Staging of Non-Hodgkin's Lymphoma

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ATTITUDES toward the staging of non-Hodgkin's lymphoma are undergoing significant modification as clinicians and investigators attempt to assess the results of 10 yr of very active and fruitful clinical trials. The non-Hodgkin's lymphomas are now understood to consist of a complex group of diseases of variable cellular origin, variable natural history, and widely divergent patterns of response to chemotherapy and radiotherapy. Because of these divergent clinical features, no rigid or routine staging plan is appropriate for all patients with non-Hodgkin's lymphoma; in particular, the role of staging laparotomy, a morbid and expensive procedure, requires re-evaluation in the "good prognosis" categories of disease. It will be the purpose of this review to discuss the indications for and the yield of specific diagnostic procedures in the major pathologic subgroups, and to indicate how this information may be integrated with the therapeutic alternatives to arrive at a staging strategy.

GENERAL CONSIDERATIONS

A general scheme for staging classification (the Ann Arbor classification) has been applied to both Hodgkin's disease and non-Hodgkin's lymphoma, and is presented in Table 1. While the Ann Arbor scheme is extremely useful in defining the patient composition of clinical trials, there exists considerable uncertainty at present as to whether the distinction between the various stages is prognostically important for all histologic groups. For example, the distinction between stage III and stage IV non-Hodgkin's is of little importance in determining therapy, since patients with stage III disease are not curable with total nodal radiotherapy. Most patients with stage III disease are treated with either systemic chemotherapy (as in the case of histiocytic lymphoma)[1] or with palliative involved field or total body radiotherapy, (as utilized for the nodular lymphomas or diffuse well-differentiated lymphocytic lymphoma).[2] Certain other factors not explicitly recognized by the Ann Arbor classification, such as the bulk of tumor[3] and the specific sites of organ involvement (bone marrow versus skin, etc.), may have a more profound influence on the prognosis than does the distinction between stage III and stage IV disease.

The Rappaport scheme for pathologic classification of subtypes of disease will be used as the basis of this discussion in view of its wide acceptance in the United States and its proven prognostic significance. In general, patients with nodular type patterns of lymph node involvement and those with smaller cell types (the well-differentiated, intermediate, or poorly differentiated lymphocyte) have a more indolent clinical course than those with a diffuse pattern of nodal replacement and a larger cell type (histiocytic or lymphoblastic). The good and poor prognosis categories as currently recognized in protocols at the National Cancer Institute are listed in Table 2. Since accurate histopathologic classification forms the basis for later decisions regarding staging and treatment, it is essential to reach agreement on this point prior to completion of staging. Repeat lymph node biopsies may be necessary to settle uncertainties.

CLINICAL STAGING

Complete clinical staging should be performed on all patients with non-Hodgkin's lymphoma, including a careful history, physical examination, blood counts and chemistries, and radiologic studies as indicated below. The patient should be questioned about the date of first appearance of lymph node enlargement and the rate of subsequent tumor growth, as this information may influence the choice of therapy, and indeed the decision to institute treatment, in the good prognosis group of patients.[4] The oncologist should give particular attention to recording the site and size of all abnormal lymph nodes, including the epitrochlear, femoral, and

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Table 1. The Ann Arbor Staging Classification

Stage I
Involvement of a single lymph node region (I) or localized involvement of a single extranodal organ/site (I_E).

Stage II
Involvement of more than one lymph node region on the same side of the diaphragm (II) or of one or more lymph node regions and localized involvement of an extralymphatic organ/site (II_E) on the same side of the diaphragm.

Stage III
Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (III_S) or by localized involvement of an extralymphatic organ/site (III_E) or both (III_{SE}).

Stage IV
Diffuse or disseminated involvement of one or more extralymphatic organ/site with or without lymph node involvement.

popliteal sites that are not usually involved in Hodgkin's disease. Certain clinical correlations must be kept in mind during the physical examination. Pre-auricular nodal enlargment is often associated with disease in the Waldeyer's ring area. Primary lesions of extra-nodal sites such as bone or skin (usually of the diffuse histiocytic category) are frequently associated with involvement of regional lymph nodes. Patients with skin disease, either as primary lesions or as secondary sites, often have multiple cutaneous lesions that may be at quite widely spaced sites. Thus a careful inspection of the skin, with biopsy of suspicious lesions, is necessary in patients with diffuse types of histopathology, and particularly in those with known skin involvement.

Table 2. Histologic Classification and Prognosis

Good Prognosis*	Poor Prognosis*
Nodular poorly differentiated lymphocytic (NPDL)	Nodular histiocytic (NH)
Nodular mixed lymphocytic–histiocytic (NM)	Diffuse histiocytic (DH)
Diffuse well differentiated lymphocytic (DWDL)	Diffuse mixed lymphocytic–histiocytic (DM)
Diffuse poorly differentiated lymphocytic (DPDL)	Pleomorphic or stem cell
	Lymphoblastic

*Good prognosis connotes an expectation of greater than 1-yr median survival with palliative radiotherapy or single-agent chemotherapy. Poor prognosis implies a median survival of less than 1 yr if complete remission is not achieved by aggressive therapy.

Peripheral blood counts and chemistries, while helpful in the attempt to detect organ dysfunction, are not reliable indicators of organ involvement with tumor due to the fact that lymphoma usually produces little alteration in the function of these tissues. Some abnormality in the blood counts is found in only 37% of patients with bone marrow infiltration by lymphoma.[5] Approximately 50% of patients with an abnormal blood count will not have bone marrow involvement on biopsy. Peripheral blood smear examination yields evidence of malignant cells in approximately 15% of patients, primarily those with small cell types of lymphoma such as nodular or diffuse poorly-differentiated lymphocytic lymphoma (NPDL or DPDL).[5,6]

RADIOLOGIC STUDIES

Chest x-rays should be performed in all patients, but yield positive information in only 26% of patients (Table 3). The most frequent abnormalities are hilar or mediastinal adenopathy (18%), pleural effusion (8%), and parenchymal lesions (4%). Parenchymal lesions and effusions require pathologic verification; a chylous or transudative effusion that lacks malignant cells does not change the pathologic stage of the patient. Pulmonary parenchymal lesions that are associated with hilar lymph node involvement, and which involve only one hemithorax, are considered to be disease in extension from the lymph nodes and do not change the patient's stage of disease. Full lung tomograms are usually not needed to search for occult parenchymal nodules in the presence of a completely normal chest x-ray in view of the infrequency of parenchymal disease in these patients, but probably should be done in any patient with extensive mediastinal or hilar adenopathy. Suspected mediastinal or hilar adenopathy on plain films may require tomographic evaluation (either conventional or computerized) to determine the presence and extent of involvement.

Routine bone films have largely been replaced by bone scanning, a technique with greater sensitivity. Bone lesions are particularly common in patients with diffuse histiocytic lymphoma;[7] in a recent series from the National Cancer Institute, 10 out of 40 or 25% of patients with this diagno-

Table 3. Pretreatment Chest X-Ray and Lymphangiogram in 170 Consecutive Patients[7]

Pathologic Category (No. Patients)	Chest Film (%)				Lymphangiogram* (% positive)
	Normal	Adenopathy	Effusion	Parenchymal Lesion	
Nodular subtypes (81)	70	23	8	2	90
Diffuse subtypes					
Mixed and histiocytic (47)	74	17	9	6	61
Other pathologies (42)	81	12	5	0	75
All patients (170)	74	18	8	3	78

*137 of 170 patients were studied.

sis had bone lesions detected radiologically; all 10 of these lesions were seen on bone scan, while bone films showed the lesions in only 8 patients. Thus, as an initial procedure it is unnecessary to do both plain films and scan. A positive bone scan should be confirmed by plain films and biopsy if possible.

Bipedal lymphangiography is a particularly valuable procedure in staging of non-Hodgkin's lymphoma. Retroperitoneal disease is often undetected by physical examination. Recognition of abdominal disease may be an important factor not only in determining stage but also in providing impetus for further evaluation of renal function, particularly in patients with favorable histology who are candidates for conservative therapy.

Lymphangiography is a highly accurate technique for evaluating intra-abdominal lymph nodes, as has been verified by comparison of x-ray results with the findings during staging laparotomy.[7–10] Foamy enlargement of nodes is the most accurate indicator of lymphomatous involvement; filling defects or absence of filling with collateral lymphatic drainage are also signs of malignant disease, although less specific for lymphoma. An accurate assessment of abdominal lymph nodes has been reported in 83%–90% of patients studied, in three large series in which the x-ray's interpretation was verified by laparotomy;[8–10] nodes deemed abnormal by lymphangiography were histologically involved with lymphoma in over 90% of cases, while patients with a negative study (who constitute a minority of those examined) have about a 20%–30% chance of abdominal involvement at laparotomy.

The incidence of lymphangiographic positivity varies with histologic type for patients with non-Hodgkin's lymphoma, and ranges from about 90% for patients with nodular types of disease to 57% for those with diffuse histiocytic lymphoma (Table 3).[7] Most patients with positive lymphangiograms have clinically palpable adenopathy below the diaphragm so that an advance in stage occurs in only 10% of patients.

The lymphangiogram is useful not only for assessment of para-aortic lymph nodes, but is also an accurate predictor of the chances of finding intra-abdominal lymphoma in extranodal sites or in splenic, portal, or mesenteric lymph nodes. In the National Cancer Institute series,[7] 81% of patients with a positive lymphangiogram who were clinical stage III prior to laparotomy had disease in liver, ascites, or lymph nodes outside the para-aortic chain at laparotomy, while only 18% of patients with negative lymphangiograms had similar findings at laparotomy. The Stanford oncology group has shown a similar positive correlation between lymphangiography and mesenteric lymph node involvement.[9] These findings have important implications for staging and treatment; there appears to be little reason, aside from research consideration, for undertaking staging laparotomy in patients with a positive lymphangiogram in view of the high likelihood of finding disease in sites outside traditional irradiation ports. The unfavorable results of nodal irradiation for treatment of stage III disease further militate against the use of staging laparotomy in these patients, since systemic therapies would be indicated regardless of the findings at laparotomy.

The side-effects of lymphangiography should be kept in mind in considering its use for patients with non-Hodgkin's lymphoma. Forty percent of patients develop fever within 24 hr. Lipid microemboli probably occur in all patients, but may become significant in patients with extensive tumor replacement of abdominal lymphatics and with collateral circulation. Patients with known

pulmonary disease, asthma, or massive mediastinal involvement should have lesser amount of dye used; in cases of extreme pulmonary compromise, the oncologist should consider either CAT scanning or gallium scanning as an alternative.

Of the various alternatives to lymphangiography,[67] gallium scanning is of some value in patients with histiocytic lymphoma, in which 60%–80% of involved nodal sites will be visualized.[11,12] In the lymphocytic or mixed types of lymphoma, this test is highly unreliable; less than 50% of involved nodal sites will be detected. Lesions in or near the liver may be obscured by the normal accumulation of gallium in the liver. Iliac lymph nodes are also difficult to interpret because of the usual accumulation of gallium in the cecum and sigmoid colon. Thus, gallium scans are a poor substitute for lymphangiography in patients with NHL.

Abdominal CAT scans offer a second and probably a better alternative to lymphangiography. In the largest comparative series published to date, Best et al.[13] found that 9 of 45 patients with a negative CAT scan and a negative lymphangiogram had positive abdominal nodes at laparotomy; two patients with a positive CAT scan but negative lymphangiogram had positive lymph nodes at surgery. In addition, CAT scans appear to provide a truer estimate of the size of involved nodes (often underestimated by lymphangiography) and may detect abnormal nodes in the mesentery, porta hepatis, or splenic hilum.[14] Thus the CAT scan may be an acceptable substitute for lymphangiography when the latter procedure can not be obtained, although, like lymphangiography, CAT scanning has a substantial false negative rate.

A third alternative to lymphangiography is inferior venacavography, a procedure that permits delineation of masses in the right retroperitoneum. Clinical experience with this technique is less extensive than with lymphangiography; it has the additional disadvantage of providing only a negative impression of enlarged nodes rather than a direct view, and is not in common clinical use.

It is important to note that the lymphangiogram is useful not only for purposes of staging but also for determining the response to therapy. Serial flat plates of the abdomen provide an inexpensive and rapid index of tumor response, and thus have advantages over CAT scans, gallium scans, or inferior venacavography.

In patients with proven intra-abdominal disease of diffuse histopathologic pattern, it is important to rule out the presence of a primary lesion in the bowel or stomach. Such lesions may cause significant bleeding or may perforate as a consequence of necrosis secondary to therapy,[15] and should be resected prior to treatment if surgically feasible. Barium studies of the upper and lower bowel are indicated as a first step in the search for an intestinal primary lesion, with subsequent endoscopic biopsy and cytologic study of suspicious lesions. A combination of endoscopic cytology (obtained after abrasion of the suspicious lesion) and biopsy was successful in diagnosing a malignancy in 14 or 15 patients with gastric lymphoma, and provided the specific diagnosis of malignant lymphoma in 12 of 15 patients.[16] These results represent a considerable improvement over the yield of blind cytologic studies of gastric aspirates. It should be kept in mind that lymphoma cells are easily confused with anaplastic carcinoma cells in cytological preparations.

BONE MARROW EVALUATION

One of the major findings of exhaustive staging studies, and indeed an important reason for the decline of interest in staging laparotomy in non-Hodgkin's lymphoma, is the approximately 50% incidence of bone marrow[5,17,18] and hepatic involvement.[7] The incidence of bone marrow metastases in lymphoma is highest in patients with lymphocytic types of histology (40%–100% depending on specific type) (Table 4), and lowest in those with diffuse histiocytic lymphoma. Each subtype of disease tends to have an identifiable pattern of bone marrow involvement. Patients with NPDL have a predominance of paratrabecular location of tumor, while in patients with DPDL the involvement assumes a more diffuse than focal pattern in most cases.[5] Bone marrow metastases in patients with diffuse histiocytic lymphoma and diffuse mixed lymphoma occur in a diffuse pattern and may be associated with focal or diffuse myelofibrosis. While bone marrow involvement is less frequent in diffuse histiocytic lymphoma, its detection has

Table 4. Bone Marrow Biopsy and Liver Biopsy in Non-Hodgkin's Lymphoma[7]

Pathologic Category	Bone Marrow* Positive/Tested (%)	Liver† Percutaneous	Liver† Peritoneoscopy [Positive/Tested (%)]	Liver† Laparotomy
Nodular				
Poorly differentiated lymphocytic	19/48 (40)	14/45 (31)	6/28 (21)	7/18 (39)
Mixed	11/24 (46)	4/21 (19)	7/17 (41)	1/9 (11)
Histiocytic	1/7 (14)	0/6 (0)	3/6 (50)	0/2 (0)
Diffuse				
Well differentiated lymphocytic	6/6 (100)	2/4 (50)	0/1 (0)	
Poorly differentiated lymphocytic	15/28 (54)	5/15 (33)	5/7 (71)	1/2 (50)
Mixed	2/6 (33)	1/4 (25)	2/5 (40)	0/2 (0)
Histiocytic	6/39 (15)	2/33 (6)	3/26 (12)	0/11 (0)
Stem cell	4/7 (57)	0/3 (0)	0/1 (0)	—
Total	64/165 (39)	28/131 (21)	26/91 (28)	9/44 (22)

*100 of 165 patients had bilateral biopsies.

†Biopsies were performed sequentially.

importance not only for staging but also because of its strong correlation with later spread of disease to the meninges and central nervous system.[19] Lumbar puncture with cytologic examination should be performed in patients with diffuse types of lymphoma having advanced stage, and particularly in those with bone or bone marrow involvement.

Because of the focal nature of bone marrow involvement, clot sections alone are inadequate for staging purposes. For example, in the NCI series, clot sections were positive in only 22% of NPDL patients who had a positive biopsy(s); in those with diffuse types of histology, a higher fraction (approximately 2/3) had positive clot sections in the presence of a positive biopsy, perhaps reflecting the more diffuse nature of the bone marrow infiltrate. In view of the clinical importance of bone marrow evaluation and the focal nature of metastases, more than one biopsy should be obtained for evaluation. For patients having two biopsies, between 10% and 20% will have positive findings in only one biopsy;[5,17] assuming an even chance of obtaining the positive biopsy on the first attempt, a second biopsy should increase the number of positives by 5%–10%.

Overall, bone marrow biopsy can be expected to advance approximately 25% of patients to stage IV, since some of those with marrow metastases will have previously been classified as stage IV on the basis of other sites of extranodal disease. The shift to stage IV occurs predominantly in patients with stage III disease and in those with "good prognosis" or indolent types of disease. In these patients it is then unnecessary to proceed with further staging, unless the documentation of liver involvement has importance in the choice of therapy. For most clinical protocols this is not the case.

HEPATIC STAGING

Intensive efforts to identify hepatic metastases in non-Hodgkin's lymphoma have led to recognition of a surprisingly high incidence of involvement in the more indolent categories of disease[7] (Table 4). The yield increases as the size and number of specimens increase. Percutaneous biopsy reveals disease in approximately 30% of patients with NPDL or DPDL, but in only 6% of patients with histiocytic lymphoma. Peritoneoscopy-directed biopsies add an additional 30% or higher percentage of positives after a negative percutaneous biopsy. Laparatomy in patients having a negative biopsy by the nonsurgical techniques (percutaneous or peritoneoscopy) reveals an additional 20% positive liver biopsies, primarily in patients with NPDL who have a positive lymphangiogram prior to biopsy. By all biopsy techniques, patients with diffuse histiocytic lymphoma have a much lower incidence of

liver metastases than the other major categories of disease.

STAGING LAPAROTOMY

There can be no doubt that the staging laparotomy has been of great value in enhancing our understanding of the clinical behavior of the non-Hodgkin's lymphomas. Several prospective studies of this procedure have demonstrated the propensity of lymphoma to involve nonaxial lymph nodes as well as spleen and liver.[7,9,20] In addition, laparotomies have helped to define the accuracy of other staging procedures, particularly the lymphoangiogram and nonsurgical liver biopsies. Finally, multiple tissue biopsies obtained at laparotomy have revealed a surprisingly high divergence (20%) of tumor histology.[9,21] The presence of a more aggressive histology in an intra-abdominal lymph node may significantly alter the natural history of the patient's disease although the implications of divergent histology are not well understood at this time.

However, staging laparotomies are usually not essential in staging of patients with non-Hodgkin's lymphoma, and only rarely provide direct therapeutic benefit, although, as mentioned previously, resection of a primary bowel lesion may prevent later complications. Moreover, patients with non-Hodgkin's lymphoma are generally older than those with Hodgkin's disease and, thus, postoperative complications are more common. While surgical mortality has been approximately 0.5%, significant morbidity, primarily in the form of pneumonia, pulmonary embolism, pancreatitis, subdiaphragmatic abscess, or gastrointestinal bleeding, has been reported in 11%–40% of patients in three larger series.[7,9,20] However, the primary factors that account for the limited use of laparotomy in non-Hodgkin's lymphoma are the high yield of less morbid procedures and the recognition that precise definition of organ involvement probably has limited importance in treatment planning for most of these patients.

Following careful clinical evaluation, including lymphangiography, bilateral bone marrow biopsies, and percutaneous liver biopsy, over 80% of patients with non-Hodgkin's lymphoma will be categorized as stage III or stage IV.[7] Since these patients are treated with chemotherapy in most centers, staging laparotomy is not indicated. Staging laparotomy could be considered for the remaining 20% of patients who are stage I or II, but only if they are to be treated with local, rather than systemic, treatment on the basis of their early stage of disease. The reader is referred to more complete discussions of the therapeutic alternatives for localized non-Hodgkin's lymphoma elsewhere in this issue.

Between 17% and 28% of all patients who are stage I or II prior to laparotomy will advance in stage because of laparotomy findings.[7,20] The frequency of positive findings is somewhat higher in patients with nodular forms of lymphoma than in those with diffuse types of disease.[7] The procedure probably has its greatest usefulness in the diffuse histiocytic class of patients, since fully 1/3 of this group will remain in stage I or II after a complete sequence of staging procedures, including laparotomy, and may be candidates for local radiotherapy.[7]

In considering the use of staging laparotomy, the medical oncologist must be involved in the planning of the procedure, and must call attention to the specific lymph nodes and tissues he wishes to have biopsied or removed. In patients who have undergone lymphangiography, the position and identity of lymph nodes removed should be evaluated during the procedure by obtaining a flat plate examination of the abdomen. In the non-Hodgkin's lymphomas, particular care must be taken to inspect the mesentery, as well as porta hepatis and the splenic pedicle, for suspicious nodes since these areas are frequently positive at laparotomy.[7,10,20] Ascites should be obtained for cytologic evaluation if present, as this may be the only site of intraabdominal disease.[7]

In summary, the oncologist must assume responsibility for determining the specific procedures and proper sequence to be utilized in the staging workup, based on a clear conception of the therapeutic alternatives available for the patient. While the primary justification for any procedure must be the impact of results on therapeutic decisions, complete staging information is desirable in research trials, as this information may be of future value in allowing identification of prognostic factors and in providing a precise characterization of the population being treated. However, in our view, these benefits cannot be used to justify laparotomy.

REFERENCES

1. DeVita VT, Chabner BA, Hubbard SP, et al: Advanced diffuse histiocytic lymphoma, a potentially curable disease. Lancet 1:248, 1975

2. Anderson T, Bender RA, Fisher RI, et al: Combination chemotherapy of non-Hodgkin's lymphoma: Results of long-term follow-up. Cancer Treat Rep 61:1057–1066, 1977

3. Fisher RI, DeVita VT, Johnson BL, et al: Prognostic factors for advanced diffuse histiocytic lymphoma following treatment with combination chemotherapy. Am J Med 63:177–182, 1977

4. Portlock CS, Rosenberg SA: No initial therapy for stage III and IV non-Hodgkin's lymphomas of favorable histologic types. Ann Intern Med 90:10–13, 1979

5. Coller BS, Chabner BA, Gralnick HR: Frequencies and patterns of bone marrow involvement in the non-Hodgkin's lymphomas: Observation on the value of bilateral biopsies. Am J Hematol 3:105–119, 1979

6. McKenna RW, Bloomfield CD, Brunning RD: Nodular lymphoma: Bone marrow and blood manifestations. Cancer 36:428–440, 1975

7. Chabner BA, Johnson RE, Young RC, et al: Sequential nonsurgical and surgical staging of non-Hodgkin's lymphoma. Ann Intern Med 85:149–154, 1976

8. Bonadonna G, Pizetti F, Musumeci R, et al: Staging laparotomy in non-Hodgkin's lymphomata. Br J Cancer 31 (supp 2): 252–260, 1975.

9. Goffinet DR, Warnke R, Dunnick NR, et al: Clinical and surgical (laparotomy) evaluation of patients with non-Hodgkin's lymphomas. Cancer Treat Rep 61:981–992, 1977

10. Moran EM, Ultmann JE, Ferguson DJ, et al: Staging laparotomy in non-Hodgkin's lymphoma. Br J Cancer 31 (supp 2):228–236, 1975

11. Turner DA, Fordham EW, Amjad A, et al: Gallium-67 imaging in the management of Hodgkin's disease and other malignant lymphomas. Semin Nucl Med 8:205–218, 1978

12. Longo DL, Schilsky RL, Blei L, et al: Gallium-67 scanning has limited usefulness in staging patients with non-Hodgkin's lymphoma. Am J Med (in press)

13. Best JJK, Blackledge G, Forbes WS, et al: Computed tomography of abdomen in staging and clinical management of lymphoma. Br Med J 2:1675–1677, 1978

14. Schaner EG, Head GL, Doppman JL, et al: Computed tomography in the diagnosis, staging, and management of abdominal lymphoma. J Computer-Assisted Tomography 1:176–180, 1977

15. Hande KR, Fisher RI, DeVita VT, et al: Diffuse histiocytic lymphoma involving the gastrointestinal tract. Cancer 41:1984–1989, 1978

16. Cabre-Fiol V, Vilardell F: Progress in the cytological diagnosis of gastric lymphoma. Cancer 41:1456–1461, 1978

17. Dick F, Bloomfield CD, Brunning CD: Incidence, cytology, and histopathology of non-Hodgkin's lymphomas in the bone marrow. Cancer 33:1382–1398, 1974

18. Jones SE, Rosenberg SA, Kaplan HS: Non-Hodgkin's lymphoma. I. Bone marrow involvement. Cancer 29:954–960, 1972

19. Bunn PA, Schein PS, Banks PM, et al: Central nervous system complications in patients with diffuse histiocytic and undifferentiated lymphoma: Leukemia revisited. Blood 47:3–10, 1976

20. Castellani R, Bonadonna G, Spinelli P, et al: Sequential pathologic staging of untreated non-Hodgkin's lymphomas by laparoscopy and laparotomy combined with marrow biopsy. Cancer 40:2322–2329, 1978

21. Fisher RI, DeVita VT, Young RC, et al: Natural history of non-Hodgkin's lymphoma with divergent histologies at staging evaluation. Proc Am Assoc Cancer Res 20:250, 1979