Bone Marrow Involvement in Hodgkin's Disease: An Analysis of 135 Consecutive Cases

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Purpose: To describe the incidence of primary bone marrow involvement (BMI) in Hodgkin's disease (HD) and its correlation with clinical and laboratory features present at diagnosis, and to evaluate the prognostic relevance of BMI.

Patients and Methods: Between 1983 and 1991, 2,307 patients with HD were treated according to two trial generations (HD1-3 and HD4-6) of the German Hodgkin's Lymphoma Study Group (GHSG).

Results: One hundred thirty-five cases of primary BMI were observed. The incidence of BMI was 4.8% in the HD4-6 study generation, which included all stages. Among stage IV patients, 32% had BMI. Among those with BMI, other organs were also involved in 33%. Among all patients, the presence of BMI was significantly associated with B symptoms, lymph nodes on both sides of the diaphragm, mixed cellularity histologic subtype, leukocytopenia, anemia, thrombocytopenia, lactate dehydrogenase (LDH) level more than 400 U/L, and erythrocyte sedimentation rate (ESR) more than 40 mm/h. BMI was negatively correlated with a large mediastinal tumor (3.7% *v* 20.0% in non-BMI cases). Eighty-seven of 108 (81%) assessable patients with BMI achieved a complete remission (CR). This compares favorably with the overall CR rate in all stage IIIB/IV patients. Among stage IV patients, BMI has no prognostic relevance with regard to freedom from treatment failure and overall survival. Twenty-one patients with BMI relapsed after having achieved a CR. Only five of these (24%) again had a positive bone marrow biopsy.

Conclusion: The prognosis of patients with BMI is not worse than the prognosis of other advanced-stage HD patients. BMI alone does not define a special high-risk group in which a different treatment approach is indicated.

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BONE MARROW involvement (BMI) has been recognized as an unfavorable prognostic sign since the time when bone marrow biopsies gained widespread use in the staging of malignant lymphomas.[1-3] In most large series of patients with untreated Hodgkin's disease (HD), the incidence of BMI was in the range of 5% to 15%.[3-8] BMI has been reported to be associated with B symptoms and advanced disease, whereas the histologic subtype of nodular sclerosis was relatively infrequent.[3,5,8] In a more recent analysis of stage IV patients, BMI was again recognized as an independent unfavorable prognostic factor as far as survival was concerned.[9] Current strategies in HD aim to improve the prognosis of patients with advanced-stage disease using dose-intensified protocols with or without autologous transplantation.[10-12] In this retrospective study, we reviewed the data of 135 consecutive patients with primary BMI diagnosed between 1983 and 1991 and evaluated clinical and laboratory features and outcome. Patients with BMI deserve special consideration, since the overall outcome of stage IV patients is not yet satisfactory and, therefore, some or all of these patients might qualify for new treatment strategies.

PATIENTS AND METHODS

Between 1983 and 1991, 2,307 patients from 132 participating centers were entered onto two successive trial generations of the German Hodgkin's Study Group (GHSG) (HD1-3, 1983 to 1988; HD4-6, 1988 to 1992). Clinical staging was performed according to the Ann Arbor guidelines.[13] Data from all patients were collected centrally. The histopathologic diagnosis of HD was reviewed by a panel of hematopathologists. The results of this review for the first study generation were recently published and confirmed the diagnosis of HD in 92% of patients.[14] Three percent of cases were eliminated because a non-Hodgkin's lymphoma was diagnosed. The use of immunohistochemistry was optional, but performed if considered necessary by the members of the panel. For staging, computed tomographic (CT) scans of thorax and abdomen and abdominal ultrasound were performed. Lymphangiography was recommended, especially in cases of infradiaphragmal involvement. Most patients had a bone scan, and all patients had a liver biopsy. At most centers, a bone marrow biopsy was performed unilaterally at the posterior iliac crest using a Jamshidi needle. Bone marrow biopsies were reviewed only if considered necessary by the panel of pathologists.

In the HD1-3 study generation, patients between the ages of 15 and 65 years were included. A staging laparotomy was recommended for clinical stages (CS) I, II, and IIIA. Patients with early-stage disease (I and II without risk factors) underwent radiation therapy and were not documented in detail.

Patients with intermediate-stage disease (I, II with risk factors, and IIIA) were treated with combined modality (two double cycles

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Table 1. Histologic Subtypes of HD

Stage	Histologic Subtype				
	LP	NS	MC	LD	UC
IV + BMI	3.0	37.3*	49.3*	0	10.4
IV total	1.5	62.6	27.2	0	8.7
I-IV	3.2	70.0	22.1	0.4	4.3

NOTE. Nine hundred eighty-seven cases were reviewed by a panel of hematopathologists, including 195 patients with stage IV disease and 67 with BMI; data are given as percentages.

Abbreviations: LP, lymphocytic predominance; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocytic depletion; UC, subtype not classified.

*Statistically significant, see text.

of cyclophosphamide, vincristine, procarbazine, and prednisone [COPP]/doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD] plus extended-field irradiation). Risk factors were defined as follows: (1) large mediastinal mass (mediastinal diameter of one third of the maximal thoracic diameter on anteroposterior [AP] chest radiograph); (2) massive splenic involvement (diffuse infiltration or infiltration with five nodules); and (3) extranodal disease.

Patients with advanced-stage disease were treated with eight cycles of chemotherapy (four double cycles of alternating COPP/ABVD) or six cycles of chemotherapy (three double cycles COPP/ABVD) and 20 Gy of involved-field radiation. In the COPP protocol, which was given instead of MOPP, mechlorethamine was replaced by cyclophosphamide (650 mg/m^2 on days 1 and 8). The HD1-3 study generation has been described previously.[15] The HD4-6 study generation included patients between the ages of 15 and 75 years.

In the HD4 protocol for early-stage disease, patients without special risk factors in pathologic stages (PS) IA-IIB were treated with extended-field radiation therapy.

In the HD5 protocol for intermediate-stage disease, patients in CS/PS IIIA or earlier stages in the presence of risk factors were included. Risk factors were defined as in the HD1-3 protocols; in addition, a high erythrocyte sedimentation rate ([ESR] > 50 mm/h if no B symptoms present or > 30 mm/h in case of B symptoms) and three or more involved lymphatic areas were considered. These patients were treated with four cycles of chemotherapy (two cycles each of COPP/ABVD or two cycles of COPP/ABV/ifosfamide, methotrexate, etoposide, and prednisone [IMEP]) and subsequent extended-field irradiation.

The HD6 protocol was given to patients with stages IIIB/IV disease and consisted of four double cycles of COPP/ABVD or four rapidly alternating triple cycles of COPP/ABV/IMEP. Subsequent radiation therapy was administered only to initial bulky disease, slow responding areas, or residual masses (30 Gy). In the COPP/ABV/IMEP study arm, COPP was started on day 1, ABV on day 15, and IMEP on day 29 (ifosfamide 1 g/m^2 on days 29 to 33, methotrexate 30 mg/m^2 on day 31, etoposide 100 mg/m^2 on days 29 to 31, and prednisone 40 mg on days 29 to 35), with the entire cycle repeated on day 43. Complete remission (CR) was defined as the complete regression of all evidence of lymphoma (especially normalization of bone marrow biopsy); a residual mediastinal lymphadenopathy was compatible with a CR if it was unchanged for at least 3 months. Patients were considered assessable for response if they had completed chemotherapy and radiation therapy (if applicable) and were observed for at least 3 months or failed to respond to the intended therapy (see following).

Statistical Methods

For univariate analysis, the Pearson χ^2 and Mann-Whitney U tests were used when appropriate. Freedom from treatment failure was defined as the time from registration to any of the following events: progression during therapy, not achieving CR at the end of therapy, relapse, or death from any cause. Failure time and survival curves were compared using the Cox-Mantel test. Step-up logistic regression analysis was used to assess the independent contribution of various patients' characteristics at diagnosis to predict BMI.

RESULTS

Incidence of BMI

Among 2,307 patients with HD, 135 cases of primary BMI were identified. If only the HD4-6 study generation, which includes early as well as advanced stages, is analyzed, the incidence of BMI was 4.8% (82 cases among 1,739 patients). If only stage IV patients are analyzed,

Table 2. Clinical Characteristics of Patients With BMI

Characteristic	Stage					
	IV + BMI		IV		I-IV	
	No.	%	No.	%	No.	%
B symptoms	113/135	83.7	299/422	70.9§	1077/2307	46.7§
1 lymphatic area	8/134	6.0	8/418	1.9	217/2284	9.5
≥ 2 lymphatic areas*	32/134	23.9	137/418	32.8	1031/2284	45.1
≥ 2 lymphatic areas†	94/134	70.1	273/418	65.3	1036/2284	45.4
Massive splenic involvement	39/135	28.9	105/422	24.9	332/2307	14.4
Large mediastinal mass	5/135	3.7	81/422	19.2§	523/2307	22.7§
Bulk (≥ 5 cm)‡	37/82	45.1	158/269	58.7¶	913/1739	52.5

*On 1 side of diaphragm.

†On both sides of diaphragm.

‡Information only available for HD4-6 protocols.

§$P < .00001$ v IV + BMI.

¶$P < .0027$ v IV + BMI.

Table 3. Incidence of BMI According to CS/PS

Stage*	No.	%
I A	1/168	0.6
II A	5/552	0.9
III A	12/405	3.0
IV A	4/105	3.8
I B	7/49	14.2
II B	15/309	4.8
III B	51/495	10.3
IV B	40/226	17.7

*Before bone marrow biopsy result was known.

the relative incidence of BMI was 32.0% (135 cases among 422 patients).

Histologic Subtypes

Details on histologic subtypes are listed in Table 1 (only slides of lymph node tissue reviewed by the panel of hematopathologists are included). In stage IV disease with primary BMI, the subtype of mixed cellularity was more frequent and the subtype of nodular sclerosis less frequent than among all patients and among all stage IV patients ($P < .001$, χ^2 test).

Presenting Clinical Characteristics

Eighty-eight patients were male and 47 female. This male incidence of 65.2% compares with a male incidence of 60.0% of all stage IV patients and a male incidence of 56.9% in the HD4-6 protocols (no significant difference). The age distribution of patients with BMI showed no major difference from patients without BMI: in the HD1-3 protocols, the median age in BMI was 34.7 years, compared with 33.7 years for all stage IV patients and 29.7 years for all patients; in the HD4-6 protocols, the median age for BMI was 42 years, compared with 36 years for all stage IV patients and 32 years for all patients.

Further clinical characteristics are listed in Table 2. Most patients with BMI had B symptoms and advanced lymphatic disease. Bulky disease and massive splenic involvement were relatively frequent. A large mediastinal tumor was rarely associated with BMI (3.7% *v* 19.2% among all stage IV patients and 22.7% among stage I to IV patients; $P < .001$). In 44 patients with BMI (32.6%), other stage IV disease was detected: 26 cases with liver, 11 with bone, and 10 with lung involvement. The incidence of BMI was calculated for clinical stage as determined before knowing the result of the bone marrow biopsy (Table 3): these results show that B symptoms and advanced disease are associated with BMI, although the incidence of BMI in earlier stages, eg, stage IB, is not negligible.

Table 4. Mean Laboratory Values in Patients With/Without BMI

	BMI	No. BMI
ESR (mm/h)	65.8*	40.0
Alkaline phosphatase (U/L)	277.2*	182.9
LDH (U/L)	289.7*	216.4
Leukocytes (g/L)	8.5*	10.5
Hemoglobin (g/dL)	11.7*	13.0
Thrombocytes (g/L)	320.7*	373.9

*Statistically significant difference, $P < .0001$, Mann-Whitney *U* test.

Radiologic Features of BMI

Bone scintigraphy was performed in 98 patients and abnormalities were detected in 21 (21.4%). In 10 of these patients, osteolytic bone lesions could be verified on conventional radiographs.

Nuclear magnetic resonance imaging of bone marrow was performed in seven patients (pelvis and vertebral marrow) and showed abnormal results in all cases.

Table 5. Frequency of BMI According to Laboratory Values

Variable	No.	%	P*
ESR (mm/h)			
< 40	39/1,114	3.5	< .0001
≥ 40	93/1,156	8.0	
Alkaline phosphate (U/L)			
< 230	85/1,819	4.6	< .0001
≥ 230	46/391	11.7	
LDH (U/L)			
< 240	61/1,409	4.3	
240-400	34/441	7.7	< .0001
≥ 400	15/94	15.9	
Hemoglobulin (g/dL)			
Male			
< 12	37/259	14.2	< .0001
≥ 12	49/1,056	4.6	
Female			
< 10.5	21/122	17.2	< .0001
≥ 10.5	26/838	3.1	
Leukocytes (g/L)			
< 4	22/82	26.8	
4-10	72/1,219	5.9	< .0001
≥ 10	40/979	4.1	
Thrombocytes (g/L)			
< 150	21/65	32.3	
150-500	101/1,845	5.4	< .0001
≥ 500	11/355	3.0	
Leukocytes and thrombocytes (g/L)			
Leukocytes < 4, thrombocytes < 150	9/16	56.2	
Leukocytes ≥ 10, thrombocytes ≥ 500	9/272	3.3	< .0001
Any other	117/2,003	5.8	

*Pearson χ^2 test.

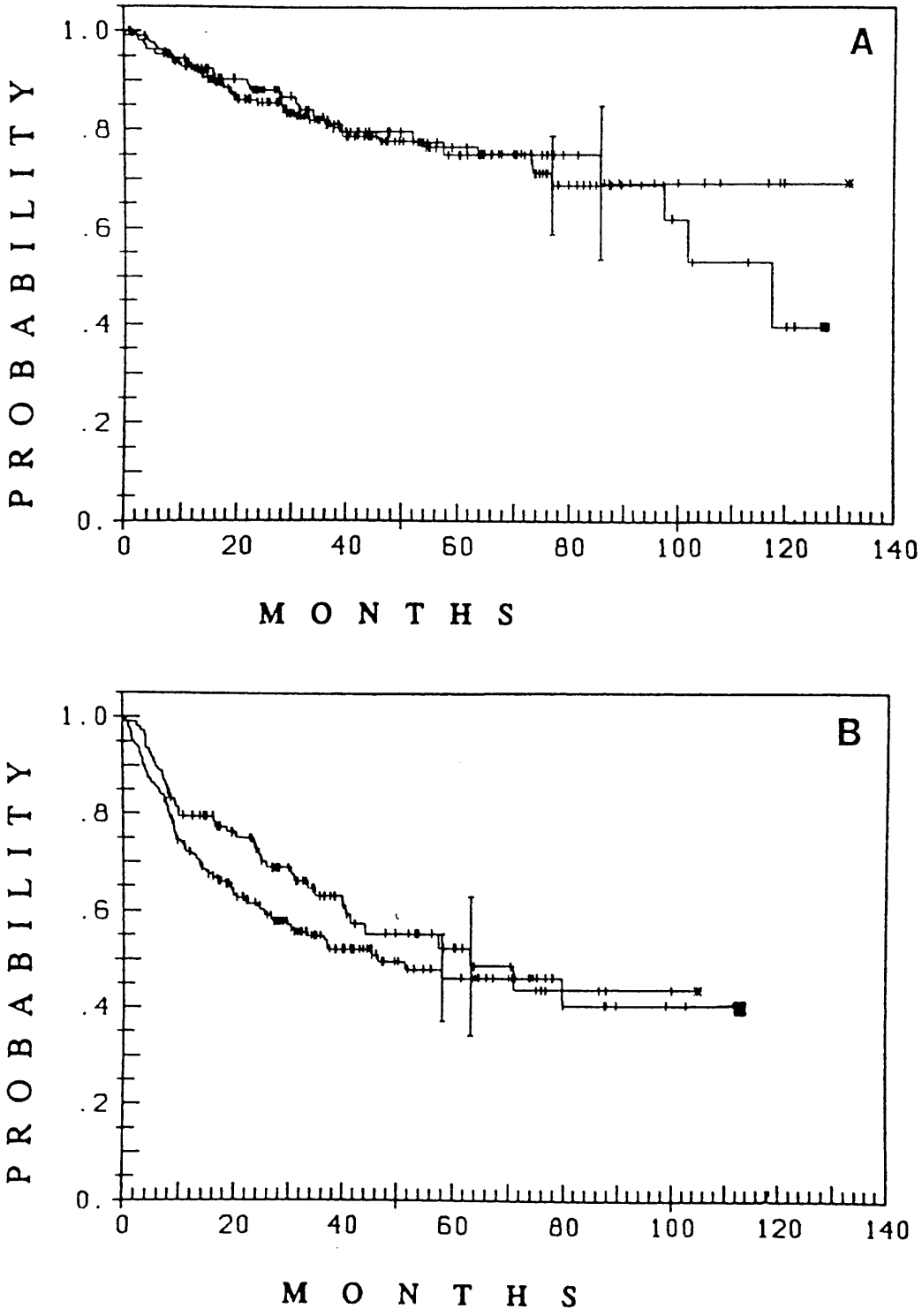

Fig 1. Overall survival (A) and freedom from treatment failure (B) curves for stage IV with BMI (*, n = 108, 42 failures, 21 deaths) and without BMI (■, n = 213, 98 failures, 46 deaths). Cox-Mantel tests: (A) $P = .52$ and (B) $P = .16$ not significant. Crossbars depict 95% confidence intervals.

Laboratory Features of BMI

Compared with bone marrow biopsies, routine bone marrow aspirates were insensitive in detecting BMI in HD: diagnostic changes were observed in only 27 of 85 cases in which aspirates were made in addition to biopsy (31.8%).

In a univariate analysis, patients with and without BMI were compared according to different laboratory values (Table 4). Patients with BMI had a higher ESR, alkaline phosphatase level, and lactate dehydrogenase (LDH) level, and lower hemoglobin, leukocyte, and thrombocyte counts than patients without BMI. Patients with an elevated ESR, alkaline phosphatase level, or LDH level, or leukocytopenia or anemia, had a significantly increased risk of BMI. In the infrequent case of leukocytopenia and concurrent thrombocytopenia, nine of 16 patients had BMI (Table 5).

Table 6. Incidence of BMI Various Historic Groups of HD Patients, 1974 to 1991

Reference	Years	Stages Included	Incidence	
			No.	%
19	1964-76	I-IV	53/1,200	4.4
18	1970-81	ND	18/370	4.8
8	1977-84	I-IV	13/182	7.1
6	1975-78	IIB-IV	16/185	8.6
4	1971-80	I-IV	49/480	10.2
7	1978-88	III-IV	13/125	10.4
2	1965-72	ND	19/174	10.9
5	1975-86	I-IV	16/120	13.3
3	1968-75	ND	15/107	14.0
Present series	1988-92	I-IV	82/1,739	4.8

Abbreviation: ND, no data given.

Logistic Regression Analysis

Logistic regression modeling with a step-up selection procedure was used in an attempt to predict the presence of bone marrow involvement. The following parameters in the order of selection have independent predictive value: systemic symptoms ($P < .00005$), thrombocyte counts (coded: $-1 < 150$; $0 = 150$ to 500, $1 > 500$ g/L ($P < .00005$), large mediastinal tumor ($P < .00005$; negatively correlated), LDH level ($P = .0004$, continuous variable), stage before bone marrow biopsy ($P = .0014$) and hemoglobin level ($P = .0088$).

Although the goodness of fit of this model is satisfactory, the discrimination of BMI and non-BMI cases is not particularly good, probably because the crude incidence of BMI is low among all stages (4.8%). The median of the predicted probability of non-BMI is 98% among non-BMI cases, in contrast to 86% among BMI cases. The model may not be used to define a group of patients with virtually no risk of BMI and does not characterize a group of high BMI risk.

Treatment Results

Taking together patients treated according to the HD3 and HD6 protocols, 87 of 108 assessable patients with BMI achieved a CR (80.6%). Four patients obtained partial remissions with the standard induction protocol, and the remaining 17 patients had progressive disease. The CR rate for patients with BMI compares favorably with the CR rates for all stage IV patients of 73.5% and for stage IV/IIIB combined of 79.7%. Freedom from treatment failure and overall survival of patients with BMI was not different when compared with patients with stage IV without BMI or stage III B/IV without BMI. The survival and freedom from treatment failure curves for stage IV with or without BMI are shown in Fig 1A and B.

In the observation period, which lasted from 1983 to 1993, 21 of 87 patients relapsed. Among these 21 patients, only four again had a positive bone marrow biopsy (23.8%). Among all stage IV patients (n = 236), 55 have relapsed (23.3%). Of the total group of 135 patients, two developed second malignancies, both with progressive HD.

DISCUSSION

To our knowledge, this is the largest series yet of patients with HD and BMI. Among 2,307 patients entered from our multicenter study group, 135 showed BMI. The incidence of 4.8% BMI in the HD4-6 protocols, which also include early stages, is somewhat lower than in most series, which may be explained by the fact that most series do not include patients with early-stage disease. Details about the incidence of BMI in various series are listed in Table 6. The international data base for HD, in which data of more than 14,000 patients are collected, gives an incidence of BMI of 3.7% and 9.2% according to clinical or pathologic staging.[16] BMI is one of the major reasons for stage IV classification in HD, and other organs (lung, liver, and bone) are diffusely involved in approximately one third of cases. The male predominance of our patients and a median age of 34 to 36 years confirm data from other series of patients with BMI or stage IV disease.[2,3,9,17] BMI is associated with so-called unfavorable histologic subtypes of HD; this confirms data from smaller series of patients with BMI.[2,3,18,19] As noted previously, BMI is associated with B symptoms and advanced disease.[2,3,5,8] However, a large mediastinal mass is rare in HD with BMI. This may relate to the biologic properties of the malignant cells, since a mediastinal tumor often remains localized, whereas BMI in most cases indicates disseminated disease. Similarly, the histologic subtype of nodular sclerosis predominates in mediastinal disease[20,21]

Table 7. CR and Survival Rates in Advanced-Stage HD With BMI

Reference	Years	Stages	CRs		Survival Rate (%)
			No.	%	
19	1964-76	IV + BMI	21/48	43.8	45
2	1965-72	IV + BMI	13/18	72.2	ND
9	1969-83	IV + BMI	6/14	42.9	18
18	1970-81	IV + BMI	11/14	78.6	42
6	1975-84	IIB-IV	152/185	82.2	77
17	1974-82	IV	72/88	81.2	ND
25	1975-88	III-IV	163/227	71.8	73
7	1978-88	III-IV	114/125	91.2	79
Present series	1983-91	IV + BMI	87/108	80.6	71
Present series	1983-91	IIIB-IV	79/607	79.7	70

NOTE. Survival at 5 years estimated from published data.
Abbreviation: ND, no data available.

and is infrequent in BMI. The value of bone marrow biopsy in the staging of early HD has been questioned[5,8]; however, our results show that even in early stages (eg, stage IB), a significant number of positive biopsies occur. Patients with stages IA or IIA disease without bulk have a low risk of BMI; however, in these patients, the outcome would be changed most if a positive biopsy was missed. Consistent with the systemic nature of BMI, the laboratory features of an elevated ESR, LDH, and alkaline phosphatase level, and leukocytopenia, anemia, and thrombocytopenia, were observed. The histologic and clinical features of myelofibrosis were described as a presenting sign of HD with BMI.[22] Although no patient showed typical myelofibrosis, in the rare cases of leukocytopenia and thrombocytopenia, more than 50% of patients had BMI.

Using current treatment and staging strategies, it appears from our data that BMI, at least in a multicenter setting, can no longer be considered as an unfavorable prognostic factor within advanced-stage HD. In the past, some,[6,9] but not all,[18] studies had identified BMI as an unfavorable prognostic criterion. In a recent study in which the effect of low-dose involved-field irradiation as an adjunct to chemotherapy was studied, BMI again had no effect on remission duration.[23] Reasons for this apparent discrepancy may be the treatment received (MOPP or other MOPP-based combination regimens in the earlier studies). The CR rate of 80.6% obtained in this multicenter study group compares favorably with the overall CR rate in patients with advanced stages in this and other series. A detailed comparison is listed in Table 7. BMI has no different prognosis from other advanced stages. To select patients who will fail to respond to the standard induction protocol or who will relapse early, other biologic and/or clinical characteristics need to be evaluated. Previous BMI does not exclude patients from undergoing stem-cell or bone marrow transplantation, since, as shown in our group of patients, only a minority will again relapse in the bone marrow. Recently, the value of magnetic resonance imaging to detect BMI was established[24]; by directing biopsies to suspicious areas, it may also enhance the detection of low-grade involvement. Altogether, it may be more important to detect BMI in early than in advanced stages, because patients with advanced-stage will be treated by chemotherapy in any case.

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