Non-Hodgkin's Lymphoma
An Approach to Staging and Therapy

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Progress in the management of non-Hodgkin’s lymphomas (NHL) has been less impressive than the dramatic advances in the control and cure of Hodgkin’s disease. Unlike Hodgkin’s disease, it has not yet been documented whether NHL tends to spread along contiguous lymph nodes. Recent evidence suggests that hepatic and marrow involvement may frequently be observed at diagnosis in patients with the lymphocytic types of NHL, in contrast to Hodgkin’s disease, which is usually limited to the lymph nodes at presentation. Although disseminated NHL may respond to the same chemotherapeutic regimens as Hodgkin’s disease, response has been noted in a smaller percentage of patients and for a shorter duration of time. Despite these limitations, however, advances in histologic classifications as well as clinical and pathologic staging have broadened our understanding of the non-Hodgkin’s lymphomas, and will hopefully lead to improved survival.

The Hodgkin’s disease staging system introduced at Ann Arbor can be readily applied to the study of NHL.

(Table 1.) Stages I and II denote involvement of one or more lymph node regions, respectively, on the same side of the diaphragm. Stage III includes disease limited to the lymph nodes, but on both sides of the diaphragm; involvement of the spleen is noted specifically. Stage IV indicates lymph node and visceral involvement (such as marrow or liver). Involvement of only one organ, such as the stomach or bowel, does not signal Stage IV disease, but rather Stage I(, (E = extranodal). This distinction is especially important since up to one-third of the non-Hodgkin’s lymphomas may arise in extralymphatic sites.

To simplify the analysis of NHL, all histologic types are grouped together. It must be recognized, however, that several disorders are involved. Non-Hodgkin’s lymphomas can be classified by cell type (Table 2.): lymphocytic, well differentiated; lymphocytic, poorly differentiated; histiocytic; or mixed-cell. These lymphomas may also be classified as nodular or diffuse, according to the overall histologic pattern. (Figs. 1a, 1b, 1c, 1d.) “Histiocytic lymphoma” refers to the cell type previously termed reticulum cell sarcoma. The relative incidence of each histologic type of NHL is presented in Table 3.

Many studies have confirmed the clinical value of this classification by showing that patients with various histologic
types of NHL have different patterns of visceral involvement and response to therapy. Thus, the hematopathologist plays an essential role in the initial evaluation of these patients.

**Staging**

**History and Physical Examination**
A history of a lump or other mass, recurrent infections, an episode of herpes zoster, as well as unexplained anemia or bleeding may be initial clues to the diagnosis of NHL. The findings of lymphadenopathy, splenomegaly or hepatomegaly is suggestive, but lymphoma may also present as an abdominal mass, a tumor of Waldeyer’s ring (nasopharynx, adenoids and tonsils), or as a discrete lesion of either the lung or central nervous system.

A complete and careful physical examination of all lymph nodes, especially those that lie outside conventional radiotherapy fields, such as the epitrochlear nodes, is essential. Unfortunately, physical examination alone usually cannot detect hepatic and splenic disease, and is almost worthless in uncovering retroperitoneal disease.

Following the histologic diagnosis of NHL, but prior to treatment, the extent of disease must be evaluated. As is true for all cancers, the extent of clinical evaluation must be guided by the type of therapy proposed. In patients considered for aggressive curative treatment, extensive evaluation is appropriate. In those whose age and underlying medical problems limit therapy to local palliation, few investigative procedures are indicated. If Stage IV disease has been documented (Table 1.), no further staging is necessary. Additional noninvasive tests, however, may detect local disease, requiring immediate intervention.

| Stage  | Description                                                                 |
|--------|-----------------------------------------------------------------------------|
| I      | Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (\(I_E\)). |
| II     | Involvement of two or more lymph node regions on the same side of the diaphragm (III) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (III_E). |
| III    | Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an extralymphatic organ or site (III_E) or by involvement of the spleen (III_S) or both (III_Se). |
| IV     | Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Reasons for classifying the patient as Stage IV should be identified. |

**Note:** In Hodgkin’s disease, all patients are subclassified A or B to indicate the absence or presence, respectively, of (1) unexplained weight loss of more than 10 percent body weight; (2) unexplained fever with temperatures above 38°C; (3) night sweats.
While knowledge of therapeutic options is essential, anticipating findings may also determine the extent of staging which should be pursued. Table 4 lists the incidence of various stages found in each type of NHL, and contrasts it to that in Hodgkin’s disease.

Laboratory Studies

Routine tests, including a complete blood count and liver and renal function tests, should be obtained in all patients. Examination of the blood may reveal anemia, possibly the first sign of lymphomatous replacement of the bone marrow or an autoimmune hemolytic process; the detection of lymphoma cells indicates that leukemic transformation has occurred. Abnormal liver function tests may suggest lymphomatous involvement of the liver or coexistent hepatic disease, requiring a closed liver biopsy, which may otherwise be omitted. A patient with a liver biopsy positive for lymphoma is classified as Stage IV, and no further staging is necessary.

Abnormal renal function may be the first hint of ureteral compression, urate nephropathy, hypercalcemic nephropathy or the nephrotic syndrome. Since widespread lymphoma can occur in the presence of normal liver and renal function tests, and since the abnormalities detected by these tests are not specific for NHL, further laboratory studies are usually indicated.

Bone Marrow Examination

Many patients, including those who present with apparently localized disease, may have extensive lymphatic as well as bone marrow involvement. The superiority of marrow biopsy over marrow aspiration in detecting marrow involvement has been demonstrated. In our experience, bone marrow involvement is present at diagnosis in more than 60 percent of patients with poorly differentiated lymphocytic lymphoma, but is infrequent in patients with histiocytic or mixed-cell lymphoma. Since a positive marrow biopsy establishes Stage IV disease, it should be performed early in the evaluation. (Fig. 2.)

Radiographic Studies

Chest X-rays may reveal mediastinal, hilar or parenchymal involvement by lymphoma. Once demonstrated, tomodograms help delineate the extent of intrathoracic involvement, revealing whether parenchymal disease represents visceral dissemination (Stage IV) or in-

Fig. 1a. Nodular lymphoma. Although normal nodal architecture is destroyed, a nodular pattern may still be recognized. (Low power view.)

Fig. 1b. Diffuse lymphoma. No nodularity is seen. (Low power view.)
vasion contiguous to diseased lymph nodes (Stage I<sub>E</sub>, II<sub>E</sub> or III<sub>E</sub>). This distinction is of therapeutic importance since contiguous spread of parenchymal disease may be managed by radiotherapy rather than systemic chemotherapy.

The intravenous pyelogram (IVP), inferior venacavagram (IVC) and lymphangiogram are of value in detecting retroperitoneal disease. An IVP should be performed in all patients, even if Stage IV disease has been proven by other methods, since obstructive uropathy secondary to malignant lymphoma is an emergency situation requiring local radiotherapy prior to definitive management. (See patient histories A. and B. on pages 328-329.)

An inferior venacavagram is the most reliable method for diagnosing retroperitoneal disease; when judged abnormal on the basis of displacement or extrinsic compression of the main trunk or the iliac veins, pathologic confirmation has almost always been found at laparotomy. The IVC is especially valuable in assessing the upper abdominal region, which is not well evaluated by lymphangiography. (Patients A. B. and C.) However, sensitivity is low: approximately 50 percent of cases with normal inferior venacavagrams had retroperitoneal disease at staging laparotomy.

The lymphangiogram is almost as accurate as the IVC. Despite a somewhat lower percentage of false positive findings, retroperitoneal disease is found at staging laparotomy in only one-third of patients with normal lymphangiograms. Because it is associated with embolism of fatty material to the lungs, lymphangiography is contraindicated in patients over 65 years old or those with chronic lung disease. (Patients A. and B.)

Radioisotopic Studies
Nuclear medicine studies have provided an additional dimension to the clinical assessment of lymphoma, although their accuracy is less than optimal. Technetium-99m (99mTc) is routinely used to scan the liver and spleen. Only one-half of cases with hepatomegaly or a focal defect on the 99mTc scan had liver involvement confirmed by open liver biopsies. (Patients D. and E.) Approximately one-fifth of patients with normal scans have focal lymphomatous involvement of the liver.
Both nodular and diffuse forms exist. Nodular lymphomas were previously termed (giant) follicular lymphoma. Table 3.

Relative Incidence of Histologic Types

| Histologic Type                  | Nodular | Diffuse |
|----------------------------------|---------|---------|
| Well-differentiated lymphocytic  | Rare. Usually chronic lymphocytic leukemia |
| lymphoma                         |         |         |
| Poorly differentiated lymphocyte | 30 percent | 30 percent |
| Mixed-cell lymphoma              | 5 percent | 5 percent |
| Histiocytic lymphoma             | Rare    | 30 percent |

*Both nodular and diffuse forms exist. Nodular lymphomas were previously termed (giant) follicular lymphoma.

When splenomegaly, increased Gallium-67 uptake or decreased 99mTc uptake (Patient E.) were used as criteria of disease in the spleen, three-fourths of the positive studies were confirmed; more than one-third of the negative studies were associated with lymphomatous involvement of the spleen. Bone scans may be helpful but, unless confirmed by biopsy, impossible to interpret. Table 5 summarizes the accuracy of inferior venacavagram. lym-
Table 4. Relationship Between Histology and Stage of Disease at Presentation

| Histology                  | Stage       |
|---------------------------|-------------|
|                           | Stages I and II | Stage III | Stage IV |
|                           | (Percent)    | (Percent) | (Percent) |
| Non-Hodgkin’s Lymphoma    |             |           |           |
| Poorly differentiated lymphocytic lymphoma-nodular | 15 | <15 | >70 |
| Poorly differentiated lymphocytic lymphoma-diffuse | 15 | <15 | >70 |
| Histioytic lymphoma       | <50         | >50       |           |
| Hodgkin’s Disease         | 60          | 30        | 10       |

Table 5. Accuracy of Diagnostic Tests in Non-Hodgkin’s Lymphomas*

| Test               | Accuracy on positives (percent) | Accuracy on negatives (percent) |
|--------------------|---------------------------------|---------------------------------|
| Inferior venacavagram | 93                              | 47                              |
| Lymphangiogram      | 83                              | 67                              |
| Liver scan          | 50                              | 82                              |
| Spleen scan         | 77                              | 61                              |
| Gallium scan        | 82                              | 59                              |

*Based on a series of 57 staging laparotomies performed at the University of Chicago. Accuracy indicates clinical impression of test confirmed by pathologic stage. For example, 93 percent of inferior venacavograms interpreted as positive were confirmed on pathologic section; 47 percent considered clinically negative were found to be negative and the balance, 53 percent, were positive.

phangiogram, liver scan, spleen scan and total-body 67Gallium scanning (Patients D. and F.)

Staging Laparotomy
The clinical value of staging laparotomy has yet to be demonstrated, but its investigative use has led to several observations: staging laparotomy is associated with change to a less advanced stage in approximately 10 percent of patients, and to a more advanced stage in 30-40...
percent. In approximately 60 percent of patients with abdominal disease, mesenteric nodes are involved.

While these findings suggest clinical value, two reservations must be recognized. (1) Many changes in stage are of no therapeutic significance (i.e., Stage I to II, Stage III to IIIa). (2) Discoveries of more advanced disease may reflect the value of bone marrow biopsies done at
the time of laparotomy, and not the value of laparotomy per se. If limited disease (Stages I and II) is to be treated by radiotherapy, and advanced disease (Stages III and IV) by chemotherapy, clinical staging can be used with greater than 90 percent accuracy. As stated previously, the extent of evaluation must be determined by the type of treatment being considered, and may vary among institutions.

Therapy
Management of the non-Hodgkin’s lymphomas depends on the extent of disease. Since many studies have included patients whose staging workup was less than ideal, only limited data regarding treatment of adequately staged patients with NHL are available. The following broad guidelines represent our approach to the control and cure of NHL by radiotherapy or chemotherapy.

Stages I, II, and IIe
Few patients have Stage I or II disease, but their prognosis is clearly the most favorable. Five-year survivals above 80 percent have been reported in Stage I patients treated with supervoltage (cobalt-60) radiation at doses of 3,500 to 4,000 rads, given at a rate of 1,000 rads/week to the entire primary site and a large margin of surrounding tissue. It has not yet been demonstrated whether treatment of involved fields only or more extensive radiotherapy offers maximum benefit to these patients. The role of adjuvant chemotherapy is presently under investigation in some centers.

Stages III, IIIe, and III, and II, and IIe
It is very difficult, at present, to assess the proper treatment for these patients. Theoretically, radiotherapy may be appropriate if disease is limited to the lymph nodes. Of course, it must first be assumed that the lymphomas, like Hodgkin’s disease, are responsive to radiotherapy and that widespread lymphatic disease may occur in the absence of visceral dissemination. The latter phenomenon has not been substantiated to occur with significant frequency.

Based on lessons learned in Hodgkin’s disease, megavoltage radiotherapy from a linear accelerator source is preferable to supervoltage cobalt-60 radiotherapy. A special abdominal port, rather than a classical “inverted-Y” is necessary to include the porta hepatis

(Text continued on page 333)
**Fig. A1.** The axis of the left kidney is almost parallel to the left psoas shadow on IVP. This is the normal inclination of the renal shadow. The lower pole of the right kidney is tilted laterally, the upper pole slightly medially.

**Fig. A2.** The left collecting system lies posteriorly, partly overlying the spine; the other is elevated ventrally. (Lateral view.)

**Fig. A3.** The inferior venacavagram shows lateral displacement of the upper portion of the inferior vena cava. (Frontal view.)

**Fig. A4.** The lymphangiogram indicates a collection of abnormal enlarged lymph nodes at the level of L3,4 (Oblique view.)

**IN SUMMARY:** Patient A has a retroperitoneal mass on the right side demonstrated by displacement of the kidney and upper urinary tract on intravenous pyelogram. In addition, the inferior venacavagram reveals another mass somewhat higher and in the midline, not detected by IVP. The presence of more distal nodes, also not shown by the intravenous pyelogram, is demonstrated on the lymphangiogram.
**Fig. B1.** IVP reveals that the axis of both kidneys is approximately parallel to the psoas shadow. The ureters run distally almost parallel to the spine. This may be normal, but it is unusual. Some medial displacement is seen, especially on the right side. Note the partially calcified gallstones. (Supine view.)

**Fig. B2.** The inferior venacavagram shows a slight elevation of the inferior vena cava from the lumbar spine. Also note more distally a slight elevation of the right ureter by enlarged lymph nodes. (Oblique view.)

**Fig. B3.** Enlarged incompletely filled, “foamy” lymph nodes extending from the iliac chain diffusely over the spine. (Supine view.)

**Fig. B4.** Oblique view of Fig. B3.

**IN SUMMARY:** The information provided by the intravenous pyelogram can be considered equivocal at best for the diagnosis of retroperitoneal tumor. The inferior venacavagram provides more convincing evidence; disease is definitively demonstrated on lymphangiogram.
The mass is seen markedly elevating and narrowing the lumen of the inferior vena cava, indicating the lobular outline of the tumor. (Oblique view)

IN SUMMARY: The extent and space of the mass are well demonstrated by this technique. The inferior venacavagram is the most reliable radiologic method for assessing retroperitoneal disease. This examination is more expeditiously and simply performed than lymphangiography and is considered safer in older patients.

Fig. C1. A huge, lobulated retroperitoneal mass is found on inferior venacavagram, displacing the inferior vena cava toward the right and indenting its outline. (Supine view)

Fig. C2. The mass is seen markedly elevating and narrowing the lumen of the inferior vena cava, indicating the lobular outline of the tumor. (Oblique view)

Fig. E. Liver and spleen scan performed after the injection of eight mCi 99mTc sulfur colloid. A.B, and C correspond to the anterior, posterior and right lateral projection of the liver. Abnormal features: enlarged liver and the loss of pliability (not shown here), inhomogeneous distribution of activity throughout the organ. D.E and F correspond to the anterior, posterior and left lateral projection of the spleen. Abnormal findings: enlargement of the spleen with multiple areas of decreased uptake.

IMPRESSION: Abnormal liver and spleen scan. Hepatosplenomegaly with multiple areas of decreased uptake in both organs consistent with lymphomatous involvement.
Fig. D1. Bone scan performed with a rectilinear scanner three hours after the injection of $^{99m}$Tc Diphosphonate. Patient D. is a young woman known to have lymphoma. Normal features: activity in the midline of the thorax responding to the simultaneous projection of the sternum and the thoracic spine; activity visualized bilaterally in the abdomen, that corresponds to the radiopharmaceutical excreted through the kidneys; activity is also seen in the bladder. Because the patient is young, there is bilateral and symmetrical activity in the metaphyseal areas of the upper and lower extremities. Abnormal features: increased uptake in the proximal portion and mid-shaft of the left femur; abnormal accumulation of activity in the mid-shaft of the right tibia.

**IMPRESSION:** Abnormal bone scan. The increased uptake in the left femur and the right tibia most likely correspond to bony involvement from known lymphomatous disease.

Fig. D2. Gallium scan performed 72 hours after intravenous injection of five mCi of $^{67}$Gallium citrate. Abnormal findings: bilateral accumulation of activity in the thorax (right lung field and left lower lung); abnormal uptake in the right lobe of the liver, and massive accumulation of activity in the abdominal masses. Abnormal uptake is also demonstrated in the left femur and right tibia. Extensive tumor involvement above and below the diaphragm interferes with the liver in the uptake of $^{67}$Gallium citrate.

**IMPRESSION:** Abnormal scan, consistent with massive lymphomatous involvement in the thorax, abdomen and skeleton.

Fig. F. $^{67}$Gallium citrate scan performed 72 hours after the IV administration of five mCi. This case demonstrates normal and homogeneous distribution of activity throughout the liver and slightly less uptake in the spleen. The central area of activity in the face corresponds to normal uptake by the nasopharyngeal mucosa. Abnormal findings are in the thorax, left axilla, left supra- and infraclavicular areas.

**IMPRESSION:** Abnormal scan compatible with lymphomatous involvement.
Table 6. Drugs Effective in the Chemotherapy of Lymphoma

| Drug                  | Toxicity                      |
|-----------------------|-------------------------------|
|                       | Common                        | Infrequent                    |
| Alkylating agents     |                               |                               |
| Cyclophosphamide      | Myelotoxicity, nausea, vomiting, alopecia | Hemorrhagic cystitis          |
| Nitrogen mustard      | Myelotoxicity, severe nausea, vomiting |                               |
| Chlorambucil          | Myelotoxicity                 |                               |
| Vinca alkaloids       |                               |                               |
| Vincristine           | Peripheral neuropathy, ileus, alopecia |                               |
| Vinblastine           | Myelotoxicity                 |                               |
| Anti-tumor antibiotics|                               |                               |
| Adriamycin            | Myelotoxicity, nausea, vomiting, total alopecia | Dose-dependent cardiotoxicity |
| Bleomycin             | Stomatitis                    | Fever and hypotension with initial doses; dose-dependent pulmonary fibrosis |
| Antimetabolites       |                               |                               |
| Cytosine arabinoside  | Myelotoxicity                 | Cirrhosis                     |
| Methotrexate          | Myelotoxicity, stomatitis     |                               |
| Nitrosoureas          |                               |                               |
| BCNU, CCNU            | Myelotoxicity (4-6 wks.)      |                               |
| Others                |                               |                               |
| Procarbazine          | Myelotoxicity                 | Antabuse-like syndrome        |
| Imidazole carboxamide | Myelotoxicity                 | Nephrotoxicity                |
| Corticosteroids       | Fluid retention, immunosuppression | Peptic ulcer, cataracts      |
and the mesenteric nodes, which are frequently involved. (Fig. 3.) An experienced radiotherapist, trained in radiobiology, should determine the high doses of radiation that must be delivered to large volumes of tissues with minimal toxicity; referral to a center with appropriate experience in this treatment is often necessary. Patients with histiocytic, diffuse lymphoma who have Stage III disease (and possibly all patients with diffuse lymphoma) should be excluded from this approach as a high incidence of extranodal progression during or immediately after treatment and low survival rates have been observed.

An alternative therapeutic approach for these patients involves chemotherapy, usually a multi-drug regimen. Combination chemotherapy is based on the principle that because toxicities involve different systems multiple agents may combine their effectiveness with minimal side-effects. For example, cyclophosphamide and procarbazine primarily cause bone marrow toxicity. Vincristine may lead to peripheral neuropathy and constipation, whereas the major side-effects of prednisone include salt retention, gastric ulceration and immunosuppression. The dose schedules involved in the most commonly used chemotherapy regimens are presented schematically in Fig. 4. Because drug toxicity may require frequent dose modification, the "COPP" and "CVP" regimens are best administered by experienced chemotherapists.

Stage IV

Patients with disseminated disease are generally treated with chemotherapy, although palliative radiotherapy for local complications may also be useful in immediate management. Multi-drug regimens are commonly used, but well-controlled studies have not yet resolved the ideal number of drugs or their schedule of administration. That most effective drugs are myelotoxic is the major constraint on combination therapy. Several regimens, which include cyclophosphamide, vincristine and prednisone, have been used to produce complete remission in up to 68 percent of patients. The median disease-free survival in these patients is more than three years. The value of adding or substituting procarbazine, bleomycin, imidazole carboxamide, methotrexate, cytosine arabinoside or Adriamycin is currently under investigation. Once patients have proved refractory to combination therapy, further palliation may be achieved by other agents used either singly or in combinations not previously employed. (Table 6.)

In contrast, more conservative treatment with single agents, such as chlorambucil or cyclophosphamide, may be more appropriate for patients whose histologic type suggests less aggressive disease, for example, poorly differentiated lymphocytic lymphoma-nodular. In elderly patients or those with coexistent medical problems that significantly limit life expectancy, less aggressive therapy is most appropriate.

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