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Original Paper

Retrospective Assessment of Quality of Life and Treatment Outcome in Patients with Hodgkin's Disease from 1969 to 1994

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We determined the current quality of life (QoL) of patients with Hodgkin's disease treated at the Innsbruck University Hospital between 1969 and 1994 at a mean time of 9.1 ± 7.0 years after their initial treatment. Further aims of our study were to assess potential differences in objective treatment outcome and QoL between patients treated with chemo-, radio- or combined modality therapy and those enrolled in randomised clinical trials or treated according to standard procedures. The QLQ-C30, a health-related and validated self-report questionnaire developed by the Study Group on Quality of Life of the European Organization for Research and Treatment of Cancer (EORTC) was mailed to a cohort of 194 survivors out of a total of 225 patients with Hodgkin's disease; 126 of them (64.9%) returned the completed questionnaire. The 5- and 10-year overall survival rates for the total group of 225 patients were 94.3% and 84.9%, respectively. Irrespective of stage, higher relapse-free survival rates were observed in patients receiving combined modality treatment ($P = 0.025$). Five-year relapse-free survival rates were 96.6% for patients enrolled in clinical trials and 82.8% for patients treated outside of randomised studies ($P = 0.037$ in univariate and $P = 0.064$ in multivariate analysis). Patients treated with combined modality regimens had reduced QoL scores in comparison with those treated with either radiation or chemotherapy alone, but QoL parameters did not differ between patients enrolled in clinical trials and those treated according to standard procedures. Patients with Hodgkin's disease had an excellent long-term prognosis and very high QoL scores a mean of 9.1 years after treatment of their disease. The improved relapse-free survival rates achieved by combined modality regimens must be carefully weighed against the accompanying reduced QoL, since lower relapse rates did not translate into a survival advantage. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: Hodgkin's disease, quality of life assessment, self-report questionnaires, EORTC QLQ-C30, randomised clinical trials, therapy modalities
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INTRODUCTION

IN THIS CENTURY, there has been a steady and significant improvement in the prognosis of patients suffering from Hodgkin's disease. The proportion of long-term disease-free survivors has increased from 5% in the early 1930s [1] to more than 90% of patients with localised disease and to approximately 70% of patients with advanced stage disease in the late 1980s and early 1990s [2]. This progress results from the development of effective chemotherapeutic regimens such as MOPP (nitrogen mustard, vincristine, procarbazine, prednisolone) [3] and ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) [4] and better irradiation techniques [5, 6]. Further improvement of treatment strategies was

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achieved by the systematic large prospective clinical trials designed to test the most effective combination of cytotoxic drugs [4, 7–9] and the efficacy of treatments combining adequate chemo- and radiotherapy [10]. As a consequence of the excellent treatment outcome, more attention has been directed to the long-term consequences and unfavourable side effects of curative radio- and chemotherapy. This is of particular importance, since the median age of patients with this disease increases the probability of their living long enough to develop secondary cancers [2], leukaemias [11], cardiac failures and coronary heart disease following irradiation to the chest and/or the administration of anthracycline-containing cytotoxic regimens [5, 12]. More recently, the effects of disease and therapy on quality of life (QoL) have also been recognised as an important issue, with special interest being focused on fertility [13–15], sexual behaviour [16, 17] and psychosocial re-integration of successfully treated patients [16]. For these reasons, modification of current therapeutic regimens to make them more tolerable, with fewer short- and long-term side-effects for low-risk patients, and the use of more aggressive protocols in the small group of primary high-risk patients, are being planned for the future [18, 19]. Since the efficacy of these strategies will have to be tested in large, multicentre, randomised clinical trials, it will be important to define and differentiate between the short- and long-term influence of the disease *per se*, the impact of the various treatment strategies and the effect of the enrolment of patients in clinical trials on QoL parameters. With the numbers of patients tested in clinical trials increasing and the legal requirements on informed consent of patients growing, it will become important to develop procedures for reducing psychological stress and the deterioration of QoL which are specific for the disease and/or medical management strategies.

For these reasons we conducted a retrospective analysis of objective outcome and QoL parameters in patients treated and followed up at the Innsbruck University Hospital between 1969 and 1994 with the following aims: (1) to analyse the current QoL in patients who had been treated for Hodgkin's disease, as measured by the well-defined QoL instrument EORTC QLQ-C30 [20]; (2) to determine the influence of clinical parameters for risk estimation on treatment outcome; (3) to investigate the impact of the application of different treatment modalities on the rates of the recurrence of the disease and on QoL. We also tried to determine whether patients enrolled in clinical trials and those treated according to standard procedures but not included in clinical trials differed from each other with regard to their QoL in the long term as well as relapse-free survival.

PATIENTS AND METHODS

Patients

The Out-patient Department of Haematology and Oncology at the Innsbruck University Hospital has been treating patients with Hodgkin's disease since 1969. Since this time, this department has developed into the preferred primary care and reference centre for patients with established or suspected Hodgkin's disease for a population of approximately 1 million people. When the present investigation was started, the electronic cancer registry system of the Province of Tyrol contained a list of 254 patients treated at our institution, 225 of them were eligible to participate in the study as complete and updated case histories were available and 194 of them were alive. Clinical data of all patients with complete records are listed in Table 1 and data are broken down

Table 1. *Demographic and clinical data of patients*

	In trial*	Outside trial*	Total sample
Number	$n = 62$	$n = 163$	$n = 225$
Sex			
Female	39 (62.9%)	87 (53.4%)	126 (56.0%)
Male	23 (37.1%)	76 (46.6%)	99 (44.0%)
Mean (± S.D.) age at diagnosis (range)	35.0 ± 12.3 (15–64) years	37.6 ± 17.5 (6–89) years	36.9 ± 16.3 (6–89) years
Mean time (± S.D.) from diagnosis (range)	4.2 ± 1.5 (0.9–7.0) years	12.9 ± 6.8† (1.0–34.0) years	10.5 ± 7.0 (0.9–34.0) years
Ann Arbor stages			
Stage I	7 (11.3%)	20 (12.3%)	27 (12.0%)
Stage II	35 (56.5%)	70 (42.9%)	105 (46.7%)
Stage III	10 (16.1%)	48 (29.4%)	58 (25.8%)
Stage IV	10 (16.1%)	25 (15.3%)	35 (15.6%)
B symptoms	24 (38.7%)	65 (39.9%)	89 (39.6%)
Treatment modalities			
Chemotherapy	6 (9.7%)	57 (35.0%)‡	63 (28.0%)
[stages I/II/III/IV(%)]	[0.0/16.7/33.3/50.0]	[1.8/18.2/43.6/36.4]	[1.6/18.0/42.2/37.7]
Radiotherapy	15 (24.2%)	55 (33.7%)	70 (31.1%)
[stages I/II/III/IV(%)]	[26.7/73.3/0.0/0.0]	[26.4/62.3/11.3/0.0]	[26.5/64.7/8.8/0.0]
Combined modality treatment	41 (66.1%)	51 (31.3%)†	92 (40.9%)
[stages I/II/III/IV(%)]	[7.3/56.1/19.5/17.1]	[6.1/53.1/30.6/10.2]	[6.7/54.4/25.6/13.3]
Laparotomy	18 (29.0%)	85 (52.1%)†	103 (45.8%)
Liver biopsy	57 (91.9%)	97 (59.5%)‡	154 (68.4%)
Risk factors	36 (58.1%)	32 (19.6%)‡	68 (30.2%)
Relapse	2 (3.2%)	40 (24.5%)‡	42 (18.7%)

*Numbers of patients are given and percentages are provided in brackets. The numbers of patients in German Hodgkin Study Group (GHSG) studies who completed the questionnaire are as follows: HD4, 11; HD5, 20; HD6, 10; HD8, 3; HD9, 1. Statistical differences between patients in and outside clinical trials: †$P < 0.01$; ‡$P < 0.001$. S.D., standard deviation.

according to participation in clinical trials or subject to conventional treatment strategies. All 194 surviving patients were formally invited to participate in this evaluation and were sent a self-report questionnaire by mail (see below). To avoid any possible bias, the names of the patients were withheld from the analysts. Sociodemographic data were available for the 126 patients answering the questionnaire.

Histological diagnosis

Histological diagnosis was based on representative tissue samples, followed the Rye criteria [21] and was established by expert haematopathologists. Since the description of subtypes I and II of nodular sclerosis, the differentiation as described by MacLennan and colleagues [22] has been incorporated into the diagnosis. The accuracy of the histological diagnosis was retrospectively checked again by an independent expert pathologist in 50% of representative cases chosen at random. The diagnosis of Hodgkin's disease was confirmed in all cases. Histological subtype did not influence treatment decisions.

Treatment strategies

Before July 1988. Prior to July 1988, patients were treated according to the relevant international standard procedures, with staging and treatment strategies being continuously adapted to changing standards [23]. This was particularly true for restrictions in explorative and staging laparotomy. In brief, patients with limited stage disease were usually staged surgically and treated with radiotherapy alone. Chemotherapy was added in case of mediastinal bulky disease. Advanced stages of disease were treated with chemotherapy alone, with irradiation added to sites of primary bulk and active residual disease. COPP (cyclophosphamide, vincristine, procarbazine, prednisone)/ABVD, MOPP/ABVD or MOPP were the preferred chemotherapeutic regimens. Details of treatment are given in Table 1. It was the usual practice to inform patients verbally about their disease and treatment procedures.

After July 1988. Since 1 July 1988, it has been the policy of the hospital to include all patients in international, randomised, phase III clinical trials. The protocols met the requirements of the local ethics committees and were carried out according to the relevant laws regulating clinical trials. Written informed consent was obtained from all patients. Staging was performed according to the recommendations of the Ann Arbor Committee [24] with minor modifications (e.g. regular performance of bone marrow biopsies).

Patients with pathologically confirmed localised disease and without well-defined clinical risk factors (i.e. large mediastinal mass, E stages, ≥ 3 lymph node areas involved, massive splenic involvement and elevated erythrocyte sedimentation rate (i.e. first hour values ≥ 50 in A and ≥ 30 in B stages)) were enrolled in the HD 4 protocol of the German Hodgkin's Study Group (GHSG) ($n = 16$) [25]. In the presence of risk factors, patients with clinical stages I and II were treated according to the GHSG HD 5 and later on according to the HD 8 protocol ($n = 26$) [26]. In stages III and IV of the disease, patients were enrolled into the HD 6 ($n = 18$) [26] and later into the HD 9 trial ($n = 2$) of the GHSG [27].

Routinely scheduled follow-ups (i.e. quarterly during the first 3 years after initial diagnosis, twice a year during years 3–5 and once annually thereafter) were identical for all patients.

Assessment of QoL

The 194 survivors of Hodgkin's disease were sent a letter by the principal investigator explaining the aims of the study and inviting patient participation. 126 patients responded which meant that QoL data were available for 64.9% of surviving patients (equivalent to 56.0% of the 225 patients with complete records available and to 49.6% of all 254 patients listed in the cancer registry). The core questionnaire (QLQ-C30) from the European Organisation for Research and treatment of Cancer (EORTC) Quality of Life Study Group [20] was used for the assessment of QoL. This instrument is especially suitable for the measurement of QoL in patients with malignant diseases and has previously shown good psychometric qualities in formal studies. The QLQ-C30 has proved to be highly reproducible and applicable across language and cultural barriers [28]. It is multidimensional, patient-based and designed for self-administration. The 30 items in the questionnaire cover the most diverse areas of life (see Subscales); patients were asked to answer these questions as applying to the time period of the immediately preceding week. The EORTC QLQ-C30 consists of: the Gutman scale for answering eight items (possible answers: yes or no), a four-step Likert scale for answering 20 items (possible answers: not at all, little, moderate, very much) and a seven-step Likert scale in the case of two items. In the analysis of the single items, five function subscales, one subscale 'global QoL' and nine symptoms subscales were calculated. All subscales and individual item scores were linearly converted to a 0–100 scale. For the functional and overall QoL scales, a higher score represents a higher level of functioning and QoL. For the symptom scales and single items, a higher score reflects a higher level of complaints and extent of impairment.

Statistics

In order to examine the comparability of sociodemographic and clinical data between the groups who returned the questionnaires and those who did not and between those who participated in clinical trials and those who did not with respect to continuous and ordinal variables, the Mann–Whitney U test for independent random samples was employed. In the case of discrete variables, systematic group differences were investigated by means of the chi-square test. For QoL variables, the simple comparison of groups (e.g. in and outside of randomised clinical trials) was supplemented by an analysis of covariance including relevant sociodemographic (age, sex) and clinical variables (presence of B symptoms, risk factors, relapse, stage of disease, protocol of treatment). The evaluation of the influence of parameters such as age at diagnosis, clinical risk factors, Ann Arbor stages, trial participation and treatment modalities on relapse-free and overall survival were determined using the Kaplan–Meier method. The statistical significances for differences concerning these parameters were calculated applying the log-rank test. Additional analyses with the Cox regression method [29] (covariates: age at diagnosis, gender, the presence of risk factors or B symptoms, stages of disease, clinical trial participation and treatment modality) were performed. All calculations were carried out using the SPSS computer program (SPSS Inc.).

RESULTS

Characterisation of the various groups of patients

Differences in clinical parameters as well as in treatment strategies for all 225 patients and separately for patients in

and outside clinical trials are given in Table 1. Both groups were well balanced as regards age and distribution of stages, but differed in clinically relevant risk factors which were more often present in patients included in clinical trials (58.1% versus 19.6%, $P < 0.001$). However, patients enrolled in clinical trials (HD 4–HD 9) more frequently underwent liver biopsy ($P < 0.001$), while staging laparotomy was more regularly carried out in patients treated according to standard procedures ($P < 0.01$, Table 1). Combination of chemo- and radiotherapy was more often applied in the GHSG protocols than was considered adequate for patients treated outside clinical trials ($P < 0.01$, Table 1). Patients in clinical trials were more homogeneous with regard to the chemotherapeutic regimens they received, since 91% of study participants were treated with either COPP/ABVD or COPP/ABV/IMEP (ifosfamide, methotrexate, etoposide, prednisone), whereas patients outside clinical trials received a wider variety of chemotherapy regimens with 'standard' COPP/ABVD (20.2%), MOPP/ABVD (17.3%) and MOPP (26.9%) constituting the most frequently applied regimens. These differences are clearly the result of the specific design of the study protocols and do not reflect a bias in the selection of patients.

The clinical parameters shown in Table 1 were all separately analysed for 126 patients answering the QoL questionnaire and were found to be equally distributed between this subset and the total group of 225 patients. A statistically significant difference could not be observed in any of the categories compared ($P > 0.05$ for all tests). The following additional sociodemographic data could be obtained in this group of 126 patients answering the questionnaire: 11.1% were living alone, 75.4% with a partner, 4% with children, 7.9% with their parents and 1.6% in a sheltered home. Concerning their educational status, 46.3% had attended elementary school and 35.8% had completed an apprenticeship; 6.5% and 11.4% had finished high school or a college/university, respectively. Patients treated in clinical trials or according to standard procedures did not differ concerning these parameters ($P > 0.1$ for all tests).

Clinical outcome of patients enrolled in or outside clinical studies

The results of treatment in terms of overall survival were excellent for the total group of patients (5-year overall survival: 94.3% (95% confidence interval (CI) 91.1–97.5%); 10-year overall survival: 84.9% (95% CI 78.9–90.9%)) irrespective of their stage of disease ($P = 0.93$; Table 2). Patients older than 60 years were characterised by a reduced overall survival but did not differ from other age groups in relapse-free survival (Table 2). Differences in treatment strategies for patients in and outside clinical trials did not result in differences in remission rates (complete response rates 97.8% versus 89.8%) or overall survival (5-year survival rates for patients in and outside randomised clinical trials 95% versus 95.4%; $P = 0.67$). The 5-year relapse-free survival rates were 96.6% for trial participants and 82.8% for patients treated outside clinical trials. This difference was statistically significant in the univariate analysis ($P = 0.037$), but the difference failed to reach significance in a multivariate analysis using age, risk factors, Ann Arbor stages and treatment modality as other independent variables ($P = 0.064$, Table 2).

Table 2. Influence of various clinical parameters on relapse-free and overall survival for all eligible patients (n = 225)*

	Relapse-free survival				Overall survival			
	5 years	95% confidence interval	Log-rank test	Cox regression	5 years	95% confidence interval	Log-rank test	Cox regression
Age at diagnosis (years)†								
0–25	86.1%	77.1–95.1			100%	88.5–100		
26–40	80.1%	70.3–89.9	$P = 0.68$	$P = 0.50$	95.8%	91.2–100	$P < 0.0001$	$P < 0.0001$
41–60	94.1%	87.6–100			100%	96.5–100		
> 60	78.2%	54.4–100			61.8%	38.9–84.7		
Presence of risk factors‡								
Yes	87.4%	76.4–98.4	$P = 0.73$	$P = 0.12$	88.7%	79.8–97.6	$P = 0.0001$	$P = 0.0001$
No	84.7%	78.8–90.6			97.3%	94.7–99.9		
Ann Arbor stages§								
Stage I	92.1%	81.6–100			95.8%	87.8–100		
Stage II	84.5%	76.3–92.7	$P = 0.13$	$P = 0.14$	95.6%	91.3–99.9	$P = 0.93$	$P = 0.38$
Stage III	79.8%	69.1–90.5			96.5%	91.7–100		
Stage IV	92.8%	83.2–100			93.2%	84.0–100		
Trial participation¶								
In trial	96.6%	92.0–100	$P = 0.037$	$P = 0.064$‖	95.0%	89.4–100	$P = 0.67$	$P = 0.65$
Outside trial	82.8%	76.6–89.0			95.4%	92.0–98.8		
Treatment modality								
Radiotherapy	80.7%	70.8–90.6			100%	94.9–100		
Chemotherapy	80.7%	69.8–91.6	$P = 0.025$	$P = 0.041$	93.0%	86.3–99.7	$P = 0.12$	$P = 0.71$
Combined modality treatment	93.8%	88.5–99.3			96.1%	91.7–100		

*Results are given for all 225 patients entered in the database of the Cancer Registry of Tyrol between 1969 and 1994 and evaluable for clinical data, i.e. overall and relapse-free survival. †Subgroup analysis revealed patients > 60 years of age had the highest risk of death. ‡Clinical risk factors were defined as follows: presence of elevated erythrocyte sedimentation rate, large mediastinal mass, E stages, ≥ 3 lymph node areas involved and massive splenic involvement (for detail see Patients and Methods). §Histological subtypes did not influence clinical outcome (P = n.s.). ¶Details of the design of the German Hodgkin's Study group (GHSG) studies HD 4, HD 5, HD 6, HD 8 and HD 9 are given in Patients and Methods and have been published elsewhere [25–27, 53]. ‖Omitting the influence of treatment modality on relapse-free survival, the P value became 0.038 in the Cox regression model.

Patients treated with combined modalities (i.e. chemo- in addition to radiotherapy) relapsed significantly less frequently compared with those treated with chemo- or radiotherapy alone ($P = 0.025$, Table 2). This effect of combined modality treatment was more pronounced in stages I and II ($P = 0.005$) than in advanced stages of the disease ($P = 0.26$). However, irrespective of the stage of disease, overall survival was identical for these three groups of patients (Table 2, $P = 0.12$).

QoL parameters at the time of analysis

A mean (±standard deviation, S.D.) of 9.1 ± 7.0 years after the start of treatment, scores on QoL parameters were very high in all subscales (mean ± S.D.: physical functioning: 90.5 ± 19.4; role functioning: 87.3 ± 29.2; emotional functioning: 74.7 ± 23.5; cognitive functioning: 89.2 ± 18.5; social functioning: 88.2 ± 22.4) and thus in the global QoL (82.0 ± 17.9). QoL scores were not influenced by the time interval between the time of treatment and the analysis of the current QoL. In fact, patients 2–5 years after treatment and those more than 5 years after the beginning of therapy did not differ in their assessment of the current QoL (e.g. global QoL scores (mean ± S.D.): < 2 years after treatment: 79.6 ± 23.1; 2–5 years after treatment: 82.4 ± 14.9; > 5 years after the end of therapy: 82.2 ± 18.6, $P > 0.1$). Taken together, these results may indicate rapid improvement of QoL after treatment in patients with Hodgkin's disease.

Influence of relapse and staging procedures on QoL

41 out of 225 (18.2%) patients investigated had experienced at least one relapse and 19 (46.3%) of these completed the questionnaires. QoL parameters for these patients did not differ significantly from the values obtained for patients who were still in the first continuous complete remission (e.g. global QoL scores: 81.5 ± 8.1 versus 84.7 ± 17.0, $P = 0.43$). Global QoL scores were not influenced by the performance of staging laparotomy (82.4 ± 17.6 versus 81.1 ± 18.3 in patients with clinical versus pathological staging, $P =$ n.s.) or by the performance of any surgical procedure in addition to the extirpation of lymph nodes (83.8 ± 17.6 versus 80.4 ± 18.1 in patients with versus without additional surgery, $P =$ n.s).

QoL in patients enrolled in or outside clinical trials

Overall, the patients' scores on the QoL parameters were high and differences between patients treated in and outside clinical trials were statistically non-significant in all subscales (e.g. mean ± S.D. for global QoL scores: 82.0 ± 17.9 versus 83.5 ± 14.6, $P > 0.1$).

Treatment modalities and differences in QoL scores

Using the QLQ-C30, analysis of the current QoL of patients treated with either chemotherapy, radiotherapy, or a combined modality protocol revealed more pronounced deficits in physical functioning (Table 3) and significantly higher rates of dyspnoea, pain and fatigue in patients treated with combined modality regimens (Table 3).

DISCUSSION

Modern treatment strategies in patients with Hodgkin's disease have significantly improved relapse-free and overall survival rates. Therefore, the analysis of QoL parameters in long-term survivors [30, 31], a comparison of such results with those obtained in other diseases and the determination of sociodemographic factors and therapeutic modalities which have an impact on QoL have attracted scientific interest. Such comparisons, however, are difficult because of the large variety of methods used in QoL questionnaires currently available. As a result, it is not surprising that heterogenous conclusions have been drawn from such analyses carried out with patients suffering from Hodgkin's disease. Using multiple instruments with proven psychometric properties, Olweny and colleagues recently reported that patients more than 12 months after treatment were comparable with their healthy neighbours in terms of physical well being and QoL and that they fared significantly better than patients suffering from coronary heart disease [16]. Using the brief symptom inventory, however, Kornblith and associates found that at least 22% of 277 eligible patients fulfilled the criteria for psychiatric illness [32].

In the face of such conflicting reports and in order to allow better comparison of our results with those of future investigations or those obtained in other diseases, our analysis was

Table 3. Results of quality of life self-estimations by patients with Hodgkin's disease treated with radiotherapy (RT), chemotherapy (CT) or combined modality (CMT)

	RT		CT		CMT		Statistical difference	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	CMT versus RT	CMT versus CT
Physical functioning	96.32	10.25	89.03	21.19	87.37	22.24	$P < 0.05$	n.s.
Role functioning	97.22	11.62	80.65	35.77	84.55	31.73	n.s.	n.s.
Emotional functioning	75.44	21.92	73.92	23.84	74.71	24.65	n.s.	n.s.
Cognitive functioning	91.23	13.83	88.71	20.36	88.01	20.35	n.s.	n.s.
Social functioning	94.74	14.55	84.41	26.15	85.96	23.94	n.s.	n.s.
Global quality of life	86.62	14.18	81.45	19.45	79.24	18.97	n.s.	n.s.
Fatigue	18.21	21.77	26.16	25.10	31.11	30.50	$P < 0.05$	$P < 0.05$
Nausea and vomiting	3.51	7.90	1.61	8.98	7.60	18.38	n.s.	n.s.
Pain	6.58	14.78	9.68	17.09	17.84	28.84	$P < 0.05$	$P < 0.05$
Dyspnoea	14.91	20.06	12.90	22.24	26.32	33.18	$P < .01$	$P < 0.05$
Sleep disturbance	22.81	26.96	22.58	27.74	22.22	31.71	n.s.	n.s.
Appetite loss	7.02	19.23	1.08	5.99	10.53	24.53	n.s.	n.s.
Constipation	12.28	23.79	8.60	17.14	10.53	22.85	n.s.	n.s.
Diarrhoea	2.63	9.11	8.60	22.72	9.94	25.17	n.s.	n.s.
Financial impact	7.02	20.73	13.98	29.53	16.37	27.55	n.s.	n.s.

S.D., standard deviation; n.s., not significant.

based on the self-report QoL questionnaire QLQ-C30, which has widely been used in assessing QoL of cancer patients and which has demonstrated transcultural reproducibility [28]. Our results indicate high scores on QoL parameters in all subscales analysed by means of the QLQ-C30 questionnaire in survivors of Hodgkin's disease and after a mean period of 9.1 years from the time of the initial diagnosis. This high level of QoL and its rapid improvement over time are indicated by the fact that more than 2 years after treatment, the results of the assessment of the current QoL were not further influenced by the time interval between therapy and completion of the questionnaire (see Results). Although our results need confirmation in prospective trials, they are in line with previous longitudinal analyses of QoL scores reporting a substantial decrease in psychological morbidity within 1 year after treatment [33] and even a significant improvement of QoL in 88% of patients undergoing bone marrow transplantation [34]. When the potential influence of treatment concepts on the balance between relapse-free and overall survival, on the one hand, and on QoL, on the other, is investigated, adjustments must be made for the distribution of sociodemographic data and clinical risk factors (Table 1) since they might impact on the choice and efficacy of treatment as well as on QoL. When all our 225 eligible patients were analysed, Ann Arbor stages and histological subtypes were without influence on relapse-free and overall survival (Table 2). The presence of clinical risk factors as defined by GHSG, however, was associated with an inferior overall survival rate (Table 2). Single institute and registry-based data have identified age above 40 years [35], above 45 years [36], or above 50 years [37, 38] as a risk factor for reduced survival rates in patients with Hodgkin's disease. This has been attributed to an increased number of relapse rates (e.g. after radiotherapy [39]) and an even higher simultaneous increase in causes of death other than Hodgkin's disease in the study of Guinee and colleagues [40], to a higher rate of secondary neoplasias [41], to an increased comorbidity and toxicity of therapy in the elderly population [2, 35, 40] or to inadequate staging or treatment of these patients in other reports [38, 42]. In our study, the reduction in overall survival of patients beyond the age of 60 years was not caused by a lower response or an inferior relapse-free survival rate as compared with the age groups < 25, 25–40 and 40–60 years, respectively (Table 2) and it was not caused by an inadequate dose adjustment of the treatment protocol. Thus, Hodgkin's disease *per se* did not compromise the objective treatment outcome in older patients, a finding which is in line with reports for complete remission patients by Erdkamp and associates [37], but in contrast to the study by Walker and colleagues [38].

Randomised phase III clinical trials are the gold standard for the testing of innovative therapies [43] and have enabled the adequate tailoring of radio- and chemotherapy and a substantial improvement in the treatment outcome of Hodgkin's disease. They will remain the mainstay for the achievement of further progress in the treatment of this disease and in risk stratification [44]. With the increased perception of QoL as a central goal not only in palliative [45] but also in curative cancer therapy of young patients, cooperative trial groups will be supplementing their phase III trials with tests for QoL [46]. However, little is known about the potential bias introduced in ascertaining QoL from such randomised trials and in making generalisations about all patients with Hodgkin's disease based on the results of such trials. Such bias might arise from the fact that only a limited number of cancer patients (estimated to be less than 1%) are enrolled in clinical trials [47]; preselection processes employed by investigators may compromise the intention of recruiting representative patients [46]; and investigations have not been carried out regarding the influence of participation in clinical trials on QoL parameters. The possibility of such an influence cannot be excluded, since such participation will often require not only more intensive staging procedures but also provide patients with more detailed information concerning short- and long-term side-effects of therapy on physical health, probability of relapse, secondary cancer or leukaemia, infertility and potential disablement in children. Considerations of relapse or progression of the disease may arouse substantial negative emotions [48]. Randomisation may also create anxiety in patients and lead them to question whether choice of treatment was appropriately made in their cases; indeed it was rejected as an option by 90% of early stage breast cancer patients who were asked about their choice of treatment alternatives in case of progression [48]. To some extent at least, monocentric long-term analysis of all patients seen at an institution may help avoid such bias.

In a univariate analysis, our retrospective analysis showed prolonged relapse-free survival rates for patients participating in clinical trials (5-year relapse-free survival 96.6% versus 82.8%, $P = 0.037$, Table 2). This was not due to a different composition of the two groups with respect to demographic (age, sex) or clinical (stage, presence of risk factors) variables other than treatment. Investigating the possible reasons for such an improved outcome in patients treated in clinical trials, a multivariate analysis was carried out. The results from Cox regression showed that the more frequent application of combined modality treatment in clinical trials at least partly explained the more favourable outcome in study participants. In fact, the statistical significance of 'study participation' disappeared (according to the $P = 0.05$ criterion) when taking treatment modality (chemotherapy, radiotherapy, combined treatment modality) into account (Table 2). Such a favourable influence of the more frequent ($P < 0.01$) application of combined treatment modality on relapse-free but not on overall survival in our study participants is what can be reasonably expected, since patients relapsing after radiotherapy alone may undergo efficient and successful salvage therapy (Table 2). This observation is also in line with data from a recent meta-analysis [49]. However, considering the fact that the actual change in the significance level for the influence of study participation on relapse-free survival between univariate and multivariate analysis was considerably low (from $P = 0.037$ to $P = 0.064$, Table 2), treatment modality alone is not sufficient to explain the improved relapse-free survival of study participants and other possible reasons must also be considered. Patients in clinical trials were more homogeneous with regard to the chemotherapeutic regimens they received, since 91% of study participants were treated with either COPP/ABVD or COPP/ABV/IMEP, whereas patients outside clinical trials received a wider variety of chemotherapy regimens with 'standard' COPP/ABVD (20.2%), MOPP/ABVD (17.3%) and MOPP (26.9%) constituting the most frequently applied regimens. Although the long time interval during which patients were recruited precludes the calculation of exact dose intensities of the chemotherapeutic regimens on relapse-free and overall survival, it may be assumed that in the treatment of patients

in trials, the treatment plan was more strictly adhered to and a higher dose intensity applied. In fact, reductions of the standard dosages of MOPP or MOPP-like regimens have been associated with identical complete remission rates but substantially reduced disease-free survival rates in retrospective analyses [50, 51] and recent controlled clinical trials have provided evidence for an improved outcome in patients treated with dose-escalated COPP/ABVD [52] or with the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) regimen [53], thus underlining the role of dose intensity in this disease. Evidence has been provided that patients treated in trials are more likely to receive standard doses of chemotherapy whilst patients outside trials are more likely to be undertreated [54]. Furthermore, it is well known that deviations from the standard dosage of irradiation delivered and of the field size chosen may occur frequently even in controlled clinical trials with a centralised radiation plan and may impact significantly on the relapse rate [25]. Although not proven, such differences between the actual and the planned or even ideal irradiation plan may occur even more frequently outside clinical trials. Finally, patients willing to participate in trials may be selected by or predisposed to an attitude for more stringent adherence to a treatment plan. In general, our data are in line with results from other investigators, who reported improved outcome for patients with multiple myeloma [55] and non-small cell lung cancer [56] treated in clinical trials.

In terms of QoL, our patients in and outside clinical trials did not differ in any subscale of the QLQ-C30 when analysed in a multivariate analysis. Although patients not included in randomised studies more frequently underwent staging laparotomy (Table 2), this procedure and surgical interventions *per se* were without influence on QoL parameters. Based on these results, we assume that there is no negative impact of aggressive clinical staging, randomisation and the increasingly detailed nature of informed consent involved in clinical trial participation on QoL during treatment as well as on its improvement over time.

When investigating the influence of treatment modalities on QoL parameters, it was observed that the combined modality treatment was more often associated with a lower physical functioning score than radiotherapy alone (Table 3) and also caused more severe complaints of fatigue, pain and dyspnoea than radio- and/or chemotherapy alone. This may be explained by the cumulative pulmonary toxicity of cytotoxic agents such as bleomycin and irradiation, on the one hand [57], and of vinca-alkaloids, bleomycin or anthracyclines [58] in conjunction with radiotherapy on gastrointestinal function, on the other. Combined modality treatment was applied with similar frequency in patients with localised (I, II; 42.6%) and in those with advanced stages of disease (III, IV; 38.9%) and the presence of B symptoms, risk factors and other parameters listed in Table 2 were without influence on QoL parameters. Thus, the observed deterioration in QoL was not caused by disease conditions requiring combined modality treatment but rather by the treatment itself.

Patients undergoing chemotherapy and irradiation experienced significantly lower relapse rates than those treated with either modality alone. Thus, two aspects with opposing influence on QoL have to be weighed against each other: the aggressive therapeutic approach of combined treatment modality designed to avoid staging laparotomy and relapse resulting from an underestimation of the spread of the disease by clinical staging, and the psychological and social stress caused by relapse as well as the additional toxicity of salvage therapy. These considerations, in conjunction with the efficacy of salvage chemotherapy, have led the investigators of the EORTC Hodgkin's lymphoma group to question the usefulness of staging laparotomy in low-risk patients with limited stage disease [59, 60]. However, as yet there are no data on QoL which support aggressive staging or the more frequent application of primary combined modality treatment for the purpose of reducing relapse rates or the need for salvage treatment at a later period of time. Our results demonstrate that the differences in frequencies of staging laparotomies in patients in and outside clinical trials and, furthermore, surgical procedures *per se*, remained without influence on QoL. In contrast to a previously reported negative influence of relapse [61] or severe illnesses after treatment completion [32] on psychosocial adaptation, in our study the occurrence of relapses did not negatively affect the patients' social or psychological status. Considering the fact that improvement in relapse-free survival rate did not further increase overall survival, the persistent and negative influence of the more frequent application of combined modality treatment on QoL life might outweigh its beneficial effect on relapse-free survival. Whether this trade-off also holds true for the latest concepts of combined modality treatment with their significant reduction in field size and volume of irradiation and their probably improved chemotherapeutic regimens awaits final proof by phase III clinical trials accompanied by stringent assessment of QoL.

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