patients who received full doses or nearly full doses of chemotherapy is small (27–51% in different groups), the findings are consistent with the importance of dose intensity or of administration of full doses of chemotherapy.

The other findings of interest relate to postmastectomy radiotherapy. Survival was not at all different in patients with ≥ four nodes who received radiotherapy. There was a suggestion of a radiotherapy effect with fewer locoregional recurrences ($P = 0.067$). This difference is not significant by conventional tests of significance; a study with a larger number of recurrences would be required to detect a true reduction in locoregional recurrence of this magnitude. The expense and toxicity of postmastectomy radiotherapy [7], as well as its modest effect in reducing locoregional recurrence when given in addition to chemotherapy, do not support its routine use. Limiting its use to groups of patients at higher risk of recurrence after mastectomy and chemotherapy than those in this study would seem judicious.

In summary, the results of this prospective study indicate no advantage for 12 as compared with 6 months of adjuvant CMF chemotherapy in women with breast cancer and positive axillary nodes. There is a suggestion of a decrease in locoregional recurrence from postmastectomy regional radiotherapy given before 6 months of CMF chemotherapy, but there was no effect on survival. A study with a larger number of recurrences would be needed to detect a true reduction in locoregional recurrence of the magnitude seen in this one.

1. Vélez-García E, Moore M, Vogel CL, *et al.* Postmastectomy adjuvant chemotherapy with or without radiation therapy in women with operable breast cancer and positive axillary nodes: the Southeastern Cancer Study Group (SECSG) experience. *Breast Cancer Res Treat* 1983, **3**, 49–60.
2. Vélez-García E, Moore M, Vogel C, *et al.* Post-surgical adjuvant chemotherapy with or without radiation therapy in womem with breast cancer and positive axillary nodes: a Southeastern Cancer Study Group (SECSG) experience: In Salmon SE, Jones SE, eds. *Adjuvant Therapy of Cancer* IV. Orlando, Grune and Stratton, 1984, 273–282.
2. Vélez-García E, Carpenter JT, Moore M, *et al.* Postsurgical adjuvant chemotherapy with or without radiotherapy in women with breast cancer and positive axillary nodes: progress report of a Southeastern Cancer Study Group (SEG) trial. In Salmon SE, ed. *Adjuvant Therapy of Cancer* V. Orlando, Grune and Stratton, 1987, 347–355.
4. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J Royal Stat Soc, Series* A 1972, **135**, 185–207.
5. Cox DR. *Analysis of Binary Data*. London, Methuen, 1970, 58–71.
6. Henderson IC. *Adjuvant Systemic Therapy of Early Breast Cancer in Breast Diseases*, Harris JR, Hellman S, Henderson IC, Kinne DW, eds. Philadelphia, JB Lippincott Co, 1991, 448–450.
7. Fisher B, Rockett H, Fisher ER, Wickerham DL, Redmond C, Brown A. Leukemia in breast cancer patients following adjuvant chemotherapy or postoperative radiation: the NSABP experience. *J Clin Oncol* 1985 **4**, 1640–1658.

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Vincristine is Associated with the Risk of Azoospermia in Adult Male Survivors of Childhood Malignancies

Jukka Rautonen, Aarne I. Koskimies and Martti A. Siimes

Of 55 males, currently above 18 years of age, diagnosed with and treated for different malignancies in childhood between 1960 and 1985 at a single institution, 28 (51%) were azoospermic. The age of the patient, testicular irradiation, four different therapeutic agents (L-asparaginase, cyclophosphamide, doxorubicin, vincristine) and one combination (MOPP, nitrogen mustard, vincristine, procarbazine, prednisone) were each associated with the risk of azoospermia. However, in multivariate analysis vincristine had the statistically most significant independent effect on the risk of azoospermia, the risk being 5-fold (95% confidence limits 1.3–18.8, $P = 0.02$) that in patients who had not received vincristine. The risk of azoospermia in patients who had received cyclophosphamide was 3.4-fold (0.95–12.3, $P = 0.06$) and in those who had received testicular irradiation it was 8.2-fold (0.75–90.9, $P = 0.09$) that of others. Normospermia (22% of patients) was not incompatible with any of the more commonly used modes of therapy. We conclude that vincristine may have a previously unrecognised important role in causing azoospermia, possibly irreversible, when administered in childhood or adolescence.
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INTRODUCTION

TESTICULAR IRRADIATION and various chemotherapeutic agents used in the treatment of malignant diseases are known to cause temporary or even permanent disturbances in spermatogenesis [1–12]. However, most studies have included only patients who received treatment as adults, and very little is known about fertility in adult male survivors of malignancies of childhood [13–17]. Since the toxic effect of any agent or treatment modality may be different on a prepubertal or pubertal as opposed to a mature testis, it is crucial to assess the toxic effects of individual agents in the pediatric population as well. Unfortunately the simultaneous use of many drugs makes this task difficult. We have attempted to overcome this difficulty by using statistical multivariate methods, not used in previous studies, to identify

the factors having an independent effect on semen quality and quantity in 55 adult male survivors of malignancies of childhood.

PATIENTS AND METHODS

Patients and treatment

Our series comprised all 55 males who had been diagnosed and treated for different malignant diseases at the Children's Hospital, University of Helsinki, from 1960 to 1985, and who agreed to semen analysis. The study protocol was approved by the ethical committee of the Children's Hospital. The median age of the patients at initial diagnosis had been 10 years with a range from 1 day to 15 years, and at the time of study it was 20 (18–43) years. Median length of follow-up was 11 (2.5–30) years; 85% of the patients had been followed up for at least 5 years and the majority (60%) had been followed for more than 10 years. The diagnoses included leukaemia (n = 11), lymphoma (n = 12), Wilms' tumour (n = 9), neuroblastoma (n = 7), different sarcomas (n = 13), and others (n = 3; papillary thyroid carcinoma, spinal glioma, and malignant blue naevus). The treatment in each case had consisted of different combinations of surgery, irradiation therapy, and various cytostatic agents. Of the 7 patients who had received testicular irradiation, 6 had received bilateral irradiation, 1 having received 21 Gy and 5 received 24 Gy, and 1 patient had undergone a unilateral orchiectomy and irradiation (24 Gy) of the remaining testis. Of the 12 patients with central nervous system irradiation, 11 had received cranial irradiation (24 Gy) and 1 patient with spinal glioma had received craniospinal irradiation (40 Gy). 17 patients had received subdiaphragmatic irradiation therapy (9 with Wilms' tumour, 3 with lymphoma, 2 with neuroblastoma, and 3 with different sarcomas).

Semen analysis

One semen specimen was collected from each patient by masturbation, either at the clinic or at home immediately before the clinic appointment, after an abstinence period of at least 3 days. The parameters determined included ejaculate volume, sperm density, total sperm count, percentage of mobile sperm, grade of motility, lifetime, agglutination, percentage of sperm with morphologically abnormal heads, midpieces, and tails, and total percentage of abnormal sperm [18]. Normospermia was defined as: (1) ejaculate volume $\geq$ 2.0 ml; (2) sperm concentration $\geq 20 \times 10^6$/ml; (3) sperm motility $\geq$ 50%; (4) life span $\geq$ 48 h; and (5) structural anomalies in $<$ 50% of sperm cells. All five requirements had to be fulfilled; thus, patients with, e.g. slightly decreased sperm count and those with normal counts but decreased ejaculate volume were not considered normospermic. Azoospermia was defined as the total absence of sperm cells.

Statistical methods

The differences in the incidence of azoospermia between various groups were analysed with the likelihood ratio χ^2 test and the differences in sperm count or concentration or in ejaculate volume with analysis of variance (ANOVA). Linear correlation coefficients were calculated to study the association between sperm count and age or duration of follow-up. Multiple linear regression analysis was performed to identify the factors independently associated with ejaculate volume, sperm count and sperm concentration; a logarithmic transformation of the latter two was used. Logistic regression analysis was used to identify the factors associated with azoospermia. All multivariate analyses were done in a forward-stepping manner, all variables being available for inclusion in the model. After the model was completed, we tested whether the inclusion of interaction terms, e.g. age and vincristine receipt, would further improve the model. Since the association between age at diagnosis and the risk of testicular damage was not linear, age was not regarded as a continuous variable in the regression analyses. Instead, a following classification was used: 0–1 year (n = 11), 2–5 years (n = 10), 6–10 years (n = 12), 11–13 years (n = 14), and 14–16 years (n = 8).

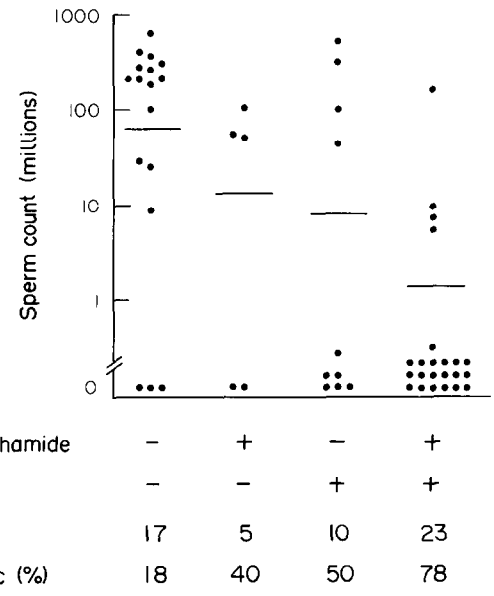

Fig. 1. The effect of cyclophosphamide and vincristine therapy on sperm count in adult males cured of cancer in childhood. The horizontal bars denote the mean value in each group.

RESULTS

Of the 55 patients, 28 (51%) were azoospermic. Total sperm cell counts in the remaining 27 patients ranged from 10000 to 650×10^6. The correlations between sperm count and the duration of follow-up (r = 0.14, P = 0.3) or age at diagnosis (r = −0.14, P = 0.3) were not statistically significant.

In multivariate analysis only the use of vincristine ($P < 0.01$) and cyclophosphamide (P = 0.01) were shown to be independently associated with sperm count; the effects of these agents seemed to be additive (Fig. 1). Neither their mutual interaction nor their interaction with age at diagnosis were statistically significant. There was an inverse relationship between vincristine dose (in mg/m^2) and sperm count (r = −0.42, P = 0.002). Of the 7 patients who had received testicular irradiation, 6 were azoospermic, and all of these had received vincristine (n = 2) or cyclophosphamide (n = 1) or both (n = 3); the 1 patient who had received only testicular irradiation was normospermic.

Sperm concentrations in the 27 patients who were not azoospermic ranged from 10000 to 425×10^6/ml (median 67×10^6/ml). In multivariate analysis, vincristine was the only agent independently associated with sperm concentration. The mean concentration in all patients who had received vincristine

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Table 1. Diagnosis, age at diagnosis, and risk of azoospermia in males cured of cancer in childhood.

		Azoospermic	
	n	(%)	*P*
All patients	55	51	
Diagnosis			0.10
Leukaemia	11	64	
Lymphoma	12	58	
Wilms' tumour	9	22	
Neuroblastoma	7	57	
Sarcoma	13	62	
Other	3	0	
Age at diagnosis (years)			0.05
0–1	11	55	
2–5	10	20	
6–10	12	58	
11–13	14	43	
14–16	8	88	

was 12.5 × 10^6/ml as compared with 76.8 × 10^6/ml in the others ($P < 0.001$).

Patients cured of leukaemia tended to be azoospermic more often than the others (Table 1), although this difference was not statistically significant. Age at diagnosis also had an effect on subsequent fertility (Table 1). Further, many individual therapeutic agents were associated with azoospermia (Table 2). The risk of azoospermia was 100% in the few patients whose therapy had included MOPP (nitrogen mustard, vincristine, prednisone, and procarbazine) or cisplatin. However, vincristine was identified by multivariate analysis as having the statistically

Table 2. The association between different therapeutic agents and risk of azoospermia in males cured of cancer in childhood

	Present		Absent		
		Azoospermic		Azoospermic	
Risk factor	*n*	(%)	*n*	(%)	*P*
Irradiation					
Abdominal	17	47	38	53	0.70
Cranial	12	59	43	49	0.56
Mediastinal	7	71	48	48	0.24
Testicular	7	86	48	46	0.04
Actinomycin D	16	44	39	54	0.50
Cytarabine	5	80	50	48	0.16
L-Asparaginase	7	86	48	46	0.04
Bleomycin	1	100	54	50	0.24
Cisplatin	2	100	53	49	0.10
Cyclophosphamide	28	71	27	30	0.002
Doxorubicin	18	72	37	41	0.03
6-Mercaptopurine	14	50	41	51	0.95
Methotrexate					
High-dose	10	60	45	49	0.52
Per oral	12	50	43	51	0.94
MOPP*	3	100	52	48	0.04
Vincristine	33	70	22	23	<0.001

*MOPP = Nitrogen mustard, vincristine, procarbazine and prednisone.

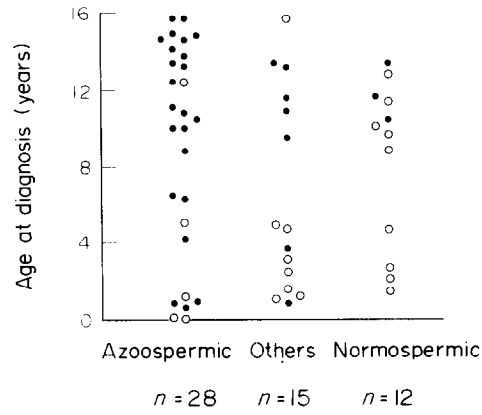

Fig. 2. The association between age at diagnosis, vincristine therapy, and fertility in males cured of cancer in childhood. Patients who had received vincristine are marked with black circles and those who had not with white circles. Azoo = azoospermic, Other = oligozoo-, asthenozoo-, or hypospermia, Normo = normospermic.

most significant independent effect on the risk of azoospermia, the risk being 5-fold (95% confidence limits 1.3–18.8, $P = 0.02$) that of other patients. The risk of azoospermia in patients having received cyclophosphamide was 3.4-fold (0.95–12.3, $P = 0.06$) and in those having received testicular irradiation 8.2-fold (0.75–90.9, $P = 0.09$) that of others. Neither age at diagnosis nor the interactions between age and the receipt of vincristine, cyclophosphamide, or testicular irradiation, had an independent effect on the risk of azoospermia. It may be seen in Fig. 2 that in each age group there was an association between vincristine and risk of azoospermia.

The median volume of ejaculate in the patients was 2.0 ml with a range from 0.25 to 5 ml. In 18 patients (33%) the volume was abnormally low. Two factors, abdominal irradiation and cyclophosphamide therapy, were identified as having an independent effect on the ejaculate volume (Fig. 3). Abdominal

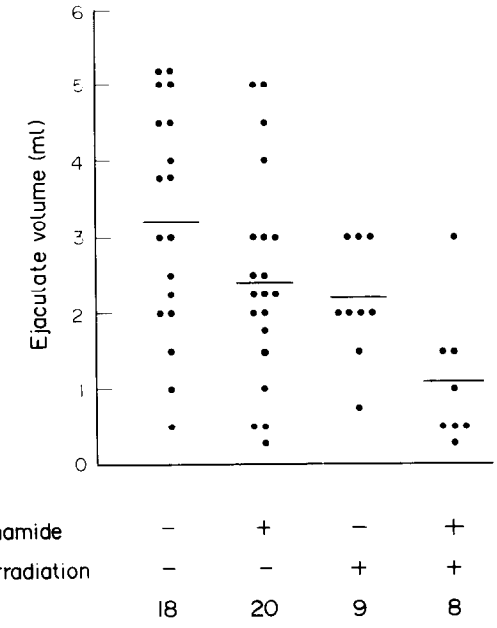

Fig. 3. The effect of cyclophosphamide and abdominal irradiation on ejaculate volume in adult males cured of cancer in childhood. The horizontal bars denote the mean value in each group.

irradiation decreased the volume by an average of 1.2 ml (95% confidence limits 0.4–1.9 ml, $P = 0.002$) and cyclophosphamide by an average of 0.9 ml (0.2–1.5 ml, $P = 0.01$). Testicular irradiation, other cytostatic agents, and abdominal or retroperitoneal surgery had no significant effect on the volume after these two factors were taken into account. There was no correlation between ejaculate volume and sperm concentration ($r = 0.06$, $P = 0.7$).

Of the 27 patients who were not azoospermic, none had more than 50% structurally abnormal sperm cells (median 25%, range 10–49%). In 4 patients sperm motility was abnormally low, and in 5 patients the life span of sperm cells was diminished to less than 48 h. No risk factors were associated with these abnormalities. Only 12 patients (22%) were normospermic. Normospermia was not incompatible with any of the more commonly used modes of therapy. Of the 3 patients treated with surgery only, 2 were normospermic and 1 was azoospermic.

DISCUSSION

Our results show that half of the male survivors of malignancies of childhood are azoospermic. Since at the time of the study therapy had been discontinued in most patients for at least 5 years, it is reasonable to assume that the azoospermia is permanent. In addition to the azoospermic patients, almost one third had abnormal findings in semen analysis, leaving only 22% of the males normospermic.

The most interesting result of our study is undoubtedly the significant risk of azoospermia associated with use of vincristine. To our knowledge, this association has not been previously reported. In experimental studies in mice vincristine does not seem to be very spermatotoxic [19]; however, the extrapolation of results derived from animal studies for use in humans is not straightforward as illustrated by doxorubicin, a drug found to be very spermatotoxic in mice [19] but much less so in humans [20]. It should be noted that vincristine is also included in MOPP, widely known to be very spermatotoxic [7–9]; the effect of vincristine may have gone unnoticed, being masked by the effects of nitrogen mustard and procarbazine [11, 21].

The association between age at diagnosis and risk of subsequent azoospermia, although not statistically significant, is interesting. It could be speculated that the prepubertal testis is less vulnerable to spermatotoxicity than the pubertal testis; however, at least with the use of cyclophosphamide this does not appear to be true [10]. Further, the absence of an independent association between age at diagnosis and risk of azoospermia in the present study does not support the speculation. It should be recognised that our series, even if larger than those previously reported, is still too small to allow for definite conclusions, and the results obtained must be treated cautiously. It is possible, therefore, that the boys treated during puberty incur a higher risk of azoospermia than those treated before the onset of puberty. The situation is perhaps reversed in the lower end of the age spectrum, as indicated by Fig. 2, boys aged < 1 year being at greater risk of azoospermia regardless of the therapy used.

Sperm production in adult male survivors of malignancies of childhood has recently been analysed in two studies. In the first one [15] data on vincristine were not presented. In the second one [16] the authors stated that vincristine did not appear to affect spermatogenesis; however, of the 15 patients in their series who had received vincristine and on whom semen analysis was done, all but 1 were azoospermic. The latter study illustrates the difficulties in assessing the individual toxic effect of a single drug often used in combination with other drugs.

In our series, 1 patient was azoospermic despite treatment which consisted only of surgery, whereas another was normospermic in spite of having received large doses of vincristine (52.5 mg/m^2) and cyclophosphamide (27 000 mg/m^2), and cranial irradiation (2400 cGy). Further, the only patient who had received testicular irradiation (2400 cGy) without vincristine and cyclophosphamide was normospermic. These findings emphasise the marked individual differences in susceptibility to the spermatotoxic effects of different agents.

One third of the patients demonstrated low volume on their semen analysis. This finding could have been the result of retrograde ejaculation, ejaculatory tract obstruction, damage to the autonomic innervation required for normal ejaculation, or incomplete specimen collection. The association between ejaculate volume and abdominal irradiation and cyclophosphamide indicates that the low volume can not be attributed solely to problems in specimen collection. At the time of the study, serum testosterone levels were normal in all patients (data not shown) making testosterone deficiency an unlikely cause of decreased ejaculate volume. It is interesting that abdominal or retroperitoneal surgery was not associated with alterations in ejaculate volume. The mechanisms underlying these associations remain unknown. Regardless of the mechanism, however, very low ejaculate volume may contribute to impaired fertility.

We conclude that vincristine may have a previously unrecognised role in causing azoospermia, possibly irreversible, when administered in childhood or adolescence. However, the existence of marked individual differences in susceptibility to the spermatotoxic effects of chemotherapeutic agents or testicular irradiation should be emphasised.

1. Sandeman TF. The effects of *X*-irradiation on male human fertility. *Br J Radiol* 1966, **39**, 901–907.
2. Lu CC, Meistrich ML, Thames HD. Survival of mouse testicular stem cells after gamma or neutron irradiation. *Radiat Res* 1980, **81**, 402–415.
3. Richter P, Calamera JC, Morgenfeld MC, Kierszenbaum AL, Lavieri JC, Mancini RE. Effect of chlorambucil on spermatogenesis in human with malignant lymphoma. *Cancer* 1970, **25**, 1026–1030.
4. Bajorunas DR. Disorders of endocrine function following cancer therapies. *Clin Endocrinol Metab* 1980, **9**, 405–430.
5. Thachil JV, Jewett MAS, Rider WD. The effects of cancer and cancer therapy on male fertility. *J Urol* 1981, **126**, 141–145.
6. Shamberger RC, Sherins RJ, Rosenberg SA. The effects of postoperative adjuvant chemotherapy and radiotherapy on testicular function in men undergoing treatment for soft tissue sarcoma. *Cancer* 1981, **47**, 2368–2374.
7. Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Boardwell CG. The effect of Hodgkin's disease and combination chemotherapy on gonadal function in the adult male. *Cancer* 1982, **49**, 418–422.
8. Waxman JHX, Terry YA, Wrigley PFM, *et al.* Gonadal function in Hodgkin's disease: long-term follow-up of chemotherapy. *Br Med J* 1982, **285**, 1612–1613.
9. da Cunha MF, Meistrich ML, Fuller LM, *et al.* Recovery of spermatogenesis after treatment of Hodgkin's disease: Limiting dose of MOPP chemotherapy. *J Clin Oncol* 1984, **2**, 571–577.
10. Watson AR, Rance CP, Bain J. Long term effects of cyclophosphamide on testicular function. *Br Med J* 1985, **291**, 1457–1460.
11. Horstman MG, Meadows GG, Yost GS. Separate mechanism for procarbazine spermatotoxicity and anti-cancer activity. *Cancer Res* 1987, **47**, 122–131.
12. Meistrich ML, Chawla SP, da Cunha MF, *et al.* Recovery of sperm production after chemotherapy for osteosarcoma. *Cancer* 1989, **63**, 2115–2123.
13. Whitehead E, Shalet SM, Morris Jones PH, Beardwell CG, Deakin

DP. Gonadal function after combination chemotherapy for Hodgkin's disease in childhood. *Arch Dis Child* 1982, **57**, 287–291.
14. Matus-Ridley M, Nicosia SV, Meadows AT. Gonadal effects of cancer therapy in boys. *Cancer* 1985, **55**, 2353–2363.
15. Jaffe N, Sullivan MP, Ried H, *et al.* Male reproductive function in long-term survivors of childhood cancer. *Med Pediatr Oncol* 1988, **16**, 241–247.
16. Aubier F, Flamant F, Brauner R, Caillaud JM, Chaussain JM, Lemerle J. Male gonadal function after chemotherapy for solid tumors in childhood. *J Clin Oncol* 1989, **7**, 304–309.
17. Siimes MA, Rautonen J. Small testicles with impaired production of sperm in adult male survivors of childhood malignancies. *Cancer* 1990, **65**, 1303–1306.
18. World Health Organization. *WHO Laboratory Manual for the Examination of Human Semen and Semen–cervical Mucus Interaction.* Cambridge, Cambridge University Press, 1987.
19. Lu CC, Meistrich ML. Cytotoxic effects of chemotherapeutic drugs on mouse testis cells. *Cancer Res* 1979, **39**, 3575–3582.
20. da Cunha MF, Meistrich ML, Ried HL, Gordon LA, Watchmaker G, Wyrobek AJ. Active sperm production after cancer chemotherapy with doxorubicin. *J Urol* 1983, **130**, 927–930.
21. Meistrich ML, Finch M, da Cunha MF, Hacker U, Au WW. Damaging effects of fourteen chemotherapeutic drugs on mouse tesis cells. *Cancer Res* 1982, **42**, 122–131.

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

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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.
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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].

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