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Skeletal-related events and mortality among older men with advanced prostate cancer

Eberechukwu Onukwugha[a,*], *Candice Yong*[a], *C. Daniel Mullins*[a], *Brian Seal*[b], *Diane McNally*[a], *Arif Hussain*[c,d]

[a]*Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, 220 Arch Street, Baltimore, MD 21201, USA*
[b]*Bayer HealthCare Pharmaceuticals, Inc., USA*
[c]*University of Maryland School of Medicine, 685 West Baltimore Street, Baltimore, MD 21201, USA*
[d]*Veterans Affairs Medical Center, Baltimore, MD 21201, USA*

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ABSTRACT

Objective: Skeletal-related events (SREs) are defined as a cluster of events including clinical diagnoses and treatment. Using claims data, the burden of SREs as a group has been reported among patients with cancer. We investigate the mortality impact of subcomponents of SREs, a topic that has received limited attention among older men.
Materials and Methods: We analyzed prostate cancer (PCa) and all-cause mortality among men diagnosed with metastatic PCa from 2000 to 2007 using Surveillance, Epidemiology, and End Results data linked with 1999–2009 Medicare data. We created three measures of pathological fracture (PF), spinal cord compression (SCC), and bone surgery (BS) that differed in the use of claims-based bone metastasis information. We reported covariate-adjusted hazard ratios (HRs) using the full sample and a propensity score-matched sample (PSMS).
Results: Application of inclusion/exclusion criteria resulted in 7062 men in the full sample (1776 in the PSMS). PCa-specific (all-cause mortality) was 54% (80%) at a median follow-up of 609 days. SRE prevalence ranged from 9.7% to 17.1% across the measures. In a PCa mortality model, the HR associated with an SRE ranged from 1.07 (0.98–1.16) to 1.31 (1.18–1.45). The HRs for SCC and PF were statistically significant and positively associated with PCa-specific mortality. The results for BS depended on the measure. Results for SCC and BS, but not for PF, were preserved using a PSMS.
Conclusions: The relationship between SREs and mortality among older men with metastatic PCa was driven by SCC and depended on the definition used to measure SREs.
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1. Introduction

The incidence of prostate cancer is strongly correlated with age and about 60% of cases are diagnosed in men sixty-five years and older.[1] Additionally, two-thirds of prostate cancer-related deaths occur in men aged seventy-five or above.[2] Prostate cancer-related deaths often involve cases in which the cancer has metastasized or spread to distant sites. Among

* *Corresponding author at:* University of Maryland School of Pharmacy, 220 Arch Street, Office Level One, Baltimore, MD 21201, USA. Tel.: +1 410 706 8981; fax: +1 410 706 5394.
E-mail address: eonukwug@rx.umaryland.edu (E. Onukwugha).

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individuals diagnosed with cancer, metastases are more likely to spread to the skeleton.[3] In fact, 60 to 84% of cases of metastatic disease involve the bone.[4] Patients who develop bone metastasis (BM) are at risk of skeletal-related events (SREs) such as pathologic fractures (PF), bone surgery (BS), radiation therapy to the bone, and spinal cord compression (SCC).[5,6] SREs are associated with considerable morbidity, including severe bone pain and impaired mobility, and have been shown to negatively affect health-related quality of life including physical, functional, and emotional well-being.[7,8] A number of studies have shown that SREs not only impact patient quality of life but can also affect cancer-specific and overall survival.[6,7,9–12]

The subcomponents of SREs include clinical events (e.g., spinal cord compression, pathological fracture) and treatment (e.g., bone surgery, radiation therapy) which can differ in their relationship with mortality. There is limited evidence regarding the mortality impact of subcomponents of SREs among older men. In addition, there has been limited attention paid to the incorporation of BM information from claims data, which is typically used in anchoring clinical diagnosis, treatment, and procedure codes for the purpose of identifying an SRE. When using observational claims data to study the relationships between SREs and mortality, the extent to which conclusions depend on the approach used in anchoring SREs to BM is important to investigate given that claims-based algorithms used to anchor SREs to BM have not been validated.

We undertook the present study based on the linked Surveillance, Epidemiology, and End Results (SEER) and Medicare claims data to better understand the relationship between SRE subcomponents and mortality among older patients. In the absence of a validated claims-based definition of an SRE, different claims-based definitions were used to identify an SRE. The measures differed in how they incorporated claims-based information related to BM. Although this study evaluated men with metastatic prostate cancer (PCa), the study question is applicable to claims-based studies involving other cancers with skeletal metastasis such as breast and lung cancers.

2. Materials and Methods

2.1. Population

This retrospective cohort analysis of linked cancer registry and Medicare data examined treatment of men at least 66 years of age diagnosed with incident PCa between 2000 and 2007 as listed in the SEER cancer registries. The cohort was limited to men alive at diagnosis with incident stage IV metastatic (M1) PCa according to the American Joint Committee on Cancer Tumor-Node-Metastasis stage, 3rd and 6th editions.[13,14] Treatment-related data from 1999 to 2009 were extracted from linked Medicare claims. Additional inclusion criteria were: 1) continuous enrollment in Medicare Parts A and B during 12 months prior to and including the month of diagnosis; 2) not enrolled in a health maintenance organization (HMO) during the pre-period; and 3) no history of other cancers within 5 years prior to PCa diagnosis. Individuals were censored if they enrolled in an HMO or lost Part A and/or B enrollment at any time following the diagnosis date, or if the end of the study period (December, 2009) was reached.

2.2. Variables

The primary outcome variable was PCa-specific mortality. All-cause mortality was investigated as a secondary outcome. The key independent variable used in the survival models was evidence of an SRE, defined as PF, SCC, or BS. The reference category included men who did not have a PF, SCC, or BS following the PCa diagnosis. Given the inability to differentiate receipt of radiation to the prostate gland from receipt of radiation to the bone using codes available in claims data, we did not investigate palliative radiation therapy to the bone as an SRE in the present study.

The three subcomponents (i.e. PF, SCC, BS) were identified by searching MEDPAR, NCH (Carrier), and outpatient facility claims for the relevant diagnosis and procedure codes. All claims from the diagnosis period to the end of follow up were examined. Claims were consolidated based on the bone subgroup involved: vertebral column, humerus (upper arm), femur (upper leg), radius/ulna (lower arm), tibia/fibula (lower leg), or other/unspecified. A validation study for an algorithm to identify vertebral compression fractures noted the importance of separating subsequent new compression fractures from follow up visits related to the first new compression fracture.[15] The current study employed a gap approach to separate new fracture events to the same bone from prior fracture events to the same bone and for which the patient could still be receiving treatment.

For weight-bearing bones (i.e., femur, vertebrae, or tibia/fibula) we grouped claims for the same bone into one event if the start date for the subsequent claim was less than 183 days following the end date for the previous claim. When the bone was not weight-bearing (i.e., radius/ulna, humerus, or unspecified) claims were combined into one episode when the gap was less than 90 days. The gaps for consolidating claims into episodes were determined by the typical treatment length associated with the healing time for specific bone types and a review of studies investigating the validity of fracture event definitions using administrative claims data.[15,16] For an episode having two or more SRE subcomponents, a hierarchy (see Fig. 1) similar to the method used in a previous study was applied to assign the episode to a specific SRE component.[17]

An SRE was defined in three different ways as follows: (1) the first PF, SCC, or BS episode occurring concurrent with or following the first BM claim; (2) an SRE episode that includes a BM ICD9 diagnosis code of 198.5 (secondary malignant neoplasm of bone and bone marrow) on the claim; or 3) an SRE episode that follows the diagnosis of incident M1 PCa. The first definition, our primary, is similar to prior studies where the SRE is anchored to a prior/concurrent BM claim.[6,12] Definition #2 is more restrictive and #3 is less restrictive, respectively. We disaggregated the primary definition depending on whether a BS procedure code appeared concurrently with the PF or SCC episode to yield five additional measures: PF with BS, PF without BS, SCC with BS, SCC without BS, and BS only.

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