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Laparoscopy and laparotomy combined with bone marrow biopsy in staging Hodgkin's disease

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Summary

The relative merits of laparoscopy with liver and spleen biopsy and staging laparotomy were studied in 91 unselected patients with Hodgkin's disease. Laparoscopy with liver and spleen biopsy were combined with needle biopsy of the bone marrow and laparotomy was combined with open bone marrow biopsy. In 65 untreated patients six out of seven with liver or marrow disease, or both, were shown to have extranodal lymphomas in these sites by laparoscopy plus needle marrow biopsy. Among 26 patients who had been treated this finding occurred in six out of 10 patients. Spleen biopsies during laparoscopy detected infiltration by lymphoma in 14 out of 37 (38%) patients with diseased spleens. Morbidity was higher after laparotomy than after laparoscopy. Laparoscopy produced abdominal bleeding secondary to splenic biopsy in two patients. All patients with Hodgkin's disease should be subjected to laparoscopy plus needle marrow biopsy before undergoing laparotomy.

Introduction

Accuracy in staging Hodgkin's disease has been improved recently by the use of laparotomy with splenectomy and multiple tissue biopsies, including open bone marrow biopsy. Though essentially devoid of major surgical complications laparotomy has not been accepted by all centres as a routine staging procedure for surgically low-risk patients with clinical stage I, II, and III disease.

In 1970 the National Cancer Institute group in the USA began to study the value of laparoscopy in detecting liver involvement in patients with untreated Hodgkin's disease. Their most recent results¹ showed that hepatic disease in 47 untreated patients was shown with the same frequency by multiple liver biopsies as that reported by wedge biopsy at laparotomy. They concluded that laparoscopy could be an alternative to laparotomy in establishing stage IV disease.

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Since bias from retrospective comparative evaluations cannot be entirely eliminated, and the American series was preselected for more advanced disease, we decided to combine both laparotomy and laparoscopy in a series of untreated and treated patients with Hodgkin's disease to establish more clearly the relative merits of both staging procedures.

Patients and methods

The study was carried out on 91 unselected patients aged 13-69 years who were admitted to the Instituto Nazionale Tumori from 1 October 1973 to 31 March 1975. The patients fell into two groups: 65 patients had never been treated; and 26 patients had been treated and were either incompletely staged in other hospitals or relapsing from primary treatment.

Clinical diagnostic evaluation included routine haematological studies, chest x-ray examination, skeletal survey, and leg lymphography. Liver radionuclide scans were performed in 37 patients and spleen scans in 24. Scans were usually performed when we thought that they could add further information to help us define the clinical stage more accurately. All patients were staged according to the clinical criteria proposed at Ann Arbor.

One to three days before laparoscopy a posterior iliac crest bone marrow biopsy was performed with Jamshidi needle. Laparoscopy was performed in all patients. Classic staging laparotomy with open iliac crest marrow biopsy was carried out in patients with negative histological findings in the liver on laparoscopy and the bone marrow on needle biopsy.

The Wolf cold light endoscope was used. The procedure was performed in the morning, after an overnight fast. The pneumoperitoneum was created by 2-3 litres of carbon dioxide through the insertion of a Veress needle into the left lower quadrant of the abdomen. Under local lignocaine hydrochloride (Xylocaine) anaesthesia the laparoscopy trocar was inserted 1-2 cm above the umbilicus in the midline. To avoid intraperitoneal adhesions in patients who had undergone abdominal surgery through midline laparotomy the entry of the trocar was placed laterally on the right. Liver and spleen biopsies were performed with the Tru-cut needle (Travenol Laboratories). When abnormal areas were present a specimen was also taken from the liver edge with a Palmer forceps. The biopsy needle was introduced 2 cm medially to the intercept of the right midclavicular line with the costal margin for liver biopsy and in the left ninth intercostal space at the intercept with the anterior axillary line for spleen biopsy. Only in seven patients was a single liver biopsy specimen obtained. In the remaining patients one or more specimens were obtained from each hepatic lobe (2 in 36 cases, 3 in 26, 4 in 15, 5 in 6, and 6 in 1). Splenic biopsies (1 in 46 patients, 2 in 29, and 3 in 1) were usually obtained from the medial aspect of the lower pole without use of adrenaline. In patients with tumour nodules on the surface of the liver or spleen specimens were first obtained from abnormal areas. In most patients the procedure was completed within 20 minutes.

Results

Table I presents the findings of sequentially combined staging procedures in untreated patients. Specimens from the spleen could not

TABLE I—Findings on liver, spleen, and marrow biopsy in untreated and treated patients

Clinical stage or site of disease	No of patients	No with positive findings on:			No with stage modification	No with positive findings on Laparotomy		No of additional patients found on laparotomy to have spleen disease	No with positive findings on open marrow biopsy	No with stage modification
		Laparoscopy		Needle marrow biopsy						
		Liver	Spleen			Liver	Spleen			
Untreated patients										
I	19	0/19	1/15		1	0/19	6/19	5		5
II	21	0/21	1/17		1	1/21	3/21	2		3
III	11	2/11	2/11	2	3	0/8	5/8	5		0
III _s	1	0/1	1/1		0	0/1	1/1	0		0
IV	13	2/13	2/10	3	10	0/10	4/10	3		9
Total	65	4/65 (6%)	7/54 (13%)	5/65 (8%)	15/65 (23%)	1/59 (2%)	19/59 (32%)	15/59 (25%)	0	17/59 (29%)
No with extranodal disease			6 (9%)			1 (2%)				
Treated patients										
Lymph nodes	15	1/14	4/12	1		3/13	9/13	5	2	
Liver (± nodes)	10	3/10	3/7	4		1/5	3/5	2		
Spleen (± nodes)	1	0/1	0/1			0/1	1/1	1		
Total	26	4/25 (16%)	7/20 (35%)	5/25 (20%)		4/19 (21%)	13/19 (68%)	8/19 (42%)	2/19 (11%)	
No with extranodal disease			6 (23%)			5 (26%)				

be obtained during laparoscopy in nine patients because the spleen was not sufficiently visible. In another two patients samples were not adequate for histological examination. Biopsies during laparoscopy showed hepatic involvement in 4 out of 65 patients (6%) and splenic infiltration in 7 of the 54 patients (13%) in whom spleen biopsy was feasible and adequate. Needle bone marrow biopsy was interpreted as positive for Hodgkin's disease in five patients: in two patients, one with stage III and one with stage IV disease bone marrow was apparently the only site of extranodal lymphoma, while in the remaining patients (stage III (1), stage IV (2)) marrow infiltration was associated with liver infiltration. Splenic involvement alone was detected in four patients.

Laparotomy was performed in 59 patients with negative findings in the liver after laparoscopy or negative findings in the marrow after needle biopsy or both. Only one patient previously classified as having clinical stage IIB disease showed liver involvement on wedge biopsy after negative findings on needle biopsies at laparoscopy. Splenectomy, besides confirming all positive histological findings seen after laparoscopy, detected splenic disease in 15 further patients (25%). Open bone marrow biopsy showed nothing abnormal in any patient with negative findings on needle biopsy.

Thus by combining laparoscopy with needle marrow biopsy 6 out of 65 patients (9%) were shown to have true (pathological) stage IV disease. By including the patients with positive findings on splenic biopsy but no liver or bone marrow involvement the clinical stage was modified in 15 of the 65 (23%) patients (to a worse stage in 5 patients, to a better stage in 10). By detecting one case of liver involvement that had not been found on laparoscopy, subsequent laparotomy contributed to establish stage IV disease in 2% of patients, and through the demonstration of additional splenic disease laparotomy modified the clinical stage in 17 out of 59 (41%) patients (to a worse stage in 8 patients, to a better stage in 9).

Table I also shows the results in 26 restaged patients. Laparoscopy detected liver disease in 4 out of 25 (16%) patients and spleen involvement in 7 out of 20 (35%) biopsied patients. Needle marrow biopsy yielded positive findings in five (20%) patients, and in two of them bone marrow was apparently the only site of extranodal disease. Subsequent laparotomy carried out in 19 patients with negative findings on liver and marrow biopsy showed that the liver was involved in four and spleen in eight additional patients who had been negative on laparoscopy. Open iliac crest bone marrow biopsy showed positive findings in two patients who had had negative findings on needle biopsy. The false-negative findings of laparoscopy plus needle marrow biopsy occurred in 21% (4 out of 19) of patients for liver, 42% (8 out of 19) for spleen, and 11% (2 out of 19) for marrow.

Histologically positive liver specimens were documented in 2 out of 10 patients with lymphocytic predominance, 7 out of 48 with nodular sclerosis, 3 out of 21 with mixed cellularity, and 1 out of 12 with lymphocytic depletion. There were positive spleen findings in, respectively, 3 of the 10, 22 of the 48, 10 of the 21, and 2 of the 12. The incidence of positive hepatic and splenic findings during laparoscopy was not dependent on the number of biopsies performed.

In the 13 patients with positive liver biopsy findings the spleen was affected in 10 cases and the bone marrow in 6. In one patient positive

findings on bone marrow biopsy was associated with splenic infiltration. These correlations confirm the high association of splenic lymphoma with liver and marrow involvement.²

The value of liver and spleen scans in predicting the involvement by lymphoma may be summarised as follows: histologically documented hepatic involvement was present in 3 of the 13 (23%) patients with positive and in 4 of the 24 (17%) patients with negative liver scans; surgical staging proved that both patients with a positive scan had splenic disease, while 9 of the 22 (41%) patients with negative scans showed Hodgkin's disease in the spleen at either laparoscopy or laparotomy. Liver function tests failed to indicate the presence of liver metastases in most patients.

Table II shows the comparative evaluation of complications. In patients subjected to laparoscopy no morbidity was found in 96%. Three patients showed abdominal bleeding, and in two of them an immediate laparotomy was required. In patients subjected to laparotomy no side effects attributable to the procedure were observed in 69%. Two patients required a second laparotomy, one for postoperative bleeding from the suture at the level of splenic hilus, and the other because of intestinal occlusion produced by adhesions among the loops. The incidence of postoperative atelectasis, pleural effusion, and pneumonia was similar to that reported in another series.³

TABLE II—Complications of laparoscopy and laparotomy

	Laparoscopy (n = 91)	Laparotomy (n = 77)
None	87 (96%)	54 (69%)
Abdominal bleeding:		
From liver	1	
From spleen	2	
From splenic hilus		1
Atelectasis ± pneumonia		12
Atelectasis ± pleural effusion		7
Left pleural effusion		2
Hepatitis (traumatic)	1	1
Pancreatitis		1
Wound infection		1
Intestinal occlusion		1

Discussion

Our results show that in Hodgkin's disease laparoscopy detected hepatic disease in more than half the patients (eight out of 13) with liver metastases before they underwent laparotomy. Furthermore, since laparoscopy was systematically combined with needle marrow biopsy the number of patients requiring laparotomy was further diminished, and stage IV disease was established without surgical exploration of the abdomen. By sequentially combining both surgical procedures we confirmed some of the initial findings of the American investigators.¹

Laparotomy was advocated first by the Stanford group² and is performed in many centres to detect an occult splenic involve-

ment. Patients with Hodgkin's disease in the spleen represent a high-risk group for concomitant or subsequent hepatic and marrow disease^{2,3} and are therefore candidates for combined radiotherapy and chemotherapy. The high correlation of splenic disease with positive liver and marrow findings is also emphasised by our results. Therefore laparotomy is indicated in Hodgkin's disease not only to confirm or exclude liver disease but also to show the presence of an otherwise occult splenic lymphoma. For this reason we attempted to explore the yield of splenic biopsies through laparoscopy and found that this procedure detected infiltration by lymphoma in about one-third of patients with diseased spleens.

The relative merits of laparoscopy and laparotomy should also be compared in terms of the morbidity of each procedure. Laparotomy caused more complications than laparoscopy. Two patients in each group required exploratory laparotomy for episodes directly related to the staging procedure. Splenectomy also increases the incidence of varicella-zoster infection, especially in patients undergoing combination chemotherapy, and may be followed in few patients by fulminant infections.⁴ Laparoscopy, besides being devoid of such complications, may reduce the stay in hospital.⁵

In conclusion, laparoscopy plus needle marrow biopsy in

Hodgkin's disease could replace the traditional exploratory laparotomy with splenectomy and multiple tissue biopsies in at least two-thirds of patients with extranodal disease and in about one-third of those with splenic disease. All patients should therefore be subjected to this combined procedure as a screening technique for pathological staging and restaging before undergoing laparotomy. Exploratory laparotomy remains an accepted and necessary procedure only for patients negative on pre-operative laparoscopy and needle marrow biopsy. Splenic biopsy during peritoneoscopy should no longer be considered an almost invariably hazardous procedure except in patients with a large and congestive spleen.

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Weight gain and the sleeping electroencephalogram: study of 10 patients with anorexia nervosa

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Summary

The relation between reduced nutritional intake, with consequent weight loss, and sleep disturbance was studied by comparing certain sleep encephalogram patterns in a group of inpatients with anorexia nervosa before, during, and after a regimen of refeeding with a normal diet to a matched population mean weight. At low body weights patients had less sleep and more restlessness, especially in the last four hours of the night. During refeeding and weight gain slow-wave sleep initially increased and then tended to decrease during the final stage of restoration of weight back to matched population mean levels. With the overall weight gain, however, there was a significant increase in length of sleep and rapid eye movement sleep, the latter increasing especially during the later stages of weight gain. These results reaffirm that insomnia, and especially early morning waking, is associated with low body weight in anorexia nervosa, and their implications are discussed with particular reference to a hypothetical association between various anabolic profiles and the need for differing components of sleep.

Introduction

Patients with anorexia nervosa have a pattern of sleep different from that of most young people. They tend to have disturbed sleep in the middle third of the night and to wake early. This disturbance is unrelated to mood but is probably related to the severity of the nutritional disturbance.¹ When the weight of such patients is restored to normal in association with bed rest and a normal diet the sleep pattern reverts to normal; these changes are again unrelated to mood. Conversely, obese people losing weight on a diet begin to sleep less, especially in the second half of the night.² Admittance to hospital, like mood and mood change, does not seem to affect these changes. It has also been shown³ that, irrespective of diagnosis, mentally ill patients who lose weight because of their illness also sleep less, especially in the second half of the night; in particular they experience more sleep interruptions, longer periods of interrupted sleep, and earlier waking. Among those who gain weight the converse is true.

Excessive somnolence is a recognised accompaniment of the Kleine-Levin syndrome,⁴ the syndrome of megaphagia and hypersomnia,⁵ and, more debatably, the Pickwickian syndrome.⁶ Eating is a recognised precipitant of some narcolepsy attacks.⁷ Recently it has been shown that a bedtime milk cereal drink leads to an increase in sleep, especially in the second half of the night.^{8,9}

We report here a study of the sleeping electroencephalogram (EEG) changes associated with aspects of nutritional and weight change in patients with anorexia nervosa. A preliminary study of five patients showed that it was predominantly slow-wave sleep that was increased when the weight of such patients was restored towards normal. Most of these patients failed to achieve matched population mean weights, however, and their refeeding diets were often high in protein and fat and low in carbohydrate.¹⁰ We expected therefore that we would once again find a positive association between weight gain and increased sleep;

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