

Bone Marrow Transplantation in Patients with Multiple Myeloma: Prognostic Significance of MR Imaging

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OBJECTIVE. This study in myeloma patients treated with myeloablative therapy and bone marrow transplantation assessed the prognostic value of MR imaging before and after treatment of the bone marrow and the prognostic value of an index reflecting changes on MR images obtained before and after treatment.

SUBJECTS AND METHODS. MR images (T1-weighted images before and after injection of gadolinium and T2*-weighted images) of the spine and pelvis were obtained 1 month before and 1 month after marrow transplantation in 25 consecutive patients with stage III myeloma. Pre- and posttreatment MR imaging patterns of marrow involvement (normal, focal, diffuse), number of focal lesions, and a "marrow evolution index" (0–8 on the basis of comparison of the lesions [number, size, contrast enhancement] and of the surrounding marrow background on pre- and posttreatment MR images) were determined. Hematologic and MR imaging parameters were correlated with the quality of response to treatment (complete versus partial remission) and with relapse-free and overall survival.

RESULTS. Response quality did not differ among categories of patients determined on the basis of MR images. Individual MR imaging parameters did not correlate with response duration and survival. Patients with a low marrow evolution index had significantly longer relapse-free ($p < 10^{-3}$) and overall survival ($p = 0.005$) than patients with a high index.

CONCLUSION. Individual MR imaging parameters before and after treatment had no prognostic significance in our series of myeloma patients treated with marrow transplantation. Comparison of MR images before and after treatment using a marrow evolution index may help predict response duration and survival.

Treatment of multiple myeloma has for years consisted of the chemotherapy combination of melphalan and prednisone [1]. Attempts have been made to improve treatment by combining multiple alkylating agents. Despite higher response rates, these multidrug regimens failed to improve survival, and myeloma remains an incurable malignancy, with a median survival that does not exceed 3 years [2–5]. In the past 10 years, several studies have shown that high-dose cytotoxic chemotherapy (high-dose myeloablative melphalan regimens) induced higher response rates and that bone marrow or peripheral blood stem cell transplantation reduced the toxicity of these high-dose regimens [6–8]. Randomized studies further showed that high-dose therapy significantly improved response duration and overall survival [9–11]. Accordingly, this therapeutic approach has gained wide acceptance as treatment for multiple myeloma.

We undertook this prospective study in a homogeneous series of myeloma patients treated with high-dose cytotoxic chemotherapy and bone marrow transplantation to assess the prognostic value of MR imaging of the bone marrow before and after treatment.

Subjects and Methods

Patients and Treatment

Between November 1993 and November 1998, 25 consecutive patients with Durie-Salmon [12] stage III multiple myeloma were enrolled in this study. The characteristics of the patients are listed in Table 1.

Five patients received allogeneic human leukocyte antigen-identical sibling transplants, and 20 patients received an autologous peripheral blood stem cell transplant. Five patients had primary unresponsive disease, four patients had resistant relapse, and 16 patients had achieved remission after the initial treatment. Before the high-dose cytotoxic chemotherapy and bone marrow transplantation, all patients had un-

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TABLE 1 Patient Characteristics at Transplantation

Characteristic	Value	Range
Sex: male/female	15/10	
Age (yr) ^a	52 ± 7	28–65
Monoclonal component: IgG/IgA/BJ	17/5/3 ^b	
Hemoglobin (g/dL) ^a	11.5 ± 1.6	7.4–14.6
Calcium (mg/dL) ^a	9.4 ± 1.7	8.4–14.2
Medullary plasmacytosis (%) ^a	42 ± 16	16–92
β ₂ -microglobulin (mg/dL) ^a	2.9 ± 1.2	1.5–6.4
C-reactive protein (mg/dL)	1.0	0.0–16.0
Quality of response: complete/partial	14/11	

^aMedian ± standard deviation.^bNumber of patients.

dergone at least four to six cycles of standard first-line chemotherapy: vincristine, doxorubicin, and dexamethasone. The bone marrow transplantation conditioning regimens consisted of the IV administration of high-dose melphalan (140 mg/m²) in all patients, with total body irradiation in 18 patients. Maintenance therapy of interferon-α was started after hematologic reconstitution in 12 patients.

Assessment of Response to Treatment and Patient Follow-Up

Response to therapy was determined using the criteria of the Eastern Cooperative Oncology Group [13]. Partial response was defined as a 50% or more decrease of the monoclonal protein in serum or urine or more than 50% reduction of bone marrow infiltration (in non-secretory myeloma). Complete response was defined as no monoclonal protein measurable in serum, 10 times concentrated urine by immunofixation analysis, and less than 5% plasma cells with no abnormal morphology in bone marrow smears. These plasma cells had to be polyclonal on immunofluorescence staining.

According to these criteria, 14 patients achieved a complete remission and 11 achieved a partial remission. After transplantation, patients were followed up monthly at our hematology unit. In patients with complete remission, "relapse" was defined on the basis of the reappearance of detectable monoclonal protein, the appearance of other symptoms of myeloma, or the appearance of new lytic lesions or progression of existing lesions on radiographic skeletal surveys. In patients with partial remission, relapse was defined as an increase of more than 25% of the monoclonal peak. The median relapse-free survival was 502 days (range, 77–1379 days). The median overall survival was 879 days (range, 153–2164 days). By the time of this study, 15 patients had relapsed and six had died. All deaths were considered related to the disease.

Bone Marrow MR Imaging

All patients underwent prospective MR imaging studies of the spine and pelvis at a median of 4 weeks

(range, 3–6 weeks) before and 5 weeks (range, 4–8 weeks) after marrow transplantation. MR imaging was performed on a 0.5-T unit (Gyrosan NT; Philips Medical Systems, Best, The Netherlands).

T1-weighted spin-echo MR images were obtained of both the cervicothoracic and lumbosacral spine in the sagittal plane using a dedicated phased array coil in the receive-only mode (TR/TE, 400/20; 384 × 512 matrix; four signals acquired; 5-mm-thick sections; 0.5-mm interslice gap; and 400-mm field of view). T2*-weighted gradient-echo MR images were also obtained (540/27; flip angle, 30°). In the pelvis, T1-weighted spin-echo and T2*-weighted gradient-echo MR images were obtained in the coronal plane using a body coil (192 × 256 matrix; four signals averaged; 6-mm-thick sections; 0.6-mm interslice gap; and 400-mm field of view).

In patients with bone marrow abnormalities, T1-weighted spin-echo MR images of the thoracic and lumbar spine and pelvis were repeated immediately after the IV administration of 0.1 mmol/kg of gadoterate meglumine (Dotarem; Guerbet, Aulnay-sous-Bois, France). Patients with unequivocal normal bone marrow status on MR images did not receive a contrast material injection.

MR Image Analysis

All MR images of the spine and pelvis were reviewed by two radiologists. The patients were classified into three categories according to the MR imaging patterns of spinal bone marrow involvement. The three patterns were the normal pattern, characterized by an intermediate to high marrow signal intensity on T1-weighted images and a normal intermediate signal intensity on T2*-weighted images; the focal pattern, characterized by the presence of nodular lesions of at least 5-mm in diameter and of low signal intensity on T1-weighted images and high signal intensity on T2*-weighted images in an otherwise normal-appearing bone marrow; and the diffuse pattern, characterized on T1-weighted images by a diffuse lowering of the marrow signal intensity, which becomes identical to or lower than the signal of the intervertebral disks, and on T2*-weighted images by diffusely or focally increased signal intensity. In patients with the focal pattern, the sizes (maximal diameters) of the spinal and pelvic lesions were measured, and the mean and median of these values were noted. Enhancement of the lesion signal intensity was assessed after contrast material injection and was categorized as either diffuse homogeneous, only peripheral, or absent. The surrounding "background" marrow was further studied without taking into account the focal lesions and was qualified as being either normal-appearing or diffusely altered if it showed high signal intensity or abnormally decreased signal intensity, respectively, on T1-weighted MR images.

Four MR imaging parameters were evaluated to assess bone marrow changes on MR images before and after marrow transplantation: lesion number, size, contrast enhancement, and appearance of the bone marrow background, independently of focal lesions (Figs. 1–3). A score of 0, 1, or 2 was given if the number of focal lesions decreased, remained un-

changed, or increased, respectively, on MR studies before and after transplantation. A score of 0, 1, or 2 was given if the mean lesion size decreased, remained stable, or increased, respectively. A score of 0, 1, or 2 was given if the number of lesions showing diffuse contrast enhancement decreased, remained stable, or increased, respectively, compared with the number of lesions showing lack of enhancement or only peripheral rim enhancement. A score of 0, 1, or 2 was given if the marrow background showed evolution from diffuse alteration to normal appearance, remained stable, or showed evolution from normal appearance to diffuse alteration, respectively.

A "marrow evolution index" ranging from 0 to 8 was determined for each patient after summation of these four values.

Statistical Analysis

The chi-square test was used to compare complete and partial remission rates among the various subgroups. Relapse-free and overall survival were estimated using the Kaplan-Meier method. The influence of MR imaging findings and of hematologic parameters on survival was analyzed using the log-rank test.

Results

MR Imaging Appearance of the Bone Marrow Before and After Treatment

Before treatment, the MR imaging pattern of bone marrow involvement was normal in seven patients and abnormal in 18 (14 focal, 4 diffuse). After treatment, the MR imaging pattern was normal in 10 patients and abnormal in 15 (12 focal, 3 diffuse). The median number of focal lesions was two (range, 0–18) before treatment and one (range, 0–14) after treatment. The median marrow evolution index was 3 (range, 1–8). This index was less than 4 in 15 patients, and greater than or equal to 4 in 10 patients.

Correlation with the Quality of Response

After treatment, 14 patients achieved complete remission and 11 patients achieved partial remission. The proportion of patients presenting either complete or partial response did not differ according to the pre- and posttransplantation MR imaging appearances of the bone marrow, number and size of focal lesions, and changes in marrow appearance on MR images before and after transplantation (Table 2). No correlation was observed between biologic data (serum levels of β₂-microglobulin, C-reactive protein, calcium, hemoglobin, and monoclonal protein) before transplantation and quality of response.

Correlation with the Relapse-Free and Overall Survival

Table 3 illustrates univariate analysis of the prognostic influence of MR imaging and clinical and therapeutic parameters on re-

MR Imaging of Bone Marrow Transplantation

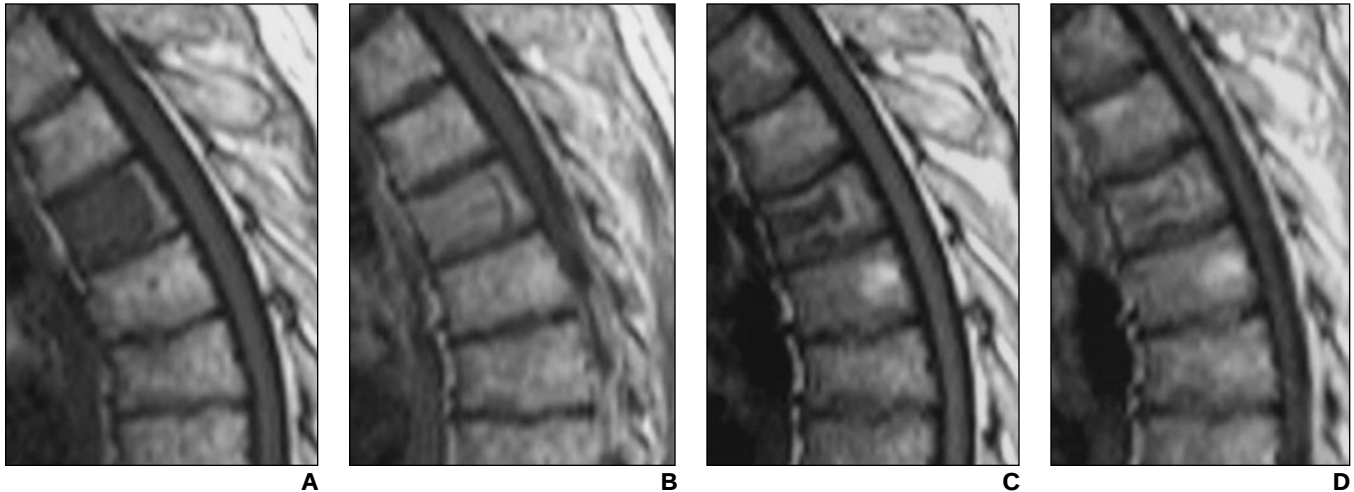


Fig. 1.—52-year-old man with multiple myeloma.

A. Pretransplantation sagittal T1-weighted spin-echo MR image (400/20, TR/TE) shows large focal area of low signal intensity in T5-vertebral body.

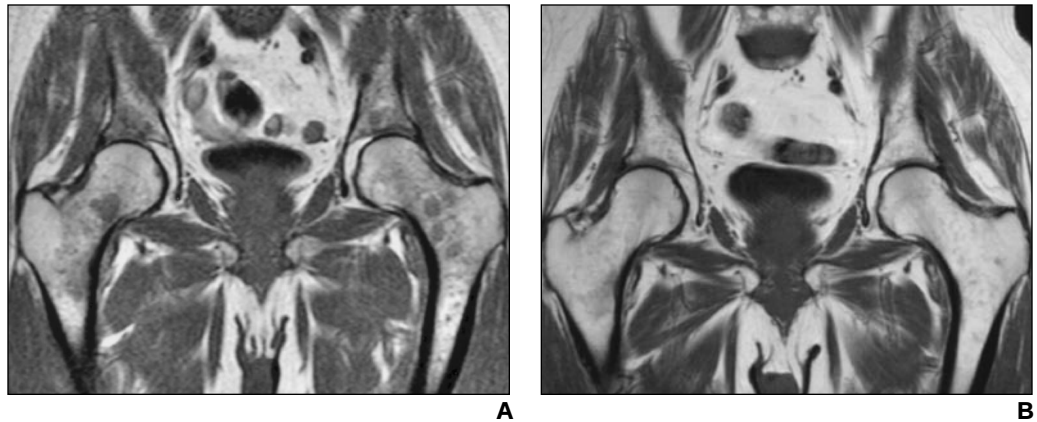
B. Contrast-enhanced T1-weighted MR image shows diffuse lesion enhancement.

C and D. Posttransplantation MR images obtained before (**C**) and after (**D**) contrast material injection show reduction in lesion size and contrast enhancement.

Fig. 2.—56-year-old man with multiple myeloma.

A. Coronal T1-weighted spin-echo MR image before transplantation shows numerous focal areas of low signal intensity in both femoral necks and acetabular roofs.

B. Corresponding MR image after transplantation shows that foci have disappeared.



sponse duration and overall survival. Individual MR imaging parameters before and after treatment had no prognostic value. Changes in lesion size, number, and contrast enhancement, and changes in the MR imaging appearance of the marrow background, had no prognostic value. Patients with a marrow evolution index of less than 4 had a significantly longer response duration ($p < 10^{-3}$) and overall survival ($p = 0.005$) than did those with an index greater than or equal to 4 (Figs. 4 and 5).

Patients with β_2 -microglobulin levels less than 3 mg/dL had significantly longer response duration ($p = 0.004$) and a trend toward a longer survival ($p = 0.06$) than those with β_2 -microglobulin levels greater than or equal to 3 mg/dL (Fig. 6). Achievement of complete remission was also associated with a trend toward longer response duration ($p = 0.06$).

Fig. 3.—50-year-old man with multiple myeloma.

A. Sagittal T1-weighted spin-echo MR image of lumbar spine before transplantation shows abnormal diffuse low signal intensity in vertebral bodies.

B. Corresponding MR image after transplantation shows conversion to normal high-signal-intensity marrow.

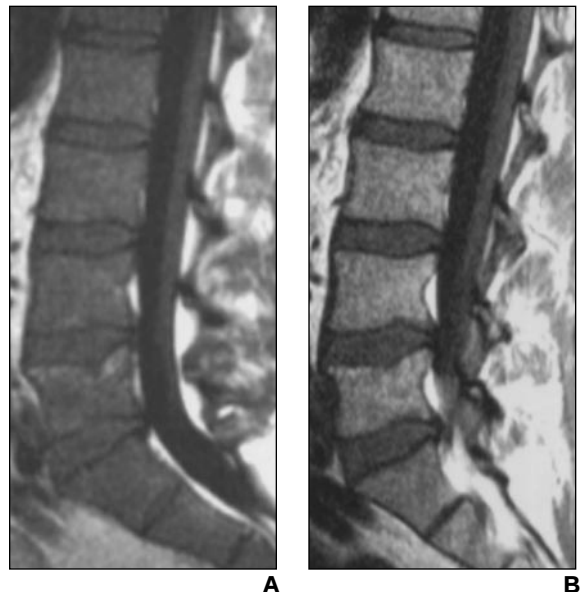


TABLE 2

Prognostic Value of MR Imaging Parameters and Serum β_2 -Microglobulin Levels in Predicting Quality of Response After Bone Marrow Transplantation in Multiple Myeloma Patients

Parameter	No. of Patients	Remission		<i>p</i>
		Complete	Partial	
MR imaging pattern before treatment				
Normal	7	4	3	NS
Abnormal	18	10	8	
MR imaging pattern after treatment				
Normal	10	6	4	NS
Abnormal	15	8	7	
Marrow evolution index				
<4	15	9	6	NS
≥ 4	10	5	5	
β_2 -microglobulin level				
<3 mg/dL	15	10	5	NS
≥ 3 mg/dL	10	4	6	

Note.—NS = not significant.

TABLE 3

Univariate Analysis of the Prognostic Value of Clinical and MR Imaging Parameters

Parameter	Response Duration	Overall Survival
MR imaging pattern before treatment (normal/abnormal)	NS	NS
MR imaging pattern after treatment (normal/abnormal)	NS	NS
No. of focal lesions before treatment	NS	NS
Marrow evolution index (</ ≥ 4)	10^{-3}	0.005
β_2 -microglobulin level (</ ≥ 3 mg/dL)	0.004	0.06
C-reactive protein (</ ≥ 0.6 mg/dL)	NS	NS
Calcium (</ ≥ 12 mg/dL)	NS	NS
Total body irradiation (+/-)	NS	NS
Response quality (complete/partial)	0.06	NS
Interferon- α after transplantation (+/-)	NS	NS

Note.—*p* values are according to the log-rank test; NS = not significant.

Discussion

The wide variety in survival rates of multiple myeloma patients and the need to define the optimal therapeutic strategy explain the need for valuable prognostic factors. The Durie and Salmon staging system and the serum levels of β_2 -microglobulin and C-reactive protein enable confident evaluation of life expectancy of myeloma patients [12, 14]. However, these parameters have limitations, which accounts for the constant search for better estimates of individual patient survival, especially when considering most recent intensive therapeutic approaches, such as bone marrow transplantation [15].

The MR imaging appearance of the bone marrow and its prognostic significance have been evaluated in multiple myeloma patients treated with conventional chemotherapy [16–18]. Little has been written about the evaluation of bone marrow using MR imaging in the setting of bone marrow transplantation in myeloma patients. Agren et al. [19] obtained MR images of the bone marrow in 20 patients before and after (in 13 cases) bone marrow transplantation, but a large variety in sequences, in contrast material injection, in studied anatomic areas, and in time intervals with respect to the bone marrow transplantation precluded any definitive analysis of the predictive value of MR images in these patients. Our study of the potential prognostic value of bone marrow MR imaging in a homogeneous series of patients undergoing high-dose cytotoxic chemotherapy and bone marrow transplantation has two main results. First, it shows that individual MR imaging parameters before and after treatment do not have significant prognostic

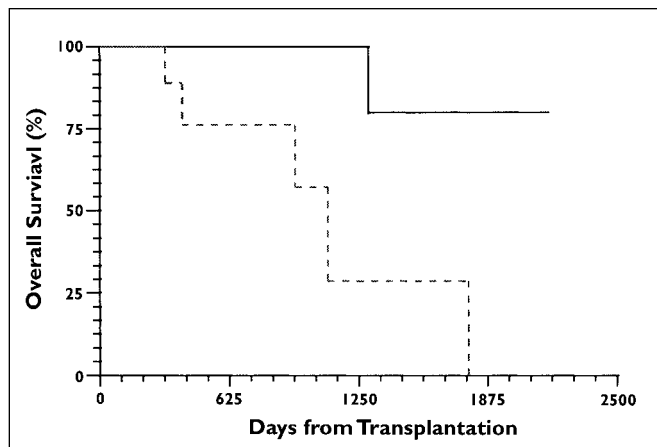


Fig. 4.—Graph shows Kaplan-Meier estimation of overall survival in 25 multiple myeloma patients treated with high-dose cytotoxic chemotherapy and bone marrow transplantation, according to marrow evolution index (MEI) obtained by comparison of MR images before and after treatment ($p = 0.005$). Cut-off value of 4 was chosen (solid line, MEI < 4; dotted line, MEI ≥ 4).

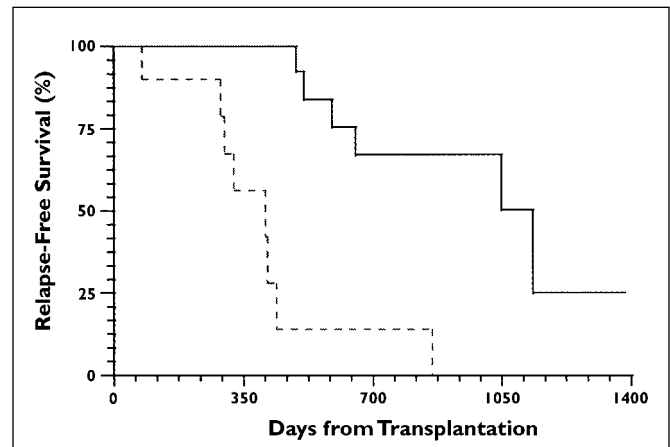


Fig. 5.—Graph shows Kaplan-Meier estimation of relapse-free survival in 25 multiple myeloma patients treated with high-dose cytotoxic chemotherapy and bone marrow transplantation according to marrow evolution index (MEI) obtained by comparison of MR images before and after treatment ($p < 0.001$). Cut-off value of 4 was chosen (solid line, MEI < 4; dotted line, MEI ≥ 4).

MR Imaging of Bone Marrow Transplantation

value. Second, careful comparison of MR images before and after treatment yielded information relevant to the duration of response and overall survival.

In our study, none of the MR imaging parameters before and after treatment had individual prognostic value. The MR imaging patterns before transplantation did not correlate with survival. Our results also show that residual marrow abnormalities may be observed on MR images after bone marrow transplantation and the administration of high-dose myeloablative chemotherapy, in the same way that they occur after conventional chemotherapy regimens [16, 17, 20]. The clinical relevance of these residual abnormalities after transplantation may be questioned, because patients with these abnormalities did not appear to have a poorer outcome than those with normal posttransplantation MR imaging findings.

The originality of our work relies on careful comparison of precisely scheduled pre- and posttreatment MR imaging studies, with characterization of the evolution of four different MR imaging parameters. Indeed, conversion of a diffuse to a focal or normal MR imaging pattern of marrow involvement, reduction in lesion size and number, absent or only peripheral lesion enhancement on contrast-enhanced MR images have been shown in association with a response to standard chemotherapy [17, 20]. None of these changes on MR images before and after transplantation have prognostic value if isolated. The novel finding is that an index combining the various changes in marrow and lesion appearance on the MR images before and after treatment provides valuable prognostic information. A future step should aim at determining the respective contribution to prognosis of each of the four MR imaging features.

One limitation of our study is that, given the limited number of patients and limited follow-up, multivariate analysis of the prognostic value of clinical, biologic, cytogenetic, and MR imaging findings could not be performed. Whether MR imaging parameters will add original information to the many existing prognostic variables requires further evaluation in an ongoing long-term study. The serum β_2 -microglobulin levels before treatment have prognostic significance in our study. This finding to some extent validates our study population because β_2 -microglobulin—an excellent indicator of tumor burden and one of the most important prognostic factors in myeloma patients treated with standard therapy—has been repeatedly shown to be a strong independent prognostic factor for

relapse-free and overall survival after bone marrow transplantation [9, 21, 22].

The choice of T2*-weighted gradient-echo MR imaging must be discussed. The sensitivity of this sequence for myeloma lesion detection has been repeatedly emphasized, especially on medium-field-strength MR imaging scanners [18, 23, 24]. At higher field strengths, focal field inhomogeneities caused by trabecular bone will lead to signal intensity loss, and other sequences might be recommended, such as fat-suppressed T2-weighted spin-echo and short inversion time inversion recovery MR images [25].

In conclusion, this study shows that individual MR imaging parameters before or after treatment do not have prognostic value in patients treated with high-dose cytotoxic chemotherapy and marrow transplantation. Residual marrow abnormalities may be observed on MR images after treatment, and these abnormalities do not negatively affect survival. Determining and comparing the four parameters on MR images before and after treatment provide a simple index that can help predict response duration and survival. Conversely, this noninvasive approach could help recognize patients at a high risk for early relapse.

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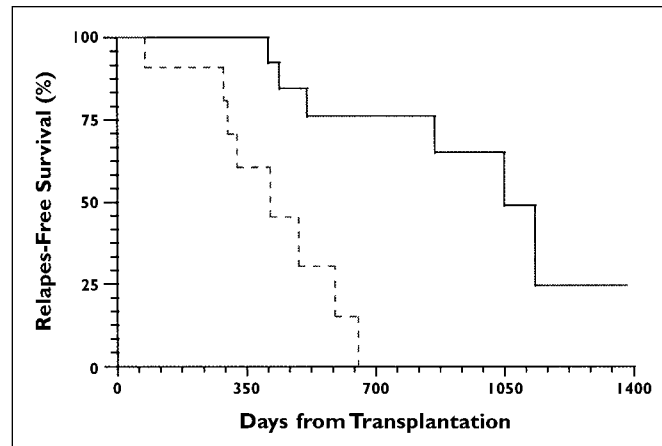


Fig. 6.—Graph shows Kaplan-Meier estimation of relapse-free survival in 25 multiple myeloma patients treated with high-dose cytotoxic chemotherapy and bone marrow transplantation according to serum β_2 -microglobulin levels before treatment ($p = 0.004$). Cut-off value of 3.0 mg/dL was chosen (solid line, β_2 -microglobulin level < 3.0 mg/dL; dotted line, β_2 -microglobulin level $\geq$ 3.0 mg/dL).

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