Immunoglobulin G (IgG) Subtype Is Associated with a Favorable Survival Prognosis in Patients Irradiated for Spinal Cord Compression from Myeloma

DIRK RADES[1], ANTONIO J. CONDE-MORENO[3], NIKLAS GEBAUER[2], TOBIAS BARTSCHT[2], JON CACICEDO[4], BARBARA SEGEDIN[5] and STEVEN E. SCHILD[6]

Departments of [1]Radiation Oncology and [2]Medical Oncology, University of Lübeck, Lübeck, Germany; [3]Department of Radiation Oncology, Consorcio Hospital Provincial de Castellón, Castellón, Spain; [4]Department of Radiation Oncology, Cruces University Hospital, Barakaldo, Vizcaya, Spain; [5]Department of Radiotherapy, Ljubljana Institute of Oncology, Ljubljana, Slovenia; [6]Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.

Abstract. *Aim: This study was performed to investigate the prognostic impact of the myeloma subtype on the survival prognosis of patients with spinal cord compression (SCC) from myeloma. Patients and Methods: In 238 patients irradiated for SCC from myeloma, the myeloma subtype and 10 additional characteristics were evaluated for survival. These characteristics were fractionation of radiotherapy, age, time from myeloma diagnosis to SCC, presence of extra-osseous lesions, additional osseous lesions, gender, time to developing motor weakness, ability to walk, number of vertebrae affected by SCC and performance status. Results: Immunoglobulin G subtype was associated with significantly better survival than other subtypes both at 1 year (80% vs. 50%) and at 2 years (56% vs. 30%) following radiotherapy of SCC (p<0.001). In the subsequent Cox regression analysis, myeloma subtype maintained significance (risk ratio=2.44; 95% confidence interval=1.56-3.85; p<0.001). Conclusion: This study identified myeloma subtype as being an independent prognostic factor of survival in patients with SCC from myeloma.*

Patients with myeloma account for 10-15% of all patients presenting with malignant spinal cord compression (SCC) (1). Myelomas are very radiosensitive tumors. Therefore, these patients were excluded from a randomized trial comparing radiotherapy (RT) alone to RT preceded by decompressive surgery (2). It is widely accepted that RT alone is the standard treatment of SCC from myeloma (1). For RT, conventional irradiation or stereotactic body radiation therapy (SBRT) are available techniques. However, a practical guideline from the American Society for Radiation Oncology recommended that SBRT for SCC should not be used outside clinical trials (3). SBRT may result in late morbidity such as myelopathy and vertebral body fractures (4, 5). Therefore, the vast majority of patients with malignant SCC, including those with SCC from myeloma, receive conventional RT. If conventional RT is administered, several fractionation regimens are in use. It is well-recognized that patients with a poor survival prognosis should receive short-course RT and those with a more favorable prognosis, long-course RT (6-8). The most common long-course RT program is 3 Gy × 10 over 2 weeks. However, a previous study suggested that patients with an extraordinarily good prognosis benefit from RT regimens with total dose greater than 30 Gy, such as 2 Gy × 20 and 2.5 Gy × 15 (9). To be able to deliver the most appropriate RT to each patient with SCC from myeloma, the RT regimen should be adapted to the patient's survival prognosis. For precise estimation of survival, independent prognostic factors of survival are very helpful. Several prognostic factors have already been identified (10). The present study investigated the potential role of the myeloma subtype as an additional independent predictor of survival in patients irradiated for SCC from myeloma in the largest series of such patients reported so far.

Correspondence to: Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany. Tel: +49 4515006661, Fax: +49 451 5003324, e-mail: Rades.Dirk@gmx.net

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Patients and Methods

Two-hundred and thirty-eight patients who presented with weakness of one or both legs due to SCC from vertebral myeloma were included in the present retrospective study. The patients received RT alone with either a short-course (8 Gy ×1 or 4 Gy × 5) or a long-course (3 Gy × 10, 2.5 Gy × 15 or 2 Gy × 20) RT regimen. In

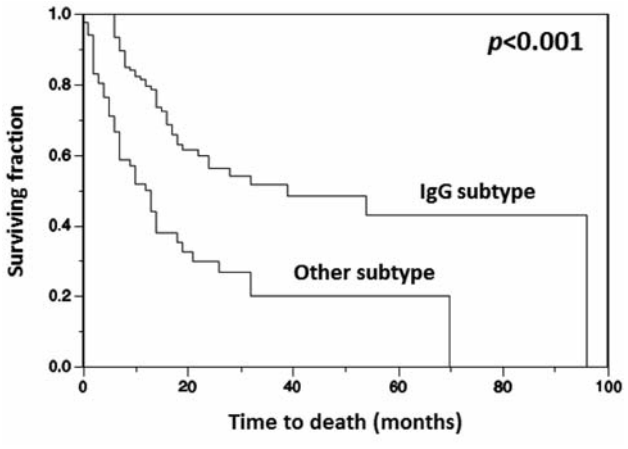

Figure 1. *Kaplan–Meier curves for survival according to myeloma subtype. The p-value was calculated with the log-rank test.*

addition to the RT regimen, 10 further characteristics were evaluated for survival including the myeloma subtype (IgG *vs.* other), age (≤64 years *vs.* >64 years, median age=64 years), time from myeloma diagnosis to SCC (≤15 months *vs.* >15 months), extra-osseous lesions prior to RT of SCC (no *vs.* yes), additional osseous lesions prior to RT of SCC (no *vs.* yes), gender, time to developing motor weakness prior to RT of SCC (≤14 days *vs.* >14 days), ability to walk prior to RT of SCC (not ambulatory *vs.* ambulatory), number of vertebrae affected by SCC (1 and 2 *vs.* ≥3) and Eastern Cooperative Oncology Group performance score (ECOG 1 and 2 *vs.* ECOG 3 and 4). The main focus was to determine if there was an association between myeloma subtype and survival. All of these characteristics were analyzed with respect to survival with Kaplan–Meier analysis and the log-rank test (univariate analysis). Those characteristics that achieved significance ($p<0.0045$=alpha level of 0.05 after Bonferroni's adjustment) were subsequently included in a Cox regression analysis to identify the independent predictors of survival.

Table I. *Univariate analysis of survival.*

	At 1 year (%)	At 2 years (%)	*p*-Value
Myeloma subtype			
IgG (n=153)	80	56	
Other (n=85)	50	30	<0.001
Age			
≤64 years (n=125)	75	62	
>64 years (n=113)	68	56	0.34
Time from myeloma diagnosis to SCC			
≤15 months (n=128)	78	67	
>15 months (n=110)	66	51	<0.001
Extra-osseous lesions			
No (n=218)	77	63	
Yes (n=20)	0	0	<0.001
Additional osseous lesions			
No (n=91)	81	70	
Yes (n=147)	67	52	<0.001
Gender			
No (n=88)	63	55	
Yes (n=150)	78	61	0.21
Time to developing motor weakness			
≤14 Days (n=112)	59	44	
>14 Days (n=126)	83	71	<0.001
Ability to walk			
Not ambulatory (n=69)	52	30	
Ambulatory (n=169)	80	70	<0.001
Number of vertebrae affected by SCC			
1-2 (n=112)	74	65	
≥3 (n=126)	71	54	0.17
ECOG performance score			
1-2 (n=150)	85	76	
3-4 (n=88)	49	28	<0.001
Fractionation regimen			
Short-course RT (n=84)	69	62	
Long-course RT (n=154)	74	58	0.68

SCC: Spinal cord compression, ECOG: Eastern Cooperative Oncology Group, RT: radiotherapy.

Results

Seven of the investigated characteristics were positively associated with survival in the univariate analysis, including IgG subtype ($p<0.001$, Figure 1), time from myeloma diagnosis to SCC of >15 months ($p<0.001$), no extra-osseous lesions prior to RT of SCC ($p<0.001$), no additional osseous lesions prior to RT of SCC ($p<0.001$), slower development of motor weakness prior to RT of SCC ($p<0.001$), ability to walk prior to RT of SCC ($p<0.001$), only 1 or 2 vertebrae affected by SCC ($p<0.001$) and an ECOG performance score of 1 or 2 ($p<0.001$). The results of the entire univariate analysis are shown in Table I.

In the subsequent Cox regression analysis, myeloma subtype ($p<0.001$), extra-osseous lesions prior to RT of SCC ($p<0.001$), additional osseous lesions prior to RT of SCC ($p=0.021$), the ability to walk prior to RT of SCC ($p<0.001$) and the ECOG performance score ($p<0.001$) proved to be significantly associated with survival. The time to developing motor weakness showed a trend ($p=0.059$) for association. The results of the complete multivariate analysis are given in Table II.

Discussion

During recent years, a great amount of research has been performed to improve the outcome for patients with myeloma (11-15). Myeloma of the vertebral body may lead to destruction of the bone, resulting in damage of the posterior wall of the affected vertebrae, leading to SCC. Out of all patients with SCC, every 7th to 10th patient has SCC from myeloma (1). When compared to patients with malignant SCC from other tumors, those with myeloma generally have a more favorable survival prognosis. Furthermore, myeloma is

Table II. *Multivariate analysis of survival*.

Factor	Risk ratio	95% CI	*p*-Value
Myeloma subtype: IgG *vs*. other	2.44	1.56-3.85	<0.001
Time from myeloma diagnosis to SCC: >15 months *vs*. ≤15 months	1.24	0.64-1.01	0.29
Extra-osseous lesions: No *vs*. yes	4.74	2.45-8.67	<0.001
Additional osseous lesions: No *vs*. yes	2.02	1.11-3.72	0.021
Time developing motor weakness: >14 days *vs*. ≤14 days	1.24	0.99-1.57	0.059
Ability to walk: Ambulatory *vs*. not ambulatory	2.67	1.67-4.27	<0.001
ECOG performance score: 1-2 *vs*. 3-4	3.30	2.05-5.36	<0.001

CI: Confidence interval, SCC: spinal cord compression, ECOG: Eastern Cooperative Oncology Group.

more radiosensitive than solid tumors. Therefore, patients with SCC from myeloma deserve specific consideration. Because of its extraordinary radiosensitivity, SCC from myeloma is generally treated with RT alone rather than decompressive surgery followed by RT (2). When delivering RT, it is important to use a fractionation regimen tailored to a patient's individual situation in order to provide optimal treatment results. Beside other factors such as patient comorbidity, performance status and distance to the radiotherapy department, the patient's remaining lifespan should be considered. To provide optimal patient care, it is crucial to know a patient's remaining lifespan as precisely as possible. For estimating this, prognostic factors are quite helpful. Several factors have been identified for patients with SCC from myeloma. In a previous study, a significant positive impact on the survival of these patients was reported for ECOG 1 or 2 ($p<0.001$), ability to walk prior to RT of SCC ($p<0.001$), no further osseous myeloma lesions at the time of RT ($p<0.001$) and no extra-osseous myeloma lesions at the time of RT of SCC ($p<0.001$) (10). In addition to these clinical factors, genetic markers were reported to be of prognostic significance. Myelomas with deletions 1p and 17p, as well as translocations t(4;14), t(14;16) und t(14;20) according to fluorescence *in situ* hybridization analysis were associated with worse prognoses (16, 17). This also applied to deletion those with 13q, deletion 17q and monosomy 13, when identified by chromosomal analysis.

In the current study, which includes the largest cohort of patients with SCC from myeloma, we identified an additional predictor of survival, the myeloma subtype. Patients with SCC from an IgG myeloma had a significantly better survival than patients with other subtypes. This new prognostic factor will likely further facilitate greater personalization of care for SCC from myeloma. Since the myeloma subtype was a highly significant and independent predictor, one may consider optimizing an existing survival score which was specifically designed for patients with SCC from myeloma, with the addition of myeloma subtype to that score (18).

In conclusion, this study identified a new independent predictor of survival in patients with SCC from myeloma. This new factor can contribute to a more precise estimation of an individual patient's survival time and to a more appropriate tailoring of treatment to the patient's personal situation.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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