



RESEARCH ARTICLE

Comparative Analysis of Harms Associated with Conservative Management and Immediate Treatment among Low Risk Localized Prostate Cancer Patients: A Population Based Study

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Abstract

Purpose: To examine urinary, rectal, erectile side effects and cancer specific survival in localized prostate cancer patients who were treated with immediate treatment or conservative management.

Methods: Using the Surveillance Epidemiology and End Results Medicare-linked database, a total of 6,868 patients aged ≥ 66 years diagnosed with low risk localized prostate cancer in the year 2004 and 2005 were identified. Patients who received either immediate or delayed treatment (> 6 months after diagnosis) were followed for 5-years to determine toxicities and survival. Propensity score matching was used to adjust for selection bias associated with treatment type received. The presence of toxicity in each cohort was determined using logistic regression. The Cox proportional hazard model was used to estimate prostate cancer specific survival rates.

Results: Overall, 735 patients received delayed treatment and 6,133 patients received immediate treatment. Multivariate logistic regression analysis showed that the conservative management group was found to have lower odds for urinary complications (odds ratio: 0.82, p value < 0.0001), rectal complications (odds ratio: 0.77, p value < 0.01) and erectile toxicities (odds ratio: 0.64, p value < 0.01) compared to the immediate treatment group within 5-years of diagnosis. The results of survival analysis showed that there was no additional hazard of dying due to prostate cancer in conservative management within a 5-year period among studied patients than those in the immediate treatment group (Hazard ratio: 0.74, p value: 0.27).

Conclusion: Patients aged ≥ 66 years diagnosed with low risk prostate cancer are not at additional risk of dying due to prostate cancer within a 5-year period if kept on conservative

management or delayed treatment. It is critical to choose appropriate treatment for disease management and it should account for patient preferences for the potential side effects of treatment options.

Keywords

Prostate cancer, SEER-Medicare, Treatment outcomes, Conservative management

Introduction

Prostate cancer is the second leading cause of noncutaneous cancer related deaths among men in the United States [1]. The National Cancer Institute has estimated that there will be approximately 180,890 new cases of prostate cancer and approximately 26,140 will die of it in 2016 [2]. Prostate cancer leads in terms of costs as well. The overall direct cost of prostate cancer in the United States in 2010 was estimated to be more than \$12 billion in annual costs [3]. In 2020, the direct cost of prostate cancer is projected to be \$19 billion [3]. Currently, most prostate cancers are detected by a blood test that measures Prostate Specific Antigen (PSA), and digital rectal examination [4]. More than half of cancers detected with PSA screening are localized, not aggressive at diagnosis, and unlikely to become life threatening [5]. However, 90% of patients receive immediate treatment for prostate cancer such as surgery or radiation therapy resulting into tremendous overtreatments [5,6]. In many patients, these overtreatment's have



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substantial short-term and long-term effects without any clinical benefit.

Appropriate management of screen detected, early-stage, low to intermediate risk prostate cancer is an important public health issue given the number of men affected and the risk for adverse outcomes, such as diminished sexual function and loss of urinary control. Potential strategies to eliminate overtreatment include more widespread implementation of observational therapies. Currently, clinicians rely on two observational strategies as alternative to immediate treatment of early-stage prostate cancer: Watchful waiting and active surveillance. Watchful waiting involves relatively passive patient follow-up, with palliative interventions when any symptoms develop. Active surveillance typically involves proactive patient follow-up in which PSA levels are closely monitored, prostate biopsies may be repeated, and eventual treatment is anticipated. As prostate cancer often has an indolent natural history, it makes observational management strategies more appealing [7]. The life time risk of being diagnosed with prostate cancer is about 17%, while the corresponding risk of dying of this disease is 3% [8,9]. This evidence suggests that conservative management may be an important treatment consideration of the sizable majority of men diagnosed with localized prostate cancer.

Watchful waiting in low-risk prostate cancer is not new to the field. However, active surveillance is a new emerging strategy that focuses on relatively young individuals rather than the sicker older population. Despite its potential as a reasonable treatment choice active surveillance has been used in only about 10% of the patients, perhaps because of a limited understanding of and contemporary data on the anticipated course and outcomes of this approach. Long term outcomes and effects on quality of life have not been well characterized [8,10]. The Institute of Medicine's Committee on Comparative Effectiveness Research has identified treatment for localized prostate cancer as a high-priority research area [11]. The objective of the current study was to compare conservative management with the immediate treatment based on long term clinical outcomes mainly disease and treatment related toxicities. The rationale behind this study is that it may add evidence to choose an appropriate regime for patients diagnosed with low risk localized prostate cancer.

Methods

Data sources

Data for this study was obtained from the National Cancer Institute's Surveillance Epidemiology Ends Re-

sults (SEER) program database linked to Medicare administrative claims from 2003 to 2009. The SEER program captures clinical, demographic and survival information of approximately 28% of the US population and is 98% complete for case ascertainment [12]. The Medicare program covers approximately 97% of the persons aged 65 years and older [13]. This study was approved by the University of Georgia's Institutional Review Board as well as by the SEER-Medicare for Data Use Agreement with National Cancer Institute. As the data did not contain personal identifiers, informed consent was not requested by the Institutional Review Board.

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

Study participants

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

Table 1: ICD-9 and CPT/HCPCS codes used to identify treatment modality.

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

Table 2: ICD-9 and CPT/HCPCS codes used to identify complications.

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

Outcomes assessment

Both incident and prevalent cases of urinary, rectal and erectile complications were assessed separately in both cohorts. Urinary complications were defined as having incontinence, obstruction, irradiation cystitis, bladder hemorrhage, urinary fistulas or urinary tract infections. Rectal complications were defined as having rectal hemorrhage, ulcers, fistulas or bowel incontinence. Erectile complications were defined as having impotence. These complications were identified using appropriate ICD-9 diagnoses codes as well as based on Common Procedure Terminology (CPT)/HCPCS codes of invasive procedures performed to repair these complications. The medical codes for diagnoses and procedures performed for the complications are provided in [Table 2](#). Patient's dates of diagnosis and death were obtained from the SEER's PEDSF file.

Statistical analyses

Demographic and clinical variables across study cohorts were compared. A chi-square test was used to compare categorical variables and a t-test was used to compare continuous variables. As the aim of this study was to compare treatment outcomes, propensity score matching was used to address the issue of selection bias and generate comparable study arms. In this two-step procedure, the probability of receiving treatment (conservative management vs. immediate treatment) was first calculated based on multivariate logistic regression that included the patient's demographic information such as age, race, income, and tumor related information (e.g., grade, tumor extension and tumor size) as predictors of receiving treatment. The obtained probability scores were then used in analyzing outcomes. Risk of complications such as urinary, rectal and sexual dysfunction was estimated using logistic regression. A Cox proportional hazard model was used to estimate the prostate cancer specific survival rate in both the cohorts. All analyses were performed using SAS statistical software (version 9.3, SAS Institute, Cary, NC).

Results

The study population included 6,868 patients who were diagnosed with incident prostate cancer between 2004 and 2005 and fit into the eligibility criteria. Conservative management and immediate treatment cohorts

consisted of 735 and 6,133 patients respectively. [Table 3](#) describes the baseline characteristics of the study cohorts. The majority of eligible patients were aged 66 to 74 years and white in both the cohorts. Approximately 97% of the patients in both cohorts had either a moderately or intermediately differentiated tumor grade. All patients had localized prostate cancer. Tumor size was not recorded in more than 85% of patients in both cohorts. There was no nodal involvement in all the eligible patients. In terms of comorbidity burden, the majority of patients had either 0 or 1 comorbid condition. There were more married individuals in the immediate treatment group than the conservative management cohort. There was no significant difference in the proportion of patients who had T1 or T2 a staging in both the treatment arms.

Risk of adverse outcomes

Patients diagnosed with prostate cancer were followed for a 5-year time period to measure adverse events in both cohorts. Adverse events studied included urinary, rectal and erectile complications. Rates of urinary, rectal and erectile complications were 55.51%, 20.27% and 6.12%, respectively, for conservative management patients. Immediate treatment patients were found to have urinary, rectal and erectile rates of 57.26%, 25.04% and 10.75% respectively. [Table 4](#) presents crude rates of complication diagnoses and invasive procedures performed for both cohorts.

[Table 5](#) shows the results of the logistic regression predicting urinary complications based on the treatment arms, demographic, and tumor related variables adjusted with propensity scores. Odds of urinary complications were statistically significantly lower in the conservative management than the immediate treatment group (odds ratio: 0.82, $p < 0.01$).

Patients aged from 66 to 79 years were found to have significantly lower odds of urinary complications than those above 80-years-old. Patients with null or moderate comorbidity were found to have reduced odds of urinary complications than those with more than one comorbidity. Black patients compared to whites had reduced odds of urinary complications. Single patients were found to have higher odds of having urinary complications than married patients. Results related to rectal complications are pre-

Table 3: Clinical and demographic characteristics of patients with clinically localized prostate cancer.

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

Table 4: Crude rates for complication diagnoses and invasive procedures.

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

sented in [Table 6](#). Conservative management was found to have a lower odd of rectal complications compared to the immediate treatment group (odds ratio: 0.77, $p < 0.01$). Compared to whites, black and patients with other ethnicities were found to have reduced odds of rectal complications. Those with null or moderate comorbidity were found to have lower odds of getting rectal complications than those with higher comorbidity. Factors associated with rates of erectile complications are presented in [Table 7](#). Conservative management was found to be less likely to have erectile complications than the immediate treatment group (odds ratio: 0.64, $p < 0.01$). There was not a statistically significant difference between blacks and whites regarding erectile complications. However, patients with other ethnicities (other than black) were found to have reduced odds of having erectile complications than whites.

Patients aged from 66 to 79 years were found to have higher odds of erectile complications than those above 79 years of age. Patients with null or one comorbidity had higher odds of having erectile complications than those with higher comorbidity.

Survival analysis

Data for survival analysis are presented in [Table 8](#). These data represent up to a 5-year follow up period from time of diagnosis. Patients who were in the conservative management group did not differ significantly from those in the immediate treatment group in terms of prostate cancer specific mortality at any point in time (Hazard ratio: 0.74, p value: 0.27) within the 5-year time period. However, our study found that black patients compared to whites had higher hazard of dying due to

Table 5: Logistic regression analysis of urinary complications and predictors using propensity score.

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

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

Table 6: Logistic regression analysis of rectal complications and predictors using propensity score.

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

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

prostate cancer within 5-year time period (Hazard ratio: 2.54, p value: 0.01). Patients aged from 66 to 79 years were found to have better survival experience than those aged above 79 years within the study time period. We also found that patients with null or one comorbidity had a reduced hazard of dying due to prostate cancer than those with greater than one comorbidity.

Discussion

Our study of prostate cancer patients diagnosed between 2004 and 2005, with a 5-year follow up, has focused on whether urinary, rectal, or erectile complication rates differ between conservative management and immediate treatment groups. Further, this study

assessed the survival experiences of both treatment groups. Prostate cancer is considered a disease of older men and the median age at diagnosis reported is 72 years [14]. Thus, SEER-Medicare population is representative of the population of interest. Results of the current study suggest that patients who opt for delayed treatment are less likely to have urinary, rectal, and erectile complications compared to those in immediate treatment within 5-year treatment period. Current study also found that the delayed treatment group does not have higher prostate cancer specific mortality within 5-year time period than the immediate treatment group. It has been reported in previous studies that radical prostatectomy and radiation therapy affect a pa-

Table 7: Logistic regression analysis of erectile complications and predictors using propensity score.

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

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

Table 8: Cox proportional hazard model to assess hazard of dying due to prostate cancer adjusted with propensity scores.

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

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

tient's bowel, urinary and sexual function tremendously and thereby affect the patient's quality of life [15]. Men in the intermediate risk category face the most challenging decisions regarding treatment and physicians recommend working backward from the known side effects associated with each treatment option [15]. Prostate cancer itself can affect bladder and sexual function [16]. Urinary incontinence is the most common symptom of prostate cancer and its severity depends on the type of the disease. Tumor growth can also damage the nerves that control the erection and thus leave a patient unable to engage in sexual activity.

As patients live longer with low-risk localized prostate cancer, they live with sequel of the treatments they

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

find any claims related to drugs such as sildenafil citrate, tadalafil citrate or vardenafil to treat erectile dysfunction. Patient preferences for outcomes among competing treatment strategies may be an important factor that drives treatment decisions.

There are patients who want to avoid therapy induced distressful symptoms even when faced with a reduced prospect of survival. Some men give full priority to survival even though the survival gain may be very small. Recently, Bill-Axelsson, et al. presented extended follow up results of the Scandinavian Prostate Cancer Group study number 4 (SPCG-4) [19]. This trial randomized patients to watchful waiting or radical prostatectomy between 1989 and 1999. They found a substantial reduction in mortality after the radical prostatectomy group was followed for up to 23.2 years among men younger than 65 years of age. They did not find a significant difference in mortality rate between radical prostatectomy and watchful waiting among low risk localized prostate cancer patients. However, our study is different than SPCG-4 trial or other studies that have compared immediate treatment options with watchful waiting program [9,20]. We combined different immediate treatment options into one category. Further, we had a conservative management group that included both watchful waiting and active surveillance options. Acceptance of active surveillance or watchful waiting depends on a patient's physical and psychological well-being. Both strategies offer the opportunity to delay treatment. However, watchful waiting is reserved for those who cannot tolerate aggressive treatment and are offered hormonal therapy upon cancer progression. On the other hand, active surveillance involves curative treatment upon cancer progression. It is difficult to separate patients who received watchful waiting versus active surveillance from the claims database as both groups receive frequent PSA screening. As a result, both treatment options in this study are combined as a conservative management approach.

Several potential limitations of this study should be considered when interpreting these results. Large administrative data sets such as Medicare data contain data originally intended for billing purposes. Procedures or treatments that do not incur any costs are not reported as there is no financial incentive to document them. Treatment date that we identified from the claims data represent the claims date and may not necessarily correspond to the actual date the treatment was initiated. Thus identifying delayed treatment based on 6 month cut off time may not be accurate. Complication rates obtained using these data represent underestimates as not all patients are likely to receive treatments for complications. The treatment modalities were not randomized in the study. However, the issue of selection bias was addressed using propensity score matching. We could not differentiate patients who had watchful waiting or active surveillance as an observational strategy.

This may bias the results because patients in watchful waiting are more likely to receive hormonal treatment and are at higher risk of having serious side effects or even death. We acknowledge that our study follow up period was restricted to 5-years which may not be a long enough time to capture all possible events for slowly growing prostate cancer. The study was limited to Medicare eligible patients aged 66 years or older and those receiving care through the traditional, fee-for-service system, limiting the utility of the finding to older patients not enrolled in managed care programs. In this study, we did not measure the average time of receiving treatment in the delayed treatment group or time interval of developing urinary, rectal or erectile side effects in both the groups. In the future we aim to measure that time interval and compare immediate treatment with delayed treatment cohort by estimating number of cases of metastatic cancer prevented.

Conclusion

Treatment options for patients diagnosed with low to intermediate risk prostate cancer include i) Immediate treatment with either radical prostatectomy or radiation therapy and ii) Observational strategies such as active surveillance or watchful waiting. Our study suggests that the conservative management approach should be considered for patients who prefer less likely to have urinary, rectal, and erectile side effects. Prostate cancer specific mortality does not differ significantly among patients diagnosed with localized and well differentiated prostate cancer and who receive either immediate treatment or observation treatment within 5-year from diagnosis. Choosing the appropriate treatment regimen for disease management is critical and should account for (i) The patient's tumor characteristics such as its grade or aggressiveness, (ii) Patient age, overall health and remaining life expectancy and (iii) Patient preferences for the potential side effects of treatment options.

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