

The significance of a residual mediastinal mass following treatment for aggressive non-Hodgkin's lymphomas

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ABSTRACT: The chest radiographs of 252 patients with aggressive non-Hodgkin's lymphoma, prospectively treated according to one of three protocols of combination chemotherapy, were reviewed to determine the incidence and prognostic significance of mediastinal abnormalities following treatment.

Residual mediastinal masses were defined as any abnormality, greater than 2 cm in diameter, that had initially responded to chemotherapy and then remained stable in size for at least three months after its maximal response, together with the disappearance of all other clinical and biological signs of active lymphoma.

At the end of treatment, 21 (8%) patients had some residual mediastinal abnormality. The predominant histological pattern was the diffuse large cell subtype ($p < 0.001$). Disease free survival and overall survival for these patients were similar to those observed among patients in complete remission without a persisting radiological mass after treatment.

We conclude that mediastinal residual masses after completion of treatment for aggressive lymphoma are frequent and do not indicate a poorer prognosis. Such patients can be observed clinically without any need for additional chemotherapy or radiotherapy.

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The mediastinum is a frequent site of involvement in patients with aggressive non-Hodgkin's lymphomas (NHL). Large or bulky mediastinal involvement at presentation is thought to be of adverse prognostic significance and associated with a higher risk of relapse after treatment [1]. However, intensive chemotherapy has considerably modified the course of these aggressive diseases. Such regimens, as the C_2H_2OP protocol [2], have been associated with long-term survival rates in excess of 50%. More recently, with a median follow-up of 23 months, the LNH-84 protocol [3] has been associated with a 2 yr survival rate of 67%.

The mediastinum may not return to normal after treatment. The introduction of newer and more sensitive radiographic technology, such as computed tomography (CT) and magnetic resonance imaging (MRI), has improved the detection of very small lesions. However, this increased precision may sacrifice specificity. The finding of a radiographically detectable residual mass when all other evidence of disease has disappeared is a common problem in NHL patients and may lead some physicians to biopsy the mediastinum or administer additional chemotherapy or radiation. Whilst they may effectively indicate persisting active disease for which additional treatment is required, alternatively, these residual

mediastinal abnormalities may simply represent fibrotic residua; such findings are frequent after treatment of some solid tumours, such as testicular cancer [4].

This study analyses the experience in aggressive NHL patients of Hôpital Saint-Louis, who initially presented with a mediastinal mass. After completion of therapy, they were left with a radiologically detectable mass, whilst otherwise in a clinical complete response (CR). We sought to determine the prognostic significance of these residual mediastinal abnormalities.

Patients and methods

Patients

From January 1980 to December 1989, 252 patients with aggressive non-Hodgkin's lymphoma were treated at Hôpital Saint-Louis in Paris (France). Eligibility criteria were the diagnosis of intermediate or high-grade non-Hodgkin's lymphoma, according to the working formulation [5], stage I with tumour mass ≥ 10 cm or stages II to IV for intermediate grade NHL, all stages for high-grade NHL, no contraindication to doxorubicin and no previous chemotherapy or radiotherapy unless recent and

localized. No upper limit was given for age but patients should not present abnormalities of major organs that contraindicated high doses of doxorubicin or cyclophosphamide. All pathological diagnoses were reviewed and confirmed by a specialized group of pathologists.

Of the 252 patients, 166 were male (66%) and 86 were female (34%). Median age was 47 yrs. Initial staging procedures included physical examination; complete blood cell count and routine blood chemistry; posteroanterior and lateral chest roentgenograms, bone marrow biopsy and cerebrospinal fluid examination; thorax and abdominal CT was routinely used after 1984. Other tests, e.g. endoscopy, bone scan, were performed when clinically indicated. The histological subtypes were:

follicular large cell	12 patients	(5%)
diffuse small cleaved cell	15 patients	(6%)
diffuse mixed	54 patients	(21%)
diffuse large cell	114 patients	(45%)
immunoblastic	30 patients	(12%)
lymphoblastic	15 patients	(6%)
small noncleaved cell	12 patients	(5%)

Clinical stage was decided at a multidisciplinary lymphoma staging conference which included medical oncologists, radiation therapists, radiologists, and pathologists. The extent of disease was determined by consensus.

We defined a stable residual mass as any mediastinal abnormality >2 cm in diameter on the posteroanterior or lateral chest X-ray or CT scan of the thorax, that had initially responded to combination chemotherapy, and had then remained stable in size for at least 3 months after reaching its maximal response, together with the disappearance of all other clinical and biological signs of active lymphoma. All patients were regularly re-evaluated clinically and radiographically (with chest X-ray performed every month and CT scan every 3 months, from 1984).

All radiographs were reviewed by one researcher (J.F.). At presentation, the size of the mediastinum on a posteroanterior chest radiograph was measured at its widest diameter. The transthoracic diameter was measured at its widest point, just above the domes of the diaphragm. The ratio of these two numbers was used in classifying the mediastinal width as <33% or ≥33% of the transthoracic diameter. Measurements of mediastinal width were then made on each serial film. The width of the stable residual mass was defined as the product of multiplying the two largest diameters of the mass, measured on the chest X-rays or on the CT scan.

Treatment

The treatment plan consisted of combination chemotherapy. Patients were treated according to one of three successive protocols, C₂H₂OP, LNH-84 and LNH-87, as a function of the year of diagnosis. Each of these protocols was based on a similar sequence. Induction included three or four courses of intensive polychemotherapy (Table 1).

Table 1. — Comparative induction courses of the three treatment protocols used

Drugs	C ₂ H ₂ OP	LNH-84	LNH-87
Doxorubicin mg·m ⁻²	90	75	75
Cyclophosphamide mg·m ⁻²	1800	1200	1200
Vindesine mg·m ⁻²	4	4	4
Bleomycin mg	0	20	20
Prednisone mg·m ⁻²	300	300	300

A consolidation phase of sequential chemotherapy began one month after the last induction course. Only patients treated with the C₂H₂OP protocol received radiotherapy at the end of chemotherapy treatment if a CR was not achieved or a residual mass observed.

Statistical methods

The date when the trial observations ceased was October 1st, 1990. Disease-free survival was calculated from the date of randomization to the date of progression or death. Survival analysis was estimated by the method of KAPLAN and MEIER [6]. Log-Rank and generalized Wilcoxon tests [7] were used to establish the significance of unadjusted differences in survival for each variable. These results were obtained using the BMDP package (Statistical Software, Los Angeles, CA, USA).

Results

Of the 252 patients with aggressive lymphoma treated at Hôpital Saint-Louis, 58 (23%) had mediastinal masses at presentation. At the end of treatment, 21 (8%) had some residual mediastinal abnormality. Five had been treated with the C₂H₂OP protocol, 10 with the LNH-84 protocol and six with the LNH-87 protocol. There was no significant difference in the initial staging of these patients, whatever the year of diagnosis and treatment. Table 2 displays the initial characteristics of these 21 patients. The predominant histological pattern was the diffuse large cell subtype (p<0.001). The area of the mediastinal residual mass ranged from 4–63 cm² with a mean of 23 cm².

Fifteen patients did not relapse; the mediastinal widening remained stable without any significant difference between the different histological subtypes. The same applied to four patients among them who had received mediastinal radiotherapy.

Six of the patients with a residual mediastinal mass relapsed (29%). The histological subtype was always of the diffuse large cell pattern. All of these patients received salvage chemotherapy. Two of them presented as relapse in the mediastinum and, subsequently, the disease rapidly disseminated and these two patients died 9 and 16 months after initial diagnosis. The other four did not appear to relapse at the site of the initial mediastinal mass but nearby, as judged by CT scan. One of the four, initially treated in 1983, had previously received mediastinal radiotherapy at the end of the induction chemotherapy. Only one of these patients died of lymphoma (19 months after diagnosis); unfortunately, a fourth death was by suicide in a patient with a stable second CR.

Table 2. — Initial characteristics of the 21 patients with a residual mediastinal mass

Age yrs	19–58
Median	35
Sex:	
Male	12
Female	9
Clinical Staging:	
I	3
II	13
III	2
IV	3
B symptoms	6/15
LDH >1.25 × normal	16
Mediastinal bulky ≥33%	16
Histological subtypes:	
diffuse large cell	17
lymphoblastic	3
diffuse mixed	1
Treatment protocol:	
C ₂ H ₂ OP	5
LNH 84	10
LNH 87	6

LDH: lactate dehydrogenase. B symptoms: night sweats, weight loss >10%, fever >38°C.

Thus, seventeen of these 21 patients (81%) are alive, after a median follow-up of 36 months. Overall survival (fig. 1) as well as disease-free survival (fig. 2) for these 21 patients were similar to those observed among patients in complete remission without a persistent radiological mass after treatment.

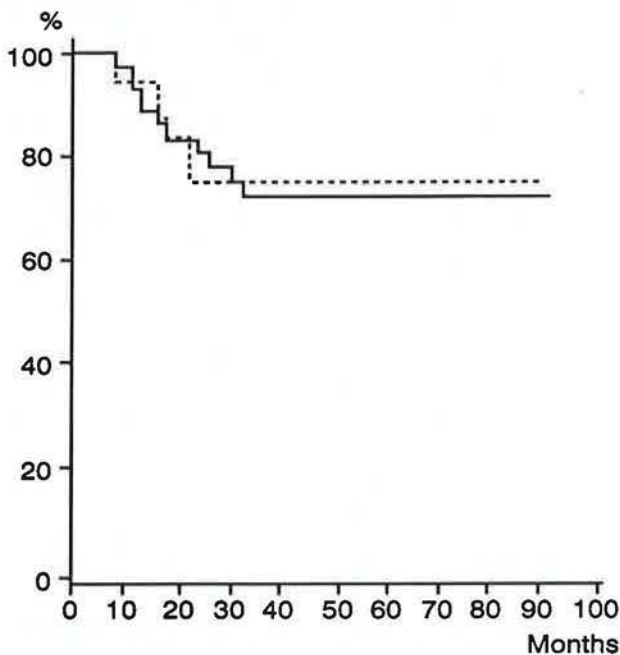


Fig. 1. — Overall survival for the 166 patients in complete response (CR) according to the presence of persistent radiological mediastinal mass (RM) after chemotherapy. : with RM; — : without RM.

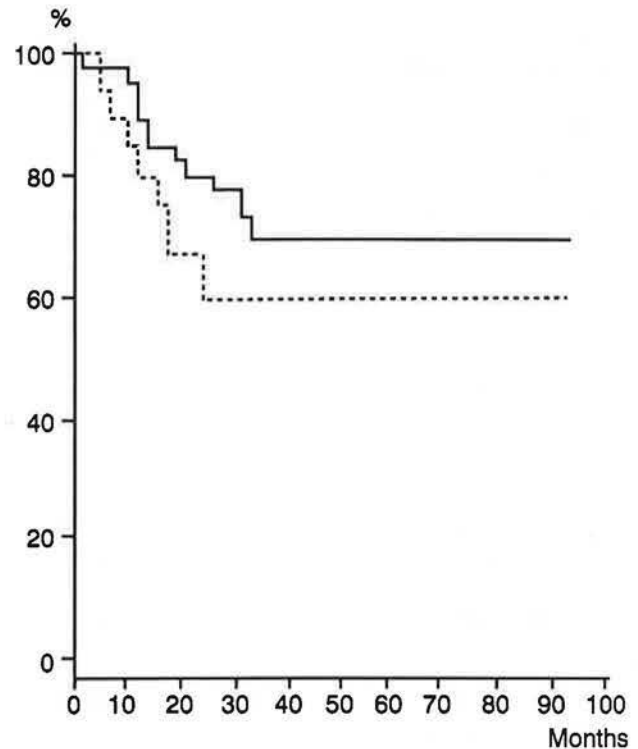


Fig. 2. — Disease-free survival for the 166 patients in complete response (CR) according to the presence of persistent radiological mediastinal mass (RM) after chemotherapy. : with RM; — : without RM.

Discussion

Mediastinal involvement is common in NHL and although response to induction therapy is usually rapid, residual mediastinal abnormalities are frequently observed on the post-treatment chest radiograph, which raises the possibility of persistent disease. The significance of this residual mass remains a challenge for the evaluation of these patients with a high expectation of cure, and raises the question of salvage therapy (e.g. autologous bone marrow transplantation and/or radiotherapy).

The same phenomenon is already known to occur after chemotherapy for testicular carcinoma. Here, the common practice is to resect residual pulmonary or intra-abdominal masses following chemotherapy. Such a policy in patients achieving an excellent, but less than complete, response found residual carcinoma in 15 out of 41 patients [8]. The remaining patients had only necrosis-fibrosis, or mature teratoma.

A similar issue has been illustrated for the malignant lymphomas, especially in patients treated for Hodgkin's disease (HD). JOCHELSON *et al.* [9] retrospectively analyzed the chest roentgenograms of 65 patients treated for HD with initial mediastinal adenopathy [9]. On completion of treatment, 57 (88%) of the 65 patients had some residual mediastinal abnormality. However, these patients did not have a higher incidence of recurrence. The study by RADFORD *et al.* [10] addresses the issue of residual mediastinal masses in 110 patients

treated for advanced HD with chemotherapy and/or radiotherapy. Residual mediastinal abnormalities occurred in 64% of patients at the completion of treatment. The presence of a mediastinal abnormality following treatment did not predict relapse. Recently, ORLANDI *et al.* [11] reviewed the chest radiograms of 102 patients with HD presenting with mediastinal involvement at diagnosis. Thirty nine cases (38%) showed residual mediastinal widening at the end of therapy. The isolated intrathoracic relapse rate was 11% for patients without residual mass as compared to 20.5% for those with residual widening ($p=0.3$).

Few data are available concerning residual masses after chemotherapy for aggressive NHL. VEMATSU *et al.* [12] treated four patients with extensive mediastinal NHL. After completion of treatment, follow-up CT showed a residual mediastinal mass in all four patients, who have remained alive and well for more than 19 to 45 months without any supplemental treatment.

These data are in complete accordance with ours, since we did not find any negative prognostic significance for residual mediastinal masses observed among 21 patients heavily treated for aggressive lymphoma. Nevertheless, some patients relapse in the site of the residual mass, which means that active disease was persisting. Therefore, it is important to identify patients whose residual masses have a high likelihood of relapse. An accurate estimate of residual viable tumour would facilitate the use of appropriate second-line therapy [13].

Computed tomography of the thorax has had a remarkable impact on the determination of extent of disease in lymphoma. After completion of treatment, it can demonstrate better than chest radiography the persistence of residual mediastinal abnormalities. However, it is generally considered to be unable to distinguish between fibrous tissue and viable neoplasm [14], except when it shows their cystic nature [15]. The use of MRI could be complementary to the CT scan and increase the specificity of the clinical diagnosis. Finally, gallium scanning could be the best test for the identification of viable residual disease in lymphoma patients, but requires further evaluation [16-18].

We conclude that mediastinal residual masses after completion of treatment for aggressive lymphoma are frequent and do not suggest a negative prognostic significance. According to a strict application of our criteria for stable disease, a patient in clinical CR with a stable residual mediastinal mass can be observed radiologically, thus avoiding a diagnostic thoracotomy.

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References

- Cabanillas F, Burkes JS, Smith TL, Moon TE, Butler JJ, Rodriguez V. - Factors predicting for response and survival in adults with advanced non-Hodgkin's lymphoma. *Arch Intern Med*, 1978; 138: 413-418.
- Gisselbrecht C, Lepage E, Fermand JP, Ferme C, Castaigne S, D'Agay MF, Seligmann M, Boiron M. - Intensive induction treatment in non-Hodgkin's lymphomas with various grade of malignancy. In: Non-Hodgkin's Lymphomas (1984). New techniques and treatments. Sotto eds., Fourth Cancer Research Workshop, Basel, Grenoble, 1985; pp. 195-199.
- Coiffier B, Gisselbrecht C, Herbrecht R, Tilly H, Bosly A, Brousse N. - LNH-84 regimen: a multicenter study of intensive chemotherapy in 737 patients with aggressive malignant lymphoma. *J Clin Oncol*, 1989; 7: 1018-1026.
- Motzer R, Bosl G, Heelan R. - Residual mass: an indication for further therapy in patients with advanced seminoma following systemic chemotherapy. *J Clin Oncol*, 1987; 5: 1064-1070.
- The Non-Hodgkin's Lymphoma Pathologic Classification Project: National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. *Cancer*, 1982; 49: 2112-2135.
- Kaplan E, Meier P. - Non-parametric estimation from incomplete observations. *J Am Stat Assoc*, 1958; 53: 457-480.
- Mantel N. - Evaluation of survival data and two new rank-order statistics arising in its consideration. *Cancer Chemother Res*, 1966; 50: 163-170.
- Einhorn LH, Williams SD, Mandelbaum I. - Surgical resection in disseminated testicular cancer following chemotherapeutic cytoreduction. *Cancer*, 1981; 48: 904-908.
- Jochelson M, Mauch P, Balikian J, Rosenthal D, Canellos G. - The significance of the residual mediastinal mass in treated Hodgkin's disease. *J Clin Oncol*, 1985; 3: 637-640.
- Radford JA, Cowan RA, Flanagan M, Dunn G, Crowther D, Johnson RJ, Eddleston B. - The significance of residual mediastinal abnormality on the chest radiograph following treatment for Hodgkin's disease. *J Clin Oncol*, 1988; 6: 940-946.
- Orlandi E, Lazzarino M, Brusamolino E, Caldera D, Morra E, Dore R, Di Giulio G, Bernasconi C. - Residual mediastinal widening following therapy in Hodgkin's disease. *Hematol Oncol*, 1990; 8: 125-131.
- Vematsu M, Kondo M, Tsutsui T, Murase T, Yoroze A, Hiramatsu H, Fujii H, Hashimoto S. - Residual masses on follow-up computed tomography in patients with mediastinal non-Hodgkin's lymphoma. *Clin Radiol*, 1989; 40: 244-247.
- Canellos GP. - Residual mass in lymphoma may not be residual disease. *J Clin Oncol*, 1988; 6: 931-933.
- Lewis E, Bernardino ME, Salvador PG, Cabanillas FF, Barnes PA, Thomas JL. - Post-therapy CT detected mass in lymphoma patients: is it viable tissue? *J Comput Assist Tomogr*, 1982; 6: 792-795.
- Baron RL, Sagel SS, Baglan RJ. - Thymic cysts following radiation therapy for Hodgkin's disease. *Radiology*, 1981; 141: 593-597.
- Wylie BR, Southee AE, Joshua DE, McLaughlin AF, Gibson J, Hutton BF, Morris JG, Kronenberg H. - Gallium scanning in the management of mediastinal Hodgkin's disease. *Eur J Haematol*, 1989; 42: 344-347.
- Kaplan E, Jochelson MS, Herman TS, Nadler LM, Stomper PC, Takvorian T, Andersen JW, Canellos GP. - Gallium-67 imaging: a predictor of residual tumor viability and clinical outcome in patients with diffuse large cell lymphoma. *J Clin Oncol*, 1990; 8: 1966-1970.
- Nedellec G, Lioure B, Bussy E, De Revel T, Carlioz R, Gaillard JF, Auzanneau G. - Evaluation of residual masses after lymphoma treatment: the contribution of gallium 67 tomoscintigraphy. *Nouv Rev Fr Hematol*, 1990; 32: 187-190.