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Prognostic significance of tumor burden assessed by whole-body magnetic resonance imaging in multiple myeloma patients treated with allogeneic stem cell transplantation

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Abstract

Allogeneic stem cell transplantation is a disputed but increasing therapeutic option in patients suffering from multiple myeloma in Europe. To study possible predictors of survival, 79 patients were investigated using whole-body magnetic resonance imaging to assess the visible tumor burden before and after allogeneic stem cell transplantation. Statistical analysis of clinical and imaging parameters included Cox regression models and distribution of survival time estimates (Kaplan-Meier method). Log rank test was used to determine the prognostic impact of the presence of focal lesions on survival. A higher tumor burden according to the lesion count was associated with a shorter overall survival (univariable/multivariable Cox regression: 1st magnetic resonance imaging p=0.028/ p=0.048; 2nd magnetic resonance imaging p=0.008/ p=0.024). Focal infiltration pattern itself seemed to be an additional adverse prognostic factor for overall survival (2nd MRI p=0.048), although no definite cut-off could be defined. Kaplan-Meier estimates at 60 months of follow-up show a significant difference (Log rank p=0.04) for overall survival rates between patients with focal infiltration (32%) and those without (75%). Since this subgroup of patients may benefit from maintenance therapy, adoptive immunotherapy, or local interventions, whole-body imaging is an appropriate and highly recommendable diagnostic approach for detection of prognostically relevant lesions before and after treatment.

Introduction

In the era of emerging immunologic treatment options in hematology and oncology, one of the first approaches in this field namely allogeneic stem cell transplantation (alloSCT) remains a largely disputed but still promising therapeutic option. Results from clinical trials comparing outcome after autologous and alloSCT in patients with multiple myeloma (MM) have been ambiguous. Whereas in some studies allogeneic transplantation in first-line led to at least a superior progression free survival (PFS), the outcome was similar or even inferior to autologous SCT in others [1-6]. In the relapsed setting only one small study was able to show a superior PFS [7]. Nevertheless, alloSCT is being increasingly used in some European countries, especially as second line treatment and beyond [8]. In some of the studies survival curves revealed a plateau with patients achieving a long-term remission interpreted by some researchers as cure. Treatment-related mortality, however, is high compared to autologous transplantation, ranging from 10% in some first-line studies to up to 33% in the relapsed setting. Therefore, the International Myeloma Working Group recommended alloSCT only for eligible patients with early relapse after autologous SCT and within the setting of clinical trials [9]. This considered, it will be necessary to discriminate patients who will probably benefit from the treatment from those who will not. Measurement of tumor burden as a surrogate for possible remission or relapse is an ongoing matter of debate and is mostly indirect, as through immunoglobulin production/ free light chains, CRAB criteria etc. Quantification can also be attempted through the percentage of plasma cells in bone marrow, but is prone to sampling errors due to a focal growth pattern, as it is found in a significant number of patients [10]. Monitoring of minimal residual disease including multi-color flow cytometry (MFC) and next generation sequencing (NGS)-based detection provides prognostic information but goes along with the same problem of potential sampling error [11-13]. To identify the localization of malignant foci in the organism, modern imaging techniques play a major role in diagnostics and follow up. As a consequence, these methods have been included in the updated diagnostic and response criteria [14,15]. Whole-body magnetic resonance imaging (WB-MRI) is

of great value in early diagnosis and detection of residual disease since it has been shown that bone marrow infiltration detected by MRI is of prognostic significance [16-18]. Previously, an agreement between serological response and changes in imaging has been proven, and it has also been shown that residual focal lesions after therapy (autologous SCT) are of prognostic significance for overall survival (OS) [19]. Additionally, MRI has the advantage that it implies neither radiation exposure nor contrast agent administration and can therefore be performed repeatedly without harm [20]. In the present study, we examined bone marrow infiltration in WB-MRI in patients before and after allogeneic SCT in addition to clinical and molecular risk constellation. Our intention was to learn whether the number of focal lesion before alloSCT or the number of persisting focal lesions thereafter is a possible predictor of survival. Finally, MRI might help to identify patients who will benefit from this treatment, or, in the post-transplant setting, who might need additional treatment.

Methods

Patient cohort

In this single-institution-imaging-study, 79 patients were evaluated and had undergone WB-MRI before and after alloSCT between 7/2004 and 9/2013. 68 were in stage III (86%) and 11 in stage II (14%) according to Durie- Salmon [21]. Study approval was obtained from the institutional review board of the University of Heidelberg/Germany, and informed consent was waived due to the retrospective nature of this evaluation. For therapy regimes see Table 1, clinical remission status is shown in Table 2.

Imaging protocol and evaluation

Diagnostic whole-body-MRI examinations were performed on 1.5T scanners (Avanto, Siemens Medical Solutions, Erlangen/Germany) including a coronal T1-weighted turbo-spin-echo sequence, coronal T2-weighted, fat-attenuated turbo-inversion-recovery magnitude

(TIRM), and morphologic sagittal sequences (Table 3). No contrast medium was given. Protocol details have been published previously [17, 22].

Focal lesions and diffuse infiltration patterns were assessed separately for each acquisition date by two radiologists, with 4 and 25 years of experience in oncologic imaging, blinded to the response, in consensus reading as previously described [19, 23, 24]. Focal lesions were counted as myeloma infiltrates if they were hypointense in T1w as well as hyperintense in T2w fat-attenuated sequences, and >5 mm in diameter. Supplementary information is available online.

Statistical analysis

For the analysis of prognostic significance of parameters at 1st MRI, PFS and OS were calculated from the date of allogeneic transplantation on, including 79 patients. OS was defined as time to death from any cause, and PFS as time to progression of disease or death, whichever occurred first. For parameters at 2nd MRI, OS and PFS were counted from the landmark time point 250 days after alloSCT. Patients who were in progression even before or at the 2nd MRI were excluded from this part of the analysis. The 2nd MRI was only included if it had been performed within 250 days after alloSCT.

Log-rank test was used to determine the prognostic impact of the presence of focal lesions on survival, and the distribution of survival times was estimated with the Kaplan-Meier method. Survival rates for PFS and OS at 24 and 60 months since alloSCT and landmark were compared. Prognostic impact was assessed with univariable and multivariable Cox regression models. Hazard ratio for the number of focal lesions was scaled to increments of 10 lesions. Multivariable models included the following additional covariates: Durie- Salmon stage, elevated LDH-levels, age, ISS (II/III vs. I), cytogenetic high-risk, treatment auto-alloSCT upfront each before alloSCT, and remission status according to the IMWG-criteria (VGPR or better) at the corresponding examination date of MRI assessment. A separate model was fitted for each time point (1st/2nd MRI) and MRI parameter (focal lesions yes vs. no/number of focal lesions). For multivariable models, missing values of clinical parameter

values were imputed using multivariate imputation by chained equations as implemented in the R package based on 100 imputation runs [25]. All tests were two-sided; *P*<0.05 was considered statistically significant. All analyses were carried out with statistical software R 3.2 (R Foundation for Statistical Computing, Vienna/Austria. URL https://www.R-project.org/).

Results

Clinical parameters

Mean time interval between 1st MRI and alloSCT was 29 days (range 0 -113). Response was assessed according to the guidelines of the International Myeloma Working Group adding "near complete remission" (Table 2;[15]). Median follow-up was 83.5 months (72.0-113.6). Fifty-seven (72.2%) patients had recurrent disease during follow-up. In total 65 events for PFS and 51 deaths were observed (64.5%). Out of the 79 patients (median age 53 years/ range 29-65, 30 female/ 49 male patients) who had an initial MRI, 63 also completed the follow-up examination, 48 of them in an acceptable time frame (< 250 days after alloSCT). 39 patients of those 48 had no progression until the 2nd MRI. Median time between alloSCT and 2nd MRI was 183 days (range 105- 238 days). For these 39 patients, 32 PFS events and 23 deaths were observed during follow-up. Median follow-up time in this subgroup was 76 months.

Univariable analysis of prognostic factors is shown in Table 4. A higher stage of disease according to the classification of Durie- Salmon (III versus II) resulted in earlier progression after alloSCT (HR 3.10, p=0.016). Prognostic factors before alloSCT influencing OS include an increase of LDH level (per 100U/L increment, HR 1.4, p=0.025). A less favorable outcome was also found for patients who did not undergo auto-alloSCT up front (HR 2.45, p=0.039).

Multivariate analysis (Table 4) supported an influence of the Durie- Salmon stage at 1st MRI on PFS (HR 3.48, p=0.023), and of the therapy regime on OS (HR 2.73, p=0.035). Other factors as age, LDH, remission status and cytogenetic risk constellation did not reach statistical significance.

MRI findings

At initial imaging, focal lesions were detected in 66 out of 79 patients (83.5%), and diffuse infiltration patterns in 60 patients (76%). After alloSCT, myeloma-suspicious focal lesions were visible in 27 out of 39 patients (69.2%), and none in 12 (30.8%). 28 patients had signal alterations compatible with diffuse infiltration (71.8%). A figure with T1-weighted images of a patient with multiple lesions at various locations is includes in the supplementary material.

Of the 39 patients without clinical progression, 8 had no lesions in neither the baseline nor the follow-up MRI scan. In 27 patients, one or more lesions were found at baseline and at the follow-up scan. In 4 patients one or more lesions were present at baseline and resolved after alloSCT. An example of a focal remission is shown in Figure 1, images of a patient with progressive disease in follow-up MRI is included in the supplementary material.

Univariable regression analysis (Table 5) could not detect statistically significant influence of MRI findings on PFS. Statistical results for presence of one or more focal lesion after therapy and of increasing number of focal lesions at 1st and 2nd MRI suggested an effect with HR >1 but this did not reach statistical significance.

A higher number of focal lesions at baseline and follow-up on the other hand were associated with a shorter OS (Table 5, HR 1.22, p=0.028; HR 1.46, p=0.008 respectively, per 10 lesion increase). Presence of at least one focal lesion after therapy also yielded a negative prognostic effect on OS (Table 5, HR 2.98; p=0.048). This is also seen in the Kaplan-Meier plot for OS and presence of any focal lesion at second MRI, which is shown in Figure 2. Kaplan-Meier survival rates for PFS and OS at 24 and 60 months of follow up are presented in Table 6. If any focal lesion was detectable on the second MRI, the OS rate was 63% after 24 months and 32% after 60 months. If no focal lesions had been detected (log-rank, p=0.04), 92% of the patients were alive after 24 months, and 75% after 60 months.

Multivariable analysis supported the adverse prognostic influence on OS for increasing number of lesions (by 10) at both time points (HR 1.24, p=0.048; HR 1.56, p=0.024, respectively). Furthermore, increased risk without reaching statistical significance was found for PFS and OS considering presence of focal lesion at 1st MRI (HR 1.96, p=0.097; and HR

2.26, p=0.098), and for higher numbers at baseline (PFS, increase by 10 lesions: HR 1.21, p=0.058).

Diffuse infiltration pattern showed no impact on PFS (1st MRI p=0.720, 2nd MRI p=0.699) or OS (1st MRI p=0.151, and 2nd MRI p=0.238).

Patients with decreasing numbers of focal lesions (19/39) between MRIs did not have a better prognosis than other patients with focal infiltration at baseline imaging. Patients with resolving lesions showed slightly better PFS than patients with no lesions at both MRIs but without statistical significance (HR 0.42 p= 0.280). No statistically significant difference was found for patients with none versus persisting lesions (HR 1.41, p=0.44), meaning radiologically stable patients.

Discussion

Given that multiple myeloma is so far not curable in the majority of patients, not even with autologous SCT, alloSCT remains as a last resort in the attempt to definitely eradicate the disease. However, a relatively high treatment-related mortality and morbidity and a still significant percentage of relapsing patients has led to the recommendation to apply this treatment only in eligible patients with early relapse after autologous SCT and within clinical trials [9]. Hence, it is important to identify those patients who might benefit from alloSCT.

Prognostic significance of tumor burden

The intention of the current analysis was to study the prognostic relevance of focal lesions as a measure of tumor burden in multiple myeloma in the setting of alloSCT. MRI examinations before and after allogeneic stem cell transplantation were therefore retrospectively reviewed with a long follow-up. Results of univariable and multivariable analyses verified that a higher tumor load at baseline as well as follow-up-MRI is of adverse prognostic significance for OS. This is supported by indirect measurements of tumor burden, like increasing LDH-levels or a

high M-component production rate, as being included in the Durie- and Salmon Staging system, which was used for these patients by the time of recruitment.

In patients who did not progress immediately after transplantation, the detection of a focal infiltration pattern (at least one focal lesion/ any lesion) in bone marrow after therapy seems to be an additional adverse factor. OS after 5 years was 75% in patients without focal lesions in second MRI, compared to 32% for patients with detectable lesions. This remarkable difference goes in line with the research by Walker et al. who concluded that a higher number of focal lesions in untreated newly diagnosed patients was unfavorable for survival, although in our present study no cut-off point for number of lesions could be defined. Patients with resolving lesions resembling imaging response, showed slightly better PFS without statistical significance, probably due to limited eligible patients with complete imaging. Patients with any focal lesion after therapy and especially a higher tumor load on MRI are at higher risk of progression and shorter OS, independently of molecular tumor activity. Therefore, patients might be selected for and hopefully profit from continuous therapy to prevent or at least delay relapse. Additionally, localized relapse has been shown to occur despite sustained molecular remission, which can be reliably detected through follow-up imaging [26].

Comparison to findings in PET/CT and autologous SCT

The results of the present analysis also support previous findings that residual lesions after autologous SCT are of adverse prognostic significance. This is true for MRI as well as PET/CT [19, 27, 28]. The mentioned results have led to the implementation of imaging findings into the updated recommendations for assessment of treatment response in patients with multiple myeloma [15]. The rationale behind this recommendation is also that an assessment of minimal residual disease usually is performed on bone marrow samples acquired from the iliac crest. Those samples, however, might miss accumulations of malignant cells i.e. focal lesions in other parts of the body. Since alloSCT aims at a cure of myeloma, the achievement and therefore the assessment of the deepest possible response is crucial. Our findings in the alloSCT setting are supporting results of Patriarca et al., who evaluated 54 patients before

and after allogeneic SCT with PET/CT and were able to show that patients with a complete remission in imaging have a significantly longer PFS and OS than those in whom any PET-positive lesions had remained (2- year PFS: 51% versus 25%, P=0.03; 2-year OS: 81% versus 47%, P=0.001; [29]). In recently published data of the IFM/DFCI Trial, PET/CT normalization before maintenance was also associated with better PFS and OS [30].

Combined results so far suggest that residual disease after therapy increases the risk of relapse, as we previously also discussed for patients after autologous SCT, although results for PFS were only of borderline statistical significance in our current study [19].

Role of cytogenetic risk factors and therapy regime

Interestingly, some of the well-established risk factors like high risk cytogenetics by Fluorescence in situ hybridization and ISS had no prognostic effect in our cohort. Although we did observe an increased risk (HR >1) for high-risk FISH, this did not reach statistical significance. Deletion 17p13 and translocation t(4;14) were considered high-risk cytogenetic aberrations. The influence of translocation t(14;16) was not investigated due to a high number of missing values because at time of first diagnosis of most of the patients (beginning in 2004) FISH was not yet standard of care in our department. It has nonetheless also been shown that a possible success of alloSCT is independent on the cytogenetic risk profile [31]. Furthermore, a less favorable outcome was seen in patients who did not undergo auto-alloSCT up front. Poorer outcome in the relapsed setting has been stated previously by Franssen and colleagues, who also did not see any differences in outcome for patients with high risk cytogenetics, as was the case in our own investigation [32].

Limitations and future directions

A limitation of the present MRI study is the limited number of cases. But it has to be considered that in comparison to other treatment options, few patients are eligible for alloSCT and we can present the biggest cohort with MRI imaging so far, as recruited in one of the biggest myeloma centers in the world. Also, we would like to discuss the mere

morphologic evaluation applied in this study, making it difficult to separate active tumor lesions from pre-treated lesions without residual vital cells. Our own investigations (not published) attempting to differentiate those types of lesions were not successful so far, and one should be cautious, because progression can possibly arise from inactive cystic-transformed lesions as well. Furthermore, repopulating blood-building bone marrow in vertebrae or even long bones can morphologically resemble focal myeloma lesions and makes the interpretation challenging. Functional MRI sequences such as diffusion weighted imaging (DWI) were not regularly available in this study, but are highly recommendable in a scientific setting. Since the use of contrast agents is limited in myeloma patients, as renal impairment is a potential symptom of the disease, DWI seems especially promising. It does not require contrast agents, but still can give qualitative and quantitative information about the bone marrow and has been shown to be a useful technique for detecting diffuse and multifocal marrow infiltration in patients with myeloma, with equal or higher sensitivity, when compared to PET [33, 34]. According to Cassou-Mounat et al. the detection rate of PET can even be improved by the implementation of 18F-fluorocholine in diagnostics. In their pilot study the recent metabolic tracer could detect more lesions when compared to 18F-fluorodeoxyglucose [35]. Further studies are needed and are currently conducted in our institutions to assess the development and remission of lesions in DWI and PET in this context.

In addition to focal infiltration, diffuse bone marrow infiltration is seen in many myeloma patients. In our cohort, we could not detect an impact of a diffuse infiltration pattern on the patients' outcome. Although conventional MRI has previously been shown to be more accurate than FDG PET/CT for the detection of diffuse marrow infiltration, due to the possible reconstitution of the bone marrow after previous therapy and transplantation, pathological or therapeutically induced diffuse signal changes could not be reliably distinguished [36]. Therefore, further analysis will surely be a topic of future research.

Conclusion

In general, it seems that a focal infiltration pattern and an increased tumor load represented by increasing focal myeloma bone marrow lesions, shortens OS. In conclusion, we recommend imaging using whole body MRI before and after allogeneic SCT, since patients with prognostically relevant lesions and higher tumor burden before and after treatment may independently from serological response benefit from maintenance therapy, donor lymphocyte infusions (DLI), or local interventions to consolidate remission.

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Tables

Table 1: Therapy regime

Systemic therapy and transplantation	n	%
alloSCT after 1st relapse	20	25.3
alloSCT after > 1st relapse	10	12.7
Auto-allo SCT upfront	16	20.2
Auto-allo after 1st relapse	20	25.3
Auto-allo after > 1st relapse	13	16.5
	79	100

Abbreviations: allo, allogeneic; auto, autologous; n, number; SCT, stem cell transplantation.

Table 2: Remission status at baseline and follow-up

	1st MRI		2nd MRI	
	n	**%**	**n**	**%**
CR	10	12.7	10	20.8
nCR	7	8.9	4	8.3
VGPR	8	10.1	10	20.8
PR	43	54.4	15	31.2
MR	3	3.8	1	2.1
SD	4	5.1	-	-
PD	4	5.1	8	16.7
	79	100	48	100

Abbreviations: CR, complete remission; MR, minimal response; MRI, magnetic resonance imaging; n; number; nCR, near complete remission; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial remission.

Table 3: Imaging protocol

MRI-sequence	T1-w TSE cor	T2w-TIRM cor	T2-w FLASH sag
TR/TE	627ms/11ms	3340ms/109ms	402ms/12ms

Abbreviations: cor: coronal; FLASH: T2*-weighted fast low angle shot; MRI: magnetic resonance imaging; sag: sagittal; TE: echo time; TIRM: turbo inversion recovery magnitude; TSE: turbo spin echo; TR: repetition time. Depending on the patient´s height, acquisition included only proximal parts of the lower extremities.

Table 4: Clinical parameters influencing progression free survival and overall survival

Clinical Parameters	Univariable Cox model		Multivariable Cox model	
	HR (LCL-UCL)	p- value	HR (LCL-UCL)	p-value
PFS				
Age	1.02 (0.99-1.05)	0.248	1.02 (0.99-1.06)	0.232
Durie-Salmon Stage: III vs. II	3.10 (1.23-7.77)	**0.016**	3.48 (1.19-10.16)	**0.023**
ISS: 2/3 vs. 1	0.98 (0.55-1.77)	0.956	0.88 (0.47-1.65)	0.687
ISS: 2 vs. 1	1.23 (0.66-2.31)	0.516		
ISS: 3 vs. 1	0.63 (0.26-1.50)	0.295		
High LDH	0.94 (0.49-1.82)	0.862	1.13 (0.57-2.26)	0.723
Increase of LDH level (per 100 U/L increment)	1.18 (0.90-1.55)	0.221		
FISH: high risk vs. low risk	1.41 (0.78-2.57)	0.255	1.17 (0.62-2.21)	0.633
Status of remission at baseline: VGPR and better vs. other	0.73 (0.42-1.27)	0.269	0.70 (0.37-1.33)	0.275
Status of remission at 2nd MRI: VGPR and better vs. other	0.50 (0.24-1.06)	*0.069*	0.53 (0.17-1.69)	0.285
Therapy: other vs. auto-alloSCT upfront	1.87 (0.95-3.68)	*0.071*	1.68 (0.79-3.55)	0.178
OS				
Age	1.01 (0.98-1.05)	0.515	1.00 (0.96-1.04)	0.968
Durie-Salmon Stage: III vs. II	2.10 (0.76-5.85)	0.154	2.83 (0.78-10.24)	0.113
ISS: 2/3 vs. 1	0.97 (0.49-1.93)	0.941	0.96 (0.47-1.99)	0.919
ISS: 2 vs. 1	1.03 (0.49-2.15)	0.939		
ISS: 3 vs. 1	0.85 (0.31-2.35)	0.757		
High LDH	1.53 (0.72-3.26)	0.267	1.33 (0.58-3.08)	0.500
Increase of LDH level (per 100 U/L increment)	1.40 (1.04-1.87)	**0.025**		
FISH: high risk vs. low risk	1.56 (0.79- 3.10)	0.202	1.23 (0.52-2.92)	0.634
Status of remission at baseline: VGPR and better vs. other	1.13 (0.62-2.06)	0.698	1.32 (0.65-2.71)	0.443
Status of remission at 2nd MRI: VGPR and better vs. other	0.99 (0.43-2.30)	0.981	0.91 (0.31-2.66)	0.861
Therapy: other vs. auto-alloSCT upfront	2.45 (1.05-5.76)	**0.039**	2.73 (1.08-6.95)	**0.035**

Analysis included univariable and multivariable Cox regression model. Results for models at 1st MRI (prior to alloSCT) are given, except for Status of remission at 2nd MRI, which is based on the model at landmark. Results for multivariable model are based on the model with number of focal lesions as MRI parameter. No relevant differences in results were found when considering presence of focal lesions (yes/no) as MRI parameter instead.
Deletion 17p13 and translocation t(4;14) were considered high-risk cytogenetic aberrations. The influence of translocation t(14;16) was not investigated due to a high number of missing values. The only two patients with documented t(14;16) also had del17p13.
Abbreviations: AlloSCT, allogeneic stem cell transplantation; auto, autologous; FISH, Fluorescence in situ hybridization; HR, hazard ratio; ISS, international staging system; LCL, lower 95% confidence level; LDH, Lactate dehydrogenase; PFS, progression free survival; OS, overall survival; UCL, upper 95% confidence level; U/L, units per litre; VGPR, very good partial response.

Table 5: Imaging findings

		Univariable Cox model		Multivariable Cox model	
PFS		HR (LCL-UCL)	p- value	HR (LCL-UCL)	p-value
MRI 1	Presence of focal lesion	1.56 (0.80-3.08)	0.195	1.96 (0.89-4.31)	*0.097*
	Increasing number of focal lesions by 10	1.15 (0.97-1.36)	*0.099*	1.21 (0.99-1.47)	*0.058*
MRI 2	Presence of focal lesion	1.83 (0.83-4.03)	0.131	1.40 (0.52-3.78)	0.506
	Increasing number of focal lesions by 10	1.19 (0.90-1.57)	0.223	1.19 (0.75-1.89)	0.457
OS					
MRI 1	Presence of focal lesion	1.96 (0.83-4.60)	0.123	2.26 (0.86-5.94)	*0.098*
	Increasing number of focal lesions by 10	1.22 (1.02-1.45)	**0.028**	1.24 (1.00-1.54)	**0.048**
MRI 2	Presence of focal lesion	2.98 (1.01-8.79)	**0.048**	2.79 (0.84-9.33)	*0.095*
	Increasing number of focal lesions by 10	1.46 (1.10-1.94)	**0.008**	1.56 (1.06-2.28)	**0.024**

Abbreviations: Progression free survival (PFS) and overall survival (OS). Univariable and multivariable analysis of hazard ratio (HR) are shown with lower and upper 95% confidence level (LCL and UCL). MRI1: 79 patients; MRI2: 39 patients.

Table 6: Survival rates

	Focal lesion	Follow-up (time/months)	PFS Survival rates (LCL-UCL)	OS Survival rates (LCL-UCL)
MRI 1	yes	24	0.34 (0.24-0.48)	0.62 (0.51-0.75)
		60	0.16 (0.09-0.29)	0.36 (0.26-0.51)
	no	24	0.54 (0.33-0.89)	0.77 (0.57-1.00)
		60	0.37 (0.18-0.77)	0.68 (0.47-1.00)
MRI 2	yes	24	0.16 (0.07-0.39)	0.63 (0.47-0.84)
		60	0.16 (0.07-0.39)	0.32 (0.18-0.56)
	no	24	0.50 (0.28-0.88)	0.92 (0.77-1.00)
		60	0.37 (0.17-0.83)	0.75 (0.54-1.00)

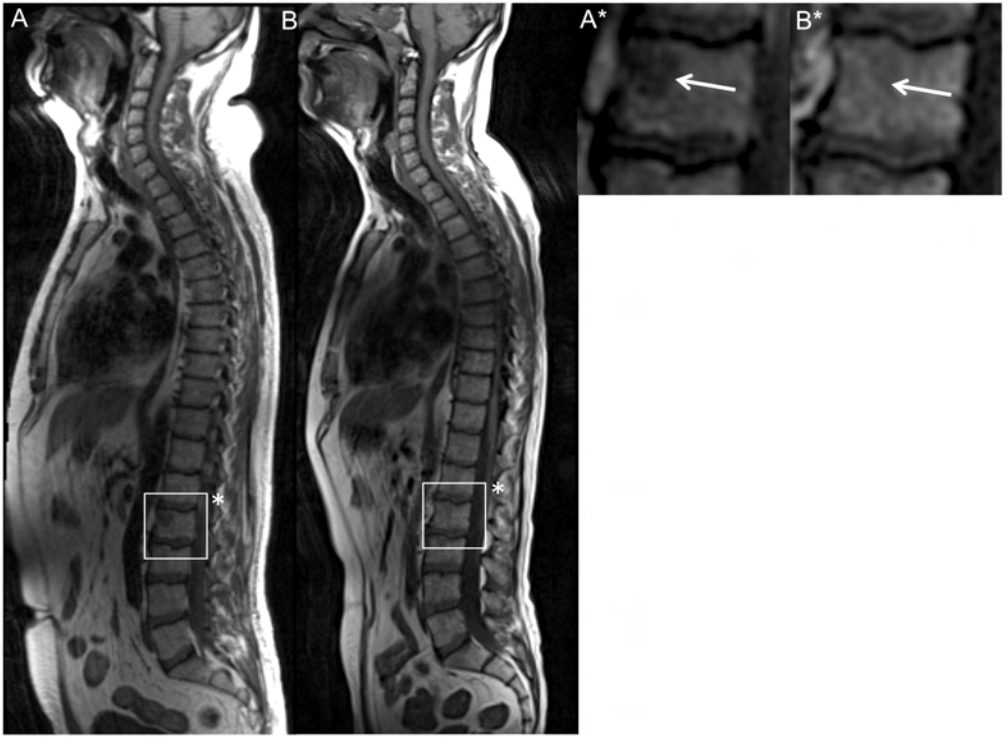
Abbreviations: See Table 4.

Figure legends

Figure 1: 2nd lumbar vertebra with focal remission after therapy
(A) 39- year-old patient before alloSCT; * magnification shows hypointens lesion in bone marrow
(B) 6 months after alloSCT no focal lesion was detected. Also, note weight loss with reduction of abdominal and subcutaneous fat tissue after therapy

Figure 2: Kaplan-Meier graph for influence of presence or absence of focal lesions in 2nd MRI on OS. Censored patients are indicated with small vertical marks.

Supplementary information is available online.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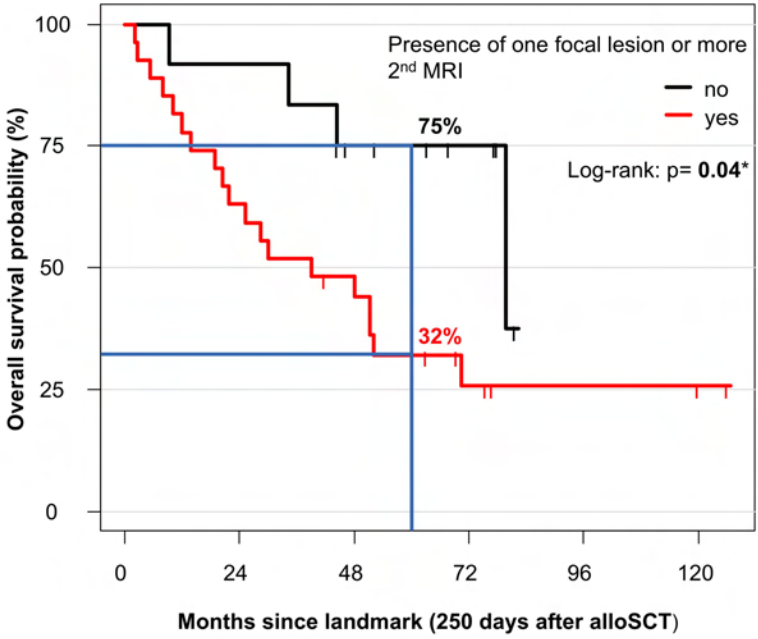
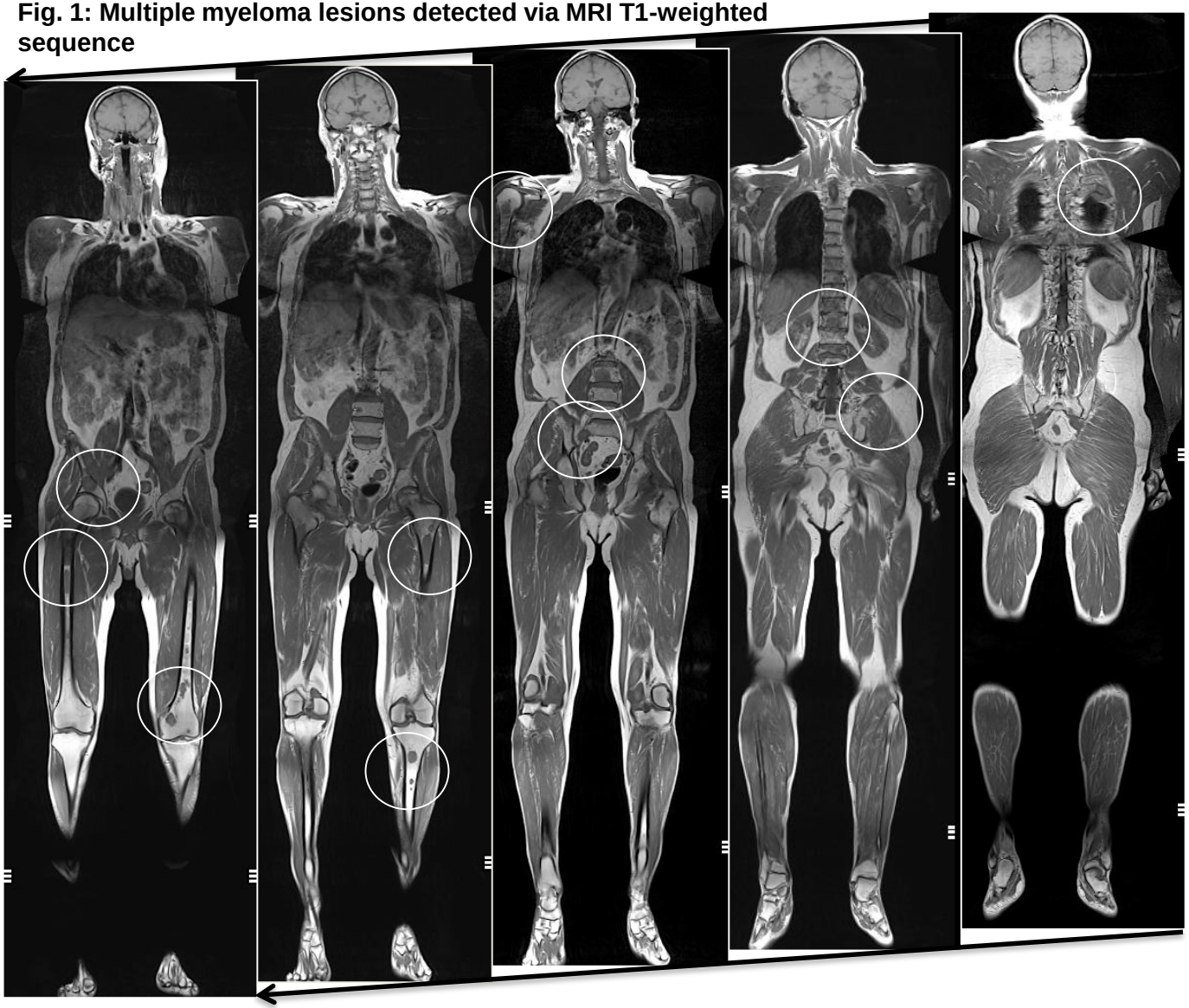

Presence of one focal lesion or more
2nd MRI
no
yes
75%
32%
Log-rank: p= 0.04*
Overall survival probability (%)
100
75
50
25
0
0
24
48
72
96
120
Months since landmark (250 days after alloSCT)

Fig. 1: Multiple myeloma lesions detected via MRI T1-weighted sequence

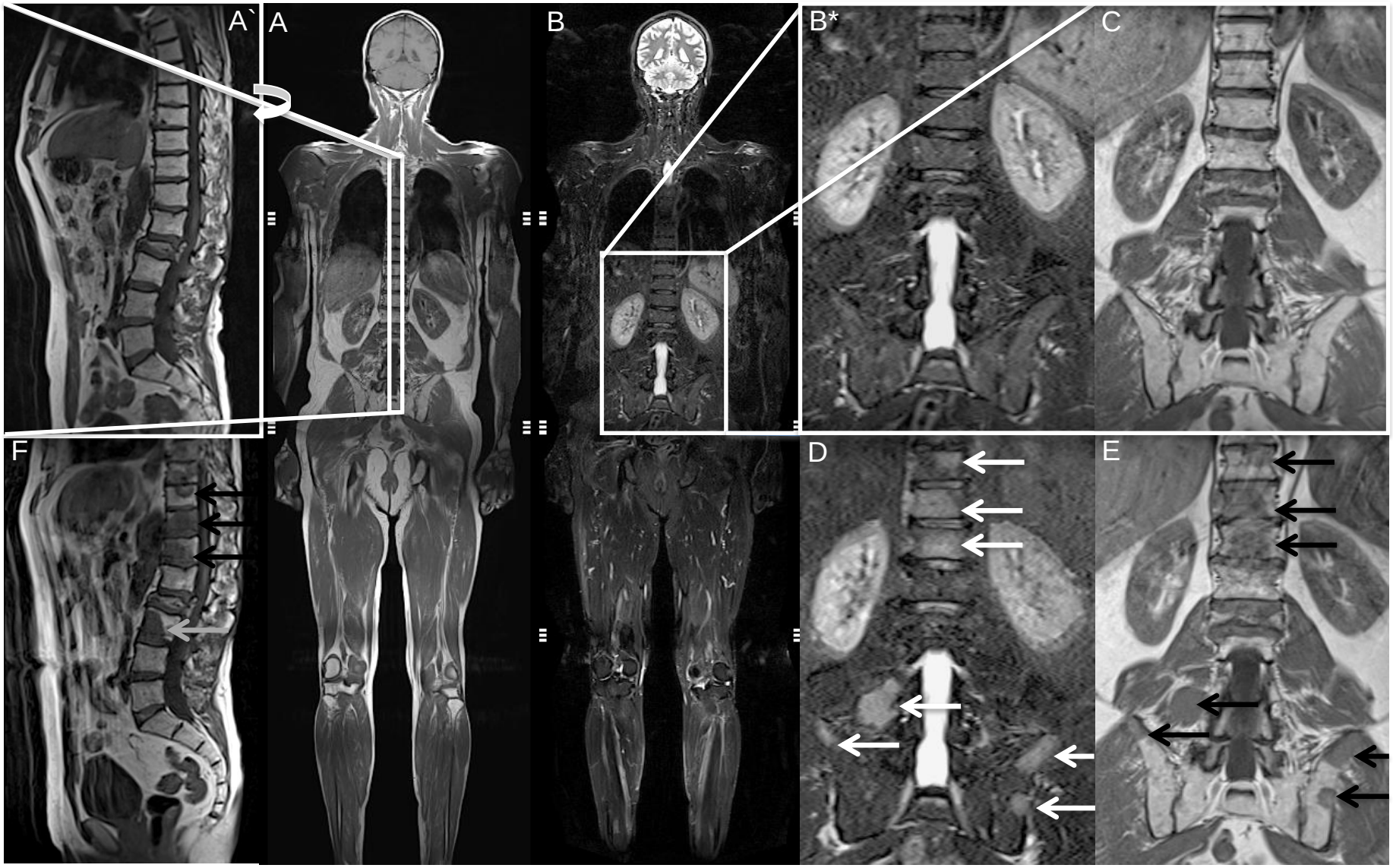


Coronal whole-body images showing multifocal T1w-hypointense multiple myeloma lesions, which in this patient were located in the tibia, femur, pelvis, vertebrae, humerus, and left ribs.

Myeloma infiltrates were diagnosed if they were hypointense in T1w as well as hyperintense in T2w fat-attenuated sequences, and >5 mm in diameter after standardized criteria from Stäbler et al. (AJR Am J Roentgenol., 1996) and Baur et al. (Cancer, 2002).

In the applied protocol coronal T1w- and T2-TIRM as well as sagittal T2w images were acquired (please refer to Table 3). Axial series are not included standardly, but in case of cortical destruction and suspected spinal compression. Artefacts, degenerative or other benign changes were not included. Lesions which could not clearly be defined as suspicious were not counted.

Fig. 2: Progressive disease



Coronal whole-body MRI with T1-w (A) and T2-TIRM sequences (B) of a 60- year old male patient; (B*) shows magnification of pelvis and spine; (C) corresponding magnified image of T1-w image at the same date proofs normal bone marrow.
(D) and (E) depict focal progression in follow up after alloSCT (black and white arrows)
Sagittal T1w- image at follow-up (F) confirms spine lesions, whereas at baseline exam only pre-existing compression fracture of L2 was seen (A`). Lesions were not counted if they lay in locations typical for degenerative changes.