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Clinical features as a predictor of laparotomy findings in supradiaphragmatic stage I and II Hodgkin's disease

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Clinical features (sex, age, histology, B-symptoms, the number of lymph node areas involved, supradiaphragmatic site of disease and laboratory findings) have been correlated with staging laparotomy (SL) findings in 95 adult patients with supradiaphragmatic Hodgkin's disease (HD), clinical stage I and II seen at the Institute of Oncology, Ljubljana in the years 1974–1989. Sex and age ware the only significant independent predictors of positive SL. On the basis of these observations, low risk (less than 15 %), intermediate risk (16–50 %) and high-risk (more than 50 %) groups for predicting positive SL can be defined. These observations could be considered for treatment planning as well as selection of patients for SL.

Key words: Hodgkin's disease; staging laparotomy; clinical predictors

Introduction

Although staging laparotomy (SL) is known to be the most accurate method for staging of Hodgkin's disease (HD) in the abdomen, it cannot be ignored that this relatively aggressive method is associated with certain morbidity and, albeit rare mortality, should therefore be avoided whenever possible. Despite the controversial opinion on the indications for this method, its value in the cases when ist outcome governs the choice of treatment is indisputable. It would be a great advantage if among patients with supradiaphragmatic clinical stage (CS) I and II those with low and high risk of occult abdominal disease could be recognised on the basis of clinical data. In these cases, the method of treatment could be chosen without SL. To address this question, we have analysed data from 95 patients and correlated the presenting features with laparotomy findings; the obtained results were compared with those reported by other authors.

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Patients and methods

In the period 1974–1989, 219 adult patients with supradiaphragmatic HD CS I and II were treated at the Institute of Oncology in Ljubljana. SL was performed in 43 % (95/219), i.e. in less than a half of them. Of these, 51 were

males and 44 females, aged 15–63 years (mean 32 yrs). All 95 laparotomized patients had histologically confirmed diagnosis.[1]

Preoperative evaluation included a complete history, physical examination, routine laboratory tests, chest X-ray, bone marrow biopsy, pedal lymphography, Gallium scintiscan of the body, and recently also computer tomography and/or ultrasonography of the abdomen.

Stage was determined according to the Ann Arbor classification.[2] Five supradiaphragmatic lymph node areas were defined for the needs of this study: 1. left neck and/or supraclavicular; 2. right neck and/or supraclavicular; 3. left axillary and/or subclavicular; 4. right axillary and/or subclavicular; 5. mediastinal and/or left/right/bilateral hilar lymph nodes. Bulky mediastinal disease was defined as the largest transversal diameter exceeding one third of the trans-thoracic diameter at the level of the 5th/6th thoracic vertebral body.

SL consisted of splenectomy, liver biopsy, lymph node biopsy and bone-marrow sampling.

Laparotomy findings were correlated with age, sex, histology, B-symptoms, the number of lymph node areas involved, the localization of supradiaphragmatic disease, and some laboratory tests (sedimentation, hemoglobin, serum copper and albumins).

Chi-square and Yates' correction of Chi-square were used for statistical analysis. Logistic regression analysis (LRA) was used to test the effect of each variable independently, and to estimate the risk of positive laparotomy in various clinical subgroups. Statistics were calculated by means of BMDP program.[3]

Results

Laparotomy findings

Of the 95 supradiaphragmatic CS I–II patients who underwent pretreatment SL, 34% had occult abdominal HD (Table 1).

The percentage of positive SL was statistically significantly higher in male patients, aged 40 years or more, with mixed-cell HD type (Table 2.)

The outcome of SL was not found to be statistically significantly influenced by sedimentation rate nor by the values of serum hemoglobin, copper and albumins (Table 3).

Supradiaphragmatic localization of HD did not exert a statistically significant effect on the outcome of SL either in CS I (Table 4) or in CS II (Table 5).

Logistic regression analysis (LRA)

By LRA, sex ($p = 0.0001$) and age ($p = 0.05$) were the only independent significant predictors of positive laparotomy in CS I–II. On the basis of these factors the predicted risk estimates were shown (Tables 6 and 7).

Discussion

The objective of the present investigation was to define high- and low-risk CS I–II patients of occult abdominal disease on the basis of their clinical features on admission.

Males were shown to be at a significantly higher risk of occult subdiaphragmatic disease than women (Table 2). This observation in consistent with other reports.[4–9]

The findings one the influence of age on the outcome of SL are inconsistent. We have shown (Table 2) that the rate of positive SLs is increasing by age, being significantly higher in patients at an age of $\geq$40 years than in younger ones. Some authors[10] confirm this observation while others claim just the opposite,[4] or even report a higher rate of positive SLs in patients under 20 years of age.[6] It is not clear, however, whether the studies reporting findings different from ours also included children, which might be the cause of the observed difference.

Our patients with CS I–II and mixed cellularity histological type presented with a significantly higher percentage of HD in the abdomen than patients with nodular sclerosis type (Table 2), which has been also confirmed by some other authors.[5, 7, 8, 10] Those who have been investigating the influence of histology separately for CS I and II report interesting results: histological type correlates with SL outcome in

Table 1. Hodgkin's disease clinical stage I–II; Results of laparotomy.

CS	No. of pts	Unchanged stage		Upstaging		Upstaging %
		PS I No.	PS II No.	PS III No.	PS IV No.	
I	36	20	0	15	1	44
II	59	0	43	16	0	27
Total	95	20	43	31	1	34

CS = clinical stage

Table 2. Hodgkin's disease clinical stage I–II (n = 95): Laparotomy findings by clinical features.

Clinical features	CS I–II No.	Postlaparotomy stage PS I–II No.	PS III No.	PS IV No.	Stage change %	Chi^2	df	p
Age (yrs)								
≤19	12	10	2	0	17			
20–39	59	42	16	1	29	Trend		
40–59	21	11	10	0	47	3.810	1	0.0504
≥60	3	0	3	0	100			
Age (yrs)								
15–39	71	52	18	1	27			
≥40	24	11	13	0	54	4.8666	1	<0.05
Sex								
Males	51	26	24	1	49			
Females	44	37	7	0	16	10.1579	1	<0.01
*Histology								
LP/NS	55	43	12	0	22			
MC/LD	35	17	17	1	51	7.1591	1	<0.01
Symptoms								
A	86	58	27	1	33			
B	9	5	4	0	44	0.1206	1	>0.1
No.of lgl areas involved								
1	36	20	15	1	44			
2	34	23	11	0	32	Trend		
3	19	16	3	0	16	1.521	1	0.2175
≥4	6	4	2	0	30			
No.of lgl areas involved								
1	36	20	15	1	44			
≥2	59	43	16	0	27	2.2789	1	>0.1

*Histologically unclassified (5/95) are not included.

CS = clinical stage, PS = pathological stage, LP/ND = Lymphocyte predominant and Nodular sclerosis, MC/LD = Mixed cellularity and Lymphocyte depleted

CS I but not in CS II.[6] The lowest percentages of positive SLs were found in patients with CS I and LP histological type: 0%,[7] 5%[5] and 16%.[6]

Table 3. Hodgkin's disease clinical stage I–II (n = 95): Laparotomy findings by laboratory results.

Clinical features	CS I–II No.	Postlaparotomy stage PS I–II No.	PS III No.	PS IV No.	Stage change %	Chi^2	df	p
SR								
0–15	29	20	8	1	28			
16–30	15	9	6	0	27	Trend		
31–50	21	18	3	0	14	0.747	1	0.3873
51–70	15	10	5	0	33			
≥70	15	6	9	0	60			
Hb								
<100	4	3	1	0	25			
101–120	17	11	6	0	35	Trend		
121–140	42	31	11	0	26	0.4490	1	0.502
141–180	32	18	13	1	44			
Cooper								
normal	45	26	18	1	4			
increased	44	33	11	0	25	2.2330	1	0.1
Albumins								
normal	54	36	17	1	33			
decreased	36	23	13	0	36	0.0205	1	>0.1

SR: mm/hr; range 2–132; $\bar{X}$ = 38.5; Median = 33; SD = 29.3
Hb: g/l; range 97–169; $\bar{X}$ = 135; Median = 132; SD = 16.5
Copper (in 89/95 pts): μmol/l; normal 11–26.7; range 10–48; $\bar{X}$ = 27.9, Median = 26.8; SD = 7.82
Albumins (in 90/95 pts): g/l; normal 35; range 21–58; $\bar{X}$ = 35.8; Median = 36; SD = 6.4

CS = clinical stage, PS = pathological stage

Table 4. Hodgkin's disease clinical stage I (n = 36): Laparotomy findings by site.

Site		CS I No.	Stage change No.	%	Chi^2	df	p
Neck	L	12	6/12	50	0.3272	1	>0.1
	R	13	4/13	31			
Axilla	L	1	1/1	100	–	–	–
	R	2	1/2	50			
Neck or axilla	L	13	7/13	54	0.5056	1	>0.1
	R	15	5/15	33			
Mediastinum	yes	8	2/8	25	0.2526	1	>0.1
	no	28	12/28	43			
Neck	R + L	25	10/25	40			
Axilla	R + L	3	2/3	67	1.634	2	>0.1
Mediastinum		8	2/8	25			

Compared to patients with CS I, in those with CS II subdiaphragmatic disease is reported to be significantly more frequent;[4, 5, 8] moreover, the rate of positive SLs is increasing by the number of regions involved. Other authors[6] have not confirmed those findings, possibly due to the fact that only patients with less that three involved regions were included into the study.

Table 5. Hodgkin's disease clinical stage II (n = 59): Laparotomy findings by site.

Site		CS II No.	Stage change No.	%	Chi^2	df	p
Neck bilat.		2	1/2	50	–	–	–
Neck unilat. + mediastinum		26	8/26	31	0.0037	1	>0.1
Neck bilat. + mediastinum		9	2/9	22			
Mediastinum	no	14	4/14	29	0.0417	1	>0.1
	yes	45	12/45	27			
Mediastinum size	bulky	11	1/11	9	2.442	2	>0.1
	not bulky	29	8/26	31			
	undefined	8	3/8	37			

CS = clinical stage

Table 6. Hodgkin's disease clinical stage I–II (n = 95): Predicted risk of positive laparotomy, based on sex* and age*.

Sex	Age yrs	Stage change Observed No.	%	Predicted %
Males:	≤20	2/6	33	28
	21–39	11/27	41	44
	40–59	10/16	63	62
	≥60	2/2	100	77
Females:	≤20	1/7	14	8
	21–39	5/31	16	15
	40–59	0/5	0	27
	≥60	1/1	100	43

* derived from logistic regression analysis.

positive SL (Table 2) than those with CS II, though the difference is insignificant. The reason may be in our definition of supradiaphragmatic lymph node areas (see Patients and Methods).

Opinions on the influence of B-symptoms on SL outcome are also controversial. We – as well as some other authors,[5] could not prove a significantly higher percentage of positive SL in patients with B-symptoms while others did.[4, 7, 8, 10] We also did not confirm the influence of sedimentation rate, serum hemoglobin, copper and albumins on the outcome of SL (Table 3). Only one such study[8] has been found in the available literature, which also

Table 7. Hodgkin's disease clinical stae I–II (n = 95): Predicted risk of positive laparotomy, based on sex* and age.*

Risk degree	Risk factor	Stage change Observed No.	%	Predicted %
High	male + ≥40 yrs	12/18	67	62–77 (69.5)
Medium	male + <40 yrs or female + ≥40 yrs	13/33 1/6	36	28–44 (36) 27–43 (35)
Low	female + <40 yrs	6/38	16	8–15 (11.5)

* derived from logistic regression analysis

Our results also fail to confirm the above cited findings; on the contrary, we have found that patients with CS I have higher percentage of

failed to prove any influence of sedimentation rate, serum copper and LDH values on the outcome of SL.

The results of some investigations[4–6] reveal an interesting observation that none of the patients with a single localization of HD in the mediastinum (CS I) had positive SL (in one of the previously mentioned studies[4] this applies only to females). Therefore, in Stanford (U.S.A.) SL has not been performed in such patients since 1973. Ours (Table 4) as well as the findings of other investigators[8, 10, 11] support this observation since the percentage of positive SLs was lower in patients with a single mediastinal HD site than in those without mediastinal involvement, though in our case the difference was not statistically significant. In patients with CS I the side of localization, i.e. either left of right, did not influence the outcome of SL (Table 4) which is in accordance with the results of other studies.[4-6] We did not evaluate the influence of the size and localization of cervical lymph nodes on the outcome of SL since these data were not available. The results of some studies[6–8] lead to an interesting conclusion that patients with CS I and lymph node involvement above the hyoid cartilage have statistically significantly less positive SLs than those with localizations under the hyoid cartilage, and that patients with lymph nodes >5 cm in diameter have subdiaphragmatic disease more frequently than those with smaller lymph nodes;[6] the latter observation, however, has not been confirmed by other authors.[8]

In patients with CS II the situation is different. As evident from our study (Table 5) and those of others,[6] the outcome of SL is neither influenced by the size of lymph nodes[6, 8] nor by the presence or absence of HD in the mediastinum.

By LRA, sex and age were the only independent significant predictors of positive laparotomy in our CS I–II patients. On the basis of these factors the predicted risk estimates for positive SL are shown (Tables 6 and 7). The higher risk in males is particularly evident in those exceeding 40 years of age, with a predicted chance of positive laparotomy of 69.5 %. At the other end of the spectrum, females under 40 years of age have a predicted risk of 11.5 %.

To our knowledge, there are only four studies[4–6, 8] where the predictors of positive laparotomy have been analysed by means of multivariate analysis. On the basis of these factors some authors predicted risk estimates for positive SL.

Summarising ours and the above four studies, we can draw the following two conclusions:

1) Clinical features predicting a low risk of positive SL in CS I are as follows: female sex, and irrespective of sex: mediastinal site, nonbulky upper neck nodes, and LP histological type.

2) Clinical features associated with a high risk of positive SL in CS I–II are as follows: male sex (confirmed by all studies), age (the evidence for that is controversial: <20 years,[6] >27 years,[5] ≥40 years[our results]), a greater number of involved regions (inconsistent evidence: 2 or more,[4] 3 or more,[8] 4 or more[5]), mixed cellularity and lymphocite depleted histological type,[8] and B-symptoms.[4, 8]

Conclusion

Our study and the review of existing literature were aimed to identify the patients who do not require SL, i.e. those in whom the selection of treatment metod can be based solely on the evaluation of risk of abdominal HD involvement. Patients with low risk would require radiotherapy alone, and high-risk patients chemotherapy. The objective to define high- and low- risk patients on the basis of clinical features has been only partly realized.

The above findings have shown that the definitions of risk groups are unreliable due to incomplete agreement between different studies, which could be attributed to the following reasons:

1) Most of the studies were done on a small number of patients.

2) In some studies, CS I and CS II were analysed separately, which is correct, while in others CS I–II were pooled together owing to the small number of patients in a particular center.

3) The clinical features analysed were not always the same.

Nevertheless, the most reliably definable is the group of patients at a low risk of positive SL. A prospective multicentric study on a larger number of patients would be required to allow more rigorous statistical analysis, which however seems hardly feasible as SL has been mostly abandoned nowadays.

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