PAPERS AND ORIGINALS

Intensive investigation in management of Hodgkin's disease

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Summary

Ninety-eight patients with clinically localised Hodgkin's disease underwent laparotomy and splenectomy to determine the extent of microscopic spread. In 68 patients the procedure was carried out for untreated disease apparently confined above the diaphragm. Abdominal disease cannot be confidently excluded on the basis of non-invasive investigation at presentation. Clinical assessment of splenic disease was unreliable unless gross splenomegaly was present. Pedal lymphography was accurate in assessing para-aortic and iliac disease but of no value in assessing other intra-abdominal lymph node involvement, including that of the mesenteric lymph node. Trephine bone marrow biopsy findings were normal in all patients before surgery, and only one patient was found to have diseased bone marrow by Stryker-saw biopsy at operation. Liver disease was identified at operation in nine patients, some of whom were asymptomatic with clinically undetectable splenic and nodal disease. Detailed clinical staging failed to detect disease in one-third of patients who underwent laparotomy.

These studies show that if radiotherapy is to remain the

treatment of choice for disease truly localised to lymph nodes a detailed staging procedure, including laparotomy and splenectomy, remains essential. The value of this potentially curative treatment is considerably diminished in the patient who has been inadequately staged.

Introduction

Certain principles of treatment are now well established in the management of Hodgkin's disease. Radiotherapy has become the treatment of choice for disease confined to the lymph nodes system,^{1 2} while chemotherapy is preferred for more extensive disease.³ Intensive use of one form of treatment may preclude effective use of the other; and the risk of further neoplasm is slightly increased in patients receiving both radiotherapy and chemotherapy.^{4 5}

To give the best treatment, the extent of the disease must be precisely defined. Clinical assessment is inaccurate since microscopic disease remains undetected. Nevertheless, radiological assessment is helpful in determining whether disease is present above the diaphragm, and since extended-field radiotherapy given to the "mantle" area permits a degree of diagnostic error in patients who present with disease in the neck, axilla, or mediastinum, more detailed staging of the kind which might be obtained by limited thoracotomy would be of little therapeutic value. The accurate assessment of abdominal disease has more important therapeutic implications: lymphangiography and percutaneous liver biopsy are not completely accurate,^{6 7} so a negative result will not exclude abdominal disease with the high degree of certainty necessary if radiotherapy is to be curative. There is, therefore, a strong case for performing splenectomy and a staging laparotomy in patients presenting with predominantly supradiaphragmatic disease who are clinically amenable to treatment with radiotherapy. We report here our experience of intensive staging procedures and the influence of staging on patient management.

Patients and methods

Patients referred to St Bartholomew's Hospital with a tissue diagnosis of Hodgkin's disease were staged clinically.^{8 9} The histology was reviewed (AS) and classified according to the Rye nomenclature.¹⁰

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One hundred and twenty-nine patients were considered to have localised nodal disease (clinical states I-IIb) or extensive nodal involvement without symptoms of Hodgkin's disease (clinical stage IIIA). Relevant symptoms were fever, night sweats, and weight loss.⁸ Further definition of the extent by laparotomy, splenectomy, lymph node biopsies, and liver and bone marrow biopsy was recommended for this group. Surgical staging was not undertaken in patients with extensive nodal disease with symptoms (stage IIb) or in patients with extranodal involvement by Hodgkin's disease (stage IV).

LYMPHOGRAPHY

Ninety patients underwent bipedal lymphography using a total dose of Lipiodol not exceeding 14 ml. Ventilatory capacity was tested clinically, radiologically, and functionally before the investigation. A blind review by two observers categorised the lymphogram as positive, negative, or equivocal. The prelaparotomy films were compared with those obtained after surgery (excised nodes being marked by metal clips), and the correlation between radiological abnormality and node histology was noted. Non-opacified but histologically involved nodes were also noted.

Criteria for nodal involvement were: (a) nodal enlargement with separation of contrast-filling sinuses ("foamy" appearance); (b) filling defects other than at the node hilum (seen on at least two different projections); (c) absence of node filling, often associated with abnormal collateral vessels. Additional signs were: (d) filling of nodes at abnormal sites; and (e) displacement of nodes from the vertebral column. Slightly enlarged iliac nodes alone were insufficient to warrant a positive lymphographic diagnosis because of the high incidence of this pattern with non-specific inflammatory change.

ASSESSMENT OF LIVER DISEASE

Patients with abnormalities of liver size, liver function, bromsulphthalein excretion, or scanning defects underwent percutaneous biopsy. A positive finding or consistent abnormality of two of the clinical indices was considered evidence of liver disease, and the patient was exempted from further surgical staging.

ASSESSMENT OF BONE MARROW DISEASE

All patients underwent bone-marrow aspirate and Gardner-needle trephine biopsy at presentation. Those with evidence of Hodgkin's disease did not undergo staging by laparotomy. Features of marrow disease were a loss of normal marrow architecture, with replacement by cellular fibrous tissue and an absence of normal marrow elements in affected areas. The presence of Reed-Sternberg cells was not required.¹¹

TABLE I—Correlation between pre-operative lymphogram and histological involvement of para-aortic and iliac glands shown at laparotomy

	No of patients	Histology		"Error"
		Affected	Not affected	
Positive lymphogram	24	22	2	8
Negative lymphogram	58	4	54	7
Equivocal	8	2	6	
Total	90	28	62	

TABLE II—Correlation between prelaparotomy assessment of lymphogram and histological involvement of para-aortic and iliac lymph glands

Histology	Total No of patients	Assessment					
		Correct		Incorrect		Equivocal	
		+ Lymphogram + biopsy	- Lymphogram - biopsy	+ Lymphogram - biopsy	- Lymphogram + biopsy	+ Biopsy	- Biopsy
Lymphocyte predominance	15	5	9	0	1	0	0
Nodular sclerosis	46	10	30	2	1	0	3
Mixed cellularity	27	5	15	0	2	2	3
Lymphocyte depletion	2	2	0	0	0	0	0

+ = Positive. - = Negative.

LAPAROTOMY AND SPLENECTOMY

The spleen and splenic hilar lymph node were removed. Biopsy specimens were taken from nodes in the iliac and para-aortic group and also from nodes that are not normally shown on a lymphogram—for example, those in the coeliac axis, mesentery, cystic duct, omentum. Biopsy sites were marked with tantalum clips. Wedge and needle biopsies of the liver were performed, and a Stryker-saw bone-marrow biopsy specimen was taken from the iliac crest through a separate incision. In women the ovaries were transfixed behind the uterus.

PREPARATION AND INTERPRETATION OF SPECIMENS

After fixation representative blocks from obvious deposits were taken. In the absence of obvious tumour blocks were made from several sections of the tissue. The presence or absence of Hodgkin's disease, the degree of reactivity of lymphoid tissue, and the presence of granulomatous foci were reported. A pleomorphic cellular infiltrate in the portal tracts and sinusoids of the liver was insufficient evidence of liver disease in the absence of diagnostic Reed-Sternberg cells in the biopsy specimen.

TREATMENT

Patients with nodal disease confined to one side of the diaphragm (pathological stage I-IIb) received either mantle or inverted-Y radiotherapy. Splenic irradiation was not included, and thus splenectomy was an essential part of the surgical procedure.

Patients with extensive nodal involvement and symptoms of Hodgkin's disease (stage IIb) or with extranodal disease (stage IV) were treated with combination chemotherapy.¹²

Results

LYMPHOGRAPHY

Of the 58 lymphograms regarded as negative, 54 were confirmed to be negative at laparotomy (7% error). In four patients nodes thought to be unaffected were histologically positive (table I). One patient had microscopic involvement of one para-aortic node, one had a unilateral lymphogram for technical reasons, and two would still be considered negative on retrospective lymphographic review. Twenty-four lymphograms were considered to be positive, and the findings in 22 were confirmed at laparotomy. The remaining two patients had negative findings (8% error). Nodes considered to be affected on these last two lymphograms were not biopsied, and in this respect the laparotomy rather than the lymphogram may have been misleading. Eight lymphograms were considered to be equivocal (9% of total). After laparotomy two patients had positive findings and six were negative.

Of the 54 patients with no involvement of the para-aortic or iliac nodes detected by lymphography or laparotomy, 14 had involvement of the non-opacified splenic hilum, coeliac axis, or mesenteric nodes (26%). Only one of the 14 had a palpable spleen, though 13 showed microscopic disease of the spleen. Thus lymphography showed para-aortic and iliac disease with considerable accuracy. But as an indicator of overall abdominal involvement it gave an incomplete result in at least 26% of cases owing to occult disease in the spleen, splenic hilum, or coeliac axis lymph nodes, none of which opacify at pedal lymphography and would therefore remain undetected without laparotomy.

The lymphography and laparotomy findings in relation to histological type of Hodgkin's disease are summarised in table II. Forty-six

TABLE III—Representation of histological types in patients undergoing laparotomy for Hodgkin's disease

Histology:	Lymphocytic predominance	Nodular sclerosis	Mixed cellularity	Lymphocytic depletion	Miscellaneous	Total
No (%) of specimens	23 (21)	48 (44)	33 (30)	2 (2)	4 (4)	110 (100)

of the 90 patients (51%) had nodular sclerosing disease. Within this group only one patient with a negative lymphogram had a positive biopsy finding at laparotomy (2% staging error). Nothing was found at laparotomy in the three patients with equivocal lymphograms. Twenty-seven cases were of mixed cellularity (30%). In this group two patients with a negative lymphogram were found to have pathological involvement (7% error). Of the five with equivocal lymphograms, two were found to have pathological involvement after surgery.

LAPAROTOMY AND SPLENECTOMY

Nineteen of the 129 patients with localised disease had medical contraindications to surgical staging. Table III shows the histological types of the remaining 110 patients. Twelve further patients were subsequently excluded from the analysis for the following reasons: the diagnosis was made at laparotomy (4); inadequate biopsies were taken (4); there were diagnostic errors or unsuspected findings (4). Thus 98 patients were available for analysis. They fell into four categories: 68 patients were untreated and had disease above the diaphragm; six underwent "early laparotomy" immediately after mantle radiotherapy for disease above the diaphragm; six had disease presenting only below the diaphragm; and 18 had relapsed.

CHANGE OF STAGE

Of the 68 patients who had staging laparotomies for previously untreated disease with a supra-diaphragmatic presentation, 24 (36%) had their stage changed (table IV). This was anticipated but none the less significant, since treatment is determined according to the anatomical extent of disease. In 20 (83%) the change was an increase in stage because of occult disease in the abdomen; in four (17%) we found that the clinical assessment of abdominal involvement was incorrect. Eight of the 24 in clinical stage I and nine of the 26 in stage II were changed to stage III. Three stage III patients were classified as stage IV after laparotomy.

TABLE IV—Results of pretreatment staging laparotomy for Hodgkin's disease above diaphragm

Clinical stage	No of patients	Pathological stage		
		Same	Increased	Decreased
IA	23	16	7	0
IB	1	0	1	0
IIA	22	14	8	0
IIB	4	3	1	0
IIIA	18	11	3	4
Total	68	44 (64%)	20 (30%)	4 (6%)

The finding of disease below the diaphragm was perhaps not surprising, but the few patients with clinically diagnosed intra-abdominal disease who did not have abdominal involvement were interesting. Three had clinical splenomegaly, which was pathologically innocent. Two had false-positive lymphograms, and one had an equivocal lymphogram. In the 36 months after laparotomy three of the four patients have remained disease-free. One relapsed four months after radiotherapy with recurrence in the treated area and in the lung. When analysis was extended to include all 98 laparotomies, 37 patients (37%) had their stage altered by surgery.

CLINICAL ASSESSMENT AND LAPAROTOMY STAGING

Splenomegaly

The most significant discrepancy between the findings at clinical assessment and at laparotomy was in the detection of disease within

the spleen (table V). Only 70% of clinically enlarged spleens were involved, while a clinically undetectable spleen contained Hodgkin's disease in 40% of cases.

The detection and importance of splenic involvement are controversial. It has been suggested that nodal involvement in the abdomen occurs relatively rarely in the absence of splenic disease^{13 14} and that the spleen becomes affected fairly early in the course of the disease. Thirty-one of our 68 untreated patients had abdominal disease, and six of these had nodal involvement in the absence of splenic disease.

TABLE V—Accuracy of clinical Assessment of intra-abdominal disease in 98 patients presenting with Hodgkin's disease (clinical stage I-III A)

	Clinical assessment	Pathological assessment	Accuracy
Lymph nodes:			
Involved	24	22	92%
Non-involved	58	54	93%
Equivocal	8	2 involved/ 6 non-involved	
Spleen:			
Involved	10	7	70%
Non-involved	88	53	60%
Liver:			
Involved			
Non-involved	98	9	9%

The remainder had an affected spleen, either as the sole evidence of disease (four cases) or with extrasplenic involvement as well.

The spleen was affected in 42 of the whole series (43%) and in 25 of those who underwent laparotomy for untreated supradiaphragmatic disease (37%), thus confirming the high incidence noted by others.¹⁵ Clinically apparent splenomegaly may be reliably considered to indicate involvement only when the spleen weights over 500 g. On the other hand, spleens of 70 g may be affected by Hodgkin's disease (see figure).

Splenic size assessed by weighing after laparotomy in patients with Hodgkin's disease.

TABLE VI—Correlation between isolated supradiaphragmatic presentation and presence of abdominal disease at laparotomy

Presentation site	No of patients	No negative at laparotomy	No positive at laparotomy	Distribution of abdominal disease			
				Non-opacified nodes	Para-aortic plus iliac nodes	Spleen	Liver
Left neck	15	10	5	5	2	5	
Right neck	5	2	3	3		3	
Mediastinum	2	2					
Axilla	1	1					
Thymus	1		1			1	

Lymphography

Lymphography has proved accurate in predicting disease in the para-aortic and iliac glands, but it is difficult to interpret equivocal lymphograms and assess disease in areas that do not normally opacify. Disease in such non-opacified sites in the absence of gross abnormalities in the upper lumbar nodes has been noted to be unusual,¹⁶ but 18 of the 31 untreated patients positive at laparotomy showed disease in the spleen alone, the spleen plus non-opacified nodes, or non-opacified nodes alone. Six patients became classified as pathological stage III because of affected mesenteric nodes (3 patients), cystic duct nodes (2), or a lesser omental node (1) in association with splenic disease.

Liver

Laparotomy showed that nine of the 98 patients had hepatic disease. All patients with liver disease had a diseased spleen and abdominal lymph nodes. The spleens weighed from 195 to 1660 g (median 408 g).

Five of the 68 patients presenting with supradiaphragmatic nodes were found to have liver disease. In three cases this was associated with splenic and para-aortic disease recognised on clinical assessment. Two who were considered to be clinically free of abdominal disease, however, were shown to have disease of the liver, spleen, and non-opacified nodes only. One of the five had symptoms on presentation.

Thus asymptomatic patients with clinically localised disease may have dissemination detected solely by laparotomy. This contrasts with the observations of Hellman¹⁷ but further endorses the unreliability of preoperative assessment of liver involvement.⁷

Bone marrow

Only one patient with clinical stage III disease, was found to have marrow disease. There was no indication of this on the pre-laparotomy blood count, aspirate, or trephine biopsy. This patient also had splenic and nodal involvement with mixed cellularity disease. In all other cases the Stryker-saw result did not modify the prelaparotomy marrow assessment.

PRESENTING FEATURES AND LAPAROTOMY FINDINGS

It has been suggested that certain presenting features may be associated with a low risk of abdominal disease, and their identification might therefore spare some patients from surgical staging.^{18 19}

Clinical stage 1 disease—Twenty-four of the untreated patients with supradiaphragmatic disease were clinically classified as having stage I disease. Five of the 15 patients with disease clinically localised to the left cervical nodes showed abdominal disease (table VI). Mixed cellularity histology was present in all, and only one of the five had symptoms of Hodgkin's disease. Three of the five patients presenting with right cervical nodes had infradiaphragmatic disease. All were asymptomatic. Mixed cellularity was present in two and nodular sclerosis in one. Abdominal disease was present in the one patient with an isolated thymic presentation.

Symptoms—Of the 68 patients undergoing surgical staging for disease presenting above the diaphragm, five had symptoms of Hodgkin's disease and two of these showed abdominal disease. Eighteen of the asymptomatic patients had abdominal disease. Symptoms were present in all six patients presenting with infradiaphragmatic disease. Twenty-four laparotomies were done for staging in relapse or for staging after initial treatment had been undertaken. Of the seven symptomatic patients, five had abdominal disease. Abdominal disease was present in 12 of the 17 patients without symptoms.

COMPLICATIONS OF LAPAROTOMY

No deaths occurred that might be attributed directly to the procedure.

The major complications were respiratory problems associated with small effusions at the left base after splenectomy (table VII). Thrombocythaemia was common, but thrombotic complications rare. One case of deep vein thrombosis was associated with dissection for a node biopsy; subsequent venography showed a thrombus in apposition to the tantalum clip.

TABLE VII—Complications of staging laparotomy and splenectomy in 98 patients

	No of patients		No of patients
Pulmonary embolus	1	Wound dehiscence	1
Deep vein thrombosis	3	Intestinal obstruction	1
Chest infection	10	Pneumothorax	1
Haemorrhage	1	Urinary retention	1
Subphrenic abscess	1	Urinary tract infection	1
Empyema	1		

Discussion

The efficacy of radiotherapy in controlling localised Hodgkin's disease has been amply shown. Treatment fails if an inadequate dose is given¹ or active disease is omitted from the radiation field.

Although combination chemotherapy has greatly improved the outlook for advanced disease, the long-term results are not yet clear, so we need, at present, to give "curative" radiotherapy to the maximum number of patients. This must not, however, be done at the expense of overlooking disease that is not clinically apparent. The major difficulty in staging is assessing intra-abdominal disease. Definition of liver or bone-marrow disease is of prime importance, as chemotherapy then becomes the treatment of choice. Similarly, disease of the abdominal lymph nodes is important in determining the necessity for infradiaphragmatic radiotherapy and the field size required.

The value of lymphography in detecting intra-abdominal disease has been established.^{20 21} Lymphography accurately assessed disease of para-aortic and iliac lymph nodes in over 90% of patients. The failure of lymphography to show disease subsequently established in these sites represents a genuine error. Nevertheless, the demonstration of normal nodes in the presence of an abnormal lymphogram requires cautious interpretation, as non-representative biopsies may give misleading information. A few (9%) lymphograms yielded equivocal results. Most of these assessments turned out to be negative.^{13 15 22 23}

The demonstration of normal para-aortic and iliac nodes by lymphography does not exclude the presence of disease in the other abdominal nodes. In about a third of patients disease was shown after laparotomy in sites that do not opacify on the lymphogram. Thus the lymphogram cannot be used to assess total abdominal node disease but may be relied on for an accurate interpretation of the state of para-aortic and iliac nodes.

Biochemical indices and percutaneous biopsy are known to give an unreliable preoperative assessment of liver disease.⁷ In our series we tried to exclude before operation those patients with suspected hepatic involvement. Similarly, patients with established stage IIIB disease were not subjected to laparotomy.

Despite such selection, nine unsuspected cases of liver disease occurred in the whole group, five of them among the 68 patients with untreated supradiaphragmatic disease. Most of these cases were asymptomatic. Like others, we found no liver disease without concomitant splenic and nodal involvement.

Similar selection to exclude patients with bone-marrow disease was exercised by preoperative trephine biopsy on all patients. Only one case of bone-marrow disease was subsequently discovered by Stryker-saw biopsy.

Clinical assessment of spleen size as an indication of involvement by Hodgkin's disease proved to be totally unreliable unless massive splenomegaly was present. Impalpable spleens contained disease and palpable spleens were disease-free often enough to make the assessment meaningless. We could not define characteristics at presentation which would exempt surgical staging on the grounds of a negligible risk of abdominal disease. The presence or absence of symptoms of Hodgkin's disease was not a reliable indication of the extent of disease.

An incidental finding at five laparotomies was non-caseating miliary granulomata in spleen, nodes, or liver.¹⁵⁻²⁴ Comparison of clinical assessment and subsequent laparotomy findings indicates that over a third of the patients had clinically unsuspected abdominal disease. This disease would have been unaffected if treatment had been planned according to clinical assessment of the extent of disease.⁶⁻¹⁴⁻¹⁵ This error is reflected in the disease-free survival figures for our patients treated with radiotherapy after clinical or pathological (post-laparotomy) assessment of disease extent. At 36 months the figures were 60% and 82% respectively.

These results confirm the failure to define the extent of disease solely by clinical means and indicate that when either mantle or inverted Y radiotherapy fields are used, the absence of Hodgkin's disease in the untreated areas must be established beyond doubt. In this context the disclosure of disease by surgical staging outweighs any upset caused by the procedure. The application of total nodal and splenic irradiation would obviate

the need for such scrupulous staging. But this would result in overtreating most patients presenting with localised disease and would be inappropriate in the 10% of patients in whom disseminated disease is established by operative means.

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Increased insensible water loss in newborn infants nursed under radiant heaters

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Summary

Urine osmolality was studied in 38 babies nursed in conventional incubators or cots and 18 nursed under an overhead radiant heat shield. Among 50 babies receiving a similar fluid intake in the first 48 hours of life mean urinary osmolality was significantly higher in the radiant heater group. In babies weighing less than 1500 g a trend towards higher urinary osmolalities was recorded in those nursed under radiant heaters even though they had received al-

most double the fluid intake of the incubator group. Severe hypernatraemia occurred in four of the five babies weighing less than 1000 g who were nursed under radiant heaters but in none of the seven babies of similar birth weight nursed in incubators.

These findings are consistent with previous observations of an increase in insensible water loss in babies nursed under radiant heaters and emphasise the importance of providing enough extra water for these infants and the need for close monitoring of their fluid balance. The latter may be done at the bedside by measuring urinary specific gravity with a hand refractometer.

Introduction

Recent estimations of insensible water loss in the newborn period have suggested that infants of low birth weight may lose over 60 ml/kg/24 hours.¹⁻² These values are much higher than those found by others.³⁻⁴ An increase in insensible water loss in babies nursed under radiant heaters compared with that in

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