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Trends and Outcomes of Modern Staging of Solitary Plasmacytoma of Bone

Rahma Warsame, Morie A Gertz, Martha Q. Lacy, Robert A. Kyle, Francis Buadi, David Dingli, Philip R. Greipp, Suzanne R. Hayman, Shaji K. Kumar, John A. Lust, Stephen J. Russell, Thomas E. Witzig, Joseph Mikhael, Nelson Leung, Steven R. Zeldenrust, S. Vincent Rajkumar, and Angela Dispenzieri

Division of Hematology and Internal Medicine (R.W., A.D., M.A.G., M.Q.L., R.A.K., F.B., D.D. P.R.G., J.A.L., S.V.R., S.J.R. T.E.W., N.L., S.R.H., S.R.Z, Mayo Clinic, Rochester, MN) and Mayo Clinic, Scottsdale, AZ (J.M.).

Abstract

Over the years, the definition of solitary plasmacytoma of bone (SPB) has shifted in part due to more modern testing capabilities. We hypothesized that outcomes data based on antiquated testing would not reflect outcomes using modern staging. To address both how widely applied adequate diagnostic staging is and what the progression rates of SPB as defined with state-of-the-art staging are, we performed a retrospective chart review of those patients with a diagnosis of SPB seen at our institution over the past decade. Two groups were studied: all patients with SPB (n=127); and those patients referred to our institution for an indication other than progression (n=91). The median PFS for those two groups were 26 months and 42 months, respectively. At baseline, only a minority of patients had state-of-the-art staging. The 5 patients with both modern imaging and a negative bone marrow had a 21 month PFS of 100%. Patients with plasmacytoma plus--one plasmacytoma but bone marrow consistent with monoclonal gammopathy of undetermined significance--fair worse than true SPB. The use of modern staging appears to be beneficial in the initial staging of SPB, and there may be a role for PET/CT in future diagnostic work up.

INTRODUCTION

Solitary plasmacytoma of bone (SPB) is a rare neoplasm that comprises less than 5% of all plasma cell neoplasms.(1) The diagnostic criteria for this disorder have evolved over time, especially due to the greater availability of more sensitive testing. Historically, the diagnostic criteria were as follows: a solitary lesion of bone due to biopsy proven clonal plasma cells; bone marrow not consistent with multiple myeloma; normal skeletal survey (and MRI of spine and pelvis if done); and no anemia, hypercalcemia, or renal impairment attributable to plasma cell disorder. (2) These criteria have been revised such that more patients with occult disseminated disease are excluded.(1),(3) Specifically, an absence of

Correspondance, Angela Dispenzieri, M.D, 200 First Street SW, Rochester, MN 55905, Telephone: 507 284-2179, Fax: 507 266-4972, dispenzieri.angela@mayo.edu.

Conflict of interest

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clonal plasma cells in the iliac crest biopsy and a normal magnetic resonance imaging (MRI) spine and pelvis are required to qualify for the diagnosis.(1),(3) Older series allowed for inclusion of patients with up to 10% bone marrow plasmacytosis and up to 2 bone lesions. (4–6)

Using the older more permissive definitions, the reported 10 year disease free survival rates were between 16–46% after radiation therapy or surgery with adjuvant radiation.(4, 7–10) These rates should represent an overestimation of progression for those patients with SPB, who are classified using modern definitions. (1, 3) To address both how widely applied adequate diagnostic staging is and what the progression rates of SPB as defined with state-of-the-art staging is, we studied those patients with a diagnosis of SPB seen at our institution from 2000 to 2009.

PATIENTS AND METHODS

One hundred and seventy-nine patients labeled as SPB, who received care at the Mayo Clinic between January 1, 2000 and December 31, 2009, were identified by electronic retrieval from our myeloma data base. For the purpose of this study, patients were included if they had: biopsy proven plasmacytoma; no evidence of systemic disease on skeletal survey; and fewer than 10% plasma cells on bone marrow biopsy. Patients with osteosclerotic myeloma (POEMS), patients with >10% plasma cells on bone marrow biopsy, or systemic features including anemia, hypercalcemia or renal disease that were related to the plasma cell neoplasm were excluded.

One hundred and twenty-seven patients were included in the final analysis. Fifty-two cases were excluded for the following reasons: more than one lesion on plain skeletal radiographs (n=18); or more than 10% bone marrow plasma cells on biopsy (n=38). Given that some patients were referred to the Mayo Clinic at the time of progression, the sub-group of 91 patients, who were referred not for the purpose of progressive disease, was also considered separately. Those patients, who had clonal plasma cells in the bone marrow at a level of less than 10%, akin to a co-existing monoclonal gammopathy of undetermined significance, or those with inadequate imaging were considered to have ‘plasmacytoma plus.’ Those with state-of-the-art imaging—either MRI spine and pelvis, MRI whole body, or PET-CT—documenting only one plasmacytoma were considered to have ‘true SPB.’

The clinical data, radiographic imaging, laboratory assays were compiled, reviewed and compared for all patients by RW and AD. For those patients without follow-up information within 6 months, referring physicians were contacted for additional information and the Social Security Death Index was utilized to verify whether patients were still alive if no additional information could be obtained.

Statistical analysis was undertaken using the JMP software package (SAS, Cary, NC, USA). Survival was calculated from the date of diagnosis and assessed by the method of Kaplan and Meier and compared by log rank test. Categorical variables were compared with Chi squared or Fishers tests as appropriate. All p values were 2-sided with a significance level of

0.05. Differences between continuous variables were determined by Kruskal-Wallis test. Multivariate analysis was by Cox regression models.

RESULTS

PATIENT CHARACTERISTICS

Patient characteristics are shown in Table 1. Ninety-one were seen at the Mayo Clinic Rochester within 90 days of their diagnosis of SPB, including 30 whose diagnosis was made at the Mayo Clinic. Thirty-six were referred to Mayo at the time of progression. The median age was 59 years (range: 28 to 83), and 76% were male. Of the 127 patients included in this study 121 patients were treated with radiation therapy including 31 patients who had radiation as adjuvant therapy after surgery; five of the remaining six sought treatment elsewhere and radiation therapy could not be confirmed; and one was treated with only surgery. The radiation dose was available for only 85 patients. The median radiation dose administered was 46 Gy (range: 20 to 60 Gy).

SURVIVAL AND PROGRESSION

Eighty-five patients (67%) have progressed, and 33 have died (Figure 1A). Median follow-up of surviving patients is 56 months (range 7 to 128 months). All but six of the deaths occurred in patients with progression to myeloma. Of these six, one died in a motor vehicle accident, another of complications of dementia, and 4 died of causes unknown to us. The 5-year OS was 74%, and the median PFS was 26 months (Figure 1A).

Since more than 25% of the patients had been referred to our clinic at the time of progression, we separately assessed the group of 91 patients whose first visit to our clinic was not associated with progression. At a median follow up of 54 months 21 have died and 49 have progressed. The 5-year OS and the median PFS were 78% and 42 months, respectively (Figure 1B).

The types of progression for the 85 patients who progressed were: diffuse myelomatous bone disease, 27 patients; diffuse marrow involvement and/or rising monoclonal protein levels consistent with multiple myeloma, 40 patients; local recurrence of plasmacytoma, 10 patients; another solitary plasmacytoma in another area of the body, 3 patients; or two or more additional plasmacytomas without any evidence of systemic involvement or bone marrow plasmacytosis consistent with macrofocal multiple myeloma, 5 patients.

QUALITY OF BASELINE DIAGNOSTIC EVALUATION DEFINES OUTCOMES

All 127 patients were included to address the question of adequate staging, with the understanding that an unknown number of patients may have been excluded from our data set by state-of-the-art staging moving them from a diagnosis of plasmacytoma to multiple myeloma before enrollment into the plasmacytoma data base.

At baseline, 48 percent of patients had studies to exclude a clone residing in the iliac crest bone marrow sample, four patients (3%) had MRI of spine/pelvis or whole body MRI, and 13 percent had PET/CT. Therefore, none had a diagnostic work-up consistent with current

guidelines, i.e. negative MRI pelvis/spine or MR whole body and documented absence of clonal plasma cells in the bone marrow.

The absence of clonal plasma cells in the bone marrow was prognostic. Overall, of the 61 patients tested for bone marrow clonality, 37 were negative and 24 had clonal cells detected. PFS was incrementally superior among patients with a negative bone marrow as compared to those who did not have clonality tested or those with a positive bone marrow both in the total group (42 versus 24 versus 15 months, $p=0.01$ Figure 2A) and in the sub-group not referred specifically for progression (50 versus 63 versus 14 months, $p=0.0002$; Figure 2B). Extent of bone marrow plasmacytosis was prognostic for PFS in both the overall group (median PFS 36 versus 21 months for those with fewer than 5% bone marrow plasmacytosis, $p=0.03$, data not shown) and in the 91 patients (57 versus 32 months, $p=0.0002$, Figure 2C).

Among the four patients who had a negative MRI spine/pelvis or MR whole body, none had 'true SPB' since one had clonal bone marrow plasma cells documented, two had more than 5% bone marrow plasmacytosis without any testing for clonality, and the fourth had fewer than 5% bone marrow plasmacytosis without testing for clonality. With follow-up times of 31, 37, 73 and 101 months, only one of these 4 patients has progressed to MM at 5 months. One of these patients had an additional sacral plasmacytoma discovered by MRI along with 9% bone marrow plasmacytosis; she has not progressed with 73 months follow-up.

Seventeen patients had baseline PET/CT performed. In the group of 127 patients, a negative PET/CT alone did not predict for lack of progression (PFS 30 versus 18 months, $p=NS$, figure 3A); however, among the 91 patients referred to Mayo before progression a negative PET/CT alone performed better (PFS 57 versus 23 months, $p=0.07$ Figure 3B). Of the 17 patients with negative PET/CT, 5 had 'true SPB' with documented absence of clonal bone marrow plasma cells. The other 12 had 'plasmacytoma plus:' 9 with clonal plasma cells documented; and 3 with no testing for clonality performed. As shown in Figure 3C, none in the first group has progressed with a median follow-up of 21 months (range 6.7, 69). The combination of negative PET/CT and negative bone marrow had good predictive value for a lower likelihood of progression.

OTHER PROGNOSTIC FACTORS

Other factors that were tested as predictors for PFS are shown in Table 2. On univariate analysis, the presence of clonal plasma cells on bone marrow aspiration, bone marrow plasmacytosis greater than or equal to 5%, a detectable monoclonal protein on urine protein immunofixation, and radiation dose were prognostic for PFS. On multivariate analysis, the three factors that predicted for a shorter progression free survival were clonal plasma cells in bone marrow, a detectable monoclonal protein in the urine and a higher radiation dose delivered. Too few patients ($n=25$) had a serum immunoglobulin free light chain tested at baseline to include it in the multivariate model. Radiation dose was available for only 73% of patients. Inexplicably, the patients receiving the highest doses of radiation were those more likely to progress.

DISCUSSION

We retrospectively analyzed 127 Mayo Clinic patients seen in the past decade to ascertain both the frequency of state-of-the-art plasmacytoma diagnostic work-up and whether such an evaluation would have a favorable impact on prognosis. One would anticipate that this testing should distinguish true solitary plasmacytoma of bone from patients with either macrofocal myeloma, plasmacytoma plus, or early stage multiple myeloma and therefore result in better prognosis. Only 5 patients in our cohort had staging sufficient to call them true solitary plasmacytoma of bone since only a minority of patients had MRI spine/pelvis, PET/CT or bone marrow studies to document clonal marrow involvement. The retrospective nature of this study makes it impossible to know the true denominator of how many patients with a preliminary diagnosis of SPB had appropriate testing and were upstaged to myeloma and, therefore, excluded from our series. Despite this limitation, we found that at baseline those patients with true SPB as defined by either a negative PET/CT or MRI and documented absence of clonal plasma cells on iliac crest aspirate/biopsy had an excellent progression free survival with none of these patients progressing at a median follow-up of 21 months.

In spite of the fact that approximately a quarter of patients in our series were referred to our clinic at the time of progression, our 5-year OS of 74% is comparable to that of 3 previous series of patients with SPB, ranging from 74% to 87%. (8), (9, 11). In addition our PFS rates of 26 months and 42 months for all patients and those not referred specifically for progression, respectively, are comparable or superior to the 18 to 21 months cited in the literature. (9, 11, 12) Most notable in our series, however, is the 21-month PFS rate of 100% among the small sub-group of patients who had SPB based on state of the art staging with PET/CT and negative bone marrows.

Due to a paucity of patients who had MRI spine/pelvis, we could not test how effective the current plasmacytoma staging recommendation of negative MRI spine/pelvis is. The literature would suggest that MRI is beneficial and a more sensitive imaging modality of the axial skeleton than conventional radiography. It is better at detecting myeloma over normal marrow and can be used to evaluate disease status in SPB (13). Mouloupoulos et. al demonstrated that MRI was superior in revealing additional areas of malignant lesions in the thoracic and lumbar spine in patients with SPB. (14) Another series had seven of eight patients staged with conventional radiography develop multiple myeloma, in contrast to one of seven who were staged using MRI. (10)

PET/CT is also known to be a valuable imaging tool in cancer. In a recent study comparing various imaging techniques, PET/CT scans were able to detect myelomatous involvement in areas that were out of the field of view for MRI in 35% of patients, but in 30% patients PET/CT scans failed to show abnormal areas in the spine pelvis compared to standard MRI. (15) A prospective comparison between MRI and PET/CT for appraisal of plasmacytoma was done in 2007. (16) This study found an equivalent or higher sensitivity, specificity, positive predictive value and negative predictive value for baseline staging of plasmacytomas with PET/CT as compared to MRI. This study, however, was limited by small sample size (n=23). In another study 20 additional plasmacytomas were discovered

that was negative on traditional staging techniques in 4 patients that influenced treatment regimens. (17) Although the current guidelines require MRI of the spine and pelvis for initial diagnosis of SPB, PET/CT is a technique that should be considered.

The definitions for bone marrow involvement among patients with SPB have been vague at best. Older definitions allowed for fewer than 10% bone marrow plasma cells. More recent criteria require no clonal bone marrow plasma cells, but there are limited studies that have applied those criteria.(18) With the modern definitions of SPB and multiple myeloma, there is lack of terminology for those patients in the gray area between true SPB and Durie Salmon Stage I myeloma. Our data illustrate that those patients, who have one plasmacytoma but have bone marrow consistent with monoclonal gammopathy of undetermined significance, fair worse from true SPB. We have therefore coined a new moniker, plasmacytoma plus, to describe this group of patients. In summary, our hypothesis was that the historical outcomes of SPB are confounded by inadequate initial evaluation and staging. The use of modern staging incorporating PET/CT, flow cytometry and immunohistochemistry appears to be beneficial for documenting true SPB and distinguishing it from plasmacytoma plus allowing for a more accurate estimation of outcomes. Large prospective studies are required to better assess the role of these techniques in evaluating and staging SPB.

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Figure 1. Overall survival (OS) and progression free survival (PFS)

A. For all 127 patients

B. For the subset of 91 patients referred to the Mayo clinic for initial evaluation

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Figure 2. The influence of bone marrow findings on PFS

A. Bone marrow clonality among all 127 patients

B. Bone marrow clonality among subset of 91 patients referred to the Mayo clinic for initial evaluation

C. Bone marrow plasmacytosis less than 5% among subset of 91 patients referred to the Mayo clinic for initial evaluation

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Figure 3. Influence of PET-CT scans on PFS

A. All patients

B. Among subset of 91 patients referred to the Mayo clinic for initial evaluation

C. Influence negative PET-CT scan combined with bone marrow clonality. Patients with 'true SPB' (dotted line) fare better than those with 'plasmacytoma plus' (solid and broken lines)

Table 1

Patient characteristics

	All patients, n (%)	Referred not at progression, n (%)	Referred due to progression, n (%)	P value
Number of patients	127	91	36	
Male	96 (76)	71 (78)	25 (69)	NS
Median Age, years *	59 (28, 83)	57 (28, 83)	60 (28, 78)	NS
Year of diagnosis				
2000–2004	62 (48)	41 (66)	21 (34)	NS
2005–2009	65 (52)	50 (34)	15 (23)	NS
Months between diagnosis and Mayo evaluation *	4.5 (0, 95)	1.7 (0, 40)	13.8 (1.3, 95)	<0.0001
Follow up, months *	50 (6, 128)	50 (6, 123)	50 (10, 128)	NS
PET/CT	17 (13)	16 (18)	1 (3)	0.04
MRI Spine/Pelvis	4 (3)	3 (3)	1 (3)	NS
Site of Plasmacytoma				
Axial skeleton	104 (83)	71 (79)	33 (92)	NS
Long bones	23 (18)	20 (22)	3 (8)	NS
Serum M protein size, g/dL	0 (0, 2.9)	0 (0, 3.5)	0 (0, 2.9)	0.016
SIFE or SPEP positive	65 (75)	52 (78)	13 (65)	NS
UIFE result (pos/neg/ND)	39/16/72	32/15/41	1/7/28	0.008
Baseline BM aspirate/biopsy				
Not done	8 (6)	7 (8)	1 (3)	NS
Plasma cells, % *	2 (0, 9)	2 (0, 9)	0 (1, 8)	NS
Clonality testing done	61 (48)	52 (58)	9 (25)	0.004
Documented BM clone	24 (19)	21 (23)	3 (9)	0.001
Documented negative BM	37 (29)	31 (34)	6 (17)	0.04
Treatment received				
Radiation therapy	121 (95)	85 (93)	36 (100)	0.03
Surgery alone	1 (0.7)	1 (1)	0 (0)	NS
Surgery + radiation	31 (24)	25 (31)	6 (17)	NS

* Expressed as median (range)

BM, bone marrow; MRI, magnetic resonance imaging; SIFE, serum immunofixation; SPEP, serum protein electrophoresis; UIFE, urine immunofixation

Table 2

Univariate and Multivariate Risk factors for progression for the subset of 91 patients with SPB

	Univariate		Multivariate	
	RR (95%CI)	P	RR (95%CI)	P
Clonal plasma cells in bone marrow (vs negative or not tested)	3.46 (1.81, 6.29)	0.0003	2.63 (1.34, 4.85)	0.006
BMPC (GTE 5%)	1.61 (1.0, 2.5)	0.03	NA	NS
Urine	1.71 (1.09, 2.65)	0.02	1.86 (1.09, 3.13)	0.02
Radiation dose	1.00 (1.07, 1.07)	0.04	1.04 (1.01, 1.08)	0.02

Other factors tested, which were not significant: Diagnosis year, Rochester by 3 months, initial place of diagnosis, age, gender, site of plasmacytoma, size of plasmacytoma, MRI pelvis/spine, CT done, PET done