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Solitary plasmacytoma: should new approaches in diagnosis and treatment be adopted?

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ABSTRACT

Background: Radiotherapy (RT) is the gold standard for solitary plasmacytomas (SP) with great local control. The influence of radiotherapy as well as factors on multiple myeloma (MM) progression is unknown.

Materials and methods: We present a retrospective study of 27 patients with SP (bone-SBP- and extramedullary-SEP-), treated since 1995 to 2021. We aim to analyze prognostic factors affecting local control and progression to MM in patients treated with radiotherapy (RT).

Results: Mean age was 57.3 years. 22 were SBP and 5 SEP. 13 patients were treated with definitive RT, and 14 with a combination of RT and systemic treatment and/or surgery. Local control was observed in 91.5% of cases. 28% experienced progression to MM. With a median follow up of 61.4 months [39.5, 121.6], 5-years MM-free-survival was 81 ± 8%; no individuals progressed further 50 months since diagnosis. Large tumor bulk (> 5 cm) and type (SBP 36% *vs*. SEP 0%) were associated with progression. Progression was not affected by doses greater than 46 Gy and/or surgery. An immunophenotype different from IgG kappa was predictive of less progression (p = 0.031) in Cox regression analysis adjusted for age, RT dose and tumor bulk > 5 cm. Patients with positron emission tomography-computed tomography (PET-CT) staging showed less MM progression, without statistical differences.

Conclusion: RT achieves more than 90% of local control. The immunophenotype IgG kappa showed more risk of progression to MM. Initial staging with PET-CT seems to lead to a better identification of SP. The inclusion of bad prognosis patients in clinical trials would determine the role of adjuvant chemoimmunotherapy in SP treatment.

Key words: solitary plasmacytoma; multiple myeloma; radiotherapy; IgG kappa; PET-CT

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Introduction

Solitary plasmacytoma (SP) is a plasmatic tumor with exclusively local involvement in bone or soft tissue, without radiological evidence of bone involvement at another level [1, 2], without organ involvement (hypercalcemia, renal failure or anemia) [1, 3], with absent or minimal (< 10%) bone marrow infiltration [3]. Histologically, it is composed of a sheet of monoclonal plasma cells at different stages of maturation [4].

It is a rare tumor; it accounts for less than 5% of plasma cell neoplasms [1–3] and has an annual incidence of < 450 cases in the United States [3]. It affects more frequently men between the ages of 50 and 60 [5].

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Two separate entities have been categorized: bone solitary plasmacytoma (SBP) and soft tissue-extramedullary plasmacytoma (SEP) [2], the first being the most frequent (70 *vs.* 20–30% [1, 2]) and with a higher risk of progression to multiple myeloma (MM) at 5 years (56 *vs.* 30%, p = 0.021 [2, 6], practically reaching a rate of 100% at 15 years [1, 7]). The most common bone location is the axial skeleton, the most frequent location of the SEP is the head and neck region (paranasal sinuses, nasal cavity and nasopharynx) [2, 4, 5, 8, 9].

Historically, the diagnosis has been made by skeletal survey. With the evolution of diagnostic techniques and greater availability, computed tomography (CT), magnetic resonance imaging (MRI) [10] and, more recently, positron emission tomography (PET)/CT, have been progressively incorporated.

Regarding treatment, the standard of care in most cases is exclusive radiotherapy [1, 2], with doses between 40–50 Gy with excellent long-term local control (79–91%) [1, 2, 11, 12]. The 5-year overall survival rate is 78% [2, 3, 7], with a 5-year local control of 81-96% with no differences between the two entities [9, 10, 14], and a 5-year progression-free survival to MM of 53% [2, 7].

The purpose of our study is to analyze in a group of patients survival rates, progression to MM, and prognostic factors of the disease, as well as to study the impact of incorporating new diagnostic studies, both imaging and molecular, and their possible influence on the evolution of the disease.

Materials and methods

Patient cohort and study design

The present retrospective observational study involved a population of 27 patients with solitary plasmacytoma who were assessed and treated in a tertiary hospital in Madrid (Spain) between 1995 and 2021. Initially, 42 patients were selected; excluded from the analysis were those who met criteria for MM at the time of diagnosis, who had other hematological malignancies, who were misclassified with solid tumors of other origins and patients with insufficient clinical information. The entire cohort had been treated with radiotherapy, and we had their signed informed consent to use their clinical data for research studies.

Data analysis

General data were collected (sex, date of birth, age at diagnosis, general clinical situation at diagnosis according to the Eastern Cooperative Oncology Group (ECOG) scale, as well as data related to tumor characteristics at diagnosis [tumor size, type (bone or extramedullary), location, quantitative bone marrow infiltration by pathology and by flow cytometry], immunohistochemical and molecular characteristics (percentage of plasma cells by flow cytometry, plasma cell immunophenotype, serum monoclonal component, presence of Epstein Barr virus), laboratory values [levels of serum calcium, albumin, total serum protein, lactate dehydrogenase (LDH), beta 2 microglobulin, serum creatinine, hemoglobin, leukocytes, platelets, kappa and lambda light chains, serum free light chain ratio, immunoparesis, proteinuria, urine immunofixation, urine light chains], imaging technique used for diagnosis (skeletal survey, CT, MRI, PET/CT), characteristics of the treatment received (type of treatment, start and end dates of radiotherapy, total treatment time, dose administered equivalent dose in 2 Gy fractions (EQD2), number of fractions, type of fractionation, radiotherapy technique, volume of treatment, lymph node irradiation), and outcome parameters [tumor response, toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 scale], serum paraprotein persistence after treatment, type — local *vs.* MM — of progression, date of progression, last follow-up date, clinical situation at last follow-up and cause of death if applicable).

Statistical analysis

Data were analyzed using the SPSS statistical program, version 25 (SPSS, Inc., Chicago, IL, USA).

Quantitative results were expressed by mean and standard deviation or by median and interquartile range. We used the Kolmogorov-Smirnov test to determine if the quantitative parameters had a normal distribution. The percentages and absolute values were presented as qualitative parameters.

Categorical variables were compared using the Chi-square test and Fisher's exact test, as appropriate. The Student's t-test for independent variables was used to analyze whether the means of two data sets were significantly different.

Survival, progression to multiple myeloma, and the association with variables such as age,

tumor size greater than 5 cm, presence of an immunophenotype other than IgG kappa, or the radiation therapy dose, were calculated with Kaplan Meier analysis and Cox regression. The covariates included in the multivariate analysis were selected based on clinical criteria and the results of the univariate analyses.

In all analyses $p < 0.05$ was considered statistically significant, with a confidence interval of 95%.

Results

A total of 27 patients were analyzed, 20 were male (74%). The mean age at diagnosis was 57.3 years (40–83.8). The patients clinical and functional status at the time of diagnosis, according to the ECOG scale, was 0 in 8 (29%), 1 in 14 (52%), 2 in 4 patients (15 %) and 3 in one case (4%).

82% of the tumors (n = 22) were SBP, and 18% (n = 5) were SEP. 40.7% of them were located in the vertebrae, 18.5% in the head and neck region, 14.8% in the pelvis, 11.1% in the ribs, 11.1% in the upper extremities and 3.7% in the lung. Mean size was 114 mm (12.67–390.52), 59.3% of the tumors were greater than 5 cm and just 3.7% greater than 20 cm.

At time of diagnosis analytical profiles were as described in Table 1.

Different imaging techniques were used for diagnosis, such as skeletal survey, CT, MRI and PET/CT, with the latter diagnostic technique being performed in 48% of patients.

After analyzing the biopsies of solitary plasmacytoma, the immunohistochemistry distribution was as follows: immunoglobulins (Ig) IgG kappa 40.7%, IgG lambda 11.1%, IgA 7.4%, kappa 14.8% and lambda 18.5%. The bone marrow infiltration by plasma cells determined by cytomorphology was 2% (1, 5). Flow cytometry was performed in 59.3% of the patients. The proportion of plasma cells by flow cytometry was 0.31% (0.18, 0.70), presenting pathological immunophenotype in 14.8% of cases. 76.2% of the patients presented serum monoclonal component, with a median of 0.02 mg/dL (0.0, 0.42). Urine immunofixation was positive in 35.5%. The ratio of serum free light chains was less than 8 in 93.8% and greater than 20 in 6.3%. No cases of immunoparesis were detected.

Exclusive radiotherapy was performed in 48.1% of the patients, exclusive surgery in 3.7% and combined treatment in the remaining ones, which could be radiotherapy combined with surgery, with

Table 1. Patients characteristics

Variables	Global (n = 27)
Age [years]	57.3 ± 12.1
Sex [n (%)]	
Male	20 (74.1)
ECOG [n (%)]	
0	8 (29.6)
1	14 (51.9)
2	4 (14.8)
3	1 (3.7)
Immunophenotype PC [n (%)]	
Kappa	4 (16)
Lambda	5 (20)
Ig G kappa	11 (44)
Ig G lambda	3 (12)
Ig A	2 (8)
Serum calcium [mg/dL]	9.25 ± 0.42
Serum albumin [g/dL]	4.14 ± 0.37
Total serum proteins [g/dL]	7.2 (6.9, 7.7)
LDH [U/L]	196.1 ± 54.54
B2 microglobulin [mg/L]	2 (1.3, 2.24)
Cr [mg/dL]	0.87 ± 0,2
Hb [g/dL]	14.58 ± 1.44
Serum free light chains [mg/dL]	
Kappa	3.21 (1.57, 4.46)
Lambda	1.66 (1.14, 3.25)
Urine free light chains [mg/dL]	0.0 (0.0, 7.8)
PET scan [n (%)]	
Yes	13 (48.1)
No	14 (51.9)
Treatment received [n (%)]	
Radiotherapy	13 (48.15)
Surgery	1 (3.7)
Combined treatment (Radiotherapy and/or surgery and/or systemic treatment)	13 (48.15)
Dose n (%)	
≤ 46 Gy	11 (44)
> 46 Gy	14 (56)
Fractionation [n (%)]	
Normofractionation	22 (88)
Hypofractionation	3 (12)
MM progression [n (%)]	
Yes	8 (29.6)
No	19 (70.4)

ECOG — Eastern Cooperative Oncology Group scale; PC — plasmatic cell; LDH — lactate dehydrogenase; Cr — creatinine; Hb — hemoglobin; WBC — white blood count; Gy — Gray; PET — positron emission tomography scan; MM — multiple myelom

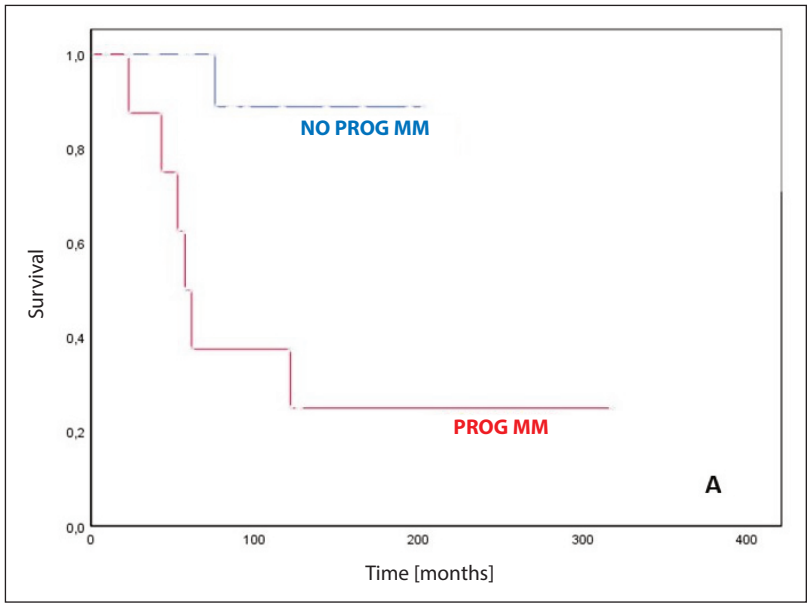

Figure 1. Overall survival according to progression (PROG) to multiple myeloma (MM) (p* = 0.002)

systemic treatment or both. The patients who received radiotherapy were treated with a dose of 45 Gy (40, 46.5), 56% of the cases received a dose greater than 46 Gy, conventional fractionation in 88%, in 22 fractions (20, 23), in a total treatment time of 31 days (28, 35.5), and a mean volume of 195 cc (163, 1108). 84% received conformal 3D radiotherapy, 8% IMRT and 8% 2D. 2 patients received lymph node irradiation associated with local tumor irradiation.

88.5% of the patients presented complete response to treatment, and 11.5% showed stable disease. Toxicity profile of the radiotherapy treatment was favorable, with 52% of the patients presenting no toxicity, 20% grade 1, 24% grade 2 and 4% grade 3, with no cases of grade 4 or higher toxicity.

With a median follow up of 61.37 months [39–121], 5-year MM-free-survival was 81±8%; no individuals progressed further 50 months since diagnosis. In 2 cases (7.4%) progression was local; one of them subsequently progressed to myeloma. In the remainder (n = 7), progression was to multiple myeloma, all cases occurring in bone-type plasmacytomas. Among the patients who progressed, 2 of them died from the disease. At the end of follow-up, 66.7% of the patients were without evidence of disease and 18.5% were still alive but with multiple myeloma (Fig. 1).

The comparative analysis showed that the subgroup of patients who did not complete their diagnosis with a PET/CT had higher rates of progression than those who did (42.9% *vs.* 15.4%, p = 0.127). Achieving a complete response after local treatment was not associated with a lower risk of progression to MM. None of the patients who progressed had received systemic treatment. The subgroup of extramedullary plasmacytomas presented greater overall survival than bone plasmacytomas (p = 0.162) (Fig. 2).

IgG kappa immunophenotype was associated with larger tendency to progression to myeloma 71.4% *vs* 28.6%, although not statistically significant (p = 0.102). In the multivariate analysis, the presence of an immunophenotype different from IgG kappa was a protector from progression to myeloma regardless of age, larger tumor size, or the dose of radiotherapy received, hazard ratio (HR) 0.079 (p*= 0.032). No other variable was a predictor of progression to myeloma in the multivariate analysis.

Discussion

The diagnosis and treatment of solitary plasmacytomas have not undergone substantial changes in the last 20 years. The high rate of progression from solitary plasmacytoma to multiple myeloma after radical treatment with radiotherapy invites us to identify the profile of patients who present a higher risk of progression and to consider whether an in-

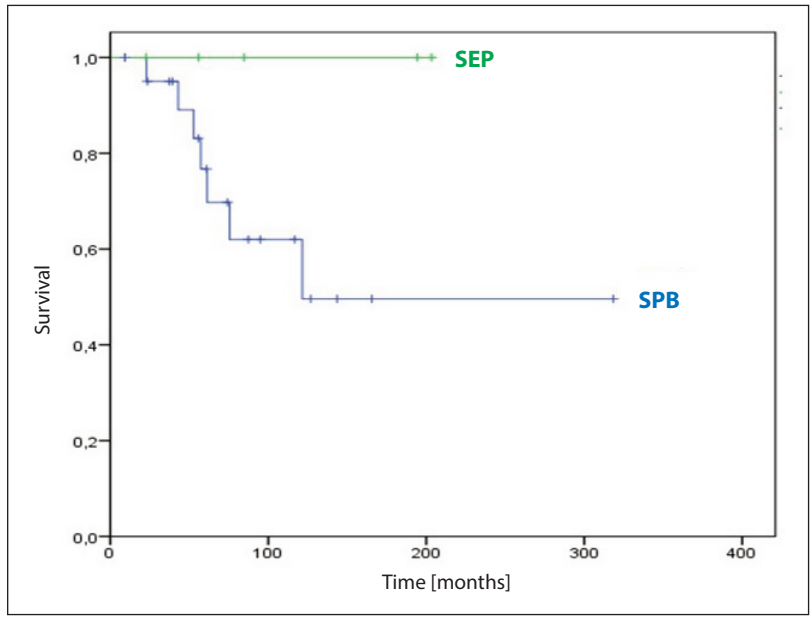

Figure 2. Overall survival according to bone (SPB; blue line) *vs*. extramedullary (SEP; green line) solitary plasmacytoma in 27 patients; p = ns

tensification of treatment could reduce this evolution to MM. On the other hand, the relatively high percentage of early relapse (14.8% during the first 2 years in our series) raises the possibility that staging with classical techniques, such as skeletal survey, may be insufficient to detect hidden disease.

PET studies are increasingly applied for the diagnosis of solitary plasmacytoma, given its high sensitivity (86.7–93.3%) [15]. The most recent update of the MM NCCN clinical practice guidelines (version 03.2023) recommend the performance of FDG PET/CT as the first option for initial diagnostic workup in extramedullary solitary plasmacytomas and as a second option for solitary bone plasmacytomas, if whole body MRI is not available [16]. It should be taken into account that PET also has limitations, such as difficulty in detecting tiny lytic bone lesions, especially those close to the skull, or less sensitivity than MRI for detecting early diffuse bone marrow infiltration [1, 15]. In our series, there was a higher rate of progression in patients in whom PET was not performed (42.9%) than in those who did have such study (15.4%). This may be due to cases of underdiagnosed disseminated disease, which has been described in previous papers. Schirrmeister et al. in 2003 prospectively studied 15 patients; in 5 of them the PET/CT showed 20 lesions that had not been detected with conventional imaging tests [17]. Nanni et al. modified the diagnosis from solitary plasmacytoma to MM in 43% of their patients after performing a PET [18]. In 35% of the patients analyzed by Kim et al. the PET results influenced their treatment [19]. In view of these results, it seems relevant to complete the diagnostic workup with a PET/CT, to improve staging and adequacy of treatment.

A high percentage of patients with solitary plasmacytoma, mainly SBP type [1, 20], progress to MM during the first years after diagnosis (median 1.6 years [range 0.28–12.03] [20, 21] 5 years MM free survival (MMFS) of 44.1% and 10 years MMFS of 36.7% [22]). Some poor prognostic factors that increase the risk of progression to multiple myeloma have been described. The most frequently described are: bone type [2], age over 60 years (p= 0.03) [9, 21], presence of serum paraprotein at diagnosis (60% progression to MM at 5 years *vs*. 39 %, p = 0.016) [2], bone marrow involvement (56–70% progression rate to MM at 2–3 years) [23, 24], an abnormal serum free light chains (SFLC) ratio at diagnosis [25], elevated B2 microglobulin (p = 0.03) [7], tumor size greater than 4 or 5 cm [7, 9, 26], radiotherapy dose below 45 Gy [7, 27, 28], and persistence of paraprotein after radiotherapy treatment ≥ 5g/L [10, 29].

There is little evidence showing an association between plasmatic cell´s immunophenotype and progression to MM. In the present study, we ob-

served that IgG kappa plasmacytomas had a greater tendency to progress to MM than other types, so we grouped the cases in two: IgG kappa or another Ig type. In univariate analysis, having an immunophenotype different from IgG kappa appeared as an independent protective factor for progression to MM, HR 0.143 (0.027–0.760) (p* = 0.023). This data was confirmed in the multivariate analysis HR 0.079 (0.008–0.808) (p* = 0.032). On the contrary, Gun Suh et al., 2012, observed better progression free survival to MM in those patients with bone plasmacytomas and IgG immunophenotype than in those with other immunoglobulin subtypes (p = 0.04) [7]. Previously, Greipp et al., 2005, demonstrated better survival in patients with MM and IgG immunophenotype over IgA or light chains [30]. Therefore, there is insufficient evidence to allow for an intensification of treatment of solitary plasmacytomas based on immunophenotype.

In our series, age was also associated with progression to MM in the univariate analysis, HR 1.082 (1.011–1.158) (p* = 0.022). This aligns with previous studies, such as the multi-institutional of Ozsahin et al. who analyzed 258 patients, in which older age was associated with greater progression to MM, lower progression-free survival, and lower overall survival [9], and the study by Tsang et al. which presented a HR 1.1 (p = 0.0013) for disease-free survival, and HR 1.05 (p = 0.037) for myeloma-free rate [26] in older patients. In the same way, an association between younger age and higher MM-free survival was demonstrated in a multicenter study with 80 patients, HR 0.295 (p = 0.027) [21].

In our study, as in the studies of Alghisi et al. 2020 or Kilciksiz et al. 2008 [20, 21], tumor size > 5 cm, B-2 microglobulin, hemoglobin, SFLC ratio, or radiotherapy treatment dose were not predictors of progression to MM.

A strength of our series is that it is one of the few that study the poor prognostic factors of evolution to MM, as well as the association between performing a PET study at the diagnosis of PS and progression to MM. Up to now, it has not been possible to demonstrate any predictive factor for progression to MM, which would justify therapeutic intensification, for instance incorporating systemic treatment to primary treatment. As weaknesses, the small sample size, or the retrospective and single-center nature of the study do not allow us to make recommendations on the management of these tumors.

From the radiotherapy treatment point of view, its excellent results on local control and low rate of toxicity, possibly improved by the development of IGRT, allow radiotherapy to continue to be considered standard of care for PS, especially for SEP.

Given the low incidence of PS, multicenter prospective studies should be carried out to allow us to establish prognostic associations which could help improve the evolution of this disease. However, our study emphasizes the importance of PET staging with the aim of ruling out subclinical disease and starting early treatment on patients who present as MM. In addition, identifying the immunophenotype as a prognostic factor for progression to MM or the influence of paraprotein persistence after RT treatment should be incorporated as predictive variables for progression to MM in future studies.

Conclusion

RT has demonstrated a local control rate of over 90%, underscoring its efficacy in the treatment of SP. However, a higher risk of progression to MM has been observed in cases with the IgG kappa immunophenotype. This finding suggests the importance of considering immunophenotyping as a key predictive factor when assessing the risk of progression to MM in patients with SP.

The use of PET-CT in initial staging appears to offer significant advantages in the accurate identification of solitary plasmacytomas. This technique, with its high sensitivity, could play a crucial role in the detection of subclinical lesions and contribute to a better approach in the early management of patients with SP.

A promising avenue for clinical research in the treatment of SP is the potential inclusion of patients with poor prognosis in clinical trials. This strategy could provide valuable insights into the potential role of adjuvant chemotherapy and immunotherapy in the treatment of solitary plasmacytomas. The identification and categorization of these high-risk patients could be fundamental to the personalization and improvement of treatment options, thereby opening the door to more advanced and effective approaches.

In conclusion, radiotherapy is highly effective in the local control of solitary plasmacytomas, while immunophenotyping and the initial use of PET-CT are emerging as critical aspects in assessing the risk of progression to multiple myeloma and improving lesion identification. Exploration of additional therapeutic strategies, such as adjuvant chemotherapy and immunotherapy, by enrolling high-risk patients in clinical trials may represent a significant breakthrough in the treatment of solitary plasmacytomas.

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Conflict of interests

The authors have no relevant financial or non-financial interests to disclose. All authors have approved the final article.

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Authors contribution

Co-Authors: C.G.S: — conceptualization, methodology, supervision; V.E.D.P. — investigation; L.B.G. — validation; P.M.N — resources; F.F. — investigation; C.E.C. — writing-review and editing

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