Risk factors for progression of solitary plasmacytoma of bone to multiple myeloma in the spine: A population-based study

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Abstract

Background: Spine SBP is a primary spinal malignant tumor. Risk factors associated with progression of solitary plasmacytoma of bone (SBP) to multiple myeloma in spine remains unknown. This study therefore aimed to identify the risk factors associated with progression of solitary plasmacytoma of bone (SBP) to multiple myeloma in the spine.

Methods: Data of 1543 patients diagnosed with spine SBP between 1992 and 2013 was obtained from the Surveillance, Epidemiology, and End Results (SEER) database for analysis. Risk factors associated with progression of SBP to multiple myeloma (MM) were then identified using univariate and multivariate regression analysis methods.

Results: Out of the 1543 patients diagnosed with spine SBP, 659 of them progressed to MM. The overall rate of progression to MM was 42.51%. Univariate and multivariate regression analysis revealed that age, race, gender and chemotherapy were independent risk factors associated with SBP progression to MM.

Conclusion: Old aged patients, patients belonging to the white race, female patients and those undergoing chemotherapy were identified to be at a high risk of progression to MM. This information will assist clinicians in evaluating patients’ risk of SBP progression to MM at the point of diagnosis and advise them accordingly.

Background

Plasmacytomas are malignant tumors characterized by clonal proliferations of plasma cells. They can be classified into three groups: multiple myeloma (MM), extramedullary plasmacytoma (EMP) and solitary plasmacytoma of bone (SBP) [1]. SBP’s account for approximately 5% of plasmacytomas. The ratio of male to female patients diagnosed with SBP is 2:1 [2, 3]. Spine SBP is a mass of neoplastic monoclonal plasma cells in spinal bones. Nearly 70% of SBP’s primarily occur in the spine commonly in the thoracic
vertebrae of red marrow-containing bones [4-6].

Previous study reported that patients diagnosed with SBP have high risk of progression to MM [7]. 50 - 60% of patients diagnosed with SBP develop to MM [7]. Knobel et al., reported that the median time of SBP development to MM was 21 months. 51% of patients had probability of SBP developing to MM within 5 years [8]. In the same line, Bertanha et al., reported the average time of SBP development to MM was 41 months. SBP in the spine have a high likelihood to progress to MM than SBP in other bone sites. For instance, Yang et al., reported a case of rapid progression of solitary plasmacytoma to MM in lumbar vertebra. To the best of the authors’ knowledge, information regarding risk factors associated with progression of SBP in the spine is still lacking.

As such, the Surveillance, Epidemiology, and End Results (SEER) database was used to enroll enough spine SBP patients for the study. This was done because obtaining enough patients diagnosed with spine SBP for the study was a big challenge. The SEER database has been widely used as an effective tool for analysis of rare cancers [11-13]. This study aimed to identify factors associated with increased risk of progression of spine SBP to MM. The study is expected to provide more information that will assist clinicians in evaluating patients’ risk of SBP progression to MM at the point of diagnosis.

Methods

Patients cohort

A population-based search for patients diagnosed with primary spinal bone tumor was performed in the National Cancer Institute’s SEER database (with additional treatments) [http://seer.cancer.gov]. The database contained numerous cancer data derived from 18 cancer registries across the United States. The cancer registries covered approximately 30% of the US population. The SEER database had widely been used and validated independently for analysis of primary spinal bone tumor. The study did not require
approval from the internal review board because the SEER database uses publicly available information with no personal identifiers. ICD-O-3 codes were reviewed for all patients to identify the histological subtypes of “solitary bone plasmacytoma (9731/3)”. Site-specific codes were first used to identify all primary spinal bone tumors. The codes were; C41.2 for the vertebral column and C41.4 for pelvic bones, sacrum, coccyx and associated joints. Data on SP-bone staging (extension of disease (EOD)) was limited to only two main categories; “local” and “distant”. However, patients with “distant” involvement were not of interest because spine SBP is a localized single mass of monoclonal plasma cells in the spine. Cognizant to this, patients designated as “distant” were excluded from the study. Patients diagnosed with second or later primary cancer, those diagnosed using a death certificate or autopsy results, those with unknown survival time and those of unspecified race were also excluded. Patients whose spine SBP progressed to MM were also identified (Figure 1).

Statistical analysis

The incorporated variables of the group of patients whose spine SBP progressed to MM and that of those whose spine SBP didn’t progress to MM were compared using the chi-squared test. Univariate logistic regression analysis of the age, year of diagnosis, gender, race, marital status, grade, radiotherapy sequence, surgery, radiotherapy and chemotherapy of the patients was used to identify possible risk factors associated with SBP progression to MM. Multivariate logistic analysis was then applied to further evaluate the risk factors identified in the univariate logistic regression analysis. Statistical analyses were performed using SEER*Stat version 8.3.4 (NCI., Bethesda., MD), SPSS version 23 (IBM Corp., Armonk, New York, USA) and R version 3.3.1 (Institute for Statistics and Mathematics, Vienna, Austria) software. Differences between groups were deemed to be statistically significant when the p value was less than 0.05 (p<0.05).
Results

**Patients baseline characteristics**

8195 patients diagnosed with spinal bone tumor between 1983 and 2015 were retrieved from the SEER database. 2147 patients diagnosed as SBP were then selected for another round of screening. Among these patients, 604 were categorized as “distant” or were of unknown race and hence were excluded. The remaining 1543 patients diagnosed with spine SBP were then included in the study. We identified Patients whose SBP progressed to MM were identified using their cause of death (COD) and their ID’s being found in both SBP and MM patients’ databases. Finally, 659 patients whose spine SBP progressed to MM were identified (Figure 1).

Patients characteristics are listed in Table 1. 966 (62.6%) patients were aged above 59 years. Their median age at the point of diagnosis was 63.9 years. 1206 (78.16%) patients were diagnosed between 2003 and 2015. Histologically, 580 (37.59%) patients were of pre-B cell grade while 921 (59.69%) were of unknown grade. Based on gender, 968 (62.73%) patients were males while the rest 575 (37.27%) were females. Moreover, 989 (64.1%) patients were married. 1236 (80.1%) patients were white. Upon diagnosis, 476 (30.85%) patients underwent surgery, 1275 (82.63%) patients underwent radiotherapy while 320 (20.74%) patients underwent radiotherapy after surgery. Nonetheless, 336 (21.78%) patients underwent chemotherapy.

**Risk factors associated with SBP progression to MM**

Univariate logistic regression analysis revealed that age, race, gender and chemotherapy were all significantly associated with SBP progression to MM (p<0.05) (Table 2). After controlling for confounding variables using multivariate logistic analysis, age, gender, race and chemotherapy was identified as independent risk factors for SBP progression to MM (p<0.05) (Table 2).
Multivariate logistic analysis revealed an increased risk of SBP progression to MM among patients aged 45-59 years old (OR = 1.953, 95% confidence interval [CI] of 1.254 to 3.044), 60-74 years old (OR = 2.787, 95% CI of 1.812 to 4.287), 75-89 years old (OR = 2.877, 95% CI of 1.825 to 4.536) and those above 90 years (OR = 4.350, 95% CI of 1.590 to 11.901). Patients belonging to the white race (OR = 2.032, 95% CI of 1.079 to 3.826), female patients (OR = 1.272, 95% CI of 1.027 to 1.576) and patients who had undergone chemotherapy (OR = 1.593, 95% CI, 1.243 to 2.042) also had an increased risk of SBP progression to MM.

Discussion

In this study, univariate and multivariate logistic analysis revealed that old age, belonging to the white race, being female and undergoing chemotherapy were risk factors that increased the likelihood of SBP progression to MM. All factors were independent of each other. These findings were consistent with those of who reported that old age was an independent risk factor for worse prognosis of SBP patients [17-19]. Similarly, Knobel et al., reported that younger patients with tumors located in the vertebral column had a better outcome when treated with moderate-dose radiotherapy [8]. El-Fattah et al., analyzed the risk factors of plasmacytoma mortality using a large population-based study. They found that the age of the patient, black-American race and bone plasmacytomas were significant risk factors associated with low overall survival of patients diagnosed with plasmacytoma [20]. In the same line, Kilciksiz et al., reported that young age was an independent good prognostic factor for progression of SBP to MM [19]. This study revealed that there is a close association between old age and increased likelihood of SBP progressing to MM. These findings partially explained the poor prognosis of plasmacytoma in older patients. However, Bertanha et al., found that patients who progressed to MM were younger than those who did not. In their study, the average time of progression to
MM was 41 months [9]. However, the evidence of the risk factor analysis was low because the small sample size of the two groups was only compared using the t test analysis. In our multivariate analysis, SBP patients belonging to the white race had a higher risk of its progression to MM. This was attributed to the high incidence of SBP among the white race individuals. In addition, the rate of SBP progression to MM in female patients was slightly higher than that in male patients. This suggested that progression of SBP to MM could be partially gender dependent. In the same line, SBP patients under chemotherapy regimens were also at a higher risk of progression to MM.

The mean age of patients diagnosed with spine SBP was 63.6 years. The ratio of male to female patients diagnosed with SBP was 1.68:1 indicating that spine SBP often occurred in older men. This was a large-scale population retrospective study that was limited to positive SBP diagnosis done between 1992-2013. This was done to reduce diagnosis errors and ensure that the follow-up time after diagnosis was more than 5 years.

**Limitations**

Despite the insightful data obtained in this study, it had some limitations. Some risk factors such as tumor size, persistent myeloma and serum free light chain ratio were not available in the SEER database [21]. In addition, there was no data on surgical approaches and time of surgery are available in the database although there were reports of surgical procedures performed. Moreover, the SEER database lacked data on the range and dose of radiation therapy and other treatment methods such as immunotherapy and hormone therapy. Despite these shortcomings, the study generated invaluable information regarding the risk factors associated with SBP’s progression to MM.

**Conclusions**

Evidently, this study is the largest analysis done to evaluate the progression of spine SBP patients to MM. represents the largest series with risk factors for progression to MM on
patients with SBP in spine. Old aged patients, patients belonging to the white race, female patients and those undergoing chemotherapy were identified to be at a high risk of progression to MM. Indeed, this information will assist clinicians in evaluating patients’ risk of SBP progression to MM at the point of diagnosis and advise them accordingly.

Abbreviations

SBP: solitary plasmacytoma of bone; SEER: Surveillance, Epidemiology, and End Results; MM: multiple myeloma; EMP: extra-medullary plasmacytoma; HRs: hazard ratios; CIs: confidence intervals

Declarations

Acknowledgments

None.

Availability of data and materials

Limited Use Agreement for Surveillance, Epidemiology, and End Results (SEER) Program (https://seer.cancer.gov) SEER*Stat Database. The data can be used publicly.

Ethics approval and consent to participate

Anonymized cancer registry data were analyzed in this study, therefore not requiring ethics approval. No patient identifying information is reported.

Consent for publication

Not Applicable.

Availability of data and materials
Please contact corresponding author Jianyuan Jiang for data requests.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

LX and JYJ conceived the study idea. LX, JYJ and HLW performed data mining, and statistical analyses. JYJ and CJZ interpreted results of statistical analyses. LX drafted the initial manuscript. LX and JYJ made critical comment and revision for the initial manuscript. LX had primary responsibility for the final content. LX and HLW are co-first authors. JYJ is correspondence author. All authors reviewed and approved the final manuscript.

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Tables

Table. 1 Characteristics of patients with solitary plasmacytoma of bone (SBP) in spine by progression to multiple myeloma (MM).
| Characteristic                        | N (%) | Progression to MM | No progression to MM | P      |
|--------------------------------------|-------|-------------------|----------------------|--------|
| **Year**                             |       |                   |                      | 0.450  |
| 1992-2002                            | 337(21.84) | 150               | 187                  |        |
| 2003-2013                            | 1206(78.16) | 509               | 697                  |        |
| **Age**                              |       |                   |                      | 0.000  |
| <45                                  | 138(8.94)   | 32                | 106                  | *      |
| 45-59                                | 439(28.45) | 168               | 271                  |        |
| 60-74                                | 606(39.27) | 284               | 322                  |        |
| 75-89                                | 341(22.10) | 164               | 177                  |        |
| >89                                  | 19(1.23)    | 11                | 8                    |        |
| **Race**                             |       |                   |                      | 0.038  |
| White                                | 1236(80.10) | 546              | 690                  | *      |
| Black                                | 246(15.94)  | 96                | 149                  |        |
| Asian or Pacific Islander            | 53(3.43)    | 14                | 39                   |        |
| American Indian/Alaska               | 9(0.58)     | 3                 | 6                    |        |
| **Gender**                           |       |                   |                      | 0.009  |
| Female                               | 575(37.27)  | 270               | 305                  | *      |
| Male                                 | 968(62.73)  | 389               | 579                  |        |
| **Marital status**                   |       |                   |                      | 0.706  |
| Married                              | 989(64.10)  | 433               | 556                  |        |
| Divorced                             | 127(8.23)   | 51                | 76                   |        |
| Single                               | 184(11.92)  | 74                | 110                  |        |
| Others                               | 243(15.75)  | 101               | 142                  |        |
| **Grade**                            |       |                   |                      | 0.292  |
| Pre-B cell                           | 580(37.59)  | 238               | 342                  |        |
| Grade 1                              | 14(0.91)    | 6                 | 8                    |        |
| Grade 2                              | 8(0.52)     | 6                 | 2                    |        |
| Grade 3                              | 10(0.65)    | 6                 | 4                    |        |
| Grade 4                              | 10(0.65)    | 3                 | 7                    |        |
| Unknown                              | 921(59.69)  | 400               | 521                  |        |
| **Radiotherapy sequence**            |       |                   |                      | 0.990  |
| Before surgery                       | 32(2.07)    | 14                | 18                   |        |
| After surgery                        | 320(20.74)  | 136               | 184                  |        |
| Other or unknown                     | 1191(77.19)| 509               | 682                  |        |
| **Surgery**                          |       |                   |                      | 0.890  |
| Yes                                  | 476(30.85)  | 185               | 251                  |        |
| No                                   | 1107(71.74) | 474              | 633                  |        |
| **Radiotherapy**                     |       |                   |                      | 0.152  |
| Yes                                  | 1275(82.63) | 534              | 741                  |        |
| No or unknown                        | 268(17.37)  | 125               | 143                  |        |
| **Chemotherapy**                     |       |                   |                      | 0.000  |
| Yes                                  | 336(21.78)  | 172               | 164                  | *      |
| No or unknown                        | 1207(78.22)| 487              | 720                  |        |

**Abbreviations:** MM multiple myeloma

Note: * p<0.05 (n=1543)

Table 2 Univariate and multivariate logistic regression analysis for patients with solitary plasmacytoma of bone (SBP) in spine by progression to multiple myeloma (MM).
| Characteristic | Univariate analysis |  | Multivariate analysis |  |
|----------------|---------------------|---|-----------------------|---|
|                | OR (95%CI)          | P  | OR (95%CI)            | P  |
| Year           |                     |    |                       |    |
| 1992-2002      | Reference           |    | Reference             |    |
| 2003-2013      | 0.910 (0.714-1.161) | 0.450 | Reference             |  |
| Age            |                     |    |                       |    |
| <45            | Reference           |    | Reference             |    |
| 45-59          | 2.054 (1.323-3.188) | 0.001* | 1.953 (1.254-3.044)  | 0.003* |
| 60-74          | 2.922 (1.908-4.475) | 0.000* | 2.787 (1.812-4.287)  | 0.000* |
| 75-89          | 3.069 (1.959-4.808) | 0.000* | 2.877 (1.825-4.536)  | 0.000* |
| >89            | 4.555 (1.688-12.292)| 0.003* | 4.350 (1.590-11.901) | 0.004* |
| Race           |                     |    |                       |    |
| White          | Reference           |    | 2.032 (1.079-3.826)  | 0.028* |
| Black          | 0.814 (0.615-1.077) | 0.150 | 1.660 (0.845-3.259)  | 0.141 |
| Asian or Pacific Islander | 0.454 (0.244-0.844) | 0.013* | Reference             |    |
| American Indian/Alaska Native | 0.632 (0.157-2.538) | 0.518 | 1.147 (0.250-5.270)  | 0.860 |
| Gender         |                     |    |                       |    |
| Female         | Reference           |    | 1.272 (1.027-1.576)  | 0.027* |
| Male           | 0.759 (0.616-0.935) | 0.009* | Reference             |    |
| Marital status |                     |    |                       |    |
| Married        | Reference           |    | Reference             |    |
| Divorced       | 0.862 (0.591-1.255) | 0.438 |                     |    |
| Single         | 0.864 (0.627-1.190) | 0.370 |                     |    |
| Others         | 0.913 (0.687-1.214) | 0.532 |                     |    |
| Grade          |                     |    |                       |    |
| Pre-B cell     | Reference           |    | Reference             |    |
| Grade 1        | 1.078 (0.369-3.146) | 0.891 |                     |    |
| Grade 2        | 4.311 (0.863-21.542)| 0.075 |                     |    |
| Grade 3        | 2.155 (0.602-7.721) | 0.238 |                     |    |
| Grade 4        | 0.616 (0.158-2.406) | 0.486 |                     |    |
| Unknown        | 1.103 (0.894-1.362) | 0.360 |                     |    |
| Radiotherapy sequence | Reference |    | Reference             |    |
| Before surgery |                     |    | Reference             |    |
| After surgery  | 0.950 (0.457-1.977) | 0.892 |                     |    |
| Other or unknown | 0.960 (0.473-1.947) | 0.909 |                     |    |
| Surgery        |                     |    |                       |    |
| Yes            | Reference           |    | Reference             |    |
| No             | 1.016 (0.812-1.271) | 0.890 |                     |    |
| Radiotherapy   |                     |    |                       |    |
| Yes            | Reference           |    | Reference             |    |
| No or unknown  | 1.213 (0.931-1.580) | 0.153 |                     |    |
| Chemotherapy   |                     |    |                       |    |
| Yes            | Reference           |    | 1.593 (1.243-2.042)  | 0.001* |
| No or unknown  | 0.645 (0.506-0.822) | 0.000* | Reference             |    |

**Abbreviations:** MM multiple myeloma, OR odds ratio, CI confidence interval, NI not included

**Note:** * p<0.05 (n=1543)
Figures

SEER database

Site code: C41.2, C41.4

Spinal bone tumor n=8195

ICO-O-3 9731/3 malignant

Solitary bone plasmacytoma n=2147

Excluded: Extension distant and Unknown race Year (1992-2013)

Study population n=1543

Study population of SBP of spine N=1543

Cases of MM N=111868

Cases of SBP of spine with progression to MM N=659

Cases of SBP of spine without progression to MM N=884

Figure 1
The flow diagram demonstrates the process of selecting patients from the SEER database.