The Staging of Hodgkin’s Disease

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Summary

The interpretation of the clinical status of Hodgkin’s disease is based on the histology of the involved node, the patient’s age and sex, the anatomic extent of the disease, and the presence or absence of systemic symptoms. The necessary survey of the patient at the time of diagnosis includes symptomatic history, complete physical examination, laboratory studies, and X-ray examinations including lymphangiography. The usual stagings of Hodgkin’s disease are: Stage I, localized disease; Stage II, regional disease above or below the diaphragm; Stage III, disease both above and below the diaphragm; and Stage IV, extranodal disease. Subtype A refers to the absence, and B to the presence, of symptoms.

Accurate staging is of importance in suggesting prognosis, determining the most effective forms of treatment, and in providing a basis for comparison of the clinical experiences of different clinics.

Clinical Stages of Hodgkin’s Disease

Hodgkin’s disease runs a variable clinical course, perhaps more so than that of any other form of neoplastic disease. Craver has applied the old clinical maxim about syphilis to Hodgkin’s disease: “Know this and you know medicine” (4). Clinicians, for many years, have tried to characterize the different clinical pictures of Hodgkin’s disease for prognostic and therapeutic purposes. These efforts have reached their culmination in the present concept of staging, as defined by Peters (17, 18) and modified by Kaplan (12, 13). Table 1 shows the 1950 classification of Peters and her modification in 1958 to include the symptomatic status of the patient. Kaplan’s additional stages include Stage 0, where all evidence of disease is removed by the biopsy, and Stage IV, which contains the extranodal manifestations of Hodgkin’s disease. As reported by Lee et al. (15), staging accuracy has been remarkably upgraded by the use of lymphangiography. While staging is a relatively straightforward procedure, its implications deserve some discussion as related to the complex aspects of Hodgkin’s disease.

Diagnosis of Hodgkin’s Disease

The diagnosis of Hodgkin’s disease is suspected by the physician but made by the pathologist. In rare instances the diagnosis of Hodgkin’s disease has been strongly suggested by the clinical findings, and for various reasons, treatment was initiated before a histologic diagnosis was obtained. In 3 such cases, pathologic examination proved the clinical impression incorrect; subsequent examination by the pathologist revealed sarcoidosis, carcinoma of the lung, and reticulum cell sarcoma.

The Reed-Sternberg cell is the hallmark of Hodgkin’s disease, and in establishing the diagnosis it takes precedence over any clinical finding. The Reed-Sternberg cell suggests that the pathogenesis of Hodgkin’s disease may be unique and separate from other neoplastic diseases, an assumption also implicit in the organization of a special conference on Hodgkin’s disease. In clinical practice, it may be assumed that some cases of Hodgkin’s disease are missed or misdiagnosed because the Reed-Sternberg cells were not found, whereas other cases were diagnosed in error because a Reed-Sternberg-like cell was interpreted as the real thing. There is thus uncertainty, in some cases, about the diagnosis; instances have occurred where expert pathologists have retreated from a diagnosis of Hodgkin’s disease when it appeared to be incompatible with the clinical findings. These are exceptional situations, however, and most cases of Hodgkin’s disease present a well-defined pathologic picture with no need for indecision on the part of a competent pathologist. While we are dependent on the pathologist for the diagnosis of the unique entity known as Hodgkin’s disease, in some series that diagnosis has been in doubt, based on subjecting the slides to review by a panel of pathologists, in about 20% of the patients (8).

Clinical Manifestations and Stages

Physicians appreciated early the importance of the initial physical findings and symptoms in individual patients in anticipating the clinical manifestations and course of the disease. Reed (19), in her report in 1902 describing the characteristic cells of Hodgkin’s disease, referred to 2 clinical stages.

One is progressive enlargement of the lymphatic glands, almost always beginning in the cervical area. “The disease affects progressively the neighboring glands, apparently following the normal lymphatic distribution... During the first stage of the disease, which may be prolonged over months, the general physical condition is apparently normal, even while the glands are increasing rapidly.

“The second stage of the disease, marked by progressive asthenia, cachexia, and anemia, invariably develops, usually after one or more years, but occasionally after a very brief period of glandular growth... Irregular or continuous fever is the rule, attributable to the inflammatory nature of the disease.”

Ziegler’s (23) description of the clinical course of Hodgkin’s disease in 1911 was modified by Longcope and McAlpin (16). The disease was differentiated into 7 clinical pictures: “(a) an acute form; (b) a localized form; (c) a generalized form; (d)
TABLE 1
STAGING CLASSIFICATIONS IN HODGKIN’S DISEASE

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>No detectable disease, owing to excisional biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>Involvement of a single lymph node region or a single lesion elsewhere in the body</td>
<td>Involvement of a single site or lymphatic region</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>Involvement of 2 or more proximal lymph node regions of either the upper or lower trunk</td>
<td>Involvement of 2 or 3 proximal lymphatic regions</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>Involvement of ( \frac{3}{2} ) or more lymph node regions of both upper and lower trunk</td>
<td>Involvement of 2 or more distant lymphatic regions</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Disease above and below the diaphragm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These clinical pictures can be shown to correspond to the current classification of the stages of Hodgkin’s disease.

1. LOCALIZED FORM. “The cervical nodes are most often affected. The solitary masses grow slowly for two or three years, and the disease assumes a chronic course.”

2. MEDIASTINAL FORM. This form “represents one variety of the localized form in which the mediastinal nodes are especially involved. The patient presents a remarkable picture with all the symptoms and signs of mediastinal tumor—cough, dyspnea, orthopnea, pain and other evidences of pressure.”

3. GENERALIZED FORM. “There is an extension of the localized process to neighboring groups of nodes and the disease becomes more or less generalized.”

These forms correspond roughly to Stages I and II.

4. ACUTE FORM. “Death may occur within a few weeks, or at most months. In this form the enlargement of the lymph-nodes is often remarkably wide-spread, but not very great.”

5. LARVAL OR LATENT FORM. “In this type the disease is confined more or less exclusively to the thoracic or abdominal lymph-nodes. The superficial nodes may escape completely. The symptoms are varied and often indefinite. Abdominal pains, jaundice, diarrhea, or effusions into the pleural and abdominal cavities may occur. The spleen and liver are often enlarged. Fever is frequently present. Some of the most pronounced examples of remittent fever occur in this type.”

The acute and larval forms may be incorporated in Stages II-B and III-B.

Longcope also describes 2 additional forms, which were confined to the spleen or involved bone and bone marrow. These forms, as well as other extranodal manifestations of Hodgkin’s disease, would represent Kaplan’s Stage IV. These are early examples of the continuing efforts to classify Hodgkin’s disease.

These classifications are based on the extent of detectable disease and the presence or absence of constitutional symptoms and signs. Craver (3) divided the disease into 3 classes: Class I, localized disease; Class II, regional disease, all apparent disease being above or below the diaphragm, with or without constitutional signs and symptoms; and Class III, generalized disease with constitutional signs and symptoms. Healy et al. (9) has followed a similar classification. Shimkin et al. (21) defines Stage...
TABLE 2
FAVORABLE AND UNFAVORABLE FACTORS

<table>
<thead>
<tr>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Young adult</td>
<td>Elderly</td>
</tr>
<tr>
<td>Outdoor occupation</td>
<td>Abnormal or depressed blood picture</td>
</tr>
<tr>
<td>Normal blood count</td>
<td>Rapid progression of disease</td>
</tr>
<tr>
<td>Long history of localized disease</td>
<td>Generalized disease, or abdominal presentation</td>
</tr>
<tr>
<td>Localized to 1 side of neck, not at the base</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Weight gain after 1st course of treatment</td>
<td>Symptomatic: fever, itching, anorexia, weakness</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Signs: splenomegaly, involvement of pulmonary parenchyma, multiple cutaneous nodules</td>
</tr>
</tbody>
</table>

II as regional disease without constitutional symptoms; the occurrence of symptoms places the patient in Stage III. It is often difficult to distinguish between Stages I and II-A, and Easson and Russell (5) have lumped them together. Their classification appears to be based simply on the presence or absence of constitutional signs and symptoms.

While Peters' (18) stage classification is of great practical value, a number of important factors of prognostic significance are not considered, particularly in the wastebasket Stage III. These include such factors as the sex of the patient (the course of the disease is generally slower in females), the duration of signs or symptoms before the diagnosis is made (the longer the prediagnostic history, the better the prognosis, presumably because the disease is evolving more slowly), age (the disease progresses more rapidly in older patients), the exact location of the presenting lymph nodes, and the completeness and duration of response to therapeutic procedures. The weighing of some of these factors, as adapted from Craver (4), is listed in Table 2.

While they are of general value in predicting the clinical course, Finkbeiner et al. (6) were unable to find any single reli-

CHART 1. Relation of clinical stages to estimated survival in Hodgkin's disease. The estimated % of patients in Stages I-III, with or without symptoms, but staged with the addition of lymphangiography. The clinical course is estimated for patients in Stage I, for those who have progressed from Stages I to II, I to III, and from II to III, and for those presenting in Stage III. Do patients who present in Stage I and then recur after treatment progress more slowly when they enter Stage II or Stage III than patients who present initially in these stages? The abscissa refers to the % of patients remaining in the stage estimated on the basis that 100% are in the stage at zero time. Patients in Stage III remain there. The last column refers to the total mortality in each stage from the clinical onset of the disease, with a range suggested by several studies. Thus far, adequate data to establish the correctness of the graph are not available.
TABLE 3

Estimated % of Patients Surviving 5 and 10 Years

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>60-70</td>
<td>50-60</td>
</tr>
<tr>
<td>Stage II-A (lymphangiogram negative)</td>
<td>50-60</td>
<td>40-50</td>
</tr>
<tr>
<td>Stage II-B, III</td>
<td>15-30</td>
<td>5-10</td>
</tr>
</tbody>
</table>

TABLE 4

Estimated Number* of Patients Surviving 5 and 10 Years

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>4.2</td>
<td>3.6</td>
</tr>
<tr>
<td>Stage II-A (lymphangiogram negative)</td>
<td>9.6</td>
<td>7.9</td>
</tr>
<tr>
<td>Stage II-B, III</td>
<td>15.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Total</td>
<td>30.0</td>
<td>16.7</td>
</tr>
</tbody>
</table>

* Based on 100 patients.

Patients Presenting in Various Stages of Hodgkin's Disease (%)

Retrospective interpretation of staging from different institutions or even within the same institute is difficult; classification of stages vary from investigator to investigator, and lymphangiography within the past 3 years has profoundly modified the incidence of clinical stages. Aisenberg, in his review of Hodgkin's disease (1), concludes that at the time of presentation about 20% of the patients are Stage I, 20% in Stage II, and 60% in Stage III. If a normal lymphangiogram is essential to qualify for Stages I and II-A, the probable incidence of these stages is closer to 25-30%, and about 60-70% of the patients when 1st seen are in Stage III with constitutional signs and symptoms (2, 4, 5, 7, 9-11, 14, 18, 21). Estimates of the incidence of Stages I, II, and III are shown in Chart 1; about 9% of the patients are estimated to present with extranodal lesions (Stage IV, Kaplan).

Relation of Stages to Clinical Course

Hodgkin's disease is specifically staged at the time of diagnosis in order to plan the appropriate therapeutic program. Correct staging of localized disease is stressed by the radiotherapists, because these patients may have a prolonged response to treatment. But, in order to determine the importance of treatment in the several stages, untreated control patients are needed. Since they are obviously impossible to obtain, the probable course of the several stages of Hodgkin's disease must be interpreted in treated patients. Localized Hodgkin's disease usually extends to regional nodes and then disseminates (20). Symptoms appear to be related to the volume of tumor present, but also, they occur commonly in patients with retroperitoneal disease or bone marrow involvement. Sometimes, severe symptoms are found with little detectable Hodgkin's disease; possibly at this stage the process is diffuse. The rate of evolution of the disease varies in each patient. Stage I may remain localized for many years without treatment, and the localized disease, when it extends or recurs, may do so more slowly than in patients who present with Stage III disease. Furthermore, the possibility must be considered that when Hodgkin's disease appears in another site in someone who had been treated successfully for local disease years before, it may not be a metastasis, but reinitiation of the disease. While Hodgkin's disease usually begins in a local area, the hypothetical initiating factor may be a systemic one. Reinduction may be a possible explanation when Hodgkin's disease, recurring in a new area after a long disease-free period, behaves in a more aggressive manner than the original process. Detailed information on the pattern of progression of the various forms and stages of Hodgkin's disease must be accumulated, and the modifications in the
natural course of the disease as a result of treatment must be interpreted as best one can. Aisenberg (1) has tabulated the 5- and 10-year survivors by stage at the time of diagnosis. While these available data are not highly consistent, I have tried to develop some broad estimates for purposes of orientation (Table 3).

On the basis of the estimated distribution of patients in each stage, 5- and 10-year survivors are estimated as seen in Table 4. If these estimates are reasonable, there should be an equal number of patients alive who presented in Stages I and II-A and in Stages II-B and III at 5 years, but by 10 years the ratio should be close to 2.5:1.

Conclusions

Chart 1 summarizes the stages of Hodgkin's disease, the estimated incidence in each stage, and the estimated 5- and 10-year survival rates. The incidence of constitutional signs and symptoms in relation to each stage is noted. These figures are a personal estimate, which will be validated or corrected in due course. Chart 1 also suggests the need to determine the clinical course of Stage I patients after entering Stages II and III, and Stage II patients who enter into Stage III. Do patients tend to follow the temporal course common to each stage, or do patients progressing from Stage II-A to III, for example, show a slower pace of the disease than those presenting initially in Stage III?

At present we are still in a data-collecting period. Opinions concerning staging, the clinical evolution of Hodgkin's disease, the significance of the various constitutional signs and symptoms and the benefits from various forms of treatment require validation. As the pathologic criteria of diagnosis, the staging technics, and the principles of therapy of localized Hodgkin's disease are standardized, the collection of reliable data should be vastly improved. Institutions can then pool data, obtained and recorded in a comparable manner, for analysis.

It may be worth listing the diagnostic procedures and follow-up examinations followed in our own clinics (Table 5).

A clinical classification of the various forms of Hodgkin's disease is essential, and the staging technic is for the present both practical and widely accepted. It is of interest at this time to refer to another summary statement on Hodgkin's disease.

“We regret the impossibility of giving more exact figures as to ultimate recoveries, but as 67 per cent of these patients have come to us within the last two years, and as our work before that time was less standardized, the reason is obvious.

“Apparently greater benefits are being obtained as experience increases and methods and judgment improve. We are of the opinion that in about 20 per cent of all cases as we see them recovery is a possibility at present.

“Earlier diagnoses, and the recognition that Hodgkin's disease, if treated promptly and radically, is curable would raise this percentage materially without any change in the treatment outlined above. More definite laboratory and clinical knowledge of this disease as a morbid physiologic process, and clearer conceptions of the defensive mechanisms which combat it, are needed to further an effective rational therapy” (22).

Yates and Bunting (22) wrote this in 1917, and I am unable to add anything important to their conclusions.

References

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