

ORIGINAL RESEARCH ARTICLE

Long-term outcome of patients with solitary plasmacytoma treated with radiotherapy: A population-based, single-center study with median follow-up of 13.7 years

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Abstract

In this single-center, population-based, and retrospective study, we analyzed the outcome of 49 patients with solitary bone plasmacytoma (SBP) and 28 patients with solitary extramedullary plasmacytoma (SEP), all treated with radiotherapy. Laminectomy was performed in 18/30 SBP patients with vertebral involvement and tumour resection in 10 SEP patients. Overall survival and cause of death for each patient were compared to 5 sex-, age-, and residency-matched individuals from the normal population. Response (complete and partial) was achieved in 94% of SBP and 96% of SEP patients. Relapse rates were higher in SBP (65%) compared to patients with SEP (18%) ($P < .01$). Only one in-field relapse was identified for the whole series. Ten- and 15-year overall survival, progression free survival (PFS) and multiple myeloma free survival (MMFS) for patients with SBP were 60%/41%, 25%/17%, and 33%/33%. Corresponding values for patients with SEP were 67%/54%, 57%/44%, and 91%/91%. SBP patients had significantly shorter PFS and MMFS compared to SEP patients ($P < .01$ for both). Only two of the SEP patients developed multiple myeloma and no patient in the whole series progressed to multiple myeloma later than 10 years after diagnosis. Unlike for SEP, the major cause of death among SBP patients was multiple myeloma (49%). Compared to matched normal population, no increased risk of death from secondary malignancies or cardiovascular disease was observed. Positive predictors in SBP patients were for overall survival age <60 years, combined laminectomy and radiotherapy and radiotherapy dose >40 gray, for PFS tumour size <6 cm and combined laminectomy and radiotherapy and for MMFS tumour size <6 cm. Radiotherapy confers excellent local control in both SEP and SBP patients; however, the challenge is to prevent development of multiple myeloma in patients with SBP.

KEYWORDS

multiple myeloma, plasmacytoma, prognostic factors, radiotherapy, survival

1 | INTRODUCTION

Solitary plasmacytoma (SP) is a rare neoplastic disorder accounting for $<5\%$ of all plasma cell malignancies.¹ Most patients present with a solitary bone plasmacytoma (SBP). However, in one-third of the patients, the neoplasia occurs in extraosseous tissue thus called solitary extramedullary plasmacytoma (SEP). Most common sites for SBP are bones with active bone marrow hematopoiesis such as the vertebral spine, ribs, skull, pelvis, femur, clavicle, and scapula. In SEP, tumours often occur in the upper aero-digestive system.^{2,3} The risk of progression to multiple myeloma (MM) is higher in SBP compared to SEP and occurs after a median time of 2 years.^{4,5}

Although radiotherapy has become the standard treatment for SP, there is no standard recommended dose. The median dose of radiation applied in studies, which included both SBP and SEP ranged between 40 and 45 gray (Gy),^{2,6-9} in studies with only SBP between 40 and 50 Gy^{4,10} and in studies with only SEP between 50 and 56 Gy.¹¹⁻¹³ There is no clear evidence to support that adding chemotherapy can improve the outcome.⁸ In a cohort of 53 SP patients treated with radiotherapy, reported 5-year overall survival (OS) and progression free survival (PFS) were 72% and 53%, respectively, in SBP patients compared to 88% and 88% for SEP patients.² In another report, which included 38 patients with SP, 5-year OS and MM free survival (MMFS) were 70% and 36%, respectively, in SBP versus 87% and 71% in SEP.⁵

Unlike in our study, the follow-up time in these series has not exceeded 10 years.

In the present paper, we report long-term outcome, including cause of death and incidence of second primary malignancies in 77 patients with SP treated with radiotherapy as well as prognostic factors for death and progression.

2 | MATERIAL AND METHODS

2.1 | Patients

Patients with histologically verified SBP (49 patients [64%]) and SEP (28 patients [36%]) identified from the Oslo University Hospital lymphoma registry and treated with radiotherapy from 1980 until 2010 were included. In this period, radiotherapy for SP has been centralized to our hospital, covering the South-Eastern region of Norway with 2.6 million inhabitants. Inclusion criteria were (1) single area of bone destruction (SBP) or extramedullary mass (SEP) due to monoclonal plasma cell neoplasia; (2) bone marrow aspirate and biopsy with <10% plasma cells; (3) no other bony destruction on skeletal survey; (4) absence of anemia, hypercalcemia, and renal impairment due to plasma cell dyscrasia; (5) absence or low serum (<30 g/L) or urinary level of monoclonal immunoglobulin by serum and urine electrophoresis and immunofixation. Procedures performed at diagnosis included medical history, physical examination, complete blood count, biochemical tests, and skeletal survey including X-ray of the long bones, bone marrow aspiration, and biopsy. Either magnetic resonance imaging or computed tomography scan of involved area was performed in all patients. Five patients who had received chemotherapy in addition to radiotherapy were not included.

2.2 | Pathology

All biopsies from involved sites and bone marrows were assessed by expert hematopathologists at our institution. Histopathological diagnosis was confirmed by the presence of neoplastic monoclonal plasma cells in the involved tissue. Bone marrow biopsies were obtained from the iliac crest and bone marrow aspirations from either the iliac crest or the sternum.

2.3 | Radiotherapy

All patients received involved field photon beam radiotherapy with a curative intent and with 2 Gy/fraction. The planning treatment volume included the radiologically visible macrotumour with a sufficient margin, ie, for vertebral SBPs, the 2 adjacent vertebrae were included. Regional lymph nodes were not included. There were no significant differences between SBP and SEP patients in regard to median radiotherapy dose, which was 40.0 Gy and 45.5 Gy, respectively.

2.4 | Data collection and follow-up

A total of 97 cases with SP were retrieved from our hospitals lymphoma registry. After reviewing the medical records, 77 patients met the inclusion criteria for our study. Additional data was collected from

radiotherapy records, local hospitals, and family doctors. Information on date and cause of death was updated from Statistics Norway. Moreover, information on second primary malignancies was acquired from Norwegian Cancer Registry. Second primary malignancy was defined as any malignant disease other than plasma cell disorders, diagnosed after SP.

Performance status was determined by WHO/ECOG (World Health Organization/Eastern Cooperative Oncology Group) criteria.¹⁴

Response to radiotherapy was evaluated according to Cheson criteria 2 to 3 months after end of treatment.¹⁵ Most patients were evaluated for response by either magnetic resonance imaging or computed tomography scan (X-ray before 1986). Patients were then followed with visits 2 to 3 times a year on the first 2 years and then twice yearly until 5 years. Follow-up data were recorded from the diagnosis until death or the end of the study follow-up at December 31, 2015.

Survival and cause of death for each patient was compared to 5 age-, sex-, and residency-matched individuals from the general population. Information on dates and causes of death for matched controls was available only until the end of 2012.

2.5 | Statistical analyses and clinical endpoints

Overall survival was defined as the time from date of diagnosis until death from any cause. Progression free survival was defined as the time from diagnosis until progression either to new SP or MM or to death from any cause. All other events were censored. MMFS was calculated from the time of diagnosis to progression to MM. All other events were censored.

Survival curves were generated using the Kaplan-Meier method and differences in survival were assessed by log-rank test.

Associations between categorical variables were analyzed with chi-square tests. All tests were 2 sided. *P* values < .05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics Version 22 and Stata SE Version 14.

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics are shown in Table 1. The median observation time was 13.7 years for all patients, 12.7 years for SBP patients, and 14.3 years for SEP patients. Corresponding observation times for patients alive by the end of the study were 14.7, 14.7, and 16 years. Almost one-half of patients with SBP and two-thirds of patients with SEP were 60 years or older, and there was a male predominance in both subgroups (78% in SBP and 75% in SEP). Among SBP patients, involvement of vertebral spine was most common (30 patients, 61%). The remaining 19 patients (39%) had the following nonvertebral disease locations: bones of the pelvic girdle (6 patients), long bones of extremities (4 patients), clavicle and sternum (6 patients each), rib bone (2 patients), and scapula (1 patient). Most patients with SEP (93%) had involvement of the head and neck region: nasopharynx (6 patients), paranasal sinuses (5 patients), nasal cavity (3 patients), thyroid gland, soft palate, tonsil, and vocal cord (2 patients each), and lacrimal gland,

TABLE 1 Patient characteristics

Diagnosis		All patients No. (%)	SBP No. (%)	SEP No. (%)	P Value ^a
Total		77 (100)	49 (64)	28 (36)	N/A
Age, year	Median (range)	61 (25-80)	58 (25-80)	64 (3-79)	.03
	<60	35 (46)	27 (55)	8 (29)	
	≥60	42 (54)	22 (45)	20 (71)	
Gender	Male	59 (77)	38 (78)	21 (75)	.80
	Female	18 (23)	11 (22)	7 (25)	
WHO performance status	0	37 (48)	15 (30)	22 (79)	<.01
	1	24 (31)	18 (37)	6 (21)	
	≥2	16 (21)	16 (33)		
Size of tumour, cm	<6	55 (71)	29 (59)	26 (93)	<.01
	≥6	22 (29)	20 (41)	2 (7)	
M-protein in serum and/or urine	Negative	39 (51)	16 (33)	23 (82)	<.01
	Positive	38 (49)	33 (67)	5 (18)	
Involved region ^b	Vertebral spine		30 (61)		N/A
	All the others		19 (39)		
Treatment	RT	49 (64)	31 (63)	18 (64)	.93
	SRT	28 (36)	18 (37)	10 (36)	
Median RT dose in Gy, range	Overall	40 (30-52)	40 (30-52)	40 (40-50)	.76
	40.0 (30.0-40.25)	43 (56)	21 (43)	15 (54)	
	45.5 (41.2-52.0)	34 (44)	28 (57)	13 (46)	
Follow-up time, years	Median (range)	13.7 (0.2-34.9)	12.7 (0.2-28.3)	14.3 (1.7-34.9)	N/A

Abbreviations: gy, Gray; N/A, not applicable; RT, radiotherapy; SBP, solitary bone plasmacytoma; SEP, solitary extramedullary plasmacytoma; SRT, surgery and radiotherapy.

^aP values are from chi-square test comparing SBP and SEP groups within corresponding rows.

^bOnly for SBP patients.

parotid gland, pituitary gland, and tongue base (1 patient each). The remaining 2 patients with SEP had involvement of lung and the supraclavicular node region, respectively. Laminectomy was performed in 18 (37%) patients with SBP. Indications for laminectomy were structural instability or impaired neurological function. Excisional biopsies or tumour resections were performed in 9 (36%) of patients with SEP. The remaining patients had needle biopsies. All surgical interventions were performed prior to radiotherapy except in one case with vertebral SBP who underwent post radiation laminectomy.

M-component was detected in serum and/or urine protein in 38 (49%) patients, but the amount was quantifiable in only 14/38 patients (13 patients with SBP and 1 with SEP): 10 patients with IgG (median, 9.8 g/L and range, 0.2-17 g/L), 3 patients with IgA (6.3, 7.4, and 12.3 g/L, respectively), and 1 patient with IgM (13 g/L). One or more polyclonal immunoglobulin isotype was suppressed with values under the lower normal limit in 4 patients with vertebral SBP.

3.2 | Response to radiotherapy and relapse after the primary treatment

The overall response rate (ORR) in the SBP group was 94% with 57% complete responses. Likewise, ORR was 96% in the SEP group with more patients achieving complete response (CR) (86%) ($P = .01$) compared to SBP. Only 1 patient in each category did not have a measurable response to radiotherapy. Evaluation of response was not available in 2 patients with SBP who died shortly after treatment from unrelated causes. Favorable factors for ORR in patients with SBP were age <60 years and WHO performance score 0-1 compared to age ≥60 years ($P = .05$) and WHO performance score ≥2 ($P = .01$),

respectively. Corresponding factors in SEP patients were tumour size <6 cm ($P < .01$), negative M-component ($P = .03$), and WHO performance score 0 ($P = .05$), respectively.

Relapse of SP or progression to MM occurred more frequently in the SBP group (65%) than among patients with SEP (18%) ($P < .01$), and 29/32 relapses presented as MM in the SBP group compared to 2/5 in the SEP group. In the SBP group, 3 out of 32 relapses presented as SBP at a new location; one of these was close to the primary radiation field. No in-field relapse was recorded. One of these 3 patients developed MM 18 months later. In the SEP group, 3 out of 5 relapses presented as a new SP, 1 distant from, 1 near, and 1 within the primary radiation field. The patient with in-field relapse had SEP of the left nostril and relapsed 1 year after 45 Gy radiotherapy. Complete surgical resection resulted in a new CR and the patient was relapse-free and alive at the end of the study. None of these 3 patients developed subsequent MM.

3.3 | Survival analysis

For all patients, the OS at 5, 10, and 15 years was 79% (95% confidence interval [CI], 70-88), 63% (95% CI, 52-74) and 46% (95% CI, 34-58), respectively. Progression free survival was 57% (95% CI, 46-68), 36% (95% CI, 46-68), and 27% (95% CI, 17-37), and MMFS was 64% (95% CI, 53-75), 54% (95% CI, 42-66), and 54% (95% CI, 42-66), respectively. Survival curves for both SBP and SEP are shown in Figure 1. Although there was no significant difference in OS between the groups, patients with SEP had a significantly superior PFS and MMFS compared to SBP patients. After 15 years, 33% of SBP and

91% of SEP had not developed MM. Importantly, no patients relapsed or progressed to MM later than 10 years after diagnosis.

3.4 | Predictive factors for survival in SBP and SEP

Results of univariate and multivariate analysis are shown in Table 2. In univariate analysis for the SBP group, the OS was significantly superior for patients younger than 60 years. This was confirmed in multivariate analysis (hazard ratio [HR], 5.78; 95% CI, 2.11-15.86). The multivariate analysis further showed superiority for patients who received radiotherapy and surgery compared to radiotherapy alone (HR, 4.67; 95% CI, 1.22-17.85) and patients who received a median dose of 45.5 Gy compared to those given a median dose of 40 Gy (HR, 2.96; 95% CI, 1.02-8.57). Tumor size less than 6 cm and combined surgery and radiotherapy were positive predictors for PFS (HR, 2.35; 95% CI, 1.07-5.14 and HR, 3.12; 95% CI, 1.2-8.11, respectively). Regarding MMFS, the only predictive factor in multivariate analysis was tumour size more than 6 cm (HR, 3.01; 95% CI, 1.18-7.68).

Age younger than 60 years predicted longer OS for SEP patients, but this was not confirmed in multivariate analysis. Patients with WHO performance score 0 had a significantly superior OS in both univariate and multivariate analysis (HR, 22.16; 95% CI, 2.69-182.3), as did combined surgery and radiotherapy (HR, 9.55; 95%

CI, 1.2-75.63). For PFS, the only positive predictor was WHO status 0 (HR, 17.78; 95% CI, 2.79-113.32).

3.5 | Mortality in patients as compared to controls

At the last follow-up 20 (41%) patients with SBP and 12 (43%) of patients with SEP were still alive. Multiple myeloma was the most common cause of death in SBP patients (49%) followed by cardiovascular disease (CVD) (24%), miscellaneous causes (14%), and other malignancies (14%), while CVD was the most common cause of death in SEP (44%) followed by miscellaneous causes (31%). Only 1 patient with SEP died of MM, while 3 died of other malignancies.

The overall median age at death as recorded by the end of 2012 for SBP patients was 79 years as compared to 83 years in age and sex matched controls ($P < .01$). Corresponding results for SEP were 83 and 83 years. There were no significant differences between patients and controls concerning death due to CVD or another malignancy neither for SBP nor for SEP.

3.6 | Second primary malignancies

Nine patients with SBP and 2 patients with SEP were diagnosed with a second primary malignancy: prostate cancer (3 patients), squamous cell carcinoma of skin (2 patients), and esophageal, sigmoid, rectal,

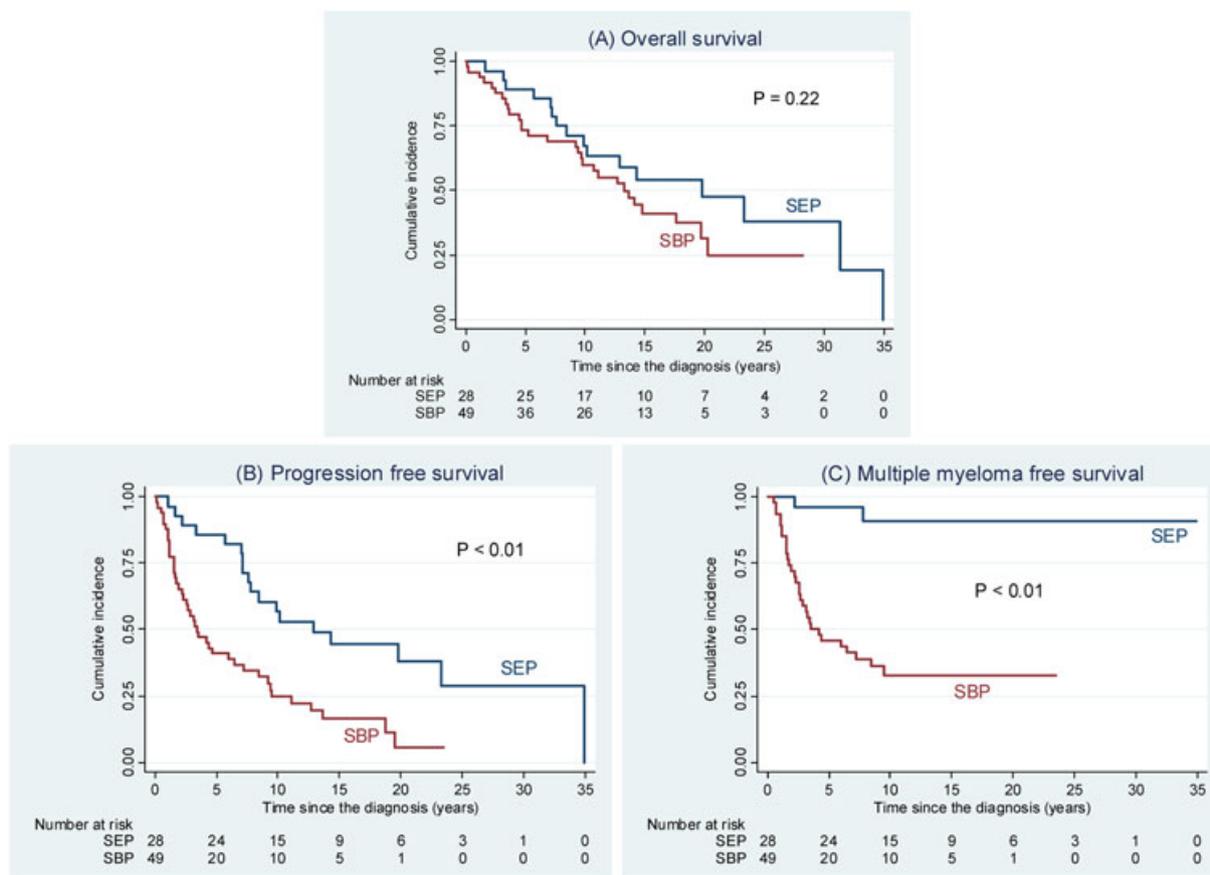


FIGURE 1 Kaplan-Meier survival curves showing comparison between patients with solitary bone plasmacytoma (SBP) and solitary extramedullary plasmacytoma (SEP) regarding (a) overall survival, (B) progression free survival and (C) multiple myeloma free survival

TABLE 2 Results from univariate and multivariate survival analysis

Variable		Overall survival		Progression free survival		Multiple myeloma free survival	
		SBP	SEP	SBP	SEP	SBP	SEP
Age, <60/≥60 years	P value for UVA	<.01	<.01	.05	.27	.66	.52
	P value for MVA	<.01	NS	NS	NS	NS	NS
	HR (95% CI) for MVA	5.78 (2.11-15.86)	NS	NS	NS	NS	NS
Gender, male/female	P value for UVA	.37	.81	.39	.80	.60	.45
	P value for MVA	NS	NS	NS	NS	NS	NS
	HR (95% CI) for MVA	NS	NS	NS	NS	NS	NS
WHO performance status, 0/≥1	P value for UVA	.62	<.01	.45	<.01	.97	.06
	P value for MVA	NS	<.01	NS	<.01	NS	NS
	HR (95% CI) for MVA	NS	22.16 (2.69-182.3)	NS	17.78 (2.79-113.32)	NS	NS
Tumour size, <6/≥6 cm	P value for UVA	.70	.92	.15	.81	.08	.69
	P value for MVA	NS	NS	0.03	NS	.02	NS
	HR (95% CI) for MVA	NS	NS	2.35 (1.07-5.14)	NS	3.01 (1.18-7.68)	NS
M-protein, positive/negative	P value for UVA	.91	.37	.42	.52	.03	.71
	P value for MVA	NS	NS	NS	NS	NS	NS
	HR (95% CI) for MVA	NS	NS	NS	NS	NS	NS
Treatment, SRT/RT	P value for UVA	.43	.06	.21	.32	.33	.73
	P value for MVA	.02	.03	.02	NS	NS	NS
	HR (95% CI) for MVA	4.67 (1.22-17.85)	9.55 (1.20-75.63)	3.12 (1.2-8.11)	NS	NS	NS
Median RT dose, 45.5 Gy/40Gy	P value for UVA	.90	.91	.18	.85	.22	.99
	P value for MVA	.04	NS	NS	NS	NS	NS
	HR (95% CI) for MVA	2.96 (1.02-8.57)	NS	NS	NS	NS	NS
Location, vertebra/others	P value for UVA	.98	X	.95	X	.41	X
	P value for MVA	NS	X	NS	X	NS	X
	HR (95% CI) for MVA	NS	X	NS	X	NS	X

Abbreviations: HR, hazard ratio; MVA, multivariate analysis; NS, not significant; RT, radiotherapy; SBP, solitary bone plasmacytoma; SEP, solitary extramedullary plasmacytoma; SRT; surgery and radiotherapy; UVA, univariate analysis; X, not analyzed. NB: HR mentioned only for MVA. P values in UVA are from log-rank test comparing the 2 groups and are mentioned regardless significance level. P values in MVA are from Cox regression model and mentioned only when statistically significant.

urothelial, cervix, and breast cancer (1 patient each). None of the second primary cancers was located near or in the primary radiation field.

4 | DISCUSSION

In this single-center, retrospective study with a median observation time of 13.7 years, we report the outcome of 49 patients with SBP and 28 patients with SEP treated with radiotherapy. Overall response rates were 94% in SBP patients and 96% in SEP patients. Relapse or progression to MM occurred in 61% of SBP patients compared to only 7% of SEP patients. We only observed one in-field relapse and no in-field secondary malignancies. Interestingly, no patients in the 2 groups developed MM later than 10 years after diagnosis. Unlike for SEP patients, the major cause of death in the SBP group was MM. Compared to controls, the risk of death due to CVD or second malignancy was not increased.

In previous reports, on outcome for patients with plasmacytoma, mostly with limited patient numbers, follow-up time has been shorter than in the present study. While some series show no significant difference between SBP and SEP regarding OS^{5,16} others shows favorable

OS for SEP.^{2,17} Although the rate of progression to MM in our study was much higher in the SBP group, we did not find a significant difference in OS between the 2 groups. This might be caused by a 6-year higher median age of the SEP group. In line with other reports, we observed an inferior PFS and/or MMFS for patients with SBP compared to SEP.^{2,16,17} Bony lesions are usually difficult to measure, and response assessment might be obscured by slow repair.¹⁸ Accordingly, long-term local control, PFS and MMFS might be more reliable measures to evaluate treatment effects in these patients. Katodritou et al reported outcome of 65 SBP and 32 SEP patients treated in 12 different Greek centers with a median follow-up of 5 years. Unlike our study, 48% of their patients received chemotherapy alone or combined with radiotherapy.⁸ The overall 5- and 10-year OS, PFS and MMFS were comparable to what we found. Furthermore, PFS and MMSF were significantly superior for SEP compared to SBP and with no significant difference in OS. The only risk factor for progression to MM in that study was suppressed polyclonal immunoglobulin at the time of diagnosis. Only 4 patients had slightly suppressed polyclonal immunoglobulin in our series and their outcome was not different from the rest of the study population (data not shown). We found that tumour size above 6 cm was a negative predictor for progression to MM in

SBP but not in SEP. Negative impact of tumour size on progression to MM has also been shown in at least one previous study.¹⁹ Others have shown a negative impact of tumour size ≥ 5 cm on local failure.²⁰ Although late progression to MM, even after 10 years have been reported in previous studies,^{9,17} none of our patients developed MM after 10 years. This might indicate that patients who do not progress to MM within 10 years are in fact cured. In our study, treatment with surgery and radiotherapy was predictive for improved OS and PFS in patients with SBP but only for OS in SEP patients. In 1 previous study, on 67 patients with SEP in the head and neck region, the only positive significant predictive factor for OS was combined radiotherapy and surgery.¹² In 2 other studies including both SEP and SBP surgery in addition to radiotherapy did not have any impact on survival. However, only 4%² and 8%⁵ underwent surgery in these 2 studies. In an analysis of 1164 patients with SBP from SEER database with surgery performed in 35% of patients, there was no significant improvement in OS for combined surgery and radiotherapy compared to radiotherapy alone.²¹ Based on data from our study and previous series, it remains an open question whether combining surgery and radiotherapy has impact on survival in SP patients.

Presence of measurable M-component 1 year after treatment has been reported to confer inferior prognosis after treatment for SP.^{22,23} This would be expected, since continuous production of myeloma protein indicates residual disease. We do not have data on this in our patient cohorts.

At present, the preferred dose of radiation for SP patients has not been clearly defined. We observed prolonged OS for the group of SBP patients who received a median radiation dose of 45.5 Gy compared to those who received a median dose of 40 Gy. However, radiotherapy dose did not influence long-term local control, PFS, or MMFS. Further, only 1 out of 77 patients in our cohort had an in-field relapse and this patient received 45 Gy. This strongly suggests that the radiation doses applied in our study was adequate. We did not find any dose-survival relationship for the SEP patients. Of note, only 1 patient in the whole series suffered from an in-field relapse, suggests that the dose of radiation applied in our study had been adequate. In a study on 17 patients with SEP, Tournier-Rangard et al showed improved local control with radiation dose ≥ 45 Gy.²⁴ In another study including 46 patients with SP from Princess Margaret Hospital, radiotherapy doses ≤ 35 Gy was associated with increased risk of local failure.²⁰ In contrast, 2 other series have not shown a clear relationship between radiation dose on local control.^{2,9} On the basis of the results from our study and other reports, we currently apply 40 Gy as a standard dose for SBP and SEP pending results from future randomized prospective trials.

While 1 study has indicated possible increased risk of second primary malignancies¹¹ after radiotherapy for SP, we did not find any evidence to support this. Additionally, we did not observe an increase in mortality from second primary malignancies compared to matched controls. Moreover, there was no increased risk of death from CVD compared to controls. Our data suggest that radiotherapy with relatively small fields can be regarded as a safe in respect to risk of secondary malignancies and CVD.

Although a retrospective single-center study like ours may confer a potential risk of selection bias, we find this less likely since our institution is the only referral center for SBP and SEP in the South-Eastern

part of Norway. However, the statistical power of our analyses are somewhat compromised by the small sample size, especially for the SEP patients.

In conclusion, we have shown that radiotherapy is feasible and a safe treatment option and results in excellent long-term local control both in the SEP and SBP subgroups of plasmacytoma. Unlike for SEP, progression to MM remains a major problem for SBP and the focus of future studies should be to explore new strategies to prevent systemic disease.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

DAB performed the research. DAB, HH, WG, and AK designed the research study. DAB analyzed the data. DAB, AK, WG, and HH wrote the paper.

ETHICS STATEMENT

The study was approved by the Data Protection Officer at Oslo University Hospital and Regional Committee for Medical and Health Research Ethics, South East, Norway (Project number 2012/1957). The study conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

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