Mediterranean Journal of Hematology and Infectious Diseases

Review Articles

Solitary Plasmacytoma

Sara Grammatico, Emilia Scalzulli and Maria Teresa Petrucci

Hematology, Department of Cellular Biotechnologies and Hematology, "Sapienza" University, Rome, Italy

Competing interests: The authors have declared that no competing interests exist.

Abstract. Solitary plasmacytoma is a rare disease characterized by a localized proliferation of neoplastic monoclonal plasma cells, without evidence of systemic disease. It can be subdivided into solitary bone plasmacytoma if the lesion originates in bone, or solitary extramedullary plasmacytoma if the lesion involves a soft tissue. The incidence of solitary bone plasmacytoma is higher than solitary extramedullary plasmacytoma. Also, the prognosis is different: even if both forms respond well to treatment, overall survival and progression-free survival of solitary bone plasmacytoma are poorer than solitary extramedullary plasmacytoma due to its higher rate of evolution in multiple myeloma. However, the recent advances in the diagnosis of multiple myeloma can better refine also the diagnosis of plasmacytoma. Flow cytometry studies and molecular analysis may reveal clonal plasma cells in the bone marrow; magnetic resonance imaging or 18 Fluorodeoxyglucose positron emission tomography could better define osteolytic bone lesions. A more explicit exclusion of possible occult systemic involvement can avoid cases of misdiagnosed multiple myeloma patients, which were previously considered solitary plasmacytoma and less treated, with an unavoidable poor prognosis.

Due to the rarity of the disease, there is no uniform consensus about prognostic factors and treatment. Radiotherapy is the treatment of choice; however, some authors debate about the radiotherapy dose and the relationship with the response rate. Moreover, the role of surgery and chemotherapy is still under debate. Nevertheless, we must consider that the majority of studies include a small number of patients and analyze the efficacy of conventional chemotherapy; few cases are reported concerning the efficacy of novel agents.

Keywords: Solitary Plasmacytoma, Myeloma, Radiotherapy, Osteolytic Lesions.

Citation: Grammatico S., Scalzulli E., Petrucci M.T. Solitary Plasmacytoma. Mediterr J Hematol Infect Dis 2017, 9(1): e2017052, DOI: http://dx.doi.org/10.4084/MJHID.2017.052

Published: August 23, 2017 **Received: May 16, 2017** **Accepted: July 21, 2017**

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nc/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Correspondence to: Maria Teresa Petrucci, MD, Hematology, Department of Cellular Biotechnologies and Hematology, Via Benevento 6, 00161 Rome, Italy. Tel +39 06 49974430, Fax +39 06 441639810. E-mail: petrucci@bce.uniroma1.it

Incidence, Signs and Symptoms and Diagnostic Criteria. Solitary plasmacytoma (SP) is an uncommon type of plasma cell (PC) dyscrasia that accounts for approximately 2-5% of all PC disorders.[1-3] It is characterized by a localized proliferation of neoplastic monoclonal PCs, with no radiologic evidence of additional skeletal lesions, absence of signs and symptoms of multiple myeloma (MM), present in the CRAB manifestation (hypercalcemia, renal insufficiency, anemia and/or bone lesions), and a bone marrow examination morphologically normal or having a very low clonal PC infiltration (less than 10%).[4,5]

Due to the rarity of this disease, there are few studies about it and not a true consensus about the prognostic factors and treatment. Here, a literature

review was performed to identify relevant articles about SP. PubMed, National Guideline Clearinghouse Cochrane Database of Systematic Reviews and ClinicalTrials.gov electronic databases were used for the search. Also oncology and hematology conference proceedings (European Hematology Association (EHA), American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH) and International Myeloma Working Group (IMW) were used. The search was restricted to documentation published in human subjects. Case reports were excluded. In **Table 1 A** and **1 B** the key points of the most relevant articles (limited to those published over the last 20 years) are summarized.

SP can be subdivided into two entities: solitary bone plasmacytoma (SBP) and solitary extramedullary plasmacytoma (SEP), depending on whether the lesion originates in bones or soft tissues.[6] The incidence of SBP is approximately 40% higher than SEP.[3]

The median age at diagnosis of SP is 55-60 years, significantly lower than in MM patients; the male to female ratio varies from 1,2:1 to 2:1.[3,6,7-10]

Some authors report a higher incidence rate of SP in the black race, around 30% more than white race;[3,9,10] African American to Caucasian incidence rates ratio to develop SP was found to be approximately 1.25/1.30.[9,10] Incidence in Asian population is lower than previous ones; however, its cohort of patients studied is small (about 5.4%).[3] In fact, it is important to consider that the majority of studies refer to a predominantly Caucasian population.

SBP most frequently occurs in the axial skeleton, such as a vertebra, while SEP is observed in the head and neck, and these two entities have a clinical course and prognosis that are quite different from each other.[2,3,5-7,11-17]

All these data reported are prevalently based on historical studies; there are few series reported in the most recent years. However, last year, de Waal et al. reported the experience between 1988 and 2011 in the northern area of the Netherlands about 76 SP patients, confirming the historical data. Median age was 61 years (range 26–87), and 60% were male; 66% had an SBP, localized in the axial skeletal in 78% of these patients. In the SEP patients, the plasmacytoma was most frequently located in the oropharynx or nasopharynx (65%).[18]

In the largest and most recent cohort analyzed, Thumallapally et al. published a retrospective study of 1691 SP diagnosed in the United States of America (USA) from 1998 to 2007, analyzing and reporting data from the Surveillance, Epidemiology and End Results (SEER) database, a population-based registry in the USA. The median age at diagnosis was 60.38 ± 14.22 years. The male to female ratio was 1.7:1. The cohort was predominantly Caucasian (80%) followed by African American (14%) and other races (5.4%). More favorable outcomes were recorded for Caucasians and patients of other races relative to the African American cohort, but these differences were not statistically significant (59.1% vs. 57.6%, p = .083). Bone was the most common site of involvement (57.78%). Additionally, 831 (49%) and 146 (8%) patients had axial and appendicular skeletal involvement, respectively, while PC proliferation in soft tissues was noted in 540 patients (32%). In patients with SEP, the most commonly encountered site was the upper airway tract (12%).[10]

Signs and symptoms that patients usually refer are a pain due to: bone destruction, spinal cord and/or nerve root compression or compression and enlargement of the soft tissue involved.

Diagnosis of SP needs:

- history and physical examination,
- complete blood count, white blood cell differential, platelet count,
- serum chemistry for creatinine, albumin, corrected calcium,
- serum LDH and Beta-2 microglobulin,
- serum quantitative immunoglobulins and serum protein electrophoresis,
- 24-h urine for total protein, Bence Jones protein, and urine protein electrophoresis,
- serum Free Light Chain (FLC) assay,
- bone marrow aspiration and biopsy,
- skeletal survey [at least radiography, and/or computed tomography (CT), magnetic resonance imaging (MRI) or 18 Fluorodeoxyglucose positron emission tomography (FDG-PET)].

In particular, diagnosis of SBP requires a solitary bone lesion confirmed by the skeletal survey, the clonal PC infiltration lower than 10% proven by biopsy, and lack of myeloma-related organ dysfunction.

Diagnosis of SEP requires a tissue biopsy indicating monoclonal PC histology, bone marrow

Table 1A. Keypoints of the most relevant articles from 1999 to 2009.

Authors	Characteristics	Key points
Liebross et al, 1999.[13]	22 patients with SEP.	LC is achieved in 95% of cases and disease never reappears in regional nodes. The 5-year rate of freedom from progression to MM is 56% and the median survival is 9.5 years.
Galieni et al, 2000.[7]	46 patients with SEP.	The disease is most frequently localized in the upper airways. Incidence in males and females is similar. The therapeutic strategy varies, although the most frequent form of treatment is local radiotherapy. The 15 year survival rate is 78%.
Tsang et al, 2001.[37]	46 patients with SP: 32 with SBP and 14 with SEP.	Bone presentation and older age are predictive of progression to MM and poorer DFS. Tumor size (< 5 cm) affects LC rate. Anatomic location do not predict outcome. Lower radiotherapy dose (<35 Gy) is not associated with a higher risk of local failure.
Dingli et al, 2006.[16]	116 patients with SBP.	Abnormal serum FLC ratio and persistence of M protein are negative prognostic factors.
Knobel et al, 2006.[41]	206 patients with SBP.	In multivariate analyses, favorable factors are younger age and tumor size < 5 cm for survival; younger age for DFS; anatomic localization (vertebra vs. other) for LC. Older age is the only predictor for MM. There is no dose-response relationship for doses 30 Gy or higher, even for larger tumors.
Ozsahin et al, 2006.[38]	258 patients with SP: 206 with SBP and 52 with SEP.	On multivariate analyses, the favorable factors are younger age and tumor size <4 cm for OS; younger age, extramedullary localization, and radiotherapy for DFS; small tumor and radiotherapy for LC. Bone localization is the only predictor of MM development. There is no dose–response relationship for doses >30 Gy, even for larger tumors.
Kilciksiz et al, 2008.[8]	80 patients with SP: 57 with SBP and 23 with SEP.	On multivariate analyses, the favorable factors are radiotherapy dose of ≥50 Gy and radiotherapy + surgery for PFS and younger age for MFS. For the SBP patients the favorable factor is younger age for MFS. Radiotherapy at ≥50 Gy and radiotherapy + surgery may be favorable prognostic factors on PFS.
Dores et al, 2009.[3]	Incidence rates, incidence rates ratios and 5-year relative survival for plasmacytoma overall and by site – SBP and SEP – in the SEER Database (1992− 2004).	Incidence of SBP is 40% higher than SEP. Compared with Whites, the Black race incidence rate is ~ 30% higher for SP. 5-year relative survival varies significantly by age (<60/60+ years).
Jawad et al, 2009.[9]	1164 SP patients identified in the SEER database (1973-2005).	5- year survival for patients that don't progress to MM is significantly better. Age > 60 years is the only factor that correlates with progression of disease.

SP: solitary plasmocytoma; SBP solitary bone plasmacytoma; SEP solitary extramedullary plasmacytoma ; LC local control; MM multiple myeloma, DFS disease-free survival; FLC free light chain; Gy Gray; OS overall survival; PFS progression-free survival; MFS myeloma-free survival; SEER Surveillance, Epidemiology and End Results.

Table 1B. Keypoints of the most relevant articles published in the last decade.

Authors	Characteristics	Key points
Suh et al, 2012.[42]	38 patients with SP: 16 with SBP and 22 with SEP.	SBP patients more frequently progress to MM than SEP patients. Radiotherapy with doses ≥40 Gy demonstrates better LC in SBP. In the multivariate analysis, elevated β2-microglobulin is a significantly unfavorable prognostic factor affecting OS.
Hill et al, 2014.[28]	OMD measured by MFC in 50 SBP patients.	Progression has been documented in 72% of patients with OMD vs 12.5% without. Monoclonal ULC are similarly predictive of outcome because progression has been documented in 91% vs 44% without.
Katodritou et al, 2014.[43]	97 patients with SP: 65 with SBP and 32 with SEP.	OS, MMFS, PFS and PFRS are better for SEP than SBP. In the multivariate analysis, prolonged PRFS and young age are positive predictors of OS. Achievement of CR is the only positive predictor of PRFS. Immunoparesis is the only negative predictor of progression to MM. The addition of chemotherapy or novel agent-based treatment increases toxicity without offering any survival advantage over radiotherapy.
Li et al, 2015.[53]	38 patients with SP: 16 with SBP and 22 with SEP.	Radiotherapy alone is associated with significantly higher 5-year LPFS, MFS, PFS and OS.
De Wall et al, 2016.[18]	76 patients with SP, 34% with SEP and 66% with SBP.	SBP patients have a higher risk of developing MM. No association could be shown between angiogenesis parameters and progression to MM.
Finsinger et al, 2016.[27]	53 patients with SP: 35 with SBP and 18 with SEP.	SBP patients have a significantly worse OS and PFS compared to SEP patients. On univariate analysis, bone disease and size (≥5 cm) impact negatively on PFS. Bone disease also affects OS. In multivariate analysis bone location is the only independent prognostic factor for PFS and OS.
Paiva et al, 2016.[29]	OMD measured by MFC in 64 patients with SP: 35 with SBP and 29 with SEP.	Flow-positive SBP patients have significant higher risk to develop MM. No significant differences have been observed among SEP cases.
Thumallapally et al, 2017.[10]	1691 SP patients identified in the SEER database (1998-2007)	In univariate analysis the survival outcomes are better for younger male patients who receive radiotherapy with surgery. Patients who receive neoadjuvant radiotherapy have increased survival rates compared to those receiving adjuvant radiotherapy. The 5-year survival rates for patients with axial plasmacytoma are superior when radiotherapy is combined with surgery. In the multivariate analysis, age <60 years and treatment with either radiotherapy or surgery show superior survival rates. Age >60 years is associated with a lower 5-year survival in patients who progress to MM.

SP: solitary plasmocytoma; SBP solitary bone plasmacytoma; SEP solitary extramedullary plasmacytoma ; LC local control; MM multiple myeloma; Gy Gray; OS overall survival; PFS progression-free survival; MFS myeloma-free survival; OMD occult bone marrow disease ; ULC urinary light chains; PFRS plasmacytoma relapse-free survival; LPFS local progression-free survival; MFC multiparameter flow cytometry; SEER Surveillance, Epidemiology and End Results.

clonal PC infiltration less than 10% of all nucleated cells, the absence of osteolytic bone lesions or other tissue involvement without CRAB.

Recent advances have improved the precision of diagnosis. Flow cytometry studies and molecular detection of heavy- and light-chain gene rearrangements may reveal clonal PCs in the bone marrow. MRI or FDG-PET that are more sensitive tests than conventional skeletal survey could better define patients with systemic disease at diagnosis.[19] In addition, quantitation of kappa and lambda chains not bound to intact immunoglobulin molecules in the serum (FLCs), can define more precisely the diagnosis of MM. This test allows the determination of clonality based on the involved/uninvolved serum FLCs ratio, which needs to be ≥100 according to the most recent diagnostic criteria of MM.[20]

Solitary extramedullary and bone plasmacytoma show non-specific CT and MRI imaging findings. Usually, the MRI appearance of SBP is consistent with that of a focal area of bone marrow replacement; the signal intensity is similar to muscle on T1-weighted images and hyperintense about muscle on T2-weighted images. MRI is the modality of choice for soft tissue evaluation; also, MRI of the axial skeleton has been shown to be superior to whole body X-rays and is recommended in patients with SBP of the spine and suspected cord or nerve root compression.[21] FDG-PET is the modality of choice for assessment of the skeletal abnormalities.[22-25] Recently an abnormal involved serum FLC value and the presence of at least two hypermetabolic lesions on FDG PET at diagnosis of SP were reported as the two predictors of early evolution.[26]

Some patients with SP have a small monoclonal protein (also called M protein) detectable in the serum and/or in the urine; more frequently SBP than SEP. The percentage in SBP varies from 24% to 72% of patients in different reports; levels of uninvolved immunoglobulins are usually normal.[6,16] In SEP M protein is detected less frequently (about 20% of cases).[7,13,27] Moreover, Dingli et al. reported in 116 SBP that the FLC ratio was normal in 53% patients and abnormal in 47%. Patients with an abnormal FLC had a higher incidence of monoclonal protein in the urine ($p < 0.001$) and a larger serum M- protein ($p = 0.04$).[16]

Finally, Hill e Paiva reported the importance of multiparameter flow cytometry (MFC) for detecting clonal PCs in the bone marrow;[28,29] the presence of "minimal occult" bone marrow disease indicates a high risk of progression for SBP patients and could suggest a tailored of patients' follow-up. Conversely, flow diagnostic criteria may also allow the accurate identification of "true" SP, characterized by flow-negative bone marrow and absence of M protein, which would represent a signature for the possibility of cure.

Therefore, nowadays, a correct diagnosis of SP must include the modern techniques as MFC and FLC detection in addition to FDG-PET or MRI for the study of bone lesions. Here we present a possible diagnostic algorithm for SP divided into three different steps of examinations (**Figure 1)**.

Prognostic Factors. For SP, it is hard to identify prognostic factors. Several authors reported various parameters that influence the outcome of these patients, such as age, lesion size, localization (bone or soft tissue) and the presence of M protein at the onset and that could disappear after therapy.[5,13,17,22,30-39] However, these adverse prognostic features have not been consistent between series.[13,31,36,40,41]

In our previous study, in univariate analysis, the only adverse prognostic factor for overall survival (OS) was the bone localization rather than the extramedullary localization. In fact, we could demonstrate a statistically significant difference between the two groups regarding 5- and 10-year OS probability, with SEP showing a longer survival probability. Regarding progression-free survival (PFS), the two adverse prognostic factors in univariate analysis were bone disease and the larger size of the lesion (>5 cm). In multivariate analysis, the only significant independent prognostic factor was the bone localization compared to the extramedullary localization, both regarding OS and PFS. It must underlie that we identified some important differences between SBP and SEP patients, particularly a prevalence of serum M protein and larger tumor size in SBP. We did not observe significant differences in terms of OS and PFS between patients with age greater or lower than 60 years.[27]

SBP versus (vs.) SEP. Other authors reported poor prognosis of SBP in comparison with SEP. Ozsahin et al. reported in SBP a median time to

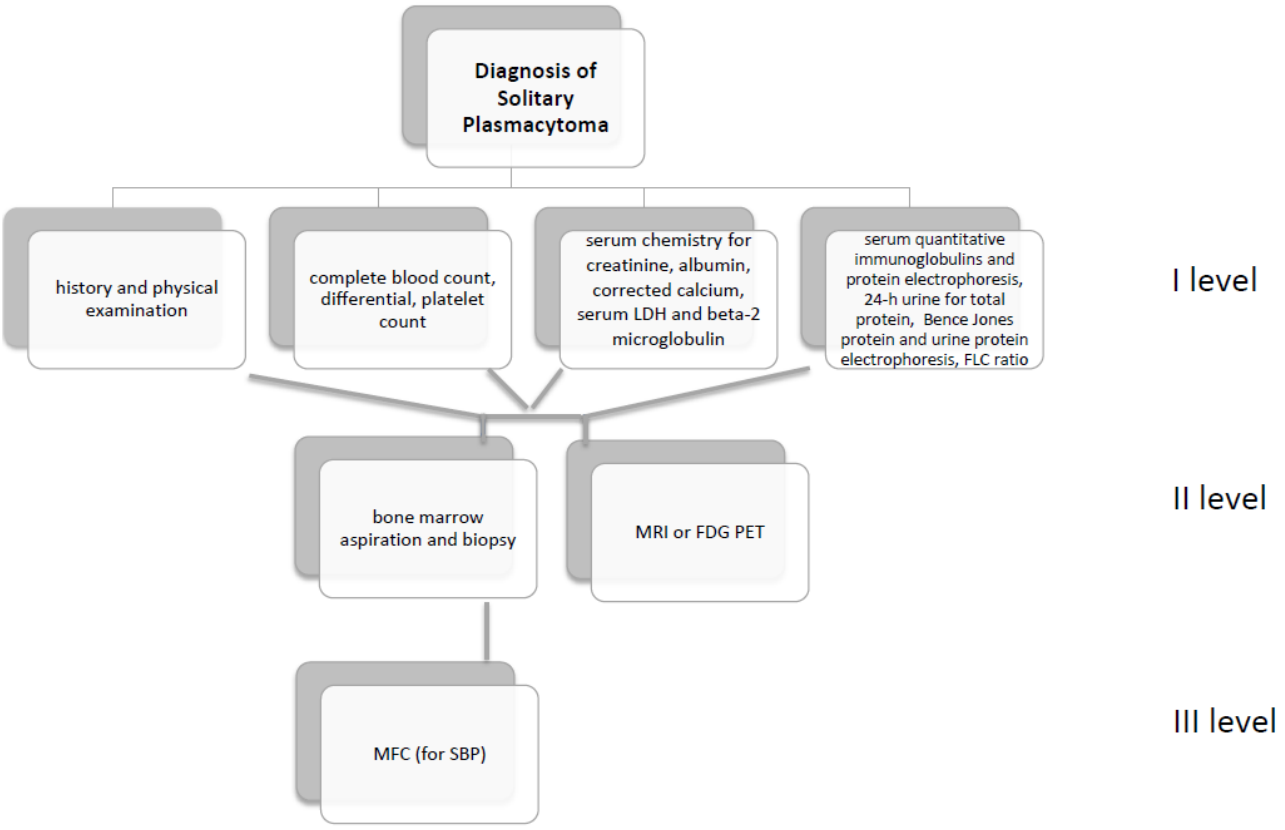

Figure 1. Diagnostic algorithm for SP divided in 3 different steps.

MM development of 21 months (range 2–135), with a 5-year probability of 45%. The 5-year OS, disease-free survival (DFS) and local control (LC) rate (considered as the resolution of the tumor mass and associated symptoms in the treatment area, with no subsequent evidence of local tumor progression) was 74%, 50%, and 86%, respectively. SBP had a significantly higher risk of progression to myeloma at a rate of 65–84% in 10 years and 65–100% in 15 years. In spite of a curative treatment, the median time to progression to MM was 2 to 3 year.[38] However, some authors reported that the median OS in patients with SBP was 10 years, and 10% to 20% of patients died of unrelated causes.[6]

Also, a recent review by Suh et al. confirmed that SBP progressed more frequently to MM compared with SEP (p = 0.02). In fact, the Myeloma-free survival (MFS) rate of SEP was 71.2 % both at 10-year and 5-, whereas the rates of SBP were at 10-year 36.4 % and 0 %, at 5, respectively. The median time of MFS in SBP was 36 months, while SEP was not attained because of its low progression rate to MM. The median time of progression to MM following diagnosis was 45 (range, 8–142) and 25 (range, 4–108) months in SEP and SBP, respectively. The 5- and 10-year PFS rates for all patients were 43 % and 25 %, respectively. Patients with SBP demonstrated worse PFS rates compared with SEP patients; however, this difference was not statistically significant (p = 0.16).[42] Also, the Greek experienced recently reported a 5 and 10-year OS of 92% and 89% in SEP and 86% and 69% in SBP, respectively (p = 0.2). The 5- and 10-year MFS probability was 90% and 70% for patients with SEP vs. 59% and 50% for patients with SBP, respectively (p = 0.054). Overall, the 5- and 10-year OS probability, plasmacytoma relapse-free survival (PRFS), PFS and MFS was 84% and 78%, 72% and 58%, 58%, and 43%, and 70% and 59%, respectively. In addition, in this study, impairment of humoral immunity (immunoparesis), defined as a suppression of at least one uninvolved immunoglobulin (i.e., for IgG<700 mg/dL, for IgA <70 mg/dL and IgM<40 mg/dL), was the only negative predictor of progression to MM.[43]

On the contrary, less than 30% of patients with SEP develop systemic progression; some groups reported that the median time to progression to systemic disease is approximately 2 years.[2,33,44] Liebross et al. reported an LC rate in 95% of patients with SEP. MM developed in 32%: the 5-

year rate of freedom from progression to MM was 56%, and the median survival was 9.5 years.[13] Galieni et al. achieved complete remissions in 85% patients, 11% of partial remissions and 4% of non-response to therapy. Local recurrence or recurrence at other sites occurred in 7.5% and 10% of patients, respectively. Moreover, 15% of patients developed MM. The 15-year survival rate was 78%, and the diffusion-free survival was 83%.[7]

Recently de Wall et al. confirmed all these data in his cohort of 76 SP patients. Among SBP patients, 70% progressed to MM with a median time to progression of 19 months (range 5–131). In SEP patients, 3 (12%) progressed to MM after 6, 33 and 71 months. The 5-year PFS was significantly different between SBP and SEP (38% vs. 93%, p = 0.0001). However, the OS between SBP and SEP was not significantly different (p = 0.294) with an OS of 70% vs. 81% at 5 years and 64% vs. 77% at 10 years, mainly because 4 SEP patients died within 5 years of diagnosis due to disorders unrelated to MM. No association with progression to MM was observed except for the location of the plasmacytoma.[18]

Moreover, this year, the German group examined the survival of patients with rare PC and plasmacytoid malignancies (SP, MM, and lymphoplasmacytic lymphoma) in Germany compared to that in the USA in a period from 1998 to 2012. In Germany, patients with SP had a 5-year relative survival (RS) of 56.5%, with a lower survival for intraosseous (47.7%) versus extraosseous (62.0%). Five-year RS estimated for USA patients with SP was higher at 62.3%, with survival for patients with intraosseous SP at 60.4% and extraosseous SP at 67.8%. Survival trends between 2003 to 2007 and 2008 to 2012 were compared. Five-year age-adjusted RS for patients with LPL/SP increased in Germany, from 69.2% between 2003 and 2007 to 74.2% in the period 2008 to 2012. In the USA, overall 5-year age-adjusted RS for these conditions went from 73.3% to 76.8%. Similar increases were seen for both men and women. However, 5-year RS increased more for patients with LPL with smaller increases observed for SP. A better identification of SP might be related to the survival improvement.[45]

Table 2 A and **B** summarize the results of the most relevant series of SBP and SEP cases, highlighting the better results for SEP regarding LC rate, progression to MM and OS.

Age, sex, and race. Numerous studies reported a substantial impact of age on the outcome; age> than 55 or 60 years is considered poor prognostic factor.[3,9,17,38,41,46] Recently, Thumallapally et al., in the retrospective analysis on 1691 SP, noted the highest survival rates for the younger age group (<40 years), while patients aged 60 years or older had the most unfavorable outcomes (87.45% vs. 45%, p < 0.05). Moreover, males had a higher chance of survival than females (63.7% vs. 52.9%, p < 0.05), and Caucasians and other races had more favorable outcomes respect to the African American cohort, but these differences were not statistically significant (59.1% vs. 57.6%, p = 0.083).[10] Recently, El-Fattah et al. also reported black race as a poor prognostic factor.[46] However, in the past, Dores did not find differences in survival between males and females or whites and blacks,[3] while Jawad reported poorer prognosis for races different from Caucasian or African American, even if other races represented only the 4.2% of the cohort analyzed in the study.[9]

Tumor size and localization. Different authors agree on the importance of tumor size as a prognostic factor[33,38,41] and the impact of extramedullary involvement vs. bone involvement.[36,38]

For example, Tsang et al. showed that patients with lesions < 5 cm had an LC rate of 100%, whereas patients with larger tumors had a rate of nearly 40%;[37] similar results were obtained by Knobel et al..[41] Other reports suggested a more favorable prognosis for SBP of the appendicular than an axial skeleton in some,[30] but not all studies confirmed this.[41] In a recent large retrospective USA study, there was no substantial difference in 5-year relative survival between SBP occurring in the axial or appendicular skeleton.[3]

M protein and FLC. Wilder et al. reported that, in multivariate analysis, the persistence of M protein more than one year after radiotherapy was the only independent adverse prognostic factor for MFS (p = 0.005) and cause-specific survival (p = 0.04). Most patients with M protein that persisted for more than one year after radiotherapy were diagnosed with MM within 2.2 years of treatment.[30,47]

Dingli et al. created a risk stratification model based on 2 variables of FLC ratio and M protein

Table 2. Results of the largest series of solitary bone plasmacytoma- SBP (**table 2 A**) and solitary extramedullary plasmacytoma - SEP (**table 2 B**). SEP shows better LC, MMP and OS than SBP.

Table 2A

SOLITARY BONE PLASMACYTOMA

Authors	N.	FU (m)	LC (%)	MMP (%)	OS (%)
Bataille et al, 1981 [30].	114	>120	88	58	68
Frassica et al, 1989 [31].	46	90	89	54	45
Galieni et al, 1995 [34].	32	69	90	43	49
Tsang et al, 2001 [37].	32	96	78	64	/
Wilder et al, 2002 [47].	60	94	90	60	59
Knobel et al, 2006 [41].	206	54	79 (at 10 y)	72	52
Ozsahin et al, 2006 [38].	206	56	74	72	52
Kilciksiz et al, 2008 [8].	57	28	94	4,1y	68
Suh et al, 2012 [42].	16	50	80	100	33
Katodritou et al, 2014 [43].	65	60	58	79	69
Li et al, 2015 [54].	16	55	/	30	84
De Wall et al, 2016 [18].	26	89	/	70	64
Finsinger et al, 2016 [27].	35	107	/	57	51

Table 2B

SOLITARY EXTRAMEDULLARY PLASMACYTOMA

Authors	N.	FU (m)	LC (%)	MMP (%)	OS (%)
Liebross et al, 1999 [13].	22	/	95	32	56
Galieni et al, 2000 [7].	46	118	92	15	78
Tsang et al, 2001 [37].	14	96	93	16	/
Ozsahin et al, 2006 [38].	52	56	68	36	72
Kilciksiz et al, 2008 [8].	23	28	95	7.4y	89
Suh et al, 2012 [42].	22	50	77	29	87
Katodritou et al, 2014 [43].	32	60	69	21	89
Li et al, 2015 [54].	22	55	/	6	94 (at 5y)
De Wall et al, 2016 [18].	50	89	/	12	77
Finsinger et al, 2016 [27].	18	107	/	5	88

FU: follow-up. LC: Local Control. M: months. Y: years. MMP: multiple myeloma progression (at 10y). OS: overall survival (at 10y).

level. Patients with a normal FLC ratio at baseline and M protein level less than 5 g/L at 1 to 2 years following diagnosis were considered low risk, patients with either risk factors were considered intermediate risk and high risk with both risk factors. The corresponding progression rates at 5 years were significantly different in the low, intermediate, and high groups: 13%, 26%, and 62%, respectively ($p < 0.001$).[16]

Occult Bone Marrow Disease (OMD). Recent studies have demonstrated that more careful examination of the bone marrow in SBP patients identified a clonally related PC population in 68% of the patients. The presence of this occult bone marrow disease (OMD) is of prognostic significance and is highly predictive of progression to MM, with a time to progression of 18– 26 months.[28,29] The high predictive value of OMD and the short PFS supports the potential use of the systemic treatment in addition to local radiotherapy in this high-risk group of SBP.

Paiva et al. examined 64 patients newly diagnosed with SP, 35 with SBP and 29 with SEP, respectively. MFC on the bone marrow was performed; an antigen combination including CD19, CD38, CD45, and CD56 was systematically evaluated, allowing for identification of the bone marrow PCs compartment by strong CD38 expression and intermediate side-scatter signal, and detection of clonal PCs by the recognition of aberrant phenotypic expression profiles. Patients were defined as flow-positive when ≥ 20 PCs were detectable by MFC, at a sensitivity level of 10^{-4}. Clonal PCs were detected in 28 of the 64 patients with SP (44%; flow-positive), and slightly more frequently in those cases with SBP (49%) compared with SEP (38%). Among patients with SBP, 71% displaying clonal PCs progressed into MM, in contrast to only 6% among flow-negative patients ($p < 0.001$). Median time to progression (TTP) was significantly shorter if bone marrow clonality was present (26 months vs. not reached; hazard ratio, 17.4; $p < 0.001$). Among patients with SEP, only 20% of flow-positive cases evolved into MM as compared with 6% of flow-negative patients, and TTP was not significantly different. Therefore OMD evaluation seems to be relevant only in SBP cases. It is important to notice that there was no correlation between the level of M protein and the number of clonal PCs in the bone marrow.[29]

In the same year, Hill et al. analyzed 50 patients with SBP with MFC. OMD was defined as a discrete population of phenotypically aberrant PCs comprising >30% of total bone marrow PCs. Aberrant phenotype PCs, indicative of OMD, were demonstrable in 34 of 50 (68%) patients. Progression was documented in 72% (26/34) of patients with OMD compared with 12.5% (2/16) without, and the median TTP was 26 months vs not reached ($p = 0.003$).[28]

The presence of urinary light chains (ULC) was also predictive of progression because it was documented in 91% (10/11) of patients with ULC vs. 44% (15/34) without (median TTP, 16 vs. 82 months, $p < 0.001$). When both parameters were assessed, progression was documented in 75% (24/32) of patients with OMD and/or ULC but in only 7.7% (1/13) who lacked both parameters (median TTP, 23 months vs. not reached $p = 0.001$).

However, it is important to have a common flow method for the detection of clonal PCs.[48]

Therapy.

Radiotherapy. Due to the rarity of the disease, there are no randomized studies regarding the best treatment approach, and the available data from small case series are somewhat controversial.

Radiotherapy is the treatment of choice for SP, although its efficacy has been tested only in small retrospective series.[5,14,41,49] So far, no clear relationship has been documented between response and radiotherapy dose. Some authors suggested a dose of 40-50 Gy for smaller lesions and >50 Gy for larger lesions (>5cm).[5,14,22,31,41] In contrast, others authors have shown that <35 Gy are effective for lesions <5cm, while lesions >5 cm should be treated with >40-50 Gy.[32,33,37] The multicentre study of the Rare Cancer Network, which has analyzed more than 258 patients with SP and a series of 46 SP patients treated at the Princess Margaret Hospital, produced no evidence of improvement regarding LC with radiotherapy doses >30-35 Gy.[37,38] This datum is in contrast with other series where it is asserted that radiotherapy doses >45-50 Gy provide better local response rates.[32,33] In our series, patients received a median dose of 41 Gy (range 21-88), substantially in agreement with the data reported

in the literature without differences between lower or higher doses of 40 Gy.[27]

Considering the most recent published works, Kilciksiz et al. reported the 10-year probability of OS of 73% in all patients with SP, 68% in 57 patients with SBP, and 89% in 23 patients with SEP, respectively. The corresponding median PFS values were 3.5 years (95% CI: 2.25–4.81), 3.2 years (95% CI: 1.99–4.37), and 7.4 years (95% CI: 0.57–14.33), respectively. On multivariate analysis, only the radiation therapy without surgery and lower radiation doses (<50 Gy) were significantly associated with lower PFS ($p = 0.035$ and $p = 0.044$). The median MFS values were 4.8 years (%95 CI 1.46–8.24), 4.09 years (%95 CI:2.41–5.77), and 7.45 years (%95 CI: 0.00–14.98) for SP group, SBP and SEP subgroups, respectively.[17]

At the same time, Suh et al. didn't observe a significant dose–response relationship in patients with SEP; however, radiation doses ≥40 Gy significantly increased the 5-year LC rates compared to radiation doses <40 Gy in patients with SBP (100 % vs. 60 %, $p = 0.04$).[42]

Surgery and radiotherapy. Even data about the role of the surgery in SP are controversial. Surgery, a milestone for the histologic diagnosis (biopsy or partial/total deletion of the lesion), is considered a specific treatment for plasmacytomas for distinct localizations (spine with neurological damage, upper airway that cannot be treated with radiotherapy, or vertebral fractures that require stabilization).[42,50]

Radical surgery of SEP of the neck and head with curative intent is often a mutilating procedure; because these tumors are highly radiosensitive, radical surgery should be avoided. However, for SEP of other sites, surgical removal, if feasible, could be considered. Because these cases are rare, it is unclear whether additional treatment with radiotherapy is necessary for resected SEP with clear surgical margins.[2,17]

Alexiou et al. reviewed 714 cases with lesion found in the upper aerodigestive tract and other 155 found in other body regions. Patients with non-upper aerodigestive tumor had a similar risk of recurrence no matter they received radiotherapy, surgery or combined treatments. Interestingly, for upper aerodigestive tract SEP, higher OS and PFS were detected in those receiving surgery plus radiotherapy.[12] In addition, a research including 57 SBP and 23 SEP showed that surgery plus radiotherapy resulted in significantly longer PFS, compared with radiotherapy alone (median PFS 7.4 years vs. 2.6 years).[8] Also, Sasaky et al. reported that radiotherapy combined with surgery was the lone significant prognostic factor for OS of SEP in the head & neck area ($p = 0.04$).[50]

More recently, Gerry et al. reported that SEP in the head & neck area responded better to surgery than radiotherapy or surgery plus radiotherapy,[51] while some researcher held a contrary opinion.[52,53]

Li et al. revealed that radiotherapy alone could be considered as a more effective treatment for SP over surgery; also Jawad et al. did not report an advantage of surgery alone or radiotherapy plus surgery in SBP.[54]

Recently, in the retrospective study by Thumallapally et al. 825 patients (49%) received radiotherapy and 197 (12%) underwent surgery, while 359 patients (21%) required both radiotherapy and surgery. According to the localization treatment varied; SBP patients received radiation prevalently only. Patients with SEP of upper airway tract and the central nervous system received radiotherapy plus surgery prevalently; whereas those with the lower airway tract involvement received radiotherapy only or neither radiotherapy nor surgery, and those with gastrointestinal tract localization were more frequently treated with surgery only. The survival rates of patients treated with radiotherapy were significantly higher than those of patients who did not receive radiotherapy (64.4% vs. 48.6%, $p < 0.05$). Moreover, patients who received neoadjuvant radiotherapy had a greater chance of 5-year relative survival than those who received adjuvant radiotherapy (86% vs. 73%, $p < 0.05$). A significant difference in survival was also observed in patients who underwent surgery when compared to patients who did not (69.7% vs 57.4%, $p < 0.05$). Analyzing the 5-year relative survival of different treatment modalities in relation to the primary site, patients with axial skeletal involvement treated with a combination of radiotherapy and surgery had a higher survival rate (70.5%) than those who received only radiotherapy (61.5%) or surgery (46.4%) ($p < 0.05$). Patients with upper and lower airway tract involvement had a higher survival with surgery alone when compared to combination therapy and radiotherapy (96.7%, 100% $p < 0.05$ and $p < 0.01$,

respectively). Patients with involvement of the appendicular skeleton (63.6%), central nervous system (92.6%) and other sites (excluding gastrointestinal, skin and connective tissues, lymph nodes) (64.4%) had an increased survival rate when treated with radiation alone ($p = 0.024$, $p < 0.05$, $p = 0.004$, respectively). In contrast, patients diagnosed with soft tissue SEP and lymph node SEP obtained better survival outcomes when received a combination treatment ($p = 0.69$ and $p = 0.83$, respectively), but the differences were not statistically significant. In the multivariate Cox regression treatment with either radiotherapy (HR 0.597, $p < 0.001$) or surgery (HR 0.764 $p < 0.001$) were all independent predictors of higher OS. Combination therapy did not appear to be significant in the multivariate analysis (HR 1.226, 95% CI 0.966-1.552, $p = 0.094$). Five hundred – fifty-three patients (32.7%) had progressed to MM during the median follow-up of 9.7 years.[10]

Chemotherapy. To date, the role of chemotherapy remains controversial; some authors suggest its combination with local radiotherapy also for patients with initial SBP. There is only one prospective study that has suggested a benefit of combined treatment compared to radiotherapy alone.[55] Here, 53 patients with SBP were randomly assigned to be treated with either local radiotherapy with doses ranged from 40 to 50 Gy to achieve LC of disease (28 patients) or the same radiotherapy schedule followed by melphalan and prednisone given every 6 weeks for 3 years (25 patients). After a median follow-up of 8.9 years, DFS and OS were improved in patients who were treated with combined therapy; 22 patients remain alive and free of disease in the combined treatment group compared to only 13 patients in the radiotherapy group ($p < 0.01$). Another retrospective study showed favorable effects related to melphalan-based chemotherapy in preventing MM development[32] but in a small series of patients. Other studies did not report any benefits of chemotherapy.[33,35,37,43] Also in our study, we failed to observe significant differences in favor of chemotherapy compared to radiotherapy.[27]

Regarding the use of novel agents, the Greek group reported the experience of 97 SP. Eighty patients (82.5%) received radiotherapy alone or in association with chemotherapy or surgery. Twenty-seven patients received novel agents: particularly 22 bortezomib-based regimens and 5 immunomodulatory drugs (IMiDs). However, the addition of chemotherapy or novel agents increased toxicity without offering any survival advantage over radiotherapy.[43]

The Mayo Clinic group has recently shown a strong correlation between a high degree of bone marrow angiogenesis and a more rapid progression to MM, in histological specimens from patients with SBP.[56] Thus, the use of drugs that inhibit angiogenesis and/or act on the bone marrow microenvironment (such as IMiDs and proteasome inhibitors) may represent a novel therapeutic approach also in SP.

Discussion. SBP and SEP are rare forms of localized PC dyscrasia; these two entities have a clinical course and prognosis that are quite different from each other. The updated guidelines recommend to exclude the possibility of a systemic disease: therefore, all patients with plasmacytoma should undergo a complete staging that includes: at least whole body X-rays of the skeleton, bone marrow biopsy and blood tests to rule out full-organ damage. However, given the recent innovations regarding a diagnosis for MM, a spine MRI or FDG-PET, serum FLC ratio, immunoglobulin levels and MFC should be introduced even for the diagnosis of plasmacytoma (**Figure 1)**. In fact, a better definition of a possible systemic disease, often underestimated, should reduce the percentage of patients with SP that evolve in MM. Percentage of evolution in MM is higher in SBP (more than 60%) respect to SEP (less than 30%), with a lower PFS and OS of SBP than SEP. In general progression to MM develop in 2-3 years.

Due to the rarity of the disease, there are no randomized studies about the best treatment approach, and data reported in the literature are controversial. Radiotherapy is the treatment of choice for SP, but no clear relationship has been documented between response and radiotherapy dose. For SBP it is recommended treatment with radical radiotherapy, with a margin of at least 2 cm and a dose of 40 Gy in 20 fractions. For SBP >5 cm, a higher dose of up to 50 Gy in 25 fractions should be considered.[5]

Surgery is contraindicated in the absence of structural instability or neurological compromise. However, due to the development of modern spinal fixation systems over the last decade,

surgical treatment is now a feasible and successful option for patients who develop pain caused by structural compromise within the vertebra, vertebral instability, neurological compromise or both. Loss of structural integrity requires some forms of stabilization procedure; in cases of neurological compromise, decompression is also required. The choice of surgery and approach needs to be tailored to the specific situation of each patient, the general fitness, and clinical conditions; also the site and the extent of the tumor must be evaluated. Moreover, if surgery is required, it should be carried out before starting radiotherapy because surgery is more difficult in patients who have received radiotherapy and initial surgery may sometimes compromise radiotherapy, e.g. by the placing of metal supports.[5]

Patients with a bulky disease or not responding to radiotherapy could benefit from chemotherapy; however, studies are limited, and its role is controversial. The better prognosis of patients with SEP compared to SBP allows speculating that these are indeed two different diseases also from a biologic point of view. It is possible to suggest that SEP patients probably can be treated with surgery or radiotherapy alone, while SBP patients, who more frequently have an extensive disease, should be treated with chemotherapy after surgery and/or local radiotherapy, to prevent disease progression. Moreover, the potential use of the systemic treatment in addition to local radiotherapy could be suggested in the high-risk group of SBP with OMD. About chemotherapy, it is important to consider the possibility of using novel agents, taking into account the well-documented role that angiogenesis plays in several hematologic disorders, particularly in PC dyscrasias. However, there are some small series of cases treated with bortezomib-based regimens and fewer cases treated with IMiDs.[43,57,58] Here we report a hypothesis for a therapeutic algorithm (**Figure 2)**.

Radiotherapy remains the treatment of choice for both SBP and SEP; surgery should be indicated only in particular and feasible cases. Chemotherapy should be considered in cases of bulky disease at the onset or in high-risk patients.

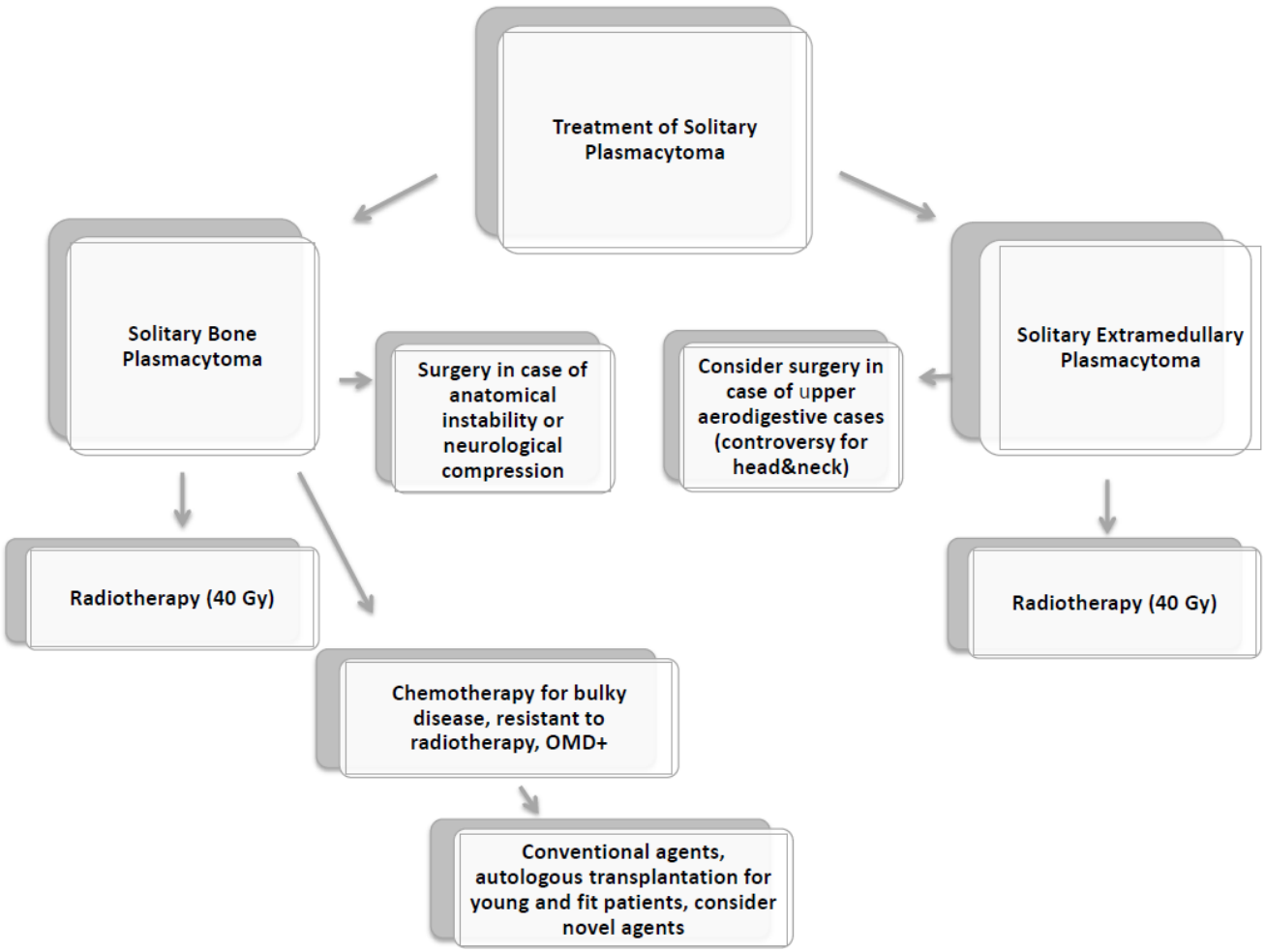

Figure 2. Therapeutic algorithm for SP (SBP and SEP).

According to the data reported in the literature, we can consider high-risk patients cases with abnormal FLC ratio and M protein level of at least 5 g/L,[16] the presence of OMD,[28,29] or presence of at least two hypermetabolic lesions on FDG-PET.[26] The patients with disease resistant to radiotherapy could benefit from chemotherapy too. New drugs could lead to optimal results, as for MM; also, autologous stem cell transplantation should be considered in young and fit high-risk or resistant SBP patients. However, larger prospective clinical studies need to be performed to refine our understanding of SP (taking into account that SBP and SEP could be considered as two different entities) and to optimize management of affected patients, in particular, the role of novel agents for the treatment of this disease.

References:

1. Knowling MA, Harwood AR, Bergsagel DE. Comparison of extramedullary plasmacytomas with solitary and multiple plasma cell tumors of bone. J Clin Oncol. 1983;1:255-62. https://doi.org/10.1200/JCO.1983.1.4.255 PMid:6668499
2. Dimopoulos MA1, Hamilos G. Solitary bone plasmacytoma and extramedullary plasmacytoma. Curr Treat Options Oncol. 2002;3:255-9. https://doi.org/10.1007/s11864-002-0015-2
3. Dores GM, Landgren O, McGlynn KA, Curtis RE, Linet MS, Devesa SS. Plasmacytoma of bone, extramedullary plasmacytoma, and multiple myeloma: incidence and survival in the United States, 1992-2004. Br J Haematol. 2009;144:86-94. https://doi.org/10.1111/j.1365-2141.2008.07421.x PMid:19016727 PMCid:PMC2610331
4. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ, Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BG, Miguel JF. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15:e538–48. https://doi.org/10.1016/S1470-2045(14)70442-5
5. Soutar R, Lucraft H, Jackson G, Reece A, Bird J, Low E, Samson D; Guidelines Working Group of the UK Myeloma Forum.; British Committee for Standards in Haematology.; British Society for Haematology. Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. Br J Haematol. 2004;124:717-26. https://doi.org/10.1111/j.1365-2141.2004.04834.x PMid:15009059
6. Dimopoulos MA, Moulopoulos LA, Maniatis A, Alexanian R. Solitary plasmacytoma of bone and asymptomatic multiple myeloma. Blood. 2000;96:2037-44. PMid:10979944
7. Galieni P, Cavo M, Pulsoni A, Avvisati G, Bigazzi C, Neri S, Caliceti U, Benni M, Ronconi S, Lauria F. Clinical outcome of extramedullary plasmacytoma. Haematologica. 2000;85:47-51. PMid:10629591
8. Kilciksiz S, Celik OK, Pak Y, Demiral AN, Pehlivan M, Orhan O, Tokatli F, Agaoglu F, Zincircioglu B, Atasoy BM, Ozseker N, Yersal O, Niang U, Haydaroglu A; Turkish Oncology Group-Sarcoma Working Party.Clinical and prognostic features of plasmacytomas: a multicenter study of Turkish Oncology Group-Sarcoma Working Party. Am J Hematol. 2008;83:702-7. https://doi.org/10.1002/ajh.21211 PMid:18543343
9. Jawad MU, Scully SP. Skeletal Plasmacytoma: progression of disease and impact of local treatment; an analysis of SEER database. J Hematol Oncol. 2009;2:41. https://doi.org/10.1186/1756-8722-2-41 PMid:19778427 PMCid:PMC2759950
10. Thumallapally N, Meshref A, Mousa M, Terjanian T. Solitary plasmacytoma: population-based analysis of survival trends and effect of various treatment modalities in the USA. BMC Cancer. 2017;17:13. https://doi.org/10.1186/s12885-016-3015-5 PMid:28056880 PMCid:PMC5216567
11. Wiltshaw E. The natural history of extramedullary plasmacytoma and its relation to solitary myeloma of bone and myelomatosis. Medicine (Baltimore). 1976;55:217-38. https://doi.org/10.1097/00005792-197605000-00002
12. Alexiou C, Kau RJ, Dietzfelbinger H, Kremer M, Spiess JC, Schratzenstaller B, Arnold W. Extramedullary plasmacytoma: tumor occurrence and therapeutic concepts. Cancer. 1999;85:2305-14. https://doi.org/10.1002/(SICI)1097-0142(19990601)85:11<2305::AID-CNCR2>3.0.CO;2-3
13. Liebross RH, Ha CS, Cox JD, Weber D, Delasalle K, Alexanian R. Clinical course of solitary extramedullary plasmacytoma. Radiother Oncol. 1999;52:245-9. https://doi.org/10.1016/S0167-8140(99)00114-0
14. Hu K1, Yahalom J. Radiotherapy in the management of plasma cell tumors. Oncology (Williston Park). 2000;14:101-8, 111; discussion 111-2, 115.
15. Chao MW, Gibbs P, Wirth A, Quong G, Guiney MJ, Liew KH. Radiotherapy in the management of solitary extramedullary plasmacytoma. Intern Med J. 2005 Apr;35(4):211-5. https://doi.org/10.1111/j.1445-5994.2005.00804.x PMid:15836498
16. Dingli D, Kyle RA, Rajkumar SV, Nowakowski GS, Larson DR, Bida JP, Gertz MA, Therneau TM, Melton LJ 3rd, Dispenzieri A, Katzmann JA. Immunoglobulin free light chains and solitary plasmacytoma of bone. Blood. 2006;108:1979-83. https://doi.org/10.1182/blood-2006-04-015784 PMid:16741249 PMCid:PMC1895544
17. Kilciksiz S, Karakoyun-Celik O, Agaoglu FY, Haydaroglu A. A review for solitary plasmacytoma of bone and extramedullary plasmacytoma. ScientificWorldJournal. 2012;2012:895765. doi: 10.1100/2012/895765. https://doi.org/10.1100/2012/895765
18. de Waal EG, Leene M, Veeger N, Vos HJ, Ong F, Smit WG, Hovenga S, Hoogendoorn M, Hogenes M, Beijert M, Diepstra A, Vellenga E. Progression of a solitary plasmacytoma to multiple myeloma. A population-based registry of the northern Netherlands. Br J Haematol. 2016;175:661-7. https://doi.org/10.1111/bjh.14291 PMid:27605358
19. Moulopoulos LA, Dimopoulos MA, Weber D, Fuller L, Libshitz HI, Alexanian R. Magnetic resonance imaging in the staging of solitary plasmacytoma of bone. J Clin Oncol. 1993;11:1311-5. https://doi.org/10.1200/JCO.1993.11.7.1311 PMid:8315427
20. Dispenzieri A, Kyle R, Merlini G, Miguel JS, Ludwig H, Hajek R, Palumbo A, Jagannath S, Blade J, Lonial S, Dimopoulos M, Comenzo R, Einsele H, Barlogie B, Anderson K, Gertz M, Harousseau JL, Attal M, Tosi P, Sonneveld P, Boccadoro M, Morgan G, Richardson P, Sezer O, Mateos MV, Cavo M, Joshua D, Turesson I, Chen W, Shimizu K, Powles R, Rajkumar SV, Durie BG; International Myeloma Working Group. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia, 2009; 23:215-224. https://doi.org/10.1038/leu.2008.307 PMid:19020545
21. Dimopoulos MA, Hillengass J, Usmani S, Zamagni E, Lentzsch S, Davies FE, Raje N, Sezer O, Zweegman S, Shah J, Badros A, Shimizu K, Moreau P, Chim CS, Lahuerta JJ, Hou J, Jurczyszyn A, Goldschmidt H, Sonneveld P, Palumbo A, Ludwig H, Cavo M, Barlogie B, Anderson K, Roodman GD, Rajkumar SV, Durie BG, Terpos E. Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. J Clin Oncol 2015;33: 657–64. https://doi.org/10.1200/JCO.2014.57.9961 PMid:25605835
22. Vogl TJ1, Steger W, Grevers G, Balzer J, Mack M, Felix R. MR characteristics of primary extramedullary plasmacytoma in the head and neck. AJNR Am J Neuroradiol. 1996 Aug;17(7):1349-54. PMid:8871723
23. Lu YY, Chen JH, Lin WY, Liang JA, Wang HY, Tsai SC, Kao CH. FDG PET or PET/CT for detecting intramedullary and extramedullary lesions in multiple Myeloma: a systematic review and meta-analysis. Clin Nucl Med 2012;37:833–37. https://doi.org/10.1097/RLU.0b013e31825b2071 PMid:22889770
24. Agarwal A. Neuroimaging of plasmacytoma. A pictorial review. Neuroradiol J. 2014;27:431-7. https://doi.org/10.15274/NRJ-2014-10078 PMid:25196616 PMCid:PMC4236876
25. Cavo M, Terpos E, Nanni C, Moreau P, Lentzsch S, Zweegman S, Hillengass J, Engelhardt M, Usmani SZ, Vesole DH, San-Miguel J,

Kumar SK, Richardson PG, Mikhael JR, da Costa FL, Dimopoulos MA, Zingaretti C, Abildgaard N, Goldschmidt H, Orlowski RZ, Chng WJ, Einsele H, Lonial S, Barlogie B, Anderson KC, Rajkumar SV, Durie BG, Zamagni E. Role of 18F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group. Lancet Oncol. 2017;18:e206-e217. doi: 10.1016/S1470-2045(17)30189-4. https://doi.org/10.1016/S1470-2045(17)30189-4
26. Fouquet G, Guidez S, Herbaux C, Van de Wyngaert Z, Bonnet S, Beauvais D, Demarquette H, Adib S, Hivert B, Wemeau M, Berthon C, Terriou L, Coiteux V, Macro M, Decaux O, Facon T, Huglo D, Leleu X. Impact of initial FDG-PET/CT and serum-free light chain on transformation of conventionally defined solitary plasmacytoma to multiple myeloma. Clin Cancer Res. 2014;20:3254-60. https://doi.org/10.1158/1078-0432.CCR-13-2910 PMid:24714772
27. Finsinger P, Grammatico S, Chisini M, Piciocchi A, Foà R, Petrucci MT. Clinical features and prognostic factors in solitary plasmacytoma. Br J Haematol. 2016;172:554-60. https://doi.org/10.1111/bjh.13870 PMid:26684545
28. Hill QA, Rawstron AC, de Tute RM, Owen RG. Outcome prediction in plasmacytoma of bone: a risk model utilizing bone marrow flow cytometry and light-chain analysis. Blood. 2014;124:1296-9. https://doi.org/10.1182/blood-2014-04-566521 PMid:24939658
29. Paiva B, Chandia M, Vidriales MB, Colado E, Caballero-Velázquez T, Escalante F, Garcia de Coca A, Montes MC, Garcia-Sanz R, Ocio EM, Mateos MV, San Miguel JF. Multiparameter flow cytometry for staging of solitary bone plasmacytoma: new criteria for risk of progression to myeloma. Blood. 2014;124:1300-3. https://doi.org/10.1182/blood-2014-04-567909 PMid:24876564
30. Bataille R, Sany J, Serre H. Apparently isolated plasmacytoma of bone. Clinical and prognostic data. 114 cases and review of literature (author's transl). Nouv Presse Med. 1981;10:407-11. PMid:7220335
31. Frassica DA, Frassica FJ, Schray MF, Sim FH, Kyle RA. Solitary plasmacytoma of bone: Mayo Clinic experience. Int J Radiat Oncol Biol Phys. 1989;16:43-8. https://doi.org/10.1016/0360-3016(89)90008-4
32. Mayr NA, Wen BC, Hussey DH, Burns CP, Staples JJ, Doornbos JF, Vigliotti AP. The role of radiation therapy in the treatment of solitary plasmacytomas. Radiother Oncol. 1990;17:293-303. https://doi.org/10.1016/0167-8140(90)90003-F
33. Holland J, Trenkner DA, Wasserman TH, Fineberg B. Plasmacytoma. Treatment results and conversion to myeloma. Cancer. 1992;69:1513-7. https://doi.org/10.1002/1097-0142(19920315)69:6<1513::AID-CNCR2820690633>3.0.CO;2-X
34. Galieni P, Cavo M, Avvisati G, Pulsoni A, Falbo R, Bonelli MA, Russo D, Petrucci MT, Bucalossi A, Tura S. Solitary plasmacytoma of bone and extramedullary plasmacytoma: two different entities? Ann Oncol. 1995;6:687-91. https://doi.org/10.1093/oxfordjournals.annonc.a059285 Mid:8664190
35. Shih LY, Dunn P, Leung WM, Chen WJ, Wang PN. Localised plasmacytomas in Taiwan: comparison between extramedullary plasmacytoma and solitary plasmacytoma of bone. Br J Cancer. 1995;71:128-33. https://doi.org/10.1038/bjc.1995.26 PMid:7819027 PMCid:PMC2033434
36. Bolek TW1, Marcus RB Jr, Mendenhall NP. Solitary plasmacytoma of bone and soft tissue. Int J Radiat Oncol Biol Phys. 1996;36:329-33. https://doi.org/10.1016/S0360-3016(96)00334-3
37. Tsang RW, Gospodarowicz MK, Pintilie M, Bezjak A, Wells W, Hodgson DC, Stewart AK. Solitary plasmacytoma treated with radiotherapy: impact of tumor size on outcome. Int J Radiat Oncol Biol Phys. 2001;50:113-20. https://doi.org/10.1016/S0360-3016(00)01572-8
38. Ozsahin M, Tsang RW, Poortmans P, Belkacémi Y, Bolla M, Dinçbas FO, Landmann C, Castelain B, Buijsen J, Curschmann J, Kadish SP, Kowalczyk A, Anacak Y, Hammer J, Nguyen TD, Studer G, Cooper R, Sengöz M, Scandolaro L, Zouhair A. Outcomes and patterns of failure in solitary plasmacytoma: a multicenter Rare Cancer Network study of 258 patients. Int J Radiat Oncol Biol Phys. 2006;64:210-7. https://doi.org/10.1016/j.ijrobp.2005.06.039 PMid:16229966
39. Dagan R1, Morris CG, Kirwan J, Mendenhall WM. Solitary plasmacytoma. Am J Clin Oncol. 2009;32:612-7. https://doi.org/10.1097/COC.0b013e31819cca18 PMid:19593082
40. Chak LY, Cox RS, Bostwick DG, Hoppe RT. Solitary plasmacytoma of bone: treatment, progression, and survival. J Clin Oncol. 1987;5:1811-5. https://doi.org/10.1200/JCO.1987.5.11.1811 PMid:3681369
41. Knobel D, Zouhair A, Tsang RW, Poortmans P, Belkacémi Y, Bolla M, Oner FD, Landmann C, Castelain B, Ozsahin M; Rare Cancer Network. Prognostic factors in solitary plasmacytoma of the bone: a multicenter Rare Cancer Network study. BMC Cancer. 2006;6:118. https://doi.org/10.1186/1471-2407-6-118 PMid:16677383 PMCid:PMC1479355
42. Suh YG, Suh CO, Kim JS, Kim SJ, Pyun HO, Cho J. Radiotherapy for solitary plasmacytoma of bone and soft tissue: outcomes and prognostic factors. Ann Hematol. 2012;91:1785-93. https://doi.org/10.1007/s00277-012-1510-6 PMid:22752147
43. Katodritou E, Terpos E, Symeonidis AS, Pouli A, Kelaidi C, Kyrtsonis MC, Kotsopoulou M, Delimpasi S, Christoforidou A, Giannakoulas N, Viniou NA, Stefanoudaki E, Hadjiaggelidou C, Christoulas D, Verrou E, Gastari V, Papadaki S, Polychronidou G, Papadopoulou A, Giannopoulou E, Kastritis E, Kouraklis A, Konstantinidou P, Anagnostopoulos A, Zervas K, Dimopoulos MA. Clinical features, outcome, and prognostic factors for survival and evolution to multiple myeloma of solitary plasmacytomas: a report of the Greek myeloma study group in 97 patients. Am J Hematol. 2014;89:803-8. https://doi.org/10.1002/ajh.23745 PMid:24757085
44. Weber DM. Solitary bone and extramedullary plasmacytoma. Hematology Am Soc Hematol Educ Program. 2005:373-6. https://doi.org/10.1182/asheducation-2005.1.373 PMid:16304406
45. Weberpals J, Pulte D, Jansen L, Luttmann S, Holleczek B, Nennecke A, Ressing M, Katalinic A, Merz M, Brenner H for the GEKID Cancer Survival Working Group. Survival of patients with lymphoplasmacytic lymphoma and solitary plasmacytoma in Germany and the United States of America in the early 21st century. haematologica 2017; 102:e229
46. El-Fattah MA, Aboelmagd M, Elhamouly M. Clinical risk factors of Plasmacytoma mortality: a US population-based study. Br J Haematol. 2016 Jun 13. doi: 10.1111/bjh.14189. https://doi.org/10.1111/bjh.14189
47. Wilder RB, Ha CS, Cox JD, Weber D, Delasalle K, Alexanian R. Persistence of myeloma protein for more than one year after radiotherapy is an adverse prognostic factor in solitary plasmacytoma of bone. Cancer. 2002;94:1532-1537. https://doi.org/10.1002/cncr.10366 PMid:11920511
48. Dimopoulos MA, Terpos E. Solitary bone plasmacytomas need to flow. Blood. 2014;124:1209-10. https://doi.org/10.1182/blood-2014-06-579706 PMid:25147376 PMCid:PMC4141506
49. Mendenhall WM, Mendenhall CM, Mendenhall NP. Solitary plasmacytoma of bone and soft tissues. Am J Otolaryngol. 2003;24:395-9. https://doi.org/10.1016/S0196-0709(03)00092-9
50. Sasaki R, Yasuda K, Abe E, Uchida N, Kawashima M, Uno T, Fujiwara M, Shioyama Y, Kagami Y, Shibamoto Y, Nakata K, Takada Y, Kawabe T, Uehara K, Nibu K, Yamada S. Multi-institutional analysis of solitary extramedullary plasmacytoma of the head and neck treated with curative radiotherapy. Int J Radiat Oncol Biol Phys. 2012;82:626-34. https://doi.org/10.1016/j.ijrobp.2010.11.037 PMid:21277117
51. Gerry D, Lentsch EJ. Epidemiologic evidence of superior outcomes for extramedullary plasmacytoma of the head and neck. Otolaryngol Head Neck Surg. 2013;148:974-81. https://doi.org/10.1177/0194599813481334 PMid:23482476
52. Michalaki VJ, Hall J, Henk JM, Nutting CM, Harrington KJ. Definitive radiotherapy for extramedullary plasmacytomas of the head and neck. Br J Radiol. 2003;76:738-41. https://doi.org/10.1259/bjr/54563070 PMid:14512335
53. Creach KM, Foote RL, Neben-Wittich MA, Kyle RA. Radiotherapy for extramedullary plasmacytoma of the head and neck. Int J Radiat Oncol Biol Phys. 2009;73:789-94. https://doi.org/10.1016/j.ijrobp.2008.04.077 PMid:18707826
54. Li QW, Niu SQ, Wang HY, Wen G, Li YY, Xia YF, Zhang YJ. Radiotherapy Alone is Associated with Improved Outcomes Over Surgery in the Management of Solitary Plasmacytoma. Asian Pac J Cancer Prev. 2015;16:3741-5. https://doi.org/10.7314/APJCP.2015.16.9.3741
55. Aviles A, Huerta-Guzman J, Delgado S, Fernadez A, Diaz-Maqueo JC. Improved outcome in solitary bone plasmacytoma with combined therapy. Hematol Oncol 1996, 14:111-117. https://doi.org/10.1002/(SICI)1099-1069(199609)14:3<111::AID-HON575>3.0.CO;2-G

56. Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Chandler JC, Costello C, Faiman M, Fung HC, Gasparetto C, Godby K, Hofmeister C, Holmberg L, Holstein S, Huff CA, Kassim A, Liedtke M, Martin T, Omel J, Raje N, Reu FJ, Singhal S, Somlo G, Stockerl-Goldstein K, Treon SP, Weber D, Yahalom J, Shead DA, Kumar R. Multiple Myeloma, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15:230-69. https://doi.org/10.6004/jnccn.2017.0023 PMid:28188192
57. Fukuhara S, Tazawa H, Okanobu H, Kida M, Kido M, Takafuta T, Nishida T, Ohdan H, Sakimoto H. Successful treatment of primary advanced gastric plasmacytoma using a combination of surgical resection and chemotherapy with bortezomib: A case report. Int J Surg Case Rep. 2016;27:133-136. https://doi.org/10.1016/j.ijscr.2016.08.041 PMid:27611798 PMCid:PMC5018075
58. Khaliq W1, Uzoaru I, Konchanin RP, Sapiente RA, Egner JR. Solitary extramedullary plasmacytoma of the bladder: a case report and literature. Oncology. 2010;24:832-5. PMid:20923037