original paper
Haematologica 1997; 82:676-682

HODGKIN'S DISEASE PRESENTING BELOW THE DIAPHRAGM. THE EXPERIENCE OF THE GRUPPO ITALIANO STUDIO LINFOMI (GISL)

EMILIO IANNITTO,* VINCENZO ACCURSO,* MASSIMO FEDERICO,° DANIELE VALLISA,# CARLA PIERESCA,@ SEBASTIANO F. GRAVINA,* FRANCESCO DI COSTANZO,^ ROSA DI TRAPANI,* VITTORIO SILINGARDI,° GUGLIELMO MARIANI*

**Ematologia e Centro Trapianto di Midollo, Università di Palermo; °Oncologia Medica, Università di Modena; #Divisione di Medicina I°, Ospedale Civile Piacenza; @Istituto di Medicina Interna ed Oncologia Medica, IRCCS, Pavia; ^Unità Operativa di Oncologia, Ospedale S. Maria, Terni; Italy*

ABSTRACT

Background and Objective. Infradiaphragmatic Hodgkin's disease is rare, making up 5-12% of cases in clinical stages I and II; consequently, several questions concerning prognosis and treatment strategy remain to be answered. The aim of this study was to analyze the clinical and prognostic characteristics and outcome of this condition.

Methods. A series of 282 patients with CS I-II Hodgkin's disease (HD) was investigated. In 31 patients the disease was confined below the diaphragm (BDHD), and in the remaining above the diaphragm (ADHD). The presenting features and outcomes were compared in the two groups.

Results. The BDHD group was older ($p < 0.0002$), had a higher frequency of males ($p < 0.08$) and a different histological subtype group distribution ($p < 0.0001$). Stage II BDHD patients had a worse overall survival rate (OS) than stage II ADHD patients (68.8% vs 86.6% at 8 years, $p < 0.01$) if age is not considered; patients with more than 40 years of age, in fact, had the same survival rates as those with ADHD. BDHD patients with intra-abdominal disease alone had worse prognostic factors and OS ($p = 0.12$) than patients with inguinal-femoral nodes.

Interpretation and Conclusions. Although BDHD patients present distinct features, they have the same OS and relapse-free survival rate as age-adjusted ADHD patients. According to our experience patients with stage I peripheral BDHD respond well to radiotherapy-based regimens. Those with stage II and or intra-abdominal disease are more challenging; chemotherapy or a combined therapy seem to be more suitable approaches for these patients.

Key words: Hodgkin's disease, clinical stage, prognostic factors

Hodgkin's disease (HD) is rarely found in its below-diaphragm presentation (BDHD 5-12%).[1,2] Moreover, BDHD patients are a heterogeneous group regarding the involvement of peripheral, retroperitoneal and abdominal nodes and the spleen. However, some consistent clinical features are apparent. Compared to HD stage I and II above the diaphragm (ADHD), BDHD patients are older, mostly male, and present a different distribution of histological subtypes. It is worth noting that up to 30% of patients with BDHD show the disease as confined to intra-abdominal lymph nodes (central BDHD) rather than having it extended into inguinal-femoral nodes (peripheral BDHD).[3,4] Although many studies dealing with this rare condition have been published, some questions remain unanswered, in particular: (i) do patients with BDHD have a worse outcome than those with ADHD? (ii) is current clinical staging an adequate procedure? (iii) do patients with *central* BDHD have a worse prognosis than those with *peripheral* BDHD? (iv) what is the best therapeutic strategy for BDHD? Over the last decade, there have been a number of retrospective reviews from single institutions.[1,3-17] Due to the rarity of this condition, all the published reports are retrospective, and span for periods of up to 20 years; this makes the reports heterogeneous with respect to diagnostic and treatment policies. Moreover, since most of the reports come from single institutions [third-level reference cancer center], a selection bias cannot be ruled out. Since 1988 the GISL (*Gruppo Italiano Studio Linfomi*) treatment policy for Hodgkin's lymphoma has included three prognostic categories: a) HD1: low risk patients with early disease and no unfavorable factors; b) HD2: intermediate risk patients with early disease presenting one or two unfavorable factors; c) DH3: high risk cases with advanced disease or a very unfavorable presentation. BDHD has been

Correspondence: Dr. Emilio Iannitto, Cattedra di Ematologia e Centro Trapianto di Midollo, Azienda Universitaria Policlinico Paolo Giaccone, via del Vespro 127, 90129 Palermo, Italy. Tel. international +39.91.6554409-6554423. Fax. international +39.91.6554402. E-mail: marianig@mbox.unipa.it
Acknowledgements: the authors wish to thank Mr. David Holmes for his help in the preparation of the manuscript.
Received June 3, 1997; accepted September 2, 1997.

included in our prognostic score as an unfavorable factor.

The aim of this study was to analyze the clinical and prognostic characteristics as well as the outcome of BDHD patients and compare them with the features of the ADHD patients treated at GISL centers from January 1988 to December 1995. This is, to the best of our knowledge, the first prospective multicenter study in this field.

Patients and Methods

From January 1988 to December 1995, 282 previously untreated adults with clinical stage I-II, biopsy proven HD were evaluated and registered for prospective treatment by 19 institutions of the *Gruppo Italiano Studio Linfomi* (GISL). Their ages ranged from 16 to 79. Thirty-one patients (11%) were recorded as BDHD in 11 different centers. Details of staging have been previously described.[18] The clinical stage was established according to the Ann Arbor classification, and histological subtypes were determined using Rye nomenclature.[19] As suggested by Krikorian *et al*.,[3] patients with infradiaphragmatic disease were classified according to the presence (peripheral: P) or absence (central: C) of inguinal-femoral nodes. The clinical stage routinely consisted of the compilation of historical data, physical examination, complete blood picture, multiple biochemical analysis, chest X-rays, computerized tomography (CT) of both chest and abdomen, and one side bone marrow needle biopsy. All patients with the central form, and 3 out of 17 with the peripheral form underwent diagnostic laparoscopy (LPS) or laparotomy (LPT) for the evaluation of an abdominal mass with or without systemic symptoms. No patient was splenectomized. All the tests performed for the staging procedure were repeated after therapy, with the exception of the bone marrow biopsy. According to the GISL treatment policy, on the basis of their presenting features, patients were allocated into three different prognostic groups: a) *low risk* (HD1): patients in this group were treated with radiotherapy-oriented regimen;[18] b) *intermediate risk* (HD2): this group received chemotherapy plus IF radiotherapy;[20,21] c) *high risk* (HD3): patients were treated with aggressive ten-drug chemotherapy.[22] Radiotherapy (RT) was administered by megavoltage equipment in 13 different RT divisions. The recommended dose was 36-38 Gy for the patients who also received chemotherapy, and 40-44 Gy when no chemotherapy was administered. Subtotal nodal irradiation (STNI) was: 1) for ADHD patients, a mantle field treated to a total dose of 4000-4500 cGy, followed by treatment of para-aortic and splenic pedicle nodes and treatment of the spleen at a dose of 3600 cGy, 2) for BDHD patients, a complete inverted Y-field including spleen. The median follow-up was 34 months (range 4-111) for ADHD and 53 months (range 3-89) for BDHD. The overall survival (OS) and relapse-free survival (RFS) curves were calculated using the method of Kaplan and Meier.[23] Death due to causes other than HD or therapy were not considered. Statistical significance was evaluated by the log-rank test.

Results

Clinical features, histology, stage, treatment and outcome of individual patients with BDHD are shown in Table 1. There were 21 males and 10 females with a mean age of 49.9 (range 16-79). Fourteen patients (45%) presented intra-abdominal disease, which was often accompanied by fever. Eight patients had stage I disease and 23 patients had stage II. Mixed cellularity was the most common histological subtype, accounting for 45% of cases. Three patients (9.6%) showed involvement of the spleen, and all of them belonged to the C-BDHD group (21.4%). Two C-BDHD patients were not evaluable for response because of early death. One patient who was treated with complete inverted Y RT relapsed after 6 months in the supraclavicular area and was then successfully retreated with mini mantle radiotherapy. Seven patients belonging to the BDHD group have died so far, two from the *peripheral* and five from the *central* group.

In the *peripheral* group, 1 died of adenocarcinoma with an unknown primary site (see record #18) and 1 of accidental causes (see record #6). In the *central* group one death was therapy related (see record #2: gastrointestinal bleeding due to thrombocytopenia during chemotherapy) and 1 patient (see record #1) died of progressive disease. The other three deaths were caused by infection (meningitis: record #3; sepsis: record #4; post-transfusion fulminant viral hepatitis: record #9) in patients in partial remission or progressive disease. The clinical characteristics at presentation and the therapy and survival of BDHD patients with and without involvement of inguinal-femoral nodes are compared in Table 2.

The C-BDHD group had significantly lower performance status, hemoglobin and albumin levels, but higher ESR values and incidence of B symptoms. However, no difference in median age, bulky disease or number of Ann Arbor involved areas or histological subtype distribution was found. More patients in the BDHD group received ten-drug chemotherapy, showing a statistically significant difference ($p < 0.007$). However, the overall survival of these patients was not worse than that of the P-BDHD group, although there was a trend ($p = 0.12$) due to the small number of patients (Figure 1).

In Table 3, the clinical characteristics of ADHD and BDHD patients are compared. Patients presenting BDHD were significantly older (49.9 vs 30.8 $p < 0.0002$) and were mostly males ($p=0.08$).

Table 1. Clinical features and outcome of 31 BDHD patients

Record	Sex/age	Histol.	Stage/Bulky	Presentation	LPT	LPS	Therapy	Outcome	Status	Survival (months)
1	F/75	LD	II-B/y	C	y		HD3	PG	Dead	9
2	M/58	MC	II-B	C		y	HD3	NV	Dead	3
3	M/58	LD	I-B/y	C	y		HD3	PG	Dead	3
4	F/56	NS	II-B	C		y	HD2	PR	Dead	4
5	M/26	MC	I-B/y	C	y		HD3	CR	Alive	9+
6	F/79	NS	II-B	P			HD2	NV	Dead	6
7	F/47	MC	II-A/y	C	y		HD3	CR	Alive	9
8	M/37	NS	II-A	P			HD2	CR	Alive	14
9	M/34	MC	II-B	C	y		HD2	PR	Dead	21
10	M/35	NS	I-A	P			HD2	PR	Lost	22
11	M/55	NS	I-A	P			HD1	CR	Alive	23+
12	M/52	MC	II-A	P			HD2	CR	Alive	24+
13	M/64	MC	II-A	P		y	HD2	CR	Alive	30+
14	M/29	NS	II-A	P			HD2	CR	Alive	45+
15	M/50	MC	I-A	C		y	HD1	CR	Alive	45+
16	M/50	MC	II-B	P			HD3	CR	Alive	53+
17	M/32	NS2	II-B	C	y		HD2	CR	Alive	55+
18	F/60	LP	II-A	P		y	HD1	CR	Dead	65+
19	M/35	MC	II-A	P			HD1	CR	Alive	65+
20	M/31	LP	II-A	P			HD1	CR	Lost	67+
21	F/35	MC	II-A	C		y	HD1	CR	Alive	67+
22	M/71	LP	I -A	P			HD1	CR	Alive	70+
23	F/71	LD	I -A	P			HD1	CR	Alive	75+
24	F/16	LD	II-B	C	y		HD3	CR	Alive	75+
25	M/43	MC	II-A/y	P			HD2	CR	Alive	76+
26	M/40	LD	II-B/y	C	y		HD3	CR	Alive	76+
27	F/66	MC	II-B	C	y		HD3	CR	Alive	78+
28	M/17	NS	II-A	P			HD1	CR	Alive	80+
29	F/67	MC	II-B/y	P		y	HD2	CR	Alive	82+
30	M/57	NS	II-B	P			HD3	CR	Alive	88+
31	M/60	MC	I-A	C		y	HD1	CR	Alive	89+

Moreover, histological subtype distribution showed an overall significant difference, as did albumin (cut-off 4 g/dL, p = 0.002). No difference in stage distribution was observed, though a higher percentage of patients in the BDHD group presented B symptoms. The frequency of bulky disease, number of Ann Arbor involved areas, ESR values and response rate were similar in the two groups. The ADHD and BDHD patients spread evenly over the GISL risk groups, receiving low risk (HD1) RT based treatment, intermediate risk (HD2) standard chemotherapy and IF RT, and high risk (HD3) aggressive ten-drug polichemotherapy. OS of BDHD was different from that of ADHD patients (72.6% vs 88.8% at 8 years, p < 0.003) (Figure 2). However, no difference in RFS curves was detected (data not shown).

Considering the stage, a significant difference in the OS for stage II BDHD compared to stage II ADHD patients became apparent (Figure 3). An 8-year actuarial survival rate was projected for 68.8% and 86.6% of the two groups, respectively. However, this difference disappears when stage II BDHD patients are compared to stage II ADHD patients of over 40 years of age (Figure 4). The differences in OS and RFS for stage I patients with BDHD compared to ADHD patients were not statistically significant (data not shown).

Discussion

Although the abdomen harbors a large proportion of the body's lymphoid tissue, BDHD is exceedingly rare; as a presenting feature, it accounts for no more than 12% of stage I-II patients.[3] These patients represent a heterogeneous group regarding the involvement of peripheral, retroperitoneal and abdominal lymph nodes and involvement of the spleen. In the literature, BDHD patients are report-

Table 2. Comparision of presenting features of C-BDHD and P-BDHD.

Cases	P-BDHD n=17	C-BDHD n=14	p
Age			
median	52	48.6	NS
range	(17-79)	(16-75)	
Sex M/F	13/4	8/6	NS
Symptoms B %	23.5%	64.2%	< 0.03
Stage I/II	4/13	4/10	NS
PS (K.B.)	95	75	< 0.003
Follow-up			
Median	53.6	33.3	NS
Range	7-88	3-89	
Hb < 11 g/dL	5.9%	42.8%	< 0.01
ESR > 40	18.7%	66.6%	= 0.01
LDH 250	266	0.08	
Albumin < 4 g/dL	40%	76.9%	< 0.04
Histology			
NS	7	2	0.1
LP	3	0	0.09
MC	6	8	0.2
LD	1	3	0.09
Bulky	2	5	0.2
N° involved sites	2	3	NS
CR+PR	94.1%	71.4%	NS
Surv. at 8 years	80.67%	60.58%	NS
Therapy			
HD1	7	3	NS
HD2	8	3	NS
HD3	2	8	NS

Legend. HD1: VBM+EF RT; HD2: ABVD+IF RT or CcVPP+EF RT; HD3: MOPPEBVCAD; NS: not significant.

Table 3. Comparision of presenting features of BDHD and ADHD patients.

Cases	BDHD n=31	ADHD n=251	p
Age			
Median	49.9	31.20	< 0.0002
Range	(16-79)	(18-79)	
Sex M/F	21/10	121/130	= 0.08
Stage I/II	8/23	51/200	
Symptoms B %	42%	28%	NS
PS (K.B.)	90	90	
Hb < 11 g/dL	13%	26%	= 0.06
ESR > 40	39%	38%	
LDH	250	306	
Albumin < 4 g/dL	57%	34%	= 0.02
Histology			
NS	9	154	< 0.004
LP	3	28	
MC	14	63	< 0.01
LD	5	6	< 0.001
Bulky	7/31	68/251	NS
CR + PR	80.6%	94.5%	NS
Surv. at 8 years	72.6%	88.7%	< 0.003
Therapy			
HD1	104	10	NS
HD2	92	11	NS
HD3	55	10	NS

Legend. HD1: VBM+EF RT; HD2: ABVD+IF RT or CcVPP+EF RT; HD3: MOPPEBVCAD; NS: not significant.

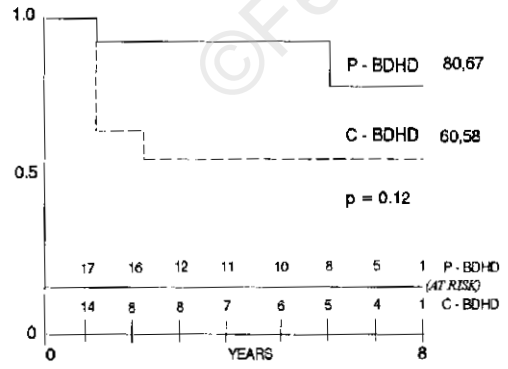

Figure 1. Kaplan-Meier plot of overall survival of P-BDHD compared to C-BDHD patients.

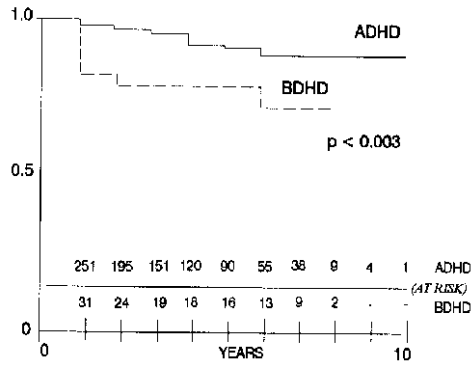

Figure 2. Kaplan-Meier plot of overall survival for patients with stage I/A-II/B ADHD and BDHD.

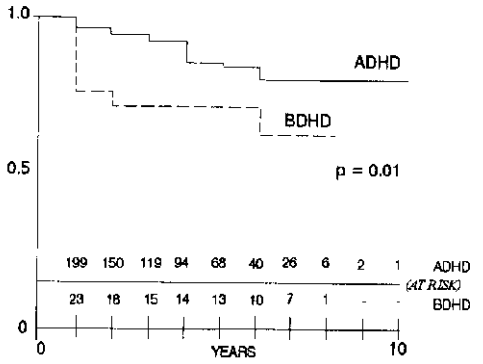

Figure 3. Kaplan-Meier plot of overall survival for patients with stage II ADHD and BDHD.

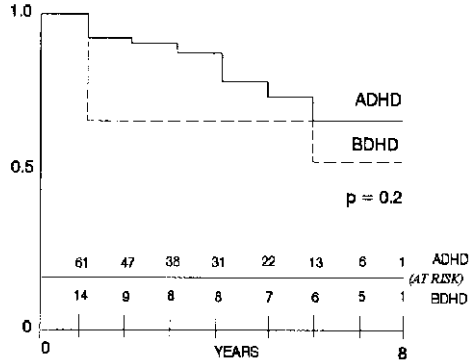

Figure 4. Actuarial survival of patients over 40 years of age with stage II BDHD compared to that of patients with stage II ADHD.

ed as being predominantly male,[1,5,6,13,15] older[1,6,8,14] than ADHD patients, with a low frequency of NS histology,[1,3,6,13,14] and poor prognosis.[8,11,16] Still, other studies did not find any difference in median age,[12,15] distribution of histology subtypes,[8,10] gender[8,14] or prognosis[1,7,13,14,17] when comparing BDHD and ADHD patients of similar stages. Our knowledge about BDHD derives from single institution retrospective studies with up to 20 years of observation. Clearly, this long period of observation may have led to pooling in the data collection of patients, as they may have been treated under different policies. These features may also be true for some recent reports.[4,16]

In the present study we have analyzed a series of CS I-II Hodgkin's disease patients enrolled in prospective trials by GISL. Moreover, infradiaphragmatic presentation was considered a negative prognostic factor evaluated with the stage, symptom histology and bulk in order to classify the patients in low, intermediate or high risk groups. Therefore, all the patients in the present analysis were subjected to the same staging and treatment policy. Eleven of all clinical stage I-II HD patients presented abdominal nodes; patients with BDHD were older and had NS histology less often than patients with ADHD. While we confirmed the male predominance assessed in the literature, we did not find a significantly different incidence of B symptoms. Of interest, is the significant prevalence of hypoalbuminemia.

Spleen involvement represents an important feature of the abdominal HD presentation. In a review of 76 BDHD patients who underwent staging laparotomy,[3] spleen involvement was documented in 28%, but only 5% of the patients were upstaged to stage IV because of liver involvement. Moreover, the analysis of the combined experience of five series reported by Liew et al.[12] indicated an incidence of spleen involvement of 7% (2/27) for CS IA, 37% for CS IIA and 62% for CS IIB. We detected spleen involvement in three patients (9.6%), all of whom belonged to stage II C-BDHD, but this figure is likely to be an underestimate because our patients were staged clinically. Only 17 out of 31 underwent surgical procedures for diagnostic purposes and no patient was splenectomized. We would also stress that in our series, all those with spleen involvement also had para-aortic disease. The data coming from series in which lymphoangiography (LAG) was routinely performed reflect the same figure.[3,4,9,11] A negative LAG in patients with inguinal-femoral disease has been correlated with a low risk (0-10%) of splenic involvement. For patients with a positive LAG, the corresponding risk has ranged from 25 to 52%. Therefore, we believe there is now enough data to consider clinical staging as an adequate approach for the majority of peripheral BDHD cases, similarly to the policy adopted for ADHD patients.[24] This is supported by the fact that either chemotherapy or combination therapy is considered the therapy of choice for CS II. For central diseases which require surgical procedure for diagnostic purposes, a more conservative approach with laparoscopy or an image-guided core needle biopsy[25] could be preferable. Indeed, in our experience, most of these patients had B symptoms, a very high risk of spleen involvement, and were therefore candidates for chemotherapy. Recent advances in diagnostic imaging techniques, such as Gallium 67 scintigraphy and positron emission tomography (PET), could be of value in the near future in staging and remission evaluation of this rare subset of HD.[26] PET, particularly, offers a

potential advantage over Gallium 67 scintigraphy in the abdomen, as interpretation of PET is normally unimpeded by massive bowel excretion of radionuclides. A question about BDHD that remains unanswered is whether[10,16,17] or not[1,7,9,13,14] this HD presentation is associated with a worse prognosis. Our series reveals a statistically significant decrease in terms of OS in patients with stage II BDHD as compared to stage II ADHD, while no differences were shown in RFS. This difference in OS, however, disappears when BDHD patients are compared to ADHD patients of over 40 years of age.

Age is a well-known adverse prognostic factor for survival, whatever the cut-off be (40 or 50 years)[27] for patients who are either clinically[27] or pathologically staged.[29] Thus, a negative prognosis may be related to the age, rather than to the site of presentation. It is still unclear why abdominal HD is so frequent in elderly men. In some reports, a worse prognosis for C-BDHD patients than for those with initial P-BDHD has been reported.[1,4,11,13,17] In our study, C-BDHD had a higher incidence of negative prognostic factors, namely anemia, hypoalbuminemia and ESR > 40 mm. Despite the fact that patients with C-BDHD had received a more aggressive treatment than P-BDHD patients (57% vs 11% ten-drug polichemotherapy p= 001), they fared worse in terms of OS (p = 0.12). No differences concerning stage, bulk, number of Ann Arbor involved areas or median age between peripheral and central BDHD were apparent. Moreover, delay in diagnosis did not differ between the two groups (data not shown). We would therefore share the opinion that the differences in the pattern of presentation and in the outcome reported are related to the abdominal presentation itself. Roos *et al.*[4] suggested that patients with pelvic disease, also, should be considered differently from those with inguinal-femoral disease, at least in terms of treatment strategy, since a high failure rate occurs, when patients are treated with limited radiotherapy. None of our patients treated with Y Rt and VBM chemotherapy failed to respond to treatment or relapsed, suggesting that this combined protocol[29] may provide a good control of microscopic disease as it has been shown for ADHD stage I-IIB. Therefore, we share the opinion that a spread of disease along the iliac node stations should be considered an important element for planning a more aggressive therapeutic approach.

In conclusion, our data indicate that BDHD is a rare condition with distinct features and adverse prognostic factors. Staging should be as uninvasive as possible and, for C-BDHD, laparotomy can be avoided. Two different groups can be distinguished concerning the therapy: 1) patients in stage I with inguinal-femoral disease, for whom clinical staging and a radiotherapy based-regimen are an appropriate approach; and 2) patients with stage II and/or intra-abdominal presentation. These are a diagnostic and therapeutic challenge with a higher risk of early death, especially if the tumor is bulky. Because of these factors, therapy for C-BDHD should include both standard chemotherapy and involved field radiation therapy.[31] If adequately treated, the outcome of these patients is similar to that of patients of comparable age and different presentation site.

References

1. Krikorian JG, Portlock CS, Rosenberg SA, Kaplan HS. Hodgkin's disease, stages I and II occurring below the diaphragm. Cancer 1979; 43:1866-71.
2. Mauch PM, Kalish LA, Kadin M, Coleman CN, Osteen R, Hellman S. Pattern of presentation Hodgkin disease. Cancer 1993; 71:2062-71.
3. Krikorian JG, Portlock CS, Mauch PM. Hodgkin's disease presenting below the diaphragm: a review. J Clin Oncol 1986; 4:1551-62.
4. Roos DE, O'Brien PC, Wright J, Willson K. Treatment of subdiaphragmatic Hodgkin's disease: is radiotherapy alone appropriate only for inguino-femoral presentation? Int J Radiat Oncol Biol Phys 1994; 28:683-91.
5. Barret A, Gregor A, McElwain TJ, Peckham MJ. Infradiaphragmatic presentation of Hodgkin's disease. Clin Radiol 1981; 32:221-4.
6. Cionini L, Magrini S, Mungai V, Biti GP, Ponticelli P. Stage I and II Hodgkin's disease presenting in infra-diaphragmatic nodes. Tumori 1982; 68:519-25.
7. Dorreen MS, Wrigley PFM, Jones AE, Shand WS, Stansfeld AG, Lister TA. The management of localised infra-diaphragmatic Hodgkin's disease: experience of a rare clinical presentation at St. Bartholomew's Hospital. Hematol Oncol 1984; 2:349-57.
8. Lanzillo JH, Moylan DJ, Mohiuddin M, Kramer S. Radiotherapy of stage I and II Hodgkin's disease with inguinal presentation. Radiology 1985; 154:213-5.
9. Leibenhaut MH, Hoppe RT, Varghese A, Rosenberg SA. Sub-diaphragmatic Hodgkin's disease: Laparotomy and treatment results in 49 patients. J Clin Oncol 1987; 5:1050-5.
10. Specht L, Nissen NI. Hodgkin's disease stage I and II with infradiaphragmatic presentation: a rare and prognostically unfavourable combination. Eur J Haematol 1988; 40:396-402.
11. Givens SS, Fuller LM, Hagemeister FB, Gehan EA. Treatment of lower torso stages I and II Hodgkin's disease with radiation with or without adjuvant mechlorethamine, vincristine, procarbazine, and prednisolone. Cancer 1990; 66:69-74.
12. Liew KH, Ding JC, Cruickshank D, Quong GG, Wolf MM, Cooper IA. Infra-diaphragmatic Hodgkin's disease, long term follow-up of a rare presentation. Aust NZ J Med 1991; 21:16-21.
13. Mai DH-W, Peschel RE, Portlock C, Knowlton A, Farber L. Stage I and II sub-diaphragmatic Hodgkin's disease. Cancer 1991; 68:1476-81.
14. Villamor N, Reverter JC, Marti JM, Montserrat E, Rozman C. Clinical features and response to treatment of infradiaphragmatic Hodgkin's disease. Eur J Haematol 1991; 46:38-41.
15. Mason MD, Law M, Ashley S, et al. Infradiaphragmatic Hodgkin's disease. Eur J Cancer 1992; 28:1851-2.
16. Enrici RM, Osti MF, Anselmo AP, et al. Hodgkin's disease stage I and II with exclusive subdiaphragmatic presentation. The experience of the departments of radiation oncology and haematology, University "la Sapienza" of Rome. Tumori 1996; 82:48-52.
17. Mauch P, Greenberg H, Lewin A, Cassady JR, Weichselbaum R, Hellman S. Prognostic factors in patients with subdiaphragmatic Hodgkin's disease. Hematol Oncol 1983; 1:205-14.
18. Gobbi PG, Pieresca C, Frassoldati A, et al. Vinblastine, Bleomycin and Methotrexate chemotherapy plus extended field radiotherapy in early, favourably presenting, clinically staged Hodgkin's patients: the Gruppo Italiano per lo Studio dei Linfomi Experience. J Clin Oncol 1996; 14:527-33.
19. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease staging classification. Cancer Res 1971; 31:1860-1.
20. Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer 1975; 36:252-9.
21. Gobbi PG, Pieresca C, Cavanna L, et al. CCNU, Vinblastine, Procarbazine and Prednisone (CVPP) with extended-field radiotherapy in the treatment of early unfavourable Hodgkin's disease. A prospective study on behalf of the Gruppo Italiano per lo Studio dei Linfomi (GISL). Haematologica 1996; 81:503-12.
22. Gobbi PG, Pieresca C, Federico M, et al. MOPP/EBV/CAD hybrid chemotherapy with or without limited radiotherapy in advanced or unfavourably presenting Hodgkin's disease: A report from the Italian

Lymphoma Study Group. J Clin Oncol 1993; 11:712-9.
23. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. Am Stat Assoc J 1958; 53:457-80.
24. Multani PS, Grossbard ML. Staging laparatomy in the management of Hodgkin's disease: Is it still necessary? The Oncologyst 1996; 1:41-55.
25. Pappa VI, Hussain HK, Reznek RH, et al. Role of image-guided core-needle biopsy in the management of patients with lymphoma. J Clin Oncol 1996; 14:2427-30.
26. de Wit M, Bumann D, Beyer W, Herbst K, Clausen M, Hossfeld DK. Whole-body positron emission tomography (PET) for diagnosis of residual mass in patients with lymphoma. Ann Oncol 1997; 8(suppl 1):57-60.
27. Wedelin C, Bjorkholm M, Biberfeld P, Holm G, Johansson B. Prognostic factors in Hodgkin's disease with special reference to age. Cancer 1984; 53:1202-8.
28. Tubiana M, Henry-Amar P, Carde JMV, et al. Toward comprehensive management tailored to prognostic factors of patients with clinical stages I and II in Hodgkin's disease. The EORTC Lymphoma Group Controlled Trials: 1964-1987. Blood 1989; 73:47-56.
29. Mauch P, Tarbell N, Weinstein H, et al. Stage IA and IIA supradiaphragmatic Hodgkin's disease: prognostic factors in surgically staged patients treated with mantle and paraaortic irradiation. J Clin Oncol 1988; 6:1576-83.
30. Horning SJ, Hoppe RT, Hancock SL, et al. Vinblastine, bleomycin and methotrexate: an effective adjuvant in favorable Hodgkin's disease. J Clin Oncol 1988; 6:1822-31.
31. Pogliani EM, Lambertenghi Deliliers G, Baldini L, et al. EBVD and alternating MOPP/EBVD with or without localized field radiotherapy in advanced or unfavorably presenting Hodgkin's disease. Haematologica 1996; 81:8-14.