Persistence of Myeloma Protein for More than One Year after Radiotherapy Is an Adverse Prognostic Factor in Solitary Plasmacytoma of Bone

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BACKGROUND. Prognostic factors for solitary plasmacytoma of bone (SPB), whether measured before or after radiotherapy (RT), have not been established. The authors analyzed multiple factors for myeloma-free survival (MFS) and cause-specific survival (CSS) in SPB patients treated with RT alone.

METHODS. Between 1965 and 2000, 60 patients with carefully staged SPB were treated with RT alone at the M. D. Anderson Cancer Center. Patient ages ranged from 29–77 years (median, 54 years), and 75% of patients had a myeloma (M) protein in the blood and/or urine. No patients showed other lesions on skeletal survey or, in recent years, magnetic resonance imaging (MRI) of the spine; marrow aspirate was normal in all patients. Radiotherapy to the solitary lesion was given to a total dose of 30–70 Gy (median, 46 Gy). The authors analyzed the impact of multiple factors on MFS and CSS, including resolution v. persistence of M protein after RT, secretory v. nonsecretory disease at diagnosis, presence v. absence of an associated soft tissue mass on computed tomography or MRI scan, magnitude of serum M protein elevation at diagnosis, age, spinal v. nonspinal location, Karnofsky performance status, total RT dose, and tumor size.

RESULTS. Median follow-up was 7.8 years (range, 1.0–25.5 years). On multivariate analysis, persistence of M protein more than one year after RT was the only independent adverse prognostic factor for MFS ($P = 0.005$) and CSS ($P = 0.04$). Most patients with M protein that persisted for more than one year after RT were diagnosed with multiple myeloma within 2.2 years of treatment.

CONCLUSIONS. Patients with M protein that persists for more than one year after RT should be monitored frequently and considered for standard chemotherapy followed by intensive consolidation therapy when they either develop symptoms or show an increasing M protein level. ***Cancer* 2002;94:1532–7.**

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Prognostic factors that are measurable before and after radiotherapy (RT) for solitary plasmacytoma of bone (SPB) have not been established due to the rarity of the disease, evolving criteria regarding the definition of SPB, and limited information in many studies regarding myeloma (M) protein levels. In addition, the importance of electrophoretic studies, immunofixation, and nephelometric quantification of immunoglobulins may not be well understood in the serial assessment of patients with SPB.[1]

Published reports of SPB commonly include patients whose di-

agnoses were established by differing criteria, with some groups using stricter definitions than others. For example, some groups require that patients with SPB have fewer than 10% plasma cells in bone marrow, and others require fewer than 5%.[2] Magnetic resonance imaging (MRI) of the thoracolumbar spine has been performed at our center since 1990 in order to assist with staging and has resulted in the detection of occult bone marrow involvement, consequently leading to the diagnosis of multiple myeloma in approximately one quarter of patients initially considered to have SPB.[3] Thus, as diagnostic criteria have become stricter, SPB has become rarer.

In the current report, we updated our findings regarding prognostic factors preceding and following RT for SPB. Unlike our prior reports,[4,5] in this report we examined: 1) only those patients treated with RT alone; 2) the impact of Karnofsky performance status and tumor size on myeloma-free survival (MFS) and cause-specific survival (CSS); and 3) the predictive ability of various prognostic factors using multivariate analysis. We concluded that persistence of M protein for more than one year after RT indicates the presence of asymptomatic multiple myeloma, and that other factors are not prognostic.

MATERIALS AND METHODS

Between 1965 and 2000, 63 consecutive, previously untreated patients with SPB were recognized at the M.D. Anderson Cancer Center. The diagnosis was based on histologic confirmation with $<$ 5% plasma cells in bone marrow and only one contiguous lesion on skeletal survey. Additional diagnostic evaluation consisted of electrophoreses of serum and urine concentrates, including immunoelectrophoresis, immunofixation, and immunoglobulin (Ig) quantifications as these procedures became available. Between 1990 and 2000, 6 out of 23 patients (26%) initially referred for SPB were excluded when MRI scans of the thoracolumbar spine revealed an intramedullary defect that had not been detected on skeletal survey. Since we focused on prognostic factors in patients treated with RT alone, we excluded three patients who had appeared in our prior report:[5] one had been treated with surgery alone and two had received chemotherapy before RT. Six more patients and up to four years of patient follow-up have been added since our prior report.[5]

Patient ages ranged from 29–77 years (median, 54 years). Of 60 patients, 37 (62%) had serum M protein; in 26 patients, the levels ranged from 0.1–1.0 g/dL, and in 11 patients the levels ranged from 1.1–2.2 g/dL. Six patients had Bence Jones protein in their urine (range, 0.01–0.08 g/day [d]) as well as an M protein in the blood. In 8 out of 60 patients (13%), only Bence Jones protein was present in urine (range, 0.02–0.70 g/d). The remaining 25% of patients had nonsecretory disease, i.e., no detectable M protein in the blood or urine on presentation.

Serial measurements of M protein were conducted at two month intervals for one year, and then at longer intervals. The disappearance of an abnormality was confirmed by immunoelectrophoresis or immunofixation[1] when that procedure became available.

In all but two cases, uninvolved serum IgG and IgA levels fell within the normal range for nephelometry,[1] IgG = 0.624–1.680 g/dL and IgA = 0.074–0.327 g/dL. Two patients had uninvolved serum IgA levels of 0.012 g/dL and 0.060 g/dL. Serum M protein levels at diagnosis for these patients were 0.5 g/dL and 1.0 g/dL, respectively. Patients with involved IgM had, by definition, Waldenström macroglobulinemia rather than SPB. Serum calcium and creatinine levels were normal in all patients. Hemoglobin was $>$ 10.0 g/dL in every case. Bony lesions ranged in size from 1.0–14.0 cm (median, 3.0 cm), the three most common sites being a vertebra (40%), pelvic bone (15%), and rib (13%). Three patients who presented with vertebral involvement received a brief course of glucocorticoids because of neurologic symptoms.

Megavoltage (1.25–25.0 MV) RT was delivered to the SPB to a total dose of 30–70 Gy (median, 46 Gy) given in daily fractions of 1.3–5.0 Gy (median, 2.0 Gy) over 8-61 days. Higher doses of RT tended to be delivered to plasmacytomas $\geq$ 5.0 cm in their greatest dimension ($P = 0.11$). One or two fields were treated in the majority of cases. For example, thoracic plasmacytomas were treated with a single posterior field, and cervical or lumbar plasmacytomas were treated with two parallel opposed fields. The margin included one adjacent vertebra in most cases where the spine was involved. The entire medullary cavity of involved bone constituted the clinical target volume in 48 out of 60 patients (80%). The medullary cavity of a long bone, e.g., rib, humerus, or femur, was typically not entirely treated in an effort to reduce treatment-related toxicity. Instead, the clinical target volume for a long bone consisted of the gross disease and usually a 2–5 cm margin along the long axis of the bone. Regional lymph nodes were excluded from the clinical target volume.

Evolution to multiple myeloma was defined by the development of multiple new bony lesions, $\geq$ 10% plasma cells in bone marrow, or rising M protein level. Chemotherapy for multiple myeloma was given on

specific protocols.[6] In accordance with other studies,[2,7,8] patients who developed a second focus of plasmacytoma remote from the primary lesion were considered to have recurrent SPB but not multiple myeloma if no additional bony lesions were found.

The two-sided Fisher exact test was used to analyze the total RT dose delivered (30.0–49.9 Gy v. 50.0–70.1 Gy) in terms of tumor size (1.0–4.9 cm v. 5.0–14.0 cm). The impact of multiple factors, including resolution v. persistence of M protein in blood and/or urine after RT, secretory v. nonsecretory disease on presentation, presence v. absence of an associated soft tissue mass on computed tomography (CT) or MRI scan, magnitude of serum M protein elevation (0.1–1.0 g/dL v. 1.1–2.2 g/dL), age (29–54 v. 55–77 years), spinal v. nonspinal location, Karnofsky performance status ($>$ 70 v. $\leq$ 70), RT dose ($\geq$ 50.0 Gy v. $<$ 50.0 Gy), and tumor size ($<$ 5.0 v. $\geq$ 5.0 cm), on MFS and CSS was analyzed using Kaplan-Meier analysis.[9] Curves were compared using the log rank test for univariate analysis.[10] The Cox proportional hazards model was used for multivariate analysis of prognostic factors that had a $P \leq 0.15$ on univariate analysis. A $P < 0.05$ on multivariate analysis was considered statistically significant.

RESULTS

The current study focused on prognostic factors preceding and following RT for SPB. Median follow-up of surviving patients was 7.8 years (range, 1.0–25.5 years). None of the soft tissue masses associated with SPB responded completely to treatment based on CT (33 patients) or MRI (18 patients) scans. The disease progressed radiographically within RT fields in 4 cases from 0.3–5.4 years (median, 1.8 years) after treatment. In three of these cases, new lytic lesions also developed outside of the radiotherapy fields. All four patients received chemotherapy when progressive disease was diagnosed. There were no recurrences at the margin of the RT fields. Only 1 out of 60 patients (2%) developed a regional lymph node recurrence. Two patients developed isolated distant recurrences of SPB and remained free of second relapse for 11.8–12.6 years following salvage RT.

Myeloma-free survival and CSS are presented in Figure 1. The 10-year local control, MFS, CSS, and overall survival rates for all 60 SPB patients were 90%, 38%, 57%, and 59%, respectively. The median durations in years of MFS, CSS, and overall survival were 4.2, 11.0, and 11.0, respectively.

In patients with nonsecretory disease, the median durations of MFS and CSS were 1.8 years and 8.5 years, respectively. Patients with nonsecretory disease tended

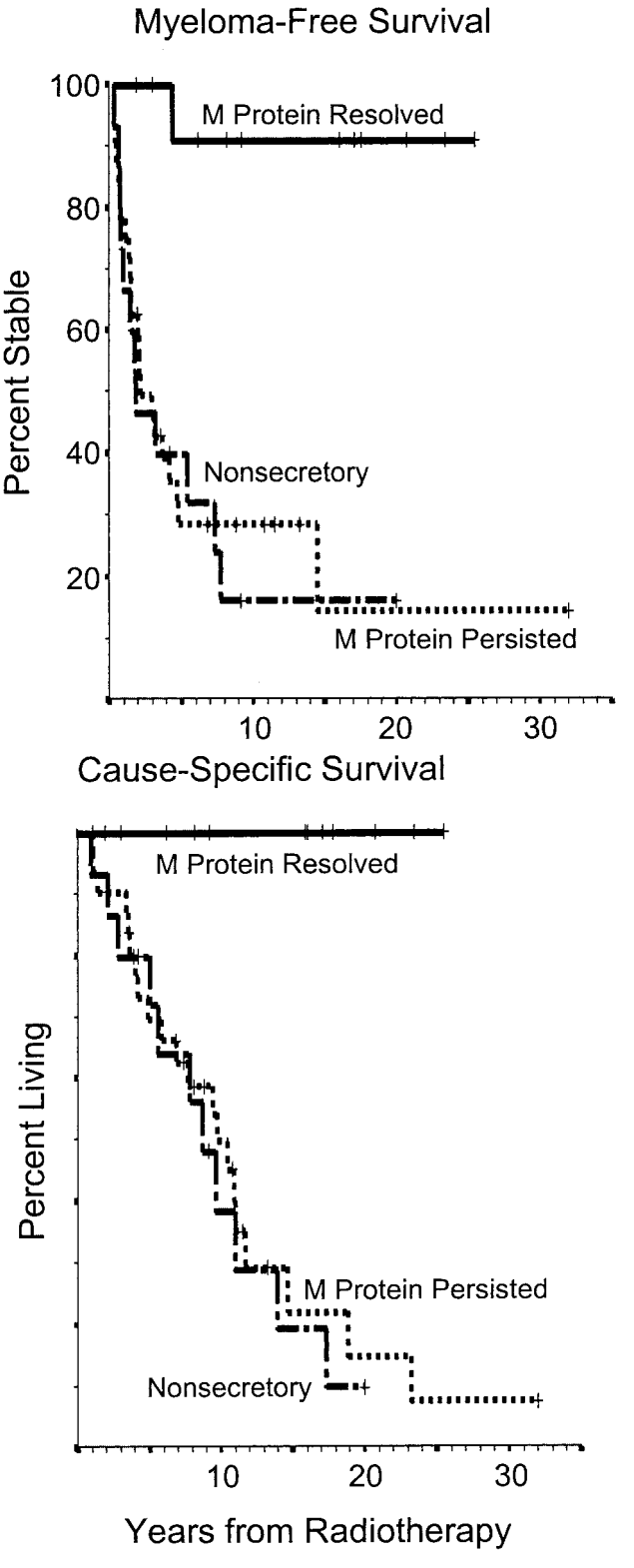

FIGURE 1. A) Myeloma-free survival ($P = 0.0005$) and B) cause-specific survival ($P = 0.0003$), both in terms of the response of myeloma (M) protein in the blood and/or urine to radiotherapy.

TABLE 1
Univariate and Multivariate Analyses of Prognostic Factors

Prognostic factor	*n* (%)	10 Year MFS (%)	Univariate *P* value	Multivariate *P* value	10 Year CSS (%)	Univariate *P* value	Multivariate *P* value
M protein in serum and/or urine after radiotherapy							
Resolved	13 (22)	91	0.0002	0.005	100	0.0001	0.04
Persisted	32 (53)	29			50		
M protein in serum or urine at diagnosis							
Yes	45 (75)	46	0.08	NS	63	0.07	NS
No	15 (25)	16			38		
Associated soft tissue mass observed on CT or MRI scan							
Yes	30 (50)	46	NS		63	0.10	NS
No	7 (12)	21			23		
Serum M protein elevation (g/dL) at diagnosis							
0.1–1.0	26 (43)	51	NS		67	0.15	NS
1.1–2.2	11 (18)	32			59		
Age (years)							
29–54	32 (53)	44	NS		64	0.15	NS
55–77	28 (47)	32			49		
Tumor location							
Nonspinal	34 (57)	31	NS		49	NS	
Spinal	26 (43)	48			69		
Karnofsky performance status							
> 70	30 (50)	30	NS		48	NS	
≤ 70	30 (50)	47			68		
Total radiotherapy dose							
50.0–70.1 Gy	28 (47)	28	NS		56	NS	
30.0–49.9 Gy	32 (53)	48			61		
Maximum dimension of solitary plasmacytoma of bone							
1.0–4.9 cm	39 (65)	41	NS		61	NS	
5.0–14.0 cm	21 (35)	33			50		

MFS: myeloma-free survival rate; CSS: cause-specific survival rate; M: myeloma; NS: not significant; CT: computed tomography; MRI: magnetic resonance imaging.

to experience worse MFS and CSS than those with secretory disease (Table 1 and Fig. 1).

The two patients with a low uninvolved serum immunoglobulin level on presentation were diagnosed with myeloma 1.6–4.8 years after RT. In both patients, serum M protein persisted for more than one year after RT.

Univariate and multivariate analyses of proposed prognostic factors preceding and following RT are presented in Table 1. Seven out of 13 patients with M protein that resolved after RT remained free of myeloma for 16.0–25.5 years. In all 13 cases, resolution occurred within 1 year. Persistence of M protein for more than one year after RT was an adverse prognostic factor for MFS ($P = 0.0005$) and CSS ($P = 0.0001$) on univariate analysis (Table 1). It was the only independent adverse prognostic factor for MFS ($P = 0.005$) and CSS ($P = 0.04$) on multivariate analysis. Most patients with persistent M protein following RT, like the patients with nonsecretory disease, developed multiple myeloma within 2.2 years of treatment (Fig. 1).

Thirty-six patients developed multiple myeloma after a median of 4.2 years following RT for SPB. Following chemotherapy, the median duration of CSS and overall survival from the date of diagnosis of myeloma were 4.8 years and 5.4 years, respectively. These survival durations are similar to those for newly diagnosed multiple myeloma patients who present with low tumor mass.[11]

One patient developed subjective, objective, management, and analytical (SOMA)[12] Grade 3 edema involving the left lower extremity after 60 Gy was given to the left ilium in daily fractions of 2.0 Gy over 40 days using anterior and posterior fields. There were no other cases of SOMA Grade ≥ 3 late toxicity due to RT. One patient was diagnosed with a pleomorphic mesenchymal sarcoma within the RT fields 17.5 years after treatment, and he died shortly thereafter.

DISCUSSION

We compared our experience regarding prognostic factors with those in other studies. Tsang et al.[8] reported that local control was more likely to be

achieved in patients with plasmacytomas < 5 cm. Moreover, Holland et al.[13] reported that MFS was better in patients with plasmacytomas < 5 cm. In the current study, tumor size was not related to outcome.

Mill and Griffith[14] observed a trend toward higher local recurrence and dissemination rates in SPB patients treated with radiotherapy doses < 50 Gy. However, serum Ig levels were not assessed in most of their cases, and other groups[5,7,15] have not confirmed their findings. As a result, dose recommendations have generally ranged between 35 and 50 Gy.[7] It is possible that no clear dose-response relationship has been demonstrated for local control or MFS because of the small number of in-field recurrences in any given study[7] and the practice of delivering higher doses of radiation to larger lesions. For example, in the current study, the 10 year local recurrence rate was only 10%, and larger lesions tended to receive higher doses of radiation. A large prospective study could help resolve the question of the optimal RT dose. In the absence of a cooperative group study or the convincing demonstration of a dose-response relationship in the literature, we recommend 45 Gy in 25 fractions over 5 weeks in accordance with the recommendations of Frassica et al.[7]

Bataille and Sany[16] reported that multiple myeloma developed more commonly in patients with neurologic problems secondary to SPB, thereby implying that performance status at diagnosis may have prognostic significance. In our SPB study, performance status was not related to MFS or CSS.

Bataille and Sany[16] also reported that involvement of the cervical, thoracic, lumbar, or sacral spine was an adverse prognostic factor. In contrast, other groups[8,17] have not identified spinal involvement as an adverse factor. Similarly, in the current study, spinal involvement did not have prognostic significance.

Some[8,16,17] groups have suggested that older SPB patients are more likely to develop progressive disease than younger patients, while others have not.[2,5,13,15,18] In the current study, age was not a prognostic factor.

Not clear is whether the presence of a soft tissue mass associated with SPB has prognostic significance. Frassica et al.[7] reported that the presence of an associated soft tissue mass on presentation did not have prognostic significance. Similarly, in the current study, the presence of an associated soft tissue mass at diagnosis was not a prognostic factor. Likewise, persistence of a soft tissue mass after treatment did not have prognostic significance, suggesting that the residual mass probably represented fibrosis in most cases. In support of our findings, Bolek et al.[15] reported that persistence of a soft tissue mass after treatment did not have prognostic significance.

Persistence of M protein for more than one year after RT was the only independent adverse prognostic factor in our study (Table 1). Two other groups[2,16] have also observed an adverse outcome in patients with persistent M protein after RT. In contrast, Frassica et al.[7] at the Mayo Clinic reported that, based on a median follow-up of 7.5 years, persistent M protein after RT in 2 out of 8 patients did not have prognostic significance. Since SPB patients can develop myeloma long after treatment,[13,15,19] e.g., one patient in the Mayo Clinic series with a rising serum M protein level was ultimately diagnosed with multiple myeloma 7.9 years after RT, longer follow-up may clarify the impact of persistent M protein after RT in the Mayo Clinic study.

In conclusion, we believe that persistence of M protein for more than one year after RT indicates that a patient most likely has multiple myeloma even though he or she is asymptomatic (Fig. 1).[4,5] Such patients should be monitored frequently and, when they develop symptoms or show an increase in their M protein level, should be considered for standard chemotherapy followed by intensive consolidation therapy.[11]

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