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► **To cite this version:**

Sonja Krause, Jens Hillengass, Hartmut Goldschmidt, Jürgen Debus, Dirk Neuhof. Radiotherapy of solitary plasmacytoma. *Annals of Hematology*, 2011, 90 (9), pp.1093-1097. 10.1007/s00277-011-1190-7. hal-00615425

**HAL Id: hal-00615425**

**<https://hal.science/hal-00615425>**

Submitted on 19 Aug 2011

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## **Radiotherapy of solitary plasmacytoma**

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**Short title:** Solitary plasmacytoma

**Abstract**

*Purpose:* Solitary plasmacytoma of the bone (SBP) or extramedullary plasmacytoma (EP) are rare neoplasms amenable to local radiotherapy. In this retrospective analysis, we report the University Heidelberg experience in the treatment of solitary plasmacytoma. *Patients and methods:* From 1995 to 2008, 18 patients were treated with local radiotherapy. Ten patients suffered from SBP, eight patients showed a single extramedullary lesion. *Results:* Local radiotherapy with a median dose of 45 Gy yielded excellent local control with only one patient suffering from local relapse. SBP and EP had significantly different 5-year multiple-myeloma-free survival rates of 36.8% and 86.7%, respectively. However, no significant difference in overall survival could be detected. *Conclusions:* Radiotherapy can achieve excellent local control of solitary plasmacytoma. Progression to multiple myeloma, especially in the case of SBP, remains to be addressed by further studies.

Solitary plasmacytoma are rare neoplasms originating from plasma cells in bone (solitary plasmacytoma of the bone, SBP) or in soft tissue (extramedullary plasmacytoma, EP). SBP constitute about 10% of plasma cell neoplasms and are mainly found in the axial skeleton [1].

EP are even more rare (about 3%) with most manifestations in the head-and-neck region [2].

Although both neoplasms originate from the same cell type, distinct features concerning progression to multiple myeloma suggest two different pathologic entities [3]

Patients typically present with symptoms caused by local tumor mass: pain and neurological deficits in the case of SBP, dysphagia, breathing problems and epistaxis in the case of EP of the head-and-neck region.

SBP and EP being rare malignant disorders, data on treatment options are sparse. However, several single- and multicenter retrospective studies report effective treatment of solitary plasmacytoma with radiotherapy.

This study is a retrospective analysis of the University of Heidelberg experience in the radiooncological treatment of solitary plasmacytoma.

### **Patients and methods**

Clinical data of all patients treated for plasmacytoma or multiple myeloma in the Department of Radiation Oncology of the University of Heidelberg from 1995 to 2008 were searched, ruling out all patients with generalised disease. Inclusion criteria were: one solitary lesion confirmed by histology (fine-needle- or open biopsy), verification of localized disease by whole-body-MRI or -CT or plain film skeletal survey, normal serum calcium, blood count and

renal function, <10% plasma cells in bone marrow biopsy, normal serum protein electrophoresis and no prior treatment for plasmacytoma.

19 patients met the inclusion criteria. One patient was lost to follow-up due to relocation abroad. Ten patients suffered from SBP, with most manifestations in the spine (seven patients), one in the sternal body, one in the skull base and one in the rib cage. Of the eight patients with EP, five had manifestations in the epi-/oropharynx, one in the orbita, one in the paranasal sinuses and one in the penile urethra. For further patient's characteristics, see Table I.

Ten patients were primarily treated with radiotherapy, in eight cases postoperative radiotherapy after partial resection or spinal decompression was performed.

Median age was 60.9 years (range: 35-81 years) and the majority of patients was male.

Radiotherapy was performed using linear accelerators. 2D-planning was used for SBP lesions. For EP lesions, 2D-planning (three patients), CT-based 3D-plans (three patients) or intensity-modulated radiotherapy (IMRT, two patients) were used.

The median applied dose was 45 Gy (range: 30 – 50.4 Gy) in single fractions ranging from 1.8 to 2.5 Gy (for details, see table II) with no difference between SBP and EP.

Clinical follow-up consisted of clinical examination, blood count and chemistry, serum protein electrophoresis and plain film skeletal survey or whole-body-MRI or -CT.

Overall survival (OS) and multiple-myeloma-free survival (MMFS) were calculated using the Kaplan-Meier method. Survival distributions were compared using the log-rank test (Statistica, StatSoft Inc., Tulsa, USA).

## **Results**

### *Follow-up*

Median follow-up was 47 months (range: 8-167 months). At last follow-up, four patients had died (three deaths were myeloma-related). Of the 14 remaining patients, eight presented with no sign of local recurrence or progression to multiple myeloma.

### *Local control*

Local control was very good with only one patient suffering from local relapse (6%). In this case, local relapse occurred seven years after development of multiple myeloma and eight years after initial treatment of vertebral bodies Th1-L2 with a total dose of 38 Gy, so that re-irradiation was possible. Yet, radiotherapy had to be stopped due to the development of perforated diverticulitis.

### *Progression to multiple myeloma*

Nine patients (50%) progressed to multiple myeloma. Median time to progression was 34.3 months (range: 2 – 154 months). Progression occurred in the majority of cases (six patients) in the first year after initial diagnosis. For all 18 patients, 2- and 5-year MMFS rates were 59.1%, the 10-year MMFS rate was 49.2%. Patients suffering from EP showed a significantly lower progression rate than SBP patients. Only two of eight patients (25%) with EP progressed to multiple myeloma, whereas seven of eight patients (70%) with SBP suffered from progression. The 5-year MMFS rates for SBP and EP were 36.8% and 86.7%, respectively ( $p=0.015$ , Figure I). Age, sex and dose applied to the lesion had no influence on multiple-myeloma-free survival on univariate analysis.

### *Overall survival*

Four patients (22.2%) died during follow-up. Three patients died of multiple myeloma, all of them initially had presented with SBP. One patient initially diagnosed with EP died of dementia.

2-year OS was 87.5%, 5-year and 10-year OS were 77.8% with no statistically significant difference between SBP and EP ( $p=0.234$ , Figure II).

### *Toxicity*

In general, local radiotherapy was tolerated very well. No grade III-IV toxicity occurred. Patients with irradiation of the head and neck mainly suffered from mild acute mucositis and skin erythema. Patients treated for bone lesions reported no side effects. None of the patients in our cohort developed secondary malignancies.

## **Discussion**

### *Local control*

In line with other retrospective studies, radiotherapy achieved excellent local control with only one patient suffering from local relapse (94% local control). In a large multicenter retrospective analysis of 258 patients with SBP/EP, Ozsahin et al. saw a 5-year local control rate of 86% [4]. Along this line, Liebross et al. reported 96% local control in patients with SBP [5] and Bachar et. al observed a 5-year freedom of local recurrence of 81% [2]. There is no reported significant difference in local control between SBP and EP. For example, Dagan et al. observed local control rates of 88% in their series of 32 patients with SBP or EP with no statistically significance between tumor types [6].

### *Progression to multiple myeloma*

We found a significantly higher percentage of patients with progression to multiple myeloma in the case of SBP (70%) compared to EP (25%). Again, this is in accord with the data published so far. In the University of Florida series, 68% of SBP patients progressed to multiple myeloma, whereas only 20% of EP patients had progressive disease [6]. In their series of 46 patients with SBP or EP, Tsang et al. saw significantly different 8-year myeloma-free survival rates of 36% and 84%, respectively [7]. Ozsahin et al. identified bone localization as a predictor for development of multiple myeloma [4].

Compared to other studies, the median time to progression of 34.3 months we saw in our patients forms the upper end of the reported range of 13 – 36 months [1,7,8,9]. Six out of nine patients with progressive disease developed multiple myeloma in the first year after diagnosis. This fact underlines the relevance of thorough pretherapeutic staging. With the introduction of whole-body MRI scans, staging sensitivity could be enhanced significantly. According to Wilder et al., up to 25% of patients initially diagnosed with solitary plasmacytoma are found to have systemic disease [10].

Given the high probability of progression to systemic disease, a small prospective study by Aviles et al. applied local radiotherapy followed by low dose prednisone/melphalan over 3 years, resulting in 12% progression to multiple myeloma compared to 54% of patients treated with radiotherapy alone [11]. However, the question of adjuvant chemotherapy for solitary plasmacytoma remains to be addressed by larger prospective studies.

### *Overall survival*

Analysis showed that 2-year-OS in our series was 87.5% and 5-year- and 10-year-OS was 77.8% with no statistically significant difference between SBP and EP. Data published so far are inconsistent: Significantly different OS rates were found by Ozsahin et al., who described 10-year overall survival rates of 72% for EP and 52% for SBP ( $p=0.04$ ) [4], and Tsang et al.,



who reported 8-year overall survival rates of 70% or 33%, respectively ( $p=0.023$ ). In contrast, neither Bolek et al. [12] nor Jyothirmay et al. [13] could detect a significant difference in OS. For an overview of all studies cited, see table III.

### *Influence of dose*

In our patient cohort, we could not detect a dose-dependence of local control. In agreement with our findings, Tsang et al. reported no higher risk of local recurrence for doses  $<35$  Gy [7] and Oszahin et al. described no dose-dependence of local control for doses  $>30$  Gy [4]. In contrast, Mendenhall et al. found that doses  $>40$  Gy resulted in 94% local control of SBP compared to 69% after  $<40$  Gy [14]. For EP, significantly better local control was reported for doses  $>45$  Gy (100% 5-year LCR vs. 55% for  $<45$  Gy) [15]. Considering the low treatment toxicity, doses of 40-50 Gy seem to be a general consensus for SBP [1,12,16] and of 40-60 Gy for EP [17,18].

### **Conclusion**

Local radiotherapy of solitary plasmacytoma results in excellent local control with low treatment toxicity. SBP and EP show distinct features concerning progression to multiple myeloma with SBP patients being at a higher risk of progression. Further studies are required to identify risk factors for progression in order to establish more individualized therapeutic strategies.

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**Legends**

- Table I. Patients' and treatment characteristics.
- Table II. Prescribed dose and fractionation scheme.
- Table III. Literature overview.
- Figure I. Multiple-myeloma-free survival for SBP and EP patients.
- Figure II. Overall survival for SBP and EP patients.

Patients' and treatment characteristics		n
Sex	Male	12
	Female	6
Age at diagnosis, median	60.9 years (range: 36-81)	
SBP	Vertebral body	7
	Skull base	1
	Sternum	1
EP	Ribs	1
	Head-and-neck	7
Primary radiotherapy	Urethra	1
	SBP	5
Postoperative radiotherapy	EP	5
	SBP	6
	EP	2

Table I. Patients' and treatment characteristics.

<b>patient</b>	<b>localisation</b>	<b>total dose (Gy)</b>	<b>single dose (Gy)</b>
1	sternum	45	2.5
2	nasopharynx	50.4	1.8
3	C4 - C6	40	2
4	nasopharynx	48	2
5	pharynx	46	2
6	Th8 – L2	38	2
7	L2 - 4	40	2
8	nasopharynx	38	2
9	Th1 - 3	40	2
10	right orbit and cheek	48	2
11	C7 – Th2	50	2
12	Th5 – 9	30	3
13	skull base	45	1.8
14	tongue	44	2
15	8th rib	50	2
16	L1-4	26 (boost 40)	2
17	paranasal sinuses	50	2
18	penile urethra	46	1.8

	<b>No. of patients</b>	<b>RT dose</b>	<b>Local control</b>	<b>MMFS</b>	<b>OS</b>
Bachar 2008	68 (only EP)	35.4 Gy median	5-y-LCR 81%	5-y-MMFS 77%	5 y 76%
Bolek 1996	37 (SBP 27, EP 10)	43.2 Gy median	LC 97%	10-y-MMFS 46% SBP, 89% EP	5-y-OS EP 100%, SBP 32%
Chao 2005	16 (only EP)	45 Gy median	LC 100%	10-y-MMFS 75%	10-y-OS 54%
Creach 2008	18 (only EP)	50.4 Gy median	LC 100%	Development of MM or plasmacytoma at distant sites 33% after median 3.1 y	10-y-OS 55%
Frassica 1989	46 (only SBP)	39.75 Gy median	LC 89%	10-y-MMFS 25%	10-y-OS 45%
Jyothirmayi 1997	30 (SBP 23, EP 7)	45 Gy median	LC EP 86%, SBP 100%	development of MM EP 43% after median 30 mo., SBP 39% after median 28 mo.	5-y-OS EP 57%, SBP 75%
Liebross 1998	57 (only SBP)	50 Gy median	LC 96%	53% development of MM after median 1.8 y	median survival 11.0 y
Liebross 1999	22 (only EP)	50 Gy median	LC 95%	5-y-MMFS 68%	Not stated, median survival 9.5 y
Mayr 1990	30 (EP 13, SBP 17)	40-60 Gy	LC EP 92%, SBP 88%	Development of MM EP 23%, SBP 53%	5-y-OS EP 58%, SBP 47%
Ozsahin 2006	258 (SBP 206, EP 52)	40 Gy median	5-y-LCR 86%	10-y-MMFS all 31%, EP 55%, SBP 25%	10-y-OS all 54%, EP 72%, SBP 52%
Tournier-Rangard 2006	17 (only EP)	52.6 Gy median	5-y-LCR 72.8 Gy	5-y-MMFS 64.1 %	Not stated
Tsang 2001	46 (SBP 32, EP 14)	35 Gy median	8-y-LCR 83%	8-y-MMFS: 50%	8-y-OS 65%
Wilder 2002	60 (only SBP)	46 Gy median	10-y-LCR 90%	10-y-MMFS 38%	10-y-OS 59%





