Introduction

The prognosis of patients diagnosed with Stage 4 prostate cancer is significantly impacted by the presence or absence of metastasis at diagnosis. Patients diagnosed with M1 (metastatic) disease have worse survival compared to patients with stage 4 (S4) M0 disease. A large study reported that the most commonly encountered metastatic sites at diagnosis were bone (84%), distant lymph nodes (10.6%), liver (10.2%), and thorax (9.1%), while 18.4% of patients had more than one organ involved [1].

Two recent studies demonstrate that the site of metastasis impacts survival rates. In a study that used Surveillance, Epidemiology, and End Results (SEER) data from 1991 to 2009, patients with visceral metastasis had poor survival compared to patients with lymph node involvement only [2]. The same study estimated that the median overall survival for lymph node, bone, visceral, and bone plus
lymph node metastasis at diagnosis were 43, 24, 16, and 14 months respectively. In a meta-analysis that pooled data from 5 phase III randomized clinical trials (RCTs), overall survival for castrate-resistant patients with lymph node only, liver ± bone, lung ± bone, bone ± lymph node, and other visceral metastasis (adrenal, brain) were 27.0, 12.1, 16.5, 20.3, and 14.4 months [3].

Several population-based observational studies have shown that bone metastasis is associated with greater risk of skeletal complications, commonly referred to as skeletal-related events (SREs), including pathologic fracture (PF), spinal cord compression (SCC), bone palliative radiotherapy (RAD), and bone surgery (BS), and contribute significantly to the burden of prostate cancer [4–6]. Zoledronic acid and, more recently denosumab, have been approved by the Food and Drug Administration since they delay onset of SREs in patients with bone metastasis [7, 8]. While it is known that patients with bone metastasis at diagnosis are at high-risk of SREs, there is limited information on the impact of other sites of metastasis at presentation on the risk of SREs. The purpose of this study was to estimate the risk of developing an SRE among S4M1 patients presenting with various sites of metastasis at diagnosis and to identify patient factors that correlated with the risk of developing SRE.

**Patients and Methods**

**Data source**

We used linked Surveillance, Epidemiology, and End Results (SEER)-Medicare datasets to study the relationship between the site of metastasis at diagnosis and risk of developing an SRE during follow-up. The SEER-Medicare database links information from the National Cancer Institute’s SEER cancer registries and Medicare claims data from the Centers for Medicare and Medicaid Services. The SEER program collects cancer incidence and mortality rates from 17 tumor registries across the U.S. covering 28% of the U.S. population [9]. Medicare claims provide information on health care services which are provided to and covered for Medicare beneficiaries from the time of Medicare eligibility until death.

**Study cohort**

This study used a retrospective cohort study design to identify patients with prostate cancer (SEER code 54). Information on the specific sites of distant metastasis in patients with M1 prostate cancer at diagnosis became available in the SEER registries of 2004 onwards, (using the derived American Joint Committee on Cancer stage grouping system, 6th edition) whereas such detailed staging information for M1 patients was not available prior to 2004 [10]. Thus, to obtain more accurate staging data this study included men aged 66 or older in SEER who were diagnosed with incident cases of M1 prostate cancer between 2005 and 2009. The 2004 cohort was excluded since it represented the first year of extracting the more ‘granular’ incident staging information from patient medical records, and hence was potentially more prone to discrepancies in documentation than during the subsequent years when more experience in extracting such data was gained. The follow-up period ended on December 31, 2010, or earlier if patients enrolled in a health maintenance organization or dis-enrolled in Medicare Parts A and B or died during this time period. Patients were required to have continuous enrollment in Medicare Parts A and B for the 12 months prior to diagnosis.

Figure 1. Cohort identification flow chart.
A/B in the year prior to diagnosis in order to assess baseline Charlson Comorbidity Index (CCI) in the year prior to diagnosis. Patients were excluded from the final sample if they had history of cancer in the 5 years prior to diagnosis, if their diagnosis month or year was unknown, or if they received a postmortem prostate cancer diagnosis (Fig. 1).

**Exposure, covariate, and endpoint definition**

We used the ‘CS Mets at DX’ measure to identify the location of distant metastasis at diagnosis among the 2005 to 2009 SEER cohort (http://web2.facs.org/cstage0204/prostate/Prostate_hal.html). SREs were identified using Medicare claims, including the International Classification of Diseases 9th version Clinical Modification and the Healthcare Common Procedure Coding System that indicated SCC, PF, BS, or RAD (Table 1), which was previously published [11]. Covariates used in the model included demographic variables (age at diagnosis, race/ethnicity, Census location), clinical variables (CCI, performance status proxies), prostate cancer variables (Gleason score at diagnosis), and treatment (androgen deprivation therapy receipt).

**Table 1. ICD-9 Codes and HCPCS codes used for identifying skeletal-related events (SRE) measures.**

| Spinal cord compression | ICD-9 | HCPCS |
|-------------------------|-------|-------|
| 3369, 7211, 7214, 72141, 72142, 72191, 7227, 72270, 72271 and 72273 |
| 63050, 63051, 22551, 22552, 63064, 63066, 61343, s2348, 63075-8, s2350, s2351, 62195, 63197, 63199, 63001, 63003, 63005, 63011, 63015, 63016, 63017, 63170, 63012, 63045, 63046, 63047, 63048, 63040, 63042, 63043, 63044, 63020, 63030, 63035, 22224, 22222, 22214, 22212, 22207, 22206, 0274t, 0275t, c9729, 0202t, 22865, 0164t, 0094t, 0097t, 63057, 63056, 63081, 63082, 63087, 63088, 63101, 63102, 63103, 63090, 63091, 63086 and 63085 |

| Pathologic fractures | ICD-9 | HCPCS |
|----------------------|-------|-------|
| 7331, 73311, 73312, 73314, 73315, 73316, and 73319 |
| 8202, 8208, 8210, 8212, 73311, 8120, 8122, 8124, 73312, 8130, 8132, 8134, 8138, 73316, 8230, 8232, 8238, 73313, 805, 806, 8200, 7331, 73310, 73319, 800, 807, 8080, 8082, 8084, 8088, 8100, 8240, 8242, 80701, 80702, 80703, 80704, 80705, 80706, 80707, 80709, 80841, 80842, 80843, and 80849 |
| Trauma/nonroutine falls/accidents | ICD-9 | HCPCS |
| 819, 828, 851, 852, 853, 854, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 8074, 9584, 80712, 80713, 80714, 80715, 80716, 80717, 80718, 80719, E800-E848, E881, E882, E883, E884.0, E884.1, E884.5, E885.0, E885.1, E885.2, E885.3, E886.0, E886.9, E888.0, and E888.1 |

**Statistical analysis**

We examined the bivariate distributions between sociodemographic, clinical, and prostate cancer-specific factors as they relate to SRE status. Sub-Hazard Ratios (SHR) of experiencing a SRE were derived using the inverse probability of treatment weighted (IPTW) Cox proportional hazards model that accounted for deaths as a competing risk and adjusted for age, race/ethnicity, androgen deprivation therapy receipt, comorbidities, performance status, Gleason score, and year of diagnosis. The IPTW was
obtained in a two-step process. We first estimated the propensity score using a logistic regression modeling the probability of androgen deprivation therapy (ADT) receipt as the dependent variable. Then the inverse of the propensity score was used to weight the sample in a Cox proportional hazards model. IPTW was important since men who received ADT were expected to be systematically different from those who did not receive ADT, therefore adjusting for selection bias. Additionally, ADT was included in the Cox proportional hazards model since men who received ADT (even after mimicking randomization) were expected to have more SREs compared to men who did not receive ADT, thus adjusting for confounding bias due to ADT. Applying IPTW and Cox proportional hazards model is a form of doubly robust estimation that protects against mismodeling [12]. Since site of metastasis influences the hazard of death, a competing risks framework was preferred because site of metastasis may have no direct influence on the hazard of SRE but can be significantly associated with cumulative probability of SRE. A cumulative incidence plot was generated for each site of metastasis based on the competing risks model. In our model, those who were lost to follow-up (HMO enrollment, Medicare Parts A/B disenrollment, or end of follow-up on December 31, 2010) were censored. All statistical analyses were performed using SAS software package (version 9.3, SAS Institute, Cary, NC) and Stata software package (version 13, Stata, College Station, TX).

**Results**

**Study sample characteristics**

Among 4404 patients (mean follow up: 16.6 months) diagnosed with incident metastatic prostate cancer, 1135 (25.8%) did not receive ADT, which is similar to what has been reported in prior SEER-Medicare studies [13, 14]. Non-Hispanic Whites, and those with lower CCI and higher Gleason scores were more likely to experience SREs (*P* < 0.05). Table 2 shows the distribution of several of the available sociodemographic, clinical, and tumor-related characteristics in SEER, as categorized by SRE status at follow-up.

**Association between metastatic site and SRE**

The distribution of various sites of metastasis among the incident cases of M1 prostate cancer patients in the final sample is shown in Figure 2. Staging information was not available in 6% of patients in this cohort. The bone, with or without lymph node and/or ‘other’ (including visceral) sites of involvement represents the most common site of distant spread, with metastasis to bone only occurring in 59% of patients at initial presentation and to bone ± other sites in 68%. Twenty percent of the sample presented with metastasis to sites other than the bone or lymph node (designated as ‘other only’ sites which would include visceral organs), whereas only a minority of patients (4.7%) had lymph node only metastasis at initial presentation. Overall, 10% of men had metastasis

| Table 2. Demographic and clinical characteristics among M1 prostate cancer men diagnosed from 2005 to 2009, by skeletal-related events status (N = 4404). |
| --- |
| Any skeletal-related event (N = 4404) |
| No (n = 2473) | Yes (n = 1931) | *P* value |
| Age |
| 66–70 | 416 17 | 356 18 | 0.06 |
| 71–75 | 457 18 | 390 20 |
| 76–80 | 499 20 | 402 21 |
| 80 + | 1101 45 | 783 41 |
| Race/Ethnicity |
| Non-Hispanic White | 1824 74 | 1530 79 | <0.01* |
| Non-Hispanic Black | 368 15 | 200 10 |
| Hispanic | 160 6 | 106 6 |
| Other | 121 5 | 95 5 |
| SEER census location |
| Northeast | 476 19 | 391 20 | 0.16 |
| South | 487 20 | 329 17 |
| North Central | 353 14 | 282 15 |
| West | 1157 47 | 929 48 |
| Married | 1427 58 | 1139 59 | 0.39 |
| Urban residence | 2160 87 | 1732 90 | 0.01* |
| Charlson comorbidity index |
| 0 | 1254 51 | 1059 55 | <0.01* |
| 1 | 462 18 | 396 21 |
| 2 | 239 10 | 161 8 |
| 3+ | 241 10 | 175 9 |
| Missing | 277 11 | 140 7 |
| Androgen deprivation therapy |
| Prediagnosis poor performance function | 706 29 | 501 26 | 0.05 |
| High PSA at baseline | 2099 85 | 1664 86 | 0.23* |
| Poorly differentiated tumor | 1457 59 | 1172 61 | 0.23 |
| Gleason score |
| 2–6 | 99 4 | 49 2 | <0.01* |
| 7 | 319 13 | 212 11 |
| 8–10 | 997 40 | 884 46 |
| Not done/unknown | 1058 43 | 786 41 |
| Year of diagnosis |
| 2005 | 482 19 | 466 24 | <0.01* |
| 2006 | 517 21 | 420 22 |
| 2007 | 460 19 | 363 19 |
| 2008 | 503 20 | 370 19 |
| 2009 | 511 21 | 312 16 |

*Significant at the *P* = 0.05 level.
to two or more ‘organ’ sites (i.e., bone, lymph node and/or ‘other’ sites) at diagnosis. On average, 44% of the final sample developed a SRE during follow-up. The proportion of patients with the different sites of metastasis at initial presentation who developed a subsequent SRE during the follow-up period is shown in Figure 2; this ranged from 29% (lymph node metastasis only) to 52% (bone and lymph node metastasis). There was a statistically significant difference between SRE rates across the seven metastatic sites ($P < 0.001$).

In the Cox proportional hazards model that accounts for death as a competing risk, it is apparent that among the prostate cancer men with different sites of metastasis those with lymph node only involvement at diagnosis were significantly less likely to develop a SRE during follow-up compared to patients presenting with bone only metastasis at diagnosis (Sub-Hazard Ratio (SHR): 0.56; 95% Confidence Interval (CI): 0.43–0.72). Patients with ‘other’ site only, bone plus lymph node, bone plus ‘other’ site ± lymph node, and lymph node plus ‘other’ site were as likely as patients with bone metastasis only to develop SREs. Lastly, although the relevant extent of disease information was missing in the ‘unknown site of metastasis’ patient group, this group was also less likely to develop SREs (SHR: 0.79; 95% CI: 0.64–0.97) compared to the bone metastasis only group (Table 3), perhaps in part reflecting that it may be more akin to the lymph node only population in terms of clinical behavior. Using the same model we have produced a cumulative incidence of SRE plot that shows the probability of developing SREs among various sites of metastasis. The probability of developing SREs within 3 years of diagnosis with Stage IV M1 prostate cancer among patients with various sites of metastasis were: lymph node only (29%), unknown site (36%), lymph node + other site (39%), other site (43%), bone only (45%), bone +other ± lymph node (47%), and bone + lymph node (50%).

**Figure 2.** Proportion of patients with the various metastatic sites at presentation and their skeletal-related events distribution.
Other predictors of developing SREs

In the multivariable Cox proportional hazards model, patients were significantly less likely to develop SREs if they were over 80 years of age (SHR: 0.83; 95% CI: 0.75–0.91), of non-Hispanic Black ethnicity (SHR: 0.77; 95% CI: 0.65–0.90), or were diagnosed in year 2009 (SHR: 0.85; 95% CI: 0.72–0.99). On the other hand, patients were significantly more likely to develop SREs if they received androgen deprivation therapy (SHR: 1.73; 95% CI: 1.48–2.02), or had a Gleason score of 8–10 (SHR: 1.5; 95% CI: 1.13–1.98) (Table 3). Interestingly, the overall prevalence of SREs decreased over time from 2005 to 2009 ($P < 0.01$).

**SRE subtypes**

Several statistically significant differences are noteworthy regarding the frequency of the different subtypes of SRE (i.e., RAD, BS, SCC, PF) with respect to certain covariates such as metastatic site, age, race, diagnosis year, and ADT receipt (Table 4). Radiation was statistically less likely among men who had lymph node only metastasis at diagnosis, were 80 years of age or older, were diagnosed with MI prostate cancer in year 2009 compared to the earlier years, or did not receive ADT for their prostate cancer. Bone surgery was statistically less likely among African American men, and those men who were diagnosed with prostate cancer in 2009. Pathologic fractures were less likely among African Americans, those less than age 80 or those who did not receive ADT. On the other hand, no significant differences with respect to spinal cord compression were found among the different covariates examined except for those MI patients who did not receive ADT (this latter group had lower incidence of SCC) (Table 4).

**Discussion**

Metastasis to the bone is a common occurrence in men with advanced prostate cancer, and is associated with significant morbidity and mortality [15–18]. One approach to understanding the clinically relevant consequences of bone metastasis is to study what has been defined as SREs. This includes certain interventions such as RAD and BS, or certain clinical events such as PF and SCC, that can occur among patients with bone metastasis. Prospective clinical trials in patients with established bone metastasis have provided important information about SREs in cancer patients [15, 19, 20]. In an effort to better understand the occurrence patterns and impact of PF, SCC, RAD, and BS in a broader prostate cancer population than what is typically defined in controlled clinical trials, we used the SEER-Medicare dataset to conduct the present analysis in a large cohort of men with stage IV M1 prostate cancer. This study took advantage of the fact that since 2004 onwards more detailed staging information on M1 patients is being captured in SEER (M1a, M1b, M1c; i.e., sites of metastasis at diagnosis).

In contrast with most prior studies where SREs have been studied in men with bone metastasis [4, 5, 15, 19–21], our study is unique in that we evaluated patients with...
different sites of metastasis, including those without bone metastasis at diagnosis, to determine the risk of developing SREs (as determined from claims data) among these different subgroups of prostate cancer patients. Using this approach, the present work documents that SREs can occur in all subcategories of M1 patients, although those with lymph node-only metastasis at presentation are significantly less likely to experience SREs compared to the other subgroups (Fig. 2, Table 3). One possible reason why men with lymph node metastasis only at diagnosis have less SREs may be due to their lower likelihood of developing subsequent bone metastasis. However, since we were not able to identify bone metastasis after diagnosis, this cannot be confirmed from the present data.

In addition to the initial sites of metastasis, we found age, ethnicity, year of cancer diagnosis and ADT receipt, can also affect the risk of developing SREs among the M1 prostate cancer cohort (Table 4). Regarding age we found that the overall lower incidence of SREs in the 80+ year old group is primarily due to the lower use of radiation amongst these patients compared to the 66–80 year old age group. Amongst African Americans, lower risk of developing PF and lower use of BS (perhaps a consequence of lower PF) account for their overall lower incidence of SREs compared to the other ethnic groups. This observation is not inconsistent with the known lower risk of fractures in African Americans compared to European Americans, perhaps reflecting inherent differences in their respective skeletal physiology [22].

Another interesting observation relates to the use of ADT. ADT is the mainstay of treatment, and in fact represents the first line of treatment for M1 prostate cancer patients. Despite this, remarkably, 25.8% of the M1 cohort did not have claims for ADT receipt, a figure that is not inconsistent with what has been reported previously by others [10, 11]. Claims reflecting all four SRE subcomponents are significantly less in the non-ADT group than in the corresponding ADT group (Table 4). The duration of follow-up for the non-ADT group is also considerably less than for the ADT group (4.9 vs. 19.5 months). Whether non-ADT patients receive lesser extent of medical services in general, as reflected by not getting a standard therapy (ADT) for their cancer in the first place and having significantly less follow-up compared to ADT patients, and whether such factors in part contribute to lower SRE-related claims across all SRE subtypes among this group, is not altogether clear but will require further study.

This study has several limitations. First, the codes used to define SREs have not been validated and are subject to further research. A Danish study validated the ICD-10 coding of bone metastasis and SREs in prostate cancer and found that the sensitivity of ICD-10 codes ranged from 44% to 55% and specificity ranged from 94% to 100% [23]. Second, there is no billing code for SREs which makes it harder to directly identify SREs, especially radiation to bone. The inability to differentiate receipt of radiation to the prostate gland from radiation to the bone will result in overestimating the prevalence of radiation. However, by only assessing S4M1 patients, we believe that the majority of our sample receiving radiation is using it for bone palliation. Third, this study did not include younger patients diagnosed with incident S4M1 or elderly...
patients who were initially diagnosed with nonmetastatic disease but developed bone metastasis during follow-up.

In conclusion, this study documents risk of SREs among elderly metastatic prostate cancer patients, irrespective of whether patients had bone metastasis at diagnosis. Although we cannot determine from these data if such patients go on to develop bone metastasis over time, these results do provide important evidence for patients and oncologists concerning SRE risk among all metastatic patients. We also identified several factors such as age and race/ethnicity that can modify the risk of SREs among metastatic prostate cancer patients. The slight decrease in SREs over time is promising. Better prevention and management of SREs can help to minimize their impact on men with advanced prostate cancer.

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**Table 4. Distribution of skeletal-related events subtype by select covariates.**

| Metastatic site            | Any SRE | RAD | BS | SCC | PF   |
|---------------------------|---------|-----|----|-----|------|
| LN only (n = 207)          | 28.50   | 16.43| NR | NR  | 9.18 |
| BM only (n = 2,583)        | 46.11   | 24.12| 2.79| 2.32| 16.88|
| Other only (n = 287)       | 41.38   | 21.08| NR | NR  | 15.56|
| BM + LN (n = 223)          | 52.02   | 28.25| NR | NR  | 17.04|
| BM + Other ± LN (n = 170) | 44.71   | 24.12| NR | NR  | 14.71|
| LN + Other (n = 69)        | 40.58   | 20.29| NR | NR  | 17.39|
| Unknown (n = 265)          | 35.47   | 17.36| NR | NR  | 13.58|
| **P value**                | <0.001  | 0.008*| 0.33| 0.65| 0.11|
| Age                       |         |     |    |     |      |
| 66–80 (n = 1372)           | 45.56   | 26.19| 2.34| 2.74| 14.29|
| 80+ (n = 1101)             | 41.56   | 18.47| 2.87| 1.96| 18.26|
| **P value**                | 0.008*  | <0.01*| 0.28| 0.1 | <0.01*|
| Race                      |         |     |    |     |      |
| Non-Hispanic White (n = 1824) | 45.62 | 23.17| 3.01| 2.59| 16.85|
| African American (n = 368) | 35.21   | 20.95| NR | NR  | 11.09|
| Hispanic (n = 160)         | 39.85   | 21.43| NR | NR  | 15.79|
| Other (n = 121)            | 43.98   | 25.46| NR | NR  | 15.74|
| **P value**                | <0.001* | 0.48| 0.008*| 0.32| 0.007*|
| Diagnosis year             |         |     |    |     |      |
| 2005 (n = 482)             | 49.16   | 25.53| 3.69| 3.38| 16.56|
| 2006 (n = 517)             | 44.82   | 23.91| 2.99| 2.45| 15.47|
| 2007 (n = 460)             | 44.11   | 23.94| 2.67| NR  | 15.19|
| 2008 (n = 503)             | 42.38   | 21.08| NR | NR  | 17.41|
| 2009 (n = 511)             | 37.91   | 19.56| NR | NR  | 15.19|
| **P value**                | <0.001* | 0.02*| 0.02*| 0.19| 0.64|
| Charlson comorbidity index |         |     |    |     |      |
| Zero (n = 1254)            | 46.09   | 25.78| 2.12| 2.67| 15.52|
| 1 (n = 462)                | 47.13   | 22.25| 3.50| NR  | 19.38|
| 2 (n = 239)                | 40.94   | 21.26| NR | NR  | 15.22|
| 3+ (n = 241)               | 43.52   | 19.43| NR | NR  | 18.91|
| **P value**                | <0.001* | 0.01*| 0.07| 0.48| 0.04*|
| ADT                        |         |     |    |     |      |
| No (n = 1135)              | 27.67   | 8.81| 3.35| 1.50| 14.01|
| Yes (n = 3269)             | 49.46   | 27.78| 2.29| 2.72| 16.67|
| **P value**                | <0.001* | <0.01*| 0.05| 0.02*| 0.035*|

NR, Not reported per data use agreement with NCI. PF, pathological fractures; SCC, spinal cord compression.

*Significant at the P = 0.05 level.
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**Conflict of Interest**

None declared.

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