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Ten-year Nodular Sclerosis Hodgkin's Disease and Second Malignancies

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Abstract—*Hodgkin's disease is one of the most curable cancers thanks to progress in radiotherapy and multi-drug chemotherapy regimens such as mechloretamine–vincristine–procarbazine–prednisone, best known as MOPP. However, long-term side-effects and treatment-induced second malignancies are of great concern. In our institution, 69 patients with nodular sclerosis Hodgkin's disease were treated over 10 years. Twenty-two per cent were stage I, 49% stage II, 23% stage III and 6% stage IV. Actuarial 10-year survival was 83% and actuarial relapse-free survival 61%. Six patients developed a second malignancy with a 10-year actuarial risk of 18%. All six cases occurred in the group treated with MOPP and extensive radiotherapy. Acute non-lymphoblastic leukemia occurred in three patients, preleukemia in two and non Hodgkin's lymphoma in one. In all of these patients, the results were quite poor. Overall survival was equally affected by Hodgkin's disease and by second malignancies. Since new multiple-drug chemotherapy regimens such as adriamycin–bleomycin–vinblastine–dacarbazine, known as ABVD, are equally effective and seem less likely to induce second hematologic malignancies, we suggest that MOPP should no longer be used as a first choice for the treatment of Hodgkin's disease, especially when in combination with radiation therapy.*

INTRODUCTION

HODGKIN'S DISEASE was described for the first time in 1832. At present, its etiology is still controversial. Improvement in diagnostic and staging procedures and progress in radiotherapy and chemotherapy have made it one of the most curable cancers. In addition to major improvements in the field of radiation oncology, the introduction of the multiple-drug chemotherapy regimens such as mechloretamine–vincristine–procarbazine–prednisone (MOPP) or adriamycin–bleomycin–vinblastine–dacarbazine (ABVD) has played the most important role in its curability, either in initially advanced stages or for relapses after radiotherapy [1–3]. In most large series, the overall survival is superior to 60% at 10 years allowing long term follow-up periods [4].

The occurence of second malignant tumors after cure for Hodgkin's disease with modern radiotherapy and chemotherapy was described first in 1972 [5]. Outcome was soon recognized to be almost invariably fatal. The carcinogenicity of alkylating agents [6] and procarbazine [7] is now well demonstrated. Furthermore, combined modality treatment with both radiotherapy and chemotherapy is also considered to favor the occurence of second acute non-lymphoblastic leukemia (ANLL), non-Hodgkin's lymphoma (NHL) and solid tumors (ST) [8–10].

We present here our 10-year experience in treating patients with nodular sclerosis Hodgkin's disease (NSHD), either with radiotherapy only or with combined modality, and report the occurence of second malignancies.

PATIENTS AND METHODS

Seventy-two previously untreated patients who were referred to the Division of Radiotherapy, Geneva University Hospital between January 1975 and December 1985 were retrospectively studied. All had NSHD which represented more than half patients with HD seen at our institution during the period considered. Other histologic subtypes were not included in order to study an homogeneous group behaving in the same pattern for relapses and therefore overall management. Three patients were excluded from this study because of advanced age which did not allow the performance of sufficient investigations and appropriate treatment. Sixty-nine patients were staged according to the Ann Arbor classification, either clinically (cs) or pathologically (ps) when a laparotomy–splenectomy was

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performed. Thirty-eight patients were entered during the first 6 years of the study and 29 during the last 5. Median rate of entry was seven patients *per annum* with a maximum of 10 patients in 1982 and a minimum of three in 1985. The following prognostic factors were identified: B symptoms (B), erythrocyte sedimentation rate (ESR) and the number of involved sites at presentation (IS). All patients received radiotherapy ($n = 69$) and in some ($n = 39$) this was combined with chemotherapy either at presentation ($n = 19$) or at relapse ($n = 11$) or at both ($n = 9$). Radiotherapy consisted in the mantle field followed by para-aortic or inverted Y fields. Doses varied from 35 to 40 Gy in 20–22 fractions with or without boost to involved areas. Patients eligible for the combined modality at presentation were mainly selected according to prognostic factors. They were those with bulky disease (5 cm) and stage I ($n = 2$), cs IIA ($n = 1$), cs IIB ($n = 3$), cs and ps IIIA ($n = 9$) and all stages IIIB ($n = 5$) and IV ($n = 4$). Three other patients with bulky ps IIA and one with non-bulky ps IIB were also treated with the combined modality. There was no formal policy as patients were most of the time under their private physicians's care. Initially, chemotherapy consisted of the MOPP regimen, however some patients were later given the ABVD regimen ($n = 7$) and some others also received several single agents like cyclophosphamide, etoposide, lomustine and others. Follow-up data were collected through personal letters or phone calls to the private physician. Six patients were lost to follow-up. Survival curves, relapse rate and second tumour occurence were computed by actuarial life table analysis [11]. Small numbers in each subgroup did not permit adequate statistical analysis in order to compare differences between curves. Detailed information regarding patients treated between 1975 and 1980 can be found in: Zulian GB, La Maladie de Hodgkin, Thèse No. 6046, Université de Genève, Suisse, 1985.

RESULTS

Mean age at presentation was 30 ± 1.5 years, 29.2 ± 2.3 years for males and 30.8 ± 2.3 for females. Average follow-up time was 5.3 ± 0.4 years. The majority of patients presented with stage II (49%) followed by stage III (23%), stage I (22%) and stage IV (6%). B symptoms were present in 28% of patients with some difference between stage I (13%), stage II (27%), stage III (44%) and stage IV (25%). ESR was 39.3 ± 3 mm at presentation with some difference according to stage, i.e. 26 ± 6 mm for stage I, 37 ± 4 mm for stage II, 53 ± 9 mm for stage III and 64 ± 7 mm for stage IV. The mean number of sites involved was three for all patients, two or less for stage I, three for stage II, five for stage III and three for stage IV (Table 1).

Table 1. Prognostic factors and stage at presentation

Stage	B symptoms	ESR (mm)	Involved sites	Number (%)
I	13%	26 ± 6	<2	15 (22%)
II	27%	36 ± 4	3	34 (49%)
III	44%	52 ± 9	5	16 (23%)
IV	25%	64 ± 7	3	4 (6%)
All	28%	39 ± 3	3	69 (100%)

Actuarial 10-year survival was 83% (72–94%, 95% confidence limit, Fig. 1): 91% for stage I, 94% for stage II, 54% for stage III and 67% for stage IV (Fig. 2). The presence of B symptoms decreases the survival to 70% only for those patients who presented them whereas survival was 88% for those who did not (Table 3). An ESR superior to 40 mm at presentation was associated with a decrease in survival to 69% whereas it was 95% for those who presented with an ESR of 39 mm or less (Table 3). When more than three sites were involved the 10-year survival rate dropped to 75% (Table 3). Statistical comparison was not done. Relapse-free survival at 10 years was 61% (47–74%, 95% confidence limit, Fig. 1). Relapse occurred 31.5 ± 3 months after initial diagnosis and relapsing patients had a raised ESR to 49 ± 7 mm at presentation, 70% had more than three sites involved and 38% had B symptoms. For the 69 patients in this study, the actuarial risk of developing a second malignancy was 18% at 10 years and occurred 57 ± 11 months after initial diagnosis of NSHD (4–32%, 95% confidence limit, Fig. 3).

In a subgroup of 39 patients who received radiotherapy combined with multiple chemotherapy either at presentation or at relapse this risk was 35% (9–61%, 95% confidence limit). Patients who suffered from a second malignancy had an ESR raised to 56 ± 14 mm at presentation, 67% had more than four involved sites and 67% had B symptoms. No second malignancy has been observed so far in the group initially treated with radiotherapy only and who never received subsequent chemotherapy ($n = 30$, Fig. 4). In the combined modality group, six patients out of 39 presented a second malignancy: three ANLL, two preleukemias and one NHL (Table 2). Two of these second malignancies occurred in patients initially treated with combined modality and who never relapsed ($n = 18$). The four others ocurred in patients who relapsed from previous complete remission but three of them were also initially treated with combined modality ($n = 21$). For these patients, outcome has been quite poor: four have already died after 3, 4, 5 and 7 months respectively and two are currently under treatment without any apparent response.

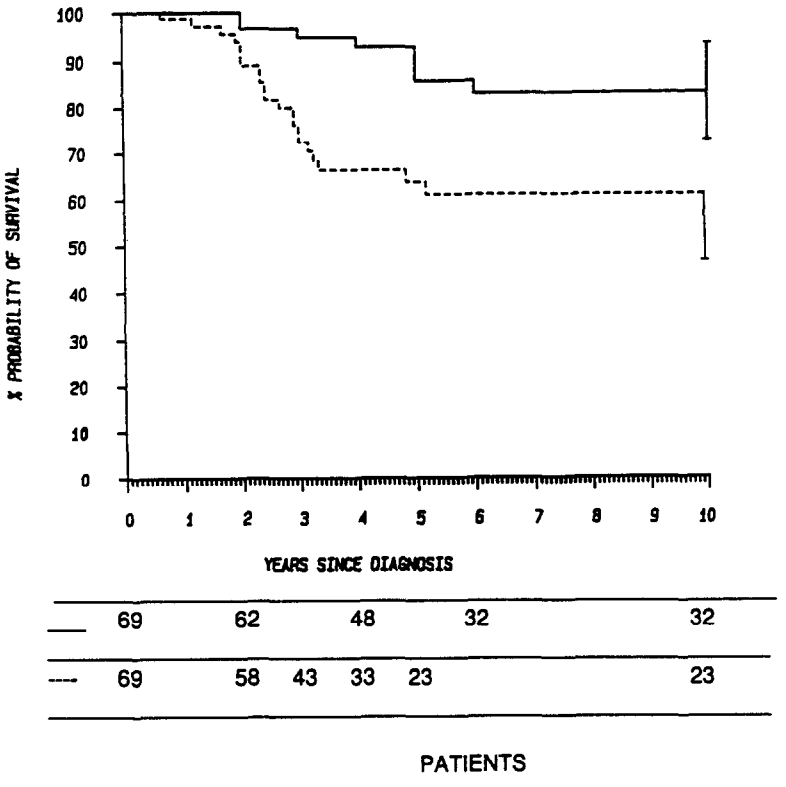

Fig. 1. Probability of survival (——) and of relapse-free survival (-----) of 69 patients who presented with NSHD over a 10-year period from initial diagnosis.

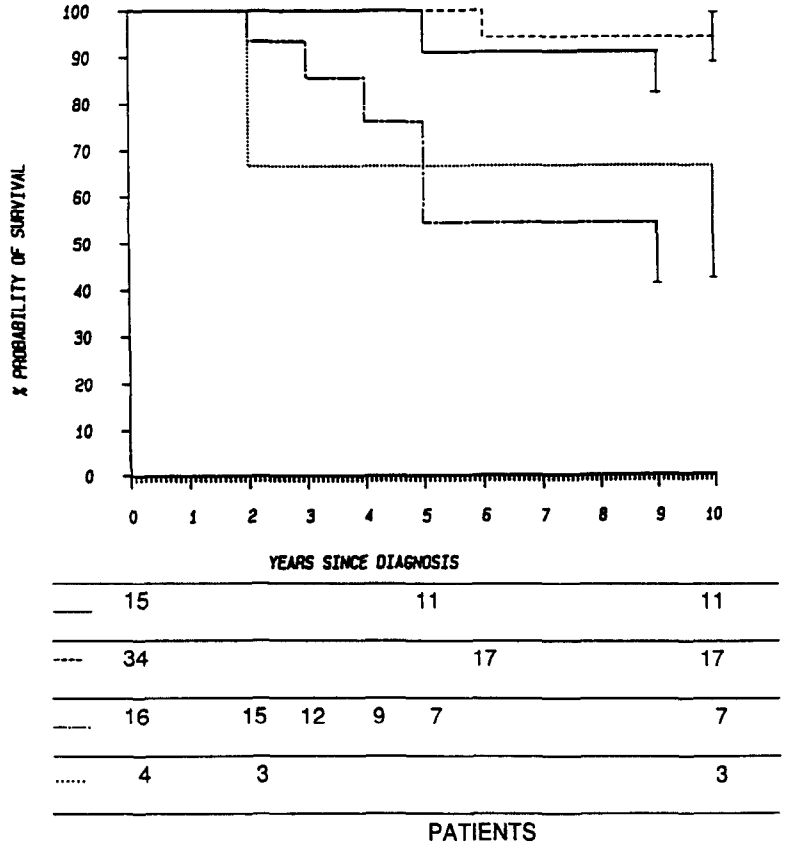

Fig. 2. Probability of survival of 15 patients with stage I (——), 34 with stage II (-----), 16 with stage III (- - - -) and four with stage IV NSHD (·····).

Table 2. Second malignancies after nodular sclerosis Hodgkin's disease

Sex, age ESR, IS stage	Initial treatment	Months until relapse	Relapse treatment	Month until second malignancy	Status at follow-up
m,30 40,4 psIIB	MOPP × 6 M 39.6 Gy Y 39.6 Gy i 12.0 Gy	38	MOPP/ABVD × 8 CCNU-VP 16 × 6 liver 20 Gy	86 NHL	Alive
m,27 40,2 psIIB	M 39.6 Gy P 39.6 Gy	24	MOPP × 8	88 ANLL	Alive
f, 17 112,8 psIIIA	MOPP × 3 M 39.6 Gy Y 9.0 Gy	35	MOPP × 2 ABVD × 5 PEC × 1	62 PL	Dead
m,43 43,2 psIIIA	M 39.6 Gy Y 39.6 Gy i 17.5 Gy MOPP × 7			22 ANLL	Dead
m,20 45,9 psIIIB	MOPP × 3 P 40.0 Gy M 39.6 Gy a 8.0 Gy BCDE × 5	14	ABM–VBL–VP16 CLB–CCNU–PM–ifosfamide–Pl iliac 40 Gy	48 ANNL	Dead
f,14 ?,5 psIIIB	MOPP × 3 COPP × 3 M 39.6 Gy Y 25.0 Gy i 3.0 Gy			36 PL	Dead

M = mantle radiotherapy; P = paraaortic radiotherapy; Y = inverted radiotherapy; i = inguinal boost; a = axillary boost; ABVD = Adriamycin® (ADM)–bleomycin–vinblastine (VBL)–dacarbazine; BCDE = bleomycin–CCNU–dacarbazine–etoposide (VP16); COPP = chlorambucil (CLB)–vincristine–procarbazine–prednisone; MOPP = mechloretamine–vincristine–procarbazine–prednisone; PEC = prednimustine (PM)–etoposide–CCNU; Pl = cisplatin; ANLL = acute non-lymphoblastic leukemia; NHL = non-Hodgkin's lymphoma; PL = preleukemia; m = male; f = female.

Table 3. Ten-year actuarial survival according to prognostic factors

B symptoms	present	(n = 19) 70%	($P < 0.01$)
	absent	(n = 50) 88%	
ESR	>40 mm	(n = 28) 69%	($P < 0.05$)
	<39 mm	(n = 30) 95%	
Involved sites	>3	(n = 36) 75%	($P > 0.01$)
	<3	(n = 32) 91%	

DISCUSSION

The data presented here derive from a single institution in managing and treating NSHD over a 10 year period. In accordance with the literature, our patients were mainly composed of young adults, however the usual male preponderance was not found. Our observed male to female ratio of 1:1.3 could simply reflect a non-specific difference due to the histologic subtype considered here.

Almost 75% of our patients presented with early stages I and II and less than 30% with B symptoms. This could perhaps be related to the slower growth pattern of NSHD compared to other histologic subtypes. As expected, a raised ESR (>40 mm), B symptoms and the number of involved sites (>3) correlated with NSHD extension as they did with relapse rate and survival.

Our overall 83% actuarial 10-year survival rate is relatively similar to the 71% in the large NSHD's Stanford's series [4].

The survival rate of stage I was affected by a single case of early abdominal relapse that could represent undetected microscopic disease at staging laparotomy.

Survival of stage II was affected by a relatively high relapse rate of 28%, in spite of a complete response rate of 70% to salvage chemotherapy after radiotherapy failures. Nevertheless, the survival of this group is likely to be worsened soon by the occurence of two observed cases of second malignancies that are currently under treatment but not responding to appropriate chemotherapy (Table 2).

Finally, stage III survival is undoubtedly influenced by late complications of the therapy. Five out of 15 patients have already died, three of them from

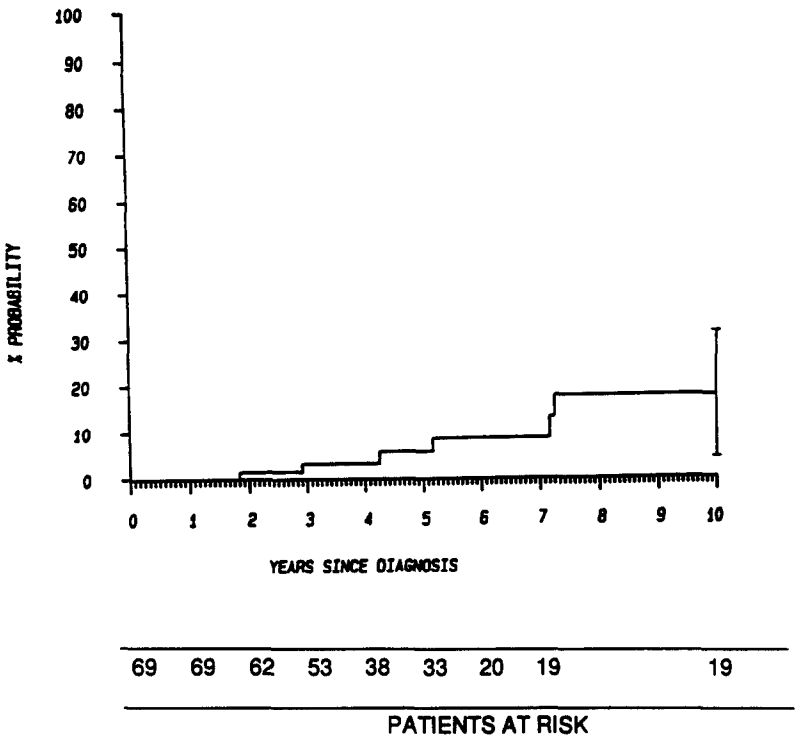

Fig. 3. Probability of a second malignancy for 69 patients who presented with NSHD over a 10-year period from diagnosis of NSHD.

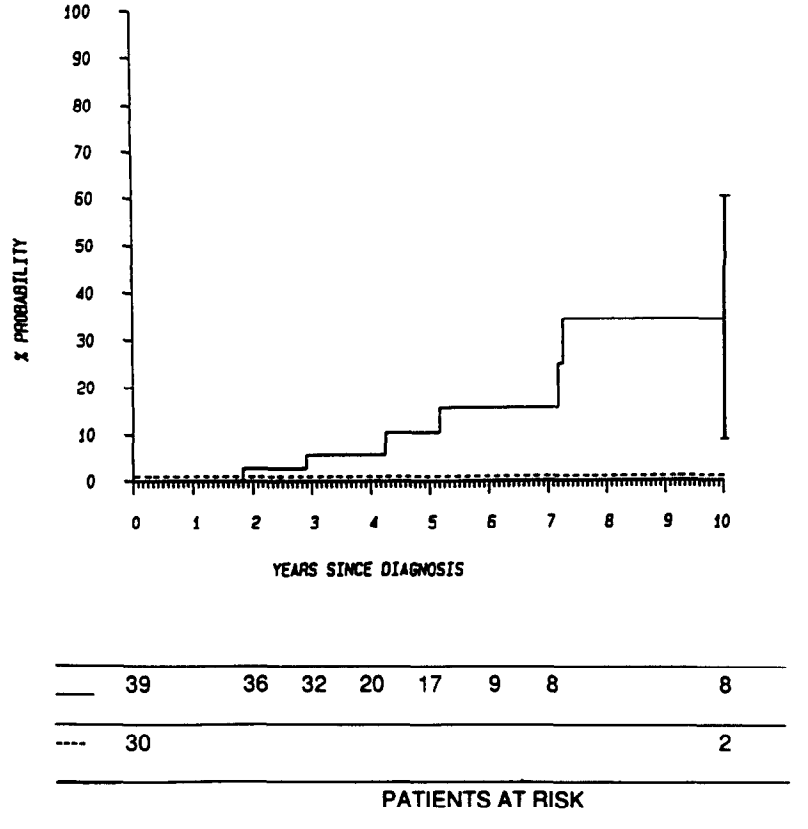

Fig. 4. Probability of a second malignancy for 39 patients who had both radiotherapy and chemotherapy (——) vs. 30 who only had radiotherapy (-----).

a second malignancy after NSHD relapse, one of them from a second malignancy without NSHD relapse and one from NSHD progression.

None of the patients who died with either preleukemia or ANLL had active NSHD. They all received a combined modality therapy including alkylating agents and procarbazine in the MOPP regimen, together with extensive supra- and infradiaphragmatic irradiation.

Thus, our overall 10-year survival was equally affected by NSHD progression (50%) and by the occurence of second hematologic malignancies (50%). This observation, albeit derived from small numbers, contrasts with a previously published study in which the death rate from progressive Hodgkin's disease exceeded the second leukemia death rate [22].

The occurence of a second malignancy was not significantly different between patients initially treated with combined modality and who never relapsed from previous complete remission (two second malignancies out of 18 patients) and those who relapsed from previous complete remission (four second malignancies out of 21 patients). The timing of combined modality therefore did not appear to influence the incidence of second malignancy in our study. We have not observed any case of solid tumor so far but our follow-up is probably short since those tumors seem to appear after 15 years [12].

Literature data indicate a cumulative risk of ANLL varying from 10 to 15% and a 4–5% probability of NHL at 10 years [8]. The peak incidence of ANLL occurs 6 years after treatment for Hodgkin's disease [20]. This contrasts dramatically with the virtual absence of second leukemia in patients treated with radiation therapy only [12] or with a combination of radiotherapy and ABVD chemotherapy [13]. Only one anecdotal case has been reported with the latter combination [14]. Accordingly, in our small subgroup of seven patients treated with this combination, no second tumor has been observed so far.

Furthermore, the ABVD regimen provides at least similar results as compared to the MOPP in patients with stage IIB, IIIA and IIIB treated with combined modality [15]. The ABVD regimen has not been shown yet to induce irreversible gonadal dysfunction but its cardiac and pulmonary toxicity certainly represents a potential risk of long-term complications [16]. With the availability of less cardiotoxic anthracycline analogs like epirubicin [17, 18] and of other agents like etoposide [19], it will soon be possible to build active regimens which will not carry the same risk as the previous ones.

In conclusion, Hodgkin's disease is a highly curable disease but its curability should not be compromised by the advent of second malignancies induced by older regimens such as MOPP or MOPP combined with radiation therapy [18]. A meticulous staging and a careful treatment selection should always be made, so that whenever possible only one modality, i.e. radiation therapy in early stages, should be used.

When chemotherapy is considered, especially if combined modality is deemed essential, MOPP and MOPP-related chemotherapy should at least be replaced by alternating combinations like MOPP/ABVD in order to reduce the amount of alkylating agents and procarbazine if not by ABVD alone. Regimens like ABVD are equally effective and less carcinogenic but are also very likely to be replaced in the near future by even less toxic combinations [21]. These regimens will then have to be tested in the treatment of early HD in order to avoid the multiple risks and complications of combined modality therapy.

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