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Treatment approaches and outcomes in plasmacytomas: Analysis using a national dataset

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Abstract

Solitary plasmacytomas are uncommon plasma cell disorders, which may present as a single bone lesion (P-bone) or extramedullary plasmacytoma (P-EM). There is a paucity of large studies analyzing prognostic factors and outcomes of plasmacytomas. While the treatment of choice is radiation therapy (RT), there is a lack of data evaluating optimal RT dose. In this study, we sought to answer these questions by utilizing the National Cancer Data Base plasmacytoma data from 2000–2011. A total of 5,056 patients were included in the study (median age 62 years; range 52–72). To obtain a pure plasmacytoma cohort, potential multiple myeloma patients were excluded from the study (bone marrow involvement, systemic chemotherapy use). P-bone constituted 70% of the patients. The median overall survival (OS) of P-EM was significantly longer than P-bone (132 vs. 85 months); and for soft/connective tissue was worse than remainder of P-EM (82 vs. 148 months). On multivariable analysis, factors associated with worse OS included older age (≥65), presence of P-Bone and treatment with a radiation dose <40 Gy.

Introduction

Plasmacytomas are an uncommon subtype of plasma cell disorders that can present as a solitary bone lesion (P-bone), an extramedullary plasmacytoma (P-EM) or multiple bone and/or extramedullary lesions as in multiple myeloma (MM). The two large studies of plasmacytomas to date consisting of approximately 1,500 patients each from the SEER database demonstrated that P-bone and P-EM constitute approximately 3% and 2% of all plasma cell malignancies, respectively.[1, 2] In terms of disease outcomes, the existing studies demonstrate a variable five-year overall survival (OS) rate of 40 to 85%.[2–7] The national

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Authorship Contributions

G.G designed the study, interpreted the data, and wrote the paper with assistance from W.I.G. and S.K; A.C.B., J.I, and S.F. performed statistical analysis; N.D.S., A.L.M., A.A.A., P.K., U.D., S.K.H., M.A.S., F.K.B., R.S.G., and R.A.K. critically reviewed the manuscript, and approved the final version.

guidelines recommend treatment of solitary plasmacytomas with radiation therapy (RT) with or without surgery.[8] However, the optimal radiation dose has been a subject of debate. In this study, our objective was to describe the patterns of clinical presentation and treatments utilized in a large population in order to then determine their impact on patient survival outcomes using the National Cancer Data Base (NCDB).

Materials and Methods

This is a retrospective study of patients with a plasmacytoma diagnosed from 2000–2011 using the NCDB participant user file. The NCDB is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which began in 1989. It is a nationwide oncology outcomes database for > 1,500 CoC-accredited cancer programs across the United States and Puerto Rico that report information to the NCDB, and contains ~70% of all new cancer diagnoses. Cases are limited to those diagnosed and/or treated within CoC-approved hospitals. The sites of plasmacytoma presentation were classified according to the International Classification of Diseases for Oncology version 3 (ICD-0–3) codes: 9731 and 9734 (http://codes.iarc.fr/).

A total of 11,500 patients with plasmacytoma were identified. In order to achieve a pure plasmacytoma cohort, potential MM patients [presence of bone marrow involvement (N=2,866); systemic chemotherapy given, recommended, or chemotherapy status unknown (N=1,951)] were excluded from the analysis. In addition, subjects with unknown or missing plasmacytoma site (N=113), and without histologic confirmation (N=177) were excluded (Figure 1). To ascertain accuracy of follow-up, we excluded patients whose treatment decisions were made at a facility outside of the reporting facility (N=400). In addition, patients who had other concomitant malignancies (N=937) were excluded. For analyses that included dose of radiation as a potential covariate, the following were excluded from OS analysis: subjects who did not receive RT (N=1,151), those with an unknown dose (N=718), and whose RT duration was unknown or those with less than 30 days of follow-up after RT (N=371). The latter were excluded as it was unclear whether they received the intended radiation dose, or if the dose was received due to imminent death.

The Kaplan-Meier method was used to estimate median OS and comparisons were made using log-rank test. The OS period was calculated from the diagnosis to the date of last contact or patient death, as reported in the NCDB. A 2-tailed P value of < .05 was considered to indicate statistical significance. Recursive partitioning survival trees were used to assess variable importance. Recursive partitioning is a classification method that can be used in the absence of classic parametric analysis.[9] As it is a non-parametric methodology, it is able to perform well in the presence of interactions between predictor variables, especially in complex diseases like plasma cell disorders. Decision trees are created by this method, which attempt to classify the data into sub-populations (partitions) based on the independent variables of interest. The variables of interest for the study cohort were age, sex, site of plasmacytoma, presence of comorbid conditions (Charlson-Deyo score), and dose of RT received. Based on the recursive partitioning results, age, RT dose, and plasmacytoma site were selected for inclusion in the final model. These variables were dichotomized and included in the multivariable survival modeling by Cox regression. Lastly, Cox regression

was used to conduct subgroup multivariable survival modeling in each site. For the subgroup(s) in which dose of radiation was found as a significant predictor of survival, a univariate regression tree with dose of radiation being the predictor was analyzed to determine dose cut-point. Statistical analyses were performed using R 3.4.2 (R Foundation, Vienna, Austria).

Results

A total of 5,056 patients were included in the study (median age 62 years; Interquartile range 52–72). Of these, 63% were males. P-bone constituted 70% of the patients, with remaining 30% presenting as P-EM. Among P-EM, most common sites of presentation were upper aero-digestive tract (45%) and connective/soft tissue (19%) (Table 1). The median OS of P-EM was significantly longer than P-bone (132 vs. 85 months; Figure 2A). Further analysis among P-EM showed that plasmacytoma of connective/soft tissue had worse OS as compared to other sites (82 vs. 148 months) (Figure 2B). Multivariate analysis of the entire cohort showed age ≥65 years and P-bone location to be associated with worse prognosis (Table 2). In addition, receipt of radiation in combination with surgery was associated with better OS than either monotherapy.

A total of 3,905 (77%) patients received some amount of RT, of which 2,816 (56%) patients were included in the analysis of radiation dose due to complete data availability (Figure 1). The median dose of RT received was 45 Gy, with some variations among disease sites (Supplementary Table T1). On multivariable analysis within the RT cohort, factors associated with worse OS included age ≥65 years, P-bone location, and radiation dose <40 Gy (Table 2). Similar to the prior analysis, receipt of surgery followed by adjuvant RT was associated with improved OS as compared to RT alone. When analyzed separately for P-bone and P-EM, age ≥65 years and RT dose <40 Gy maintained their association with worse outcomes. Of note, a higher proportion of patients with P-EM received a radiation dose ≥40 Gy than P-bone (83% vs. 72%, $p<0.001$). Among the RT cohort, further recursive partitioning survival tree analysis was performed separately for 4 age quartiles, and demonstrated OS differences based on site of plasmacytoma and radiation dose (Supplementary Figure S1–S5).

In order to ascertain appropriate radiation dose based on disease location, we pursued a subgroup analysis using regression tree models. However, due to the small sample sizes in each subgroup, we found that only the upper aero-digestive tract site had radiation dose as a significant predictor after accounting for age, sex, and comorbid conditions. The subsequent regression tree (n=402, Figure 3) showed significant difference in survival rates between those receiving 37 Gy or more and those receiving less than 37 Gy. Survival estimates at 63 months (when all in the < 37 Gy group were censored) were 84.2% (79.9 – 88.7%) and 42.0% (22.3, 79.2%), respectively.

As a further exploratory analysis, we sought to analyze other treatment modalities received by plasmacytoma patients in the main cohort of 5,056 patients. We found that surgical therapy was utilized in a proportion of patients, either as monotherapy (13%), or with adjuvant radiation therapy (28%). On multivariate analysis, adjuvant RT after surgery was

found to be associated with an improved mortality as compared to either modality as monotherapy (Table 2). As receipt of surgery can be affected by the location of the disease, we evaluated the various treatment modalities based on site of disease. A higher proportion of patients with P-EM underwent surgery alone (21% vs. 9%) and surgery in combination with RT (35% vs. 25%) as compared to P-bone. On the other hand, a higher fraction of patients with P-bone underwent RT alone as compared to P-EM (55% vs. 36%)(Table 3). However, due to the small number of patients in individual disease sites, further subgroup analysis of these treatment modalities was not feasible. In addition, approximately 10% patients did not receive any of these modalities as their planned first course therapy. This group had the worse mortality, but the reasons for non-receipt of treatment were unclear.

Discussion

Our study demonstrates that the outcomes of patients with plasmacytoma vary significantly according to disease location, age, and the dose of RT utilized. We observed a worse OS in patients with P-bone as compared to P-EM. This could be related to higher rates of progression to multiple myeloma from P-bone as compared to P-EM (>75% vs. <30%.).[10] Interestingly, presence of soft tissue/connective tissue type of P-EM was associated with outcomes similar to P-bone. The SEER database study showed a 5-year OS of 90% for P-EM arising in skin or lymph nodes, and 48% for eye/brain/central nervous system tumors.[1] Our study provides individual survival data in each of 14 sites of presentation of P-EM. This aids in the prognosis of P-EM by sites of presentation so that patients with poor prognosis (connective/soft tissue, cardiac/mediastinal, etc.) can be followed more closely to evaluate the need for systemic therapy. In addition, older age (≥65 years) was associated with worse OS as compared to their younger counterparts. This finding is similar to prior studies, and in our study, is independent of the comorbidities on regression tree analysis.

The optimal RT dose for treatment of plasmacytoma is debated, and most published series use a dose range of 30 to 60 Gy.[11–13] One of the first series of P-bone evaluated 46 cases treated with a median radiation dose of 39.75 Gy, and showed no relapses with a radiation dose > 45Gy.[11] In contrast to this, in a large retrospective study of 244 RT patients (50% P-bone), 6% of patients treated with ≤30 Gy developed local failure as compared to 13% patients treated with ≥30 Gy.[12] Among head and neck plasmacytoma (P-EM), a study of 67 patients treated with a median RT dose of 50 Gy demonstrated no correlation between radiation dose and OS.[13] In contrast, another study of 17 P-EM patients with head and neck involvement showed 100% local control with radiation dose >45 Gy, and local control was positively correlated with disease-specific survival.[14] The most recent SEER analysis showed improved 5-year OS in P-bone (appendicular skeleton) patients treated with combined surgery and RT as compared to either modality alone. It also showed that upper and lower airway tract disease had better outcomes with surgery alone compared to combination therapy. However, there was no information on dose of RT utilized, which limits drawing of meaningful conclusions. In our study, utilizing data form a large group of patients, we have shown improved outcomes with doses of ≥40 Gy in both P-bone and P-EM, supporting current practice patterns.[8] We further attempted to study the ideal radiation dose for specific sites of P-EM based on OS, but were unable to find a specific dose cut off for most sites due to the small sample sizes. The only subgroup that showed a statistically

significant cut-off point was upper aerodigestive (head and neck) disease with improved OS at a dose of >37 Gy.

In this study, we found that a proportion of patients underwent surgical treatment, either alone or with adjuvant RT. Hence, we did an exploratory analysis to investigate this in detail. In our analysis, surgery in combination with RT was associated with an improved mortality than either monotherapy. Although this was statistically significant, one has to be cautious in concluding that surgical therapy should be considered in all patients with plasmacytoma as there could be other differences in the disease and patient specific factors that could impact the receipt of surgery. On detailed analysis, we found that a higher proportion of patients with P-EM underwent surgical treatments alone or in combination with RT as compared to patients with P-bone. As the former group includes a large proportion of patients with digestive system and connective tissue disease, it may be possible that surgical excision was performed due to ease of access or local symptoms. Conversely, RT alone group had more patients with P-bone, thus contributing to the worse OS seen in that subgroup.

The strengths of our study lie in the large sample size, making it the largest plasmacytoma study to date. We are able to provide detailed information on the variable sites of presentation and treatment options utilized in this disease. In order to minimize interactions between variables, we utilized a relatively novel statistical method with the regression tree analysis to pick variables of prognostic significance. This study also enabled us to address the important question of the optimum dose of radiation for plasmacytoma, which holds true for both P-bone and P-EM. Although this dose has been recommended by national guidelines, it had not been validated in a large dataset before our study.

The primary limitations of our study are related to its derivation from a database. We did not have access to the individual patient records, which makes it difficult to completely assess for degree of bone marrow involvement, especially in cases of P-bone. We were also unable to ascertain the reason for non-receipt of RT or surgery in 10% of the patients. One of the reasons for this could be that first course therapy was not planned at the reporting facility and the patient decided to get treatment elsewhere later, which would not be captured by NCDB. Although we are able to know the site of the tumor, we do not have accurate tumor volume data, which may affect treatment choice and outcomes. Additionally, there was no information on patients who had disease progression to MM. However, we applied stringent exclusion criteria to aid in obtaining a pure plasmacytoma cohort. Due a lack of information on some of the patient and disease specific factors, our aim was not a direct comparison of surgery to RT, and was performed as an exploratory analysis to prevent bias.

Our study shows that factors that adversely affect prognosis in plasmacytoma are age ≥65 years and bone involvement of plasmacytoma. In addition, radiation doses ≥40 Gy were associated with significantly improved survival as compared to lower RT doses in the entire cohort. In the subgroup of upper-aerodigestive tract disease, a dose ≥37 Gy was found to be associated with the best OS. Hence, this study provides important information on prognostic factors in P-bone and P-EM in a large cohort of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Disclosures

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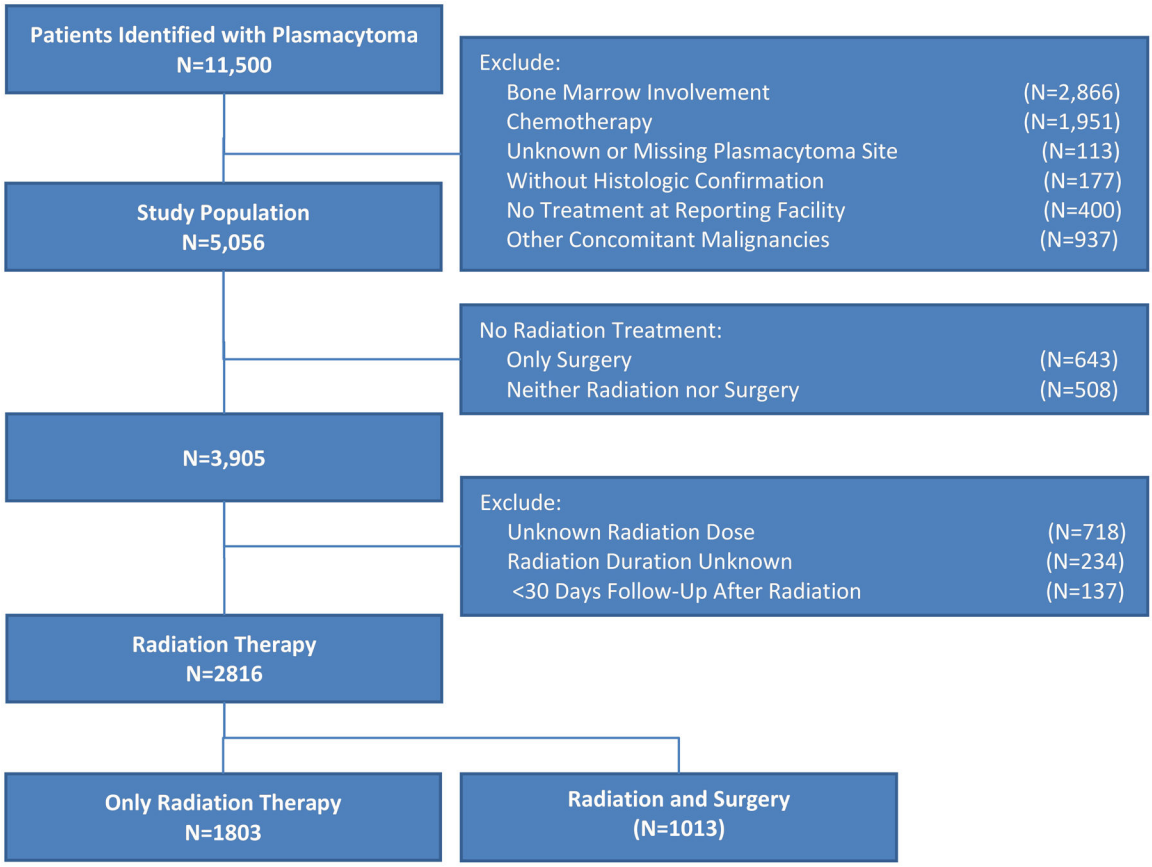

Figure 1.
CONSORT diagram for cohort selection.

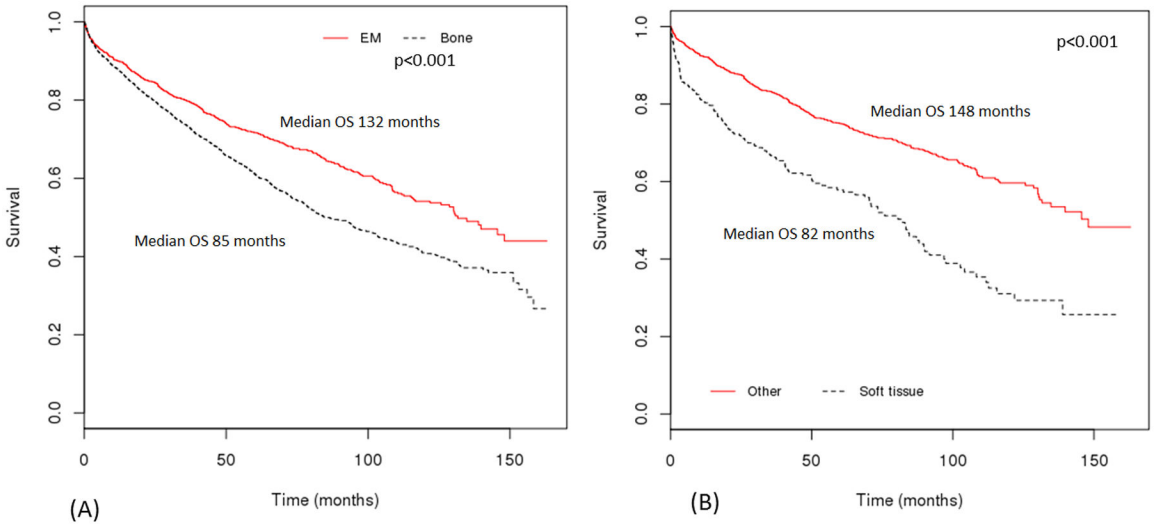

Figure 2.

Overall survival (OS) based on location of plasmacytoma (A) Extramedullary plasmacytoma (P-EM) compared to bone plasmacytoma; (B) Plasmacytoma of soft/connective tissue compared to others (P-EM other than connective/soft tissue or P-bone).

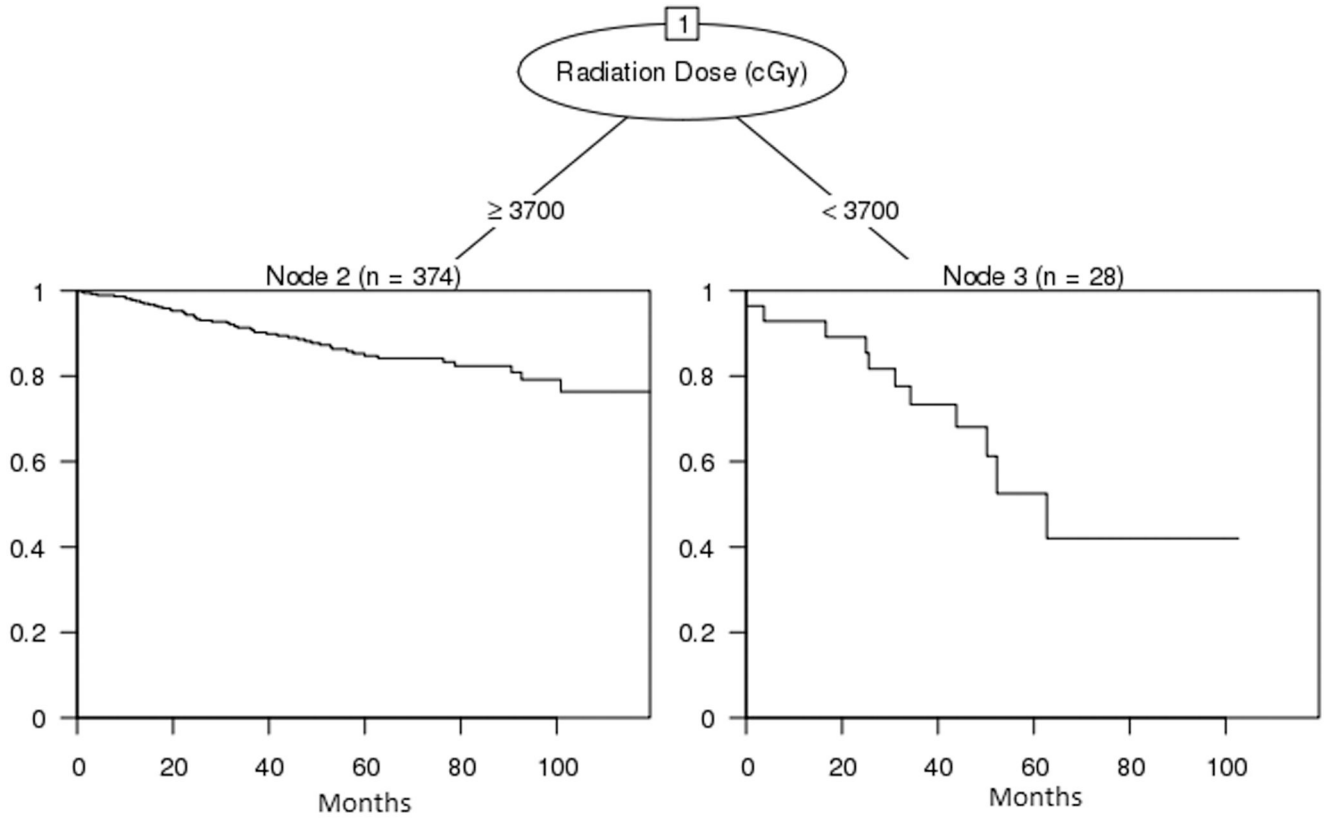

Figure 3.
Regression tree for upper aero-digestive tract site subgroup analysis of radiation dose.

Table 1.

Anatomical distribution and median overall survival (OS) of plasmacytomas.

Primary site	No. (%)	Median OS (months)	95% CI
Bone	3528 (69.8%)	85	8095
Upper aero-digestive tract	681 (13.5%)	Not reached	148-not reached
Connective/soft tissue	295 (5.8%)	82	69–92
Digestive system/hepatobiliary	122 (2.4%)	129	82-not reached
Central nervous system	115 (2.3%)	96	55-not reached
Pulmonary	84 (1.7%)	135	95-not reached
Lymph node/spleen	58 (1.1%)	Not reached	Not reached
Endocrine system	34 (0.7%)	130	90-not reached
Genitourinary	28 (0.6%)	42	16-not reached
Eye/Orbit	30 (0.6%)	Not reached	110-not reached
Cardiac/Mediastinum	22 (0.4%)	61	25-not reached
Breast	16 (0.3%)	Not reached	Not reached
Salivary glands	17 (0.3%)	109	102-not reached
Female reproductive system	14 (0.3%)	Not reached	Not reached
Male reproductive system	12 (0.2%)	42	23-not reached

Table 2.

Multivariate analysis of factors affecting survival in plasmacytoma (P- EM: Extramedullary plasmacytoma; P-Bone: Bone plasmacytoma).

Variable	No. (%)	HR (95% CI)
Age (years)		
<65	2814 (55.7%)	Referent
≥65	2242 (44.3%)	3.46 (3.14–3.81)
Location		
P-EM	1528 (30.2%)	Referent
P-Bone	3528 (69.8%)	1.48 (1.33–1.65)
Treatment		
Neither Surgery nor Radiation	508 (10.0%)	Referent
Both Surgery and Radiation	1414 (28.0%)	0.41 (0.35–0.48)
Only Radiation	2491 (49.3%)	0.53 (0.46–0.60)
Only Surgery	643 (12.7%)	0.58 (0.48–0.69)
Model for Patients With Any Radiation (N=2816)		
Radiation dose (Gy)		
<40	703 (25.0%)	Referent
≥40	2113 (75.0%)	0.62 (0.54–0.72)
Age (years)		
<65	1635 (58.1%)	Referent
≥65	1181 (41.9%)	3.17 (2.74–3.66)
Location		
P-EM	768 (27.3%)	Referent
P-Bone	2048 (72.7%)	1.47 (1.24–1.73)
Treatment		
Only Radiation	1803 (64.0%)	Referent
Both Surgery and Radiation	1013 (36.0%)	0.83 (0.71–0.96)
Model for P-Bone Primary Site (N=2048)		
Radiation dose (Gy)		
<40	572 (27.9%)	Referent
≥40	1476 (72.1%)	.66 (0.56–0.77)
Age (years)		
<65	1183 (57.8%)	Referent
≥65	865 (42.2%)	3.38 (2.87–3.98)
Model for P-EM Primary Site (N=768)		
Radiation dose (Gy)		
<40	131 (17.1%)	Referent
≥40	637 (82.9%)	0.49 (0.35–0.67)
Age (years)		
<65	452 (58.9%)	Referent
≥65	316 (41.1%)	2.79 (2.06–3.78)

Table 3.

Treatment patterns among patients with plasmacytoma (P-bone: Bone plasmacytoma; P-EM:Extramedullary plasmacytoma)

Site of plasmacytoma	Surgery + Radiation	Neither Surgery nor Radiation	Radiation alone	Surgery alone
P-Bone	886 (25.1%)	373 (10.6%)	1948 (55.2%)	321 (9.1%)
P-EM	528 (34.6%)	135 (8.8%)	543 (35.5%)	322 (21.1%) 95 (2.4%)
P-EM subgroups (n=1528)				
Breast	6 (37.5%)	0 (0.0%)	5 (31.3%)	5 (31.3%)
Cardiac/Mediastinum	3 (13.6%)	5 (22.7%)	13 (59.1%)	1 (4.5%)
Central Nervous System	64 (55.7%)	5 (4.3%)	20 (17.4%)	26 (22.6%)
Digestive System/Hepatobiliary	14 (11.5%)	22 (18.0%)	30 (24.6%)	56 (45.9%)
Endocrine System	7 (20.6%)	2 (5.9%)	13 (38.2%)	12 (35.3%)
Eye/Orbit	7 (23.3%)	0 (0.0%)	14 (46.7%)	9 (30.0%)
Female Reproductive System	3 (21.4%)	1 (7.1%)	3 (21.4%)	7 (50.0%)
Genitourinary	3 (10.7%)	4 (14.3%)	9 (32.1%)	12 (42.9%)
Male Reproductive System	1 (8.3%)	0 (0.0%)	0 (0.0%)	11 (91.7%)
Lymph Node/Spleen	22 (37.9%)	10 (17.2%)	15 (25.9%)	11 (19.0%)
Pulmonary	1 (1.2%)	18 (21.4%)	37 (44.0%)	28 (33.3%)
Salivary Glands	10 (58.8%)	0 (0.0%)	3 (17.6%)	4 (23.5%)
Connective/Soft Tissue	75 (25.4%)	44 (14.9%)	126 (42.7%)	50 (16.9%)
Upper Aero-Digestive Tract	312 (45.8%)	24 (3.5%)	255 (37.4%)	90 (13.2%)