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THE VALUE OF SEQUENTIAL BONE MARROW BIOPSY AND LAPAROTOMY AND SPLENECTOMY IN A SERIES OF 127 CONSECUTIVE UNTREATED PATIENTS WITH NON-HODGKIN'S LYMPHOMA

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Summary.—The information derived from sequential routine bone marrow biopsies and exploratory laparotomy with splenectomy in 127 consecutive untreated protocol patients with malignant lymphomata other than Hodgkin's disease is reviewed.

Of the 61 patients with diffuse lymphomata, 36% changed stage after these diagnostic procedures, usually to a more advanced stage. Of the 66 patients with nodular lymphomata, 62% had a change in stage, almost all to more advanced stages, usually as a result of bone marrow biopsy. The correlation of pathological stages to clinical stages is presented for each of the Rappaport classification subgroups and for several age groups.

The precise indications for exploratory laparotomy with splenectomy cannot yet be defined. These will have to await the results of current clinical trials, which may reveal to what degree an improvement in therapeutic results has been achieved as a result of a better knowledge of the extent of disease.

THE STANFORD experience with exploratory laparotomy and splenectomy for diagnostic and staging purposes in 69 previously untreated patients with non-Hodgkin's lymphomata has been reported (Goffinet *et al.*, 1973). This review, which supplements the data appearing in that report, is based upon a series of 91 consecutive protocol patients taken to diagnostic laparotomy among a total of 127 consecutive untreated patients from whom they were selected.

PATIENT SELECTION AND PROCEDURES

The selection of patients, criteria for eligibility for protocol study, pre-operative studies and laparotomy techniques have been described elsewhere (Goffinet *et al.*, 1973; Rosenberg *et al.*, 1971; Enright, Trueblood and Nelsen, 1970).

In summary, the following criteria were used: (1) Diagnostic biopsy was reviewed by the Stanford Division of Surgical Pathology, confirmed as a malignant lymphoma other than Hodgkin's disease and classified according to the Rappaport Classification (Rappaport, Winter and Hicks, 1956); (2) patient was previously untreated; (3) patient lived within 300 miles of the Stanford Medical Center; (4) age between 10 and 65 years, with option to accept patients to age 70 if they were in satisfactory general medical condition; (5) patient and referring physician agreed to entry into protocol after being carefully informed about the investigative nature of the diagnostic and therapeutic programmes; (6) patient did not have the clinicopathological diagnosis of chronic lymphocytic leukaemia based upon previously defined, relatively arbitrary criteria (Jones *et al.*, 1973); (7) there existed no previous or concurrent medical condition which would seriously compromise the patient's ability to withstand the diagnostic and therapeutic programme planned or the interpretation of the results of the studies.

The pre-operative evaluation included bilateral pedal lymphography and needle biopsy of the bone marrow, in addition to other and routine studies described elsewhere (Rosenberg *et al.*, 1971; Rosenberg, 1973).

The surgical staging procedures included abdominal exploration, splenectomy, wedge and needle biopsies of the liver, selected para-

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aortic and mesenteric lymph node biopsies, open iliac crest bone marrow biopsy and oophoropexy, if indicated (Enright *et al.*, 1970). Metallic clips were used to mark the splenic vascular pedicle and all lymph node biopsy sites.

In 18 patients the exploratory laparotomy was performed in another hospital as the initial diagnostic procedure. In these patients prior needle biopsy of the bone marrow and prior lymphography were not usually performed. In 8 patients in good general condition with positive needle biopsy of the bone marrow, laparotomy with splenectomy was performed for investigative purposes with the patient's informed consent. Thereafter, exploratory laparotomy was carried out only in patients who had a prior negative or equivocal needle biopsy of the bone marrow.

The terminology and classification recommended by the Ann Arbor Staging Conference was employed, designating Clinical Stage (CS) and Pathological Stage (PS). The designation " E " was used for localized extralymphatic disease as defined by Musshoff (Musshoff, 1971) and the Ann Arbor Conference. As recommended, the " B " designation for significant systemic symptoms was limited to those patients who had unexplained significant weight loss, fever and/or night sweats (Carbone *et al.*, 1971).

RESULTS

The histological subgroups of the 127 patients are shown in Table I. In several instances mixed or composite histological appearances were noted. Though this situation creates unanswered classification problems, for the purposes of this review that appearance which seemed to predominate was used for the analyses. Table I also lists the age range, the median age and the sex distribution of the 2 major subgroups, nodular and diffuse.

TABLE I.—*Non-Hodgkin's Lymphoma, Characteristics of 127 Consecutive Protocol Patients*

Histological type	Nodular	Diffuse
Histiocytic	7	37
Lymphocytic, poorly differentiated	41	12
Mixed, lymphocytic-histiocytic	18	5
Lymphocytic, well differentiated	—	5
Undifferentiated	—	2
Total	66	61
Age range	28–67 years	15–68 years
Median age	51 years	48 years
Males	33	40
Females	33	21

TABLE II.—*Non-Hodgkin's Lymphoma, Clinical* vs *Pathological Stage*

	No. of patients	% I	II	III	IV
CS	127	11	16	59	14
PS_M	104	11	15	31	43
CS or PS_M, pre-lap	73	15	23	51	11
PS_{Lap}	73	16	25	23	36
$PS_{M \text{ or } Lap}$	127	11	17	17	55

Table II compares the clinical stage of the entire group with pathological stage determined by sequential bone marrow biopsy (PS_M) and laparotomy and splenectomy (PS_{Lap}). Twenty-three patients did not have needle bone marrow biopsies before laparotomy because the procedure was done before referral to Stanford (18 patients) or because laparotomy, though carried out at Stanford, was done before accession to the protocol (5 patients).

The pathological stages after bone marrow biopsy (PS_M) show a striking shift toward the Stage IV category, primarily from the CS III group.

The pre-operative CS or PS_M distribution of the 73 patients operated upon at Stanford are compared with the pathological stage as determined by the surgical procedure (PS_{Lap}). An additional group of patients is found to have Stage IV disease usually as a result of bone marrow and/or liver involvement. There is some redistribution of patients among the Stage I, II and III groups, as will be detailed for each subgroup.

Table III compares the pre-laparotomy and post-laparotomy stages of the entire group of 91 patients taken to surgery. Table IV makes the same comparison for the 73 patients operated upon at Stanford. Tables V–VIII show the

TABLE III.—*Non-Hodgkin's Lymphoma, Effect of Laparotomy on Stage Distribution*

Pre-laparotomy stage	Post-laparotomy stage I	II	III	IV	Total
I	**11**	1		2	14
II		**16**	2	1	19
III	3	3	**20**	23	49
IV		1		**8**	9
Total	14	21	22	34	91

40% changed stage: 32% higher; 8% lower.

TABLE IV.—*Non-Hodgkin's Lymphoma, Effect of Laparotomy on Stage Distribution*

Pre-laparotomy stage	Post-laparotomy stage I	II	III	IV	Total
I	**9**	1		1	11
II		**14**	2	1	17
III	3	3	**15**	22	43
IV				**2**	2
Total	12	18	17	26	73

45% changed stage: 37% higher; 8% lower.

TABLE V.—*Non-Hodgkin's Lymphoma, Nodular Patterns.*

Clinical stage	Pathological stage I	II	III	IV	Total
I	**3**			2	5
II		**4**	2	2	8
III	1		**14**	34	49
IV				**4**	4
Total	4	4	16	42	66
%	6	6	24	64	

62% changed stage: 61% higher; 1·5% lower.

TABLE VI.—*Non-Hodgkin's Lymphoma, Nodular Lymphocytic Poorly Differentiated*

Clinical stage	Pathological stage I	II	III	IV	Total
I	**1**			1	2
II		**2**		2	4
III			**4**	29	33
IV				**2**	2
Total	1	2	4	34	41
%	2	5	10	83	

78% changed stage: all higher.

TABLE VII.—*Non-Hodgkin's Lymphoma, Nodular Mixed*

Clinical stage	Pathological stage I	II	III	IV	Total
I	**2**			1	3
II		**1**	2		3
III			**7**	4	11
IV				**1**	1
Total	2	1	9	6	18

39% changed stage; all higher.

TABLE VIII.—*Non-Hodgkin's Lymphoma, Nodular Histiocytic*

Clinical stage	Pathological stage I	II	III	IV	Total
I					—
II		**1**			1
III	1		**3**	1	5
IV				**1**	1
Total	1	1	3	2	7

changes in stage distribution as a result of the bone marrow biopsy and/or laparotomy and splenectomy in the patients with nodular histologies. Tables IX–XII show the same comparisons for patients with the diffuse histologies.

It was noted that patients with diffuse histologies under the age of 40 and especially under the age of 20 rarely had occult disease discovered by bone marrow biopsy and/or staging laparotomy. This is demonstrated in Tables XIII and XIV.

Minor and/or major operative complications have been seen in approximately one fourth of this patient group. Fortunately, operative mortality has been rare, no patient in this series having a fatal complication, though one patient not eligible for the protocol studies died in the late post-operative period (Goffinet *et al.*, 1973).

Mesenteric involvement was documented in 26 of 47 patients in whom mesenteric biopsies were obtained and identified for the pathologist. This occurred in 14 of 24 with nodular histologies and 12 of 23 with diffuse patterns.

The accuracy of lymphography within the limitations of surgical sampling of the

TABLE IX.—*Non-Hodgkin's Lymphoma, Diffuse Patterns*

Clinical stage	Pathological stage I	II	III	IV	Total
I	**8**	1			9
II		**12**			12
III	2	3	**6**	15	26
IV		1		**13**	14
Total	10	17	6	28	61
%	16	28	10	46	

36% changed stage: 26% higher; 10% lower.

TABLE X.—*Non-Hodgkin's Lymphoma, Diffuse Histiocytic Lymphoma*

Clinical stage	Pathological stage I	II	III	IV	Total
I	**5**	1			6
II		**9**			9
III	1	3	**6**	5	15
IV		1		**6**	7
Total	6	14	6	11	37
%	16	38	16	30	

30% changed stage: 16% higher; 14% lower.

TABLE XI.—*Non-Hodgkin's Lymphoma, Diffuse Lymphocytic Poorly Differentiated*

Clinical stage	Pathological stage I	II	III	IV	Total
I	**2**				2
II		**3**			3
III	1			4	5
IV				**2**	2
Total	3	3	0	6	12

TABLE XII.—*Non-Hodgkin's Lymphoma, Diffuse Lymphocytic Well Differentiated, Diffuse Undifferentiated, Diffuse Mixed*

Clinical stage	Pathological stage I	II	III	IV	Total
I	**1**				1
II					0
III				6	6
IV				**5**	5
Total	1	0	0	11	12

TABLE XIII.—*Non-Hodgkin's Lymphoma, Diffuse, Under 20 Years of Age*

Clinical stage	Pathological stage I	II	III	IV	Total
I	**1**				1
II		**6**			6
III					0
IV				**2**	2
Total	1	6	0	2	9

TABLE XIV.—*Non-Hodgkin's Lymphoma, Diffuse, Under 40 Years of Age*

Clinical stage	Pathological stage I	II	III	IV	Total
I	**4**				4
II		**9**			9
III	1	1	**6**	1	9
IV		1		**5**	6
Total	5	11	6	6	28

14% changed stage: 4% higher; 10% lower.

retroperitoneal para-aortic and iliac lymph nodes is shown in Table XV. The correlation of splenic weight to histological splenic involvement is shown in Table XVI. The larger the spleen the more likely it was to be involved with lymphoma. However, about one in 4 patients with spleens of normal size and weight had occult lymphomatous deposits. The weight range of uninvolved spleens was 40–245 g; of involved spleens 75–2400 g.

TABLE XV.—*Non-Hodgkin's Lymphoma, Lymphographic Accuracy*

Pathological/ Radiological	−/−	+/−	−/+	+/+
Nodular	9	1	3	24
Diffuse	22	1	4	9
Total	31	2	7	33

TABLE XVI.—*Non-Hodgkin's Lymphoma, Correlation of Splenic Weight and Histological Involvement*

Weight (g)	Involved	Uninvolved	Total	% Involved
≤200	12	35	47	26
201–400	4	7	11	44
>400	10	—	10	100
Total	26	42	68	38

Liver involvement was demonstrated in 15 of 84 patients in whom liver biopsy was performed, an incidence of 18%. However, liver biopsies were not obtained in a majority of patients who had demonstrated bone marrow involvement.

Of 17 patients with a positive bone marrow who did have liver biopsy, 7 (41%) had liver involvement as well. Of 14 patients with hepatic involvement who underwent splenectomy, all but one had involvement of the spleen.

DISCUSSION

The use of exploratory laparotomy and splenectomy for staging purposes in patients with Hodgkin's disease has wide acceptance. The final indications and value of the operative procedure have not been completely determined for all settings and subgroups of Hodgkin's disease, though hundreds of patients have been reported and analysed. Yet, because there are similarities in clinical features and therapeutic approaches between patients with Hodgkin's disease and those with the so-called non-Hodgkin's lymphomata, surgical staging is being performed in an increasing number of patients in the latter group. The value and role of exploratory surgery are being studied and have been reported from several groups (Hanks *et al.*, 1972; Veronesi *et al.*, 1974) including our own (Goffinet *et al.*, 1973).

Though similar in some respects, the non-Hodgkin's lymphomata differ in many ways from Hodgkin's disease. Within the group of patients with the non-Hodgkin's lymphomata there is a wide spectrum of clinical features and clinical courses. Utilizing the valuable Rappaport classification, there are 9 or 10 subgroups in the non-Hodgkin's categories, most of them having important differences each from the other. Analyses that have appeared in the literature and are presented in this report suffer from having relatively few patients in some of the subgroups.

Of great importance is the realization that the appropriate therapeutic programme for patients within each of these groups is not yet clearly defined. In the final analysis, the importance of detailed diagnostic procedures, other than to enlighten the investigators as to the nature of the disorder, is to provide more successful therapeutic approaches. We must hope for longer survival, better quality of survival and more cures as the result of our diagnostic efforts. There has not yet been sufficient time and experience to know whether these goals will result from the information gained from exploratory laparotomy and splenectomy in the non-Hodgkin's lymphomata. Yet considerable information and understanding is obtained from this diagnostic approach and in time it is hoped, indeed it seems likely, that this will result in better patient care.

More than half of the patients in this prospective protocol group have nodular lymphomata, as described by Rappaport and his colleagues (Rappaport *et al.*, 1956; Rappaport, 1966). Patients, on the average, are 15–20 years older than are those with Hodgkin's disease. Since the older patients have more difficulty with major surgery and because the nodular lymphomata, even when widespread, have relatively indolent courses, the value of the diagnostic laparotomy will have to be very definitive before it should be accepted as a routine for all patients.

There are many observations worthy of emphasis and interpretation from the data presented. The relatively young patient with diffuse lymphoma under the age of 20, and the majority (86%) of those under the age of 40, did not change in stage after diagnostic laparotomy. Of the 4 patients who did have their clinical stage changed, 3 had less disease than suspected and one patient advanced to Stage IV from Clinical Stage III.

The diffuse lymphomata differ according to cytological type, as regards the information gained from bone marrow biopsy and diagnostic laparotomy. In

the diffuse histiocytic group, which is relatively common, 30% had a change in stage (about half higher and half lower). More than half of the patients had Pathological Stage I or II which can safely be encompassed by modern irradiation techniques. In contrast, 17 of 24 patients with the diffuse lymphomata of other cytological types, and 10 of 11 of Clinical Stage III extent, were found to have Pathological Stage IV disease.

The nodular varieties also showed probable differences according to the cytological types. The largest group, those with the poorly differentiated lymphocytic type, almost always had Pathological Stage IV disease, usually with bone marrow involvement. Considering the sampling difficulties of determining bone marrow or liver involvement, it seems likely that with rare exceptions this is a generalized disease by the time the diagnosis is established. This was not true for our patients with nodular lymphomata of the mixed lymphocytic–histiocytic or pure histiocytic cell types. Only about one third of these patients could be demonstrated to have Stage IV disease and half had Pathological Stage III extent. This may have important pathogenetic and therapeutic implications.

This difference in the frequency and ease of demonstrating Stage IV disease between the nodular, poorly differentiated lymphocytic and nodular, mixed lymphocytic–histiocytic types is one of the few clinical differences we have noted between these two groups. If confirmed by our further studies and those of others, the continued separate designation of these otherwise similar histological types may be justified.

The lymphogram is still an accurate and important diagnostic procedure. Especially when clearly negative, the study is reliable. When positive, the surgeon may not be able to sample all of the abnormal or suspicious nodes adequately. This may explain some of the apparent false positive roentgenological interpretations. The lymphogram is also of great value in directing the surgeon to suspicious nodes for biopsy, in assisting the radiation therapist to plan his treatment fields, in following the response to therapy and in detecting the earliest signs of new or recurrent para-aortic disease. It should not be abandoned in favour of diagnostic laparotomy and whenever possible should be performed before the diagnostic surgery.

The lymphogram does not provide information about lymph node involvement outside the ilio-inguinal and para-aortic regions. In these lymphomata, in marked contrast to Hodgkin's disease, the mesenteric lymph nodes are involved in more than 50% of those biopsied. Routine mesenteric lymph node removal was not carried out in all of the patients in this series, but the incidence can be no less than 30% in both the nodular and diffuse varieties. The frequency of mesenteric lymph node involvement has important technical implications, should the radiation therapist decide to attempt potentially curative irradiation to known and likely sites of disease (Fu and Stewart, 1973).

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