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# The Liver in Hodgkin's Disease—I. Clinico-pathological Relations*

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**Abstract**—*A retrospective analysis of staging results from 308 patients with Hodgkin's disease (HD) was performed in order to relate clinico-pathological findings with respect to the liver to other staging results and to prognosis. Thirty-four patients had clinically enlarged liver, 80 had increased serum-enzyme levels indicating possible liver damage, but only 10 patients had biopsy-proven histologic evidence of HD in the liver (7 primary biopsies, 3 re-biopsies). Among the prognostic correlations not only advanced stage and liver infiltrates were connected to poor prognosis, but also—even in early stages—elevated serum enzyme values (S-GOT and alkaline phosphatase).*

## INTRODUCTION

WHILE our knowledge of the degree of dissemination of Hodgkin's disease was of less significance during the period when treatment was only palliative, the picture changed towards the end of the 1960s, when first high voltage radiotherapy and subsequently intensive combination therapy were found to be effective and presumably curative in a high percentage of cases.

A precise elucidation of the degree of the dissemination (stage) of the disease became necessary and since then we have—in accordance with the Ann Arbor recommendations [1, 2]—used a set of systematic staging procedures which was followed for each patient by the selection of one of several treatment programs in prospective clinical trials.

In the present study a retrospective analysis of the results of some of the staging procedures in a series of patients treated 6–14 years ago, a period which allows sufficiently long observation time, was undertaken. The study will concentrate on an analysis of the clinical, biochemical and histological findings with respect to the liver, while a subsequent study will give a more detailed account of the histopathologic findings in the liver biopsies [3].

## MATERIALS AND METHODS

Over a period of eight years, from 1966 to 1974, 308 patients with unstaged Hodgkin's disease were referred to our department, and they form the basis for the present analysis. At referral 184 patients were untreated, while 124 patients had previously received radiation therapy (85 patients), chemotherapy (9 patients) or a combination of these (30 patients). Age ranged from 3 to 84 yr (median 40 yr) and the male : female ratio was 1.32.

The diagnosis of Hodgkin's disease was made on a lymph node biopsy, subtyped according to the Rye modification of Lukes–Butler's classification [4]. Lymphocytic predominance (LP) was found in 12%, nodular sclerosis (NS) in 47%, mixed cellularity (MC) in 35% and lymphocytic depletion (LD) in 5% of the patients. Two percent could not be subtyped.

The staging procedures included haematological status, serum bilirubin, serum alkaline phosphatase, serum GOT and serum creatinine, together with roentgenogram of thorax, axial skeleton, kidneys, stomach and retroperitoneum (bipedal lymphangiography). In the clinical evaluation hepatomegaly or splenomegaly was recorded, when the liver (or spleen) by palpation was found $>2$ cm below the curvature in the medioclavicular line by at least 2 investigators. Finally, percutaneous liver biopsy was performed by the Menghini technique and iliac bone marrow biopsy with a Radner needle. The Ann Arbor staging was used with stages I–IV with the suffix A or B, depending on the absence or the presence of general symptoms such as night sweats, fever or loss of weight greater than 10% of the body weight [1, 2].

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After August 1971, supplementary explorative laparotomy was also carried out in those patients who were found to be in stage I, II or IIIA according to the above studies, and at operation, splenectomy, wedge biopsy of the liver and biopsy of the abdominal lymph nodes were performed.

The liver biopsy material thus consisted both of percutaneous liver biopsies done at the staging (primary biopsies) or later in the course of the disease, and of surgical wedge biopsies. Furthermore, autopsy material was obtained from the patients who expired at the hospital.

At the clinical evaluation, 16, 32, 27 and 25% were found to be in stages I, II, III and IV respectively.

Bipedal lymphangiography was carried out in 269 of the 308 patients and was found positive in 118 patients.

Of 83 patients who were evaluated at laparotomy, 30% had their stage altered as a result of this operation.

For each patient the period of observation comprises the time from the primary percutaneous liver biopsy to the present analysis of the material or to prior decease.

Histological technique: haematoxylin–eosin, van-Gieson–Hansen, staining for iron (Berliner blue), amyloid (alkaline Congo) and reticulin (a.m. Gordon & Sweet) were used on all biopsies. The sections were searched in at least 3 depths for infiltrates of the type listed below (together with the diagnostic criteria):

*Infiltrate of Hodgkin's disease.* Infiltrate showing characteristic structure [5, 6] with occurrence of Sternberg–Reed cells, including the mononuclear variant.

*Infiltrates suspect for Hodgkin's disease.* Pleomorphic infiltrates with atypical histiocytic cells with nuclear polymorphy and distinct nucleoli, lymphocytes, granulocytes, possibly eosinophilic, and plasma cells, but no Sternberg–Reed cells.

*Lymphocytic infiltration in the portobiliary space.* Grouped into slight, moderate and severe degrees, the presence of less than ten lymphocytes in a single space not being regarded as pathological. A few plasma cells and granulocytes, possibly eosinophilic, were accepted, but not histiocytes. The changes often varied from field to field, but were evaluated on the basis of the most pronounced changes. In some of these changes the boundary with the surrounding liver parenchyma was blurred, with necrosis of individual liver cells.

*Focal necrosis.* Necrosis of individual liver cells surrounded by a few inflammatory cells.

*Pleomorphic infiltrate.* Infiltrate consisting of histiocytes, lymphocytes, granulocytes, possibly eosinophilic, and plasma cells in varying amounts, but without occurrence of atypical histiocytic cells.

*Epithelioid cell granuloma.* Infiltrate of epithelioid cells, possibly with central fibrinoid necrosis, and the occurrence of giant cells of Langhans type or foreign body giant cells, but not containing acid–alcohol-fast rods.

In the statistical analysis of the results the following tests were used: standard Chi square test, Mann–Whitney $U$ test [7] and Gehan's test [8].

## RESULTS

Clinical examination of the size of the liver was recorded in 307 patients and it was found enlarged in 34 (for definition see Materials and Methods). Palpatory splenomegaly was demonstrated in 21 cases.

As an expression of the liver status, bilirubin, S-GOT and serum alkaline phosphatase was measured at the staging. The two enzyme values were normal in 218 patients, while one or both values were elevated (95% confidence limits) in 80 patients who had no other complicating disease which could have contributed to the enzyme elevation. Bilirubin in serum was found elevated in only one patient who showed no evidence of hemolysis.

The findings described above are partly interrelated. In Table 1 certain of the clinical findings in staging are related to the clinical stage and the lymph node histology. Positive lymphography, enlarged liver or spleen or elevated values of S-GOT and alkaline phosphatase were almost exclusively indicative of Stage III or Stage IV, most often with B-symptoms. The patient groups without enlarged liver or spleen or without elevated enzyme values were distributed over the individual stages in the same way as the total material. Concerning the lymph node histology, patients with hepatomegaly in comparison with patients without hepatomegaly showed a displacement from the two 'benign' histologies, LP and NS, to MC and LD ($P < 0.001$). On the other hand, patients with splenomegaly, positive lymphography or elevated enzyme values did not differ histologically from patients without these findings, or from the total material.

Table 2 demonstrates a positive correlation between the abnormal clinical parameters: the finding of one abnormal parameter resulted in a significantly increased incidence of pathological values of the other parameters ($P < 0.001$).

The relationship between clinical and histological parameters on the one hand and

*Table 1. Clinical findings in relation to clinical stage and lymph node histology at staging in 308 patients with Hodgkin's disease*

| Clinical findings | No. of patients | Percentage distribution of clinical stages | | | Percentage incidence of B-symptoms | Percentage distribution of lymph node histology | |
|---|---|---|---|---|---|---|---|
| | | I–II | III | IV | | LP + NS | MC + LD |
| Negative lymphography | 151 | 81 | 1 | 18 | 36 | 59 | 41 |
| Positive lymphography | 118 | 6 | 58 | 36 | 71 | 58 | 38 |
| Normal spleen | 286 | 52 | 24 | 24 | 50 | 60 | 40 |
| Splenomegaly | 21 | 0 | 62 | 38 | 86 | 48 | 43 |
| Normal liver | 273 | 54 | 25 | 22 | 49 | 63 | 36 |
| Hepatomegaly | 34 | 9 | 44 | 47 | 82 | 27 | 71 |
| Normal enzyme values | 218 | 59 | 24 | 17 | 45 | 61 | 38 |
| Abnormal enzyme values | 80 | 18 | 38 | 45 | 74 | 49 | 48 |
| Total material* | 308 | 48 | 27 | 25 | 53 | 59 | 40 |

*Two percent of the total material could not be subtyped histologically.

*Table 2. Mutual relationship between findings from lymphography, liver palpation, spleen palpation and enzyme values (S-GOT and alkaline phosphatase)*

| Clinical findings | No. of patients | Percentage incidence of positive clinical findings | | |
|---|---|---|---|---|
| | | Positive lymphography | Splenomegaly | Hepatomegaly | Elevated enzymes |
| Negative lymphography | 151 | — | 1 | 5 | 14 |
| Positive lymphography | 118 | — | 13 | 16 | 42 |
| Normal spleen | 286 | 41 | — | 9 | 25 |
| Splenomegaly | 21 | 88 | — | 43 | 52 |
| Normal liver | 273 | 41 | 4 | — | 22 |
| Hepatomegaly | 34 | 70 | 26 | — | 72 |
| Normal enzyme values | 218 | 35 | 5 | 4 | — |
| Abnormal enzyme values | 80 | 70 | 14 | 29 | — |
| Total material | 308 | 44 | 7 | 11 | 27 |

*Table 3. Clinical and histological findings at staging in 79 splenectomized patients*

| Clinical/histological findings | No. of patients | Hodgkin's disease in the spleen (79 pts) Negative (62 pts) | Positive (17 pts) | Weight of spleen (69 pts) < 250 g (50 pts) | > 250 g (19 pts) |
|---|---|---|---|---|---|
| Negative lymphography | 57 | 44 | 13 | 39 | 11 |
| Positive lymphography | 8 | 6 | 2 | 3 | 4 |
| Spleen palpation normal | 78 | 62 | 16 | 50 | 18 |
| Spleen palpation abnormal | 1 | 0 | 1 | 0 | 1 |
| Liver palpation normal | 79 | 62 | 17 | 50 | 19 |
| Liver palpation abnormal | 0 | 0 | 0 | 0 | 0 |
| Enzyme values normal | 66 | 52 | 14 | 44 | 15 |
| Enzyme values abnormal | 10 | 7 | 3 | 4 | 4 |
| Lymph node histology LP | 14 | 13 | 1 | 12 | 0 |
| Lymph node histology NS | 36 | 27 | 9 | 24 | 9 |
| Lymph node histology MC | 29 | 22 | 7 | 14 | 10 |
| Lymph node histology LD | 0 | 0 | 0 | 0 | 0 |
| Spleen without Hodgkin's disease | 62 | — | — | 41* | 12* |
| Spleen with Hodgkin's disease | 17 | — | — | 9* | 7* |

*Ten patients excluded due to lack of information on spleen weight. One of these patients had Hodgkin's disease in the spleen, the others had negative spleen histology.

spleen histology and spleen weight on the other is illustrated in Table 3. Spleen weight was determined in 69/79 splenectomized patients. Fifty out of sixty-nine were normal, and 19/69 weighed more than 250 g. Seventeen out of seventy-nine spleens (23%) contained infiltrates of Hodgkin's disease.

Among patients with negative lymphography and/or no liver enlargement by palpation and/or normal enzyme values, infiltrates of Hodgkin's disease were found in the spleen in 21–23% of the cases and an abnormal spleen weight in 22–23% of the cases. Of 78 patients without clinical splenomegaly, 16 (21%) had positive spleen findings. Only one patient had a spleen which was enlarged on palpation, in agreement with the finding at operation (spleen weight 1300 g). On the other hand, it was striking that an abnormal weight (250–1535 g) was recorded in 18 out of 68 spleens (25%) which were not enlarged on palpation at the preceding clinical examination.

Splenic Hodgkin-infiltrates were found more frequently in patients with high spleen weight (7/19 = 37%) than in patients with normal spleen weight (9/50 = 18%), but the difference was not significant ($P = 0.1$). It is remarkable that enlarged spleen was equivalent to demonstrable Hodgkin-infiltrates in less than half of the cases.

In the liver biopsies both specific infiltrates of Hodgkin's disease and a number of non-specific infiltrates, which will be discussed in a subsequent article, were demonstrated. The liver infiltrates are related to various clinical and histological findings in Table 4. Hodgkin-infiltrates were found in the primary biopsy in six patients, in a repeat biopsy in three patients and in a surgical wedge biopsy in another patient. There were no obligatory abnormal clinical findings, but B-symptoms were absent in only one patient and elevated enzyme values, positive lymphography and hepatomegaly occurred in more than half of the cases. On the other hand, it is striking that only one patient had a palpable spleen. It is likewise remarkable that 4 out of 10 patients had the more 'benign' LP or NS histology in the lymph node biopsy.

The ten patients who showed a positive liver biopsy all received chemotherapy. Six had died at the time of the present analysis, but at autopsy only four showed unchanged infiltrates in the liver, while two patients had no liver infiltrates. The other four patients with infiltrates in the liver are still in complete clinical remission.

The prognostic significance of the factors examined appears from the actuarial survival curves in Figs. 1–4. The estimated 5-yr survival for the total material was 58%. A pathological value of each of the four staging components, lymphography, enzyme determinations, liver palpation or spleen palpation, implied a clearly impaired prognosis (Fig. 2). The patient material accordingly was classified into four classes: patients in whom all the parameters

*Table 4. Clinical and histological findings in 10 patients with malignant infiltrates in the liver*

| Clinical and histological findings | Histological findings in primary biopsy, re-biopsy or wedge biopsy | |
|---|---|---|
| | Hodgkin's disease (10 pts) | Total material (308 pts) |
| Positive lymphography | 6/9* | 44%† |
| Splenomegaly | 1/10 | 7% |
| Hepatomegaly | 6/10 | 11% |
| Elevated enzyme values | 7/10 | 27% |
| B-symptoms | 9/10 | 53% |
| LP + NS | 4/10 | 59% |
| MC + LD | 6/10 | 40% |
| Died | 6/10 | 49% |
| Hodgkin's disease in liver at autopsy | 4/6 | 41% |

*One patient did not undergo lymphography.
†Percentage of total material of 308 patients.

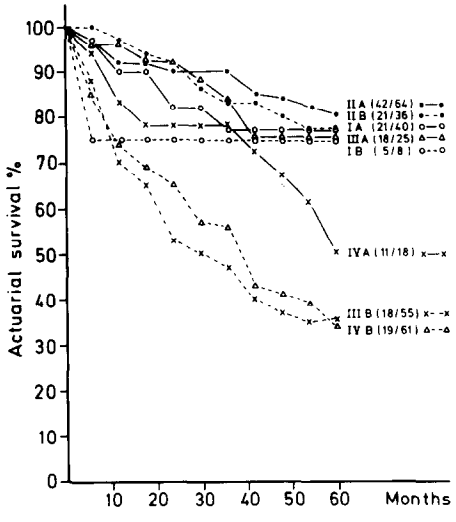


*Fig. 1. Actuarial survival of 308 patients with Hodgkin's disease according to stage of disease. The figures in parentheses indicate No. of patients alive/No. of patients in subset at onset.*

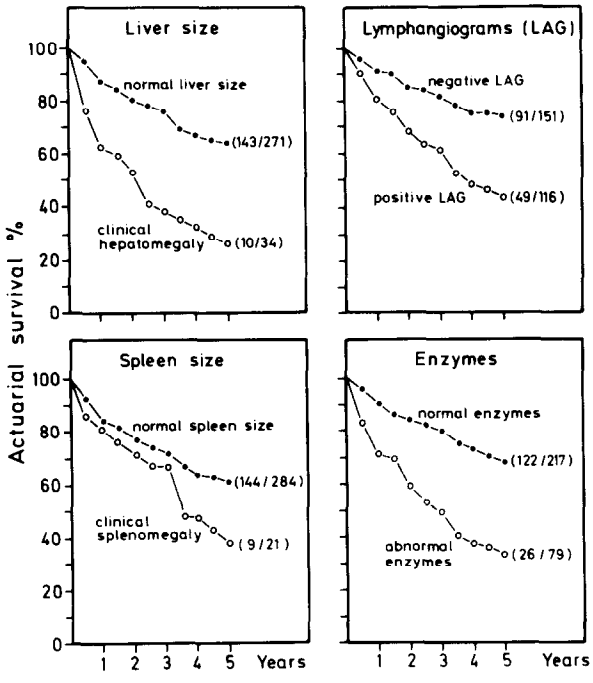


*Fig. 2. Actuarial survival of 308 patients with Hodgkin's disease according to results from staging investigations.*

mentioned were normal (class 1), patients with positive lymphography but the other parameters normal (class 2), patients with positive lymphography and palpable liver and/or spleen enlargement and/or elevated enzyme values (class 3), and patients with negative lymphography but with palpable liver and/or spleen and/or elevated enzyme values (class 4). Figure 3 shows that class 1 clearly had the best prognosis (estimated 5-yr survival, 79%), while the survival was more or less the same in classes 2, 3 and 4, and poorer than the figure of 58% for the total material. The prognoses for classes 2, 3 and 4 were more or less uniform, no matter whether one or more of the parameters examined were pathological and no matter which parameter or parameters were involved.

These prognostic classes did not coincide completely with the disease stages, although 86% of the patients in class 1 were in stages I–II and 93–95% of the patients in classes 2–3 were in stages III–IV. Almost half of the patients in class 4 were in stages I–II, in spite of hepatomegaly and/or elevated enzyme values (none of these patients had splenomegaly). In patients with abnormal enzyme values at the staging procedure, their isolated survival curves showed that under all circumstances these abnormal values signified a poor prognosis, no

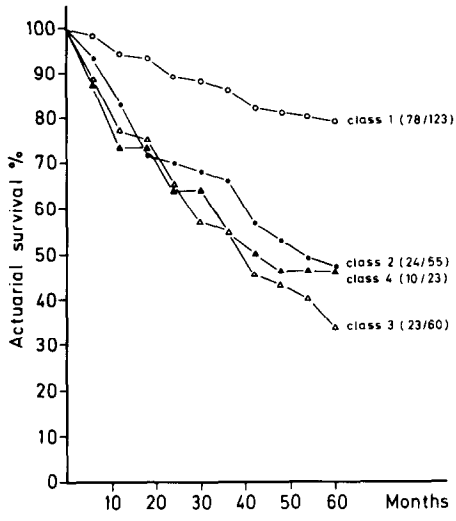


*Fig. 3. Actuarial survival of 308 patients with Hodgkin's disease according to staging characteristics. Class 1: lymphography, liver enzymes, liver size, spleen size: all normal; class 2: lymphography abnormal, other parameters normal; class 3: lymphography and liver size abnormal, spleen size, enzyme elevation normal or abnormal; class 4: lymphography normal, liver size abnormal, other parameters normal or abnormal.*

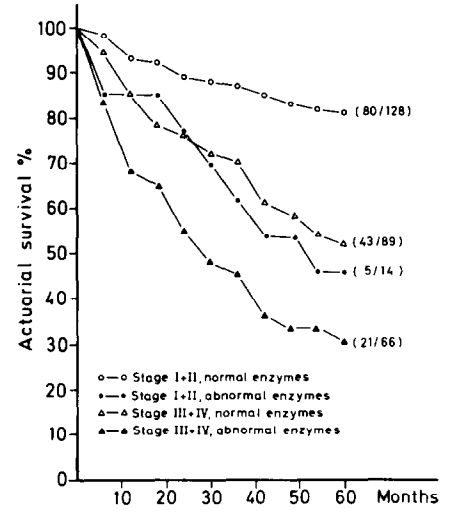


*Fig. 4. Actuarial survival of 308 patients with Hodgkin's disease according to stage and liver enzyme values.*

matter what the stage (Fig. 4). The 5-yr survival for patients in stages I–II with abnormal enzyme values was 46% compared to 81% for patients in the same stages but without elevated enzyme levels.

## DISCUSSION

The present patient material consists of all unstaged patients referred over a delimited period, and in that respect is unselected. The distribution of patients with respect to stage, general symptoms and histological subtypes corresponds to that described in other series [9–11].

In the staging, the liver was found to be enlarged on palpation in 34 patients, who on the basis of other studies were almost all in stage IIIB or IV. Infiltrates of Hodgkin's disease in the liver could be demonstrated by means of the primary percutaneous liver biopsy in only 4 of the 34 patients (12%). It is not possible to prove that in the remaining 30 patients the liver in fact had no infiltrates of Hodgkin's disease. None of the 30 patients proceeded to exploratory laparotomy, but in their subsequent course, at intervals of 1–62 months from the primary biopsy, 11 underwent a further liver biopsy, again with negative results. Of the 30 patients 24 died, and in the 18 who came to autopsy, infiltrates in the liver were revealed in 8 (44%). As this incidence corresponds to the incidence in the total material, a further development of the disease in the intervening period of 1–62 months is a more probable explanation of the infiltrates in the liver than an undiagnosed primary involvement. Even though it was only in a few patients that hepatomegaly was associated with infiltrates of Hodgkin's disease demonstrable in the biopsy specimen, the symptom was correlated with poor prognosis. At the time the material was analysed, 79% of the group with initial hepatomegaly had died, compared to 49% in the whole material. This can be explained to some degree by over-representation of advanced stages (III and IV) and more malignant histology (MC and LD) in this group, which in itself is a striking finding.

Positive lymphography likewise showed positive correlation with hepatomegaly (Table 3), but was not a prerequisite for liver infiltrates, as negative lymphography was found in 3 of the cases verified on biopsy.

The emphasis by Glatstein *et al.* that liver infiltrates do not occur without the spleen being involved at the same time[12] cannot be discussed on the basis of our material, as only one patient with positive liver findings underwent splenectomy, which showed that the spleen was involved. None of the 9 other patients with liver infiltrates had clinical splenomegaly, but as described for the surgically staged group, this was no guarantee that the spleen was not involved.

When the 10 patients in whom biopsy showed infiltrates of Hodgkin's disease in the

liver are considered, the other clinical findings were, in decreasing incidence: systemic symptoms, elevated S-GOT and alkaline phosphatase, hepatomegaly, positive lymphography, splenomegaly. Since about half of the total patient material had one or more of these findings, none of the findings (or combinations of these findings) are specific for infiltrates of the disease in the liver.

In the majority of patients (23/34) hepatomegaly was associated with elevated values of S-GOT and alkaline phosphatase, but these enzymes were found elevated in a total of 80 patients in the material. The non-specificity of such an enzyme increase corresponds to the findings in other series [13–15] and may for the advanced disease stages possibly be explained by a contribution from other types of organ infiltrates (e.g. alkaline phosphatase from bone infiltrates), but the cause of the elevated enzyme in the early stages is uncertain. At the time of investigation of our patients we did not have access to isoenzyme determination of the alkaline phosphatase. However, Aisenberg *et al.* found in electrophoresis studies that hepatic phosphatase was by far the greatest source of elevated alkaline phosphatase in patients with the early stages of Hodgkin's disease, just as they found a high incidence of elevated alkaline phosphatase in all stages in patients with the B-symptom of fever [16].

The established prognostic factors in Hodgkin's disease are: stage, histology, age and sex [9, 11, 17] and, as shown in this study, elevated levels of S-GOT and alkaline phosphatase. However, irrespective of the stage, elevated values of these enzymes do imply a reduction in the survival time. It is therefore conceivable that the elevated enzyme levels are an expression of dissemination of the disease, also in those cases where the patients are classified in stages I–II, based upon the available but clearly inadequate investigative procedures.

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