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HODGKIN'S DISEASE

Retrospective clinico-pathologic study in 149 patients

by

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It has often been postulated in recent years that Hodgkin's disease is unicentric in origin. This together with the advent of new therapeutic methods, particularly megavoltage therapy, has led to a more optimistic view of the prognosis (CRAVER 1954, HEALY et coll. 1955, SLAUGHTER et coll. 1958, KAPLAN 1962, EASSON & RUSSEL 1963, NEWALL 1965, EASSON 1966, PETERS 1966, KAPLAN & ROSENBERG 1966, MUSSHOFF & BOUTIS 1967 and STRICKSTROCK et coll. 1967). The prognosis depends on the spread of the disease (PETERS 1950, JELLIFFE & THOMSON 1955, WESTLING 1965, and ROSENBERG 1966) and its histologic type (JACKSON & PARKER 1944, LUKES et coll. 1966). The purpose of this retrospective investigation of a material of Hodgkin's disease was to assess the significance of these two factors.

Clinical material and Methods. A total of 246 patients with Hodgkin's disease were referred for treatment during the period 1944—1960. Thirty-four patients, mostly with advanced lesions, were not admitted but recommended for continuous

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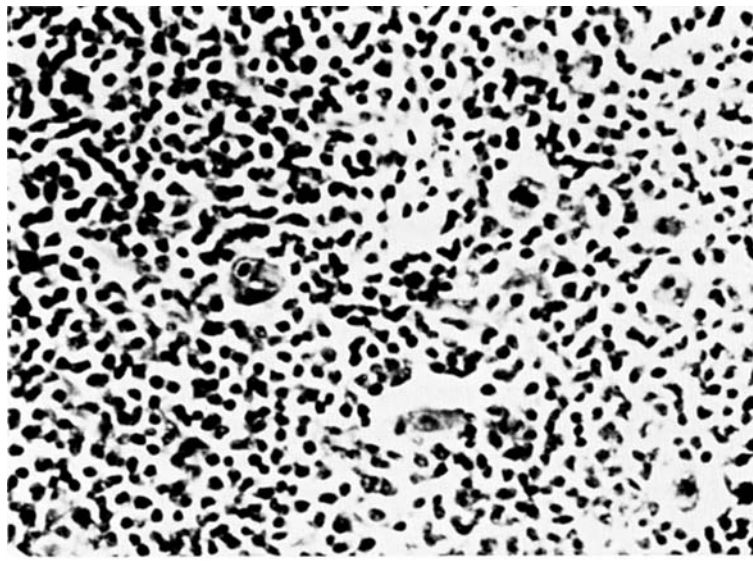

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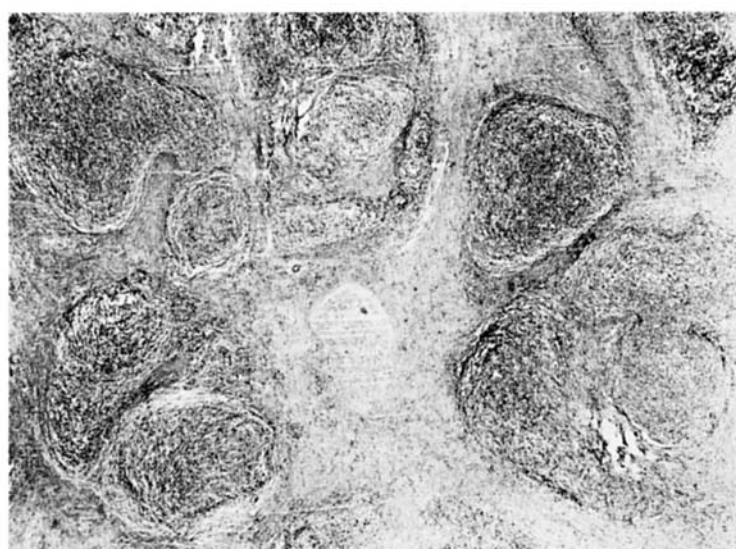


Fig. 1. Histologic appearances in Hodgkin's disease classified according to LUKES et coll. (1966). a) *Lymphocytic predominance.* Abundant lymphocytes; some atypical reticulum cells and a Sternberg giant cell. H. & E. ×400. b) *Nodular sclerosis.* Marked sclerosis with broad streaks of connective tissue shutting off nodular foci. H. & E. ×20.

treatment at their local hospitals; this left 212 patients admitted for treatment. Of these, thirty-nine had previously received treatment at other hospitals, no histologic diagnosis was available in six, and eighteen patients were not accepted as having Hodgkin's disease after re-examination of the histologic preparations. In two of these latter patients no microscopic slides were available for re-examination, in three the diagnosis proved to be not Hodgkin's disease but non-specific lymphadenitis, and in two patients the diagnoses were reticulum cell sarcoma and malignant systemic disease (not specified). In eleven of the eighteen patients, histologic examination of biopsy specimens obtained before the beginning of treatment failed to confirm the diagnosis. This left 149 patients who had previously not been treated and in whom re-examination of lymph node biopsy specimens obtained before the beginning of treatment confirmed the diagnosis of Hodgkin's disease. These 149 patients constitute the present material.

The patients were divided according to the clinical stage of the disease at beginning of treatment (JELLIFFE & THOMSON 1955 and JELLIFFE 1965) as follows:

Stage I: Lymph node involvement of only one main group, excluding intra-abdominal disease

Stage II: Lymph node involvement of two or more groups in the upper or lower half of the body, excluding intra-abdominal disease

Stage III:

A. Generalized lymph node involvement
B. Intra-abdominal involvement
C. Involvement of structures other than lymphatic
D. Constitutional symptoms for which no other reasonable cause is found.

As a rule, each patient was examined by two physicians of the department. The examination further included analysis of the blood and urine in all, roentgen examination of the lungs in 147 and cavography or urography in 11 patients. In none was lymphography before the beginning of treatment performed.

The patients were divided into various categories of forecaster index points (WESTLING 1965).

The grouping of the patients according to the histologic appearances of the initial biopsy specimens was as follows: lymphocytic predominance (L.p.), nodular sclerosis (N.s.), mixed cellularity (M.c.) and lymphocytic depletion (L.d.) (LUKES et coll. 1966) (Figs 1 to 3). The histologic re-examination of the preparations was done without knowledge of the clinical data. Only Sternberg giant cells were accepted as evidence.

Lymphocytic predominance (L.p.) is characterized by the occurrence of numerous lymphocytes. Some histiocytes without atypia may be present. On the other hand, only few other inflammatory cells, atypical reticulum cells and Sternberg giant cells are seen. This type was originally divided by LUKES et coll. (1966) into two forms, a nodular and a diffuse. We have tried to distinguish also these two forms and, among 18 patients with lymphocytic predominance, found four with the nodular form and fourteen with the diffuse form. In the further analysis of the material, these two forms were however pooled. The type previously known as paragranuloma (JACKSON & PARKER 1944) is included under the heading of lymphocytic predominance.

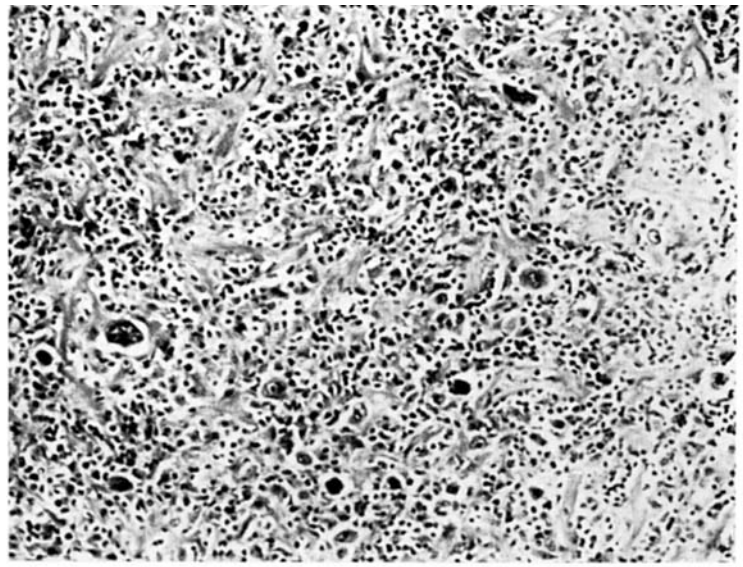
Nodular sclerosis (N.s.) is characterised by double refractive collagen connective tissue bands surrounding different-sized nodular foci in the parenchyma of the lymph node. These foci contain atypical reticulum cells, lymphocytes, leucocytes and histiocytes in varying proportions.

Mixed cellularity (M.c.) designates the granulomatous type of Hodgkin's disease with Sternberg giant cells, atypical reticulum cells, inflammatory cells and fibroblasts in roughly equal proportions and irregularly intermingled with one another.

Lymphocytic depletion (L.d.) occurs in two forms. In the one reticular form there are numerous atypical reticulum cells, while other inflammatory cells, including lymphocytes, are few. This resembles a polymorphous reticulum cell sarcoma. The previously known Hodgkin's sarcoma (JACKSON & PARKER 1944) belongs to this form. In the other form of lymphocytic depletion there is diffuse fibrosis with a few cells of all types. This probably represents a final stage. Among 20 patients with lymphocytic depletion, fourteen had the reticular form and six the diffuse fibrosis form.

It may sometimes be difficult to classify lesions, but no transitional forms were registered. All the patients were assigned to those groups in which they best fitted. It might be mentioned that none of the three patients in whom the histologic re-examination altered the diagnosis to non-specific lymphadenitis later developed clinical signs of Hodgkin's disease; furthermore, of the eight patients in whom the initial biopsy strongly suggested Hodgkin's disease but in whom it could not be verified by later biopsy, the further clinical course in six was typical of Hodgkin's disease. The histologic types of lymphocytic predominance and nodular sclerosis were observed only in lymph nodes. When other organs were involved they always had some of the other histologic characteristics.

The interval between the onset of symptoms that could reasonably be assigned



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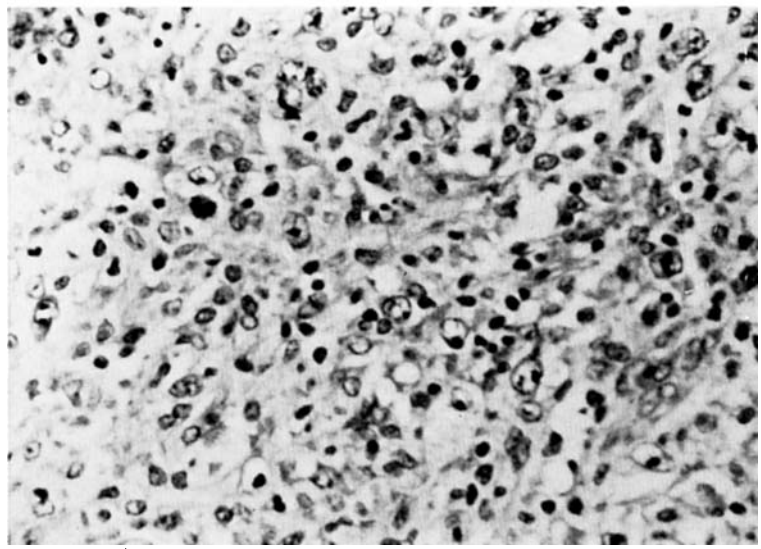

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Fig. 2. Histologic appearances in Hodgkin's disease classified according to LUKES et coll. (1966). a) *Mixed cellularity.* Several Sternberg giant cells in polymorphous granulation tissue with incipient interstitial fibrosis. H. & E. ×160. b) *Lymphocytic depletion.* Reticular form with numerous atypical reticulum cells. H. & E. ×400.

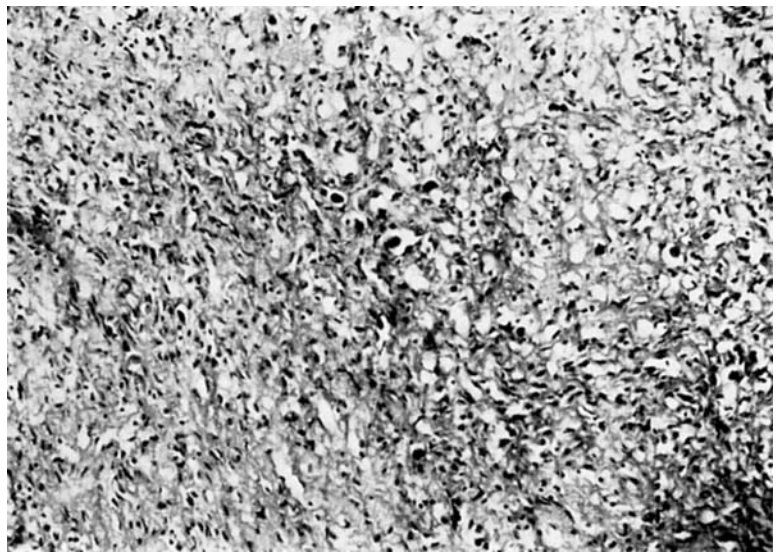

Fig. 3. Histologic appearance in Hodgkin's disease classified according to LUKES et coll. (1966). *Lymphocytic depletion.* Diffuse fibrosis with few cells and with fragments of degenerated giant cells. H. & E. ×160.

to the disease and the beginning of treatment was taken as a measure of the previous duration of the disease.

Treatment consisted mainly of radiation of the clinically involved tissues, but in two patients with advanced lesions also of total body irradiation. Roentgen was mostly used (170 kV, 0.9 mm Cu HVL) but since 1958 also ^{60}Co. When possible, the patients were given a dose thought to be sufficient to deal with the region permanently; patients with very advanced disease often received smaller doses. Five patients with advanced disease and in poor general condition received no radiation. Major operations had been performed in ten patients (thymectomy in one, pulmectomy in one, partial gastrectomy in two, resection of the intestine in two, splenectomy in three, and decompressive laminectomy in one patient). All these ten patients received postoperative radiation. Cytotoxic drugs were used mainly to relieve symptoms of advanced disease, and 76 patients were treated with cytotoxics during some phase of their disease. The drugs used were generally alkylating agents, such as nitrogen mustard, TEM and cyclophosphamide, and recently vinkaleucoblastine as well. Relapses were often treated at first with the same drug, and when this failed, another was tried. Unspecific therapy with corticosteroids, antibiotics and blood transfusions was used in advanced disease.

The patients were regularly followed up according to the schedule described by

LINDGREN (1962). The present investigation was concluded on January 1st, 1966, which means that all survivors were followed for at least 5 years. 'Followed' is here understood as the time from the beginning of treatment until January 1st, 1966, or, alternatively, until death. Of the 125 patients who died, forty-two were examined post mortem.

In the statistical analysis (Mr Eron Oxing, Department of Statistics, Lund University), differences demonstrable by the chi-square test at the 5 % level were regarded as almost significant, at the 1 % level as significant, and at the 0.1 % level as highly significant.

Results

Distribution of the material among different groups at the beginning of treatment. The 93 men and 56 women produced a quotient of 1.7, a figure given also by JELLIFFE (1965) but higher than that in the series reported by UDDSTRÖMER (1934). VIDEBAEK (1950), VOUTILAINEN & SAXÉN (1959) and WESTLING (1965). According to the Cancer Registry of Sweden, the quotient for 1960 was 1.4.

The age distribution at the beginning of treatment indicated that the age of the men ranged from 5 to 84 years (mean 46.2, median 43) and that of the women from 16 to 92 (mean 47.8, median 50). The difference in mean age between the sexes was not significant. In WESTLING's series of 250 patients the women were younger than the men, and the mean and median age of both sexes was lower than in the present material. Of the 149 patients in the present material, forty-seven (31 %) were 60 years or more at the beginning of treatment. This figure is somewhat lower than that given by the Cancer Registry of Sweden for 1960 (39 %), but much higher than those reported by UDDSTRÖMER; VIDEBAEK; VOUTILAINEN & SAXÉN, and by WESTLING (6 % to 14 %). Compared with certain series, the present material contained many men and aged persons.

When classified according to the stage of disease, twenty-one patients were assigned to stage I, fifty to stage II, and seventy-eight to stage III. There was thus 52 % in stage III, which is roughly the same as that in the series of JELLIFFE & THOMSON (55 %) and JELLIFFE (51 %). Sixty-six of the patients in stage III were assigned to this group because of the occurrence of one (42 patients) or more (24 patients) of the following types of involvement: (A) generalized lymph node involvement (39 patients), (B) intra-abdominal lymph node involvement (16 patients), and (C) involvement of structures other than lymphatic (43 patients). The remaining twelve of the 78 patients in stage III, who would otherwise have been assigned to stage I or II on clinical grounds, were allotted to stage III because of the presence of constitutional symptoms or signs

for which no other reasonable cause could be found, such as marked loss of weight, fatigue and itching, fever $\geqq 38°$ C (10 patients, in six of type Pel-Ebstein fever), hemoglobin value of $\leqq 11$ g/100 ml (8 patients), leucocytes $\leqq 4\,000$/ml (3 patients) and ESR more than 100 ml/hour (6 patients). In all the twelve patients, there were three or more such symptoms. Seven of the patients in stage I and twenty-six of those in stage II had mild loss of weight, fatigue, sweating and itching, hemoglobin value $\leqq 11$ g/100 ml, leucocytes $\leqq 4\,000$/ml and ESR > 25 ml/hour before the beginning of treatment. The ESR was raised in twenty-seven of the thirty-three patients, and in four it was as high as > 100 ml/hour. Admission had usually been preceded by biopsy which might have influenced the evaluation of the prognostic value of the ESR. The distribution of patients in stages I and II, with and without constitutional symptoms, was the same among the different histologic types.

The clinical stage distribution according to sex and age is presented in Fig. 4. The quotient males: females was 14: 7 for stage I, 26: 24 for stage II, and 53: 25 for stage III, and the distribution of the sexes among the various stages was not significantly different. The patients in stage I were mean 46.7 years (median 43) at the beginning of treatment; in stage II the mean was 40.4 (median 35) and in stage III the mean was 50.9 years (median 52). The difference in mean age of the patients in stages I and II (42.3 years) and patients in stage III (50.9 years) was significant.

On grouping of the patients according to their histologic type of lesion, the following distribution was reached:

Lymphocytic predominance	18 patients	12 %
Nodular sclerosis	31 »	21 %
Mixed cellularity	80 »	54 %
Lymphocytic depletion	20 »	13 %

In the material of LUKES et coll. consisting of 377 men aged 18 to 56 years, the frequency of mixed cellularity was much lower (26 %), while the frequency of the other types, particularly nodular sclerosis (40 %) was higher. The distribution of the histologic types in men between 18 and 56 years in the present material did not differ significantly from that of the entire material. In the series of LUKES et coll. 75 % of the patients were between 18 and 30 years. Eighteen patients of the present material were men aged 18 to 30 years. In three of these, the lesions were of histologic type lymphocytic predominance, in six type nodular sclerosis, in eight of type mixed cellularity and in one of type lymphocytic depletion. This small group thus showed better agreement regarding the distribution of different histologic types with the material of LUKES et coll. than did the present material as a whole. Mixed cellularity was the commonest type also in a recent series of patients (LANDBERG & LARSSON

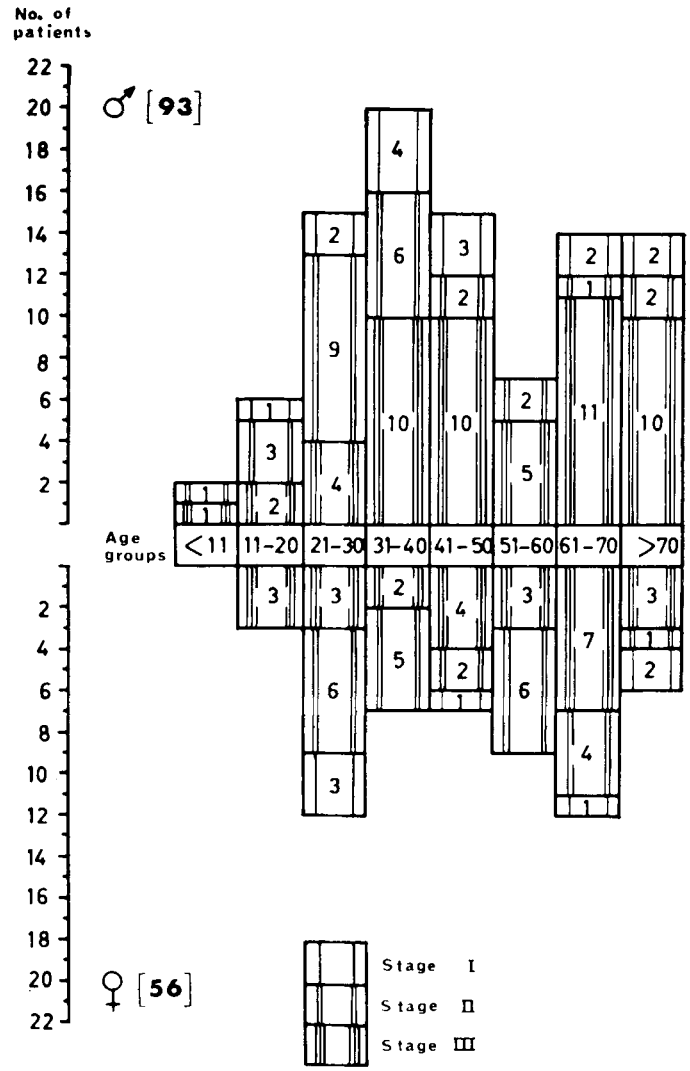

Fig. 4. Age and sex distribution of the patients grouped according to the clinical stage. The figures within the columns denote the number of patients.

1968) although in two other retrospective investigations (FRANSSILA et coll. 1967 and KELLER et coll. 1968) nodular selerosis was the commonest type.

The age and sex distribution according to the histologic type of lesions are presented in Fig. 5. The ratio between men and women with lymphocytic

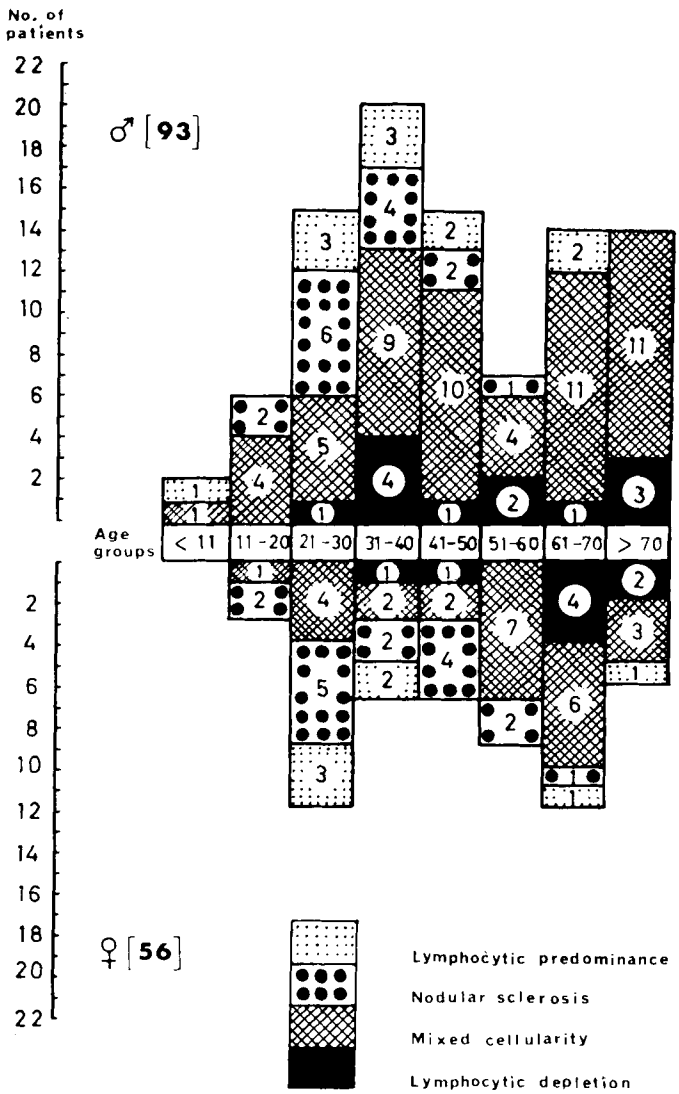

Fig. 5. Age and sex distribution of patients, grouped according to the histologic type of lesion. The figures within the columns denote the number of patients.

predominance was 11: 7, with nodular sclerosis 15: 16, with mixed cellularity 55: 25, and with lymphocytic depletion 12: 8. The distribution of the different histologic types did not vary significantly with sex within this material, while the series of FRANSSILA et coll. and KELLER et coll. had a preponderance of women with nodular sclerosis compared with other histologic types.

Table 1

Patients grouped according to clinical stage and histologic type of lesion

Histologic type	Stage I	Stage II	Stage III	Total
Lymphocytic predominance	9	8	1	18
Nodular sclerosis	4	16	11	31
Mixed cellularity	6	24	50	80
Lymphocytic depletion	2	2	16	20
	21	50	78	149

The patients in the present material with lymphocytic predominance had a mean age of 40.3 years (median 36) at the beginning of the treatment; with nodular sclerosis the mean age was 34.4 (median 31), with mixed cellularity the mean age was 50.6 (median 54), and with lymphocytic depletion the mean age was 56.7 years (median 60). Below 45 years of age, there were 13/18 patients with lymphocytic predominance, 25/31 with nodular sclerosis, 31/80 with mixed cellularity, and 6/20 with lymphocytic depletion. This difference in age distribution of the histologic types was highly significant.

The distribution of the clinical stages among the histologic types is given in Table 1. The difference in distribution among clinical stages is most marked for the types lymphocytic predominance and lymphocytic depletion so that the former was highly significantly more common in stages I and II than lymphocytic depletion. The patients with type nodular sclerosis were significantly more often in stages I and II, while those with type mixed cellularity were significantly more common in stage III.

The previous duration of the disease was (median) 2 months for patients in stage I, 3 months for patients in stage II, and 5 months for patients in stage III. For patients with lymphocytic predominance it was 6 months, for nodular sclerosis 4 months, for mixed cellularity 5 months, and for lymphocytic depletion 4 months. LUKES et coll. found a longer duration of the disease before the initial biopsy in patients with advanced disease (staging according to PETERS 1950 and PETERS & MIDDLEMISS 1958). The duration of the disease in patients with different histologic types of lesions in the present material did not differ appreciably from the values for the duration of the disease before initial biospsy in the series reported by LUKES et coll.

A survey of the patients grouped according to clinical stage and histologic type of disease and duration of the history before beginning of treatment is presented in Table 2. Three of the patients had no symptoms. Of the patients, who had had symptoms for at the most 12 months, about half were in stage III, while two-thirds of those who had had symptoms longer were in stage III. The

Table 2

Patients grouped according to clinical stage and histologic type of lesion and duration of disease before beginning of treatment

History	Histologic type	Clinical stages			Total
		I	II	III	
None (incidental finding)	Lymphocytic predominance	1			1
	Nodular sclerosis				
	Mixed cellularity		1	1	2
	Lymphocytic depletion				
		1	1	1	3
<6 months	Lymphocytic predominance	3	3	1	7
	Nodular sclerosis	3	11	6	20
	Mixed cellularity	6	13	24	43
	Lymphocytic depletion	1	2	10	13
		13	29	41	83
6—12 months	Lymphocytic predominance	3	3		6
	Nodular sclerosis		4		4
	Mixed cellularity		4	12	16
	Lymphocytic depletion	1		2	3
		4	11	14	29
> 12 months	Lymphocytic predominance	2	2		4
	Nodular sclerosis	1	1	5	7
	Mixed cellularity		6	13	19
	Lymphocytic depletion			4	4
		3	9	22	34

proportion between the number of patients in stage I and those in stage II did not differ significantly from one another regarding the previous duration of the disease. Of the eighteen patients with type lymphocytic predominance, sixteen were distributed equally among stages I and II, irrespective of the previous duration of the disease. With increasing length of history, patients with nodular sclerosis and mixed cellularity tended to be relatively more often in stage III than in stages I and II. Not until after a history of more than 12 months were patients with nodular sclerosis more often in stage III than in stages I and II. Patients with mixed cellularity were almost significantly more often in stage III than in stages I and II, and patients with type lymphocytic predominance, independent of the duration of the disease, were also most often in stage III.

Table 3

Patients grouped according to clinical stage, histologic type of lesion and clinical involvement at the beginning of treatment and present or previously treated lesions at the end of follow-up — L. p. designates lymphocytic predominance, N. s. nodular sclerosis, M. c. mixed cellularity, and L. d. lymphocytic depletion

	At beginning of treatment									
	Stage I					Stage II				
Histologic type	L.p.	N.s.	M.c.	L.d.	Total	L.p.	N.s.	M.c.	L.d.	Total
Total number of patients	9	4	6	2	21	8	16	24	2	50
Lymph nodes in neck and s. clav. fossa	6	2	4	1	13	8	16	22	2	48
Lymph nodes in axilla	3	1	1	1	6	3	5	10	1	19
Lymph nodes in mediastinum		1			1	4	14	13		31
Lymph nodes in groin			1		1			2		2
Lymph nodes in cubital or popliteal fossa								1		1
Waldeyer's tonsillar ring								1		1
Lymph nodes in abdomen										
Maxilla										
Orbita										
Thymus										
Pulm. parenchyma										
Oesophagus										
Pericard. pleura										
Thoracic wall										
Breast										
Liver										
Spleen										
Other abd. viscera										
Perineum-rectum										
Skeleton										
Skin										
Spinal canal										
Thigh muscle										

If, then, the interval between the initial symptoms and the beginning of treatment be taken as a measure of the duration of the disease, a long duration may explain advanced disease in some patients though the histologic type lymphocytic depletion had spread rapidly. However, in patients with lymphocytic predominance, despite a longer duration of the disease, this was rarely generalized at the beginning of treatment. Nodular sclerosis appeared to have spread slower than mixed cellularity.

When classifying the patients according to forecaster index points (WEST-

Table 3 *(cont.)*

Stage III					Total					At end of follow-up Total				
L.p.	N.s.	M.c.	L.d.	Total	L.p.	N.s.	M.c.	L.d.	Total	L.p.	N.s.	M.c.	L.d.	Total
1	11	50	16	78	18	31	80	20	149	18	31	80	20	149
1	9	37	14	61	15	27	63	17	122	15	29	68	18	130
	5	32	11	48	6	11	43	13	73	11	23	59	15	108
	5	15	5	25	4	20	28	5	57	9	23	41	8	81
	3	25	9	37		3	28	9	40	4	9	37	9	59
		2	1	3			3	1	4			4	1	5
							1		1		1	1		2
	1	13	2	16		1	13	2	16	3	10	31	4	48
												1		1
												1		1
	1			1		1			1		1			1
	1	12	3	16		1	12	3	16	2	8	22	4	36
			1	1				1	1				1	1
											2			2
											2	4		6
	1			1		1			1	1	1	3		5
		6	3	9			6	3	9	6	4	19	4	33
	1	5	4	10		1	5	4	10	3	5	13	5	26
		3	1	4			3	1	4	1	1	4	1	7
											1	1		2
	2	1		3		2	1		3		8	10	1	19
	3	5	1	9		3	5	1	9		5	6	1	12
											3	1		4
											1			1

LING) fifty had 0 or 1 point, thirty-five had 2 points and fifty-six patients had 3 or more points. Eight patients could not be classified, not even with substitution. The distribution among different categories of forecaster index points agrees largely with that in WESTLING's series, with minor differences, which were not significant.

Clinical manifestations and autopsy findings in patients with different histologic types of lesions. In Table 3, the number of patients in different clinical

Table 4

Patients grouped according to histologic type of lesion and stage at the beginning of treatment and histologic type and localization of the disease at autopsy. L. p.=lymphocytic predominance, N. s.=nodular sclerosis, M. c.=mixed cellularity, L. d.=lymphocytic depletion, Ret.=reticular form of lymphocytic depletion, D. f.=diffuse fibrosis form of lymphocytic depletion.

Histologic type in initial biopsy specimen	Lympho-cytic predom-inance			Nodular sclerosis			Mixed cellularity					
Patient number:	47	11	95	149	93	150	1	96	30	129	152	154
Sex:	♀	♂	♂	♂	♀	♂	♀	♂	♂	♂	♀	♀
Stage at beginning of treatment:	II	II	II	II	III	III	I	I	II	II	II	II
Histologic type in autopsy specimen	M.c.	M.c.	M.c.	D.f.	M.c.	Ret.	M.c.	Ret.	Ret.	M.c.	Ret.	Ret.
Spread of disease at autopsy												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+				+		+	+	+		+
Lymph nodes in mediastinum	+	+	+		+	+		+		+		+
Lymph nodes in retroperitoneum			+	+	+	+				+	+	
Skeleton		+	+	+		+				+	+	+
Lymph nodes in axilla				+								
Lymph nodes in mesenterium						+				+		
Lymph nodes in neck and s.clav. fossa				+	+							
Lymph nodes in groin							+					
Kidneys								+				
Lung						+						
Pleura				+						+		
Waldeyer's tonsillar ring												
Heart												
Pericardium												
Peritoneum												
Stomach												
Small intestine												
Bladder								+				
Adrenal												
Nervous system									+			

stages and of various histologic types, with different clinical manifestations at the beginning of treatment, and present or previously treated clinical manifestations at the end of follow-up are all recorded.

The most common clinical findings were lymphoma of the neck or supraclavicular fossa, which occurred in 122 patients (82 %) of the 149 at the beginning of treatment, and was noted at the end of the follow-up in 130

Table 4 *(cont.)*

														Lymphocytic depletion						Total
														Reticular			Diffuse fibrosis			
31	44	63	66	69	77	87	88	89	92	105	118	127		101	135	161	19	43	61	
♂	♂	♂	♂	♀	♂	♂	♀	♂	♂	♂	♂	♂		♂	♂	♀	♀	♂	♀	
III	III	III	III	III	III	III	III	III	III	III	III	III		III	III	III	I	III	III	
M.c.	M.c.	D.f.	M.c.	M.c.	M.c.	D.f.	M.c	M.c.	M.c.	M.c.	Ret.	M.c.		Ret.	D.f.	Ret.	D.f.	D.f.	D.f.	
+	+				+	+	+	+	+	+	+	+		+	+	+	+	+	+	28
+	+			+	+	+	+	+	+	+	+	+		+	+	+	+		+	23
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patients (87 %), and without any significant variation in frequency of the different histologic types.

The next most common finding was lymphoma of the axilla, which was present at the beginning of treatment in 73 patients (49 %) of 149, and at the end of follow-up in 108 patients (73 %). The frequency of lymphoma of the axilla at the beginning of treatment was almost significantly lower in pa-

tients with lymphocytic predominance and nodular sclerosis, but at the end of follow-up such a difference was no longer demonstrable.

Lymphoma of the mediastinum was noted at the beginning of treatment in 57 (38 %) of the 149 patients and twenty (35 %) of these fifty-seven were of the type nodular sclerosis. Twenty (65 %) of the 31 patients with nodular sclerosis had at the beginning of treatment mediastinal lymphoma, compared with 37 patients (31 %) of the 118 patients with other histologic types. The difference was highly significant. This over-representation of mediastinal lymphoma in type nodular sclerosis at the beginning of treatment was still more marked in the 71 patients with stages I and II. In 32 (45 %) of these, a mediastinal lymphoma was found at the beginning of treatment and of these thirty-two patients fifteen (47 %) had type nodular sclerosis. In 15 (75 %) of the 20 patients with type nodular sclerosis in stages I and II, a mediastinal lymphoma was thus seen at the beginning of treatment, and this localization was highly significantly over-represented among patients with nodular sclerosis compared with other histologic types (17/51 = 33 %) in stages I and II at the beginning of treatment. The difference persisted significantly, so that at the end of follow-up a mediastinal lymphoma was present in 18 (90 %) of the 20 patients with type nodular sclerosis in stages I and II, compared with 26 (51 %) of the 51 patients in stages I and II of the other histologic types. In the entire material, mediastinal lymphoma had been noted at the end of follow-up in 23 (74 %) of the 31 patients with nodular sclerosis compared with 58 (49 %) of the 118 patients with other histologic types. The difference was almost significant. Of the eight patients with nodular sclerosis in whom no mediastinal lymphoma was found, two were in stage I and II, respectively, and still had no further manifestations, while six were in stage III and died 5 to 79 months after the beginning of treatment. The high frequency of mediastinal lymphoma in patients with nodular sclerosis has been stressed by Lukes et coll., Franssila et coll. and by Keller et coll.

Lymphoma of the groin was noted at the beginning of treatment in 40 (27 %) of the 149 patients and at the end of follow-up in 59 patients (40 %). Inguinal lymphoma at the beginning of treatment was highly significantly, and at the end of follow-up almost significantly, more common in patients with mixed cellularity and lymphocytic depletion than in those with lymphocytic predominance and nodular sclerosis.

Retroperitoneal lymphoma had been diagnosed at the beginning of treatment in 16 (11)%) of the 149 patients and at the end of follow-up in 48 (32 %). The frequency was almost significantly higher for patients with mixed cellularity. It is known (Lee et coll. 1964) that cavo-urography, and particularly lymphography, may often reveal asymptomatic retroperitoneal lymphoma. The

low frequency of diagnosed retroperitoneal lymphomas in the present material at the beginning of treatment can probably be explained by the fact that cavourography was not performed so often and that lymphography was not performed at all. The figures must therefore be regarded as reflecting only the frequency of symptomatic retroperitoneal lymphomas. Still lower figures have been given by WESTLING, and by MUSSHOFF et coll. (1966).

Involvement of the lymph nodes in the cubital or popliteal fossa was present at the beginning of treatment in four, and involvement of one of the tonsils in one patient.

Tissues other than the above-mentioned lymph node groups were found to be affected at the beginning of treatment in 43 (29 %) of the 149 patients and at the end of follow-up in 90 patients (69 %). Such involvement both at the beginning of treatment and at the end of follow-up was almost significantly equally common among patients with nodular sclerosis, mixed cellularity and lymphocytic depletion but at the beginning of treatment it was significantly, and at the end of follow-up almost significantly, less common among patients with lymphocytic predominance. Involvement of the skeleton, spinal canal and of the skin was somewhat more common among patients with nodular sclerosis. FRANSSILA et coll. reported involvement of the skeleton to be more common in nodular sclerosis. The pulmonary parenchyma, the liver and the spleen were somewhat more often affected by mixed cellularity and lymphocytic depletion at the beginning of treatment, not later. The difference regarding the pulmonary parenchyma was significant.

Involvement of abdominal organs (e.g. lymph nodes, liver, spleen, stomach) was present at the beginning of treatment in one (2 %) of the 49 patients with lymphocytic predominance and nodular sclerosis, compared with 27 (27 %) of the 100 patients with mixed cellularity and lymphocytic depletion. The difference was highly significant. No such difference was, however, demonstrable at the end of follow-up.

The follow-up period for patients with lymphocytic predominance had a median of 60 months (mean 70); for nodular sclerosis the median was 63 (mean 79), for mixed cellularity it was 15 (mean 32) and for lymphocytic depletion it was 5 months (mean 13). At the end of the follow-up, six of the patients with lymphocytic predominance, ten with nodular sclerosis, seven with mixed cellularity and one with lymphocytic depletion were still alive.

Judging from the varying duration of the follow-up of the patients with different histologic types of disease, mixed cellularity, and particularly lymphocytic depletion, appear to run a faster course than lymphocytic predominance and nodular sclerosis.

Evaluable autopsy specimens were available for thirty-one of the patients. The

Table 5

Histologic type in the initial biopsy specimens and changes according to autopsy specimens in the 31 patients in this group

Histologic type at initial biopsy		Histologic type in autopsy specimen				
		Lympho-cytic pre-dominance	Nodular sclerosis	Mixed cellularity	Lymphocytic depletion	
					Reticular	Diffuse fibrosis
Lymphocytic predominance	2	—	—	2	—	—
Nodular sclerosis	4	—	—	2	1	1
Mixed cellularity	19	—	—	12	5	2
Lymphocytic depletion						
Reticular	3	—	—	—	2	1
Diffuse fibrosis	3	—	—	—	—	3
	31			16	8	7

Table 6

Patients alive 1 to 5 years from the beginning of treatment and grouped according to clinical stage

	Total number of patients	Number of patients still alive after (years)				
		1	2	3	4	5
Stage I	21	19	16	14	13	13
Stage II	50	43	33	30	28	24
Stage III	78	27	19	11	10	7

organs or organic systems involved are given in Table 4. It is clear from the table that most of the autopsies indicated that the disease had involved the spleen, liver, mediastinal and para-aortic lymph nodes. The material would not allow closer analysis of the relation between a radiation dose to an area and its effect. It should, however, be mentioned that of the twenty-four patients treated with radiation for involvement of the lymph nodes of the neck, nineteen presented no signs of local recurrence at autopsy. The histologic type was generally the same in all organs involved in a given patient.

The distribution of the histologic types in the autopsy series was compared with the histologic types at initial biopsy (see Table 5). None of the patients who had initially had lymphocytic predominance or nodular sclerosis had such types at autopsy. A shift of the material towards prognostically less favourable

Table 7

Patients alive 1 to 5 years from the beginning of treatment grouped according to the histologic type of lesion

Histologic type	Total number of patients	Number of patients alive after (years)				
		1	2	3	4	5
Lymphocytic predominance	18	16	13	11	10	9
Nodular sclerosis	31	28	22	21	19	17
Mixed cellularity	80	41	31	21	20	17
Lymphocytic depletion	20	4	2	2	2	1

histologic types had occurred, an observation in agreement with previous investigations that the disease can change in character also as regards its histologic type (HANSON 1964 and LOHMAN 1965).

Survival in the different groups. Of all the 149 patients, 44 (30 %) were alive 5 years after the beginning of treatment; twenty-three (25 %) of the 93 men and 21 (37 %) of the 56 women. The better prognosis for the women in this series, which was not significant however, was perhaps somewhat more distinct for stage II (men 10/26, women 14/24) and for type mixed cellularity (men 9/55, women 8/25), but none of the differences were significant. SHIMKIN et coll. (1955), JELLIFFE & THOMSON (1955), and FAYOS et coll. (1965) reported a better prognosis for women. The same tendency, though not statistically demonstrable, was found by PETERS (1950), PETERS & MIDDLEMISS (1958), MEIGHAN & RAMSAY (1963) and WESTLING (1965), while VIDEBAEK (1950) indicated that the prognosis was equal for both sexes.

The number of surviving patients in each of the first 5 years after the beginning of treatment are given for different clinical stages in Table 6 and for different histologic types in Table 7. These values are expressed as percentages in Figs 6 and 7.

The 5-year survival rate in different clinical stages (Table 6 and Fig. 6) was highest in stage I and lowest in stage III. The difference between stage I and stage II was not significant. The 5-year survival rate in stages I and II (52 %) did not differ statistically from the corresponding figure given by JELLIFFE (58 %). Twenty-six of the thirty-four patients in stages I and II who died within 5 years from the beginning of treatment bore clinical appearances of advanced Hodgkin's disease. Autopsy was performed in only four of the remaining eight patients. In one of these (stage II, lymphocytic predominance) death was due to myocardial infarction and there was no evidence of Hodgkin's disease, while in the other three (one in stage I and two in stage II, all of

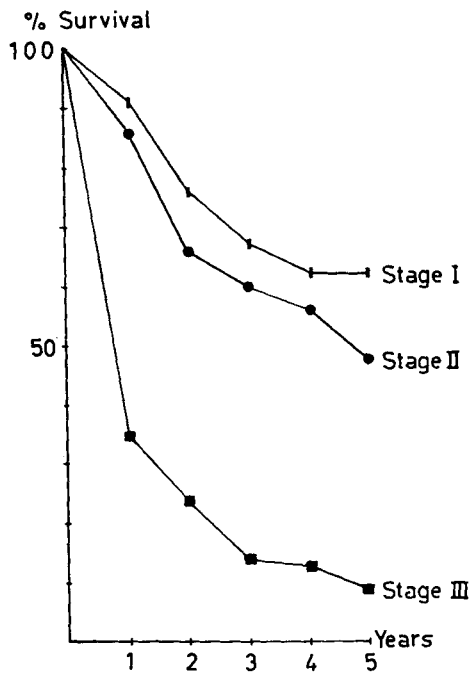

Fig. 6. Survival rate of patients 1 to 5 years after the beginning of treatment grouped according to clinical stage.

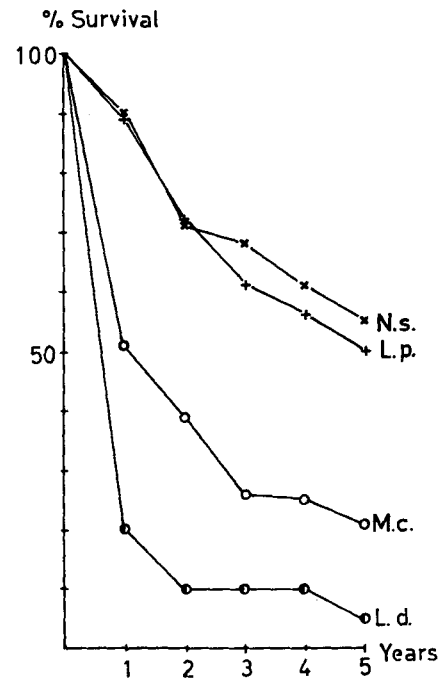

Fig. 7. Survival rate of patients 1 to 5 years after the beginning of treatment grouped according to the histologic type of lesion.

mixed cellularity type) Hodgkin's disease was demonstrated at autopsy. One patient (stage I, lymphocytic predominance) also had a soft tissue sarcoma with metastases and advanced carcinoma of the thyroid. Autopsy was not performed but the clinical course was at least compatible with Hodgkin's disease. Three patients (one in stage I and two in stage II, one with lymphocytic predominance and two with mixed cellularity) died at home and were lost to control.

Of the thirty-three patients in stages I and II who had one or two constitutional symptoms at the beginning of treatment, fifteen (45 %) were alive 5 years after the beginning of treatment, compared with twenty-two (58 %) of the thirty-eight of those in whom such symptoms had not been demonstrated. The difference was not significant.

In all the seventy-one patients in stage III who died within 5 years after the beginning of treatment the clinical picture at death was that of advanced Hodgkin's disease. Of the seven patients in stage III who survived 5 years after the beginning of treatment, three had nodular sclerosis and four had mixed

Table 8

Number of patients alive 5 years after the beginning of treatment and total number of patients grouped according to clinical stage and histologic type of lesion at the beginning of treatment

Histologic type	Stage I	Stage II	Stage III	
Lymphocytic predominance	7/9	2/8	0/1	9/18
Nodular sclerosis	4/4	10/16	3/11	17/31
Mixed cellularity	2/6	11/24	4/50	17/80
Lymphocytic depletion	0/2	1/2	0/16	1/20
	13/21	24/50	7/78	44/149

Table 9

Five-year survivals in different categories of forecaster index points (after WESTLING *1965)*

Number of forecaster index points	Total number of patients	Number of patients alive 5 years after beginning of treatment
0 or 1	50	28
2	35	9
3 or more	56	2
Not classifiable	8	5

cellularity. The reason why these seven patients were classified as stage III was that two had only generalized lymph node involvement, two had generalized lymph node involvement plus involvement of structures other than lymphatics (pulmonary parenchyma and liver) and three had involvement of structures other than lymphatics (pulmonary parenchyma, skeleton and skin, respectively). The difficulty in the evaluation of skin changes has been stressed by JELLIFFE. Of the twenty-eight patients classified as stage III because of generalized lymph node involvement and/or involvement of retroperitoneal lymph nodes two were alive 5 years from the beginning of treatment and the 5-year survival rate for this group was thus no better than for the other patients in stage III.

The 5-year survival rate for different histologic types is given in Table 7 and Fig. 7. It was the same for lymphocytic predominance and nodular sclerosis but highly significantly worse for mixed cellularity and worst for lymphocytic depletion. LUKES et coll. reported a longer median survival for types lymphocytic predominance and nodular sclerosis than for types mixed cellularity and lymphocytic depletion, and especially large differences between the nodular form of lymphocytic predominance and the diffuse fibrosis form of lymphocytic depletion. All the four patients of the present material with nodular lymphocytic pre-

dominance were alive 5 years from the beginning of treatment, while of the six with diffuse fibrosis all had died within 5 years. FRANSSILA et coll. gave similar figures for the 5-year survival. The series reported by KELLER et coll. is not comparable because of differences in the therapeutic technique.

The 5-year survival in different clinical stages was distributed among different histologic types as seen in Table 8. The possibility of a 5-year survival seems to depend both on the clinical stage at the beginning of treatment and on the histologic type of lesion. Of thirteen patients with types lymphocytic predominance and nodular sclerosis stage I, eleven (85 %) were still alive after 5 years and of the thirty-seven patients with types lymphocytic predominance and nodular sclerosis in stages I and II, twenty-three (62 %) were alive after 5 years. The corresponding figure for patients in stage III of types mixed cellularity and lymphocytic depletion was four (6 %) out of sixty-six patients. As previously mentioned, in eight of the thirty-four patients in stages I and II who died within 5 years, the cause of death could not with certainty be classified as advanced Hodgkin's disease. Three of these had lymphocytic predominance and five had mixed cellularity.

The 5-year survival in different categories of forecaster index points (WESTLING 1965) is presented in Table 9. Five of the eight patients who could not be classified were still alive at 5 years, which might help to explain why the 5-year survival rate was lower for all the three categories in the present material than in WESTLING's. The differences were not significant, however.

SUMMARY

A retrospective study of 149 patients with Hodgkin's disease indicated that the further course from the beginning of treatment depended both on the clinical stage and the histologic type of the initial biopsy specimen. The clinical staging and a differentiated histologic evaluation appear to be important in the evaluation of the prognosis of the disease.

ZUSAMMENFASSUNG

Eine retrospektive Analyse von 149 Patienten mit Hodgkins Erkrankung zeigte, dass der weitere Verlauf nach Beginn der Behandlung sowohl vom klinischen Stadium der Erkrankung als auch vom histologischen Typ der ersten Probeexcision abhing. Es ist demgemäss wichtig für die Prognose, das klinische Stadium und den histologischen Typ bei Anfang der Behandlung richtig einzuschätzen.

RÉSUMÉ

L'étude rétrospective de 149 malades atteints de maladie de Hodgkin montre que l'évolution à partir du début du traitement dépend à la fois du stade clinique et du type histologique du prélèvement biopsique initial. Il semble que la définition du stade clinique et l'établissement d'un diagnostic histologique différencié sont importants pour établir le pronostic de la maladie.

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