The homogeneous and heterogeneous risk factors for the morbidity and prognosis of bone metastasis in patients with prostate cancer

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Purpose: Using the Surveillance, Epidemiology, and End Results database (SEER) to assess the incidence and risk factors of morbidity and prognosis for bone metastases in initial metastatic prostate cancer.

Patients and methods: The records of 249,331 prostate cancer patients in the SEER database, diagnosed between 2010 and 2014, were obtained to investigate the risk factors for developing bone metastasis, and the records of 9925 of them who registered before 2013 were retrieved (with at least 1 year follow up) to explore the prognostic factors for bone metastasis. Multivariate logistic and Cox regression were used to identify risk factors and prognostic factors for bone metastases, respectively.

Results: In total, 12,794 patients (5.1%) were diagnosed with bone metastases at the initial diagnosis. Older age, unmarried status, lymph node metastasis, poor tumor differentiation grade (Gleason grade), metastases at lung, brain, and liver were all positively associated with risk for the morbidity and prognosis of bone metastasis in prostate cancer. Black race and higher T stage were positively associated with bone metastasis development; however, they were not associated with a prognosis of bone metastasis.

Conclusion: The incidence of bone metastasis in prostate cancer was approximately 5% with poor survival. The prostate cancer has homogeneous and heterogeneous risk factors for incidence and prognosis of bone metastasis, which may provide potential guidelines for the screening and preventive treatment for the bone metastasis of prostate cancer.

Keywords: bone metastases, initial prostate cancer, survival, risk factor

Introduction

Globally, prostate cancer is the second most common malignancy in males and the fifth leading cancer-related cause of death.1,2 In the US, prostate cancer is the most common malignancy in males, and takes up 19% of all newly-diagnosed male cancer cases.3 With the development of surgical technique, radiotherapy, and chemotherapy, biotherapy regimen, and supportive treatment, the survival of prostate cancer patients has increased.3,4,5 Accordingly, the higher survival rate increased the prevalence of distant metastasis. Bone metastases (BM), as one of the most common distant metastasis types, was reported to occur in at least 85% of patients who died from prostate cancer.5 BM was accepted to lead to significant morbidity, worsening patient quality-of-life.6

Usually, the three most common clinical symptoms of BM can be detected, including pain, pathologic bone fractures, and spinal cord compression.7 A large number of prostate cancer patients did not go to a doctor until they had the aforementioned symptoms. Furthermore, for asymptomatic patients, the Prostate Cancer National...
Comprehensive Cancer Network (NCCN) screening guidelines do not recommend performing routine assessment for BM.\(^9\) Hence, to build a reliable predictive system for screening performance; a study looking into the risk factors of BM in prostate cancer patients is warranted.

Currently, prostate specific antigen (PSA) has been clinically applied as the main predictor for BM.\(^9\) However, using PSA level as the inclusion criteria, the latest systematic review and meta-analysis suggested the lack of a robust definition for predicting high BM risk in prostate cancer patients.\(^10\) Meanwhile, a series of clinical studies suggested the incidence of BM in prostate patients with low PSA values (<20 ng/mL) is from 12.6% to 36.1%.\(^11\) A previous study reported, besides PSA, Gleason score can be another predictive factor in prostate cancer patients with BM.\(^14\) More BM risk factors are needed to uncover the clinical metastatic characteristics of prostate cancer, and to supplement the predictive system.

The purpose of the present study was to use the Surveillance, Epidemiology, and End Results (SEER) database to assess the incidence and the risk factors of BM in initial prostate cancer. Moreover, survival estimates and prognostic factors identification were conducted for patients who had developed BM at the time of prostate cancer diagnosis.

**Methods**

**Data source and cohort selection**

Data were obtained from the National Cancer Institute’s SEER program between 2010 and 2014, as the BM status and other sites of distant metastases were collected by SEER from 2010, and the latest data update was on December 31, 2014. We extracted data for all cases initially diagnosed as malignant primary prostate cancer between 2010 and 2014 in the study, the mean age was 66.08±9.22 years, and 190,863 (76.6%) were white. Of them, 12,794 (5.1%) were diagnosed with BM at the initial diagnosis (Table 1).

As shown in Table 1, age over 80 years, black race, unmarried, higher T stage, lymph node involvement, poor tumor differentiated grade (Gleason grade), and the presence of lung metastases, liver metastases, and brain metastases were associated with significantly greater odds of having BM at diagnosis.

**Statistical analysis**

Multivariable logistic regression was used to determine the risk factors for developing BM at diagnosis. Variables included age (≤40, 41–60, 61-80, and ≥81 years), race [white, black, American Indian/Alaska Native (AI) and Asian or Pacific Islander (API)], marital status (married and unmarried), primary tumor (T) stage (T1, T2, T3, and T4), regional lymph node stage (N0 and N1), Gleason tumor grade (Gleason score ≤6; 2= Gleason score 3+4; 3= Gleason score 4+3; 4= Gleason score 8; 5= Gleason score 9–10), and the presence or absence of lung metastases, liver metastases, or brain metastases.

Survival duration was obtained using the Kaplan–Meier method; the differences between the curves were tested by Log-rank test. To identify factors associated with mortality, multivariable Cox proportional hazards regression was performed using the aforementioned factors.

All statistical analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY, USA), and all charts of survival were prepared using MedCalc 15.2.2. Two-sided \(P\)-values less than 0.05 were considered statistically significant.

**Results**

**Incidence of bone metastases**

For the 249,331 eligible patients who were diagnosed with malignant primary prostate cancer between 2010 and 2014 in the study, the mean age was 66.08±9.22 years, and 190,863 (76.6%) were white. Of them, 12,794 (5.1%) were diagnosed with BM at the initial diagnosis (Table 1).

**Risk factors for developing bone metastasis**

As shown in Table 1, age over 80 years, black race, unmarried, higher T stage, lymph node involvement, poor tumor differentiated grade (Gleason grade), and the presence of lung metastases, liver metastases, and brain metastases were associated with significantly greater odds of having BM at diagnosis.

**Survival and prognostic factors for BM**

The mean survival of the prostate cancer patients was 28.53±17.60 months, while that of those patients with BM was only 20.44±14.57 months. Survival estimates classified by age (Figure 2A), race (Figure 2B), marital
Figure 1 Flow chart of the subject’s selection for analyzing the risk factors for the morbidity and prognosis of BM in prostate cancer patients.

Abbreviations: BM, bone metastases.
status (Figure 2C), T stage (Figure 2D), N stage (Figure 2E), tumor grade (Figure 2F), the presence of lung metastases (Figure 2G), liver metastases (Figure 2H) or brain metastases (Figure 2I) are graphically displayed. Among patients with initial bone metastasis, the median survival of those who combined with liver metastases was the shortest (Median survival=10 months, 95% CI=8.44–11.56 months).

The prognostic factors for BM are shown in Table 2. A multivariate Cox regression model showed that patients of older age, unmarried, with lymph node involvement, poor tumor differentiated grade, and the presence of lung metastases were more likely to develop BM.

Table 1 Multivariable logistic regression for analyzing the demographic and related clinical characteristics for developing BM in patients diagnosed with initial primary prostate cancer (diagnosed 2010–2014)

| Subject characteristics | No. of patients with PC (2010–2014) | OR (95%CI) | P value |
|-------------------------|-------------------------------------|------------|---------|
| Age, in years           |                                     |            |         |
| ≤40                     | 11                                  | 1.45 (1.37–1.53) | <0.001 |
| 41–60                   | 2,240                               | 1 (Reference) | 1.00    |
| 61–80                   | 7,148                               | 0.64 (0.21–1.96) | 0.43   |
| ≥81                     | 3,395                               | 1.22 (0.40–3.75) | 0.73   |
| Race                    |                                     |            |         |
| White                   | 9,652                               | 1.06 (1.04–1.08) | <0.001 |
| Black                   | 2,270                               | 1.19 (1.10–1.29) | <0.001 |
| AI                      | 91                                  | 0.97 (0.85–1.11) | 0.63   |
| API                     | 688                                 | 1.00 (0.64–1.57) | 0.99   |
| Unknown                 | 93                                  | NA         | NA      |
| Marital status          |                                     |            |         |
| Unmarried               | 4,985                               | 1 (Reference) | 1.00    |
| Married                 | 6,970                               | 0.64 (0.60–0.68) | <0.001 |
| Unknown                 | 839                                 | NA         | NA      |
| T stage                 |                                     |            |         |
| T1                      | 2,753                               | 0.91 (0.88–0.95) | <0.001 |
| T2                      | 3,502                               | 0.83 (0.77–0.89) | <0.001 |
| T3                      | 1,106                               | 0.39 (0.36–0.43) | <0.001 |
| T4                      | 1,453                               | 2.64 (2.31–3.01) | <0.001 |
| Unknown                 | 3,980                               | NA         | NA      |
| N stage                 |                                     |            |         |
| N0                      | 6,781                               | 4.80 (4.43–5.20) | <0.001 |
| N1                      | 2,932                               | 3.86 (3.37–4.41) | <0.001 |
| Unknown                 | 3,081                               | NA         | NA      |
| Gleason grade           |                                     |            |         |
| 1                       | 232                                 | 2.88 (2.81–2.96) | <0.001 |
| 2                       | 456                                 | 3.06 (2.94–3.17) | <0.001 |
| 3                       | 675                                 | 10.26 (8.60–12.25) | <0.001 |
| 4                       | 1,905                               | 29.40 (24.95–34.65) | <0.001 |
| 5                       | 4,354                               | 75.65 (64.42–88.83) | <0.001 |
| Unknown                 | 5,172                               | NA         | NA      |
| Lung Met                |                                     |            |         |
| None                    | 11,222                              | 22.39 (16.86–29.72) | <0.001 |
| Yes                     | 902                                 | 2.65 (2.05–3.46) | <0.001 |
| Unknown                 | 670                                 | NA         | NA      |
| Liver Met               |                                     |            |         |
| None                    | 11,757                              | 18.79 (12.58–28.06) | <0.001 |
| Yes                     | 483                                 | 75.35 (64.42–88.83) | <0.001 |
| Unknown                 | 554                                 | NA         | NA      |
| Brain Met               |                                     |            |         |
| None                    | 11,980                              | 28.64 (11.92–68.77) | <0.001 |
| Yes                     | 153                                 | 4.82 (4.21–5.47) | <0.001 |
| Unknown                 | 661                                 | NA         | NA      |

Note: All factors with unknown data removed from multivariable logistic regression model.
Abbreviations: BM, bone metastases; PC, prostate cancer; AI, American Indian/Alaska Native; API, Asian or Pacific Islander; Met, metastases; NA, not available.
Discussion

Based on a large population analysis, the present study firstly determined the incidence of BM at the initial diagnosis of prostate cancer patients. We found that 5.1% of prostate cancer patients were initially diagnosed with BM. Although the present study was conducted based on a large population, it may underestimate BM incidence in initial diagnosed prostate cancer patients for being unable to capture the asymptomatic cases. The BM cumulative incidence was differently reported from 0.8% to 53.6%.\textsuperscript{11,15–18} The diversity of BM cumulative incidence could be due to various causes: First, most of the prostate patients chose to go to a doctor at an advanced stage in developing countries; Secondly, a high incidence of BM can also be observed in developed countries in the 1990s.\textsuperscript{17,18} Thus, a metastatic screening for prostate cancer patients should be designed based on local economic development and local epidemiologic characteristics of prostate cancer.

A series of risk factors of initial BM in prostate cancer patients were found, including elderly patient (≥81 years), black race, unmarried, higher T stage, N stage (N1), lung metastases, brain metastases, and poor tumor differentiated grade. Thus, physicians should focus on their prostate cancer patients with these risk factors. At the same time, a skeletal scanning can be considered for the patients with high metastatic grade.
metastasis risk. Meanwhile, in future research, the factors we analyzed can be involved in the predictive system for initial BM in prostate cancer patients.

A series of prognostic factors of initial BM in prostate cancer patients, which were correlated with higher mortality risk, were found, including young (≤40 years), elderly patient (≥81 years), unmarried, N stage (N1), poor tumor grade, lung metastases, and brain metastases. The result suggested Gleason grading system’s affirmative ability on prevention prognosis of advanced cancer with BM. Based on the aforementioned prognostic factors, physicians can make a preliminary estimation for the prostate patients with initial BM.

### Table 2 Multivariable Cox regression for analyzing the mortality among primary prostate cancer patients with BM (diagnosed 2010–2013)

| Subject characteristics | No. of PC patients with BM | Survival, Median (IQR), mo | Cox HR (95% CI) | P value |
|-------------------------|---------------------------|-----------------------------|-----------------|---------|
| Age, in years           |                           |                             |                 |         |
| ≤40                     | 11                        | 27 (12.81–41.19)            | 1.43 (1.33–1.53) | <0.001  |
| 41–60                   | 1,748                     | 35 (32.65–37.35)            | 0.58 (0.14–2.32) | 0.44    |
| 61–80                   | 5,521                     | 25 (27.87–28.14)            | 0.70 (0.18–2.83) | 0.62    |
| ≥81                     | 2,645                     | 14 (13.12–14.88)            | 1.17 (0.29–4.71) | 0.82    |
| Race                    |                           |                             |                 |         |
| White                   | 7,464                     | 23 (22.14–23.86)            | 1 (Reference)   | 1.00    |
| Black                   | 1,790                     | 24 (22.37–25.63)            | 1.13 (1.01–1.26) | 0.03 |
| AI                      | 68                        | 23 (12.42–33.58)            | 0.73 (0.58–0.91) | 0.01 |
| API                     | 534                       | 34 (28.99–39.02)            | 0.77 (0.40–1.48) | 0.43 |
| Unknown                 | 69                        | 21 (30.43)                  | NA              | NA |
| Marital status          |                           |                             |                 |         |
| Unmarried               | 3,859                     | 20 (18.94–21.06)            | 1 (Reference)   | 1.00 |
| Married                 | 5,433                     | 27 (25.92–28.08)            | 0.81 (0.74–0.89) | <0.001 |
| Unknown                 | 633                       | 337 (53.24)                 | NA              | NA |
| T Stage                 |                           |                             |                 |         |
| T1                      | 2,155                     | 32 (29.80–34.21)            | 1.04 (0.99–1.08) | 0.12 |
| T2                      | 2,769                     | 28 (26.18–29.82)            | 0.94 (0.85–1.03) | 0.19 |
| T3                      | 837                       | 34 (30.48–37.52)            | 0.85 (0.74–0.98) | 0.03 |
| T4                      | 1,105                     | 19 (17.20–20.81)            | 1.23 (1.07–1.41) | 0.003 |
| Unknown                 | 3,059                     | 2,080 (68.00)               | NA              | NA |
| N Stage                 |                           |                             |                 |         |
| N0                      | 5,272                     | 28 (26.67–29.33)            | 1 (Reference)   | 1.00 |
| N1                      | 2,156                     | 25 (23.38–26.62)            | 1.11 (1.01–1.23) | 0.036 |
| Unknown                 | 2,497                     | 1,684 (67.44)               | NA              | NA |
| Gleason grade           |                           |                             |                 |         |
| 1                       | 193                       | 72 (37.30)                  | 1.26 (1.20–1.32) | <0.001 |
| 2                       | 381                       | 48 (40.20–53.80)            | 1.12 (0.79–1.57) | 0.52 |
| 3                       | 536                       | 54 (NR)                     | 1.22 (0.88–1.69) | 0.23 |
| 4                       | 1,488                     | 37 (34.33–39.68)            | 1.32 (0.98–1.78) | 0.07 |
| 5                       | 3,351                     | 25 (24.75–27.25)            | 2.03 (1.52–2.72) | <0.001 |
| Unknown                 | 3,976                     | 2,798 (70.37)               | NA              | NA |
| Lung Met                |                           |                             |                 |         |
| None                    | 8,694                     | 25 (24.15–25.85)            | 1 (Reference)   | 1.00 |
| Yes                     | 687                       | 15 (13.00–17.00)            | 1.43 (1.20–1.71) | <0.001 |
| Unknown                 | 544                       | 357 (64.44)                 | NA              | NA |
| Liver Met               |                           |                             |                 |         |
| None                    | 9,084                     | 25 (24.17–25.83)            | 1 (Reference)   | 1.00 |
| Yes                     | 388                       | 10 (8.44–11.56)             | 2.51 (2.05–3.09) | <0.001 |
| Unknown                 | 453                       | 301 (66.45)                 | NA              | NA |
| Brain Met               |                           |                             |                 |         |
| None                    | 9,257                     | 25 (24.19–25.81)            | 1 (Reference)   | 1.00 |
| Yes                     | 133                       | 11 (8.05–13.95)             | 1.80 (1.16–2.78) | 0.01 |
| Unknown                 | 535                       | 361 (67.48)                 | NA              | NA |

Note: All factors with Unknown Data removed from Cox and Kaplan–Meier model.

Abbreviations: PC, prostate cancer; BM, bone metastases; AI, American Indian/Alaska Native; API, Asian or Pacific Islander; Met, metastases; NA, not available; NR, not reached.
Among the cohort of the present study, compared with black race, white patients had significantly lower risk for developing BM at diagnosis. This may suggest that prostate cancers in white patients are likely being diagnosed at an early stage. Meanwhile, black patients with BM showed worse median survival (Table 2). The latest study looking into brain metastases in newly diagnosed breast cancer also suggested a poor median survival in black patients. Further studies looking into the potential explanations for black patients’ poor survival in metastatic tumor is needed.

Inevitably, the present study has several limitations. First, in the present study, only the presence/absence of BM based on the initial diagnosis was analyzed. The patients who developed BM later during their disease course could not be analyzed, as they may not be recorded in the SEER database. Second, the actual rate of BM in patients with prostate cancer might be underestimated. BM cannot be captured in asymptomatic prostate cancer patients. Third, the SEER database has a lack of intact baseline information. Performance status, smoking and alcohol consumption, family history, blood type, and body mass index were not provided in the SEER database. Last, but not least, the detailed diagnosis method for BM was not available.

**Conclusion**

Despite the aforementioned limitations, based on the SEER database, the present study provided the incidence risk factors and prognostic factors of BM in patients with newly diagnosed initial prostate cancer. A series of risk factors for BM in prostate cancer patients were identified, which can be potentially used for clinical prediction. Survival analysis was also conducted, and a series of prognostic factors of initial BM in prostate cancer patients were found, which can be potentially used for making an individualized treatment plan.

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**Author contributions**

XG, CZ, and XW designed the study. YX and GF collected the data. XG and XW analyzed the data. XG, CZ, and QG organized the manuscript. LL, XH, YM, FL, and GW reviewed the papers and revised the manuscript. All the authors (XG, CZ, QG, YX, GF, LL, XH, FL, YM, XW, GW) have read and approved the final manuscript. All authors contributed toward data analysis, drafting, and revising of the paper and agree to be accountable for all aspects of the work.

**Disclosure**

The authors report no conflicts of interest in this work.

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