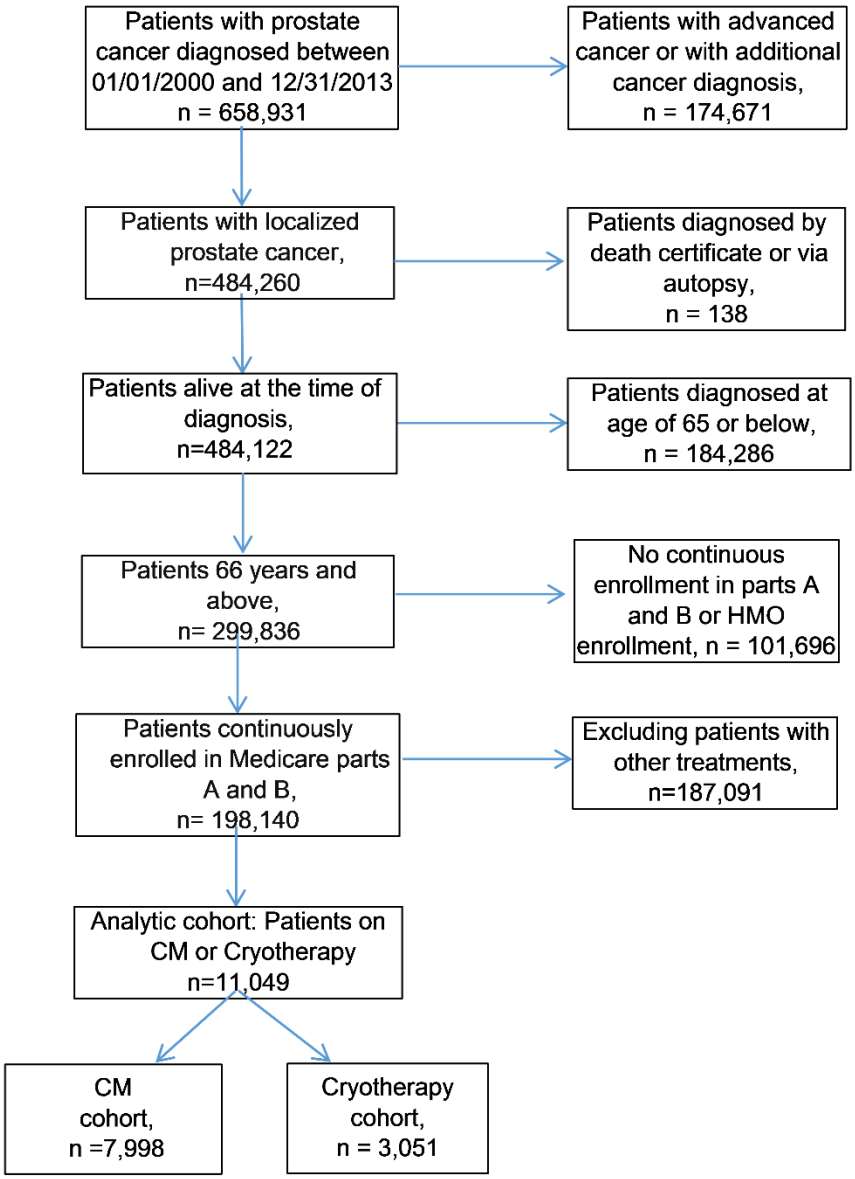
| | | | | | |
|---|---|---|---|---|---|
| Northeast | -0.025 | 0.094 | 0.98 | 0.81 - 1.17 | 0.789 |
| South | 0.0907 | 0.101 | 1.09 | 0.90 - 1.33 | 0.365 |
| Central | 0.0551 | 0.092 | 1.06 | 0.88 - 1.26 | 0.548 |
| West | - | - | - | - | - |
| **Urban residency** | | | | | |
| Yes | - | - | - | - | - |
| No | 0.0407 | 0.125 | 1.04 | 0.82 – 1.33 | 0.744 |
| **Year of diagnosis** | | | | | |
| 2000 -2004 | - | - | - | - | - |
| 2005-2009 | 0.0264 | 0.075 | 1.03 | 0.89 – 1.19 | 0.724 |
| 2010-2013 | -0.4904 | 0.215 | 0.61 | 0.40 – 0.93 | 0.023 |

Table 4.5: Generalized linear regression model for cost across terminal phase of care

| Variables | Estimate | Standard error | Cost Ratio | 95% Confidence Limits | p-value |
|---|---|---|---|---|---|
| **Treatment group** | | | | | |
| Conservative management | -0.1112 | 0.05 | 0.89 | 0.81 - 0.99 | 0.026 |
| Cryotherapy (reference) | - | - | - | - | - |
| **Age groups** | | | | | |
| 66-69 years (reference) | - | - | - | - | - |
| 70-74 years | -0.0821 | 0.0606 | 0.92 | 0.82 - 1.04 | 0.176 |
| 75-79 years | -0.0479 | 0.0615 | 0.95 | 0.85 - 1.08 | 0.435 |
| 80+ years | -0.1818 | 0.0657 | 0.83 | 0.73 – 0.95 | 0.005 |
| **Race** | | | | | |
| Caucasians (reference) | - | - | - | - | - |
| African Americans | 0.0212 | 0.0608 | 1.02 | 1.01 – 1.43 | 0.051 |
| Others | 0.179 | 0.0912 | 1.20 | 0.91 – 1.15 | 0.727 |
| **Tumor grade** | | | | | |
| Well-differentiated (reference) | - | - | - | - | - |
| Moderately differentiated | 0.1671 | 0.1695 | 1.18 | 0.66 - 1.44 | 0.893 |
| Poorly differentiated | 0.2148 | 0.1714 | 1.24 | 0.85 - 1.65 | 0.325 |
| Unknown | -0.0269 | 0.201 | 0.97 | 0.89 - 1.73 | 0.210 |
| **Tumor stage** | | | | | |
| T1 | -0.0311 | 0.0478 | 0.97 | 0.88 – 1.06 | 0.516 |
| T2 (reference) | - | - | - | - | - |
| **Charlson comorbidity index** | | | | | |
| 0 (reference) | - | - | - | - | - |
| 1 | 0.1255 | 0.0558 | 1.13 | 1.02 – 1.26 | 0.0246 |
| 2+ | 0.2913 | 0.2166 | 1.34 | 0.88 – 2.05 | 0.1785 |
| **Marital Status** | | | | | |
| Married | - | - | - | - | - |
| Unmarried/Single | -0.0044 | 0.0516 | 1.00 | 0.90 – 1.11 | 0.932 |
| **Education** | | | | | |
| First quartile (highest) (reference) | - | - | - | - | - |
| Second quartile | 0.1026 | 0.0598 | 1.11 | 0.99 - 1.25 | 0.086 |
| Third quartile | 0.0626 | 0.059 | 1.06 | 0.95 - 1.20 | 0.289 |
| Fourth quartile (lowest) | 0.1179 | 0.0594 | 1.13 | 1.01 - 1.26 | 0.047 |
| **Geographic location** | | | | | |
| Northeast | -0.0742 | 0.0601 | 0.93 | 0.83 - 1.04 | 0.217 |
| South | -0.2764 | 0.0639 | 0.76 | 0.67 – 0.86 | <.0001 |

| | | | | | |
|---|---|---|---|---|---|
| Central | -0.288 | 0.0587 | 0.75 | 0.67 – 0.84 | <.0001 |
| West | - | - | - | - | - |
| **Urban residency** | | | | | |
| Yes | - | - | - | - | - |
| No | -0.0169 | 0.078 | 0.98 | 0.84 – 1.15 | 0.828 |
| **Year of diagnosis** | | | | | |
| 2000 -2004 | - | - | - | - | - |
| 2005-2009 | 0.0279 | 0.049 | 1.03 | 0.93 – 1.13 | 0.5698 |
| 2010-2013 | -0.2176 | 0.1097 | 0.8 | 0.65 – 0.99 | 0.0473 |

## Figures




Abbreviations: CM, Conservative management;

HMO, Health Maintenance Organizations

Figure 4.1: Procedure to generate the final analytic cohort

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# CHAPTER 5

# CONCLUSIONS

This comparative effectiveness research aimed to address the uncertainties associated with treatment decision making in localized prostate cancer by generating long term evidence regarding clinical and economic benefits. In the United States, management of localized prostate cancer is a high-priority area for comparative effectiveness research.[1] Findings from this study suggests that conservative management is comparatively an effective and less expensive strategy than cryotherapy. Conservative management is associated with lower rates of treatment related side-effects and MHI, lower direct medical costs and phase specific costs, and higher survival rates. Choosing conservative management over cryotherapy could not only resolve the issues associated with the intolerance to aggressive treatments, but could also be more economical for the payers.

The purpose of our comparative effectiveness research is to help individuals make informed decisions that will improve health care at both the individual and population levels. The findings from this research are integral to patients, healthcare providers, policy makers, payers and researchers. The evidence generated could guide patients and their healthcare providers in making informed treatment decisions. Healthcare providers should actively engage in translating the available evidence to practice, not only through communication with their patients but also by practicing evidence-based decision

making. Higher value is achieved by improving outcomes, reducing costs, or both. In light of the available evidence of better clinical and economic benefits associated with conservative management, it is more likely for the patients and clinicians to have relatively low resistance to shifting care to alternative options such as conservative management. Considering the idea that older patients tend to prefer a treatment option that could improve quality of life rather than those options that maximize survival,[2,3] the evidence generated regarding treatment related side effects and mental health issues is imperative in decision making.

Results of this comparative effectiveness research could provide vital information to policy makers or purchasers of healthcare such as payers, employers, and benefits managers as it could aid them in allocating resources to structure treatments and their associated benefits. The findings from this research could provide a better understanding of the relative risks and benefits of these treatment options and support the development of evidence-based programs and policies. Payers may exercise the option to increase coverage or reduce copayments to guide treatment decision making to more cost-effective options. More resources could be allocated to additional services for patients choosing conservative management as it is a cost saving strategy. These findings are extremely relevant as the health policies are increasingly being driven by the value proposition, with a focus on the ratio of outcomes to cost. The Medicare Access and CHIP Reauthorization Act of 2015 also emphasized merit-based incentive payments, which highlights the importance of value-based care in prostate cancer.[4] Therefore, our findings are of utmost importance to the payers and policy makers in this era of value-based care.

This comparative effectiveness research has significant implications for the researchers not only in validating the research findings but also in generating newer evidence. More high quality longitudinal research is needed in this era of evidence based practice that relies on comparative effectiveness research. This research only evaluated treatment related side-effects, MHI and survival. There are many other relevant outcomes that are important such as quality of life and patient satisfaction with the treatment or quality of care received from healthcare providers. Researchers should consider these outcomes in future studies supplement the available evidence in order to inform treatment decision making. In addition, future research is needed to assess costs from patient perspectives such as out-of-pocket costs and productivity losses. Although findings from this study indicate that conservative management is a superior treatment option than cryotherapy in terms of side effects, survival, and costs, future research is warranted to conduct a more full cost-effectiveness analysis rather than a simple comparison of specific outcomes.

Therefore, in order to make comparative effectiveness research assist patients and providers in making wise choices that can improve health outcomes, exploring all the necessary patient centered outcomes is critical. Given the challenge of reducing wasteful spending in health care, policymakers must transform the vague concept of "waste" into a clearly defined set of targets that can be more precisely addressed to improve the health care system.

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# APPENDIX A

## INSTITUTIONAL REVIEW BOARD LETTER


Phone 706-542-3199

Office of the Vice President for Research
*Institutional Review Board*

**APPROVAL OF PROTOCOL**

October 14, 2016

Dear Henry Young:

On 6/14/2016, the IRB reviewed the following submission:

| | |
|---|---|
| Type of Review: | Modification |
| Title of Study: | Impact of Conservative Management versus Cryotherapy on Cost and Outcomes in Patients with Localized Prostate Cancer: A secondary data analysis of the Surveillance, Epidemiology, and End Results (SEER) Cancer Registry and Medicare Claims Database |
| Investigator: | Henry Young |
| IRB ID: | MOD00003745 |
| Funding: | None |
| Grant ID: | None |

The IRB approved the protocol from 10/14/2016.

In conducting this study, you are required to follow the requirements listed in the Investigator Manual (HRP-103).

Sincerely,

Dr. Gerald E. Crites, MD, MEd
University of Georgia
Institutional Review Board Chairperson