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Prognostic Significance of Lymphography in Stage III_s Hodgkin's Disease (HD)*

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Abstract—*Ninety-six patients with pathological stage III_s Hodgkin's disease, uniformly treated with six cycles of MOPP and TNI, were retrospectively analysed in an effort to determine whether the lymphographic aspect of lymph nodes influence the prognosis. Case material was grouped according to the presence of lymph nodes less than* 3 cm *in diameter or larger at lymphography. Five-year survival and disease-free survival were* 85 *and* 78% *for patients with small lymph node involvement, compared to* 48 *and* 30% *for patients with larger lymph nodes. The comparative analysis between the lymphographic aspect and other prognostic factors shows that large lymphographic involvement is strongly correlated with the presence of large spleen involvement* ($P < 0.0000029$), *followed by stage III_2* ($P < 0.000612$), *followed by* ≥ 5 *involved sites* ($P < 0.012$), *followed by age* > 40 yr ($P < 0.047$). *Conversely, no significant correlation was found with symptoms, histology and mediastinal involvement. Modifications of current treatment for both large and small lymph node involvement are discussed.*

INTRODUCTION

IN THE last fifteen years the prognosis and the course of Hodgkin's disease (HD) have been improved by the use of a well-defined therapeutic approach [1–3]. However, despite the encouraging development, a significant proportion of patients have still not been cured, either because they failed to respond to therapy or because they relapsed after conventional therapy [4–6]. Thus new prognostic factors in the selection of a better therapeutic approach have been explored. The prognostic value of mediastinal involvement in supradiaphragmatic HD has already been well established [7–11], especially for cases with large mediastinal involvement in which this localization was found to produce a higher risk of relapse, and for this reason a more aggressive therapeutic approach has been proposed [8, 10]. Similarly, the importance of evaluating prognostic factors in stage III had been stressed for a better definition of therapy among the groups at risk. However, no definitive results have been found in these patients [12–19].

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In order to assess the possibility of a better identification of prognostic factors we investigated retrospectively the prognostic relevance of histopathology, constitutional symptoms, age, mediastinal involvement, splenic involvement, anatomic substages and the number of involved sites correlated with the lymphographic aspect of 96 patients with stage III_s HD uniformly treated with a combination of MOPP chemotherapy and total nodal irradiation. A clear-cut correlation between the lymphographic aspect, splenic involvement and prognosis was found, providing us with the possibility of differentiating two well-defined groups of patients. These results, which form the basis of this report, are discussed with respect to the correct planning in therapy and management of such patients.

MATERIALS AND METHODS

The patients with pathologic splenic involvement form the basis of this study. One hundred and thirty-four consecutive patients with HD stage III_s were registered at the "L. e A. Seràgnoli" Institute of Haematology in Bologna between 1970 and 1980. The extent of the disease, according to the Ann Arbor clinical staging

criteria [20], was determined with conventional procedures including physical examination, chest X-rays, lymphography, bone biopsy and laparotomy with splenectomy. Bipedal lymphography was performed as described by Kinmonth [21]. Films of the lymphangiographic phase were taken immediately after injection of the contrast medium by using the same technique for all patients and consisted of antero-posterior, lateral and 45° postero-oblique projections of abdomen and pelvis. Films of lymph nodes were taken 24 hr later. Only patients with abnormal lymphography have been considered, including those with changes secondary to non-specific lesions (reactive nodes) or those with changes due to lymphoma. The lymphography was considered non-specific when the nodes were slightly to moderately enlarged and their structure was not significantly altered. The lymphography was considered specific when lymph nodes were moderately to markedly enlarged with filling defects. According to the radiographic sizes of abnormal lymph nodes, two groups of patients were identified: the first group includes patients with lymph nodes at lymphography less than 3 cm in diameter both without or with specific changes, and the second group includes patients having at least one lymph node with specific changes of 3 cm or larger in size. The lymph nodes size was determined by measuring the maximum transverse width as visualized in radiographs. Inguinal lymph nodes were excluded from the analysis because of possible errors due to the magnification of these nodes; for the others (lumbar or iliac nodes) no correction for magnification factor was applied because providing a constant radiographic technique does not give a better estimate [22]. Laparotomy with splenectomy was performed according to previous reports [4, 14]. In particular, lymph node specimens were taken from celiac, lumbar and iliac chains, and from hilus of the spleen; liver biopsy was also performed. Two groups of patients were identified according to the type of splenic involvement: the first group includes patients with large spleen involvement (three or more nodules greater than 2 cm in diameter) and the second group includes patients with small spleen involvement (less than three nodules greater than 2 cm or micronodules of any number). A further analysis was carried out by using Hoppe's methods [14, 15] in selecting the type of spleen involvement; patients having less than five nodules irrespective of the size were assigned to minimal spleen involvement while patients with five or more nodules were assigned to large spleen involvement. Data available from the lymph node specimens obtained during laparotomy allowed us to analyse according to anatomic substages and the number of involved sites. Anatomic substages III_1 and III_2 were investigated by using the same criteria of Desser *et al.* [12]. Stage III_1 included patients with involvement limited to those lymphatic structures in the 'upper' part of the abdomen, i.e. spleen, splenic nodes, celiac nodes and/or portal nodes. Stage III_2 included patients with involvement of the 'lower' abdominal nodes, i.e. para-aortic iliac or mesenteric nodes with or without involvement of the upper abdomen. Similarly we used the same procedure of Hoppe *et al.* [14, 15] to differentiate patients having five or more involved sites from those having less than five involved sites, and in particular patients were grouped according to all sites involved above and below the diaphragm. Correlations among the lymphographic aspect and the other prognostic factors were carried out and tested for their significance by using the chi squared test with correction for continuity in small groups [23]. Thirty-eight patients were excluded from the study: seven patients who had been lost at follow-up, ten patients who died without evidence of disease, 12 patients who were submitted to different therapies and nine patients with a technically incorrect (seven patients) or normal (two patients) lymphography. There were 63 males and 33 females with a median age of 34 yr. The median follow-up was 72 months. According to the symptoms, 38 were A patients and 58 were B patients. According to histology, two patients had lymphocytic predominance (LP), 66 nodular sclerosis (NS), 24 mixed cellularity (MC) and four lymphocytic depletion (LD) subtype. All patients underwent the same therapy, which consisted of six cycles of MOPP chemotherapy and total nodal irradiation (TNI) 3 months after completion of chemotherapy. MOPP was given as previously described by De Vita *et al.* [1]. Only patients who underwent more than 75% of estimated dose were included in this study. Radiotherapy was given by a ^{60}Co source and the estimated tumor dose was 3600 rad in 4–6 weeks. The radiotherapy treatment fields included the mantle and an inverted Y in which the splenic pedicle and pelvic lymph nodes were always included: prophylactic radiotherapy on the lungs and liver was not done. Complete remission (CR) was defined as disappearence of all clinical and radiological evidence of the disease for a minimum of 6 months after the therapy was completed. Whenever possible relapse was biopsy-proven and in all other cases detected through radiography. Each parameter considered was tested according to survival and relapse-free survival. Table 1 lists these parameters. Differences were evaluated by using the log rank

Table 1. *Results according to factors at risk in* 96 *patients with stage III$_s$ HD*

Parameters	Variables	Patients	5-yr survival (%)	5-yr survival (*P* value)	5-yr disease-free interval (%)	Disease-free interval (*P* value)
Age (yr)	<40	64	82	<0.025	70	<0.05
	≥40	32	58		45	
Symptoms	A	38	73	NS*	60	NS
	B	58	66		60	
Histology	NS	66	65	NS	55	NS
	MC	25	71		65	
Mediastinal involvement	yes	61	68	NS	60	NS
	no	35	73		68	
Spleen involvement	large	41	52	<0.0005	35	<0.0005
	small	55	87		76	
Substages	III$_1$	58	75	NS	68	NS
	III$_2$	38	67		56	
Involved sites	≥5	23	62	NS	55	NS
	<5	73	72		66	
Lymphography	≥3 cm	39	48	<0.0005	30	<0.0005
	<3 cm	57	85		78	

*NS = Not significant.

test according to the method extensively described by Peto *et al.* [24]. Logistic regression analysis was also performed by using Cox's method [25]. Survival and disease-free survival were calculated by life-table analysis from the date of diagnosis to relapse or death or to December 1982, according to the method described by Kaplan and Meier [26].

RESULTS

Fifty-nine patients had abnormal lymphangiograms, considered positive for Hodgkin's disease. Thirty-eight had positive laparotomy (stage III$_2$), with positive nodes obtained from the positive lymphangiogram sites at laparotomy. The remaining 21 patients with lymphangiograms considered positive for Hodgkin's disease had negative findings in the lymphangiogram sites at laparotomy: five had adequate biopsies from the para-aortic sites and were considered as 'true' false positive. The remaining 16 with positive lymphangiograms apparently did not have para-aortic node biopsies, presumable because the surgeons did not locate enlarged nodes in this area. These 21 patients were assigned to stage III$_1$ together with the remaining 37 patients without specific changes at lymphography in which the pathologic data confirmed the radiologic assumption. According to radiographic size of lymph nodes 39 patients presented with large lymph nodes at lymphography (≥3 cm width), the remaining 57 presented with smaller lymph nodes (<3 cm width). Furthermore, a massive spleen involvement was found in 41 patients and a more discrete involvement was recorded in the remaining 55; by using Hoppe's method instead, we found a large spleen involvement in 56 patients while minimal splenic disease was found in 40 patients.

The univariate statistical analysis of some prognostic factors in influencing the overall survival and disease-free survival, such as constitutional symptoms, histology, mediastinal involvement, substages and number of involved sites, did not reveal any significant correlations between the above prognostic factors and survival or relapse-free survival (Table 1). Conversely, age over 40 yr was a significant negative prognostic factor ($P<0.05$) together with massive spleen involvement ($P<0.0005$) and large lymph node involvement ($P<0.0005$) (Table 1). In fact, the probability of relapse was greater for patients with larger lymph nodes and massive spleen involvement (70 and 63% respectively) than for patients with smaller lymph nodes and small spleen involvement (20 and 25% respectively). Concurrent results were obtained with respect to death rates. In fact there were ten (17%) and nine (16%) deaths among patients with small lymph nodes and small spleen involvement respectively, compared with the 21 (54%) and 22 (54%) patients who died among the poorer risk groups. No similar results were found by grouping the patients according to Hoppe's method; in fact the relapse rates were 44 and 33% and the death rates 39 and 23% for patients with large and small spleen involvement respectively.

Logistic regression analysis performed according to Cox's method showed the amount of splenic disease as the most important factor for survival ($P<0.0000$), followed by lymph node

involvement ($P<0.0001$) and age of patients ($P<0.0135$).

Table 2 illustrates the correlations among the lymphographic aspect and the other prognostic factors tested.

The distribution among patients having lymph nodes both less or greater than 3 cm of symptoms, histology and mediastinal involvement was proportionally similar. According to age a greater proportion of younger patients had lymph nodes less than 3 cm, the P value (0.047) being moderately significant. Substage III_2 was strongly correlated with patients having large lymph node involvement ($P<0.000612$) while a more discreet correlation was found between more than five involved sites and large lymph node involvement ($P<0.012$). The most significant correlation ($P<0.0000029$) was found between the lymphographic aspect and the type of spleen involvement; in fact most patients with large lymph nodes had large spleen involvement (30/39), and most patients with small lymph nodes had small spleen involvement (46/57). However, it should be noted that in ten patients with large spleen but with small lymph nodes (<3 cm) only one relapse was recorded, while in nine patients with small spleen involvement and large lymph nodes 5/9 relapses were recorded.

Among the patients with small lymph nodes the relapse rate was higher in the supradiaphragmatic area. In fact 8 out of 12 patient who relapsed (66%) showed the recurrence of the disease in the mediastinum (3), lungs (4) or both (1); all patients had had a mediastinal involvement at diagnosis. Among the patients with large lymph nodes the relapse rate was higher in the subdiaphragmatic area (54%) or both the supra and subdiaphragmatic (28%). Below the diaphragm the most common sites of relapse were liver (5), the previously involved lymph nodes (8) or both (10).

Table 2. Correlations of lymphographic aspect and the other prognostic factors

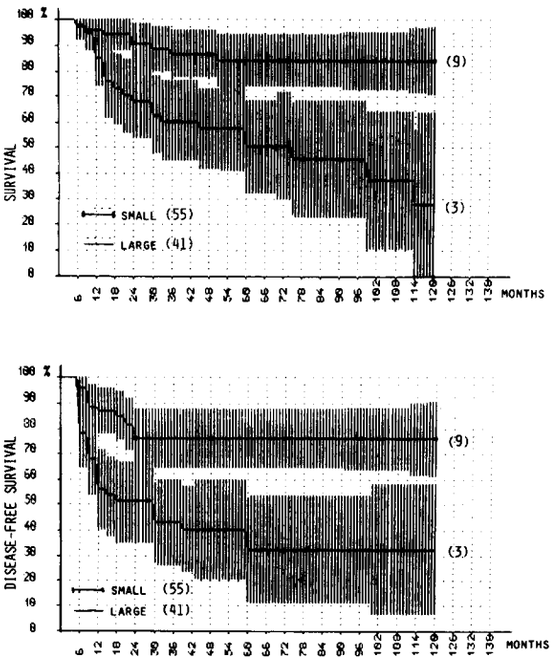
Lymph nodes size		⩾3 cm	<3 cm	P value
Age (yr)	<40	21	43	0.047
	⩾40	18	14	
Symptoms	A	16	22	0.97
	B	23	35	
Histology	NS	28	38	0.98
	MC	10	15	
Mediastinal involvement	yes	24	37	0.90
	no	15	20	
Spleen involvement	large	30	11	0.0000029
	small	9	46	
Substages	III_1	15	43	0.000612
	III_2	24	14	
Involved sites	⩾5	15	8	0.012
	<5	24	49	

Figures 1 and 2 show the difference in overall survival and relapse-free survival in accordance with the degree of spleen and lymph node involvement. The 5-yr survival and disease-free survival in patient with massive spleen involvement was 52 and 35% respectively; conversely, the 5-yr survival and disease-free survival of patients with a less evident spleen involvement was 87 and 76% respectively ($P<0.0005$). Similarly, the overall survival and disease-free survival of patients with small lymph nodes was significantly higher than that of patients with larger lymph nodes ($P<0.0005$).

DISCUSSION

This study demonstrates that the lymphographic aspect of the lymph nodes and the degree of spleen involvement may play an important role in predicting the prognosis of patients with HD in stage III with spleen involvement (III_s), since both overall survival and relapse-free survival were negatively influenced by the presence of a large lymph node involvement (⩾3 cm) or by a massive spleen involvement.

In recent years several prognostic factors have been identified in patients with HD in order to establish a better therapeutic approach and



Figs 1, 2. Survival and disease-free survival according to type of spleen involvement. Patients with small spleen involvement had survival and disease-free survival results that were significantly better than those patients with large splenic involvement ($P<0.0005$).

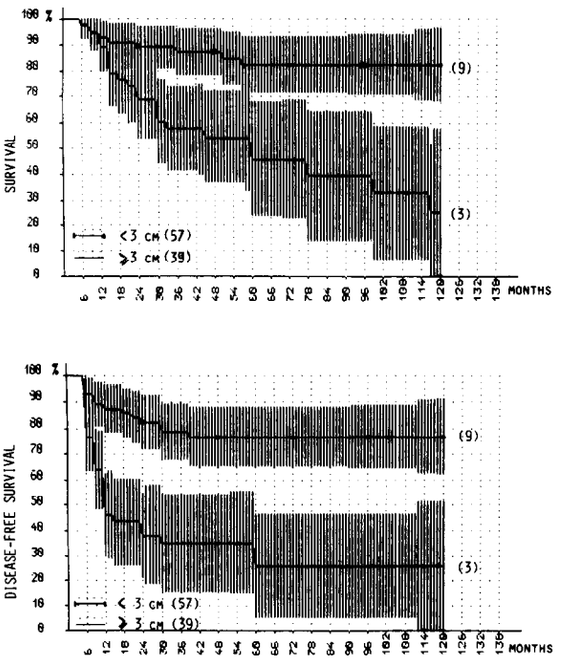
improve the survival rate especially in those patients with adverse factors [12, 14, 15, 17]. In fact, it is well-known that a higher number of involved sites, older age, a larger mediastinal involvement and presence of clinical symptoms may all play an adverse role in affecting the survival of these patients. More recently, Desser *et al.* [12] demonstrated that patients in stage III can be divided into sub-stages III_1 and III_2, where substage III_1 includes patients with involvement limited to those lymphatic structures in the 'upper' part of the abdomen, while substage III_2 includes patients with involvement of the lower abdominal nodes.

Our investigation, carried out on 96 patients with stage III$_s$ HD uniformly treated with combined chemotherapy MOPP and TNI, was unable to confirm the prognostic significance in these patients of many factors such as clinical symptoms, mediastinal involvement, histologic subtype, the number of involved sites and the anatomic substages. On the other hand, we were unable to find the same results, concerning the type of spleen involvement, as that reported by Hoppe *et al.* [15]. We think that bulky disease may be better expressed by the number and the size than by only the number of the nodules. However, our results are probably influenced by the more aggressive chemotherapeutic approach than that used by Hoppe *et al.* and definitive conclusions cannot be drawn. Undoubtedly the lymphographic identification of the lymph nodes of $\geq$3 cm diameter is consistently associated with a poorer prognosis, as is shown in Table 1 and Figs 3 and 4. Analysing the survival curves, two distinct subgroups of patients with stage III$_s$ HD can be identified: patients with small lymph nodes and small spleen involvement who showed survival figures similar to those normally observed in patients in stages I and II, and patients with massive disease who showed a survival rate similar to those observed in patients with stage IV HD. It appears that patients with lymph nodes greater than 3 cm should be considered as having a 'bulky disease' and an increased risk of relapse mainly in the sub-diaphragmatic area, as has been demonstrated in supradiaphragmatic HD with 'bulky disease' in the mediastinum that produce a high relapse rate in the local area [9, 10]. In fact in these patients in which there is a concomitant massive spleen involvement, the risk of a possible liver involvement, even if not shown by pathological analysis after laparotomy, should be taken into account as is demonstrated by the fact that the major part of our patients with liver involvement at the onset of the disease showed contemporarily a massive spleen involvement (data not shown).

Thus six cycles of chemotherapy MOPP plus TNI seem an effective treatment for patients with minimal splenic and lymph node involvement. Nevertheless, according to Hoppe *et al.* [14, 15], in our 'favourable' group of patients, especially those with minimal splenic and/or lymph node disease, chemotherapy MOPP can be reduced or abolished in order to reduce the risk of a second malignancy. On the other hand, the patients with the massive splenic and/or massive lymph node involvement probably should be treated in a different way with a more aggressive chemotherapy, including non-cross-resistant chemotherapeutic protocols with MOPP such as ABVD [27], and also a more appropriate local subdiaphragmatic radiotherapy, including the prophylactic radiotherapy on the liver as suggested by Stanford's experience [14, 15].

According to these considerations we recently started a new protocol for patients with stage III$_s$ HD; the 'low risk' patients (with small spleen involvement and small lymph nodes at lymphography) are treated with radiotherapy alone, and the 'high risk' patients (all other cases) are treated with ten cycles of MOPP and ABVD alternatively plus radiotherapy 'on bulky disease'.

In conclusion, a more careful analysis of lymphographic findings by measuring the width of the lymph nodes seems a simple and suitable



Figs 3, 4. *Survival and disease-free survival according to lymphographic aspect. Patients with small lymph nodes had survival and disease-free survival results that were significantly better than those patients with large lymph node involvement* ($P < 0.0005$).

analysis in predicting the prognosis and survival of patients in stage III_s. Furthermore, the possible prediction of type of splenic involvement by the lymphographic aspect is of great relevance to the management of such patients, including the opportunity to delay the staging laparotomy after completion of chemotherapy in patient with large lymph node involvement.

REFERENCES

1. De Vita VT, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med* 1970, **73**, 881–895.
2. Kaplan HS. Role of intensive radiotherapy in the management of Hodgkin's disease. *Cancer* 1966, **19**, 356–367.
3. Kunkle LE, De Vita VT, Young RC, Jhonson RE. Treatment of Hodgkin's disease using intensive chemotherapy followed by irradiation. *Int J Radiat Oncol Biol Phys* 1976, **1**, 619–626.
4. Rosenberg SA. The management of Hodgkin's disease. *N Engl J Med* 1978, **299**, 1246–1247.
5. Thar TL, Million RR, Hausner RJ, McKetty HB. Hodgkin's disease, stages I and II: relationship of recurrence to size of disease, radiation dose, and number of sites involved. *Cancer* 1979, **43**, 1101–1105.
6. Weller SA, Glatstein E, Castellino RA *et al.* Initial relapse in previously treated Hodgkin's disease.II. Retrograde transdiaphragmatic extension. *Int J Radiat Oncol Biol Phys* 1977, **2**, 863–872.
7. Lee CKK, Bloomfield CD, Goldman AJ, Lewitt SH. Significance of mediastinal involvement in Hodgkin's disease treated with curative radiotherapy. *Cancer* 1980, **46**, 2403–2409.
8. Lee CKK, Bloomfield CD, Nesbit ME, Levitt SH. Large mediastinal masses in Hodgkin's disease: comparison of the results of whole lung and mantle field irradiation. *Int J Radiat Oncol Biol Phys* 1979, **15**, 136–137.
9. Mauch P, Cadman R, Hellman S. The significance of mediastinal involvement in early stage Hodgkin's disease. *Cancer* 1978, **42**, 1039–1045.
10. Mazza P, Lauria F, Sciascia R *et al.* Prognostic significance of large mediastinal involvement in Hodgkin's disease. *Scand J Haematol* 1983, **31**, 315–321.
11. Valentyas E, Barrett A, McElwain TJ, Peckham MJ. Mediastinal involvement in early-stage Hodgkin's disease. *Br J Cancer* 1980, **16**, 1063–1068.
12. Desser RK, Golomb HM, Ultman JE *et al.* Prognostic classification of Hodgkin's disease in pathologic stage III, based on anatomic considerations. *Blood* 1977, **49**, 883–893.
13. Fuller LM, Gamble JF, Velazquez WS *et al.* Evaluation of the significance of prognostic factors in stage III Hodgkin's disease treated with MOPP and radiotherapy. *Cancer* 1980, **45**, 1352–1364.
14. Hoppe RT, Rosenberg SA, Kaplan HS, Cox RS. Prognostic factors in pathologic stage III A Hodgkin's disease. *Cancer* 1980, **46**, 1240–1246.
15. Hoppe RT, Cox SR, Rosenberg SA, Kaplan SH. Prognostic factors in pathologic stage III Hodgkin's disease. *Cancer Treat Rep* 1982, **66**, 743–749.
16. Levi JA, Wiernik PH. The therapeutic implications of splenic involvement in stage IIIA Hodgkin's disease. *Cancer* 1977, **43**, 2158–2165.
17. Rodgers RW, Fuller LM, Hagemeister FB, *et al.* Reassessment of prognostic factors in stage IIIA and IIIB Hodgkin's disease treated with MOPP and radiotherapy. *Cancer* 1981, **47**, 2196–2203.
18. Rosenberg SA. Prognostic factors and subgroups in Hodgkin's disease. Abstracts of International Conference on Malignant Lymphoma, Lugano, 1981.
19. Stein RS, Golomb HM, Diggs CH. Anatomic substage of stage IIIA Hodgkin's disease. *Ann Intern Med* 1980, **92**, 159–165.
20. Carbone PP, Kaplan HS, Musshof K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1966, **31**, 1860–1861.
21. Kinmonth IB. Lymphangiography in man. *Clin Sci* 1952, **11**, 13–17.
22. De Cavallio A. Spontaneous alterations in the size of lymph-nodes after lymphography. *Lymphology* 1976, **9**, 138–141.
23. Armitage P. *Statistical Methods in Medical Research.* Oxford, Blackwell Scientific Publication, 1971.

24. Peto R, Pike MC, Armitage P *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
25. Cox DR. Regression models and life tables. *JR Stat Soc B* 1972, **34**, 187–220.
26. Kaplan EL, Meier P. Non parametric estimation from incomplete observation. *J Am Stat Assoc* 1958, 457–481.
27. Bonadonna G, Zucali R, Monfardini S *et al.* Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, carboxamide versus MOPP. *Cancer* 1975, **36**, 252–259.