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Prognostic value of staging laparotomy in supradiaphragmatic clinical stage I and II Hodgkin's disease

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In the period 1974–1989, 219 patients with supradiaphragmatic clinical stage I and II Hodgkin's disease were treated at the Institute of Oncology in Ljubljana; of these 95 (43 %) patients underwent staging laparotomy. Of laparotomized patients, those with pathological stage III–IV, and of non-laparotomized, those with unfavorable prognostic factors (B-symptoms, bulky mediastinum) received chemotherapy: the remaining patients were treated by irradiation. No statistically significant difference in the survival and disease-free survival between laparotomized and nonlaparotomized patients could be found.

Key words: Hodgkin's disease; staging laparotomy; prognostic value

Introduction

Staging laparotomy (SL) is the most accurate albeit agressive diagnostic method for the verification of subdiaphragmatic spread of Hodgkin's disease (HD). There is a considerable controversy of opinions as to when and whether this method is indicated at all.

The present retrospective study is aimed to assess whether SL had any impact on survival (S), disease-free survival (DFS) and treatment modality used in patients with supradiaphragmatic clinical stage (CS) I–II HD.

Patients and methods

Our retrospective study was carried out on a series of 219 adult patients with supradiaphragmatic HD CS I–II, who underwent their primary treatment at the Institute of Oncology in Ljubljana in the period from January 1974 to December 1989. Their age ranged between 15 and 82 years (mean 36 yrs); there were 110 males and 109 females. In all the patients the diagnosis was confirmed histologically.[1]

Preoperative evaluation comprised a complete history, physical examination, routine laboratory tests, chest X-ray, bone marrow biopsy, and in the majority of patients also pedal lymphography, Ga-scintiscan of the whole body and computer tomography and/or ultrasonography of the abdomen. Stage was determined according to Ann Arbor classification.[2] Bulky mediastinal disease was defined as the largest transverzal diameter exceeding one third of the transthoracic diameter at the level of the 5th and 6th thoracic vertebral body.

Candidates for SL were nor selected at random. SL consisted of splenectomy, wedge and needle biopsy of both liver lobes, biopsy of multiple lymph nodes, biopsy of all lymph nodes that appeared to be involved with disease or involvement was suspected on lymphangiogram, bone marrow sampling and appendectomy. An oophoropexy was performed in premenopausal women. Metalic clips were placed at biopsy sites.

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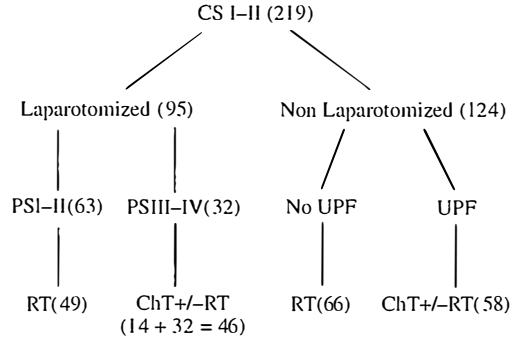
The following treatment approach was selected (Figure 1): Laparotomized patients with pathological stage (PS) I–II were treated by radiotherapy (RT), patients with PS III–IV by chemotherapy (ChT) +/–RT. In non-laparotomized patients the treatment approach was selected according to the following prognostic factors: patients with B-symptoms and/or bulky mediastinum received ChT+/–RT while the remining ones were treated by RT alone. Subtotal nodal irradiation (STNI) was almost always (81/115) the RT field chosen for patients treated only by RT. ChT used was one of MOPP-like or MOPP/ABV-like schemes. In ChT+/–RT group of patients almost all (98/104) were treated by ChT and RT.



CS = clinical stage PS = pathological stage
RT = radiotherapy ChT = chemotherapy
UPF = unfavorable prognostic factors

Figure 1. Hodgkin's disease with clinical stage I–II (n = 219): Treatment approach.

Follow up ranged from 4 to 205 months, median 64 months. Survival was defined as the lapse of time from the onset of treatment to death, or to the date of last follow-up examination. All deaths regardless the cause have been included. Disease-free survival was defined as the lapse of time from the onset of treatment to the date of the first recurrence. Complete response was defined as disappearance of all symptoms and measurable changes; partial response was defined as disappearance of measurable changes by > 50 %; progression as an increase in measurable changes by > 25 % or appearance of new sites; unchanged conditions denoted responses that could neither be defined as a partial response nor a progress.

Statistical analysis was done by means of BMDP statistic program.[3] Survival (S) and disease-free survival (DFS), as well as differences in the survival of laparotomized and nonlaparotomized patients were shown and analysed using the Kaplan-Meier method and log-rank test.[4]

Results

SL was performed in 95 (43 %) of 219 patients with CS I–II, while the remaining 124 (57 %) did not undergo laparotomy.

The laparotomized and non-laparotomized groups were homogeneous with respect to the clinical properties (Table 1), including some well established prognostic factors; the only difference noted was related to age: among those older than 60 years there were 6 laparotomized and 21 non-laparotomized patients, of these 10 were older than 70 years.

Table 1. Hodgkin's disease with clinical stage I–II (n = 219): Clinical features.

Clinical features	Non laparotomized (n = 124) n	Laparotomized (n = 95) n	p
Sex			
males	59	51	NS
females	65	44	NS
Age (yrs)			
range	15,4–82,8	15,3–63,4	
medium	39,9	32,4	0.0004
Histology			
LP/NS	86	55	NS
MC/LD	30	35	NS
unclassified/cytology	8	5	NS
B symptoms	14	9	NS
Stage			
I	39	36	NS
II	85	59	NS
Mediastinum size			
bulky	17	13	NS
undefined	16	10	NS

LP/NS = Lymphocyte predominant/Nodular sclerosis
MC/LD = Mixed cellularity/Lymphocyte depleted

The survival and disease-free survival of laparotomized and non-laparotomized patients were compared irrespective of the treatment method used; no statistically significant difference could be established (Figures 2 and 3).

Further on, we analysed S and DFS of laparotomized and non-laparotomized patients treated by radiotherapy alone. Both groups were found to be

homogeneous regarding prognostic factors and did not differ from each other as to the S and DFS (Table 2). The same applies to ChT+/–RT treated patients (Table 2).

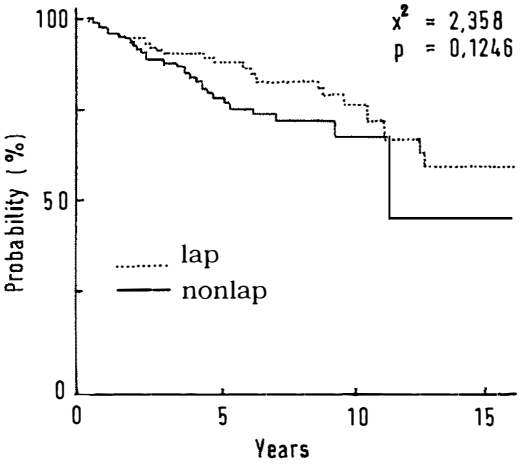


Figure 2. Hodgkin's disease with clinical stage I–II: Survival – laparotomized (59) : non laparotomized (124).

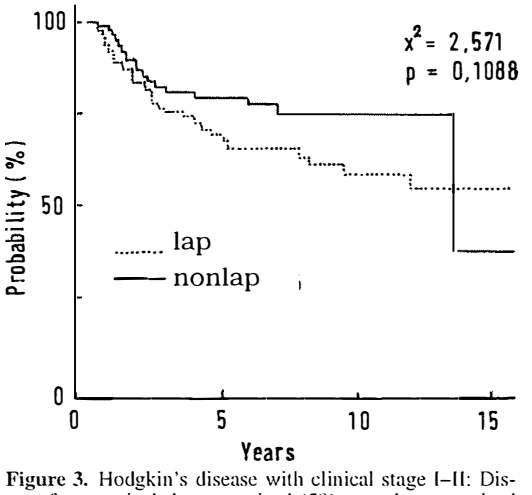


Figure 3. Hodgkin's disease with clinical stage I–II: Disease free survival: laparotomized (59) : non laparotomized (124).

Table 2. Probability of 10 yrs survival (S) and disease free survival (DFS) by treatment approach – laparotomized : non laparotomized.

	RT			ChT+/–RT		
	Lap.(49)	Nonlap.(66)	p	Lap.(46)	Nonlap.(58)	p
DFS	55 %	75 %	NS	64 %	74 %	NS
S	88 %	78 %	NS	68 %	57 %	NS

RT = radiotherapy
ChT = chemotherapy

Discussion

SL was used with the aim to identify those patients in whom radiation treatment would be effective enough to avoid chemotherapy. The laparotomized patients were treated according to the outcome of SL, while non-laparotomized ones received treatment with respect to the prognostic factors. It should be expected that the laparotomized patients have a better DFS and S in respect to non-laparotomized patients because of the exact staging. The results of our study, however, failed to confirm these expectations: (1). The laparotomized patients generally started with their first treatment a month later,[5] which is consistent with other reports.[6] (2). The number of patients receiving ChT in both groups was approximately the same (Figure 1). (3). It is essential, however, that no statistically significant difference in survival and disease-free survival could be established between the laparotomized and non-laparotomized patients (Figure 2 and 3). Review of the available literature has shown that other authors in their prevailingly retrospective and non-randomized studies also failed to prove any statistically significant differences in the survival[7–11] and DFS of both groups.[7, 9, 10] There are only two exceptions: while the first report claims DFS of laparotomized patients to be longer[8], the second one finds it to be shorter.[11] (4). No stastically significant difference in S and DFS could be established even between very comparable groups of patients in our study. These were patients without unfavorable prognostic factors treated only by RT: nonlaparotomized (n = 66) and laparotomized, PS I–II (n = 49) (Figure 1, Table 2). Second to our opinion, no statistically significant difference in S and DFS between these two groups could be established because both groups were almost always treated by STNI which involves also lymph nodes of the upper abdomen and spleen, which are the most common localisations of HD in the abdomen in supradiaphragmatic CS I–II HD patients.[5] Therefor we could conclude that if STNI is used there is no need for SL in patients with CS I–II without unfavorable prognostic factors?

The drawbacks of our study are obvious: (1). The decision for SL in CS I–II was not randomized; (2). Due to the inconsistency of the attending physicians 22 % (14/63) patients with PS I–II received ChT for having one of the unfavourable prognostic factors and thus unfortunately paid a double price by having undergone both SL and ChT (Figure 1).

But in spite of that and regardless the acceptable morbidity and non-existent mortality[5], the obtained results are not in favor of the continuation of SL practice at our institute, since our laparotomized patients do not seem to have drawn any benefit from it in comparison with non-laparotomized patients.

In view of the mentioned facts, indications for SL become questionable. We tried to find a solution to this problem in the literature, but it turned out that the question was too complex to be answered by simple "yes" or "no", and requires consideration of all pros and cons.

Arguments in favor of SL

(1) Despite new and more accurate diagnostic investigations, SL still remains the most precise method for diagnosis of subdiaphragmatic HD. Only splenectomy with histological examination enables exact evaluation of spleen involvement. Despite normal clinical findings, at least one forth of HD patients presents with spleen involvement, while only a half of those with clinically suspicious involvement actually have HD in the spleen. Using standard investigations, it is difficult to detect lymphoma in the upper abdominal lymph nodes which cannot be imaged by lymphography. SL is able to explain suspicious lymphography findings. Although HD involvement in the liver is rare, exact diagnosis is possible only by laparotomy-based biopsy.

(2) Splenectomy decreases the risk of irradiation damage to the kidney and lung base on the left as well to the heart.

(3) Oophoropexy helps to preserve fertility in women requiring irradiation to the pelvis.

(4) SL enables the selection of treatment according to the outcome, so that many patients can be spared unnecessary ChT or on the other hand ChT is not omitted in those patients who need it.

Arguments against SL

(1) SL-related morbidity and mortality; although the former is acceptable, and the latter rare in centers with adequate experience.

(2) Life-long risk of sepsis due to splenectomy.[12-17]

(3) A higher incidence of acute myeloblastic leukemia after splenectomy in patients receiving MOPP ChT.[18, 19]

(4) At least one-month delay in treatment beginning.[5, 6]

(5) In the case of recurrence after RT alone, the patient can still be cured with ChT +/– RT.[7, 20]

(6) Knowledge of prognostic factors can help us to identify at least 20 % of patients with CS I–II who require either ChT or a combined therapy.[7, 21]

(7) Knowledge of clinical properties can be used to assess the risk of HD spread in the abdomen.[22-26]

Conclusion

From all the above mentioned it is clear that SL is a diagnostic and not a therapeutic procedure. All authors are consistent in their belief that it is indicated only when the method of treatment depends on SL outcome,[18, 22-25, 27] which means that candidates for RT, i.e. therapy with less short-term and long-term side-effects than ChT, are selected on the basis of SL results. Certainly it is not justified in patients with > 50 % recurrence rate after RT alone.[27] It is also not sensible when ChT is planned regardless the SL outcome,[18, 24, 25, 27, 28] which is the case in patients with a huge mediastinal tumor mass, numerous E sites, and CS III_2A and IIIB or IV. Further, SL is not indicated in patients with CS I–II and a low risk of positive laparotomy since in such cases RT proves to be sufficient.[22, 24-26] In the present paper only some general guidelines have been given. It cannot be prescribed whether in patients belonging to either of the two groups SL should be used or not, and which treatment modality should be selected. There are great variances between different centers as to the availability and quality of diagnostic procedures, as well as to the quality of SL and competence of their diagnostic & therapeutic teams. Therefore, in every individual center indications for SL can be determined and treatment approach selected only after all the above mentioned conditions have been carefully evaluated, and all arguments for and against SL considered, taking into account the risk vs. benefit for the patient.

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