# Pure infradiaphragmatic Hodgkin's lymphoma. Clinical features, prognostic factors and comparison with supradiaphragmatic disease

Theodoros P. Vassilakopoulos
Maria K. Angelopoulou
Marina P. Siakantaris
Nikos Konstantinou
Argyrios Symeonidis
Themistoklis Karmiris
Panayiotis Repoussis
Paraskevi Roussou
Athanassios Meletios Dimopoulos
Styliani I. Kokoris
Evangelia M. Dimitriadou
Marie-Christine Kyrtsonis
Maria N. Dimopoulou
Constantinos Tsatalas
Garyfallia Kokkinis
Effimia Vrakidou
Vassiliki Grigoraki
Christos Poziopoulos
Marina Stamatellou
Dimitra Liapis
George Georgiou
Panayiotis Panayiotidis
Gerassimos A. Pangalis for the Hellenic Cooperative Lymphoma Group

*Correspondence:*
*Gerassimos A. Pangalis, MD, First Department of Internal Medicine And Department of Haematology National and Kapodistrian University of Athens, School of Medicine, Laikon General Hospital, Athens 11527, Greece.*
*E-mail: pangalis@med.uoa.gr*

*From the First Dept. of Internal Medicine and Dept. of Haematology, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece (TPV, MKA, MPS, SIK, EMD, M-CK, MND, GAP); Hematology Clinic, Theagenion Cancer Hospital, Thessaloniki, Greece (NK); Hematology Division, Dept. of Internal Medicine, University of Patras, Patras, Greece (AS); Hematology and Lymphoma Clinic, Evangelismos Hospital, Athens (TK); Hematology Clinic, Peripheral General Anticancer Hospital-Metaxa, Piraeus, Greece (PRe); Third Dept. of Internal Medicine, National and Kapodistrian University of Athens, Sotiria Hospital, Athens (PRo); Dept. of Therapeutics, National and Kapodistrian University of Athens, Alexandra Hospital, Athens (AMD); Dept.of Haematology, Democritus University of Thrace, Alexandroupolis, Greece (CT); Hematology Laboratory, Sismanoglion Hospital, Melissia, Attica, Greece (GK); Hematology Section, Hygeia Hospital, Athens (EV); Dept. of Hematology, General Hospital of Athens, Athens (VG); First Dept. of Internal Medicine, 401 Army Hospital, Athens (CP); Hematology Section, Aghios Savas Anticancer Hospital, Athens (MS); Hematology Clinic,Venizelion Hospital, Iraklion, Crete, Greece (DL); First Dept. of Propedeutic Internal Medicine, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece (GG, PP).*

Background and Objectives. Pure infradiaphragmatic Hodgkin's lymphoma (HL) is a rare disease. The prognostic impact of a purely infradiaphragmatic localization of this lymphoma is controversial. We aimed to evaluate the baseline clinicopathologic features, prognostic factors and outcome of a large series of consecutive patients with pure infradiaphragmatic HL.

Design and Methods. We analyzed 131 patients with clinical stage I/II infradiaphragmatic HL treated with ABVD or equivalent regimens with or without radiotherapy, and compared 54 of them with 444 patients with pure supradiaphragmatic disease, who were treated at the same center.

Results. Older age, clinical stage II (borderline), involvement of ≥3 sites, lymphocyte predominant histology, elevated serum $\beta_2$-microglobulin and higher International Prognostic Score were more frequent in patients with infradiaphragmatic disease than in those with supradiaphragmatic disease, while nodular sclerosis was less frequent. The complete remission rate was 100%, 97% and 82% for stages I, IIA and IIB, respectively. Only B-symptoms independently predicted for inferior failure-free survival, while inferior overall survival was independently associated with the involvement of ≥3 sites. At 10 years failure-free survival was 82±6% (vs. 85±2% for patients with supradiaphragmatic disease, $p$=0.45), overall survival was 74±8% (vs. 91±2%, $p$=0.0006), and disease-specific survival 87±5% (vs. 94±1%, $p$=0.04). In multivariate analysis the differences between infradiaphragmatic and supradiaphragmatic disease were obscured by older age and B-symptoms.

Interpretation and Conclusions. Pure infradiaphragmatic HL presents with distinct clinicopathologic characteristics. The previously reported poorer outcome may be explained by the unfavorable profile of the patients rather than the infradiaphragmatic presentation *per se*. Patients with stage IIB disease should probably be classified as having advanced HL because of the unacceptable rate of primary refractory disease.

Key words: infradiaphragmatic, Hodgkin's lymphoma, prognostic factors, chemotherapy.

Haematologica 2006; 91:32-39



Hodgkin's lymphoma (HL) is rarely restricted to infradiaphragmatic nodal areas. The incidence of such localizations among patients with clinical stage I/II HL varies from 5% to 13%.[1-28] Males older than 40 years with a histology other than nodular sclerosis have a greater probability of presenting with pure infradiaphragmatic disease.[5,7-11,25] Whether patients with pure infradiaphragmatic localization have a worse prognosis[11,12,20,22] than those with clinical stage I/II supradiaphragmatic disease remains controversial.[25,29] Important questions regarding prognostic factors and optimal treatment of pure infradiaphragmatic HL still remain unanswered, because most studies have included limited numbers of patients, treated with different modalities, usually covering periods of up to 20 years. Furthermore, this form of HL is usually excluded from randomized trials or, if included, the small number of patients precludes subgroup analysis. The largest study published so far included 106 patients treated with radiotherapy.[18] Only five series have reported on more than 50 patients with pure infradiaphragmatic HL,[13,18,24-26] and treatment approaches were either suboptimal[18] or highly heterogeneous. Thus, we decided to review the combined experience of 15 centers participating in the Hellenic Cooperative Lymphoma Group, including 163 patients with pure infradiaphragmatic HL, the majority of whom were treated with anthracycline-based chemotherapy or combined modality therapy.

## Design and Methods

### Patients and treatment strategies

Between 1984 and 2004, 163 consecutive patients with histologically confirmed clinical stage I/II pure infradiaphragmatic HL were diagnosed and treated in 15 centers in Greece. Data on 25 of these patients have

been previously reported.[1] The majority of them - 131 patients (80%) - were treated with chemo

therapy or combined modality therapy based on ABVD or equivalent regimens. Their characteristics were very similar to those of the whole patient population of 163 patients (*data not shown*). The present analysis was focused on this subgroup of 131 patients, who were treated with chemotherapy or combined modality therapy based on ABVD or equivalent regimens. Fourteen patients treated with radiotherapy alone and 18 patients treated with MOPP or ChlVPP with or without radiotherapy, approaches that are considered inferior to ABVD and equivalents,[29-34] were excluded. *ABVD and/or equivalent regimens* included ABVD (71 patients),[35] EBVD (24 patients),[36] alternating or hybrid MOPP/ABV(D) (31 patients)[32,37] and other anthracycline-containing regimens (5 patients). ABVD and equivalent regimens form the basis of current standard therapy for clinical stage I/II HL.[33,34,38]

We retrospectively evaluated demographic, clinical, histologic, and laboratory features, clinical stage,[39] the International Prognostic Score (IPS),[40] as well as the initial chemotherapy regimen, field and dose of radiotherapy, response to treatment and outcome. The diagnostic material of 64% of the patients was initially examined or reviewed in one of three referral hematopathology departments. Clinical staging was performed according to the Ann-Arbor system[39] by physical examination, chest X-rays, thoracic and abdominal computed tomography, and bone marrow biopsy. Bipedal lymphangiography was used according to the policy of each center. Other staging procedures did not differ among centers. Cases with and without inguinofemoral lymphadenopathy were considered as *peripheral* and *central,* respectively. Bulky disease was defined as a maximal lymph node diameter ≥7 cm.[29] The cut-offs for hematologic parameters and serum albumin were those proposed by the IPS.[40] In addition to individual prognostic factors, patients were also evaluated according to the prognostic stratification systems proposed by the German Hodgkin Study Group (GHSG),[34] the European Organization for the Research and Treatment of Cancer (EORTC),[38] and the International Prognostic Factor Project (IPS).[40] Clinical stage was not taken into account for the evaluation of IPS, as appropriate for localized HL.

### Statistical analysis

The flow-chart of the study including the comparisons performed between various subgroups of the overall series is outlined in Figure 1. The comparisons of clinical characteristics and between infradiaphragmatic and supradiaphragmatic cases were performed using Student's t-test, $\chi^2$ or Mann-Whitney test, as indicated. These analyses and the comparison of the outcome between infradiaphragmatic and supradiaphragmatic cases were restricted only to patients treated at the First Department of Internal Medicine and Department of Haematology, National and Kapodistrian University of Athens, Laikon General Hospital (center #1) for whom data regarding patients with supradiaphragmatic disease were recorded in our database (54 vs. 444 patients with infradiaphragmatic and supradiaphragmatic HL respectively, treated with ABVD or equivalent-based chemotherapy or combined modality treatment during the same time period; Figure 1). Complete remission was defined as the complete disappearance of all measurable disease lasting for more than 4 weeks. Failure- free survival (FFS) was defined as the time from diagnosis to failure of complete remission achievement requiring a switch to a different chemotherapy regimen, documentation of relapse or last follow-up. Overall survival was defined as the time from diagnosis to death of any cause or last follow-up. Deaths that were clearly unrelated to the disease or were not directly related to the applied treatment were censored in the analysis of disease-specific survival. Survival after failure was defined as the time from the documentation of first treatment failure to death of any cause. The various survival rates were estimated and the survival curves plotted using on the Kaplan-Meier method.[41] The univariate identification of prognostic factors was performed by the log-rank test.[42] Multivariate analysis was based on a Cox's proportional hazards model.[43]

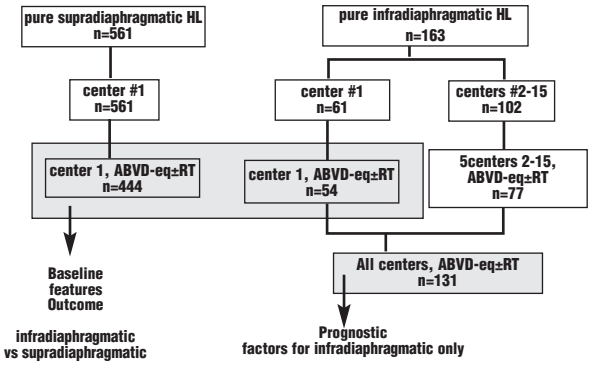


**Figure 1.** Study flow-chart. Shaded rectangles show the subgroups of patient involved in each comparison.

## Results

### Patients' characteristics

Based on data derived from a single center (Center #1; First Department of Internal Medicine and Department oh Haematology National and Kapodistrian University of Athens), the frequency of pure infradiaphragmatic disease among patients with clinical stage I/II HL was 10.8% (54/498).

Tables 1 and 2 summarize the main clinicopathologic features and tratment strategies used in the present series of patients with pure infradiaphragmatic HL. The comparison of demographic, clinical, and laboratory characteristics of patients with pure infradiaphragmatic (n=54) and pure supradiaphragmatic (n=444) HL was restricted to patients treated only at center #1, as indicated in *Methods*. Patients with pure infradiaphragmatic HL were older ($p<0.001$), more frequently had three or more involved sites ($p=0.04$), had a higher incidence

**Table 1. Baseline clinicopathologic and laboratory findings in 131 patients with pure infradiaphragmatic clinical stage I and II Hodgkin's lymphoma treated with chemotherapy or combined modality therapy based on ABVD or equivalent regimens in 15 centers.**

| *Parameter* | *Patients* | |
|---|---|---|
| | *#* | *%* |
| Age, median (range), years | 47 (14-82) | |
| ≥45 years | 73/131 | 56 |
| Gender: male | 83/131 | 63 |
| Clinical stage II | 103/131 | 79 |
| B-symptoms | 45/131 | 34 |
| Central disease | 29/131 | 22 |
| Bulky disease | 37/121 | 28 |
| Extranodal disease | 4/131 | 3 |
| ≥3 involved sites | 59/128 | 46 |
| Histology | | |
| Lymphocyte predominance | 21/131 | 16 |
| Nodular sclerosis | 60/131 | 46 |
| Mixed cellularity | 41/131 | 31 |
| Lymphocyte depletion | 2/131 | 2 |
| Unknown/unclassified | 7/131 | 5 |
| Anemia (Hb <10.5 g/dL) | 18/129 | 14 |
| Leukocytosis (≥15×10$^9$/L) | 16/129 | 12 |
| Lymphocytopenia (IPS cut-off) | 9/111 | 8 |
| Erythrocyte sedimentation rate ≥50 mm/hr | 57/121 | 47 |
| Albumin <4 g/dL | 47/116 | 36 |
| Lactate dehydrogenase elevated | 26/122 | 21 |
| β2-microglobulin elevated | 20/44 | 45 |
| GHSG (intermediate or advanced*) | 86/127 | 68 |
| EORTC (unfavorable**) | 85/126 | 68 |
| IPS ≥2 | 79/118 | 67 |
| Follow-up, median (range), months | 70 (6-209) | |

**Only two patients (4%) with infradiaphragmatic HL had advanced disease according to the GHSG classification; **Only two patients (4%) with infradiaphragmatic HL had very favorable disease according to the EORTC classification.*

**Table 2. Details of treatment strategies in patients with pure infradiaphragmatic Hodgkin's lymphoma, treated with ABVD-based chemotherapy or combined modality therapy.**

| | *Clinical Stage* | | | | | |
|---|---|---|---|---|---|---|
| *Treatment Strategy* | *I* | | *IIA* | | *IIB* | |
| | *#* | *%* | *#* | *%* | *#* | *%* |
| All patients | 28 | 100 | 58 | 100 | 45 | 100 |
| Chemotherapy only | 12 | 43 | 16 | 28 | 28 | 62 |
| Chemotherapy + radiotherapy | 16 | 57 | 42 | 72 | 17 | 38 |
| Chemotherapy cycles (#) | | | | | | |
| 3 | 1 | 4 | 2 | 3 | 0 | 0 |
| 4 | 6 | 21 | 7 | 12 | 3 | 7 |
| 5-6 | 19 | 68 | 44 | 76 | 30 | 67 |
| ≥7 | 2 | 7 | 5 | 9 | 12 | 27 |
| Radiotherapy dose (median-range; Gy) | 28 (20-46) | | 30.6 (21.6-44) | | 30 (23.3-39) | |
| Radiotherapy field | | | | | | |
| Bulky or residual disease | 0 | 0 | 4 | 7 | 0 | 0 |
| Involved field | 14 | 50 | 22 | 38 | 10 | 22 |
| Inverted Y | 2 | 7 | 15 | 26 | 5* | 11 |
| No radiotherapy due to early progression** | 0 | 0 | 1 | 2 | 2 | 4 |
| No radiotherapy | 12 | 43 | 16 | 28 | 28 | 62 |

**Plus mediastinal irradiation in one patient; ** Two out of these three patients were included in the combined modality group, based on the intention-to-treat-principle.*

of lymphocyte predominant disease ($p$<0.001) and had a lower incidence of nodular sclerosis ($p$<0.001). Patients with pure infradiaphragmatic HL presented more frequently with clinical stage II ($p$=0.08) and less frequently with bulky disease ($p$=0.07), although these differences were of borderline significance. In contrast there was no difference in gender distribution ($p$=0.23), the frequency of B-symptoms ($p$=0.98), central disease ($p$=0.96), or extranodal extension ($p$=0.19) between patients with pure infradiaphragmatic and pure supradiaphragmatic HL. There was also no difference with respect to baseline laboratory features, including anemia ($p$=0.57), leukocytosis ($p$=0.51), severe lymphocytopenia ($p$=0.87), erythrocyte sedimentation rate ≥50 mm/h ($p$=0.54), albumin <4 g/dL ($p$=0.48) or elevated lactate dehydrogenase ($p$=0.84), with the exception of elevated serum β2-microglobulin levels ($p$=0.01), between patients with pure infradiaphragmatic and pure supradiaphragmatic HL. Finally there was no difference in the distribution of patients in various subgroups defined by the GHSG ($p$=0.56) and EORTC ($p$=0.99), but patients with pure infradiaphragmatic disease had clearly higher IPS values than had patients with pure supradiaphragmatic disease ($p$=0.04).

### Complete remission rates and failure-free survival

Among patients treated with ABVD or equivalent regimens the complete remission rates were 100% (28/28), 97% (56/58), and 82% (37/45) for patients with stages I, IIA, and IIB, respectively ($p$=0.02). The complete remission rate was independent of age (80% vs. 85% for stage IIB patients aged <60 and ≥60 years). Among the 131 patients treated with chemotherapy or combined modality therapy with ABVD or equivalents, 25 had primary therapy failure or the patients had relapsed at the time of the present analysis, giving a 10-year failure-free survival of 75±5%.

The results of the univariate analysis of failure-free survival are shown in Table 3. The involvement of ≥3 sites ($p$=0.05; Figure 2A) and the presence of B-symptoms ($p$=0.03) were significantly associated with an inferior failure-free survival in univariate analysis, while stage II ($p$=0.08), and central disease ($p$=0.08; Figure 2B) had borderline significance. Combining stage and B-symptoms, a progressive decline in 10-year failure-free survival was observed from stage IA, to stage IIA and IIB (91±6% vs 76±8% vs 65±8%; $p$=0.06, Figure 2C). The GHSG ($p$=0.12) and EORTC ($p$=0.06) classifications were also marginally correlated with failure-free survival, while IPS was less discriminative ($p$=0.22), as shown in Table 3. Finally there was no difference in failure-free survival between patients treated with chemotherapy alone or combined modality therapy ($p$=0.73). In multivariate analysis only the presence of B-symptoms had independent prognostic signifi-

**Table 3.** Univariate analysis of prognostic factors in 131 patients with pure infradiaphragmatic Hodgkin's lymphoma, treated with ABVD-based chemotherapy or combined modality therapy.

| *Parameter* | *10-yr FFS(%)* | *p* | *10-yr OS (%)* | *p* |
|---|---|---|---|---|
| Age (≥45 vs <45 yrs) | 66±10 vs 83±6 | 0.13 | 47±11 vs 84±5 | 0.06 |
| Gender (male vs female) | 78±5 vs 69±11 | 0.97 | 66±7 vs 55±18 | 0.82 |
| Histology (NS vs MC vs LP) | 75±7 vs 81±9 vs 58±13 | 0.11 | 65±9 vs 69±11 vs 53±19 | 0.43 |
| Clinical stage (II vs I) | 71±6 vs 91±6 | 0.08 | 59±8 vs 92±5 | 0.14 |
| B-symptoms (yes vs no) | 65±8 vs 81±6 | 0.03 | 50±13 vs 73±7 | 0.26 |
| Localization (central vs peripheral) | 53±14 vs 82±4 | 0.08 | 61±13 vs 72±6 | 0.52 |
| Number of involved sites (≥3 vs <3) | 63±10 vs 84±5 | 0.05 | 44±11 vs 85±5 | 0.02 |
| Bulky disease (yes vs no) | 73±8 vs 76±8 | 0.22 | 50±13 vs 76±6 | 0.55 |
| Anemia (yes vs no) | 77±10 vs 74±6 | 0.72 | 82±9 vs 61±8 | 0.51 |
| Leukocytosis (≥ vs <15×10⁹/L) | 63±15 vs 76±6 | 0.25 | 68±14 vs 69±6 | 0.61 |
| Lymphocytopenia (IPS cutoff) | 67±16 vs 76±6 | 0.15 | 56±20 vs 64±8 | 0.20 |
| Erythrocyte sedimentation rate (≥ vs <50mm/hr) | 72±10 vs 78±6 | 0.85 | 56±11 vs 74±9 | 0.22 |
| Hypoalbuminemia (<4 vs ≥4g/dL) | 67±11 vs 79±6 | 0.49 | 65±10 vs 70±9 | 0.37 |
| LDH levels (elevated vs normal) | 71±9 vs 81±5 | 0.19 | 48±15 vs 79±6 | 0.10 |
| GHSG (intermediate or advanced vs early) | 69±7 vs 89±5 | 0.12 | 57±8 vs 85±7 | 0.23 |
| EORTC (unfavorable vs favorable) | 69±7 vs 91±5 | 0.06 | 59±8 vs 85±7 | 0.28 |
| IPS (≥2 vs <2) | 69±8 vs 81±8 | 0.22 | 57±9 vs 77±11 | 0.14 |

*LDH: lactate dehydrogenase; NS: nodular sclerosis; MC: mixed cellularity; LP: lymphocyte predominance.*

cance (relative risk 2.27, 95% confidence intervals 1.03-4.99, $p$=0.04).

### Overall survival

Among the 131 patients treated with ABVD or equivalent regimens, 28 have died (HL, n=15; secondary neoplasia, n=7; unrelated causes, n=6) for a 10-year overall survival rate of 65±7%. The results of univariate analysis of overall survival are shown in Table 3. Only the involvement of ≥3 sites was associated with an inferior overall survival ($p$=0.02), while older age was of borderline significance ($p$=0.06). The IPS, GHSG and EORTC classifications were not predictive of overall survival, as shown in Table 3. No difference was detected between patients treated with chemotherapy alone or combined modality therapy ($p$=0.36). In multivariate analysis the number of involved sites independently predicted for an inferior overall survival (≥3 vs. <3, relative risk 2.45, 95% confidence intervals 1.10-5.45, $p$=0.03), while older age again had borderline prognostic significance (≥45 vs. <45, relative risk 2.03, 95% confidence intervals 0.91-4.53, $p$=0.08).

### Patterns of relapse

10 out of the 131 patients had primary refractory disease, while 15 relapsed after an initial complete remission. Among the eight patients who relapsed after chemotherapy alone, five did so purely in infradiaphragmatic sites with a previously involved component, two in supradiaphragmatic sites, plus previously involved infradiaphragmatic sites, and one purely in supradiaphragmatic sites. Among the seven patients who relapsed after combined modality therapy, three relapsed purely in supradiaphragmatic sites, two in supradiaphragmatic plus previously involved infradiaphragmatic sites and two in previously involved infradiaphragmatic sites only.

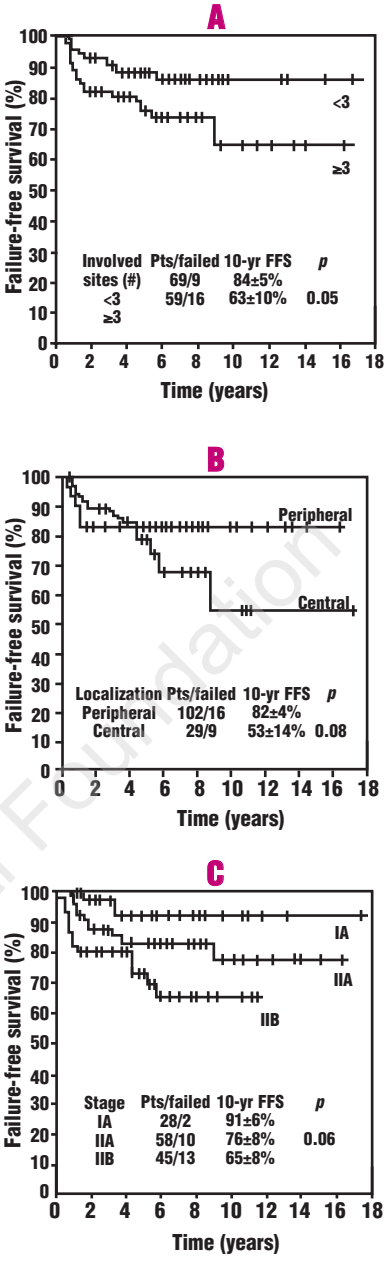


**Figure 2.** Failure-free survival of patients with pure infradiaphragmatic Hodgkin's lymphoma treated with ABVD or equivalent regimens with or without radiotherapy according to (A) the number of involved sites; (B) the presence of central localizations of the disease; (C) the clinical stage.

### Salvage therapy and survival after treatment failure

Among 25 patients in whom primary therapy failed or who relapsed after ABVD or equivalent regimens with or without radiotherapy, 16 had experienced a second progression at the time of the present analysis.

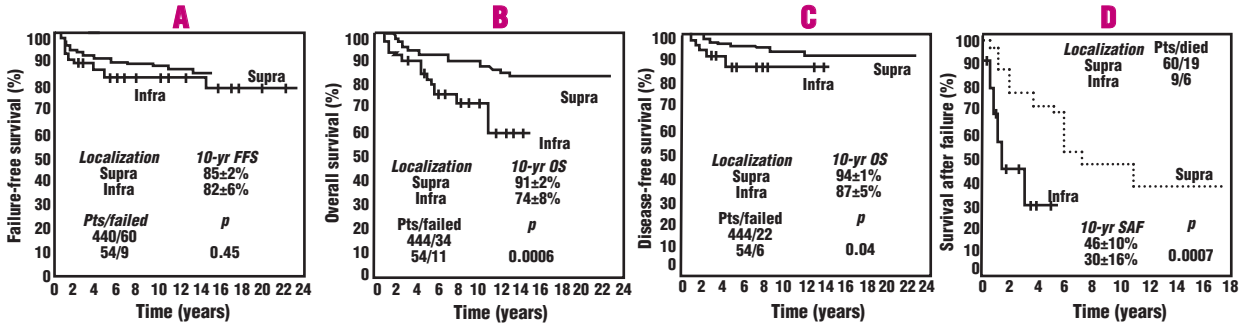


**Figure 3. A.** Failure-free survival; **B.** Overall survival; **C.** Disease-specific survival; and (**D**) Survival after treatment failure in patients with pure infradiaphragmatic and pure supradiaphragmatic clinical stage I/II Hodgkin's lymphoma. Only patients treated with ABVD or equivalent regimens with or without radiotherapy at center #1 were included.

The 10-year survival after failure was 12±10%. The median age of the patients at progression was 55 years (14-83). Seventeen patients received conventional salvage chemotherapy (16 with non-cross-resistant drugs and one with the same regimen), six received high dose therapy with autologous stem cell support after conventional salvage therapy, one patient received salvage radiotherapy, and one patient refused further treatment.

### Secondary neoplasias

Nine out of 131 patients developed secondary neoplasias, including myelodysplastic syndrome/acute non lymphoblastic leukemia (n=1, after salvage therapy), aggressive non-Hodgkin's lymphoma (n=2), lung cancer (n=2), gastric cancer (n=2), breast cancer (n=1), and melanoma (n=1). None of six solid tumors developed within radiotherapy fields.

### Survival rates in patients with infradiaphragmatic or supradiaphragmatic disease

As described in the *Methods* section, this analysis was restricted only to patients cared for in center #1, who were treated with ABVD or equivalent regimens with or without radiotherapy (54 vs. 444 patients with infradiaphragmatic and supradiaphragmatic HL, respectively; Figure 1). In univariate analysis, patients with infradiaphragmatic HL had a similar failure-free survival rate to that of patients with supradiaphragmatic disease (82±6% vs. 85±2% at 10 years, $p$=0.45, Figure 3A), but a significantly inferior overall survival (74±8% vs. 91±2% at 10 years, $p$=0.0006, Figure 3B), disease-specific survival (87±5% vs. 94±1% at 10 years, $p$=0.04, Figure 3C), and survival after failure (30±16% vs. 46±10% at 10 years, $p$=0.0007, Figure 3D). However multivariate analysis revealed that despite moderate to large differences in univariate comparisons, pure infradiaphragmatic localization had no independent effect on overall or disease-specific survival (Table 4).

**Table 4. Multivariate analysis of prognostic factors in patients with clinical stage I/II Hodgkin's lymphoma, treated with ABVD-based chemotherapy or combined modality therapy. Comparison between patients with pure infradiaphragmatic and pure supradiaphragmatic Hodgkin's lymphoma, treated at center #1.**

| *Parameter* | *Relative Risk and 95% CI* | *p* |
|---|---|---|
| Failure-free survival | | |
| B-symptoms (yes vs no) | 1.9 (1.2-3.2) | 0.009 |
| Age (≥45 vs <45 years) | 1.4 (0.8-2.4) | 0.23 |
| Infradiaphragmatic disease (yes vs no) | 1.2 (0.6-2.4) | 0.68 |
| Overall survival | | |
| Age (≥45 vs <45 years) | 5.0 (2.6-9.4) | <0.001 |
| B-symptoms (yes vs no) | 2.1 (1.2-3.9) | 0.01 |
| Infradiaphragmatic disease (yes vs no) | 1.8 (0.9-3.7) | 0.11 |
| Disease-specific survival | | |
| Age (≥45 vs <45 years) | 4.0 (1.8-8.9) | 0.001 |
| B-symptoms (yes vs no) | 2.1 (0.98-4.4) | 0.056 |
| Infradiaphragmatic disease (yes vs no) | 1.5 (0.6-3.8) | 0.41 |

*CI: confidence intervals.*

## Discussion

This analysis focused on 131 patients with pure infradiaphragmatic HL treated with chemotherapy or combined modality therapy based on ABVD or equivalent regimens, analyzing their clinicopathologic characteristics, prognostic factors, and treatment outcome in comparison to those of patients with purely supradiaphragmatic disease. To our knowledge this is the largest series of patients with pure infradiaphragmatic HL reported so far. The major advantage of our study is the application of a homogeneous treatment strategy with anthracycline-based chemotherapy, which is currently considered the standard therapy,[29-35,37,38,40,44,45] with or without radiothearapy. None of the previously published studies has included more than 60 optimally treated patients, thus rendering meaningful identification of prognostic factors difficult. Pure infradiaphragmatic disease accounted for 10.8% of all cases of clinical stage I/II HL, a finding comparable with other studies (5% to 13%).[3,5-23] We confirmed the association of infradiaphragmatic HL with older age,[3,6,10-12,16,20-22] and the inverse association with nodular sclerosing histology.[3,5,6,10,16,20,21] Pure infradiaphragmatic HL was associated with lymphocyte predominant histology, as

**Table 5. Summary of selected published series, including more than 50 patients with pure infradiaphragmatic Hodgkin's lymphoma.**

| *Parameter* | *Barton*[18] | *Liao*[24] | *Cutuli*[26] | *Darabi*[25] | *Present Study* |
|---|---|---|---|---|---|
| Time Period | 1969-1988 | 1962-1995 | 1976-1990 | 1988-1993 | 1984-2004 |
| All patients (#) | 106 | 87 | 55 | 101 | 131 |
| Radiotherapy alone (#) | 106 | 60 | 15 | 44 | 0 |
| CT/CMT, non ABVD-eq. (#) | 0 | 23 | 21 | 0 | 0 |
| CT/CMT, ABVD-eq. (#) | 0 | 4 | 19 | 57 | 131 |
| Age (median-range)¶ | 38 (7-90) | 33 (7-73) | 45 (4-79) | 39 | 47 (14-82) |
| Gender (male) | 73% | 77% | 69% | 73% | 63% |
| Stage II | 42%* | 67% | 75% | 66% | 79% |
| B-symptoms | NR* | 28% | 53% | 35% | 34% |
| Central disease | 6% | NR | NR | NR§ | 22% |
| Bulky disease | NR | 16% | NR | 49% | 28% |
| ≥3 involved sites | 14% | NR | NR | 45% | 46% |
| Histology | | | | | |
| Lymphocyte predominance | 43% | 38% | 20% | 20% | 16% |
| Nodular sclerosis | 27% | 24% | 16% | 25% | 46% |
| Mixed cellularity | 21% | 36% | 50% | 47% | 31% |
| 10-yr failure-free survival | 70% | 72% | NR** | NR§ | 75% |
| 10-yr overall survival | 71% | 75% | 61% | NR§ | 65% |

*CT, chemotherapy; CMT, combined modality therapy. NR: not reported. ¶Differences in median ages may be due to the inclusion of pediatric patients in the studies by Bartn et al., Liao et al., and Cutuli et al.; *The study by Barton et al. was restricted to patients with stage IA, IB, and IIA, treated with radiotherapy alone; **Crude failure rate 16%; §The study by Darabi et al. included patients of the HD4 and HD5 trials of the GHSG. Crude failure rates were 21% after RT alone and 33% after CMT.*

it was in other large series (Table 5), with no significant difference in the incidence of mixed cellularity disease. Patients with pure infradiaphragmatic HL presented with a higher number of involved sites, and were marginally more likely to present with stage II,[11] but not with B-symptoms,[20,22,23] compared to patients with supradiaphragmatic disease. The borderline lower incidence of bulky disease in patients with pure infradiaphragmatic HL may be the result of the lower frequency of nodular sclerosis, which is associated with bulky mediastinal masses. Although the patients with pure infradiaphragmatic HL were more frequently male the difference between genders did not reach statistical significance, in contrast to other studies.[5,6,10,19,20,22,23] As a result of the above associations, IPS values were significantly higher in pure infradiaphragmatic HL. However there was no difference in baseline laboratory parameters or the frequency of unfavorable GHSG or EORTC classification between patients with pure infradiaphragmatic and pure supradiaphragmatic disease, the only exception being the association between pure infradiaphragmatic HL and elevated serum $\beta_2$-microglobulin levels, which may be due to the strong relationship of the latter with advanced age.[46] A comparison between the present study and selected other series of patients with pure infradiaphragmatic HL is presented in Table 5 new paragraph.

Data on prognostic factors for pure infradiaphragmatic HL based on multivariate analysis have rarely been presented: Barton *et al.*[18] suggested that the number of involved sites, especially if ≥3, predicted for lower failure-free and overall survival rates in patients with stages IA/IIA treated with radiotherapy alone. Lower failure-free survival was also predicted by non-lymphocyte predominant histologies and lower radiotherapy dose (<36 Gy), while increasing age predicted for a lower overall survival. Liew *et al.*[15] identified bulky disease as the only independent prognostic factor for both failure-free and overall survival. The significance of disease bulk has been stressed by other investigators as well.[8,13] Liao *et al.*[24] reported that serum albumin and B-symptoms were independent prognostic factors for disease-free survival. Overall survival was adversely affected by advanced age, anemia, and non-lymphocyte predominant histology. However it is well recognized that some prognostic factors may no longer be valid, as more effective treatment is applied. The heterogeneous results reported in the literature regarding prognostic factors for pure infradiaphragmatic HL can probably be attributed to the variability of the applied treatments both within and among different studies, as well as the limited number of patients included in each study.

In the present analysis of 131 patients treated homogeneously with ABVD or equivalent regimens with or without radiotherapy 25 failure events were observed. Interrelated factors reflecting tumor burden emerged as predictors of failure-free survival, such as B-symptoms, stage II, involvement of ≥3 sites and central localizations of the disease. Among these, only B-symptoms had an independent impact on failure-free survival in the multivariate analysis. Furthermore, established prognostic systems, such as the GHSG and EORTC classifications, were only marginally successful in predicting the the outcome in this group of optimally treated patients (Table 3).

The optimal treatment approach for infradiaphragmatic HL has not been well established so far. The 10-year failure rate in our patients with a favorable prognostic profile according to the GHSG classification was 11% (Table 3). The 10-year failure rates in patients with clinical stages IA and IIA were 9% and 24%, respectively (Figure 2C). These figures compare favorably with a failure rate of 21%, which was recently reported by the GHSG after radiotherapy alone in pure infradiaphragmatic HL with a favorable prognostic profile.[25] They also compare favorably with the crude relapse rates of 19% and 30%, determined from a review of published reports on patients with stage IA and IIA disease treated with inverted Y or total normal irradiation alone.[3,5-13,15-17,19-24,26-28] Consequently ABVD-based approaches with or without radiotherapy appear to be superior to radiotherapy alone in patients with stage IA/IIA pure infradiaphragmatic HL, although evidence from randomized studies is lacking. Whether combined modality therapy is superior to chemotherapy alone in localized HL still remains a matter of controversy.[47,48] Our data did not reveal differences between patients treated with chemotherapy alone or combined modality treatment, but clinical stages were not evenly distributed in these groups

(Table 2), so firm conclusions cannot be drawn. Thus ABVD appears to be the treatment of choice for the subgroup of patients with stage IsA/IIA pure infradiaphragmatic HL. The optimal number of cycles of chemotherapy, the need for radiotherapy and the optimal field and dose of any radiotherapy should be further defined.

In the case of stage IIB combined modality therapy employing inverted Y or total nodal irradiation seems to be the most effective strategy, although chemotherapy alone may be equally effective. According to our data, induction treatment failed in 18% of patients with clinical stage IIB disease and this was not age-dependent. Other published reports also reveal an induction failure rate in the order of 15% for clinical stage IIB patients treated with chemotherapy or combined modality therapy. The reports also show that most relapses following chemotherapy alone or combined modality therapy have an infradiaphragmatic component.[3,5-13,15-17,19-24,26-28] Such rates of primary failure are similar to those observed in advanced HL. This suggests that pure infradiaphragmatic clinical stage IIB HL should be included in advanced stage HL. Future studies should probably focus on the use of more intensive regimens, such as BEACOPP-escalated, in patients with stage IIB pure infradiaphragmatic HL who are younger than 60-65 years.[45]

Whether patients with pure infradiaphragmatic HL have a poorer prognosis than patients with supradiaphragmatic disease of similar stage is still a matter of debate.[3,7,8,10-12,19,21-22] Since advanced age, and the number of involved sites are major prognostic factors for HL,[31,34,38,40,44,49] the inferior prognosis of patients with infradiaphragmatic disease may be related to the higher incidence of these factors.[20,24] The value of the IPS, which is partially predictive in non-advanced HL,[50,51] is clearly higher in patients with infradiaphragmatic HL. In order to avoid potential sources of institutional bias, the comparison of the outcome between pure infradiaphragmatic and pure supradiaphragmatic HL was restricted to the patients treated at center #1, where data on pure supradiaphragmatic disease were recorded in the database. Multivariate analysis demonstrated that – under treatment with ABVD and equivalent regimens with or without radiotherapy- pure infradiaphragmatic localizations were not associated with inferior failure-free survival, overall survival, or disease-specific survival in comparison to supradiaphragmatic ones after adjustment for age and B-symptoms. Thus our results suggest that the unfavorable outcome of pure infradiaphragmatic HL patients is largely explained by their adverse baseline clinical features. This view is also supported by a recent abstract from the GHSG.[25]

In summary, although the clinicopathologic features of pure infradiaphragmatic HL have been well-described, its optimal treatment is still open to discussion. Given the high rate of primary treatment failure, it might be worthwhile including younger patients with clinical stage IIB pure infradiaphragmatic HL in clinical trials of advanced disease employing more aggressive chemotherapy regimens, such as BEACOPP-escalated.[45] At present however, a careful evaluation of the existing data suggests that the outcome of pure infradiaphragmatic HL is not worse than that of its supradiaphragmatic counterpart, provided that adjustments for the remaining features of the disease are taken into account.

*All authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria. Specific responsibilities were as follows: TPV: responsibility from conception to submitted manuscript, writing of the manuscript, statistical analysis, management of clinical data covering a long follow-up period, data collection; MKA: major contribution to the writing of the manuscript, management of clinical data covering a long follow-up period, data collection; MPS, NK, AS, TK, Pre, Pro, AMD, SIK, EMD, MCK, MND, CT, GK, EV, VG, CP, MS, DL, GG, PP: management of clinical data covering a long follow-up period, data collection; GAP: study supervisor, responsibility from conception to submitted manuscript, management of clinical data covering a long follow-up period. All authors contributed to the design of the study, the writing of the manuscript. Furthermore, all authors critically reviewed and approved the final version. The authors reported no potential conflicts of interest.*

*Funding: supported in part by a grant provided by "IASIS" a non-profit organization raising funds for Research in Leukemias, Lymphomas and related disorders.*

*Manuscript received June 30, 2005. Accepted November 7, 2005.*



## References

1. Vassilakopoulos TP, Angelopoulou MK, Kontopidou FN, Siakantaris MP, Barbounis A, Hadjioannou M, et al. Pure infradiaphragmatic Hodgkin's disease. Analysis of twenty five cases and review of the literature. Haema 1999; 2:90-100.
2. Krikorian JG, Portlock CS, Mauch PM. Hodgkin's disease presenting below the diaphragm: a review. J Clin Oncol 1986;4:1551-62.
3. Krikorian JG, Portlock CS, Rosenberg SA, Kaplan HS. Hodgkin's disease, stages I and II occurring below the diaphragm. Cancer 1979;43:1866-71.
4. Pene F, Henry-Amar M, Le Bourgeois JP, Hayat M, Gerard-Marchant R, Laugier A, et al. A study of relapse and course of 153 cases of Hodgkin's disease (clinical stages I and II) treated at the Institute Gustave-Roussy from 1963 to 1970 with radiotherapy alone or with adjuvant monochemotherapy. Cancer 1980;46:2131-41.
5. Barrett 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 infradiaphragmatic nodes. Tumori 1982;68:519-25.
7. Mauch P, Greenberg H, Lewin A, Cassady R, Weichselbaum R, Hellman S. Prognostic factors in patients with subdiaphragmatic Hodgkin's disease. Hematol Oncol 1983;1:205-14.
8. Dorreen MS, Wrigley PFM, Jones AE, Shand WS, Stansfeld AG, Lister TA. The management of localized, infradiaphragmatic Hodgkin's disease: experience of a rare clinical presentation at St Bartholomew's Hospital. Hematol Oncol 1984;2:349-57.
9. 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.
10. Leibenhaut MH, Hoppe RT, Varghese A, Rosenberg SA. Subdiaphragmatic Hodgkin's disease: laparotomy and treatment results in 49 patients. J Clin Oncol 1987;5:1050-5.
11. Specht L, Nissen NI. Hodgkin's disease stages I and II with infradiaphragmatic presentation: a rare and prognostically unfavourable combination. Eur J Haematol 1988;40:396-402.
12. Frassica DA, Schomberg PJ, Banks PM, Colgan JP, Ilstrup DM, Earle JD. Management of subdiaphragmatic early-stage Hodgkin's disease. Int J

Radiat Oncol Biol Phys 1989;16:1459-63.
13. 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 prednisone. Cancer 1990; 66:69-74.
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. Liew KH, Ding JC, Cruickshank D, quong GG, Wolf MM, Cooper IA. Infradiaphragmatic Hodgkin's disease, long term follow-up of a rare presentation. Aust NZ J Med 1991;21:16-21.
16. Mai DHW, Peschel RE, Portlock C, Knowlton A, Farber L. Stage I and II subdiaphragmatic Hodgkin's disease. Cancer 1991;68:1476-81.
17. Roos DE, O'Brien P, Wright J, Willson K. Treatment of subdiaphragmatic Hodgkin's disease: is radiotherapy alone appropriate only for inguinofemoral presentations? Int J Radiat Oncol Biol Phys 1994;28:683-91.
18. Barton M, Boyages J, Crennan E, Davis S, Fisher RJ, Hook C, et al. Radiotherapy for early infradiaphragmatic Hodgkin's disease: The Australasian experience. Radiother Oncol 1996; 39: 1-7.
19. Ifrah N, Hunault M, Jais JP, Moreau P, Desablens B, Casassus P, et al. Infradiaphragmatic Hodgkin's disease: long term results of combined modality therapy. Leuk Lymphoma 1996;21:79-84.
20. Enrici RM, Osti MF, Anselmo AP, Banelli E, Cartoni C, Sbarbati S, et al. Hodgkin's disease stage I and II with exclusive subdiaphragmatic presentation. The experience of the Departments of Radiation, Oncology and Hematology, University "La Sapienza" of Rome. Tumori 1996;82:48-52.
21. Iannitto E, Accurso V, Federico M, Vallisa D, Pieresca C, Gravina SF, et al. Hodgkin's disease presenting below the diaphragm. The experience of the Gruppo Italiano Studio Linfomi (GISL). Haematologica 1997;82:676-82.
22. Kalkner KM, Enblad G, Gustavsson EG, Starkhammar H, Branehog H, Lenner P, et al. Infradiaphragmatic Hodgkin's disease: the Swedish National Care Programme experience. Eur J Haematol 1997;59:31-7.
23. Illes A, Vadasz G, Banyai A, Szegedi G. Infradiaphragmatic Hodgkin's disease. Haematologia 1997;28:117-22.
24. Liao Z, Ha CS, Fuller LM, Hagemeister FB, Cabanillas F, Tucker SL, et al. Subdiaphragmatic stage I and II Hodgkin's disease: long-term follow-up and prognostic factors. Int J Radiat Oncol Biol Phys 1998;41:1047-56.
25. Darabi K, Sieber M, Chaitowitz M, Braitman LE, Tester W, Diehl , et al. Infradiaphragmatic versus supradiaphragmatic Hodgkin lymphoma: a retrospective review of 1,114 patients. Leuk Lymphoma 2005;46:1715-20.
26. Cutuli B, Petit T, Hoffstetter S, Velten M, Dufour P, Giron C, et al. Treatment of subdiaphragmatic Hodgkin's disease: long-term results and side effects. Oncol Rep 1998;5:1513-8.
27. Hull MC, Mendenhall NP, Colgan ME: Subdiaphragmatic Hodgkin's disease: the University of Florida experience. Int J Radiat Oncol Biol Phys 2002;52: 161-6.
28. Cordoba S, Romero J, De la Torre A, Valcarcel F, Magallon R, Regueiro CA, et al. Early stage infradiaphragmatic Hodgkin's disease: results of radiotherapy and review of the literature. Radiother Oncol 2003;67:259-63.
29. Vassilakopoulos TP, Angelopoulou MK, Siakantaris MP, Kontopidou FN, Dimopoulou MN, Kokoris SI, et al. Combination chemotherapy plus low dose involved field radiation for early clinical stage Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 2004;59:765-81.
30. Carde P, Hagenbeek A, Hayat M, Monconduit M, Thomas J, Burgers MJV, et al. Clinical staging versus laparotomy and combined modality with MOPP versus ABVD in early-stage Hodgkin's disease: the H6 twin randomized trials from the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group. J Clin Oncol 1993; 11:2258-72.
31. Noordijk EM, Carde P, Mandard AM, Mellink WA, Monconduit M, Eghbali H, et al. Preliminary results of the EORTC-GPMC controlled clinical trial H7 in early-stage Hodgkin's disease. Ann Oncol 1994; 5 Suppl 2:S107-S112.
32. Canellos GP, Anderson JR, Propert KJ, Nissen N, Cooper MR, Henderson ES, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992;327:1478-84.
33. Rassidakis GZ, Medeiros LJ, Vassilakopoulos TP, Viviani S, Bonfante V, Nadali G, et al. Bcl-2 expression in Hodgkin and Reed-Sternberg cells of classical Hodgkin disease predicts a poorer prognosis in patients treated with ABVD or equivalent regimens. Blood 2002;100:3935-41.
34. Diehl V, Klimm B, Re D. Hodgkin lymphoma: a curable disease: what comes next? Eur J Haematol 2005; 75 Suppl 66:6-13.
35. Bonadonna G, Zucali R, Morfardini 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.
36. Angelopoulou MK, Vassilakopoulos TP, Siakantaris MP, Kontopidou FN, Boussiotis VA, Papavassiliou C, et al. EBVD combination chemotherapy plus low dose involved field radiation is a highly effective treatment modality for early stage Hodgkin's disease. Leuk Lymphoma 2000;37:131-43.
37. Connors JM, Klimo P, Adams G, Burns BF, Cooper I, Meyer RM, et al. Treatment of advanced Hodgkin's disease with chemotherapy-comparison of MOPP/ABV hybrid regimen with alternating courses of MOPP and ABVD: a report from the National Cancer Institute of Canada clinical trials group. J Clin Oncol 1997;15:1638-45.
38. Eghbali H, Raemaekers J, Carde P, EORTC Lymphoma Group. The EORTC strategy in the treatment of Hodgkin's lymphoma. Eur J Haematol 2005;75 Suppl 66:135-40.
39. Carbone PP, Kaplan HS, Musshof K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging. Cancer Res 1971; 31: 1860-1.
40. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. N Engl J Med 1998;339:1506-14.
41. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:185-206.
42. Peto R, Peto J. Asymptotically efficient rank invariant procedures. J R Stat Soc 1972;135(A):185-207.
43. Cox DR. Regression models and life tables (with Discussion). J R Stat Soc B 1972;34:187-220.
44. Vassilakopoulos TP, Angelopoulou MK, Siakantaris MP, Kokoris SI, Pangalis GA. Hodgkin's lymphoma: treatment and prognosis. Haema 2004; 7 Suppl 1:53-63.
45. Diehl V, Franklin J, Pfreundschuh M, Lathan B, Paulus U, Hasenclever D, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003; 348: 2386-95.
46. Vassilakopoulos TP, Nadali G, Angelopoulou MK, Siakantaris MP, Dimopoulou MN, Kontopidou FN, et al. The prognostic significance of $\beta_2$-microglobulin in patients with Hodgkin's lymphoma. Haematologica 2002;87: 701-8.
47. Meyer R, Gospodarowicz MK, Connors J, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23 4634-42.
48. Straus DJ, Portlock CS, Qin J, Myers J, Zelenetz AD, Moskowitz C, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) followed by radiation therapy (RT) vs. ABVD alone for stages I, II and IIIA non bulky Hodgkin's disease Blood 2004;104: 3483-9.
49. Vassilakopoulos TP, Angelopoulou MK, Siakantaris MP, Kontopidou FN, Dimopoulou MN, Barbounis A, et al. Prognostic factors in advanced stage Hodgkin's lymphoma: the significance of the number of involved anatomic sites. Eur J Haematol, 2001; 67:279-88.
50. Franklin J, Paulus U, Lieberz D, Breuer K, Tesch H and Diehl V. Is the International Prognostic Score for advanced stage Hodgkin's disease applicable in early stage patients? Ann Oncol 2000; 11:617-23.
51. Gisselbrecht C, Mounier N, Andre N, Casanovas O, Reman O, Sebban C, et al. How to define intermediate stage in Hodgkin's lymphoma? Eur J Haematol 2005;75 Suppl 66:111-4.