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

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Research article

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Abstract

Background: SBP of spine is a primary spinal malignant tumor. Risk factors for progression of solitary plasmacytoma of bone (SBP) to multiple myeloma in spine remains controversial. We aimed to analysis the risk factors for progression of solitary plasmacytoma of bone (SBP) to multiple myeloma in spine.

Methods: A total of 1543 patients diagnosed with SBP of spine in the Surveillance, Epidemiology, and End Results (SEER) database from 1992 to 2013 were included in the study. Factors associated of progression to multiple myeloma (MM) were assessed with univariate and multivariate methods.

Results: 1543 patients with SBP of spine were collected and 659 patients progressed to MM. The overall rate of progression to MM was 42.51%, Age, race, gender, and chemotherapy were found to be associated with disease progression to MM in the univariate analysis, greater age (45-59: OR=2.017, 95%CI, 1.287 to 3.159; 60-74: OR=2.940, 95%CI, 1.891 to 4.570; 75-89: OR=3.180, 95%CI, 1.976 to 5.118; >89: OR=5.524, 95%CI, 1.965 to 15.526), patients of white race (OR = 2.032, 95% CI, 1.079 to 3.826), female patients (OR = 1.272, 95% CI, 1.027 to 1.576), and patients received chemotherapy (OR = 1.593, 95%CI, 1.243 to 2.042) was identified as independent risk factors for SBP of spine progression to MM in the multivariate analysis.

Conclusions: Greater age, white race, female and chemotherapy was identified as independent risk factors for SBP of spine progression to MM.

Background

Plasmacytomas are malignant tumors characterized by clonal proliferations of plasma cells. Plasmacytoma can be classified into three groups: multiple myeloma (MM), extramedullary plasmacytoma (EMP) and solitary plasmacytoma of bone (SBP) [1]. Approximately 5% of plasmacytomas were SBP, in which the ratio of male to female was 2:1 [2, 3]. Nearly 70% of the SBP occurred primarily in the spine which is red marrow-containing bones, and it occurred commonly in the thoracic vertebrae [4–6].

Previous studies showed that patients with SBP have high risk of progression to MM [7]. Approximately 50%–60% of patients with SBP develop to MM [7]. Knobel et al [8] reported that median time to MM development from SBP was 21 months with a 5-year probability of 51% and Bertanha et al [9] analyzed the average time was 41 months. SBP in spine will progress more frequently to MM than SBP in other bone sites. An article by Yang et al [10] reported a case of rapid progression of solitary plasmacytoma to MM in lumbar vertebra. To the best of our knowledge, the report of risk factor on progression of SBP in spine is still lacking.

It is of great challenge to acquire a large number of patients with SBP in spine. As a result, we utilized the Surveillance, Epidemiology, and End Results (SEER) database to enroll sufficient cases for the study, The SEER database has been widely used as an effective tool for the analysis of rare cancer [11–13].

The aim of our study is to identify factors which are associated with an increased risk of progression to MM. Our work is expected to assist clinicians in evaluating patients' risk of progression to MM at diagnosis.

Methods

Patients cohort

A population-base search for patients diagnosed primary spinal bone tumor was performed in the National Cancer Institute's SEER database (with additional treatments) [http://seer.cancer.gov], derived from 18 cancer registries across the United States, covering approximately 30% of US population. Site-specific codes were first used to identify all primary spinal bone tumor: C41.2 (vertebral column) and C41.4 (pelvic bones, sacrum, coccyx, and associated joints). The SEER database was widely used and had been validated independently for analysis of primary spinal bone tumor. No internal review board approval was required in the present study because the database uses publicly available information with no personal identifiers. In our study, ICD-O–3 codes were reviewed for all cases to identify the histological subtypes with "solitary bone plasmacytoma (9731/3)". The data on SP-bone staging (extension of disease (EOD)) were limited, as "local" or "distant" were the main categories used in the database. In our work, patients with "distant" involvement were not of interest, as by definition, SBP in spine is a localized single mass of monoclonal plasma cells in spine. we excluded the cases designated as distant. We excluded cases of second or later primary cancer, those diagnosed by death certificate or autopsy, those with unknown survival time, those with unspecified race.

Statistical analysis

The incorporated variables were compared between groups with the progression to MM or without progression to MM using chi-squared test. Univariate logistic analysis was used to selected variables as possible risk factors associated with progression to MM. Multivariate logistic analysis was then applied to determine the risk factors selected in univariate analysis. Statistical analyses were performed using SEER*Stat (8.3.4., NCI., Bethesda., MD), SPSS (23., IBM Corp., Armonk, NY, USA) and R (3.3.1., Institute for Statistics and Mathematics, Vienna, Austria) software. Comparisons between groups were seemed statistically significant at $p<0.05$.

Results

Patients baseline characteristics

8195 spinal bone tumor patients diagnosed from 1983 to 2015 were collected from the SEER database. Then, 2147 patients diagnosed as SBP were selected for our study. Among these patients, 604 patients with extension distant or unknown race were excluded. Finally, 1543 patients with SBP in spine were

included in our study. We identified patients with progression to MM not only using the information (cause of death (COD)) but also finding the same patients' id between the patients with MM and the patients with SBP in spine. Finally, 659 patients with progression to MM were identified (Fig. 1).

Patients characteristics are listed in Table 1. 966 (62.6%) patients were old ages (>59), and the median age at diagnosis were 63.9 years old. 1206 (78.16%) of cases were from the year 2003 and beyond. Histologically, 580 (37.59%) of the cases were of pre-B cell grade, 921 (59.69%) were of unknown grade. 968 (62.73%) of the patients were male and 989 (64.1%) of the patients were married. 1236 (80.1%) of the patients were white. After diagnosis, 476 (30.85%) of patients received surgery, 1275 (82.63%) of patients received radiotherapy, 320 (20.74%) of patients received radiotherapy after surgery. 336 (21.78%) received chemotherapy.

Risk factors for disease progression to MM

659 (42.51%) patients who later developed to MM were identified from the cohort. Data on age, year, sex, race, marital status, grade, radiotherapy sequence, surgery, radiotherapy and chemotherapy were enrolled into the univariate logistic regression analysis. Age, race, gender, and chemotherapy were found to be associated with disease progression to MM in the univariate analysis (all $p<0.05$) (Table 2). After controlling for confounding variables using multivariate logistic analysis, age, gender, race and chemotherapy was identified as independent risk factors for disease progression to MM (all $p<0.05$) (Table 2).

Multivariate analysis demonstrated an increased risk of progression to MM among patients with 45–59 years old (OR = 1.953, 95% confidence interval [CI], 1.254 to 3.044), 60–74 years old (OR = 2.787, 95% CI, 1.812 to 4.287), 75–89 years old (OR = 2.877, 95% CI, 1.825 to 4.536), 90 years and older (OR = 4.350, 95% CI, 1.590 to 11.901), patients of white race (OR = 2.032, 95% CI, 1.079 to 3.826), female patients (OR = 1.272, 95% CI, 1.027 to 1.576), and patients received chemotherapy (OR = 1.593, 95%CI, 1.243 to 2.042).

Discussion

The prognosis of SBP varies greatly, with some patients recovering after surgical removal or local fractional radiation therapy, and others progressing to MM years later [14]. Despite treatments such as radical radiotherapy and surgery produced sufficient local control, approximal 50%–60% of patients with SBP progresses to MM [15, 16]. Thus, identifying the risk factors associated with SBP in spine progression to MM are crucial in the management and survival of patients [15]. However, to our knowledge, no study has investigated the risk factors for progression to MM in patients with SBP in spine. Based on the SEER database which covers nearly 30% of entire US population, we were able to collect relatively sufficient cases to identify potential risk factors for progression to MM. primary detection of progression to MM is important in the treatment of SBP in spine. In our study, greater age, white race, female and chemotherapy were identified as risk factors for progression to MM using univariate and multivariate logistic analysis.

Our study determined that greater age was an independent risk factor for progression to MM. Previous studies have shown that greater age is an independent risk factor for a worse prognosis of SBP patients [17–19]. Knobel et al [8] found that younger patients, especially with vertebral location, had the better outcome when treated with moderate-dose radiotherapy. An article by El-Fattahet al [20] recently analyzed the risk factor of plasmacytoma mortality according to a large population-based study. They found that age of diagnosis >60 years, black-American race and bone plasmacytomas were significant risk factors for worse overall survival. Kilciksiz et al [19] reported that younger age was an independent good prognostic factor for progression to MM. Our data revealed the association between greater age and increased likelihood of progression to MM. Our finding that older patients were more likely to present with progression to MM may partially explain the worse prognosis of older patients. However, an article by Bertanha et al [9] analyzed 103 medical records of patients, they found that patients who progressed to MM were younger than those who did not, and the average time to progression to MM was 41 months. Because the sample size was small and they only used the t test analysis to compare the two groups, so the evidence of the risk factor analysis was low. In our multivariate analysis, white race had higher risk of progression to MM, which may be attributed to the high frequency of SBP in white race. The progression to MM difference in SBP of spine may be partially gender-dependent, the rate of progression to MM in female patients is slightly higher than male patients. The progression to MM is in high risk in patients under chemotherapy.

In our study, the mean age of patients with SBP in spine is 63.6, and the male to female ratio is 1.68:1, which indicates that SBP in spine often occurred in older men. SBP of spine is a mass of neoplastic monoclonal plasma cells in spinal bones. This is a large-scale population retrospective study. We limit the time to 1992–2013, in order to reduce the diagnosis errors of diseases and ensure that the follow-up time is more than 5 years.

Limitations

Our research has some limitations. Firstly, some risk factors are not available in the SEER database such as tumor size, persistent myeloma and serum free light chain ratio [21]. Secondly, although the SEER database reports whether surgical intervention was performed, no data on surgical approaches and time of surgery are available in the database. Thirdly, data of the range and dose of radiation therapy, some other treatments such as immunotherapy and hormone therapy were also unable to obtain in the database. Despite these shortcomings, our study indicated that greater age, white race, female and chemotherapy were identified as independent risk factors for progression to MM. Our study represents the largest analysis evaluating the progression in patients with SBP of spine.

Conclusions

In conclusions, the present study represents the largest series with risk factors for progression to MM on patients with SBP in spine. Greater age, white race, female and chemotherapy were identified as

independent risk factors for progression to MM. It would be helpful for clinicians to evaluate patients' risk of progression to MM and counsel patients regarding the possibility of progression to MM at diagnosis of SBP in spine.

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.

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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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.

Competing interests

The authors declare that they have no competing interests.

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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	
2002-2013	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 Native	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			NI	
1992-2002	Reference			
2002-2013	0.910 (0.714-1.161)	0.450		
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			NI	
Married	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			NI	
Pre-B cell	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			NI	
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			NI	
Yes	Reference			
No	1.016 (0.812-1.271)	0.890		
Radiotherapy			NI	
Yes	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

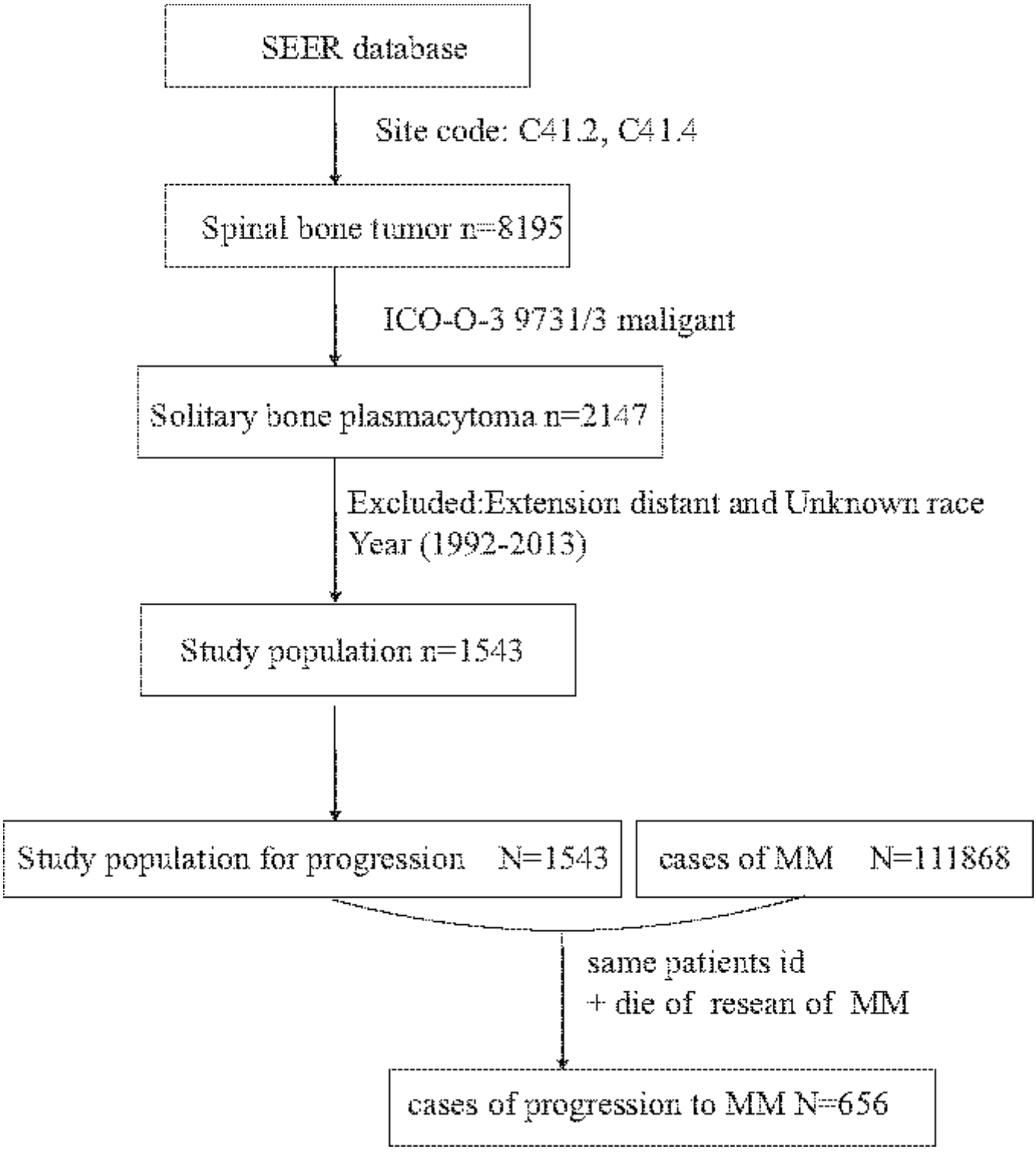

Figure 1

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