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Impact of bone events on survival in solitary bone plasmacytoma

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ABSTRACT

Background: Although much studied in multiple myeloma, bone events (BE) can also cause important morbidity in bone plasmacytoma patients. To our knowledge, the effect of BE on overall survival (OS) and progression to multiple myeloma free-survival (MPFS) also has never been studied.
Patients and Methods: Fifty-nine patients treated from 2008 to 2017 were retrospectively assessed. All patients had histological proof of disease and were treated with radical radiotherapy (RT). Available clinical information for at least 6 months follow-up or until death had to be available. BE were described as one of the following events in the index bone: fractures, osteomyelitis, chronic pain, surgery or loss of limb function after RT.
Results: Mean age at diagnosis was 57.3 years (18–80); most male (67.8%). Mean OS, bone event free-survival (BEFS), local progression-free survival (LPFS) and MPFS were 41, 36, 37 and 19 months, respectively. There were 15 deaths. BEFS ($p = 0.008$) and age>55y ($p = 0.044$) were associated with MPFS. Only BEFS correlated with OS ($p = 0.029$). BE was independently associated with both MPFS and OS in multivariate analysis.
Conclusion: BE and survival end-points were correlated. BE should be investigated in prospective trials.
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1. Introduction

Solitary plasmacytoma is a rare disease whose treatment has not had any significant evolutions in the last decades. The role of radiotherapy in the curative setting was defined in a major publication in the 1980s[1] and has since been proven to be the best practice in several other comparative trials, mostly retrospective.[2] The radiotherapy dose for curative intent has also been described over the same period[3] and remains unchanged. Thus, local control and disease cure rate as well as time for progression to multiple myeloma have been unaffected for almost 30 years.[4] Current publications try to define new approaches to this disease. Berzenje et al.[5] published in 2018 their experience with it, but their numbers, as happens to most institutions, show the same scenario as those published in the past decades.

Bone events have an impact on the quality of life for multiple myeloma (MM) patients[6] but impact on solitary plasmacytoma is not yet known. Current guidelines recommend prescription of bone-modifying agents in MM patients to prevent those events.[7] Even phase III trials have already been made to correctly address BE in this disease setting, using drugs such as zoledronic acid and denosumab[8] Nevertheless, BE incidence, mortality and currently used treatment have never been described to our knowledge. The primary goal of this study is to describe the effect of BE in survival of patients with solitary plasmacytoma.

2. Patients and methods

Between 2010 and 2017, the records of all patients with multiple myeloma or plamacytoma were retrospectively evaluated. Those who were biopsy proven and had no clinical evidence of multiple myeloma progression were assessed. The definition on multiple myeloma followed international criteria.[9] Patients with multiple lesions were excluded, as well as those with hypercalcemia, renal impairment, anemia and monoclonal bone marrow infiltration >10%.

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Included patients had to have at least 6 months follow-up on record or until death. Survival endpoints were evaluated from the date of the histopathological diagnosis: overall survival (OS), bone event free survival (BEFS), local progression-free survival (LPFS), and progression to multiple myeloma free-survival. The toxicity related to RT was evaluated according to the NCI criteria (Common Terminology Criteria for Adverse Events v4.0 - CTCAE).[10]

This project was approved by the local ethics committee (Instituto do Cancer do Estado de Sao Paulo) in November 2017 under the Brazilian federal law 466/13 Health Council Resolution and it was done under the ethical standards of the Helsinki Declaration 1975, revised in 1983.

2.1. Statistical method

The following variables were analyzed: age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, tumor location and size, type of imaging studies performed at diagnosis (radiographs, computed tomography - CT scan, positron emission tomography - PET scan, magnetic resonance imaging - MRI, ^{99m}Tc-MIBI scintigraphy - MIBI), blood plasma cells count, laboratory blood (beta-2-microglobuline, albumin, lactate dehydrogenase - LDH, creatinine, calcium, hemoglobin) and urinary (proteinuria) tests, radiotherapy dose and homogeneity, systemic treatments, and grade 3 or more late toxicities (at least 6 months after the end of treatment).

Bone event was defined as the patient having at least one of the following events in the index bone after irradiation: fracture, indication of surgery (only after RT), chronic pain, loss of function of the limb after RT or osteomyelitis. Cumulative incidence of BE, progression to multiple myeloma and death rates were recorded.

Descriptive and frequencies analysis were conducted with calculation of means, standard deviations (SD), medians and interquartile ranges (IQR). Survival estimates were calculated using the Kaplan-Meier method and the log-rank test was used for comparisons between variables. All variables with clinical significance or $p \leq 0.10$ in the univariate analysis were included in the multivariate analysis. The Cox regression method was used for the multivariate analysis. Significance level was set at 5% ($p < 0.05$). Statistical analysis was performed with the Statistical Package for the Social Sciences software (SPSS version 17, Chicago, IL, USA).

3. Results

Fifty-nine patients treated from 2008 to 2017 were retrospectively assessed. Mean age at diagnoses was 57.3 years (18–80); 67.8% were male, in an almost 2:1 ratio between males and females. Mean lesion size was 6.7 cm (1.4–22 cm). All patients were treated with external-beam radiotherapy. Most patients were treated with 45–50 Gy, with RT doses ranging from 8 Gy in a single fraction to 54 Gy in 30 fractions. Some patients also received chemotherapy, most of them due to large (> 5 cm) index lesions. All patients received chemotherapy based on cyclophosphamide, thalidomide and dexamethasone. There was no correlation between chemotherapy use and OS ($p = 0.1$), BEFS ($p = 0.908$), LPFS ($p = 0.236$) and MPFS ($p = 0.526$). More demographic information can be seen in Table 1.

Table 1
Demographic characteristics.

Variable	Number (n)	(%)	Cases of BE
Gender			
Male	40	67.8	16
Female	19	32.2	2
ECOG performance status			
0–1	48	79.6	13
2–3	5	8.4	5
4	6	12.0	0
Tumor Location			
Thoracic Spine	17	27.1	6
Lumbar Spine	5	8.4	2
Cervical Spine	2	3.3	0
Cranium	9	15.2	1
Axial bones non-vertebrae (pelvis, ribs)	17	28.8	3
Appendicular Skeleton	9	15.2	6
Staging (other than whole bone radiographs)			
PET	43	72.8	9
MIBI	26	44.0	9
MRI (index lesion)	39	66.1	16
Radiotherapy			
<30 Gy	3	5.0	2
30 Gy	6	10.1	2
30–45 Gy	15	25.4	9
45–50 Gy	34	57.6	5
>50 Gy	1	1.6	0
Chemotherapy			
Yes	23	38.9	7
No	36	61.0	11

Legend: PET = PET scan; MIBI = ^{99m}Tc-MIBI scintigraphy; MRI = magnetic resonance imaging.

Both early and late toxicities were assessed. No early grade 3 toxicities were reported. Grade 3 late toxicities occurred in 8.4% of patients. Grade 3 bladder and pulmonary toxicity occurred in one patient each and presented full resolution after clinical management with steroids. A grade 3 neurological toxicity occurred in a patient who also received chemotherapy. Two other patients presented grade 3 hematological toxicities that could not be identified because of treatment or disease progression.

The incidence of BE among our patients was 30.5% (18 patients). In 19 patients (32.2%) a BE had occurred prior to the radiation treatment. For those, only a second event was reported as BE for statistical purposes. The nature of bone events and their incidence can be seen in Table 2.

There were nine deaths during the studied period. Five patients had presented a bone event after irradiation and all except one, progression to multiple myeloma. Mean OS, bone event free-survival (BEFS), local progression-free survival (LPFS) and MPFS were 41, 36, 37 and 19 months, respectively (Figs. 1 to 3). Survivals were also reported in 5 and 10 years. For OS, BEFS, LPFS and MPFS in 5 years were 83.6%, 63%, 78.1% and 37.7%, respectively. For the same end-points in 10 years, 62.7%, 63%, 47.9% 23.6%, respectively. In the univariate analysis, none of the studied variables were associated with BEFS or LPFS (Table 3). Progression to myeloma was significantly associated with BE ($p = 0.003$) (Fig. 4) and age below 55 years

Table 2
Bone events.

Nature	Number (n)	% of BE	% in the entire sample	Mean Time to BE (months)
Disabling pain	5	27.7	8.4	5.8
Fractures	3	16.6	5.0	8.3
Osteomyelitis	2	11.1	3.3	5.4
Loss of function of the affected limb	2	11.1	3.3	4.7
Surgery	2	11.1	3.3	4.4
Spinal Cord Compression Syndrome	4	22.2	6.6	7.4
Total	18	–	30.5	4.2

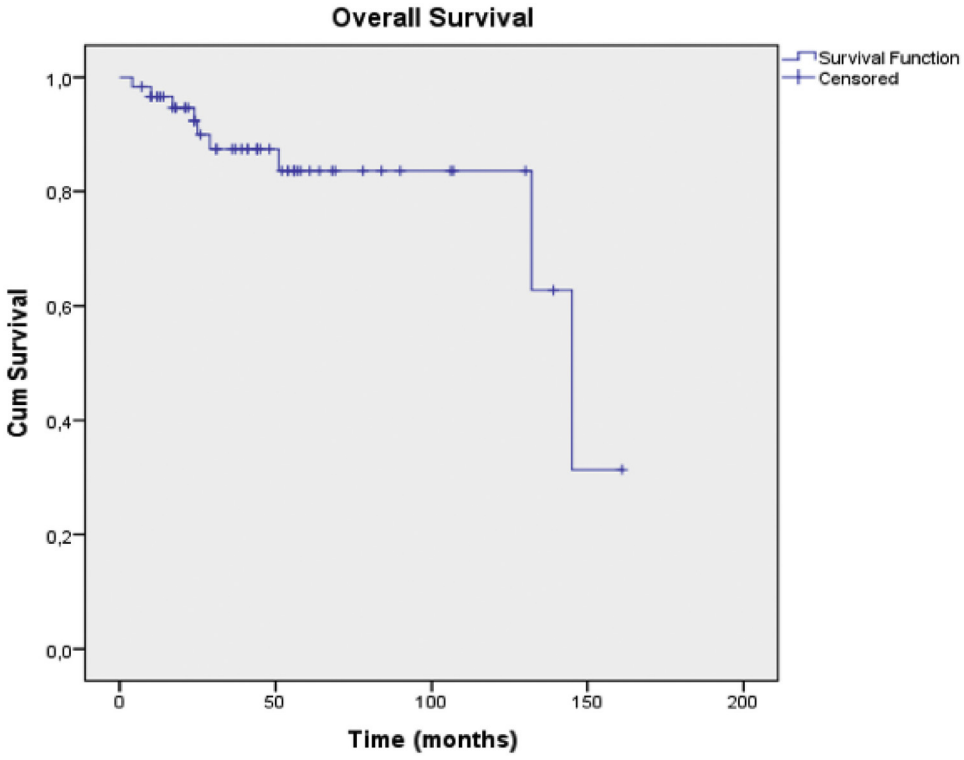

Fig. 1. Overall Survival.

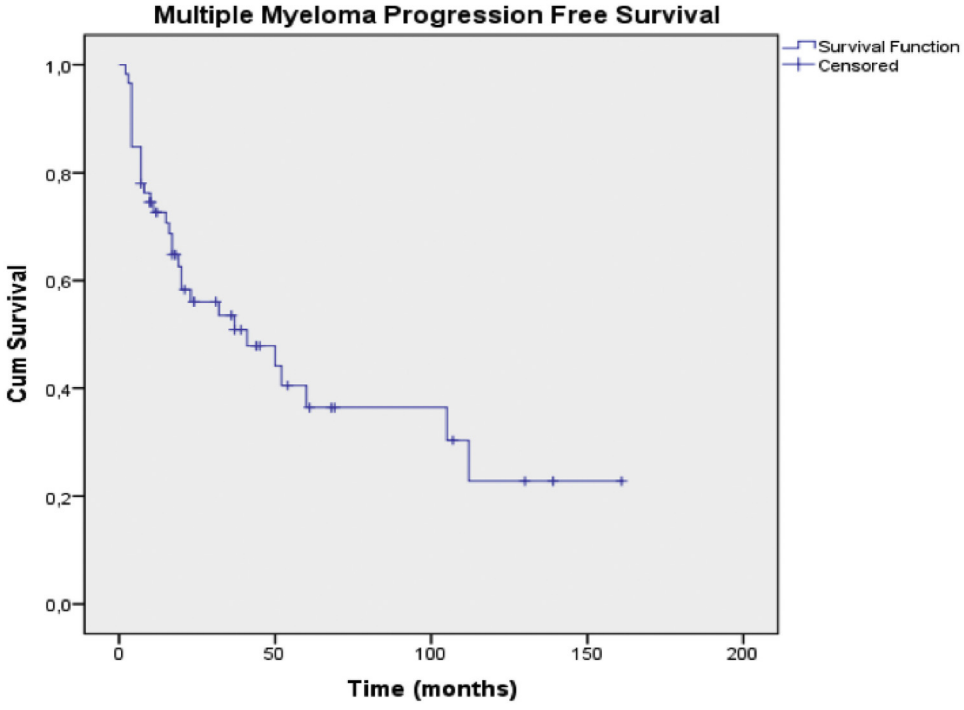

Fig. 2. Multiple Myeloma-Free Survival.

at diagnosis (p = 0.044). 13 patients with BE progressed to MM. Median time to progression to multiple myeloma was 25.0 months. Patients that had BE had a median time to progress to multiple myeloma of 21.8 months while those who had no BE had a median time of 66.73 months. OS was associated only with BE (p = 0.004) (Fig. 5). In the multivariate analysis bone event was selected as an independent adverse prognostic factor related to MPFS (p = 0.008) and OS (p = 0.029) and age below 55 years (p = 0.006) persisted as an unfavorable factor related to MPFS (Table 4).

4. Discussion

Bone events correlated directly with survival in our sample. They are not just an issue of morbidity, but they can directly impact

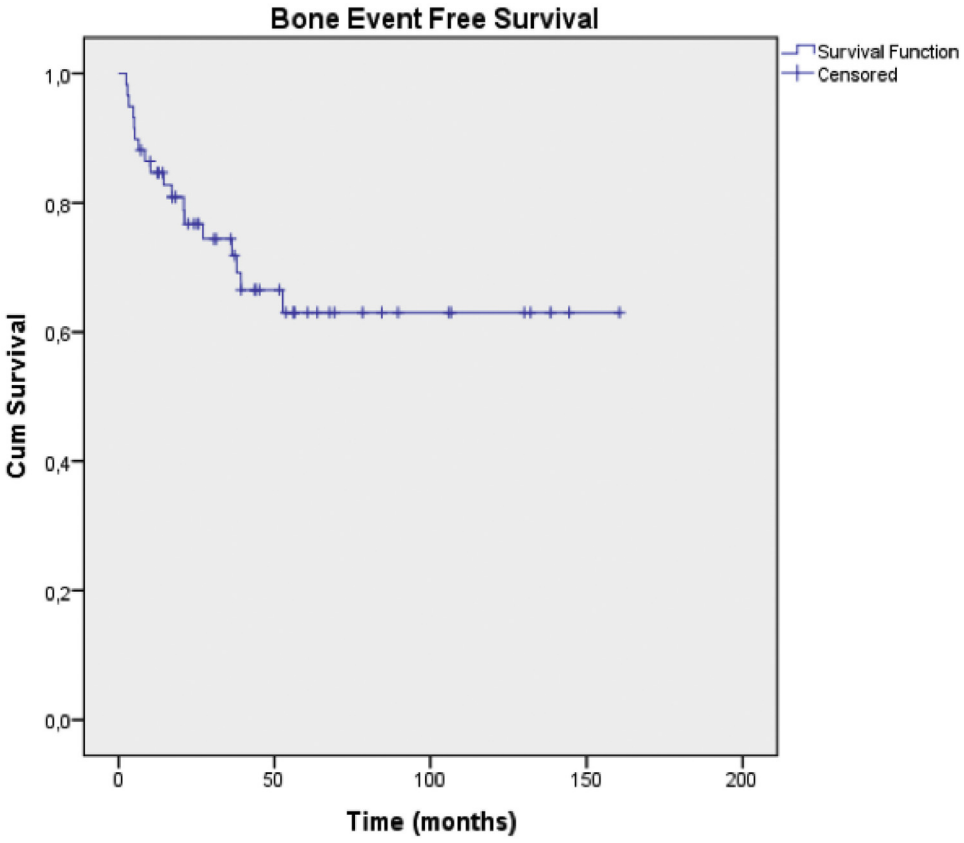

Fig. 3. Bone Event-Free Survival.

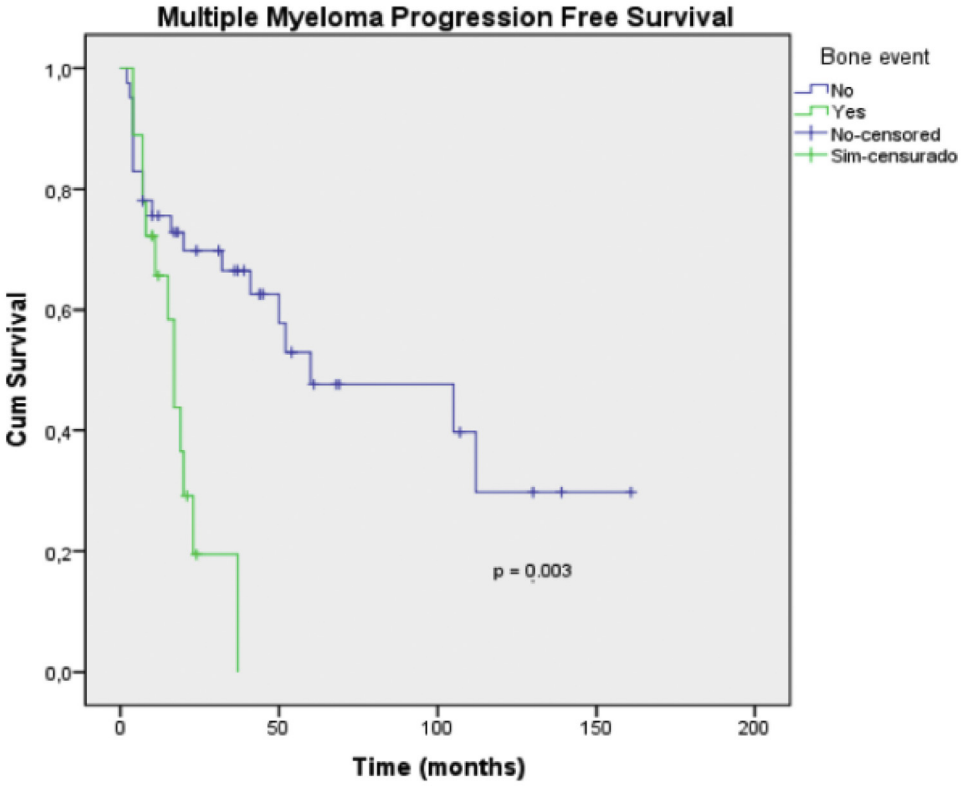

Fig. 4. Myeloma progression free survival stratified by bone events.

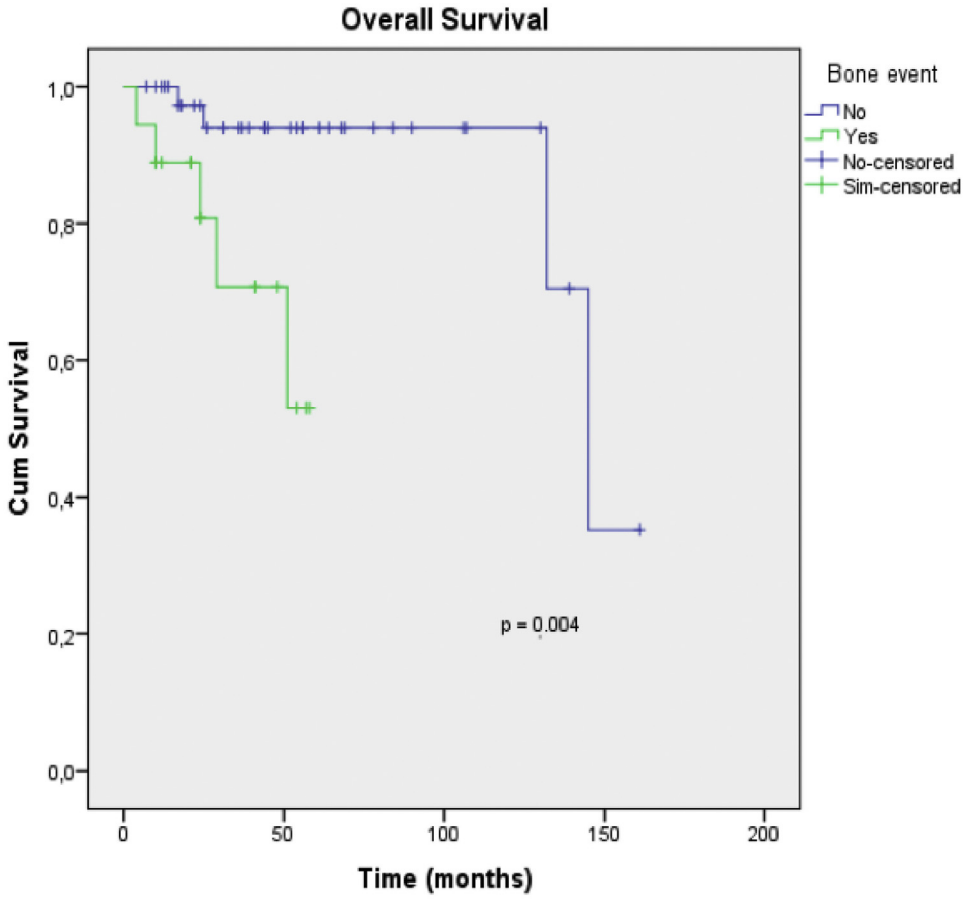

Fig. 5. Overall survival stratified by bone events.

Table 3
Bone events free survival.

	Mean (months)	5 years (%)	10 years (%)	p
BEFS (18 events)	109.0 (± 10.0)	63.0	63.0	
Gender				0.051
Male	96.8 (± 12.1)	54.8	54.8	
Female	79.6 (± 6.6)	84.2	84.2	
Age				0.735
< 55 yo	95.6 (± 13.9)	61.0	61.0	
≥ 55 yo	110.9 (± 13.0)	64.1	64.1	
ECOG				0.345
≤ 2	112.0 (± 10.5)	65.1	65.1	
> 2	39.3 (± 11.7)	44.4	44.4	
Size				0.594
< 5 cm	91.2 (± 12.9)	55.1	55.1	
≥ 5 cm	118.6 (± 17.2)	71.6	71.6	
Normal albumine				0.278
No	141.8 (± 17.6)	87.5	87.5	
Yes (≥ 3.5)	94.7 (± 9.7)	59.4	59.4	
LDH				0.517
Normal	105.1 (± 10.8)	60.7	60.7	
Abnormal	40.1 (± 2.7)	50.0	–	
Normal creatinine				0.277
No	85.0 (± 31.6)	50.0	50.0	
Yes (≤ 1.2)	100.7 (± 9.4)	63.7	63.7	
Normal calcium				0.959
No	109.1 (± 11.0)	63.1	63.1	
Yes (≥ 8.5)	96.6 (± 22.0)	61.0	61.0	
Hemoglobin				0.758
< 10	109.7 (± 30.1)	75.0	75.0	
≥ 10	107.6 (± 10.5)	61.8	61.8	
RT dose				0.725
< 40 Gy	82.8 (± 18.3)	58.4	58.4	
≥ 40 Gy	110.2 (± 11.2)	63.5	63.5	

mortality of patients with solitary plasmacytoma. It is not clear whether this direct correlation is due to mortality associated with the events; therefore, bone events being a direct cause of death among these patients; or because bone event correlates to local control and multiple myeloma progression, since it was an independent factor to both end-points, meaning that bone events are just the first event in the natural progression of this disease. Independently of the mechanism, the occurrence of bone events should be observed and taken care of in these patients. The exact influence of those events on survival still deserves further studies (Table 5).

The survival endpoints are consistent with previously published data. Literature reports a mean rate of 30-50% of patients progressing to multiple myeloma in 5 years. This can be observed in large prospective trials and in recent retrospective surveys for the last decade.[2,4,5] The rates tend to be higher with newer factors applied in the diagnosis of plasmacytoma and its differentiation to multiple myeloma, especially the introduction of bone marrow biopsy plasma cell rates and the use of beta-2-microglobulin. Our MPFS rate in 5 years was 37.7%. Only age was associated with this endpoint that was higher in an older population (55 years or more). Since our sample was staged and treated in a long period of time, differences in the diagnosis and assessment protocols can be of some importance, even though patients that did not fit in the current criteria were excluded.

Regarding our results, staging discussion was a big part of the statistical analyses. Instead of analyzing patients who were diagnosed with solitary plamacytoma in their charts, our group retrospectively reassessed staging to all patients. Some that were previously classified as solitary plasmacytoma were in fact MM and a few myeloma patients, most of them treated with 8–30 Gy RT

Table 4
Local progression free survival.

	Mean (months)	5 years (%)	10 years (%)	p
LPFS (12 events)	112.0 (± 12.1)	78.1	47.9	
Gender				0.427
Male	112.0 (± 13.3)	72.1	47.3	
Female	78.9 (± 6.7)	94.7	63.2	
Age				0.267
< 55 yo	72.3 (± 9.7)	79.0	39.5	
≥ 55 yo	122.8(± 13.4)	77.7	58.3	
ECOG				0.292
≤ 2	117.1 (± 12.3)	79.4	53.6	
> 2	69.7 (± 10.1)	66.7	0	
Size				0.084
< 5 cm	72.3 (± 12.7)	65.3	43.5	
≥ 5 cm	112.8 (± 17.2)	93.3	46.7	
Normal albumine				0.715
No	122.1 (± 22.9)	87.5	65.6	
Yes (≥ 3.5)	112.0 (± 10.6)	76.4	32.7	
Normal LDH				0.272
No	119.3 (± 7.3)	90.9	90.9	
Yes (≥ 240)	122.7 (± 13.8)	74.7	38.7	
Normal creatinine				0.813
No	98.2 (± 33.1)	53.2	53.2	
Yes (≤ 1.2)	112.1 (± 8.8)	80.9	31.5	
Normal calcium				0.857
No	118.5 (± 12.0)	73.8	65.6	
Yes (≥ 8.5)	92.0 (± 20.0)	100.0	0	
Hemoglobin				0.294
< 10	70.5 (± 1.5)	100.0	0	
≥ 10	120.1 (± 11.9)	76.4	57.3	
RT dose				0.751
< 40 Gy	92.5 (± 17.6)	64.3	64.3	
≥ 40 Gy	108.1 (± 14.1)	81.4	40.7	
Deaths				< 0.0001
No	131.7 (± 11.4)	83.4	74.1	
Yes	44.5 (± 18.4)	40.0	0	

Table 5
Toxicities.

Severe Toxicity (grade 3 and chronic as more than 6 mounths)	Number	(%)
Genitourinary	1	1.69
Gastrointestinal	0	0
Hematological	2	3.39
Neurological	1	1.69
Skin	0	0
Pneumonary	1	1.69

doses and receiving chemotherapy, were actually solitary plamacytomas in retrospect. With this procedure, our team intended to eliminate potential selection biases and population sample contamination.

A variety of radiotherapy dose was observed. Even though our institutional protocol states that the dose should be between 45–50 Gy, exception being made to vertebrae plamacytomas when dose of 44 Gy could be used, a third of patients received less bioequivalent doses. This can be explained by the fact that some patients were classified as multiple myeloma and received palliative doses to treat only bone pain before they were correctly assessed and staged. Some patients in this setting received complementary doses so the bioequivalent doses were higher than 45 Gy, but this was not the case in almost 35% of our sample. It's important to highlight that BE lacked a direct correlation with RT doses. There was no correlation between RT doses and BE or local control. Therefore, one cannot stipulate that the low doses received by some patients in our sample were responsible for BE and disease progression. Again, staging of this disease is is of utmost importance and both radiation oncology and hematology teams must apply correct criteria.

The criteria used to define bone events were more comprehensive than of other trials used in multiple myeloma. Surgery was sometimes offered to patients who were not in an emergency setting and some indications of surgery were not clear in the patients' charts. Since most trials exclude from their end-points surgeries performed for reasons not directly correlated to local progression, this can be considered as a new information derived from our cohort. In addition, osteomyelitis as a possibility of bone event was also addressed in our study. We considered this to be a very important event to describe morbidity due to the direct impact of the disease and its treatment to patients' quality of life and it also corresponded to the impact directly in the disease-specific end-points.

Our data shows new information in the management of solitary bone plasmacytoma. Since morbidity caused by bone events can be directly correlated to survival, like in other oncological settings, a multidisciplinary team is needed. Almost half of our patients were treated with doses lower than recommended for curative intent. This indicates that correct staging should be performed for any treatment decision, and the radiation oncologist should always observe criteria to multiple myeloma before favoring any treatment. Any decision made, therefore, should have the best outcome to the bone integrity in mind.

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Conflict of interest

None.

Financial disclosure

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