Predicting the Risk of Abdominal Disease in Hodgkin's Lymphoma

A Multifactorial Analysis of Staging Laparotomy Results in 255 Patients

MICHAEL C. TROTTER, M.D., GRETCHEN A. CLOUD, M.S., MAX DAVIS, M.D., SHELBY P. SANFORD, M.D., MARSHALL M. URIST, M.D., SENG-JAW SOONG, PH.D., NORMAN B. HALPERN, M.D., WILLIAM A. MADDOX, M.D., CHARLES M. BALCH, M.D.

From the Departments of Surgery, Radiation Therapy, and Biostatistics and the Comprehensive Cancer Center, The University of Alabama at Birmingham, and the Birmingham Veterans Administration Hospital, Birmingham, Alabama

There were 425 consecutive patients treated for Hodgkin's disease at this Medical Center from 1943 to 1983. Of these, 255 patients underwent a staging laparotomy and had complete preoperative clinical records. Overall, 35% had a change in stage (24% were upstaged, 11% downstaged). Twenty-nine per cent of clinical stage I patients were upstaged; 31% of stage II patients were upstaged, while <1% were downstaged; and four per cent of stage III patients were upstaged while 44% were downstaged. The diagnostic laparotomy yielded involvement in the spleen in 71% of patients with abdominal involvement, in the periaortic lymph nodes in 41%, in the liver in 11%, and the bone marrow in seven per cent. Only 12% of the 135 patients with negative laparotomies subsequently relapsed in the abdomen after a mean follow-up of 4.8 years. A multifactorial analysis was performed to identify dominant factors predicting the risk for abdominal disease. The factors best predicting abdominal involvement in stage I and II patients were: (1) antecedent symptoms ($\geq$2, 1, 0; $p < 0.00001$), (2) histological type [nodular sclerosing (NS) < lymphocyte-predominant (LP) < mixed cellularity (MC) < lymphocyte-depleted (LD); $p = 0.0009$], and (3) sex (females < males, $p = 0.01$). The clinical stage (I *vs.* II), the site of lymphoma presentation, and the age and race of the patient did not have significant predictive value for the risk of abdominal disease after the other factors were accounted for. A mathematical model was derived for identifying dominant prognostic factors for predicting the risk of abdominal disease in an individual patient setting. The lowest risk patients were asymptomatic females with NS histology (6%) or LP histology (8%), while the highest risk patients were men with multiple symptoms and either MC histology (85%) or LD histology (93%). This information can be useful in making clinical decisions in Hodgkin's lymphoma patients, especially those at an increased risk for surgery.

SURGICAL STAGING has been an important component of the pretreatment evaluation for Hodgkin's lymphoma. It is utilized at most institutions as a diagnostic procedure that is associated with virtually no mortality and with an acceptable morbidity incidence (usually less than 10%). Recently, however, the value of staging laparotomy* has been questioned by some oncologists. At a few institutions, staging laparotomy is not peformed at all,[1,2] whereas at other centers it is performed on a very selective basis.[3-6]

We evaluated the results with staging laparotomy in 255 patients with Hodgkin's disease in order to evaluate its accuracy as a diagnostic procedure and then to analyze which prognostic factors best predict the risk of abdominal disease. Our objective was to establish a quantitative estimate for abdominal Hodgkin's disease that could be used in making decisions about a staging laparotomy in an individual patient setting. Such information might enable a better selection of those patients with either a very low or a very high risk of abdominal disease so that treatment decisions might be considered in selected patients without a laparotomy.

Materials and Methods

The data for all 425 patients with Hodgkin's lymphoma treated at the University of Alabama at Birmingham between November 1943 through January 1983 were compiled into a computerized data base. Of these, 255 patients had a staging laparotomy, which was incorporated into the diagnostic work-up beginning in 1967. These operations were performed both at the University of Alabama at Birmingham and in other

This work was supported in part by a grant from the National Cancer Institute, NIH, CA-13148.

Reprint requests: Charles M. Balch, M.D., Chief of Surgical Oncology, Department of Surgery, Suite 320, Kracke Building, University of Alabama in Birmingham, Birmingham, AL 35294.

Submitted for publication: November 20, 1984.

* A more proper terminology is staging celiotomy.

TABLE 1. *Distribution of Clinical and Pathological Stages Among 255 Hodgkin's Lymphoma Patients Who Had a Staging Laparotomy*

			Pathologic Stage							
		Total	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
Total		255	48	6	85	24	40	34	4	14
	IA	48	39		1		7		1	
	IB	15		6		0		5		4
Clinical	IIA	89	1		71		15		2	
Stage	IIB	42		0		18		15		9
	IIIA	40	8		13		18		1	
	IIIB	21		0		6		14		1

referring hospitals. An additional 129 patients did not have a staging laparotomy; 93 had stage III or IV disease and were treated directly with chemotherapy often in combination with radiation therapy; 32 were judged to have a favorable prognosis (stage I or II) and were treated directly with radiation therapy, while four other patients were judged to be a poor surgical risk. Forty-one patients had insufficient records to be included in this study.

Clinical staging was based on the following evaluations: (1) history and physical exam with special attention to fever, night sweats, weight loss, and pruritis, (2) chest x-ray, (3) ^{67}gallium scan, (4) abdominal lymphangiography, (5) ultrasonography or CT scan of the abdomen, and (6) bone marrow biopsy. Since 1980, lymphangiography has been used sparingly. The Ann Arbor staging classification was used to clinically stage these patients.[7] The histological appearance was classified as either lymphocyte-predominant (LP), nodular sclerosing (NS), mixed cellularity (MC), or lymphocyte-depleted (LD).

Staging laparotomy was performed through a midline abdominal incision. Splenectomy was performed and splenic hilar lymph nodes were taken in most but not all cases. Periaortic and celiac lymph nodes were excised and iliac, mesenteric, portal, periduodenal, or any other lymph nodes were excised if they were abnormal. Wedge and needle biopsies of the liver were taken, and iliac crest bone marrow biopsy was performed.

Chi square tests were used to test the comparability of those patients with and without abdominal disease found at laparotomy with respect to age, race, sex, histology, site of disease presentation, symptoms, number of symptoms, and clinical stage.[8] A logistic regression model as described by Cox was utilized to determine those dominant prognostic factors for predicting the risk of abdominal disease in an individual patient setting.[9]

TABLE 2. *Changes in Stage After Laparotomy*

Clinical Stage	Upstaged (%)	Downstaged (%)	Same (%)
I	29	—	71
II	31	<1	68
III	4	44	52
Overall	24	11	65

Results

Results of Staging

The correlation between clinical staging and pathological staging for 255 patients is shown in Table 1. Overall, 35% of patients had a change in stage, with 24% being upstaged and 11% being downstaged (Table 2). Almost one-third of stage I and II patients were upstaged, while 44% of stage III patients were downstaged.

The anatomical sites in 91 patients where Hodgkin's disease was identified in the abdomen are shown in Table 3. The spleen was most frequently involved (71%), while periaortic nodes were involved in 41% of these patients and the splenic hilar lymph nodes contained disease in 18% of patients. Bone marrow biopsy yielded occult Hodgkin's disease in 18 patients (7%).

TABLE 3. *Sites of Abdominal Disease* Found at Staging Laparotomy in 91 Patients*

	Per cent
Spleen	71
Periaortic lymph nodes	41
Splenic lymph nodes	18
Celiac lymph nodes	16
Unspecified abdominal sites	13
Liver	11
Iliac lymph nodes	8
Iliac crest bone marrow	7
Portal lymph nodes	4
Mesenteric lymph nodes	3
Cystic lymph nodes	2

* Some patients had more than one site.

TABLE 4. *Single Factor Analysis Predicting Abdominal Disease in Clinical Stage I and II Hodgkin's Lymphoma*

Predictive Factor	P Value
Symptoms (present *vs.* absent)	0.0001
Number of symptoms (0, 1, ≥2)	0.0001
Histology (NS *vs.* LP *vs.* MC *vs.* LD)	0.0001
Age (<20, 20–40, >40 yrs)	0.01
Sex	0.02
Clinical stage (I *vs.* II)	0.70
Site of presentation (stage I)	0.70
Date of diagnosis (1967–1975 *vs.* 1975–1980)	0.74
Race	0.80

Factors Influencing the Presence of Abdominal Hodgkin's Disease

A single factor statistical analysis was used to identify those predictive factors correlating with an increased probability of abdominal disease (Table 4). The number of symptoms and the histological cell type were the most significant predictive factors ($p = 0.0001$ each). In addition, age ($p = 0.01$) and sex ($p = 0.02$) also correlated significantly with the presence of abdominal disease. Thus, older persons and men had a higher risk for abdominal disease than younger patients and women. Interestingly, the clinical stage (I *vs.* II) and the site of presentation did not predict the risk of abdominal disease (Table 4).

A multifactorial analysis of all patients with clinical stage I and II disease was then performed to identify those dominant factors predicting the risk of abdominal involvement (Table 5). The number of symptoms was the most significant predictive factor (≥2, 1, 0; $p < 0.00001$). The histological cell type was also statistically significant, with an ascending risk for NS < LP < MC < LD disease ($p = 0.0009$). In addition, women had a lower risk for abdominal disease than men, even after accounting for the other two factors ($p = 0.01$). In the multifactorial analysis, the anatomical site of presentation (*e.g.*, cervical nodes, mediastinal nodes, etc.), the clinical stage (I *vs.* II), and the patient's age and race did not correlate with a risk of abdominal disease once the other factors were accounted for.

TABLE 5. *Multifactorial Analysis Predicting Abdominal Disease in Clinical Stage I and II Patients**

	P Value
Symptoms (0, 1, ≥2)	<0.00001
Histology (NS *vs.* LP *vs.* MC *vs.* LD)	0.0009
Sex	0.01

* Other factors that were not predictive included tumor site, clinical stage, age, and race. The derived model for both clinical stage I and II patients was P (abdominal metastases) = $[1 + \exp(-1.3785 + 1.0939)$ (number of symptoms) $- 2.2066$ (XN) $- 0.8453$ (XM) $- 1.8556$ (XL) $- 0.9682$ (sex)$]^{-1}$ where sex: 1 = male, 2 = female; XN = 1 if ND, 0 if not; XM = 1 if MC, 0 if not; XL = 1 if LP, 0 if not.

TABLE 6. *Probability of Abdominal Metastases in 194 Hodgkin's Lymphoma Patients (Clinical Stage I and II)*

	No Symptoms		1 Symptom		≥2 Symptoms	
	F (%)	M (%)	F (%)	M (%)	F (%)	M (%)
NS	6	14	16	33	36	60
LP	8	19	21	41	44	67
MC	20	39	42	66	69	85
LD	36	60	63	82	84	93

Predicting the Risk for Abdominal Disease

A mathematical model was derived in order to provide a quantitative estimate of the probability for abdominal disease in different clinical settings (Table 6). The data were combined for 194 clinical stage I and II patients, since the statistical analysis showed that the clinical stage did not correlate with the risk of abdominal involvement. An entire spectrum of probability for abdominal Hodgkin's lymphoma could thus be estimated by integrating these prognostic variables. The estimated probability of abdominal disease ranged from six per cent for nodular sclerosing histology in asymptomatic women to 93% for men with lymphocyte-depletion histology and multiple symptoms (Table 6).

Follow-up Results

To estimate the accuracy of staging laparotomy, the risk for abdominal relapse was analyzed in patients undergoing long-term follow-up whose staging laparotomy showed no detectable evidence of Hodgkin's disease (pathological stage I or II). There were 135 patients who had negative laparotomies; as a result, they did not receive abdominal irradiation. Of these, 16 (12%) relapsed in the abdomen. The median time for relapse was 1.9 years. Some patients relapsed at more than one site. The mean follow-up of all patients was 4.8 years, a time period during which more than 85% of relapsed patients had already developed a recurrence. The most common sites of relapse for these 16 patients were the periaortic lymph nodes (50%), iliac lymph nodes (31%), or bone marrow (25%) as shown in Table 7. Based upon these

TABLE 7. *Postlaparotomy Relapses in the Abdomen (Stages I or II)*†† (16 Patients, or 12%, Had Negative Laparotomies)*

	Number	Per cent
Periaortic lymph nodes	8	50
Iliac lymph nodes	5	31
Bone marrow	4	25
Unspecified abdominal sites	3	19
Splenic lymph nodes	2	13
Liver	1	6
Celiac nodes	1	6

* Some patients had more than one site.

† Mean follow-up was 4.8 years for all 135 patients with pathologic stages I and II, while the mean time for relapse in the 16 relapsed patients was 1.9 years.

figures, the accuracy of staging laparotomy could be estimated at 88%, since only 12% of patients relapsed in the abdomen during the follow-up period of observation. The most frequent site of relapse was periaortic lymph nodes (50%), followed by the iliac lymph nodes (31%), and bone marrow (25%). Of the four patients who relapsed in the marrow, one did not have an iliac crest bone marrow biopsy as part of his initial staging laparotomy.

Discussion

The multifactorial analysis identified three prognostic factors that best predicted the risk of abdominal disease in stage I and II Hodgkin's disease. These were the number of symptoms (≥2, 1, 0), histologic type (NS < LD < MC < LD), and sex (females > males). The site of presentation (mediastinal, axillary, cervical, and supraclavicular) was not predictive of abdominal metastases, although others have found this to be true in a univariate analysis.[3,10]

The statistical approach used here was designed to integrate and weight these three prognostic factors so that the probability of abdominal disease could be estimated. Three groups of patients were identified. First, is a group of **low risk** patients who might be treated with radiation therapy alone. Whether this should include both mantle irradiation for upper torso disease or mantle plus upper abdomen ports was not addressed in this study. This selection might include some asymptomatic LP and NS patients (especially women) with both stage I and stage II disease where the estimated probability of abdominal disease ranges from six per cent to 19% (Table 6). Johnson and colleagues[4] also suggested that stage I and II NS patients (especially asymptomatic ones) had a sufficiently low risk for distant disease that they should be treated with radiation therapy and not undergo a laparotomy.

Second, there was an identifiable **high-risk group** of patients where the probability of abdominal disease is so high (69% to 93%) that it could be assumed to be present, and the patients treated with chemotherapy (and possibly radiation therapy) for occult disseminated disease. This selection might include symptomatic patients with LD histology (especially males), or patients with two or three symptoms and MC histology (especially males). Third, there was a subgroup of **intermediate-risk patients** who should have staging laparotomy to define the presence and extent of disease. Maximum staging then allows the physician to select the minimum curative therapy. This latter group of patients might be an appropriate subgroup in which a randomized prospective trial could be conducted to conclusively determine whether a staging laparotomy actually improves the choice of treatment and survival rates.

It should be emphasized that the endpoint of this prognostic factors analysis was the presence of Hodgkin's disease in the abdomen, not survival. It is interesting to note, however, that those factors identified in this study are similar to the results in other prognostic factors analyses that used survival rates as an endpoint, such as histology, symptoms, sex, stage, site, age, and extent of disease.[4,10–15]

The changes in stage after laparotomy and the sites of disease found in the abdomen are quite similar to those reported by others, and range from 25% to 46%.[3,16–20] The results emphasize the importance of adhering to the surgical protocol that is now used by most centers.[3,16,21,22] The spleen, splenic hilar nodes, and periaortic nodes are the most common sites of involvement. Hemisplenectomy, or partial splenectomy, is probably not an adequate staging procedure for this organ. Some oncologists have suggested that a repeat bone marrow biopsy is unnecessary, but since the preoperative needle biopsy was falsely negative in seven per cent of patients, it seems appropriate to perform a wedge excision of the iliac crest bone marrow as part of the surgical staging procedure. Of the clinical stage III patients, 44% were downstaged, largely because of false-positive lymphangiograms or gallium scans. Therefore, a staging laparotomy might be justified in clinical stage IIIA patients to verify the presence of abdominal disease.

There have been few reports with long-term follow-up after staging laparotomy. In this analysis, the surgeon could detect disease with a very acceptable false-negative rate of about 12%. This rate is an estimate only, for there are several factors that influence this figure. First, it is possible that the abdominal and marrow disease noted in these patients may have disseminated subsequent to the laparotomy as part of a more generalized disease progression. Second, some patients were treated with abdominal irradiation or systemic chemotherapy. Third, some patients are still at risk for abdominal relapse because of a follow-up observation period less than 4 years.

Those who favor a staging laparotomy emphasize that when the treatment strategy is based on clinical staging, some patients (*e.g.*, clinical stage III, pathologic stage I) might receive excessive therapy since they may actually have a lower pathologic stage. As a consequence, they might be subjected to the risks of radiation therapy and chemotherapy, such as sterility, increased organ toxicity, and the increased risk of a second malignancy.[11,17,18,22] On the other hand, those patients who are understaged might be undertreated as well, with a diminished probability for cure when they relapse. As with many controversies in medicine, the issue is not "all or none" and there may be an intermediate position that some, but not all, patients require a laparotomy in order to

make a proper treatment decision in an individual patient.

Staging laparotomy is a safe and accurate diagnostic tool for directing more specific therapy in Hodgkin's disease patients. The operative mortality should approach zero per cent and the morbidity should be less than ten per cent.[11,17,18,22–24] It is entirely possible that a more selective approach would be feasible in the future, and that patients with especially high and low risks for abdominal disease based upon prognostic factors could have their treatment decisions made without having to undergo a staging laparotomy. In our opinion, it is still an appropriate and necessary procedure for the large number of patients with intermediate risk for abdominal disease as listed in Table 6.

The approach described here provides a quantitative estimate of risk for abdominal disease that the physician can use in combination with other aspects of clinical judgment (*e.g.*, number of sites, extent, risk for surgery, number of treatment options, etc.) to make a more considered decision for an individual patient. While the probability of abdominal involvement may vary from one series to another, it does provide a mechanism for comparison between institutions and could be used to determine stratification criteria in clinical trials.

References

1. Bergsagel DE, Alison RE, Bean HA, et al. Results of treating Hodgkin's disease without a policy of laparotomy staging. Cancer Treat Rep 1982; 66:717–31.
2. Lacher MJ. Primary treatment of Hodgkin's disease with sequential radiation therapy and multidrug chemotherapy without initial laparotomy-splenectomy. Prog Clin Cancer 1982; 8:283–97.
3. Gamble JF, Fuller LM, Martin RG, et al. Influence of staging celiotomy in localized presentations of Hodgkin's disease. Cancer 1975; 35:817–25.
4. Johnson RE, Zimbler H, Berard CW, et al. Radiotherapy results for nodular sclerosing Hodgkin's disease after clinical staging. Cancer 1977; 39:1439–44.
5. Griffin T, Gerdes A, Parker R, et al. Are pelvic irradiation and routine staging laparotomy necessary in clinically staged IA and IIA Hodgkin's disease? Cancer 1977; 49:2914–16.
6. Bennett MH, MacLennan KA, Easterling MJ, et al. The prognostic significance of cellular subtypes in nodular sclerosing Hodgkin's disease: An analysis of 271 nonlaparotomised cases (BNLI Report No. 22). Clin Radiol 1983; 34:497–501.
7. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's disease staging classification. Cancer Res 1970; 31:1860–61.
8. Ostle B, Mensing R. Statistics in research. Basic Concepts and Techniques For Research Workers. 3rd ed. Iowa State University Press, 1975.
9. Cox DR. Analysis of binary data. London, Methuen, 1970.
10. Fuller LM, Hutchison GB. Collaborative clinical trial for stage I and II Hodgkin's disease: significance of mediastinal and non-mediastinal disease in laparotomy- and non-laparotomy-staged patients. Cancer Treat Rep 1982; 66:775–87.
11. Larson RA, Ultmann JE. The strategic role of laparotomy in staging Hodgkin's disease. Cancer Treat Rep 1982; 66:767–74.
12. Gospodarowicz MK, Bush RS, Bean HA, et al. Results of treatment of clinical stage I & II Hodgkin's disease (HD) at the Princess Margaret Hospital (PMH) between 1968–77 (Abstr). ASCO 1983; Vol. 212.
13. Stein RS, Hilborn RM, Flexner JM, et al. Anatomical substages of stage III Hodgkin's disease. Implications for staging, therapy, and experimental design. Cancer 1978; 42:429–36.
14. Hoppe RT, Cox RS, Rosenberg SA, et al. Prognostic factors in pathologic stage III Hodgkin's disease. Cancer Treat Rep 1982; 66:743–49.
15. Ryoo MC, Kagan AR, Wollin M, et al. Hodgkin's disease: a review of staging procedure, treatment and prognostic parameters (Abstr). ASCO 1984; 25:238.
16. Jones SE. Importance of staging in Hodgkin's disease. Semin Oncol 1980; 7:126–35.
17. Sandusky WR, Jones RCW Jr, Horsley JS III, et al. Staging laparotomy in Hodgkin's disease. Ann Surg 1978; 187:485–89.
18. Martin JK Jr, Clark SC, Beart RW Jr, et al. Staging laparotomy in Hodgkin's disease. Mayo Clinic experience. Arch Surg 1982; 117:586–91.
19. Glees JP, Barr LC, McElwain TJ, et al. The changing role of staging laparotomy in Hodgkin's disease: a personal series of 310 patients. Br J Surg 1982; 69:181–87.
20. Urlaub BJ, Mack E. Evaluation and complications of 107 staging laparotomies for Hodgkin's disease. Ann Surg 1979; 190:45–7.
21. Ferguson DJ, Allen LW, Griem ML, et al. Surgical experience with staging laparotomy in 125 patients with lymphoma. Arch Intern Med 1973; 131:356–61.
22. Cannon WB, Nelsen TS. Staging of Hodgkin's disease: a surgical perspective. Am J Surg 1976; 132:224–30.
23. Rosenstock JG, D'Angio GJ, Kiesewetter WB: The incidence of complications following staging laparotomy for Hodgkin's disease in children. Am J Roentgenol Radium Ther Nucl Med 1974; 120:531.
24. Kawarada Y, Goldberg L, Brady L, et al. Staging laparotomy for Hodgkin's disease. Am Surg 1976; 42:332–345.