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A Critique of the Value of Laparotomy and Splenectomy in the Evaluation of Patients with Hodgkin's Disease[1]

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Summary

The use of exploratory laparotomy and splenectomy has been widely adopted for the evaluation and staging of patients with Hodgkin's disease. The greatest value of the surgical procedure is to provide accurate assessment of involvement of the spleen. Although rare, in unselected untreated patients, liver involvement cannot be accurately determined without histological confirmation. Minor advantages of the procedure include supplementary information concerning the status of abdominal lymph nodes and facilitation of radiotherapy programs and possibly of chemotherapy programs. Other than as an investigative approach, the major value of the surgical procedure is to provide better diagnostic information, primarily concerning the spleen, and this is of value primarily if decisions regarding therapy are dependent on the demonstration of splenic involvement.

Introduction

The evolution of the recommended diagnostic approach for previously untreated patients with Hodgkin's disease has paralleled the development and study of aggressive therapeutic programs now available. As successively more detailed techniques have appeared and have been utilized, the value and limitations of the earlier techniques have become apparent. This has been especially so for methods of detecting intraabdominal disease. There has been enthusiasm and then reservation of the value, and necessity of inferior venacavography, bipedal lymphography and, now, exploratory laparotomy and splenectomy. These procedures developed and evaluated by clinical investigators in this field, usually as part of therapeutic protocol studies, have been rapidly adopted by medical centers and physicians, frequently without a complete appreciation of the requirements of the techniques, the morbidity of the procedures, and their indications based on available knowledge. This is the current situation for the use of exploratory laparotomy and splenectomy for patients with Hodgkin's disease.

It is timely to review the information now available pertaining to the role of exploratory laparotomy and splenectomy for the staging of untreated patients, the contribution of the procedures to our understanding of patterns of disease, and the value of this surgical approach in the total management of the disease. The acute morbidity is now well described and is minimal (3); however, the long-term effects are unknown and worthy of speculation.

Results of Exploratory Laparotomy and Splenectomy

There are now numerous reports of groups of patients subjected to these procedures in the literature, reported at meetings and by abstracts and letters (1, 2, 5, 6, 10, 13). The Stanford series now numbers over 200 patients with Hodgkin's disease. The analysis of 100 consecutive untreated patients has been published (13, 14) and included in a review by Ultmann (19) of 182 patients from 4 different centers in the United States. There are only minor differences in the results now available from the numerous medical centers, and the data from Stanford are typical and are presented in Table 1.

The most significant information gained from exploratory laparotomy and splenectomy concerns involvement of the spleen. Only one-half of the patients who are assessed to have involvement of the spleen clinically, based upon its enlargement, will have involvement of that organ when examined pathologically. Conversely, approximately 1 patient in 4 will have demonstrable Hodgkin's disease of the spleen without any clinical suspicion, preoperatively and often within a spleen or normal size. The spleen may even appear completely normal to the examining surgeon and the abnormality is evident to the pathologist only when he makes thin, 3- to 5-mm slices of the organ. This minimal involvement is seen to arise from a visibly enlarged Malpighian corpuscle. To date we have had no example of involvement of the spleen which is apparent only under the microscope but not evident grossly. One can speculate, however, that microscopic involvement does occur.

The spleen may be the only documented site of Hodgkin's disease below the diaphragm. This has occurred in 13 or 8% of 155 consecutive patients. The majority, but not all, of the patients with abdominal lymph node involvement have involvement of the spleen. Of 53 patients with Stage III disease, 43 or 81% had splenic involvement.

Some of the uninvolved spleens which were presumed to be enlarged clinically, proved to be of normal size when removed, or were up to 400 g with normal histology. In some instances, the enlarged, otherwise normal spleen was described as congested, hyperplastic, or containing noncaseating granulomata (7). The significance of an enlarged spleen not

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Table 1

Results of laparotomy in 100 consecutive untreated patients with Hodgkin's disease (13, 14)

Site	Preoperative assessment	A. Systemic symptoms absent	B. Systemic symptoms present	Total
Liver	Clinically positive	0/4[a]	1/11	1/15
	Clinically negative	1/53	1/32	2/85
Spleen	Clinically positive	2/6	6/10	8/16
	Clinically negative	11/51	9/33	20/84
Abdominal nodes	Positive lymphangiogram	8/11 (1)[b]	10/12	18/23 (1)
	Negative lymphangiogram	5/33 (4)	2/24 (1)	7/57 (5)
	Equivocal lymphangiogram	3/13 (1)	1/7	4/20 (s)

[a]No. with Hodgkin's disease/no. examined.

[b]No. in parentheses, patients with positive splenic hilar nodes but negative paraaortic node biopsy.

actually involved with deposits of Hodgkin's disease is unknown.

When there is advanced liver disease with deep clinical jaundice, massive nodular hepatomegaly, and grossly deranged liver function tests, a random needle biopsy of the liver, perhaps assisted by laparoscopy, will usually confirm the presence of Hodgkin's disease. This clinical picture, however, does not often occur in patients at the onset of their disease when initial staging and therapeutic decisions are being made. Liver involvement initially is much more subtle or occult.

Involvement of the liver by Hodgkin's disease is identified only rarely in a group of untreated patients. This occurred only 3 times in the Stanford series of 100 unselected patients subjected to exploratory laparotomy. The usual clinical determinations of liver size, liver function tests, and liver scans are unreliable. Within the limitations of surgical exploration with wedge and needle biopsies at surgery, false-negative preoperative elevations occurred in 8 of 33 instances in a selected group of patients at Stanford (5) and in 4 of 120 in Ultmann's review of unselected patients. Since the entire liver cannot be studied as can the spleen, false-positive clinical evaluations are more difficult to determine. However, this occurred in 29 of 32 patients in Ultmann's review. Clinical assessment of hepatic involvement appears to be most inaccurate in the presence of systemic symptoms, such as fever and sweats.

Apparent false-positive clinical evaluation parameters occurred in 8 of 21 patients in our selected series (5). Two of these patients have remained free of evident disease for 54 and 57 months after total lymphoid irradiation for Stage III disease. One patient developed Stage IV disease, including liver involvement 9 months after the laparotomy. Of the other 5, 2 have been free of disease for shorter periods of time and 3 have had disease activity without documented hepatic involvement. We have seen return to normal of moderate laboratory evidence of hepatic dysfunction with control of lymph node disease and symptoms by irradiation. One might speculate that there is a nonspecific effect on sensitive measures of liver function by Hodgkin's disease activity elsewhere, especially in the presence of systemic symptoms.

The nonoperative clinical assessment of Hodgkin's disease involvement of the liver is unreliable and cannot be depended upon. We must require histological verification of hepatic Hodgkin's disease, especially when its involvement would alter the therapeutic approach to the patient.

The correlation of involvement of the liver and spleen is of considerable interest and significance. We have had no examples of involvement of the liver without concomitant involvement of the spleen in untreated patients and in those later in their course who have not had a prior splenectomy. We have noted that the larger is the spleen and the greater its involvement, the more likely is the demonstrable involvement of the liver. Of 16 patients with Hodgkin's disease within spleens weighing more than 400 g, 13 or 81% have had documented hepatic tumor. It remains to be determined what the risk of liver involvement may be in those patients with minimal Hodgkin's disease of the spleen discovered at laparotomy. It appears, however, that involvement of the spleen has special pathophysiological significance and can no longer be viewed as merely another lymph node when considering the staging and management of patients with Hodgkin's disease.

One of the subjects of greatest controversy and confusion concerns the relative value of lower extremity lymphography in the light of the experience with exploratory laparotomy. There are numerous lymph node groups which are not visualized by the usual lymphographic study, including the mesenteric nodes, splenic hilar nodes, celiac axis nodes, and those in the region of the porta hepatis. In these locations, the surgical procedure supplements the information gained from the lymphogram. Frequently, the paraaortic lymph nodes are not well visualized by lymphography from the level of the 2nd lumbar vertebra and higher. However, this is also the region which the surgeon may have difficulty in adequately exploring without risking unacceptable morbidity, especially in the region of the pancreas.

By removing Ethiodol-filled lymph nodes, the surgeon can provide important material for the pathologist to confirm the roentgenologist's interpretation and, of most importance, to clarify lymphographic findings which are equivocal. In our experience, between 20 and 25% of lymphograms cannot be interpreted as definitely positive or definitely negative for Hodgkin's disease involvement. Small filling defects, especially in the most superiorly filled lymph nodes or diffuse but minor degrees of increased foaminess or granularity are the most difficult to interpret roentgenologically. If the surgeon can

remove those lymph nodes which are most suspicious and document their removal with postoperative abdominal films identifying radiopaque surgical clips, then the surgical procedure supersedes the roentgenological study for accuracy.

Rarely, a lymph node appearing completely normal roentgenologically will contain Hodgkin's disease. This occurred only twice in 57 patients in our series of 100 patients. Other series have reported a higher incidence of false-negative examinations which probably can be explained by the variable criteria used by roentgenologists for distinguishing negative from equivocal studies.

False-positive lymphographic examinations are of great importance but are difficult to determine. Before concluding that the positive lymphographic interpretation was in error, the surgeon must demonstrate that he has removed representative if not all of the opacified lymph nodes which have been interpreted as abnormal. This is sometimes difficult for the surgeon to accomplish, and in these instances the lymphogram interpretation should be utilized. We were unable to confirm the roentgenologists' positive interpretation in 5 of 28 cases in our initial report and, in our more recent consecutive series, in 6 of 23.

The lymphogram is also of importance in the planning of radiotherapy fields and the subsequent follow-up of the patient. The documentation of return to normal of paraaortic nodes after radiotherapy or chemotherapy and the earliest sign of disease activity in this occult region is of great importance in the management of patients with Hodgkin's disease (12).

For these reasons, it does not seem wise or justified to abandon lymphography in favor of exploratory laparotomy but to use both procedures as complementing each other in appropriately selected patients.

Exploratory laparotomy and splenectomy has been developed and studied as a diagnostic approach to patients with Hodgkin's disease. The advantage of removing the spleen in the subsequent management of the patient has been suggested and deserves comment (9, 15).

The radiotherapy fields which are required to encompass the spleen adequately includes some of the left lower lung and pleura and may include portions of the left kidney. There will be even more inclusion of the kidney when the spleen is large. When the radiotherapist can limit his fields to include only the identified splenic pedicle, radiation pneumonitis and pleuritis of the left lung base can be eliminated and radiation damage to the kidney can be minimized (11).

Occasionally, patients will present with significant hypersplenism and with peripheral blood count depressions too severe to permit current radiotherapy or chemotherapy programs with safety. In these cases, the splenectomy has its greatest utility. However, even the average patient will demonstrate significant increases in the peripheral white blood cell and platelet levels following splenectomy which have facilitated the delivery of wide-field radiotherapy courses (15). Although not as well documented, aggressive chemotherapy programs may also be more feasible following splenectomy (9, 14).

These advantages in the management of patients with Hodgkin's disease are minor, however, and should not be considered as the major purpose of the procedure. Splenic Hodgkin's disease can be adequately treated with irradiation, and radiotherapy and chemotherapy tolerance is adequate in patients who have not undergone surgery. There will be morbidity of the procedure, including wound dehiscence and infections, subphrenic abscess, pancreatitis, inadvertent ureteral damage, and other operative and postoperative complications. We have had only 1 death, in a previously treated patient, but a low incidence of mortality can be predicted. It is still not accurately known to what degree patients with Hodgkin's disease who have been splenectomized will have an increased incidence of infections, well described in other patients, both children and adults, who have had splenectomy (4, 20). We have already observed 4 examples of pneumococcal sepsis, 1 with intravascular coagulation, but fortunately all without mortality (M. R. Moore, personal communication). However, one boy, age 9, developed fulminant fatal *Hemophilis influenzae* sepsis with intravascular coagulation 2 years after splenectomy. He had been treated with total lymphoid irradiation followed by combination chemotherapy and had no evidence of Hodgkin's disease at autopsy.

It may be possible to select patients for exploratory laparotomy and splenectomy who are most likely to have occult abdominal disease. Patients who are older, who have systemic symptoms, who have the histological varieties of mixed cellularity or lymphocyte depletion, who have low left neck disease, or who have vascular invasion have been suggested to be at greater risk. These same clinical and pathological features, however, might be used to select patients for abdominal irradiation despite a negative exploration and might negate the value of the procedure. We do not yet know what group of patients, if any, will have such a low probability of having abdominal disease that the risk of the procedure will outweigh the gain in the therapeutic results.

The major value and utility of exploratory laparotomy and splenectomy is to determine the extent of the disease, and then only if the identification of abdominal disease would alter the therapeutic program planned. *If the therapeutic plan is to use radiotherapy only to known sites of disease, or to limit the use of radiotherapy to those patients with Stages I or II disease above the diaphragm either as a general rule, or for particular patients, then the exploratory laparotomy and splenectomy is indispensible for adequate staging and therapeutic decisions. If the therapeutic plan is to treat so-called total lymphoid fields as a general rule, or for particular patients, even in the absence of identified abdominal disease, then the surgical procedure has only the limited value of identifying the few patients with liver involvement and the facilitation of treatment to some extent.* If young women wish to preserve ovarian function and pelvic irradiation is planned, surgical oophoropexy is recommended and then the full exploration and splenectomy would seem to be justified at the time of operation (3).

It is obvious that the routine use of exploratory laparotomy and splenectomy will change the staging designations and distribution of patients at centers at which this technique is used. Patients with otherwise occult, minimal extranodal disease will be classified as Stage IV. A significant number of patients will be advanced from Stage II to Stage III, and an

almost equal number will be returned to the Stage II category, having been judged Stage III prior to surgery. The influence of the splenectomy *per se* on the subsequent behavior of Hodgkin's disease, perhaps favorable, perhaps unfavorable, is not known. Therefore, therapeutic studies and results will not be comparable from different centers unless the same diagnostic approaches are utilized by each center. Given other factors of patient selection for therapeutic trials, the need for internally controlled, randomized studies must be reemphasized.

Much of the value of the surgical approach to the staging of Hodgkin's disease has been to provide information of the patterns of disease in untreated patients. Correlations of sites of involvement, such as the spleen and the liver, the low left neck and the abdomen and the frequent bypassing of the mediastinum have been made. These observations must be confirmed and should contribute to our understanding of the nature and pathophysiology of Hodgkin's disease. The observations of focal microscopic involvement (17), vascular invasion (16), and consistency of histological patterns (8, 18) have been made because of the widespread use of exploratory laparotomy and splenectomy by groups studying these disorders. These contributions to our knowledge of Hodgkin's disease as part of careful clinical investigations do not justify the routine adoption of exploratory laparotomy and splenectomy for all patients with Hodgkin's disease, at all stages and settings of their disease, no matter what the therapeutic programs. As with all diagnostic procedures, the approach should be to individualize each patient, in the context of local and current therapeutic philosophy, and to utilize the procedure only when the small but definite risks and speculations about unknown risks appear to be less than the advantage to the patient.

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