Hodgkin's Lymphoma—Patients Assessment and Staging

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Abstract: Hodgkin's lymphoma is one of the most curable malignancies today. But treatment is associated with significant toxicity. The objective of high-quality management is to minimize treatment exposure while maximizing cure of disease. Principles of cancer staging and patient's assessment taxonomy are important to improve communication. An orderly patient evaluation and systematic recording of disease extent using the Ann Arbor classification forms the basis for treatment decision, response assessment, and clinical trials. The practice of staging in Hodgkin's lymphoma evolved over the past 40 years from clinical examination and plain imaging to modern anatomic and functional imaging. Although useful in the past, staging laparotomy, lymphangiograms, and Gallium scintigraphy have now been abandoned. Computerized tomography combined with 2-[18F]fluoro-2-deoxyglucose-positron emission tomography form the basis for anatomic disease extent assessment. Although patients' evaluation and staging at diagnosis are important, the management of Hodgkin's lymphoma involves a complex series of algorithms requiring interim and overall response assessment, careful follow-up, repeat assessment, and salvage management of recurrent disease.

Key Words: Hodgkin's lymphoma, staging, prognosis, patient assessment

(*Cancer J* 2009;15: 138–142)

Hodgkin's lymphoma is an important malignant disease. It affects young people, it is highly curable and requires meticulous assessment, treatment, and response evaluation to maximize cure, and minimize treatment-related toxicity. In the past 20 years, advances in chemotherapy and judicious use of combined modality therapy resulted in the improved overall survival of patients with Hodgkin's lymphoma.[1] Currently, more than 80% of younger patients may expect cure.[2] In this review, we will consider the taxonomy of patient assessment, staging, and response evaluation, describe the evolution of staging in Hodgkin's lymphoma, and outline the current procedures used to define disease extent.

The optimal management of any malignant disease requires careful evaluation of the disease, the patient, and available treatment options. This evaluation requires as the first step the confirmation of diagnosis with definition of the specific tumor type and any molecular tumor characteristics. The second step is assessment of disease extent. Disease extent is defined as "stage of disease." The third step is assessment of patient's general health and comorbidities that may impact treatment. Staging, as the estimation of the anatomic disease extent, is therefore only 1 component of patient evaluation and must not be confused with the overall patient assessment.

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ISSN: 1528-9117/09/1502-0138

TAXONOMY

Disease stage is defined and recorded at the time of initial presentation and diagnosis. It is important as patients with different disease stage at presentation have different prognosis, regardless of the ensuing course of disease. For example, a patient with stage I disease that recurs after treatment will have a better survival than the patient with stage IV disease who recurs. Stage is a form of shorthand language to describe disease extent. For example, in Hodgkin's lymphoma, stage I communicates disease limited to 1 lymph node region, whereas stage III communicates lymph node involvement above and below diaphragm.

In clinical practice, the term "staging" is used at any time disease extent is evaluated during the course of disease. The appropriate term for patient assessment after treatment would be "evaluation of treatment response," and at relapse, "assessment of extent of relapse." Staging (verb) as an activity describes the tests required to determine disease extent. There is also general misunderstanding of "staging" and "prognostic evaluation." Disease stage is only 1 of prognostic characteristics. Prognostic factors may be grouped into tumor related, host or patient related, and environment related.[3,4] Tumor-related factors include "tumor profile" that describes histopathological, molecular, and genetic characteristics, whereas "tumor stage" describes the anatomic disease extent.[3] The prognostic factors should be evaluated in the context of specific treatment intervention and prognosis should be defined with a specific end point in mind. For example, proposed use of chemotherapy with bleomycin and doxorubicin requires evaluation of pulmonary and cardiac function, whereas proposed use of cisplatin requires evaluation of renal function and hearing.

Cancer Staging—Principles and Use

Staging of malignant diseases was first proposed in 1920s. It was recognized then that patients with smaller localized cancers survived longer than those with extensive or disseminated disease. They were also cured with surgical resection. Pierre Denoix, father of modern TNM classification noted that the anatomic disease extent is a very powerful predictor of outcome but not the only factor.[5,6] He noted that tumor type, grade, rate of growth, and patients' symptoms were also relevant. Today, many forget that the original intent of staging classification was to describe the anatomic disease extent. Staging classification is therefore a form of language or code to communicate this. For example, in Hodgkin's lymphoma, stage I communicates disease limited to 1 lymph node region, whereas stage III communicates lymph node involvement above and below diaphragm. Knowledge of the anatomic extent of disease is essential to characterize cancer before treatment. Stage is required to develop a treatment plan. The extent of disease is relevant for assessment of outcomes with any form of treatment, although the location of disease is more important when local therapies (surgery and radiotherapy) are used.

The information about stage is used in selecting appropriate diagnostic tests. For example, patients who have advanced stage III and stage IV Hodgkin's lymphoma are recommended to have bone marrow biopsy. Staging is used to select an appropriate treatment

plan; all practice guidelines for Hodgkin's lymphoma include stage as one of the decision points for recommending treatment. Staging is necessary to be able to prognosticate and predict the outcome for an individual patient and stage information is used to establish informed consent for treatment.

Stage information is used to assess the outcome of therapeutic intervention in similar groups of patients. We use initial stage and knowledge of the outcome associated with this to select appropriate follow-up monitoring and provide patient and caregiver education. Stage information is also used in research. The analysis of patients' outcomes by stage is used to improve the efficiency of research design and data analysis and enhance the confidence of prediction. We design future studies by identifying subgroups with poor outcomes with current therapies. As all treatments for cancer are associated with some toxicity, stage information is also used to identify groups with excellent outcomes that can benefit from reduced therapy.

STAGING HODGKIN'S LYMPHOMA

Traditional staging of Hodgkin's lymphoma was based on physical examination and later imaging, which in 1960s and 1970s was with conventional x-rays with contrast (intravenous pyelogram (IVP), inferior vena cava (IVC), and lymphography) or plain tomography. Imaging was used to detect thoracic and abdominal disease, whereas the presence of peripheral lymphadenopathy was determined by careful palpation, which was a highly valued, but known as quite inaccurate clinical skill. Over the past 30 years, modern imaging with computerized tomography (CT) replaced other clinical methods.

Hodgkin's lymphoma was one of the first diseases, where clinical staging and logical progression of the disease was linked to outcomes. The early proposals for staging classification were formalized in 1971 at the Workshop on the Staging of Hodgkin's Disease held in Ann Arbor, MI. The Ann Arbor classification has been formally adopted by the Union Internationale Contre (International Union Against Cancer) Tumor Node Metastasis (UICC TNM) Committee.[7] Today, almost 40 years later, staging classification of Hodgkin's lymphoma remains relevant although imperfect. The last modifications to the Ann Arbor classification were proposed at the Cotswolds meeting in 1998 (Table 1).[8] Although the stage designation is commonly used in practice, detailed descriptors such as "X" for bulky disease are rarely used. The current approach to staging of patients with Hodgkin's lymphoma has evolved over the past 40 years. This gradual evolution was driven by changes in the management and by progress in imaging. There is general paucity of level I evidence to guide staging. To understand the practice today, it is useful to review the history of staging in Hodgkin's lymphoma.[9]

CLINICAL PRESENTATION AND PATIENT ASSESSMENT

Patients with Hodgkin's lymphoma typically present with asymptomatic lymph node enlargement, most commonly in the neck. However, if peripheral lymph node enlargement is not apparent, patients may present with systemic symptoms such as night sweats or fever. Weight loss is usually associated with advanced disease. Fever, night sweats, and weight loss have prognostic significance in Hodgkin's lymphoma, are known as "systemic" symptoms, and are present in about one third of patients. Pruritus is another relatively common presenting symptom. It used to be associated with adverse outcome, but with modern treatment, it is not. Because intrathoracic presentations are common, cough, and shortness of breath are among other presenting features. Biopsy of enlarged lymph nodes usually is diagnostic.

The clinical assessment starts with confirmation of diagnosis. A careful histopathologic assessment of the biopsy by an experienced pathologist and presence of adequate amount of tissue is paramount. Immunocytochemistry helps to differentiate between Hodgkin's and other types of lymphoma. With modern techniques, the confusion between Hodgkin's lymphoma and non-Hodgkin's lymphoma is less common than in the past.

The modern assessment of the extent of disease in Hodgkin's disease includes careful history, laboratory tests, physical examination, and imaging (Table 2).[10] Patient assessment involves the comprehensive history, specifically enquiring about presence or absence of constitutional "systemic" symptoms including unexplained fever more than 38°C, night sweats, or unintentional weight loss of greater than 10% of body weight. These 3 symptoms are classified as B symptoms and they are used in staging to indicate adverse prognosis. Other lymphoma-related symptoms, such as

TABLE 1. Cotswold Modification of the Ann Arbor Staging Classification[8]

Stage I	Involvement of a single lymph node region of lymphoid structure or involvement of a single extralymphatic site (IE)
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized contiguous involvement of only one extranodal organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by involvement of the spleen (IIIS) or by localized contiguous involvement of only one extranodal organ site (IIIE) or both (IIISE)
Stage IV	Disseminated (multifocal) involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement
Designations applicable to any stage	
A	No symptoms
B	Fever (>38°C), night sweats, unexplained loss of >10% body weight in previous 6 mo
X	Bulky disease
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

Involvement of hilar nodes on both sides constitutes stage II disease.

Bulky mediastinal disease has been defined as a thoracic ratio of maximum transverse mass diameter greater than or equal to one third of the internal transverse diameter measured at T5/6 intervetebral disc level on chest radiography. Other authors have designated a lymph node mass of 10 cm or more in greatest dimension as bulky disease.

Evidence of invasion of adjacent structures, such as bone, chest wall, or lung is an important consideration, as this may influence management. For example, a mediastinal or hilar mass that invades the adjacent lung is classified as IIE, whereas pulmonary involvement separate from adenopathy represents stage IV disease.

TABLE 2. Staging and Assessment of Patients with Newly Diagnosed Hodgkin's Lymphoma

History	Presence of systemic symptoms—fever, night sweats, and weight loss
	Pruritus and alcohol-related pain
	HIV status, cardiac, pulmonary, renal disease, hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody
Physical examination	Peripheral lymph node area, lever, and spleen
Laboratory tests	Complete blood count, LDH, liver function tests, and ESR
Imaging	CT—head and neck, chest, abdomen, and pelvis
	PET-CT
Bone marrow biopsy	Stages III–IV
	B symptoms

fatigue, pruritus, and alcohol-induced pain in involved nodal areas, should be noted, although they do not confer adverse prognosis. Laboratory studies should include a complete blood count, lactate dehydrogenase, erythrocyte sedimentation rate, alkaline phosphatase, albumin, and liver function tests. Bone marrow biopsy is indicated in selected cases of Hodgkin's lymphoma, those with advanced disease or hematologic abnormalities.

In addition, before recommending treatment, clinical assessment should assess fitness of patient to treatment, assess the degree of comorbidities, and state of vital organs. Before starting chemotherapy, the patient should have electrocardiogram (ECG), multigraded acquisition scan (MUGA) scan or echocardiogram, pulmonary function tests, thyroid, and gonadal function tests and, if relevant, semen analysis and sperm storage. None of these tests are relevant to staging per se, but they are essential in assessing the baseline condition of the patient and monitoring treatment toxicity.

The guidelines for staging of Hodgkin's lymphoma call for comprehensive physical examination. Although the physical examination may guide the initial investigations, in all instances, patients presenting with Hodgkin's disease should have full imaging studies including imaging of all major lymph node groups, thorax, and abdomen.

Because staging of Hodgkin's lymphoma evolved over the years, we will consider specific issues in staging Hodgkin's lymphoma and conclude with currently recommended procedures.

Staging Laparotomy

In 1960s and 1970s, stage I and stage II Hodgkin's lymphoma was managed with radiotherapy alone. Radiotherapy (RT) resulted in almost 100% local control, but was associated with 30% to 50% distant failure, most frequently because of the presence of occult intraabdominal disease. This and limited accuracy of imaging led to the acceptance of surgical staging of Hodgkin's lymphoma. Patients with clinically localized presentations were routinely subjected to laparotomy with splenectomy, and biopsies of the liver and paraaortic lymph nodes. The staging laparotomy in Hodgkin's lymphoma provided valuable information about the patterns of abdominal involvement. Numerous studies consistently revealed clinically occult abdominal disease in 30% to 50% of patients. This occult disease was most commonly found in the spleen. The correlation between clinical factors including the extent of supradiaphragmatic disease, presence of systemic symptoms, elevated erythrocyte sedimentation rate (ESR), age, bulk, and the findings at staging laparotomy led to the development of risk-adjusted management strategies that selectively used combined modality therapy in patients at high risk of occult abdominal disease. With time, improved imaging of the abdomen, increased use of combined modality therapy and the desire to limit the extent of radiotherapy to avoid late toxicity, eliminated the need for staging laparotomy.[9] Randomized studies showed equivalent survival for patients managed with and without staging laparotomy.[11] Although now abandoned, staging laparotomy provided useful information about patterns of disease.[9] Fundamentally, the staging evaluation should meet the needs of clinical patient management. With the availability of improved imaging with CT scanning, the availability of FDG-PET imaging, and the use of combined modality therapy in almost all patients with Hodgkin's disease, staging laparotomy is no longer relevant.

Bone Marrow Biopsy

Unlike in non-Hodgkin's lymphoma, staging bone marrow biopsy is not required in most of patients with Hodgkin's disease. Numerous studies have documented that the bone marrow involvement in patients with stage I and stage II Hodgkin's lymphoma without unfavorable prognostic factors is extremely rare and false-positive determinations are as frequent as positive.[12,13] Therefore, the bone marrow biopsy should be reserved for patients with stage III and stage IV Hodgkin's lymphoma or those stage I and stage II patients with severe B symptoms or hematologic abnormalities.

Anatomic Imaging

Lymphangiogram

In the past, lymphangiography played an important role in the assessment of infradiaphragmatic Hodgkin's lymphoma.[14] The development of lymphangiograms presented a major advance in staging of Hodgkin's lymphoma. The ability to visualize abdominal lymph nodes was useful in staging and response assessment because the contrast remained in situ for a number of months.[15–17] In 1980s, CT gradually replaced lymphangiography with no major effect on the ability to detect intra-abdominal disease.

Computerized Tomography

Today, full imaging studies in Hodgkin's lymphoma include CT imaging of all lymph node areas, including head and neck, thorax, abdomen, and pelvis.[18] In addition, if extranodal disease is suspected, magnetic resonance imaging is used to assess the extent of soft tissue, spinal canal, or brain involvement. This thorough imaging assessment of the patient serves to define the anatomic disease extent, which is essential for determining the stage. The knowledge of exact disease extent is also very useful in assessing completeness of response to treatment. The obvious limitations of anatomic imaging include inability to visualize microscopic disease, difficulties in interpreting small lymph nodes visualized on CT, and differentiating benign reactive inflammatory infiltrates, fibrosis, etc. from malignant tumor. Lymph nodes under 1 cm in diameter may also represent reactive hyperplasia, but also may harbor Hodgkin's lymphoma. Current convention calls for thoracic and abdominal lymph nodes to be considered as abnormal if they measure more than 10 mm in the short-axis diameter, and the neck, axillary, and inguinal lymph nodes if they measure more than 15 mm in short axis diameter. Clearly, smaller lymph nodes may harbor Hodgkin's lymphoma but many may be reactive.

Functional Imaging

Gallium Scintigraphy

CT and conventional x-ray imaging provides anatomic but not functional information. In the past, Gallium scintigraphy was used to define disease extent and response in Hodgkin's and other lymphomas.[19] This originated after the observation that uptake of Gallium-67 citrate was most pronounced in viable tumors. Although

used for staging, the major role of Gallium imaging in the last 2 decades was to evaluate the response of tumor to treatment rather than to stage patients. Gallium imaging was found to be poor in detecting small volume disease particularly in the abdomen, where one can find enlarged lymph nodes that are Gallium negative. The absence of Gallium uptake could be interpreted as the absence of disease.

FDG-PET Imaging

In the past 20 years, the development of PET technology led to extensive investigation of biochemical processes in vivo. PET is a noninvasive, quantitative imaging technique that can visualize biologic processes in vivo. PET has been shown to be superior to ^{67}Gallium-scintigraphy in lymphoma staging, it is easier to perform, and it delivers a lower radiation dose to the patient.[20–23] With the use of combined PET/CT equipment, disease sites can be defined both based on size criteria and their glucose metabolism.[24] FDG-PET has proven a valuable tool in the management of lymphomas.[25–27] FDG-PET is a useful modality in staging of lymphomas especially when used in conjunction with CT imaging. It is more sensitive than Gallium imaging but in studies comparing staging that includes FDG-PET and staging with modern CT imaging without FDG-PET, the change in the stage is small. In addition, there has been no report suggesting that the outcome of patients staged with and without FDG-PET differs. One should differentiate the role of FDG-PET in the initial staging from the role of FDG-PET in response assessment and guiding further therapy. Several studies have shown FDG-PET to be very sensitive in detecting areas of involvement by Hodgkin's lymphoma. In addition to detecting nodal involvement, FDG-PET is much more sensitive in detecting extranodal involvement, especially in the spleen, bone, and bone marrow. PET in general is able to detect an additional number of Hodgkin's lymphoma sites compared with conventional CT. This usually results in a modification of stage, usually increasing the stage, in about 15% to 20% of patients. Overall, management is changed in 5% to 15% of patients.[28,29] Despite the general use of FDG-PET in staging, most reports include small numbers of patients, often mixing Hodgkin's lymphoma and other lymphomas. One of the largest series is from the prospective study by the Intergruppo Italiano Linfomi.[30] The study included 186 patients from 6 Italian hematological institutions studied between 2002 and 2005. Imaging with FDG-PET was compared with the standard contrast enhanced CT imaging. In this study, overall 910 involved sites were registered with CT and 1090 sites were evaluated with FDG-PET. In this study, the sites seen on FDG-PET were confirmed with another imaging modality (magnetic resonance imaging, ultrasound). As most other studies, the gold standard of biopsy to evaluate discordant site was not used. Overall CT and FDG-PET were concordant in 84% of patients and discordant in 16%. Stage was higher with PET in 14% and lower in 1%. The planned treatment was modified based on PET results in 11 patients. Of patients staged as localized (stage I and stage II), 10 (8%) has stage changed to advanced. Contemporary management of Hodgkin's lymphoma is based on anatomic stage, presence of systemic symptoms, bulky mediastinal disease, ESR, and age. Most patients with Hodgkin's lymphoma receive chemotherapy today. Patients with stage I and stage II disease and no risk factors may receive reduced number of courses of chemotherapy followed by involved field radiotherapy. It would be interesting to see, in how many patients recommended treatment would have been insufficient when CT alone was used to determine disease stage. The current treatment policies have been developed in an era of CT imaging without PET and it is possible that the treatment recommended would compensate for deficiencies in staging. To date, no study to date compared the outcomes of patients staged with and without FDG-PET.

Despite the high sensitivity and specificity, the usefulness of FDG-PET in Hodgkin's lymphoma staging is debated. The increased use of chemotherapy negates the need for the exact definition of anatomic disease extent. However, the trend to minimizing treatment with the use of short chemotherapy and limiting radiotherapy to involved lymph nodes requires precise information on anatomic disease extent. Therefore, in most centers, FDG-PET is recommended as part of staging assessment.

SUMMARY

Current practice in staging of Hodgkin's lymphoma developed gradually over the past 40 years. Modern imaging made staging laparotomy redundant. Lymphangiograms are no longer performed, and Gallium scintigraphy is rapidly becoming obsolete. There is little argument today that CT imaging is the cornerstone of staging assessment in patients with Hodgkin's lymphoma. The art of physical examination is important, but its limitations are obvious, and therefore imaging should be used not only in the assessment of intrathoracic and intra-abdominal disease, but also to evaluate peripheral lymphadenopathy.

Change takes time, and in number of centers, Gallium scintigraphy continues to be performed, usually because FDG-PET is not approved for staging. However, because FDG-PET has become an essential tool in response assessment, it is a matter of time until all centers will adopt FDG-PET as part of imaging at diagnosis.[31]

It is important to realize that the current guidelines for patient assessment and evaluation have not been prospectively evaluated in the context of modern practice guidelines.[10] Current practice calls for minimizing treatment in patients with stage I and stage II "low risk" presentations. The risk factors include presence of B symptoms, elevated ESR, bulky disease, and age. These "risk factors" in Hodgkin's lymphomas were based on the pattern of failure with radiotherapy alone, in patients evaluated with 1980s imaging techniques, without FDG-PET. The adverse influence of B symptoms on outcomes is still poorly understood, the importance of ESR is questionable. The adverse impact of age is acknowledged but poorly understood. We should ask whether these factors are still relevant in 2009 in the era of chemotherapy and functional imaging.

The earlier review concentrated on the evaluation of patients presenting with newly diagnosed disease. It is important to note that the management of patients with Hodgkin's lymphoma involves a complex algorithms requiring interim assessment of treatment efficacy, overall response evaluation, careful follow-up to detect treatment failure early, and maximize the potential benefit of salvage treatment.[10]

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