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Development and validation of a prognostic index for fracture risk in older men undergoing prostate cancer treatment

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ABSTRACT

Objectives: Men treated with androgen deprivation therapy (ADT) or radiation therapy (RT) for prostate cancer have an increased risk for fractures. Given uncertainty as to whether specific clinical factors can identify men at increased risk, we sought to develop a prognostic index for risk of fracture in this population.

Materials and methods: We used the Surveillance, Epidemiology, and End Results-Medicare database to identify men who received ADT or RT after being diagnosed with localized prostate cancer in 2007–2009. Cox proportional hazards models tested the association of potential risk factors with fracture. In a derivation group, hazard ratios were used to assign points for factors independently related to fracture. The prognostic index was then applied to a validation group.

Results: The sample of 5824 men had a median age of 73.0 years; 82.9% were white and 8.6% had a fracture within 2 years of treatment for prostate cancer. The Cox model identified 8 variables (age, race, hormone treatment, Elixhauser score, anxiety, Parkinson's, fall-inducing medications and disability status) independently associated with fracture. In the derivation cohort, 4.3% of the sample experienced a fracture in the low-risk group, 8.9% in the intermediate group, and 19.2% in the high-risk group (C statistic, 0.749). The index was applied to the validation cohort (C statistic, 0.782).

Conclusion: The prognostic index can help to identify patients at increased risk for fracture. This underscores the importance of identifying risk factors for fracture, given the substantial variation in fracture risk in men treated with ADT or RT.

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1. Introduction

Prostate cancer is primarily a disease of aging[1]. The mean age of patients with prostate cancer is 73 years, and about 85% of patients are diagnosed after age 65 years[2]. Aging is associated with a progressive decrease of physiologic reserves that affects older patients' tolerance for cancer therapy, and, in some cases, can restrict the options for cancer treatment[3].

Fractures are a relatively common and clinically significant adverse outcome among older men with prostate cancer[4–6]. Additionally, fractures are associated with severe bone pain, limited mobility, and hospitalization for treatment, as well as negatively associated with overall survival independent of pathological stage[4,7,8]. In addition to (lower) bone density, factors associated with an increased risk of fracture include: older age, multiple coexisting conditions, history of falls and previous fractures, lower body mass index, poor functional status, and life-style factors (such as physical inactivity, smoking and alcohol use)[9–15]. Hence, a better understanding of which patients are at increased risk for fracture should be considered when selecting cancer treatments.

Androgen deprivation therapy (ADT) and radiation therapy (RT) are two forms of cancer treatment that are implicated in promoting fractures[5,15–17], and are widely used therapeutic treatment modalities for prostate cancer[18,19]. ADT, often given concomitantly with RT for men with non-metastatic disease or rising prostate-specific antigen, has been shown to reduce morbidity and possibly increase survival in men with locally advanced disease[20–22]. Although these forms of therapy exhibit cancer control benefits they can also produce negative side effects, such as weakening of the skeleton[5,9,15,18]. For example, a rapid loss of bone-mineral density due to hypogonadism occurs within the first 6 to 12 months of ADT[16,17,23]. Prior studies have demonstrated that RT also increases the risk of fractures by damaging the bone matrix[15,24]. Fracture risk-stratification for men treated with ADT or RT therefore has particular importance[5,15,16,25].

In addition to cancer treatments, older men with prostate cancer take, on average, five different medications. Polypharmacy has been linked to increased risk of falls and fractures, as well as decline in cognitive and physical functioning[3,26]. Patients taking multiple medications have an especially high risk of fractures, through several potential mechanisms. For instance, some medications have been demonstrated to decrease bone density and subsequently increase fracture risk[27–31]. Some antihypertensive medications are frequently associated with falls due to postural hypotension[32,33]. Benzodiazepines have negative effects on cognition, gait, and balance, and are also associated with a high risk of falling[28,29].

Although studies have identified risk factors for fractures in men with prostate cancer, the combined effect of these factors on fracture risk has not been adequately addressed[5,16–19,24,25]. These factors alone may not be sufficient for identifying patients at increased risk, because they fail to take into account additional significant predictors of fracture, such as poor functional status. Valid and effective prognostic indices are greatly needed—specifically, risk stratification systems for fracture designed or tested exclusively in the older population. Moreover, the recent availability of Medicare Part D data allows us to incorporate medications in addition to cancer treatment in the prognostic index to investigate specific coexisting conditions in greater detail.

To address these knowledge gaps, we performed a claims-based observational study to identify factors associated with fracture among Medicare beneficiaries receiving ADT and/or RT for prostate cancer, as this is a group of patients who face an increased risk of fracture as a result of their prostate cancer treatment. We then developed a prognostic index to assess fracture risk in these patients. Stratifying patients treated with ADT or RT for prostate cancer – based on clinical characteristics, coexisting conditions, and medication use – has the potential to identify men with increased fracture risk, thus allowing for targeted treatment interventions of the high-risk populations.

2. Materials and Methods

2.1. Study Overview and Data Source

We conducted a retrospective cohort study of men with prostate cancer who received ADT and/or RT, using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. SEER-Medicare is a database consisting of patient demographics and cancer characteristics from 17 tumor registries linked to Medicare claims that include date of service, diagnoses, and procedures from care billed by hospitals, outpatient facilities, and physicians[34]. We also used First Databank's MedKnowledge database, which contains drug information including the National Drug Codes (NDC). The Yale Human Investigation Committee approved the protocol, determining that this study did not involve human subjects.

2.2. Study Sample

We identified patients, 67 years or older, who started ADT and/or RT from April 2007 through June 2009. We restricted the study to patients with clinical tumor stage I or II who lived at least 6 months after starting ADT and/or RT. Patients who received at least one dose of medical ADT after prostate cancer diagnosis either in the form of gonadotropin-releasing hormone (GnRH) agonist, steroidal or non-steroidal anti-androgens, or who underwent orchiectomy within 9 months of prostate cancer diagnosis, were classified as ADT users. Patients who received ADT, RT or orchiectomy in the two years prior to prostate cancer diagnosis were excluded. We also excluded patients who had a fracture claim in the year prior to receipt of ADT or RT to ensure that the fracture captured in the claims data is a new or incident fracture.

2.3. Construction of Variables

We assessed the primary outcome of interest (fracture) using the International Classification of Diseases, 9th revision (ICD-9) and Healthcare Common Procedure Coding System (HCPCS) codes (Appendix 1 in the Supplementary data). We identified diagnosis and procedure codes indicative of