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Acknowledgements—This study was supported in part by the Sigrid Jusélius Foundation.

Eur J Cancer, Vol. 28A, No. 11, pp. 1841–1846, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Radiation Therapy in Clinical Stage I and II Hodgkin's Disease

Mary K. Gospodarowicz, S.B. Sutcliffe, D.E. Bergsagel and T. Chua for the Princess Margaret Hospital Lymphoma Group

A review of the Princess Margaret Hospital experience over the last 20 years in treating clinically staged patients with stage I and II Hodgkin's disease was performed to analyse the impact of patient selection and extended field radiation on relapse and survival. Of the 878 patients with stage I and II Hodgkin's disease, 521 with clinical stages I and II received radiation alone as the initial treatment. The actuarial survival for all stage I and II patients was 85.1% at 5 years and 76.2% at 10 years, and for clinically staged patients treated with radiation alone, 87.2 and 77.6%, respectively. The relapse-free rate (RFR) for all clinical stage I and II patients treated with radiotherapy (RT) alone was 70.1% at 5 years and 65.8% at 10 years. Significant prognostic factors for RFR and survival included age, stage and histology. In addition, the extent of radiation was identified as an independent prognostic factor for survival as well as for relapse. The RFR for those treated with involved field RT was 58.4% at 5 years and 50.5% at 10 years; for patients treated with mantle RT, 69.9 and 65.6%, and those treated with extended field RT 77.4 and 75.8%, respectively. In a highly selected group of patients with no adverse features, i.e. with stages IA–IIA, lymphocyte predominant or nodular sclerosis histology, erythrocyte sedimentation rate < 40, age < 50, no large mediastinal mass, and no E-lesions—the policy of mantle RT (M) and extended field RT (EF) produced comparable 5-year relapse-free rates (M, 84.9%; EF, 87.1%; $P = 0.53$). We conclude that a policy of treatment selection based upon clinicopathological prognostic factors and the use of extended field RT confers excellent results in the treatment of clinical stage I and II Hodgkin's disease.
Eur J Cancer, Vol. 28A, No. 11, pp. 1841–1846, 1992.

INTRODUCTION

IRRADIATION IS the most effective single agent for the treatment of Hodgkin's disease. Prior to the availability of effective chemotherapy (CT), all patients with Hodgkin's disease were treated with radiation therapy, with approximately 40% surviving for 5 years. Since the 1950s it has been recognised that radiotherapy (RT) can cure the majority of patients with localised stage I and II disease [1, 2]. The results of RT in the treatment of patients with clinical stage III and IV disease were unsatisfactory and for the last 20 years these patients have been managed with primary chemotherapy [3]. Thus, with the availability of curative chemotherapy, selection for treatment with RT alone has been contingent upon accurate identification of the anatomical extent of disease. This resulted in the widespread use of staging laparotomy to determine the extent of intra-abdominal involvement and, in particular, the spleen [4–7].

It has been known for many years that factors other than stage affect the prognosis of patients with early stage Hodgkin's disease. However, only in the last decade have these factors been taken into account systematically in the selection of optimal therapy. Prospective randomised studies conducted by the EORTC Lymphoma Group have validated the use of the above approach [8–11].

Correspondence to M. Gospodarowicz.
The authors are at Princess Margaret Hospital, 500 Sherbourne Street, Toronto, Ontario, Canada M4X 1K9.
This paper was presented at an international symposium on Hodgkin's disease, Royal Marsden Hospital, London, on 15–16 April 1991.
Received 22 Nov. 1991; accepted 30 Apr. 1992.

EJC(A) 28:11-D

Table 1. The pattern of referral—the distribution of previously identified independent prognostic factors over the period of the study

		1968–1977	1978–1986	*P* value*
Age	< 50	327	381	0.86
	> 50	77	93	
Histology	LP-NS	289	346	0.65
	MC-LD	105	116	
Symptoms	A	335	403	0.41
	B	69	71	

* Proportions of prognostic factors by time periods.

The use of a primary combined modality approach, i.e. chemotherapy and radiation, has resulted in a lower relapse rate than treatment with RT alone. So far, prospective randomised studies have failed to show a significant difference in overall survival for patients treated with RT alone, with chemotherapy reserved for salvage, compared with those treated with an initial combined modality approach [12–14]. Similarly, the use of staging laparotomy to determine optimal treatment has not been shown to improve survival [15]. Although RT is associated with a lower early morbidity than CT, concerns have been raised regarding late complications of RT and more specifically, combined CT and RT. Consequently, efforts are being pursued to select the optimal initial treatment required to maximise the probability of cure while minimising treatment and treatment-related complications [16, 17].

Clinical staging (CS) has been used at the Princess Margaret Hospital (PMH) for the majority of patients, with laparotomy performed in selected cases, where non-invasive staging investigations were inconclusive. Only a small proportion of patients have had surgical staging prior to being assessed [18, 19]. We have previously analysed the results of RT alone in patients with CS I and II disease treated at the PMH during 1968–1977 and 1978–1986, to determine prognostic factors and the impact of the extent of therapy on outcome [20, 21]. However, because of the small numbers of patients, ongoing selection of patients for treatment with RT alone, and the presence of multiple powerful prognostic factors confounding the analysis, it was previously difficult to assess the importance of the extent of RT in determining outcome. Therefore, to define the influence of prognostic factors and extent of RT, we have combined all patients with clinical stage I and II Hodgkin's disease treated at our institution between 1968 and 1986 for a cumulative analysis.

PATIENTS AND METHODS

Records of all patients with stage I and II Hodgkin's disease treated at the PMH between 1968 and 1986 were reviewed. A total of 878 patients were identified and none were excluded from the overall analysis because of missing data or loss to follow-up. During this time the referral pattern remained relatively stable as judged by the similarity in the distribution of important prognostic factors (Table 1). Clinical staging included a complete history and physical examination, full blood count, liver function tests, chest X-ray and lymphography. Prior to 1978, intravenous pyelogram, inferior venocavogram and liver–spleen scan were performed routinely, whereas after 1978 these were replaced by abdominal computed tomography. Gallium scanning was not used.

125 patients (14.2%) had a staging laparotomy, but there were no consistent criteria for the selection or subsequent management of these patients. The decision to perform laparotomy was often made before referral. For these reasons, this heterogeneous group was not analysed in detail. A further 9 who received palliative treatment as well as 13 patients treated with chemotherapy alone were also excluded, leaving 731 patients available for detailed analysis of prognostic factors and treatment methods.

In the early years of the review (1968–1977), RT consisted mainly of involved field techniques (IF), which for the purpose of this review include only patients who received RT to areas less than those covered by a mantle/inverted Y fields (M) or a mantle. A small number of patients received mantle and additional abdominal RT which was not standardised. In the subsequent period (1978–1986), extended field RT (EF) was used more commonly and was more standardised to cover the spleen and para-aortic lymph nodes. Overall, the most common treatment plan was that of mantle RT alone (39.7%). Involved field RT was used as part of a prospective randomised trial in 1968–1972 and later in selected cases only [22]. In the last 4 years of the review period, the majority of patients were treated with extended field RT (Table 2) [20, 21]. Chemotherapy, when used as a part of a combined modality approach or as salvage treatment, included MOPP or MOPP variants in the majority of patients.

Patients were selected for treatment with combined chemotherapy and radiation (combined modality therapy, CMT) based upon the presence of unfavourable prognostic factors. Between 1970 and 1982 those with a large mediastinal mass, multiple B symptoms, E lesions, an unusual distribution of nodal disease including those with extensive infraclavicular adenopathy, low axillary or pectoral lymph nodes, or a combination of unexplained anaemia and high erythrocyte sedimentation rate (ESR), or very extensive and bulky peripheral disease, received CMT. Based on the results of our previous study, patients over the age of 50 years and those with MC-LD histology, or patients under the age of 50 years but with both MC-LD histology and B symptoms, were also treated with CMT during the period 1982–1986 [21].

Our radiation technique has been described previously [20, 21]. The standard radiation dose delivered to involved areas was 35 Gy in 20 fractions over 4 weeks. The dose to the upper abdomen varied from 20 to 35 Gy in 20 fractions in 4 weeks. Appropriate shielding was used to protect the kidneys and liver.

For the purpose of this analysis no attempt was made to separate relapse from incomplete response to therapy. Failure to achieve a complete response was considered as relapse at the time of the completion of therapy.

Statistical methods

Survival and relapse rates were calculated using the Wilcoxon–Gehan method and were compared using the logrank test of Peto [23, 24]. Multivariate analysis was performed using adjusted logrank method [24].

RESULTS

Overall results

Between 1968 and 1986 a total of 878 newly diagnosed patients with stage I and II Hodgkin's disease were treated at the PMH. The overall actuarial survival for all patients was 85.1% at 5 years, 76.2% at 10 years and 64.4% at 20 years. The overall RFR were 68.8, 64.9 and 63.3%, respectively, and the cause-

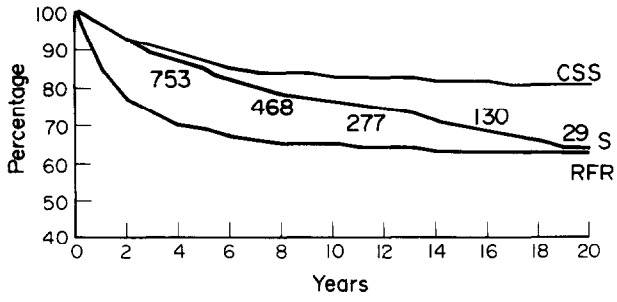

Fig. 1. Overall results in 878 patients with stage I and II Hodgkin's disease. S, Actuarial survival; CSS, cause-specific survival; RFR, relapse-free rate.

specific survival rates were 87.6, 83.3 and 80.9% (Fig. 1). The actuarial 5-year survival improved progressively over the 20-year period, from 77.1% in 1968–1972, to 85.6% in 1973–1982 and 90.8% in 1982–1986 ($P = 0.006$). The overall 5-year RFR also improved from 51.9% in 1968–1972, to 69.4% in 1973–1977, to 71.5% in 1978–1982 and 78.4% in 1983–1986 ($P < 0.0005$).

Results in radically treated CS I and II patients (RT and CMT)

The cohort of patients with clinical stage I and II disease included 731 non-laparotomy staged patients treated with either RT or CMT. Of these, 521 patients were treated with radiation alone and 210 received CMT. All 731 patients were included for the analysis of prognostic factors and for the impact of treatment on outcome.

Significantly more patients were selected for CMT in 1978–1986 (34%) than in 1968–1977 (21.9%) ($P = 0.0006$) (Table 2). Patients treated with CMT had significantly more unfavourable prognostic features: B symptoms ($P < 0.0005$), stage II disease ($P < 0.0005$), high ESR (ESR > 40; $P < 0.0005$), large mediastinal mass ($P < 0.0005$) and E lesions ($P < 0.0005$). They were, however, significantly younger (< 50 years vs. > 50 years; $P = 0.009$) than those treated with RT alone (Table 3).

The prognostic factors analysed included: age (< 50 >), stage and systemic symptoms (IA, IIA, I–IIB), gender, ESR (< 40 >), histology (LP-NS vs. MC-LD), treatment (RT, CMT), extent of RT (IF, M, EF) and time period (1968–1977 vs. 1978–1986). Of these, all factors other than gender were found to be statistically significant in univariate analysis for either survival or relapse. With multivariate analysis using the adjusted logrank method, statistically significant factors for higher risk of relapse were age (> 50), stage (IIB), histology (MC), ESR (> 40), and extent of RT (> IF), while age (> 50), stage (IIB), histology (MC) and extent of RT (> M) were predictive of lower survival (Table 4).

For patients treated between 1978 and 1986, the overall actuarial survival was superior ($P = 0.01$) and the overall RFR was better ($P = 0.0002$) than for those treated between 1968 and 1977. However, when corrected for prognostic factors including age, stage, histology, treatment (RT vs. CMT) and the extent of RT, the time period, i.e. year when treatment was delivered, did not significantly influence outcome (survival $P = 0.65$; RFR $P = 0.37$). The above findings suggest that differences in patient referral pattern, improvements in staging methods and other 'unknown' factors did not exert a significant impact on outcome, and therefore improvement in treatment results can be attributed to the improved selection of patients for radiation alone and the use of extended field RT.

For patients treated with RT alone, the 10-year RFR was significantly lower than for those treated with CMT (RT, 65.8%;

Table 2. The variation in treatment and use of laparotomy in 878 patients with stage I and II Hodgkin's disease over the study period

	1968–1977	1978–1986	*P*-value*
Radiotherapy alone	252	269	0.0001
Involved field	72	42	0.0004
Mantle or inverted Y	129	78	< 0.0005
Extended field	51	149	< 0.0005
Combined modality	71	139	0.0005
Chemotherapy alone	3	10	n.s.
Palliative treatment	5	4	n.s.
Laparotomy	73	52	0.004
Total	404 patients	474 patients	

* Distribution of patients in two time periods by treatment.

Table 3. The distribution of prognostic factors by treatment method in 731 patients treated with RT alone and CMT

		Radiation (No. of patients)	CT + RT (No. of patients)	*P* value*
Age	< 50	408	182	0.0095
	≥ 50	113	28	
Histology	LP/NS	382	151	0.71
	MC/LD	128	52	
Stage	IA	222	19	0.000
	IIA	266	111	
	B	33	70	0.000
E lesion		12	40	0.000
LMM		20	75	0.000
ESR	< 40	332	96	0.000
	X	105	46	
	≥ 40	84	68	0.000

Table 4. Prognostic factor analysis for 731 patients treated with RT alone and CMT—adjusted logrank test

	Actuarial survival		Relapse-free rate	
	Univariate *P*	Adjusted *P*	Univariate *P*	Adjusted *P*
Age	0.0000	0.0000	0.0000	0.06
Gender	0.30	0.57	0.91	0.87
Stage	0.02	0.01	0.30	0.0006
Histology	0.0000	0.02	0.0000	0.0000
ESR	0.11	0.42	0.0001	0.04
Treatment*	0.71	0.54	0.01	0.43
RT extent†	0.0000	0.02	0.0001	0.005
Time‡	0.01	0.65	0.0002	0.37

* RT alone vs. CMT.
† IF vs. M vs. EF.
‡ 1968–1977 vs. 1978–1986.

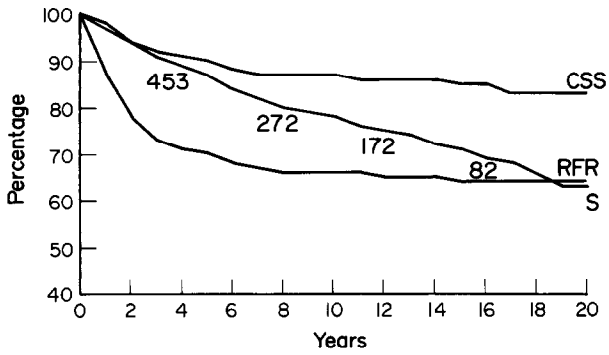

Fig. 2. Treatment results in 521 patients treated with radiation alone. S, Actuarial survival; CSS, cause-specific survival; RFR, relapse-free rate.

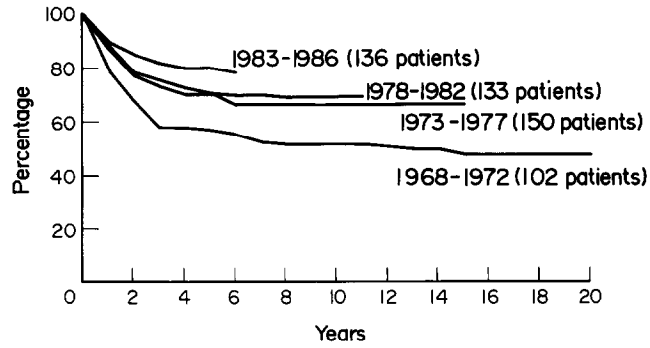

Fig. 3. Relapse-free rates for patients treated with radiation alone in consecutive time periods of the study.

CMT, 75.3%; $P = 0.016$). However, because of the imbalance in prognostic factors between these two groups, this was not significant in multivariate analysis ($P = 0.43$), although CMT was associated with a lower risk of distant relapse ($P = 0.0007$). There was no difference in the overall survival of patients treated with CMT and RT (at 10 years; RT, 77.6%; CMT, 78.2%; $P = 0.98$) even following correction for imbalance in the distribution of prognostic factors.

Results in 521 CS I and II patients treated with RT alone

The overall actuarial survival for 521 patients treated with RT alone was 87.2% at 5 years, 77.6% at 10 years and 63% at 20 years. The cause-specific survival was 89.6, 86.7 and 83.3%, and the RFRs were 70.1, 65.8 and 63.7%, respectively (Fig. 2). Patients' characteristics for this group are shown in Table 5.

The RFRs for patients treated with RT alone improved with time. In the early years of the study when involved field RT was a common treatment approach (1968–1972), the 5-year RFR was 57.3%. During 1973–1977 and 1978–1982 when the majority of patients were treated with mantle RT, the 5-year RFR was 69.7 and 71.0 %, respectively. In the cohort treated between 1983 and 1986, most receiving extended field RT, the 5-year RFR was 79.7% (Fig. 3).

The use of mantle RT rather than involved field RT was associated with a significant improvement in the 10-year RFR (M, 65.5%; IF, 50.5; $P = 0.02$) and in the 10-year actuarial survival (M, 79.9%; IF, 59.4%; $P < 0.0005$) (Fig. 4). There was further improvement in the 10-year RFR with use of extended field RT (EF 75.8%; $P = 0.037$), but this effect was not statistically significant when extended field RT was compared with mantle RT alone in a multivariate analysis, adjusting for other prognostic factors.

Previous analysis of PMH patients treated with RT alone between 1978 and 1986 demonstrated two distinct groups of patients, defined by clinical stage, age and histology, one with favourable and the other with unfavourable outcome (Table 6) [20]. Although only 10% of our patients fell in the unfavourable group, their outcome, when treated with RT alone, was significantly inferior to that for patients in the favourable group (Fig. 5).

Considering that ESR, large mediastinal mass and E lesions have also been associated with a higher local, marginal or distant relapse rate, we attempted to assess the impact of the extent of RT on the risk of relapse and survival in a 'low risk' or 'very favourable' group of patients. We have defined this group as those patients with CS IA and IIA disease, less than 50 years of age, with LP or NS histology, ESR less than 40, no large mediastinal mass, and no E lesion. The overall actuarial survival for this group of 172 patients was 90.6% at 10 years with a RFR of 76.9%. In this 'low risk' group the 10-year actuarial survival was 87.9% for those treated with IF or M, and 97.4% for those treated with EF ($P = 0.46$). The 10-year RFR for patients treated with IF was significantly lower than for those treated with M, and higher, although not significantly so, for those treated with EF (IF, 48.7%; M, 80.0%; $P < 0.0005$. EF, 87.1%; EF vs. M, $P = 0.53$).

A policy of extended field RT resulted in an improved survival in the overall population of CS I and II Hodgkin's disease

Table 5. Characteristics of 521 CS I and II patients treated with RT alone

Pathology		Stage	
LP	82	IA	222
NS	300	IIA	266
MC	121	IB	12
LD	7	IIB	21
Uncl	11		
Radiation		Sedimentation rate	
IF	114	< 40	304
M	207	> 40	112
EF	200	X	105

Age range 17–90.
Median age 31 years.
Female 237 patients.
Male 284 patients.

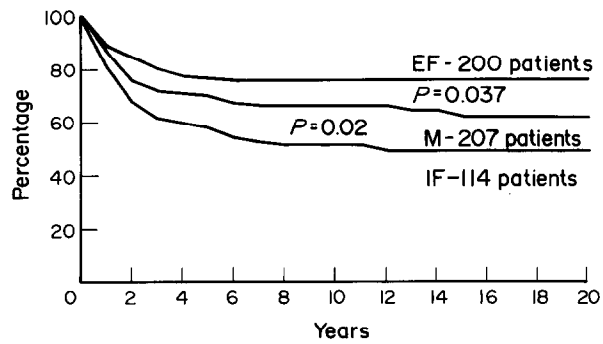

Fig. 4. Relapse-free rates for patients treated with RT alone by extent of RT.

Table 6. Definition of favourable and unfavourable subgroups for treatment with RT alone using age, stage and histology

Age	Histology	Stage IA	Stage IIA	Stage IB + IIB
< 50	LP/NS	F	F	F
	MC/LD	F	F	U
> 50	LP/NS	F	F	U
	MC/LD	U	U	U

F, favourable; U, unfavourable.

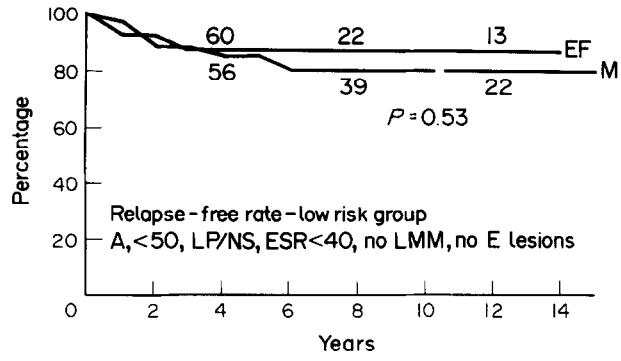

Fig. 6. Influence of extended field RT on the RFR in patients with very favourable prognostic features.

patients, but this effect was much less pronounced and not statistically significant in the very 'low-risk' group.

DISCUSSION

Clinically staged patients with localised Hodgkin's disease have a long-term survival similar to that obtained in laparotomy staged patients [15, 18]. However, the unselected use of RT alone in clinically staged patients is associated with a relapse rate of at least 30–50%. Some of the risk factors predicting relapse in clinically staged patients treated with RT alone, such as large mediastinal mass and B symptoms, are also associated with relapse in laparotomy staged patients treated with RT alone [8, 11, 25–31].

The actuarial survival of patients with stage I and II Hodgkin's disease treated at the PMH improved over the period of this review. This improvement may be attributed to the selective use of CMT in patients with unfavourable prognostic factors, who were deemed to be at a high risk of relapse following treatment with RT alone, and the use of extended field RT, especially in patients other than those with very favourable prognostic factors. Our analysis indicates that the selection of patients for treatment with extended field RT alone, based upon the absence of unfavourable prognostic features, results in an excellent RFR.

We observed that patients less than 50 years old, with favourable histology (LP or NS), without B symptoms or bulky mediastinal disease and a low ESR, had a 10-year RFR of 80% when treated with mantle RT alone. Extended field RT improved the RFR (87% at 10 years) although the effect was not statistically significant ($P = 0.53$) in this very favourable 'low-risk' subgroup, which consisted of one-third of all patients treated with RT alone (Fig. 6). It is important to note that in the group with very favourable prognostic factors, for each patient who benefited from the policy of extended field radiation, approximately 12 patients received no benefit from such treatment, as they would have been cured with mantle RT alone.

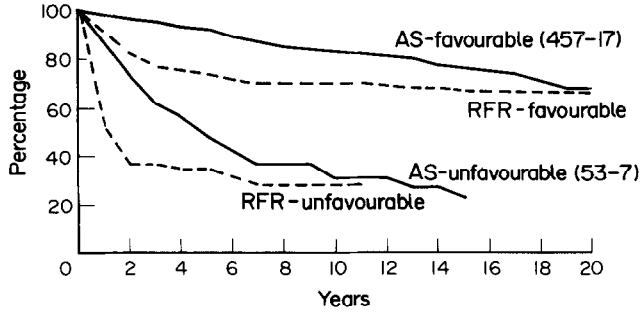

Fig. 5. Actuarial survival (S) and relapse-free rates (RFR) for patients treated with RT alone and defined as favourable or unfavourable based on combination of age stage and histology (Table 6).

We can conclude that the identification of factors predicting survival and relapse (age, stage, histology, ESR, mediastinal mass) allows the selection of patients with clinical stage I and II disease who may either achieve high control rates with RT alone or who may require CMT to achieve high relapse-free and survival rates. In practice, the use of clinically derived prognostic factors predicts both the probability of more extensive disease and the likelihood of the control by radiation of both local and distant disease. The role of laparotomy and splenectomy in defining a favourable group of patients for treatment with RT alone (PS I–II) may be offset by patient selection using multiple clinical prognostic factors and by employing extended field RT techniques. In the most favourably defined subgroup of clinical stages I and II (A, < 50 years, LP + NS, ESR < 40, no large mediastinal bulk and no E lesions), the use of extended field RT conveys no significant advantage over mantle RT alone, thereby implying a clinically selected cohort with a low risk of occult abdominal disease. The adoption of this policy of selection by multiple prognostic factors and the use of extended field RT has resulted in a reduction of the risk of relapse following RT alone for CS I and II Hodgkin's disease by 50%, and the achievement of a similar long-term control rate as for pathologically staged patients treated with RT alone.

It is apparent from studies with long-term follow-up that the risk of death from second malignancies and treatment complications eventually exceeds the risk of dying of Hodgkin's disease [32–34]. Therefore, the current focus of treatment for early stage Hodgkin's disease is an attempt to reduce treatment-related second malignancies and cardiac morbidity without compromising the probability of cure. It is not yet known whether the use of extended field RT significantly affects the serious late complication rate or, indeed, results in a rate of second malignancy higher than treatment with less extensive RT, as may be expected. Similarly, in combined modality treatment, it is not known which combination of agents, amount of chemotherapy, or dose and extent of RT is optimal. Reduction in the amount of CT and RT may be possible without compromising cure, but alternatively it may require the acceptance of a small rate of relapse.

In patients with favourable early stage Hodgkin's disease, extensive long-term follow-up will be required to assess the

impact of new treatment strategies on outcome, given that much of the mortality may result from late treatment effects.

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Acknowledgements—We thank the past and present members of the PMH Lymphoma group, who participated in the diagnosis, management, follow-up as well as the data collection of patients with Hodgkin's disease: Drs R.A. Alison, H.A. Bean, R. Blend, T.C. Brown, R.S. Bush, R.M. Clark, J. Curtis, A.J. Dembo, P.J. Fitzpatrick, R. Hasselback, C.W. Keen, J. Meharchand, A.J. Munro, B.J. Patterson, I.F. Quirt, D. Rideout, J.F.G. Sturgeon, R. Tsang, W.A. Wells, L. Yeoh and Vera M. Peters.