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14. ABSTRACT

There is increased interest in management of patients at end of life and effective methods for palliating symptoms are increasingly available. There has been very little research on the use of palliative treatments. Our team has developed the tools/methods for working with SEER-Medicare. We plan to use analytic approaches and methods to explore racial disparities in the use of palliative treatment for prostate cancer. The long-term aim of this study is to have a better understanding of the racial disparities in the receipt of proven or widely accepted palliative treatments.

15. SUBJECT TERMS

Prostate cancer, palliative care, ureteral obstruction, cord compression

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Palliative Treatment of Advanced Prostate Cancer

PROGRESS REPORT
2010-2015

Principal Investigator: Alfred I. Neugut, M.D., Ph.D.

INTRODUCTION:

New effective treatments have become available for palliative care, but disparities and variability in who receives them may be major issues as these treatments become more effective, but also more expensive and difficult to administer. For example, spinal cord compression was traditionally treated with corticosteroids and radiotherapy (RT), but recent studies have demonstrated that for selected patients surgery with RT would improve the quality of life of these patients. Are all appropriate patients receiving surgery and follow-up RT or are there subgroups that are selectively underserved, especially racial groups? And are these treatments delivered in a timely fashion and to completion? Very little research has focused on such topics in the setting of palliative care.

The long-term aim of this proposal is to have a better understanding of racial disparities in the receipt of proven or widely accepted palliative treatments. To accomplish this, we propose to use a population-based administrative database which we have used extensively in studies of curative therapies, SEER-Medicare database, to evaluate racial disparities and associated factors in the use of palliative treatment in three important palliative settings which are relatively common and have accepted effective therapeutic options.

KEY RESEARCH ACCOMPLISHMENTS:

Task1. **Administrative Preparation, Months 1-3:** **COMPLETE**

1. Purchase and upload 2009 update of SEER-Medicare database
2. Recruit new data analyst/SAS programmer
3. Recruit prostate cancer survivor/advocate to serve as consultant
4. Amend IRB approvals.

The SEER-Medicare database update was purchased and uploaded to our servers in early 2010. Analyses for Aims 1 and 2 were conducted using the SEER-Medicare files. In 2014, we obtained the MarketScan Research dataset and it is with this de-identified dataset that the analysis for Aim 3 was conducted. The MarketScan database houses data on more 180 million unique patients since 1995 and is very popular among researchers conducting comparative effectiveness studies. This database contains fully integrated patient-level data (inpatient,

outpatient, drug, lab, etc.) from commercial, Medicare supplemental and Medicaid populations. Longitudinal integrity of this database is strong, thus allowing us to examine disparities in critical palliative issues over time for a socio-economically diverse patient population.

Beverly Insel, DrPH, an epidemiologist with expertise and experience in SAS programming and epidemiologic data analysis was hired to perform analyses related to this project. When Dr. Insel left the project in 2012, she was replaced by a biostatistician/SAS programmer, Ms. Jinjoo Shim. When Ms. Shim left Columbia, she was replaced with Ms. Sowmya Vasan.

The CUMC IRB deemed this study exempt from human subjects review.

Task 2. **Communication Plan, Months 1-60:** **COMPLETE**

1. Weekly face-to-face meetings among investigators.
2. Semi-annual meetings with prostate cancer survivor consultants.
3. Semi-annual presentations at American Cancer Society Man to Man and Us Too prostate cancer support group meetings.

Weekly meetings to discuss the progress of analysis are held on Tuesdays. This has been ongoing since the initiation of the project. Discussions involve development of inclusion criteria based on variables available in the SEER-Medicare and Truven Health Analytics MarketScan databases, refinement of outcome measures, general discussion of analytic methods best suited to each individual study aim, and interpretation of findings.

A presentation was delivered by Dr. Neugut to the Us Too support group at the New York Presbyterian/ Weill Cornell Medical Center and was well received.

Task 3. **Model Creation, Months 1-60:** **COMPLETE**

1. Determine eligibility and define samples for three palliative care settings.
2. Create variables to be predictors of three palliative care interventions.
3. Create variables for receipt of three palliative care interventions.
4. Create variables for poor outcomes of palliative care interventions.
5. Data quality control and monitoring.

The specific aims of this study included: examining patients with spinal cord compression from prostate cancer and the use of surgical resection followed by radiation therapy; for patients with ureteral obstruction from prostate cancer metastases, evaluating the placement of stents or percutaneous nephrostomy; and assessment of radiation therapy use among patients with pathologic fractures due to prostate cancer.

Of these three aims, we have successfully analyzed the SEER-Medicare data with respect to the spinal cord compression and ureteral obstruction. We also undertook to study the use of

bisphosphonates in relation to skeletal-related events in prostate cancer. Due to the unreliable nature of data in the SEER-Medicare database with regard to bone metastasis, our paper was not submitted for publication. Instead, we added another aim, to examine the patterns of use of abiraterone since its approval as a palliative chemotherapy treatment for advanced prostate cancer, and investigate racial disparities in its use. This last aim is being conducted in the Truven Marketscan database.

Task 4. **Spinal Cord Compression Study, Months 9-16:** **COMPLETE**

This analysis is complete. The manuscript reporting the results of the spinal cord compression study is published (Spencer BA, Shim JJ, Hershman DL, Zaccharia B, Benson MC, Neugut AI. 2014. Metastatic epidural spinal cord compression among elderly patients with advanced prostate cancer. Support Care Cancer 22:1549-1555). The full paper can be found below in this report on pages 24-30.

This study aimed to investigate the predictors of metastatic epidural spinal cord compression (MESCC), its treatment, and impact on hospital length of stay among men diagnosed with stage IV prostate cancer. SEER-Medicare records of men >65 years of age with metastatic prostate cancer were examined; polytomous logistic regression was used to compare those with and without MESCC and those hospitalized for treatment with surgical decompression and/or radiation therapy.

Black men were more likely to develop MESCC (OR 1.75, 95% CI 1.39-2.19) than White men (Table 2, page 28 below). Older patients and those with one or more comorbidities were less likely to undergo either RT or surgery. Patients with high-grade tumors were more likely to have RT (OR 1.92, 95% CI 1.25-2.96) and those who had RT or surgery spent 11 and 29 more days, respectively, hospitalized. These findings suggest that Black men are more likely to develop MESCC but older men and those with comorbidities are less likely to be treated in the palliative care setting.

Task 5. **Ureteral Obstruction Study, Months 15-21:** **COMPLETE**

The analysis for this aim is also complete. A paper published in Supportive Care in Cancer in May 2013 reports our findings related to ureteral obstruction (Spencer BA, Insel BJ, Hershman DL, Benson MC, Neugut AI. 2013. Racial disparities in the use of palliative therapy for ureteral obstruction among elderly patients with advanced prostate cancer. Support Care Cancer 21:1303-1311). The full paper can be found below in this report on pages 15-23.

Briefly, the objective of this analysis was to investigate the predictors of the receipt of retrograde ureteral stent (RUS) and percutaneous nephrostomy (PCN) and to assess the association of the use of these therapies and survival among older prostate cancer patients. For this analysis, records of men with stage IV prostate cancer in the SEER-Medicare database were identified. Multivariable analysis was used to compare those with ureteral obstruction

treated with RUS and PCN vs. those not treated. The association between RUS, PCN, and survival was also evaluated.

We found that African American men were more likely to undergo PCN (OR 1.48, 95% CI 1.03-2.13) than Whites; older men were less likely to undergo RUS (ages 80-84 years, OR 0.41, 95% CI 0.27-0.63 and age ≥85 years, OR 0.30, 95% CI 0.16-0.54) compared to men 65-69 years; and men who received a PCN were 55% more likely to die than those who were untreated for ureteral obstruction. See Table 3 (page 20-21) in Spencer et al. below.

Our findings demonstrate a racial disparity in the treatment of ureteral obstruction among men with stage IV prostate cancer. This is the first large, population-based study to evaluate the one of the most common late complications of advanced prostate cancer. Reasons for disparate care require further examination.

Task 6. **Bisphosphonate Use Study, Months 36-48:** **COMPLETE**

See Task 3 above. This analysis looked at the use of bisphosphonates for bone fractures and whether there were racial disparities involved. In addition in the last couple of months of this year we undertook an analysis of the use of abiraterone, a new agent developed and approved for palliative chemotherapy for advanced prostate cancer patients. We are exploring its use as a function of race/ethnicity to determine whether racial disparities exist in access to this new efficacious agent. These analyses are almost complete and we will complete them shortly after the end of this grant and publish them. This analysis utilizes the MarketScan database rather than SEER-Medicare. See task 7 below.

Task 7. **Early Adoption of a New Oral Medication (Zytiga) for the Treatment of Prostate Cancer, Months 49-60:** **ANALYSIS COMPLETE**

Abiraterone (Zytiga) was approved for use in patients with mCRPC after progression with docetaxel chemotherapy in April, 2011. More recently it was approved by the FDA for use in patients with mCRPC before chemotherapy (December, 2012). We assessed the use of abiraterone in patients with prostate cancer, described the characteristics of abiraterone early adopters, examined adherence over time, and evaluated disparities in use. The abstract for this paper can be found on page 9. The paper is currently under review.

Task 8. **Final Analysis, Manuscript and Report Writing, Months 48-60:** **COMPLETE**

Final analysis and manuscript writing is complete for Tasks 4, 5 & 6. For Task 7, the analysis is complete and the first draft of the manuscript is currently being circulated for comment among the co-authors. See below for abstract.

KEY RESEARCH ACCOMPLISHMENTS:

- We examined three situations involving the palliative treatment of prostate cancer:
    - Predictors of metastatic epidural spinal cord compression, its treatment, and it impact on hospital length of stay for patients with advanced prostate cancer;
    - Predictors of the receipt of retrograde ureteral stent and percutaneous nephrostomy and their association with survival for older advance prostate cancer patients; and
    - o Use of abiraterone over time to treat metastatic castrate resistant prostate cancer.
- A fourth topic was explored, predictors of bisphosphonate use and efficacy, but not reported due to the limitations of the SEER-Medicare dataset to accurately identify bone metastasis.
- 2 publications resulted from this work and a third is being prepared for submission at this time.

REPORTABLE OUTCOMES:

2016:

Lim EA, Zhong X, Wright J, Neugut AI, Fojo AT, Hu JC, Unger JM, Hershman DL. **Diffusion of Abiraterone Use in Patients with Prostate Cancer.**

BACKGROUND:
In 2011 the Food and Drug Administration approved abiraterone, an oral CYP17 androgen synthesis inhibitor, to treat metastatic castrate resistant prostate cancer (mCRPC) after progression on docetaxel. In 2012 it was approved for mCRPC patients without prior docetaxel. We evaluated the use of aberaterone over time.

METHODS:
Patients with prostate cancer (ICD-9 185) were identified in the Truven Health Analytics MarketScan Dataset from 2009 to 2013. We assessed cumulative incidence of first abiraterone claim by age, comorbidity status, region, and health insurance type. To model abiraterone use over time we used the classic mixed influence deterministic diffusion model. Diffusion patterns of abiraterone use were evaluated in relation to landmark events. To study factors influencing use of abiraterone without prior docetaxel, we performed a logistic regression analysis.

RESULTS:
We identified 388,701 patients with prostate cancer, 3239 (0.83%) of which received abiraterone. Patients with a comorbidity score ≥1 versus 0 ($p<0.0001$) and age ≥65 versus <65 ($p<0.0001$) had higher cumulative incidence rates of abiraterone use. Abiraterone was given without prior docetaxel in 50% of patients before FDA approval for this indication. The main predictor of abiraterone use without prior docetaxel was later date of use (OR 5.57 95%CI 4.51-6.87 $p<0.0001$). Patients <65 years of age (OR 0.63 95%CI 0.53-0.75 $p<0.0001$), and those with higher copayments (OR 0.79 95%CI 0.65-0.96 $p=0.016$) were less likely to receive abiraterone without prior docetaxel. Social dynamics were a significant influence in abiraterone diffusion.

CONCLUSIONS:
We found diffusion of abiraterone occurred more quickly in older patients and those with increased comorbidities. Use of abiraterone prior to docetaxel occurred in 50% of patients initiating abiraterone therapy prior to data on efficacy in this setting.

2014:

Lim EA, Neugut AI, Shim JJ, Spencer BA, Benson MC, Tsai W-Y, Wright JD, Hershman DL. **Bisphosphonate Use in Elderly Patients with Metastatic Cancer to Bone.** (Not submitted due to limitations in the data with regard to bone metastasis).

BACKGROUND:
Bone metastases are common in patients with advanced solid tumors and increase the risk for skeletal-related events (SREs). Bisphosphonates reduce the risk of SREs. We performed a population-based study to determine predictors of bisphosphonate use and efficacy.

METHODS:
We identified subjects >65 years of age with breast, castration-resistant prostate (CRPC), and non-small cell lung cancer (NSCLC) in the SEER-Medicare database, between 2000–2007, with claims for bone metastases and bisphosphonate use (pamidronate or zoledronic acid). Optimal use of bisphosphonates was defined as receipt of ≥75% of the monthly doses within one year for those who lived one year or more after initiation.

RESULTS:
Among 9,617 patients identified, 5,788 (60%) received a bisphosphonate. In multivariable logistic regression analysis, black race (OR 0.71; 95%CI 0.60-0.83) versus white, and patients with CRPC (OR 0.74; 95%CI 0.61-0.89) or NSCLC (OR 0.38; 95% CI 0.33-0.44) versus breast cancer were less likely to receive bisphosphonates. Of those who received bisphosphonates, 3,078 (53%) had optimal dosing. Suboptimal use was associated with race (black OR 0.71, 95%CI 0.54-0.92; other OR 0.71, 95%CI 0.54-0.93 versus white) and NSCLC (OR 0.61 95%CI 0.49-0.76 versus breast cancer). Administration of bisphosphonates prior to SREs was associated with a lower risk of SREs (HR 0.85; 95%CI 0.80-0.91).

CONCLUSIONS:
We found preventive bisphosphonate use was associated with a reduced risk of SRE's however 40% of patients with bone metastases did not receive bisphosphonates. Black patients were less likely to receive bisphosphonate therapy. Reducing SRE's may be a way to decrease health care costs.

2013:

Spencer BA, Insel BJ, Hershman DL, Benson MC, Neugut AI. **Racial disparities in the use of palliative therapy for ureteral obstruction among elderly patients with advanced prostate cancer**. Supportive Care in Cancer. 2013;21(5):1303-1311

OBJECTIVES:
Palliative issues are an important but understudied issue for patients with advanced cancer. Ureteral obstruction is a complication of advanced prostate cancer, usually relieved with placement of retrograde ureteral stent (RUS) or percutaneous nephrostomy (PCN) to palliate symptoms associated with obstructive uropathy and/or renal failure. We investigated predictors of receipt of RUS and PCN and their association with survival for older advanced prostate cancer patients.

METHODS:
Using the Surveillance, Epidemiology, and End Results-Medicare database, we identified patients aged 65 or older with stage IV (n = 10,848) or recurrent (n = 7,872) prostate cancer. We used multivariable analysis to compare those with ureteral obstruction treated with RUS or PCN to those not treated and to analyze the association between RUS, PCN, and survival.

RESULTS:
Sixteen percent (n = 2,958) of the sample developed ureteral obstruction. Compared to no treatment, African Americans were more likely to undergo placement of PCN [odds ratio 1.48, 95 % confidence intervals (CI) 1.03-2.13] than Whites, but equally likely to receive a stent. Subjects of >80 years were less likely to undergo RUS (ages 80-84, 0.41, 95 % CI 0.27-0.63; ages ≥85, 0.30, 95 % CI 0.16-0.54) compared to patients 65-69 years. Subjects who received a PCN were 55 % more likely to die than those who were untreated. There was no difference in survival among those receiving RUS vs untreated. Nine percent of subjects received RUS or PCN within 30 days of dying.

CONCLUSIONS:
This is the first population-based study to demonstrate a racial disparity in the palliative treatment of advanced prostate cancer. Reasons for disparate care need to be determined so that interventions may be developed.

2013:

Spencer BA, Shim JJ, Hershman DL, Zacharia BE, Lim EA, Benson MC, Neugut AI. **Metastatic Epidural Spinal Cord Compression among Elderly Patients with Advanced Prostate Cancer.** Supportive Care in Cancer. 2014. Support Care Cancer; 22(6):1549-55.

Background:
A recent randomized trial demonstrated that for metastatic epidural spinal cord compression (MESCC), a complication of advanced prostate cancer, surgical decompression may be more effective than external beam radiation therapy (RT). We investigated predictors of MESCC, its treatment, and its impact on hospital length of stay for patients with advanced prostate cancer.

Methods:
We used the SEER-Medicare database to identify patients >65 years with stage IV (n=14,800) prostate cancer. We used polytomous logistic regression to compare those with and without MESCC and those hospitalized for treatment with surgical decompression and/or RT.

Results:
MESCC developed in 711 (5%) of patients, among whom 359 (50%) received RT and 107 (15%) underwent surgery +/- RT. Median survival was 10 months. MESCC was more likely among patients who were black (OR 1.75, 95%CI 1.39-2.19 vs. white) and had high-grade tumors (OR 3.01, 95%CI 1.14-7.94), and less likely in those younger; with prior hormonal therapy (OR 0.73, 95%CI 0.62-0.86); or with osteoporosis (OR 0.63, 95%CI 0.47-0.83). Older patients were less likely to undergo either RT or surgery, as were those with $\geq$1 comorbidity. Patients with high-grade tumors were more likely to undergo RT (OR 1.92, 95%CI 1.25-2.96). Those who underwent RT or surgery spent an additional 11 and 29 days, respectively, hospitalized.

Conclusions:
We found that black men with metastatic prostate cancer are more likely to develop MESCC than whites. RT was more commonly utilized for treatment than surgery, but the elderly and those with comorbidities were unlikely to receive either treatment.

PERSONNEL:

Last	First	Title
Hershman	Dawn	Associate Professor
Hillyer	Grace	Assistant Professor
Insel	Beverly	Res. Scientist
Jacobson	Judith	Associate Professor
Neugut	Alfred	Professor
Shim	Jinjoo	Res. Scientist
Spencer	Benjamin	Assistant Professor
Tsai	Wei-Yann	Professor
Vasan	Sowmya	Data Analyst
Zhong	Xiaobo	Data Analyst

CONCLUSIONS:

With this award from the DOD, we explored various circumstances in which palliative care was administered to patients with advanced prostate cancer. Palliative care is an increasingly important area of research at the current time. In almost all of these circumstances, we found that blacks were somewhat discriminated against in their access to the newest and best modality of intervention. The one exception was abiraterone where we could not explore this issue because MarketScan does not have race as a field. Nonetheless we did find other important predictors of getting one modality of care versus another. These studies will serve as preliminary data for future interventions to enhance the use of palliative care in patients with prostate cancer.

Support Care Cancer (2014) 22:1549–1555
DOI 10.1007/s00520-013-2112-0

ORIGINAL ARTICLE

Metastatic epidural spinal cord compression among elderly patients with advanced prostate cancer

Benjamin A. Spencer · Jin Joo Shim · Dawn L. Hershman · Brad E. Zacharia · Emerson A. Lim · Mitchell C. Benson · Alfred I. Neugut

Received: 25 March 2013 / Accepted: 25 December 2013 / Published online: 16 January 2014

Abstract
Background A recent randomized trial demonstrated that for metastatic epidural spinal cord compression (MESCC), a complication of advanced prostate cancer, surgical decompression may be more effective than external beam radiation therapy (RT). We investigated predictors of MESCC, its treatment, and its impact on hospital length of stay for patients with advanced prostate cancer.
Methods We used the SEER-Medicare database to identify patients >65 years with stage IV (n=14,800) prostate cancer. We used polytomous logistic regression to compare those with and without MESCC and those hospitalized for treatment with surgical decompression and/or RT.
Results MESCC developed in 711 (5 %) of patients, among whom 359 (50 %) received RT and 107 (15 %) underwent surgery±RT. Median survival was 10 months. MESCC was more likely among patients who were black (OR 1.75, 95 %CI 1.39–2.19 vs. white) and had high-grade tumors (OR 3.01, 95 %CI 1.14–7.94), and less likely in those younger; with prior hormonal therapy (OR 0.73, 95 %CI 0.62–0.86); or with osteoporosis (OR 0.63, 95 %CI 0.47–0.83). Older patients were less likely to undergo either RT or surgery, as were those with ≥1 comorbidity. Patients with high-grade tumors were more likely to undergo RT (OR 1.92, 95 %CI 1.25–2.96). Those who underwent RT or surgery spent an additional 11 and 29 days, respectively, hospitalized.
Conclusions We found that black men with metastatic prostate cancer are more likely to develop MESCC than whites. RT was more commonly utilized for treatment than surgery, but the elderly and those with comorbidities were unlikely to receive either treatment.

Keywords Prostate cancer · Metastatic epidural spinal cord compression · Palliative care · SEER-Medicare

The linked SEER-Medicare database was used in this study. The interpretation and reporting of these data are the sole responsibility of the authors.

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Introduction

Each year, about 4 % of men diagnosed with prostate cancer are diagnosed with distant or metastatic disease [1]. The most common site for metastatic spread in prostate cancer is bone [2]. Bone metastases can cause pain, fractures, and metastatic epidural spinal cord compression (MESCC) [3]. The resulting edema, venous congestion, and demyelination can lead to irreversible spinal cord infarction if not treated promptly. With life expectancy for patients with MESCC estimated at 4 months, the decision to relieve the compression must be

made with realistic goals [4]. However, the potential improvement in functional status (pain, ambulation, and urinary continence) and quality of life can be substantial.

Relief of spinal cord compression can be achieved either with direct surgical decompression, external beam radiation therapy (RT) or both. In 2005, a randomized trial by Patchell et al. demonstrated a benefit from circumferential decompression, as compared to posterior laminectomy, followed by postoperative RT in patients with metastatic cancer presenting with signs and symptoms of cord compression and a true displacement of the spinal cord by an epidural mass [5]. For subjects who were randomized to both surgery and RT, 84 % were able to walk after treatment as compared to 57 % in the RT alone arm (p=0.001) and this ambulation persisted for 122 days as compared to 13 days in the RT alone group (p=0.003). Though this study is the only randomized trial evaluating the use of RT versus surgery for MESCC, it has been criticized because of slow patient accrual, suggesting a recruitment bias.

The objective of our study was to identify predictors of MESCC, determine the patterns of use for surgery and RT, and investigate whether these interventions decrease the number of days spent in the hospital. We were also interested in whether disparities due to race or access to care influence the development of MESCC and its subsequent treatment.

Methods

Data source

We analyzed data from the Surveillance, Epidemiology, and End Results (SEER)—Medicare database. The SEER database includes information on cancer diagnoses, tumor histology, stage of disease, treatments, socioeconomic status at the census tract and zip code level, survival and demographic characteristics. The Medicare database provides information on Medicare A (inpatient) and B (outpatient) eligibility, reason for Medicare entitlement, and diagnoses. The physician and hospital claim files, as well as inpatient claim files, were used to search for the claims on diagnoses or surgical procedures. The SEER and Medicare databases were combined by linking these patients by their unique patient identification number.

Cohort selection

We identified individuals who were 65 years or older at the time of cancer diagnosis and received a pathologically confirmed primary diagnosis of prostate cancer (SEER Site Code 54) as their first cancer between January 1, 1991, and December 31, 2007. Patients who were enrolled in a non-Medicare health maintenance organization or not covered by Medicare Part A and B over the same period were excluded. Patients whose only reporting source was autopsy or death certificate, whose reason for entitlement was not age, or whose date of death differed between SEER and Medicare by more than 3 months were also excluded. Among the remaining 139,627 patients, we selected a cohort that was diagnosed with American Joint Cancer Committee (AJCC) stage IV prostate cancer and survived at least 90 days following diagnosis. We then identified patients who had at least one billing claim with a diagnosis of spinal cord compression (ICD-9 Code 336.9) no more than 30 days prior to the prostate cancer diagnosis. This would allow for the possibility that the cord compression was the presenting symptom for the prostate cancer.

Demographic variables

SEER-Medicare provides the age, race/ethnicity, marital status, and tumor grade as categorical variables. Age categories are ordinal with 5-year increments between categories. Race/ethnicity was described as white, black, Hispanic, and Other/Missing. Marital status at time of cancer diagnosis was categorized as Married, Single/Divorced/Separated/Widowed, or Unknown. Tumor grade was categorized as well, moderately, poorly, and undifferentiated.

Socioeconomic status

We followed the guidelines by Du et al. [6] to create a socioeconomic status score by equally weighting income, education, and poverty level provided from the 2000 census tract data. Patients were assigned a rank score from 0 to 4, with 0 being the lowest score. Approximately 1.6 % (N=233) of the cohort lacked sufficient data in one or more categories and were excluded from the analyses.

Assessment of comorbid disease

Using the comorbid conditions identified by Charlson et al. [7], we searched for diagnostic codes of the ICD-9 Clinical Modification and Healthcare Common Procedure Coding System (HCPCS) for 18 medical conditions. Each medical condition was assigned a weight and subsequently used to calculate the final index score. In order to obtain the complete diagnosis and medical claims, the physician and outpatient claims, as well as hospital claims, were included in the comorbidity calculation, as described by Klabunde et al. [8]. Claims submitted from 13 months prior to 4 months following the date of cancer diagnosis were considered in the comorbidity index calculation.

Treatment characteristics

Receipt of radiation and surgery were extracted from the Medicare database by searching the HCPCS, Current

Procedural Terminology (CPT) codes, ICD-9 Clinical Modification diagnostic codes and procedure codes from the national claims history files, outpatient statistical analysis files, and Medicare provider analysis and review files. We excluded radiation and surgery claims that were billed more than 15 days prior or 60 days following the date of diagnosis of spinal cord compression because patients could have received these treatments for medical conditions other than spinal cord compression. The CPT codes 63001, 63003, 63005, 63012, 63015–63017, 63020, 63030, 63035, 63040, 63042–63048, 63050–63051, 63055–63057, 63064, 63066, 63075–63076, 63078, 63081–63082, 63065–83088, 63091, 63101–63013, 63275–63278, 63280–63283, 63286–63287, 63290, and 63295 and ICD-9 CM codes 03.0, 03.09, 80.5, 80.51, 80.52, 80.59, 81.0 81.00 81.04, 81.05, and 81.09 corresponded to surgical decompression. The ICD-9 CM codes V58.0, V66.1, V67.1, 92.21–92.26, 92.29–92.33, and 92.39 and CPT/HCPCS codes 77401–77409, 77411–77414, 77416–77421, 77427, 77431–77432, 77435, 77470, and 77499 were used to identify patients who received radiation therapy. Based on the claims, patients were assigned to one of three treatment groups—radiation alone, surgery alone or in conjunction with radiation (+/- RT), and neither. Receipt of androgen deprivation therapy (ADT) with a GnRH agonist (HCPCS codes J1950, J3315, J9202, J9217-J9219, J9225) was assigned for patients who had at least one claim for receipt of ADT prior to the MESCC.

Statistical analysis

We used the chi-square test to compare the distributions of those who developed spinal cord compression with those who did not (see Table 1), and multivariable logistic regression to identify predictors of spinal cord compression, adjusting for the measured clinical and demographic characteristics of the patients. Polytomous logistic regression models were used to test associations between patient demographics and treatment assignment. All statistical tests were two-sided with an alpha of 0.05. Statistical analyses were performed using SAS version 9.2 (Cary, NC). We obtained approval for this study from the Columbia University Medical Center Institutional Review Board.

Results

We identified 14,800 men with stage IV prostate cancer who met our eligibility criteria. Table 1 shows their demographic and clinical characteristics. The majority of the stage IV patients were white (79 %), married (67 %), lived in an urban area (89 %), had high-grade tumors (53 %), had no comorbidities (52 %), had used ADT prior to the diagnosis of

Table 1 Socio-demographic and clinical characteristics of men >65 years with stage IV prostate cancer in SEER-Medicare, 1991–2007

Characteristic	Entire sample	Spinal cord compression sample
	(*n*=14,800)	(*n*=711)
Age	*n* (%)	*n* (%)
65–69	3,065 (20.7 %)	170 (23.9 %)
70–74	3,925 (26.5 %)	225 (31.7 %)
75–79	3,210 (21.7 %)	149 (21.0 %)
80–84	2,568 (17.4 %)	102 (14.4 %)
85+	2,032 (13.7 %)	65 (9.1 %)
Race		
White	11,745 (79.4 %)	488 (68.6 %)
Black	1,854 (12.5 %)	143 (20.1 %)
Hispanic	273 (1.8 %)	14 (2.0 %)
Other	928 (6.3 %)	66 (9.3 %)
Marital status		
Married	9,870 (66.7 %)	458 (64.4 %)
Single/divorced/widowed	4,220 (28.5 %)	235 (33.1 %)
Unknown	710 (4.8 %)	18 (2.5 %)
Residence		
Urban	13,135 (88.8 %)	654 (92.0 %)
Rural	1,665 (11.3 %)	57 (8.0 %)
Socioeconomic status		
First quintile	2,610 (17.6 %)	158 (22.2 %)
Second quintile	3,223 (21.8 %)	122 (17.2 %)
Third quintile	3,325 (22.5 %)	146 (20.5 %)
Fourth quintile	2,936 (19.8 %)	158 (22.2 %)
Fifth quintile	2,706 (18.3 %)	127 (17.9 %)
Missing		
Tumor grade		
Well/moderately differentiated	4,152 (28.0 %)	153 (21.5 %)
Poorly differentiated	7,591 (51.3 %)	351 (49.4 %)
Undifferentiated	242 (1.6 %)	15 (2.1 %)
Unknown	2,815 (19.0 %)	192 (27.0 %)
Comorbidities		
None	7,696 (52.0 %)	399 (56.1 %)
One	3,871 (26.2 %)	176 (24.8 %)
≥Two	3,233 (21.8 %)	136 (19.1 %)
Prior ADT use		
No	5,815 (39.3 %)	370 (52.0 %)
Yes	8,985 (60.7 %)	341 (48.0 %)
Prior osteoporosis		
No	12,828 (86.7 %)	57 (8.0 %)
Yes	1,972 (13.3 %)	654 (92.0 %)
Treatment		
None	NA	245 (34 %)
Radiation	NA	359 (50 %)
Surgery	NA	107 (15 %)

MESCC (61 %), and had no prior history of osteoporosis (87 %). Almost 5 % (n=711) developed MESCC, among whom 359 (50 %) underwent palliative radiation therapy and 107 (15 %) underwent surgical decompression±RT.

In the multivariable analysis, we found that MESCC was more likely to occur among those who were younger; black (OR 1.75, 95%CI 1.39, 2.19 vs. white); had undifferentiated tumors (OR 3.01, 95%CI 1.14, 7.94 vs. well differentiated); were diagnosed earlier in the cohort; did not use ADT prior to the diagnosis of MESCC (OR 0.73, 95%CI 0.62, 0.86); and had no prior history of osteoporosis (OR 0.63, 95%CI 0.47, 0.83) (Table 2).

There were 711 stage IV patients (4.8 %) who developed MESCC. Of these, 359 (50 %) underwent RT, while 107 (15 %) underwent spinal surgery. Among subjects who developed MESCC, older patients were less likely to undergo either radiation or surgery. Similarly, those with comorbidities were also less likely to undergo either radiation (2+ comorbidities: OR 0.53, 95%CI 0.34, 0.82 vs no comorbidities) or surgery± radiation (2+ comorbidities: OR 0.40, 95%CI 0.20, 0.78 vs no comorbidities). Patients with high-grade tumors were more likely to undergo RT (poorly/undifferentiated: OR 1.92, 95%CI 1.25, 2.96 vs. well/moderately differentiated) but not surgery (Table 2). In a sub-analysis of subjects (n=466) who were treated with either radiation alone or surgery±RT, age was the only significant predictor of treatment, with younger patients more likely to receive surgery (results not shown).

We performed multivariable linear regression to analyze the effect of treatment on the number of days spent in the hospital in the 12 months following the therapy (Table 3). There were 639 subjects who received either RT and/or surgery and spent a mean of 40.1 days in the hospital, not necessarily consecutively. Those who underwent RT spent an additional 11.1 days in the hospital, while patients who underwent surgery±RT spent an additional 29 days hospitalized. Patients aged 80–84 spent 10.8 days more than 65–69-year-olds in the hospital. In a multivariable Cox proportional hazards model, median survival was 10 months for the no-treatment and surgery arms, and 4 months in the RT arm (HR 1.39, 95%CI 1.17–1.66 versus no treatment). Patients with poor or undifferentiated tumors (HR 1.26, 95%CI 1.03–1.54) were also more likely to die compared to those with well to moderately differentiated tumors (results not shown).

Discussion

In our sample of elderly men with metastatic prostate cancer, 4.8 % developed MESCC; of these, 50 % were treated with RT while 15 % underwent surgery±RT. We found that black men were more likely to develop MESCC than white men, as were younger men and those without a history of osteoporosis or prior ADT use. Younger age and fewer comorbidities were associated with undergoing treatment for the spinal cord compression with either surgery or RT.

Previous studies suggest that black men present with more advanced-stage disease as compared to white men; this is thought to be largely due to poor access to healthcare [9]. While both observational [10] and interventional [11] data suggest that there is no survival difference between black and white men with advanced-stage prostate cancer, it is still possible that disparities in quality of life may result. Thus, our finding that black men with advanced prostate cancer are more likely to develop MESCC further worsens the burden of disease that blacks experience from prostate cancer.

We also found that men without a history of osteoporosis were more likely to develop MESCC. This finding seems counter-intuitive as one would expect that pre-existing osteoporosis would increase the risk of MESCC due to either frailty or pathologic fracture of a vertebral body [3]. However, this may reflect diagnostic bias; the diagnosis of osteoporosis requires men to undergo bone mineral density testing. Only 10 % of men who initiate ADT have a baseline bone density test [12]. Those diagnosed with osteoporosis are often offered treatment with bisphosphonates. Among those with prostate cancer, at least one study showed that only about half of patients received bisphosphonates for the prevention of fractures despite good evidence in its favor [13]. Of those not diagnosed, there may be a higher prevalence of untreated osteoporosis. Therefore, our finding may be due in part to diagnostic bias.

Overall, two thirds of subjects with MESCC underwent treatment with either RT alone or surgery±RT. These figures are similar to those reported by Loblaw et al., in a study of MESCC among patients with all types of cancer [14]. These relatively high treatment rates in an elderly cohort, half of whom had at least one comorbidity, suggest that the severity of the symptoms of MESCC prompted intervention.

Fifty percent of our cohort received RT while only 15 % had surgery with or without RT. Through the lens of the Patchell study, these results suggest a poorer quality of care delivered to those patients who only received RT, however this interpretation should be tempered. The majority of our sample was diagnosed before the publication of the Patchell randomized trial in 2005 [5], reducing the possible impact of that study's findings on our patient population. Also, while the Patchell study is the only randomized phase III multicenter trial evaluating the question of surgery versus RT for MESCC, the findings have been criticized as it took 10 years to recruit 50 % of the targeted accrual introducing questions of recruitment bias and validity [15]. The same group later performed a secondary analysis from the clinical trial data evaluating the role of age and treatment outcome and found that for both treatment modalities there was no difference in outcome for patients≥65 years of age [16]. Other retrospective analyses, literature reviews, and meta-analyses have been performed to help answer this question. Loblaw et al. updated their 2005

Table 2 Predictors of metastatic epidural spinal cord compression, treatment with radiation, treatment with surgery±radiation, among men diagnosed with stage IV prostate cancer in SEER-Medicare, 1991–2007

Category	Predictors of MESCC Entire cohort (n=14,800) Odds ratio with 95 % C.I.'s	Predictors of radiation vs. no treatment MESCC cohort (n=711) Odds ratio with 95 % C.I.'s	Predictors of surgery±radiation vs. no treatment MESCC cohort (n=711) Odds ratio with 95 % C.I.'s
Age			
65–69	Referent		
70–74	1.01 (0.82, 1.24)	0.76 (0.75, 1.22)	**0.52 (0.28, 0.96)**
75–79	**0.79 (0.63, 0.99)**	0.88 (0.52, 1.50)	0.68 (0.34, 1.33)
80–84	**0.63 (0.49, 0.82)**	**0.52 (0.29, 0.92)**	**0.23 (0.10, 0.55)**
85+	**0.46 (0.34, 0.62)**	**0.41 (0.22, 0.79)**	**0.06 (0.01, 0.27)**
Race			
White	Referent		
Black	**1.75 (1.39, 2.19)**	0.96 (0.59, 1.58)	0.77 (0.38, 1.56)
Hispanic	1.30 (0.75, 2.28)	1.67 (0.46, 6.09)	1.20 (0.19, 7.40)
Other	**1.80 (1.37, 2.36)**	1.53 (0.83, 2.80)	1.31 (0.55, 3.13)
Marital status			
Married	0.86 (0.72, 1.01)	0.92 (0.64, 1.34)	1.02 (0.60, 1.73)
Single/divorced	Referent		
Unknown	**0.45 (0.28, 0.73)**	0.85 (0.28, 2.59)	0.97 (0.21, 4.42)
Residence			
Rural	Referent		
Urban	1.24 (0.93, 1.66)	0.97 (0.50, 1.90)	0.61 (0.27, 1.40)
Socioeconomic status			
First quintile	Referent		
Second quintile	**0.73 (0.60, 0.94)**	0.89 (0.50, 1.59)	1.32 (0.59, 2.90)
Third quintile	0.91 (0.71, 1.18)	0.83 (0.48, 1.46)	0.92 (0.41, 2.03)
Fourth quintile	1.15 (0.89, 1.48)	0.89 (0.50, 1.58)	0.99 (0.44, 2.22)
Fifth quintile	1.02 (0.89, 1.34)	0.95 (0.51, 1.77)	0.86 (0.36, 2.09)
Tumor grade			
Well differentiated	Referent	Referent[a]	Referent[a]
Moderately differentiated	1.67 (0.73, 3.82)	Referent	Referent
Poorly differentiated	2.28 (0.99, 5.16)	**1.92 (1.25, 2.96)**[b]	1.37 (0.75, 2.51)[b]
Undifferentiated	**3.01 (1.14, 7.94)**		
Unknown	**3.88 (1.69, 8.89)**	**2.48 (1.49, 4.12)**	**2.30 (1.15, 4.62)**
Comorbidities			
None	Referent	Referent	Referent
One	0.91 (0.75, 1.09)	**0.55 (0.37, 0.83)**	0.59 (0.33, 1.04)
Two+	0.84 (0.68, 1.03)	**0.53 (0.34, 0.82)**	**0.40 (0.20, 0.78)**
Year of cancer diagnosis	**0.99 (0.97, 1.00)**	1.00 (0.97, 1.04)	1.04 (0.99, 1.09)
Prior ADT use			
No	Referent		
Yes	**0.73 (0.62, 0.86)**		
Prior osteoporosis			
No	Referent		
Yes	**0.63 (0.47, 0.83)**		

Bold entries are statistically significant

[a] The well and moderately differentiated cases have been merged as the Referent group in these two columns

[b] The poorly and undifferentiated groups have been merged in these analyses

systematic review and guidelines [17]. In it, they conclude that surgery should be considered for patients who are surgical candidates with a good prognosis, while RT should be offered to those who are non-operable, with single doses of RT given to those with poor prognosis and higher doses of RT given to those with a good prognosis. A Cochrane Review concluded that ambulatory patients with a stable spine might be treated with RT. It reported some evidence of benefit for surgery in ambulatory patient with poor prognostic factors or those who are non-ambulatory, with a short period or paraplegia, and a

Table 3 Predictors of hospital length of stay (days) (n=639) for men with stage IV prostate cancer who developed metastatic epidural spinal cord compression, SEER-Medicare, 1991–2007

	Parameter estimate	95 % C.I.
Treatment		
None	**1.00**	**Referent**
Radiation	**11.10**	**(4.21, 18.00)**
Surgery±Radiation	**28.57**	**(19.23, 37.91)**
Patient characteristics		
Age		
65–69	**1.00**	**Referent**
70–74	−1.38	(−9.50, 6.75)
75–79	−0.15	(−8.97, 8.67)
80–84	**10.76**	**(0.58, 20.95)**
85+	0.29	**(−11.94, 12.52)**
Race		
White	1.00	Referent
Black	7.47	(−1.39, 16.32)
Hispanic	−9.30	(−30.08, 11.49)
Other	**17.21**	**(6.62, 27.79)**
Marital status		
Married	**−11.08**	**(−17.64, −4.53)**
Single/divorced	1.00	Referent
Unknown	−13.63	(−32.04, 4.78)
Residence		
Rural	1.00	Referent
Urban	3.84	(−7.79, 15.48)
Socioeconomic status		
First quintile	1.00	Referent
Second quintile	−2.56	(−12.61, 7.48)
Third quintile	−5.38	(−15.25, 4.49)
Fourth quintile	−4.28	(−14.43, 5.87)
Fifth quintile	−3.01	(−13.91, 7.88)
Missing		
Tumor grade		
Well differentiated	1.00	Referent
Moderately differentiated		
Poorly differentiated	−2.90	(−10.72, 4.91)
Undifferentiated	2.81	(−6.20, 11.82)
Unknown grade		
Comorbidities		
None	1.00	Referent
One	1.66	(−5.63, 8.95)
Two+	7.26	(−0.77, 15.28)
Year of spinal cord compression diagnosis		
	0.40	(−0.20, 1.00)
Months of follow-up from spinal cord compression diagnosis		
	1.36	(0.71, 2.02)

Bold entries are statistically significant

single lesion [4]. Given the recommendations, it is understandable that the strongest predictors of undergoing either therapy in our study were younger age and fewer comorbidities. It is reassuring that race was not a predictor for receipt of therapy.

We found that patients who underwent RT or surgery spent an additional 11 and 29 days, respectively, in the hospital. This compares to 10 days for either group in the Patchell study [5]. While our study has a similar length of stay for the RT groups, patients who underwent surgery in our cohort had longer hospital stays. The difference in length of stay may reflect the difference in patient populations being studied. The Patchell study [5] included younger patients with a variety of cancers leading to MESCC (the median age in the Patchell study was 60 years); therefore, the benefit of surgery and RT for MESCC may be less applicable to older patients with advanced prostate cancer. Our hospital length of stay analysis also suggests that these indications were well chosen by the treating physicians as older men 80–84 years old who underwent surgery and/or radiation spent an extra 11 days in the hospital, as compared to 65–69-year-old patients; and there was a trend toward longer length of stay for those with 2 or more comorbidities who had surgery±RT. Since surgery and RT are palliative therapies, patients should be informed of the realistic goals of these treatments and that symptom relief may be obtained at the cost of spending more time in the hospital, a not insignificant end-of-life consideration. However, left untreated, patients with MESCC will invariably progress to paralysis, incontinence, and shorter survival [18]. It should also be noted that both surgical and radiation techniques have advanced since the publication of the Patchell study, with newer fusion techniques and single fraction radiosurgery allowing more patients to be eligible for therapeutic interventions.

A Cox proportional hazard model found that patients who received RT as treatment for MESCC were more likely to die compared to patients who received no treatment. These findings are likely due to a selection bias among patients who received RT rather than no treatment or surgery. Patients who received RT were more likely to have poorly differentiated disease (Table 2), and thus had more aggressive disease and a higher risk of dying. Interpreting these data should be done with caution.

Skeletal-related events from prostate cancer are costly, averaging $951 per episode [19]. In an accompanying cost-effectiveness analysis to the Patchell randomized trial [18], Thomas found that surgery and radiation were cost-effective, with a baseline incremental cost-effectiveness ratio of $48 per additional day of ambulation and $24,752 per life-year gained (in 2003 US dollars).

There are several limitations to our analysis. Details regarding the efficacy of therapy such as ability to ambulate before and after treatment are not available in the SEER-

Medicare database and thus only patterns of care can be examined. Our sample is also limited to men 65 years and older; therefore, our findings may not be generalizable to younger men, although the majority of cases of advanced prostate cancer are diagnosed after age 65. The CPT codes for radiation therapy are not specific to a body part and do not provide data on number of RT fractions given. Therefore, we assumed that patients who received radiation therapy within 60 days following diagnosis of MESCC were receiving treatment for the MESCC. As described above, we cannot determine if patients received oral bisphosphonates for the prevention of osteoporosis, which might have influenced the impact of osteoporosis on the development of MESCC.

In this large population-based study, we have demonstrated that black men with advanced prostate cancer are more likely than white men to develop MESCC. Older patients with spinal cord compression and those with comorbidities are less likely to be treated with either form of treatment in this palliative care setting.

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Conflict of interest None of the authors has a conflict of interest to report. No author has a financial relationship with the organization that sponsored the research. The authors have full control of the data used for analysis in this study. We agree to allow the Journal to review the data, if requested.

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ORIGINAL ARTICLE

Metastatic epidural spinal cord compression among elderly patients with advanced prostate cancer

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Abstract
Background A recent randomized trial demonstrated that for metastatic epidural spinal cord compression (MESCC), a complication of advanced prostate cancer, surgical decompression may be more effective than external beam radiation therapy (RT). We investigated predictors of MESCC, its treatment, and its impact on hospital length of stay for patients with advanced prostate cancer.
Methods We used the SEER-Medicare database to identify patients >65 years with stage IV (n=14,800) prostate cancer. We used polytomous logistic regression to compare those with and without MESCC and those hospitalized for treatment with surgical decompression and/or RT.
Results MESCC developed in 711 (5 %) of patients, among whom 359 (50 %) received RT and 107 (15 %) underwent surgery±RT. Median survival was 10 months. MESCC was more likely among patients who were black (OR 1.75, 95 %CI 1.39–2.19 vs. white) and had high-grade tumors (OR 3.01, 95 %CI 1.14–7.94), and less likely in those younger; with prior hormonal therapy (OR 0.73, 95 %CI 0.62–0.86); or with osteoporosis (OR 0.63, 95 %CI 0.47–0.83). Older patients were less likely to undergo either RT or surgery, as were those with ≥1 comorbidity. Patients with high-grade tumors were more likely to undergo RT (OR 1.92, 95 %CI 1.25–2.96). Those who underwent RT or surgery spent an additional 11 and 29 days, respectively, hospitalized.
Conclusions We found that black men with metastatic prostate cancer are more likely to develop MESCC than whites. RT was more commonly utilized for treatment than surgery, but the elderly and those with comorbidities were unlikely to receive either treatment.

Keywords Prostate cancer · Metastatic epidural spinal cord compression · Palliative care · SEER-Medicare

The linked SEER-Medicare database was used in this study. The interpretation and reporting of these data are the sole responsibility of the authors.

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Introduction

Each year, about 4 % of men diagnosed with prostate cancer are diagnosed with distant or metastatic disease [1]. The most common site for metastatic spread in prostate cancer is bone [2]. Bone metastases can cause pain, fractures, and metastatic epidural spinal cord compression (MESCC) [3]. The resulting edema, venous congestion, and demyelination can lead to irreversible spinal cord infarction if not treated promptly. With life expectancy for patients with MESCC estimated at 4 months, the decision to relieve the compression must be

made with realistic goals [4]. However, the potential improvement in functional status (pain, ambulation, and urinary continence) and quality of life can be substantial.

Relief of spinal cord compression can be achieved either with direct surgical decompression, external beam radiation therapy (RT) or both. In 2005, a randomized trial by Patchell et al. demonstrated a benefit from circumferential decompression, as compared to posterior laminectomy, followed by postoperative RT in patients with metastatic cancer presenting with signs and symptoms of cord compression and a true displacement of the spinal cord by an epidural mass [5]. For subjects who were randomized to both surgery and RT, 84 % were able to walk after treatment as compared to 57 % in the RT alone arm (p=0.001) and this ambulation persisted for 122 days as compared to 13 days in the RT alone group (p=0.003). Though this study is the only randomized trial evaluating the use of RT versus surgery for MESCC, it has been criticized because of slow patient accrual, suggesting a recruitment bias.

The objective of our study was to identify predictors of MESCC, determine the patterns of use for surgery and RT, and investigate whether these interventions decrease the number of days spent in the hospital. We were also interested in whether disparities due to race or access to care influence the development of MESCC and its subsequent treatment.

Methods

Data source

We analyzed data from the Surveillance, Epidemiology, and End Results (SEER)—Medicare database. The SEER database includes information on cancer diagnoses, tumor histology, stage of disease, treatments, socioeconomic status at the census tract and zip code level, survival and demographic characteristics. The Medicare database provides information on Medicare A (inpatient) and B (outpatient) eligibility, reason for Medicare entitlement, and diagnoses. The physician and hospital claim files, as well as inpatient claim files, were used to search for the claims on diagnoses or surgical procedures. The SEER and Medicare databases were combined by linking these patients by their unique patient identification number.

Cohort selection

We identified individuals who were 65 years or older at the time of cancer diagnosis and received a pathologically confirmed primary diagnosis of prostate cancer (SEER Site Code 54) as their first cancer between January 1, 1991, and December 31, 2007. Patients who were enrolled in a non-Medicare health maintenance organization or not covered by Medicare Part A and B over the same period were excluded. Patients whose only reporting source was autopsy or death certificate, whose reason for entitlement was not age, or whose date of death differed between SEER and Medicare by more than 3 months were also excluded. Among the remaining 139,627 patients, we selected a cohort that was diagnosed with American Joint Cancer Committee (AJCC) stage IV prostate cancer and survived at least 90 days following diagnosis. We then identified patients who had at least one billing claim with a diagnosis of spinal cord compression (ICD-9 Code 336.9) no more than 30 days prior to the prostate cancer diagnosis. This would allow for the possibility that the cord compression was the presenting symptom for the prostate cancer.

Demographic variables

SEER-Medicare provides the age, race/ethnicity, marital status, and tumor grade as categorical variables. Age categories are ordinal with 5-year increments between categories. Race/ethnicity was described as white, black, Hispanic, and Other/Missing. Marital status at time of cancer diagnosis was categorized as Married, Single/Divorced/Separated/Widowed, or Unknown. Tumor grade was categorized as well, moderately, poorly, and undifferentiated.

Socioeconomic status

We followed the guidelines by Du et al. [6] to create a socioeconomic status score by equally weighting income, education, and poverty level provided from the 2000 census tract data. Patients were assigned a rank score from 0 to 4, with 0 being the lowest score. Approximately 1.6 % (N=233) of the cohort lacked sufficient data in one or more categories and were excluded from the analyses.

Assessment of comorbid disease

Using the comorbid conditions identified by Charlson et al. [7], we searched for diagnostic codes of the ICD-9 Clinical Modification and Healthcare Common Procedure Coding System (HCPCS) for 18 medical conditions. Each medical condition was assigned a weight and subsequently used to calculate the final index score. In order to obtain the complete diagnosis and medical claims, the physician and outpatient claims, as well as hospital claims, were included in the comorbidity calculation, as described by Klabunde et al. [8]. Claims submitted from 13 months prior to 4 months following the date of cancer diagnosis were considered in the comorbidity index calculation.

Treatment characteristics

Receipt of radiation and surgery were extracted from the Medicare database by searching the HCPCS, Current

Procedural Terminology (CPT) codes, ICD-9 Clinical Modification diagnostic codes and procedure codes from the national claims history files, outpatient statistical analysis files, and Medicare provider analysis and review files. We excluded radiation and surgery claims that were billed more than 15 days prior or 60 days following the date of diagnosis of spinal cord compression because patients could have received these treatments for medical conditions other than spinal cord compression. The CPT codes 63001, 63003, 63005, 63012, 63015–63017, 63020, 63030, 63035, 63040, 63042–63048, 63050–63051, 63055–63057, 63064, 63066, 63075–63076, 63078, 63081–63082, 63065–83088, 63091, 63101–63013, 63275–63278, 63280–63283, 63286–63287, 63290, and 63295 and ICD-9 CM codes 03.0, 03.09, 80.5, 80.51, 80.52, 80.59, 81.0 81.00 81.04, 81.05, and 81.09 corresponded to surgical decompression. The ICD-9 CM codes V58.0, V66.1, V67.1, 92.21–92.26, 92.29–92.33, and 92.39 and CPT/HCPCS codes 77401–77409, 77411–77414, 77416–77421, 77427, 77431–77432, 77435, 77470, and 77499 were used to identify patients who received radiation therapy. Based on the claims, patients were assigned to one of three treatment groups—radiation alone, surgery alone or in conjunction with radiation (+/- RT), and neither. Receipt of androgen deprivation therapy (ADT) with a GnRH agonist (HCPCS codes J1950, J3315, J9202, J9217-J9219, J9225) was assigned for patients who had at least one claim for receipt of ADT prior to the MESCC.

Statistical analysis

We used the chi-square test to compare the distributions of those who developed spinal cord compression with those who did not (see Table 1), and multivariable logistic regression to identify predictors of spinal cord compression, adjusting for the measured clinical and demographic characteristics of the patients. Polytomous logistic regression models were used to test associations between patient demographics and treatment assignment. All statistical tests were two-sided with an alpha of 0.05. Statistical analyses were performed using SAS version 9.2 (Cary, NC). We obtained approval for this study from the Columbia University Medical Center Institutional Review Board.

Results

We identified 14,800 men with stage IV prostate cancer who met our eligibility criteria. Table 1 shows their demographic and clinical characteristics. The majority of the stage IV patients were white (79 %), married (67 %), lived in an urban area (89 %), had high-grade tumors (53 %), had no comorbidities (52 %), had used ADT prior to the diagnosis of

Table 1 Socio-demographic and clinical characteristics of men >65 years with stage IV prostate cancer in SEER-Medicare, 1991–2007

Characteristic	Entire sample	Spinal cord compression sample
	(*n*=14,800)	(*n*=711)
Age	*n* (%)	*n* (%)
65–69	3,065 (20.7 %)	170 (23.9 %)
70–74	3,925 (26.5 %)	225 (31.7 %)
75–79	3,210 (21.7 %)	149 (21.0 %)
80–84	2,568 (17.4 %)	102 (14.4 %)
85+	2,032 (13.7 %)	65 (9.1 %)
Race		
White	11,745 (79.4 %)	488 (68.6 %)
Black	1,854 (12.5 %)	143 (20.1 %)
Hispanic	273 (1.8 %)	14 (2.0 %)
Other	928 (6.3 %)	66 (9.3 %)
Marital status		
Married	9,870 (66.7 %)	458 (64.4 %)
Single/divorced/widowed	4,220 (28.5 %)	235 (33.1 %)
Unknown	710 (4.8 %)	18 (2.5 %)
Residence		
Urban	13,135 (88.8 %)	654 (92.0 %)
Rural	1,665 (11.3 %)	57 (8.0 %)
Socioeconomic status		
First quintile	2,610 (17.6 %)	158 (22.2 %)
Second quintile	3,223 (21.8 %)	122 (17.2 %)
Third quintile	3,325 (22.5 %)	146 (20.5 %)
Fourth quintile	2,936 (19.8 %)	158 (22.2 %)
Fifth quintile	2,706 (18.3 %)	127 (17.9 %)
Missing		
Tumor grade		
Well/moderately differentiated	4,152 (28.0 %)	153 (21.5 %)
Poorly differentiated	7,591 (51.3 %)	351 (49.4 %)
Undifferentiated	242 (1.6 %)	15 (2.1 %)
Unknown	2,815 (19.0 %)	192 (27.0 %)
Comorbidities		
None	7,696 (52.0 %)	399 (56.1 %)
One	3,871 (26.2 %)	176 (24.8 %)
≥Two	3,233 (21.8 %)	136 (19.1 %)
Prior ADT use		
No	5,815 (39.3 %)	370 (52.0 %)
Yes	8,985 (60.7 %)	341 (48.0 %)
Prior osteoporosis		
No	12,828 (86.7 %)	57 (8.0 %)
Yes	1,972 (13.3 %)	654 (92.0 %)
Treatment		
None	NA	245 (34 %)
Radiation	NA	359 (50 %)
Surgery	NA	107 (15 %)

MESCC (61 %), and had no prior history of osteoporosis (87 %). Almost 5 % (n=711) developed MESCC, among whom 359 (50 %) underwent palliative radiation therapy and 107 (15 %) underwent surgical decompression±RT.

In the multivariable analysis, we found that MESCC was more likely to occur among those who were younger; black (OR 1.75, 95%CI 1.39, 2.19 vs. white); had undifferentiated tumors (OR 3.01, 95%CI 1.14, 7.94 vs. well differentiated); were diagnosed earlier in the cohort; did not use ADT prior to the diagnosis of MESCC (OR 0.73, 95%CI 0.62, 0.86); and had no prior history of osteoporosis (OR 0.63, 95%CI 0.47, 0.83) (Table 2).

There were 711 stage IV patients (4.8 %) who developed MESCC. Of these, 359 (50 %) underwent RT, while 107 (15 %) underwent spinal surgery. Among subjects who developed MESCC, older patients were less likely to undergo either radiation or surgery. Similarly, those with comorbidities were also less likely to undergo either radiation (2+ comorbidities: OR 0.53, 95%CI 0.34, 0.82 vs no comorbidities) or surgery± radiation (2+ comorbidities: OR 0.40, 95%CI 0.20, 0.78 vs no comorbidities). Patients with high-grade tumors were more likely to undergo RT (poorly/undifferentiated: OR 1.92, 95%CI 1.25, 2.96 vs. well/moderately differentiated) but not surgery (Table 2). In a sub-analysis of subjects (n=466) who were treated with either radiation alone or surgery±RT, age was the only significant predictor of treatment, with younger patients more likely to receive surgery (results not shown).

We performed multivariable linear regression to analyze the effect of treatment on the number of days spent in the hospital in the 12 months following the therapy (Table 3). There were 639 subjects who received either RT and/or surgery and spent a mean of 40.1 days in the hospital, not necessarily consecutively. Those who underwent RT spent an additional 11.1 days in the hospital, while patients who underwent surgery±RT spent an additional 29 days hospitalized. Patients aged 80–84 spent 10.8 days more than 65–69-year-olds in the hospital. In a multivariable Cox proportional hazards model, median survival was 10 months for the no-treatment and surgery arms, and 4 months in the RT arm (HR 1.39, 95%CI 1.17–1.66 versus no treatment). Patients with poor or undifferentiated tumors (HR 1.26, 95%CI 1.03–1.54) were also more likely to die compared to those with well to moderately differentiated tumors (results not shown).

Discussion

In our sample of elderly men with metastatic prostate cancer, 4.8 % developed MESCC; of these, 50 % were treated with RT while 15 % underwent surgery±RT. We found that black men were more likely to develop MESCC than white men, as were younger men and those without a history of osteoporosis or prior ADT use. Younger age and fewer comorbidities were associated with undergoing treatment for the spinal cord compression with either surgery or RT.

Previous studies suggest that black men present with more advanced-stage disease as compared to white men; this is thought to be largely due to poor access to healthcare [9]. While both observational [10] and interventional [11] data suggest that there is no survival difference between black and white men with advanced-stage prostate cancer, it is still possible that disparities in quality of life may result. Thus, our finding that black men with advanced prostate cancer are more likely to develop MESCC further worsens the burden of disease that blacks experience from prostate cancer.

We also found that men without a history of osteoporosis were more likely to develop MESCC. This finding seems counter-intuitive as one would expect that pre-existing osteoporosis would increase the risk of MESCC due to either frailty or pathologic fracture of a vertebral body [3]. However, this may reflect diagnostic bias; the diagnosis of osteoporosis requires men to undergo bone mineral density testing. Only 10 % of men who initiate ADT have a baseline bone density test [12]. Those diagnosed with osteoporosis are often offered treatment with bisphosphonates. Among those with prostate cancer, at least one study showed that only about half of patients received bisphosphonates for the prevention of fractures despite good evidence in its favor [13]. Of those not diagnosed, there may be a higher prevalence of untreated osteoporosis. Therefore, our finding may be due in part to diagnostic bias.

Overall, two thirds of subjects with MESCC underwent treatment with either RT alone or surgery±RT. These figures are similar to those reported by Loblaw et al., in a study of MESCC among patients with all types of cancer [14]. These relatively high treatment rates in an elderly cohort, half of whom had at least one comorbidity, suggest that the severity of the symptoms of MESCC prompted intervention.

Fifty percent of our cohort received RT while only 15 % had surgery with or without RT. Through the lens of the Patchell study, these results suggest a poorer quality of care delivered to those patients who only received RT, however this interpretation should be tempered. The majority of our sample was diagnosed before the publication of the Patchell randomized trial in 2005 [5], reducing the possible impact of that study's findings on our patient population. Also, while the Patchell study is the only randomized phase III multicenter trial evaluating the question of surgery versus RT for MESCC, the findings have been criticized as it took 10 years to recruit 50 % of the targeted accrual introducing questions of recruitment bias and validity [15]. The same group later performed a secondary analysis from the clinical trial data evaluating the role of age and treatment outcome and found that for both treatment modalities there was no difference in outcome for patients≥65 years of age [16]. Other retrospective analyses, literature reviews, and meta-analyses have been performed to help answer this question. Loblaw et al. updated their 2005

Table 2 Predictors of metastatic epidural spinal cord compression, treatment with radiation, treatment with surgery±radiation, among men diagnosed with stage IV prostate cancer in SEER-Medicare, 1991–2007

Category	Predictors of MESCC Entire cohort (n=14,800) Odds ratio with 95 % C.I.'s	Predictors of radiation vs. no treatment MESCC cohort (n=711) Odds ratio with 95 % C.I.'s	Predictors of surgery±radiation vs. no treatment MESCC cohort (n=711) Odds ratio with 95 % C.I.'s
Age			
65–69	Referent		
70–74	1.01 (0.82, 1.24)	0.76 (0.75, 1.22)	**0.52 (0.28, 0.96)**
75–79	**0.79 (0.63, 0.99)**	0.88 (0.52, 1.50)	0.68 (0.34, 1.33)
80–84	**0.63 (0.49, 0.82)**	**0.52 (0.29, 0.92)**	**0.23 (0.10, 0.55)**
85+	**0.46 (0.34, 0.62)**	**0.41 (0.22, 0.79)**	**0.06 (0.01, 0.27)**
Race			
White	Referent		
Black	**1.75 (1.39, 2.19)**	0.96 (0.59, 1.58)	0.77 (0.38, 1.56)
Hispanic	1.30 (0.75, 2.28)	1.67 (0.46, 6.09)	1.20 (0.19, 7.40)
Other	**1.80 (1.37, 2.36)**	1.53 (0.83, 2.80)	1.31 (0.55, 3.13)
Marital status			
Married	0.86 (0.72, 1.01)	0.92 (0.64, 1.34)	1.02 (0.60, 1.73)
Single/divorced	Referent		
Unknown	**0.45 (0.28, 0.73)**	0.85 (0.28, 2.59)	0.97 (0.21, 4.42)
Residence			
Rural	Referent		
Urban	1.24 (0.93, 1.66)	0.97 (0.50, 1.90)	0.61 (0.27, 1.40)
Socioeconomic status			
First quintile	Referent		
Second quintile	**0.73 (0.60, 0.94)**	0.89 (0.50, 1.59)	1.32 (0.59, 2.90)
Third quintile	0.91 (0.71, 1.18)	0.83 (0.48, 1.46)	0.92 (0.41, 2.03)
Fourth quintile	1.15 (0.89, 1.48)	0.89 (0.50, 1.58)	0.99 (0.44, 2.22)
Fifth quintile	1.02 (0.89, 1.34)	0.95 (0.51, 1.77)	0.86 (0.36, 2.09)
Tumor grade			
Well differentiated	Referent	Referent[a]	Referent[a]
Moderately differentiated	1.67 (0.73, 3.82)	Referent	Referent
Poorly differentiated	2.28 (0.99, 5.16)	**1.92 (1.25, 2.96)**[b]	1.37 (0.75, 2.51)[b]
Undifferentiated	**3.01 (1.14, 7.94)**		
Unknown	**3.88 (1.69, 8.89)**	**2.48 (1.49, 4.12)**	**2.30 (1.15, 4.62)**
Comorbidities			
None	Referent	Referent	Referent
One	0.91 (0.75, 1.09)	**0.55 (0.37, 0.83)**	0.59 (0.33, 1.04)
Two+	0.84 (0.68, 1.03)	**0.53 (0.34, 0.82)**	**0.40 (0.20, 0.78)**
Year of cancer diagnosis	**0.99 (0.97, 1.00)**	1.00 (0.97, 1.04)	1.04 (0.99, 1.09)
Prior ADT use			
No	Referent		
Yes	**0.73 (0.62, 0.86)**		
Prior osteoporosis			
No	Referent		
Yes	**0.63 (0.47, 0.83)**		

Bold entries are statistically significant

[a] The well and moderately differentiated cases have been merged as the Referent group in these two columns

[b] The poorly and undifferentiated groups have been merged in these analyses

systematic review and guidelines [17]. In it, they conclude that surgery should be considered for patients who are surgical candidates with a good prognosis, while RT should be offered to those who are non-operable, with single doses of RT given to those with poor prognosis and higher doses of RT given to those with a good prognosis. A Cochrane Review concluded that ambulatory patients with a stable spine might be treated with RT. It reported some evidence of benefit for surgery in ambulatory patient with poor prognostic factors or those who are non-ambulatory, with a short period or paraplegia, and a

Table 3 Predictors of hospital length of stay (days) (n=639) for men with stage IV prostate cancer who developed metastatic epidural spinal cord compression, SEER-Medicare, 1991–2007

	Parameter estimate	95 % C.I.
Treatment		
None	**1.00**	**Referent**
Radiation	**11.10**	**(4.21, 18.00)**
Surgery±Radiation	**28.57**	**(19.23, 37.91)**
Patient characteristics		
Age		
65–69	**1.00**	**Referent**
70–74	−1.38	(−9.50, 6.75)
75–79	−0.15	(−8.97, 8.67)
80–84	**10.76**	**(0.58, 20.95)**
85+	0.29	**(−11.94, 12.52)**
Race		
White	1.00	Referent
Black	7.47	(−1.39, 16.32)
Hispanic	−9.30	(−30.08, 11.49)
Other	**17.21**	**(6.62, 27.79)**
Marital status		
Married	**−11.08**	**(−17.64, −4.53)**
Single/divorced	1.00	Referent
Unknown	−13.63	(−32.04, 4.78)
Residence		
Rural	1.00	Referent
Urban	3.84	(−7.79, 15.48)
Socioeconomic status		
First quintile	1.00	Referent
Second quintile	−2.56	(−12.61, 7.48)
Third quintile	−5.38	(−15.25, 4.49)
Fourth quintile	−4.28	(−14.43, 5.87)
Fifth quintile	−3.01	(−13.91, 7.88)
Missing		
Tumor grade		
Well differentiated	1.00	Referent
Moderately differentiated		
Poorly differentiated	−2.90	(−10.72, 4.91)
Undifferentiated	2.81	(−6.20, 11.82)
Unknown grade		
Comorbidities		
None	1.00	Referent
One	1.66	(−5.63, 8.95)
Two+	7.26	(−0.77, 15.28)
Year of spinal cord compression diagnosis		
	0.40	(−0.20, 1.00)
Months of follow-up from spinal cord compression diagnosis		
	1.36	(0.71, 2.02)

Bold entries are statistically significant

single lesion [4]. Given the recommendations, it is understandable that the strongest predictors of undergoing either therapy in our study were younger age and fewer comorbidities. It is reassuring that race was not a predictor for receipt of therapy.

We found that patients who underwent RT or surgery spent an additional 11 and 29 days, respectively, in the hospital. This compares to 10 days for either group in the Patchell study [5]. While our study has a similar length of stay for the RT groups, patients who underwent surgery in our cohort had longer hospital stays. The difference in length of stay may reflect the difference in patient populations being studied. The Patchell study [5] included younger patients with a variety of cancers leading to MESCC (the median age in the Patchell study was 60 years); therefore, the benefit of surgery and RT for MESCC may be less applicable to older patients with advanced prostate cancer. Our hospital length of stay analysis also suggests that these indications were well chosen by the treating physicians as older men 80–84 years old who underwent surgery and/or radiation spent an extra 11 days in the hospital, as compared to 65–69-year-old patients; and there was a trend toward longer length of stay for those with 2 or more comorbidities who had surgery±RT. Since surgery and RT are palliative therapies, patients should be informed of the realistic goals of these treatments and that symptom relief may be obtained at the cost of spending more time in the hospital, a not insignificant end-of-life consideration. However, left untreated, patients with MESCC will invariably progress to paralysis, incontinence, and shorter survival [18]. It should also be noted that both surgical and radiation techniques have advanced since the publication of the Patchell study, with newer fusion techniques and single fraction radiosurgery allowing more patients to be eligible for therapeutic interventions.

A Cox proportional hazard model found that patients who received RT as treatment for MESCC were more likely to die compared to patients who received no treatment. These findings are likely due to a selection bias among patients who received RT rather than no treatment or surgery. Patients who received RT were more likely to have poorly differentiated disease (Table 2), and thus had more aggressive disease and a higher risk of dying. Interpreting these data should be done with caution.

Skeletal-related events from prostate cancer are costly, averaging $951 per episode [19]. In an accompanying cost-effectiveness analysis to the Patchell randomized trial [18], Thomas found that surgery and radiation were cost-effective, with a baseline incremental cost-effectiveness ratio of $48 per additional day of ambulation and $24,752 per life-year gained (in 2003 US dollars).

There are several limitations to our analysis. Details regarding the efficacy of therapy such as ability to ambulate before and after treatment are not available in the SEER-

Medicare database and thus only patterns of care can be examined. Our sample is also limited to men 65 years and older; therefore, our findings may not be generalizable to younger men, although the majority of cases of advanced prostate cancer are diagnosed after age 65. The CPT codes for radiation therapy are not specific to a body part and do not provide data on number of RT fractions given. Therefore, we assumed that patients who received radiation therapy within 60 days following diagnosis of MESCC were receiving treatment for the MESCC. As described above, we cannot determine if patients received oral bisphosphonates for the prevention of osteoporosis, which might have influenced the impact of osteoporosis on the development of MESCC.

In this large population-based study, we have demonstrated that black men with advanced prostate cancer are more likely than white men to develop MESCC. Older patients with spinal cord compression and those with comorbidities are less likely to be treated with either form of treatment in this palliative care setting.

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Conflict of interest None of the authors has a conflict of interest to report. No author has a financial relationship with the organization that sponsored the research. The authors have full control of the data used for analysis in this study. We agree to allow the Journal to review the data, if requested.

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