Staging Non-Hodgkin Lymphoma

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ABSTRACT Non-Hodgkin Lymphomas are always treatable and frequently curable malignancies. However, choosing the most appropriate therapy requires accurate diagnosis and a careful staging evaluation. New patients with non-Hodgkin Lymphoma should have their tumors classified using the World Health Organization classification. The specific choice of therapy is dependent on a careful staging evaluation. Patients with non-Hodgkin Lymphoma are assigned an anatomic stage using the Ann Arbor system. However, patients should also be classified using the International Prognostic Index. New insights into the biology of the lymphomas in the coming years might well improve our ability to evaluate patients and choose therapy. (CA Cancer J Clin 2005;55:368–376.)
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INTRODUCTION

The development of staging was an important advance in the care of patients with cancer. The concepts of staging were developed during the 20th century and were formalized in the United States by the establishment of the American Joint Commission on Cancer in 1959. Although anatomic stage (ie, the specific sites of involvement by the cancer) was the initial focus of staging, for some cancers other factors are considered. Symptoms, the differentiation of the tumor, and the results of specific laboratory tests are now included in assigning stage to certain cancers. Staging accomplishes several important goals in cancer management. These include choosing the best therapy, allowing an accurate prognosis to be given to the patient and their family, and accurately stratifying patients to make clinical research and quality assessment possible. In addition, knowing the sites of involvement at diagnosis makes it possible to accurately restage at the end of therapy and document a complete remission.

Assigning a stage to a newly diagnosed patient with non-Hodgkin Lymphoma is no less important than for other cancers. However, the development of a staging system for non-Hodgkin Lymphoma has been a difficult and complicated process. This is, at least in part, due to the heterogeneous nature of illnesses encompassed in the term “non-Hodgkin Lymphoma.” Lymphoid malignancies are generally classified as leukemia if they involve primarily the blood and bone marrow and as lymphoma if they present as tumors in lymph nodes or other organs. However, almost all lymphoid malignancies can have either presentation and some are almost equally likely to present as a leukemia or lymphoma. In addition, immune system malignancies represent a spectrum from some of the most indolent malignancies (eg, some mucosa-associated lymphoid tissue [MALT] lymphomas) to the most rapidly progressive human cancers (eg, Burkitt lymphoma).

The first system widely utilized for staging non-Hodgkin Lymphomas was actually developed for staging Hodgkin disease and is referred to as the Ann Arbor Staging System. Although primarily an anatomic staging system, the Ann Arbor stages are modified by the presence or absence of systemic symptoms. It was adjusted over the years for the use in staging Hodgkin disease, but still represents a backbone of the staging system recommended today for non-Hodgkin Lymphomas. However, recognition that the Ann Arbor system does not subdivide some types of non-Hodgkin Lymphomas in a clinically useful way, and the recognition that other factors are important in predicting treatment outcome, led to the development of the International Prognostic Index in 1993. The recommendation for the evaluation of a new patient diagnosed with non-Hodgkin Lymphoma currently involves application of both these systems.

The current recommendations for staging non-Hodgkin Lymphoma adopted by the American Joint Commission on Cancer are published in the Cancer Staging Manual, sixth edition. These have been developed by a committee.
of experts and are reviewed on a regular basis. The membership of the committee on staging lymphoid neoplasms can be found in Table 1.

### CLASSIFICATION OF NON-HODGKIN LYMPHOMA

Our ability to classify patients with non-Hodgkin Lymphomas into clinically useful groupings has steadily improved as our understanding of the biology of the immune system has advanced. The use of histopathology to diagnose malignancies and the discovery of the Reed Sternberg cell early in the 20th century allowed a distinction between Hodgkin disease and the other lymphomas grouped together as non-Hodgkin Lymphoma. Gall and Mallory proposed a widely used system for subclassifying the non-Hodgkin Lymphomas in the 1940s. However, this system had limited clinical utility. Henry Rappaport used the presence or absence of a follicular growth pattern and the size and shape of cells to devise the first classification system with striking clinical utility. However, subsequent recognition that lymphomas were all tumors of lymphocytes and that there were different subsets of lymphocytes (ie, B, T, and NK cells) led to new systems. The most popular of these were the Lukes-Collins classification in the United States and the Kiel classification in Europe.

The use of multiple systems of classification throughout the world posed serious difficulties for therapeutic research. It was difficult or impossible to compare the results of therapeutic trials when different systems of classification were utilized. To solve this problem, the Working Formulation was developed as a compromise system. The Working Formulation adopted some aspects of the Rappaport Classification, the Lukes-Collins Classification, and Kiel Classification and was the primary system used in publications in much of the 1980s and 1990s. However, it never became as popular in Europe as in North America. The 1980s and 1990s also saw striking advances in our understanding of biology of the immune system and recognition that some lymphomas didn’t fit easily into the existing categories. The study of lymphomas carrying the t(11;14) and overexpressing the associated Bcl-1 protein led to the acceptance of mantle cell lymphoma as a specific diagnosis. The discovery of CD30 (formerly Ki-1) and the recognition that some malignancies marked by CD30 had a t(2;5) and overexpression of the ALK protein led to the acceptance of anaplastic large T/null cell lymphoma as a distinct clinical entity. Also, the description of small B-cell lymphomas occurring in association with epithelial tissue, sometimes developing in association with specific infections, led to acceptance of the concept of MALT lymphomas. Of course, the prototype MALT lymphoma occurs in the stomach and is usually associated with infection by Helicobacter pylori. None of these new lymphomas fit easily into a preexisting category in the widely used classification systems and, in fact, generally were found in several different categories.

In the 1990s, a group of hematopathologists proposed a new system to take into account advances in understanding the biology of the immune system and the recognition of these newly accepted subtypes of non-Hodgkin Lymphoma, termed the Revised European American Lymphoma (REAL) classification. Diagnoses in the REAL classification were based on morphology, immunology, and clinical characteristics. Study of the REAL classification showed that it was clinically relevant and more reproducible than previous systems.

The concepts embodied in the REAL classification were used to develop the World Health...
Organization (WHO) classification of lymphoma that is currently the gold standard throughout the world.\textsuperscript{21}

The WHO classification is presented in Table 2. It subdivides tumors into those of B-cell versus T/NK-cell origin and those with an immature or blastic appearance versus those developing from more mature stages of lymphoid development. The latter tumors, in the case of T-cell lymphomas, were referred to as “peripheral” T-cell lymphomas. Today, the first step in evaluation of any patient with non-Hodgkin Lymphoma should be classification of their tumor in the World Health Organization classification. This should include the performance of immunophenotyping and might require cytogenetics, fluorescent in situ hybridization (FISH), antigen receptor gene rearrangement studies, and other investigations. If at all possible, this should be done by an experienced hematopathologist working with an excisional biopsy of an affected lymph node or extra lymphatic tumor. Large cutting needle biopsies are an alternative in selected cases where excisional biopsy is difficult or dangerous. Fine-needle aspirates are not appropriate and should not be the basis for primary diagnosis of non-Hodgkin Lymphoma and the subsequent choice of therapy.\textsuperscript{22}

ANN ARBOR STAGING

Although originally developed for staging patients with Hodgkin disease, the Ann Arbor staging system provides the basis for anatomic staging in non-Hodgkin Lymphomas as well. However, the use of the Ann Arbor staging system for non-Hodgkin Lymphomas has a number of shortcomings. These relate in large part to the different pattern of disease seen in the non-Hodgkin Lymphomas as opposed to Hodgkin disease. For example, primary extranodal Hodgkin disease is rare, but a primary

### TABLE 2  World Health Organization Classification of Lymphoid Neoplasms

| Neoplasm Type                  | Classification                                                                 |
|-------------------------------|--------------------------------------------------------------------------------|
| **B-cell neoplasms**          | Precursor B-cell neoplasm                                                    |
|                               | Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia) |
| Mature (peripheral) B-cell neoplasms | B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma |
|                               | B-cell prolymphocytic leukemia                                                |
|                               | Lymphoplasmacytic lymphoma                                                   |
|                               | Splenic marginal zone B-cell lymphoma (with or without villous lymphocytes)   |
|                               | Hairy cell leukemia                                                           |
|                               | Plasma cell myeloma/plasmacytoma                                              |
|                               | Extranodal marginal zone B-cell lymphoma (with or without monocytoid B cells) |
|                               | Nodal marginal zone B-cell lymphoma (with or without monocytoid B cells)      |
| Follicular lymphoma           | Mast cell lymphoma                                                            |
|                               | Diffuse large B-cell lymphoma                                                 |
|                               | Burkitt lymphoma/Burkitt cell leukemia                                         |
| **T-cell and NK-cell neoplasms** | Precursor T-cell neoplasm                                                   |
|                               | Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia) |
| Mature (peripheral) T/NK-cell neoplasms | T-cell prolymphocytic leukemia                                      |
|                               | T-cell granular lymphocytic leukemia                                           |
|                               | Aggressive NK-cell leukemia                                                   |
| Adult T-cell lymphoma/leukemia (HTLV1+) | Extranodal NK/T-cell lymphoma, nasal type                                  |
|                               | Enteropathy-type T-cell lymphoma                                              |
|                               | Hepatosplenic gamma delta T-cell lymphoma                                     |
|                               | Subcutaneous panniculitis-like T-cell lymphoma                                |
|                               | Mycosis fungoides/Sezary syndrome                                             |
|                               | Anaplastic large cell lymphoma, T/null cell, primary cutaneous type            |
|                               | Peripheral T-cell lymphoma, not otherwise characterized                      |
|                               | Angioimmunoblastic T-cell lymphoma                                            |
|                               | Anaplastic large cell lymphoma, T/null cell, primary systemic type             |
extra nodal site is frequently seen in certain types of non-Hodgkin Lymphomas and is always the case in MALT lymphomas. In addition, some types of non-Hodgkin Lymphoma (eg, small lymphocytic lymphoma and mantle cell lymphoma) have bone-marrow involvement in the majority of patients, placing a disproportionally high number of patients in the highest stage. Despite these shortcomings, the Ann Arbor staging classification remains the best method available for anatomic staging of non-Hodgkin Lymphomas and has been universally adopted for this purpose.

The Ann Arbor staging system divides patients into four stages based on localized disease, multiple sites of disease on one or the other side of the diaphragm, lymphatic disease on both sides of the diaphragm, and disseminated extranodal disease (Table 3). Localized extranodal sites of involvement are recognized by a subscript E.

The definition of these stages as found in the Cancer Staging Manual is as follows: Stage I: Involvement of a single lymph node region (I), or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE) (rare in Hodgkin disease). Stage II: Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (II_E). The number of regions involved may be indicated by a subscript, for example, II_3. Stage III: Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (III_E) or by involvement of the spleen (III_S) or both (III_E,S). Stage IV: Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Any involvement of the liver or bone marrow, or nodular involvement of the lung(s) is always Stage IV. The location of Stage IV disease is identified further by specifying site according to the notations listed for Stage III.

The distinction between Stage I and Stage II involvement is based not on individual lymph nodes but on what are termed as “lymph node regions.” Lymph node regions were defined at the Rye Symposium in 1965 and have been accepted by convention since that time. The lymph node regions include right cervical (including cervical, supraclavicular, occipital, and preauricular lymph nodes), left cervical, right

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**TABLE 3  Ann Arbor Classification and the Cotswold Modifications**

| Stage | Features |
|-------|----------|
| I     | Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer’s ring) |
| II    | Involvement of two or more lymph node regions on the same side of the diaphragm |
| III   | Involvement of lymph regions or structures on both sides of the diaphragm |
| IV    | Involvement of extranodal site(s) beyond that designated E |
| For all stages | No symptoms |
| A     | Fever (>38°C), drenching sweats, weight loss (10% body weight over 6 months) |
| B     | Involvement of a single, extranodal site contiguous or proximal to known nodal site |
| For Stages I to III E | Massive mediastinal disease has been defined by the Cotswold meeting as a thoracic ratio of maximum transverse mass diameter greater than or equal to 33% of the internal transverse thoracic diameter measured at the T5/6 intervertebral disc level on chest radiography. |
| Cotswold modifications | The number of anatomic regions involved should be indicated by a subscript (eg, II_i) |
|       | Stage III may be subdivided into: III_1, with or without pleural, hilar, celiac, or portal nodes; III_2, with para-aortic, iliac, mesenteric nodes |
|       | Staging should be identified as clinical stage (CS) or pathologic stage (PS) |
|       | A new category of response to therapy, unconfirmed/uncertain complete remission (CR) can be introduced because of the persistent radiologic abnormalities of uncertain significance |
axillary, left axillary, right infraclavicular, left infraclavicular, mediastinal, hilar, periaortic, mesentery, right pelvic, left pelvic, right inguinal femoral, and left inguinal femoral. Multiple lymph nodes palpable in one of these regions would be Stage I, and involvement of two of these regions but on one side of the diaphragm would represent Stage II. Unlike Hodgkin disease, it is not uncommon for non-Hodgkin Lymphoma to involve other lymph node sites not included in the core sites from the original Ann Arbor classification. These might include epiploic, popliteal, internal mammary, occipital, submental, perauricular, and other small lymph node areas. Each of these could also be considered a separate lymph node site and used in the distinction between Stage I and Stage II.

The designation of Stage IV disease implies disseminated disease involving extranodal sites. However, by convention, involvement of the bone marrow, liver, pleura, and cerebrospinal fluid are always considered Stage IV even if the disease is isolated to that organ. Lymphatic involvement in a draining area from a primary extranodal lymphoma should be designated as $II_E$ (eg, a thyroid lymphoma with cervical lymph node involvement). Lymphoma extending beyond the lymph node capsule involving adjacent organs should also receive the E suffix and not be called Stage IV (eg, lymphoma in mediastinal lymph nodes growing directly into adjacent lung). It is true that unusual cases might lead to debate about the appropriate assignment of Stage $II_E$ or Stage IV, and sometimes even experts can disagree about which would be most appropriate.

Anatomic staging in non-Hodgkin Lymphoma can be done using history, physical examination, laboratory studies, and images, in addition to definitive proof of involvement of a particular site from biopsy. As a practical point, most patients are assigned their stage based on the results of noninvasive studies rather than having biopsies to document each apparent site of involvement.

Appropriate clinical staging includes: a careful recording of history and physical examination; appropriate images of the chest, abdomen, and pelvis; blood chemistry measurements; complete blood count; and bone marrow biopsy. The basic staging and investigation for a patient with non-Hodgkin Lymphoma includes all these studies with images usually obtained using computed tomography (CT) scans. In patients unable to safely undergo a CT scan, magnetic resonance imaging studies are often substituted. Recent advances in functional imaging using positron emission tomography scans have expanded the possibilities for imaging in non-Hodgkin Lymphoma. However, clear definitions of what constitutes a site of involvement and whether or not positron emission tomography scans can substitute for CT scans are a point for debate and investigation. Patients at high risk for central nervous system involvement should have a lumbar puncture and cerebrospinal fluid cytology performed. Bone marrow biopsy is a standard part of the clinical investigation. However, what is an appropriate bone marrow biopsy has been a point of disagreement, with some experts saying that bilateral biopsies are necessary. The most important part of a bone marrow biopsy is obtaining an adequate core for histological evaluation (ie, at least 15 to 20 mm). Whether this is done with one or multiple punctures probably does not matter. Biopsy of other sites (ie, beyond the initial excisional biopsy on which the diagnosis was based) would normally only be done if the results might modify therapy.

In the past there has been debate on how large a lymph node needed to be for it to be considered abnormal. By convention, lymph nodes greater than 1.5 cm in maximum diameter are now considered abnormal and assumed to be involved by disease. Documenting splenic involvement lymphoma can be problematic but is usually done by identifying palpably enlarged spleens or focal defects seen on imaging studies. Liver involvement is usually demonstrated by multiple defects on imaging studies consistent with involvement by neoplasm or by liver biopsy. The presence of a palpable liver or abnormal liver chemistries should not be used alone to assume involvement of the liver by lymphoma. Lung involvement is usually documented by presence of characteristic imaging abnormalities. On occasion, lung biopsy may be necessary to clarify
equivocal cases. Clinical involvement of the brain can be documented by characteristic imaging abnormalities in a patient with lymphoma known to metastasize to the brain. However, this is an unusual situation. More commonly, primary brain lymphomas require biopsy to document their presence.

Although more useful in Hodgkin disease, the Ann Arbor Staging system also designates patients as either being suffix A or B. Designation as A indicates the absence of unexplained fever with temperature greater than 38°C, drenching night sweats requiring the change of bedclothes, and unexplained weight loss of more than 10% in the 6 months before diagnosis.

**INTERNATIONAL PROGNOSTIC INDEX**

The Ann Arbor Staging system does not adequately provide prognostic information for many subtypes of non-Hodgkin Lymphoma and is far from optimal for making treatment decisions. Knowing when the disease is localized is an important factor for all types of lymphoma, but most non-Hodgkin Lymphomas are not localized and the ability to better assess the majority of patients for treatment decisions and to stratify patients in clinical trials is extremely important. In 1993, the International Non-Hodgkin Lymphoma Prognostic Index was published. This was the result of an international collaboration involving more than 2,000 patients with aggressive non-Hodgkin Lymphoma who were treated with an anthracycline-based combination chemotherapy regimen. Although originally intended for the use in patients with aggressive lymphomas, this index has utility for all types of non-Hodgkin Lymphoma and has been widely applied.

Results of the International Prognostic Index study showed that five factors were roughly equal in power in predicting treatment outcome (Table 4). These included age greater or less than 60 years, Ann Arbor Stage I and II versus Stage III or IV, none or one versus two or more sites of extranodal involvement by lymphoma, an Eastern Cooperative Oncology Group performance status (Table 5) of Grade 0 or 1 versus Grade 2 or greater, and a normal versus elevated lactate dehydrogenase (LDH). The number of adverse prognostic factors (ie, age > 60 years, advanced stage, two or more extranodal sites, poor performance status, or elevated LDH) could be simply summed because each had approximately the same power in predicting treatment outcome. Thus, a score of 0 to 5 was possible. The original publication suggested the patients be lumped into groups with a low risk (ie, score of 0 or 1), low intermediate risk (score of 2), a high intermediate group (score of 3), and a high risk (score of 4 or 5). In the original study and in previous experience, there is a highly significant impact on chances to achieve a remission, remain in

### TABLE 4  International Prognostic Index

| Prognostic Factors | Risk Category (Factors) |
|--------------------|-------------------------|
| Age > 60 years     | Low (0 or 1)            |
| Performance status > 2 | Low-intermediate (2)  |
| Lactate dehydrogenase > normal | High-intermediate (3) |
| Extranodal sites > 2 | High (4 or 5)          |
| Stage III or IV    |                         |

### TABLE 5  Eastern Cooperative Oncology Group Performance Status*

| Grade | Description                                                                 |
|-------|-----------------------------------------------------------------------------|
| 0     | Fully active, able to carry on all predisease performance without restriction |
| 1     | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work) |
| 2     | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3     | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4     | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5     | Dead                                                                       |

*As published in Oken, et al.23
remission, and overall survival based on the International Prognostic Index score. For example, patients in the low-risk group in the original publication had an 87% complete remission rate and an overall survival of 73% at 5 years versus a 44% complete remission rate and 26% survival at 5 years in the high-risk group (Table 6).3

Particularly important was documentation that the International Prognostic Index score was able to subdivide patients in Ann Arbor Stage II, III, and IV (Figure 1). The dramatic difference in treatment outcome for patients with the same Ann Arbor Stage found by utilizing the International Prognostic Index undoubtedly explains wide discrepancies in the results of some previous clinical trials. For example, in Phase II trials, several chemotherapy regimens seemed to be superior to cyclophosphamide, doxorubicin, vincristine, and prednisone in the treatment of aggressive lymphoma24–26 but yielded the same outcome in a head-to-head Phase III trial.27 In retrospect, the earlier studies almost certainly treated patients with a better prognosis, although the stages were similar.

The International Prognostic Index is presented in Table 4. This should be calculated on every new patient with non-Hodgkin Lymphoma and will have an important impact on the treatment decision.

**TABLE 6 International Prognostic Index**

| Number of Risk Factors | Complete Response Rate (%) | Five-year Relapse-free Survival (%) | Five-year Overall Survival (%) |
|------------------------|----------------------------|-----------------------------------|--------------------------------|
| All patients*          |                            |                                   |                                |
| Low                    | 0 or 1                     | 87                                | 70                             | 73                             |
| Low intermediate       | 2                          | 67                                | 50                             | 51                             |
| High intermediate      | 3                          | 55                                | 49                             | 43                             |
| High                   | 4 or 5                     | 44                                | 40                             | 26                             |
| Age-adjusted index, patients ≤60 years† | | | | |
| Low                    | 0                          | 92                                | 86                             | 83                             |
| Low intermediate       | 1                          | 78                                | 66                             | 69                             |
| High intermediate      | 2                          | 57                                | 53                             | 46                             |
| High                   | 3                          | 46                                | 58                             | 32                             |

*Adverse factors: age > 60 years, increasing lactate dehydrogenase, performance status 2 to 4, more than one extranodal site, Ann Arbor Stage III or IV.
†Adverse factors: elevated lactate dehydrogenase, performance status 2 to 4, Ann Arbor Stage III or IV.
The primary site of origin of a non-Hodgkin Lymphoma almost certainly affects the biological characteristics of the malignancy. There is no reason to believe that diffuse large B-cell lymphoma originating in different sites of the body would have the same behavior any more than we would think that all squamous cell carcinomas, regardless of origin, would have the same behavior. It is possible that different types of evaluations would be appropriate for tumors originating in different parts of the body.

The most important factor likely to change the way we evaluate patients with lymphoma is the rapidly expanding knowledge about gene expression patterns and protein expression. It is possible to imagine a time when the only evaluation of a new patient with lymphoma that would be required would be identification of the expression of certain key proteins. If drugs that specifically targeted these proteins were available, and they could cure most or all patients, other evaluation could be superfluous. Although certainly a goal for the future, it is not impossible that we could reach this point.

Whatever the future holds, at the present time an accurate staging evaluation is key to the management of a patient with newly diagnosed non-Hodgkin Lymphoma. Careful application of the systems described in this paper will lead to the best possible treatment outcome.

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