The prognostic value of mediastinal enlargement in the treatment of patients with early stage Hodgkin's disease : a population-based study

CHAPTER 4

The prognostic value of mediastinal enlargement in the treatment of patients with early stage Hodgkin's disease

A population-based study

Frans L. Erdkamp, Martin J. Houben, Wim P. Breed, Jac Th. Wijnen, Harry C. Schouten, Geert H. Blijham

Submitted

Abstract

The mediastinum is a common site of involvement in Hodgkin's disease, but conflicting results have been reported for the prognostic value of (bulky) mediastinal disease. In a retrospective population-based study of 96 patients with clinically staged I-IIIA Hodgkin's disease we investigated the prognostic impact of (bulky) mediastinal mass. In 46% of the patients mediastinal involvement was present. Complete remission rates were 95% and 94% for patients with and without mediastinal enlargement, respectively. Relapses occurred, although not statistically significant, especially more often in patients with mediastinal enlargement treated initially with radiation therapy alone. However, remission duration and survival were not adversely influenced by the presence of mediastinal disease. Analyzing, separately, the subgroup of patients with large mediastinal masses we also could not establish a significant correlation between the degree of mediastinal enlargement and remission rate, relapse-free and overall survival. In conclusion, with the limitations of a retrospective study, our data do not support the view that small versus large mediastinal disease has an impact on overall survival in patients with early stage Hodgkin's disease. Treatment decisions should therefore depend on other prognostic factors as well, particularly in the light of the observed early and late toxicities and secondary malignancies.

Introduction

A marked improvement in the overall prognosis of patients with Hodgkin's disease has been achieved during the last two decades (1,2). Over the years several prognostic indicators have been identified including the size of mediastinal involvement (1,2). Bulky mediastinal disease has been reported as a poor risk prognostic factor for relapse-free survival, particularly in early stage Hodgkin's disease (3,4,5,6,7). In some studies in addition a negative correlation with survival could be demonstrated (8,9). In the past the definition and treatment of patients with a large mediastinal mass has been variable making it difficult to formulate general recommendations (5,8,10,11). Moreover the reported data are mainly derived from single institution studies and therefore they may not be representative for the unselected population of patients with Hodgkin's disease. In the early eighties several major centers have proposed intensification of therapy at initial presentation because of the inferior relapse-free survival rates in patients with bulky mediastinal disease. However, this may increase the risk of early and late toxicities as well as secondary malignancies (2).

In order to address these problems we studied the prognostic impact of (bulky) mediastinal disease, determined in a number of ways in clinical stage I-IIIA Hodgkin's disease treated in 10 community hospitals.

Patients and Methods

Between 1972 and 1983, 182 patients with Hodgkin's disease were diagnosed in 10 community hospitals in the southeastern part of The Netherlands. From these patients a central registration system was maintained by the Comprehensive Cancer Centre South (SOOZ/IKZ). 96 patients fulfilled the entry criteria of this study being: clinical stage I-IIIA and a chest X-ray available for reviewing. All patients were studied from the date of histologic diagnosis till last follow-up or death. Median observation time was 5 years (range 3 to 14 years). In all cases the pathology was centrally reviewed and classified according to the Rye classification (12). All patients were clinically staged according to the Ann Arbor classification (13). Staging procedures such as bone marrow examination, lymphangiography and laparotomy were performed as clinically indicated; in the later years of the entry period computed tomography scanning (CT) was increasingly applied, but only from eight patients CT scans of the chest were available.

Standard postero-anterior chest radiographs from the time of diagnosis were re-examined for the presence of mediastinal involvement, the maximum mediastinal diameter with exclusion of hilar structures, chest diameter at TH5-6 and maximal chest diameter. Two methods of measuring the ratio of mediastinal mass to the thoracic transverse diameter were used. One ratio was calculated for maximal mediastinal diameter to chest diameter at TH5-6 (M1) as described by Lee et al. (9); the other method was the ratio of the maximal mediastinal mass to the chest diameter at the widest thoracic level (M2), as described by Mauch (4). For sake of uniformity and to compare our data with other studies we took generally accepted cut off points for large mediastinal mass: M1 $\geq$0.35 or M2 $\geq$0.33 (5,6). Patients with an abnormal mediastinum by chest radiograph but with M1<0.35 or M2<0.33 were defined as having small mediastinal mass.

Patients characteristics in relation to mediastinal pathology are shown in table 1. Radiation therapy was the single treatment modality in 50 patients, that is 30/52 (58%) of those without and 20/44 (45%) of those with a mediastinal mass (table 2). Patients with stages IA and IIA were treated with either mantle or inverted Y-field irradiation to a dose of 40 Gy, while patients with stages IB and

Table 1. Patient characteristics according to size of mediastinal mass in CS I-IIIA patients with Hodgkin's disease.

	mediastinal mass			
	absent	**small**	**large***	**all**
patients (n)	52	29	15	96
mean age (y)	36	30	37	34
male	31 (60%)	15 (52%)	7 (47%)	53 (55%)
histology				
LP + NS	32 (62%)	25 (86%)	12 (80%)	69 (72%)
MC + LD	20 (38%)	4 (14%)	3 (20%)	27 (28%)
clinical stage I-II	40 (77%)	25 (86%)	11 (73%)	76 (79%)
systemic symptoms	4 (8%)	10 (34%)	4 (27%)	18 (19%)
sites (n>3)	4 (8%)	9 (31%)	3 (20%)	16 (17%)
* Large mass is M1 ≥0.35.				

Table 2. Treatment according to size of mediastinal mass in CS I-IIIA patients with Hodgkin's disease.

	mediastinal mass			
	absent	**small**	**large***	**all**
patients (n)	52	29	15	96
RTX	30 (58%)	14 (48%)	6 (40%)	50 (52%)
CTX	7 (13%)	4 (14%)	3 (20%)	14 (15%)
RTX + CTX	15 (29%)	11 (38%)	6 (40%)	32 (33%)
RTX: radiation therapy, CTX: chemotherapy ; * Large mass is M1 ≥0.35.				

IIB were treated with more extensive field irradiation with or without chemotherapy. Patients with CS IIIA received either total nodal radiation therapy, chemotherapy, chiefly mechlorethamine, vincristine, procarbazine, prednisolone (MOPP) or combined modality.

The statistical analyses were performed with the BMDP package. The survival curves for all causes of death were plotted according to the Kaplan-Meier method. Survival curves were compared with the generalized Wilcoxon (Breslow) and generalized Savage (Mantel-Cox) methods. The Chi-Square test was used to compare tables (14,15).

Results

In 44 of 96 patients there was an abnormal mediastinum by chest radiograph (46%). Large mediastinal mass, which was defined as M1 ≥0.35 and M2 ≥0.33, was noted in 15 patients (16%) and 11 patients (11%), respectively. Analyzing the two calculated ratio's (M1 and M2) separately no differences in relapse or survival rates were found. Therefore, patients with a mediastinal ratio (M1) ≥0.35 (n=15) were grouped together to study further their clinical course compared to patients having smaller or no mediastinal mass. Patients with mediastinal enlargement had significantly more often systemic symptoms (P=0.009) and a higher number of involved sites (P=0.03) compared to patients with no mediastinal disease (table 1). Complete remission was achieved in 91 patients (95%). The complete remission rate for patients without mediastinal disease was 94% (49/52) compared to 95% (42/44) for patients with small or large mediastinal mass: in this latter group both failures were patients having a large mediastinal mass. Relapses as shown in table 3 occurred more frequently in patients with than without mediastinal enlargement, although this difference was not statistically significant, 31% and 18%, respectively (P=0.3). This difference was more pronounced in the group of patients treated with radiation therapy only, but was not significant (P=0.15). The relapse rate for the subgroup of patients with a large mediastinal mass was only 15% (2/13). Of the 11 patients with mediastinal involvement relapsing after radiotherapy only 4 had infield relapses, while 2 of these 4 patients also recurred outside the radiotherapy field: only one of these four patients had large mediastinal mass.

Table 3. Number of relapses of patients with complete remission in CS I-IIIA patients with Hodgkin's disease; relation with mediastinal enlargement and treatment.

	relapses (%)			
		mediastinal mass		
	absent	small	large*	all
RTX only	4/29 (14%)	6/14 (43%)	1/6 (17%)	11/49 (22%)
other	5/20 (25%)	5/15 (33%)	1/7 (14%)	11/42 (26%)
all	9/49 (18%)	11/29 (38%)	2/13 (15%)	22/91 (24%)

RTX: radiation therapy, other: chemotherapy or combined modality
* Large mass is M1 ≥0.35.

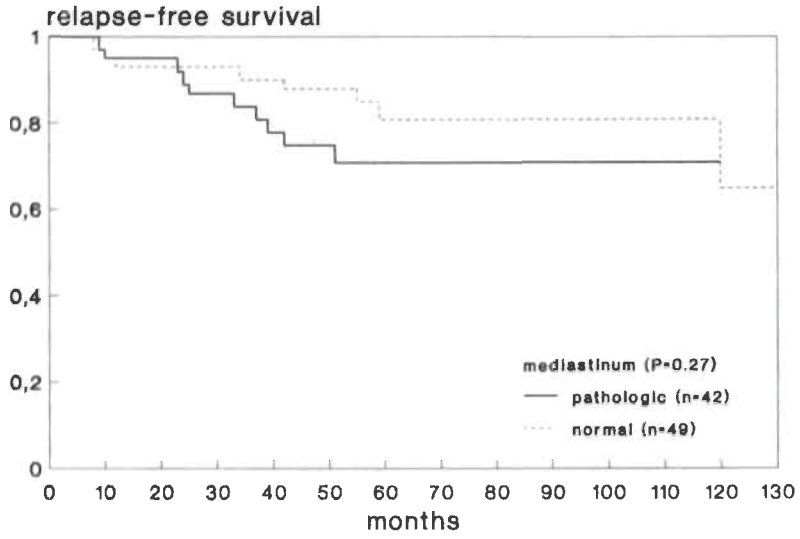

Figure 1. Relapse-free survival according to the presence of mediastinal disease in patients with clinical stage I-IIIA Hodgkin's disease.

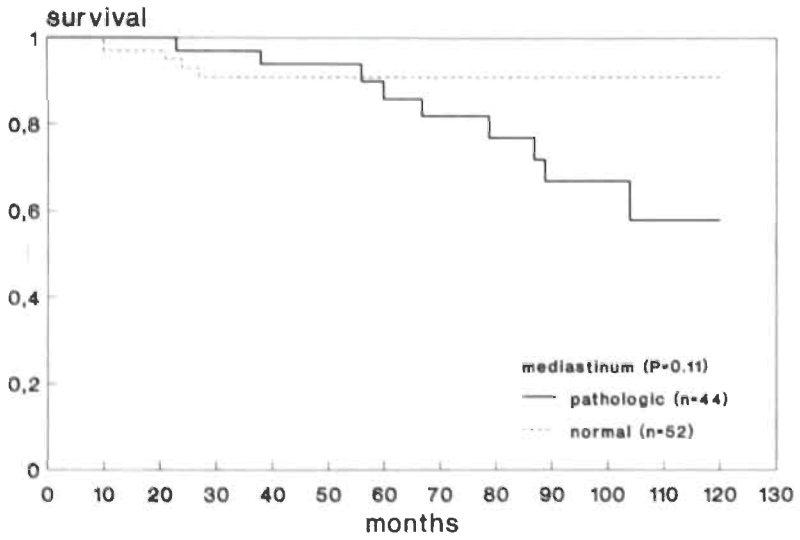

Figure 2. Survival according to the presence of mediastinal disease in patients with clinical stage I-IIIA Hodgkin's disease.

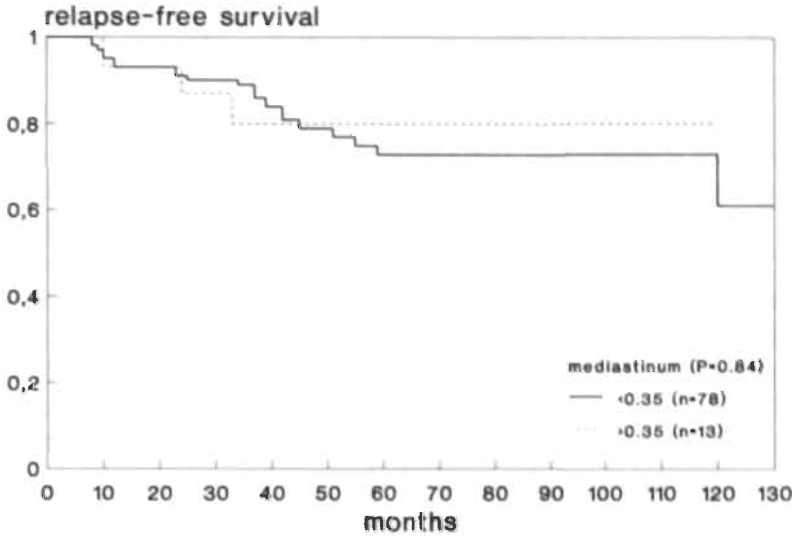

Figure 3. Relapse-free survival according to the size of mediastinal mass in patients with clinical stage I-IIIA Hodgkin's disease.

An analysis of relapse-free survival and overall survival did not show significant differences for patients with or without mediastinal involvement nor for patients with a large mediastinal mass compared to patients with small or no mediastinal enlargement (figure 1 to 4). However, comparing the survival data of patients with and without mediastinal involvement there was a tendency for a poorer survival for patients with mediastinal mass, that became apparent after 5 year (figure 4). After relapse effective salvage was possible in 7/9 (78%) of patients with initially a normal mediastinum and in only 6/11 (54%) of patients with mediastinal involvement. Although this is not significant (P=0.5) it might explain the difference in survival after a follow up of 5 to 10 years. Overall the ultimate failure rate in this study was 16% (15/96 died): 10 patients died from Hodgkin's disease, two from complications of treatment and three from intercurrent disease.

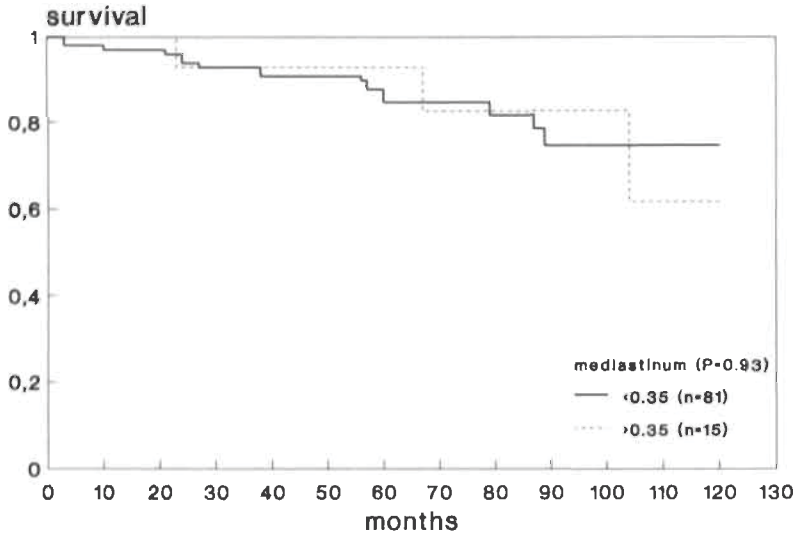

Figure 4. Survival according to the size of mediastinal mass in patients *with clinical stage I-IIIA Hodgkin's disease.*

Discussion

The mediastinum is one of the most common sites of involvement in Hodgkin's disease (1). However, the prognostic importance of the presence of a small or large mediastinal mass independent from other prognostic factors remains controversial.

In this retrospective analysis in a population-based sample of 96 patients with early stage Hodgkin's disease we could not establish a significant correlation between the presence and size of mediastinal involvement and remission rate, relapse rate and survival. This overall conclusion did not change by applying alternative methods to measure the degree of mediastinal enlargement. Our results are in line with earlier reports (11,16,17,18,19), in particular with results from a similar analysis performed by Ryoo et al (20) in patients with clinical stage I-IIIA Hodgkin's disease and large mediastinal masses. In contrast, in the late seventies and early eighties investigators from several centers were able to demonstrate an inverse correlation between relapse free survival and the presence of bulky mediastinal disease in early stage Hodgkin's disease (3-10); in two studies also the survival was affected (8,9).

The discrepancy between our results and earlier reports, who did find a relation between the degree of mediastinal enlargement and prognosis, can not be explained by differences in patient characteristics since these appear to be comparable between our study and those of major treatment centers in the USA and Europe (3-7). Treatment characteristics may affect results from retrospective analyses such as ours. Treatment schedules of our patient population were not uniform and treatment decisions could have been influenced by the presence of bulky mediastinal disease. In our series, only small treatment differences were observed for patients with or without mediastinal disease. It is true, however, that differences in relapse rate were observed in the group treated with radiation therapy only, although not significantly (P=0.15). A few centers have reported results from treatment with primary radiation therapy alone (8,11,17); only the Minneapolis group reported in a small number of patients an effect on both relapse free and overall survival (8). It can not be excluded, therefore that mediastinal enlargement is a negative prognostic factor for relapse free survival in patients treated with radiation therapy alone. Since a retrospective study such as described here and in the literature may suffer from inconsistencies across the various groups particularly with regard to patient characteristics and treatment, only a prospective randomized trial of sufficient magnitude can resolve this issue in a definitive way. However, we believe that our study and data from the literature justify the conclusion that the majority of the patients with large mediastinal masses at presentation will be overtreated when combined modality therapy is given upfront as has been recommended recently for patients with bulky mediastinal disease (21).

Apart from treatment modality also the radiotherapeutical treatment technique may to a certain extent influence chance and site of relapse. Rostock and co-workers suggested that their high intrathoracic failure rate was caused by inadequate portals of irradiation (18). Lee et al reported that seven of ten extralymphatic relapses were in the lung, six of which at the margin of the mediastinal bulk (8). In this study and the work of Ryoo et al (20) in patients with mediastinal disease, treated initially by radiation therapy, only one lung recurrence was observed in seven and twenty relapses, respectively. Improved radiation therapy may obscure earlier described negative relations between mediastinal involvement and prognosis.

The survival curve of patients with mediastinal disease showed a drop after 5 years. This drop can only to a limited extent be explained by a slightly higher relapse rate. Obviously, post-relapse events were responsible and indeed the salvage rate was lower in patients with an initially enlarged mediastinum who

relapsed. From our analysis it is apparent, that patients with mediastinal enlargement have significantly more often systemic symptoms and a higher number of involved sites. In a multivariate analysis performed by the EORTC in a population of more than 1000 patients treated between 1964 and 1982 these two factors appeared to be the only prognostic indicators for relapse (19), as was the case for total tumor burden in a recent report from the Danish Hodgkin study group (22). In our study patients with mediastinal enlargement were also slightly more often initially treated with chemotherapy (with or without radiation therapy), which may have compromised the possibility for salvage treatment. Therefore, although the drop in the survival curve after 5 years may be a real and interesting phenomena, it may well be dependent on other factors than the initially enlargement of the mediastinum.

In conclusion, our data support the view that also in the setting of community hospitals with standard levels of care mediastinal enlargement, whether small or large has no impact on overall survival. The decision whether to treat patients with Hodgkin's disease stage I to IIIA with radiation therapy or other (combined) modalities should depend on the absence or presence of other well-described factors (19,21) rather than on the presence of a mediastinal mass alone. This is important to spare these patients unnecessary toxic treatments.

References

1. Kaplan HS. Hodgkin's disease. 2nd ed. Cambridge, MA: Harvard University Press, 1980.
2. Somers R, Henry-Amar M, Meerwaldt JH, Carde P. Treatment strategy on Hodgkin's disease. Proceedings of the Paris international workshop and symposium held on june 28-30, 1989. London-Paris: John Libbey Eurotext, 1990.
3. Hoppe RT, Coleman NC, Cox RS, Rosenberg SA, Kaplan HS. The management of stage I-II Hodgkin's disease with irradiation alone or combined modality therapy: The Stanford experience. Blood 1982; 59:455-465.
4. Mauch P, Goodman R, Hellman S. The significance of mediastinal involvement in early stage Hodgkin's disease. Cancer 1978; 42:1039-1045.
5. Mauch P, Gorshein D, Cunningham J, Hellman S. Influence of mediastinal adenopathy on site and frequency of relapse in patients with Hodgkin's disease. Cancer Treat Rep 1982; 66:809-817.
6. Liew KH, Easton D, Horwich A, Barrett A, Peckham J. Bulky mediastinal Hodgkin's disease management and prognosis. Hematol Oncol 1984; 2:45-59.
7. Gomez GA, Panahon AM, Stuzman L, Moayeri H, Park JJ, Barcos M et al. Large mediastinal mass in Hodgkin's disease. Results of two treatment modalities. Am J Oncol 1984; 6:65-73.
8. Lee CKK, Bloomfield CD, Goldman AI, Levitt SH. Prognostic significance of mediastinal involvement in Hodgkin's disease treated with curative radiotherapy. Cancer 1980; 46:2403-2409.
9. Anderson H, Jenkins JPR, Brigg DJ, Deakin DP, Palmer MK, Todd IDH et al. The prognostic significance of mediastinal bulk in patients with stage I-IVB Hodgkin's disease: A report from the Manchester lymphoma group. Clin Radiol 1985; 36:449-454.
10. Thar TL, Million RR, Hausner RJ, McKetty MH. 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.
11. Fuller LM, Madoc-Jones H, Hagemeister FB, Rodgers RW, North LB, Butler JJ et al. Further follow-up of results of treatment in 90 laparotomy-negative stage I and II Hodgkin's disease patients: significance of mediastinal and non-mediastinal presentations. Int J Radiat Oncol Biol Phys 1980; 6:799-808.
12. Lukes RJ, Gompel LF, Hall TC, Rappaport H, Rubin P. Report of the nomenclature committee. Rye classification. Cancer Res 1966; 26:1311.
13. Carbone PP, Kaplan HS, Masshoff K, Smithers DW, Tubiana M. Report of the committee of Hodgkin's disease staging. Ann Arbor classification. Cancer 1971; 31:1860-1861.
14. Bishop YMM, Fienberg SE, Holland PW. Discrete multivariate analysis: Theory and practice. Cambridge, MA: MIT press, 1975.
15. Gross AJ, Clark VA. Survival distribution reliability application in the biomedical sciences. New York: Wiley and Sons, 1975.
16. North LB, Fuller LM, Hagemeister FB, Rodgers RW, Butler JJ, Shullenberger CC. Importance of initial mediastinal adenopathy in Hodgkin's disease. Am J Roentg 1982; 138:229-235.

17. Cosset JM, Henry-Amar M, Carde P, Clarke D, Le Bourgeois P, Tubiana M. The prognostic significance of large mediastinal masses in the treatment of Hodgkin's disease. The experience of the institute Gustave-Roussy. Hematol Oncol 1984; 2:33-43.
18. Rostock RA, Siegelman SS, Lenhard RE, Wharam MD, Order SE. Thoracic CT scanning for mediastinal Hodgkin's disease: Results and therapeutic implications. Int J Radiat Oncol Biol Phys 1983; 9:1451-1457.
19. Tubiana M, Henry-Amar M, van der Werf-Messing B, Henry J, Abbatucci J, Burgers M et al. A multivariate analysis of prognostic factors in early stage Hodgkin's disease. Int J Radiat Oncol Biol Phys 1985; 11:23-30.
20. Ryoo MC, Kagan AR, Wollin M, Nussbaum H, Chan PYM, Hintz BL et al. Observations on the treatment of mediastinal masses in Hodgkin's disease emphasizing site of failure. Am J Clin Oncol 1987; 10:185-193.
21. Longo DL. The use of chemotherapy in the treatment of Hodgkin's disease. Semin Oncol 1990; 17:716-735.
22. Specht L, Nordentoft AM, Cold S, Toffner Claussen N, Nissen NI. Tumor burden as the most important prognostic factor in early stage Hodgkin's disease. Relations to other prognostic factors and implications for choice of treatment. Cancer 1988; 61:1719-1727.