Long-Term Outcome of Treatment for Hodgkin's Disease: The University Hospital Sofia Experience

Dlouhodobé výsledky léčby Hodgkinovy choroby: zkušenosti z univerzitní nemocnice v Sofii

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Summary

Background: To establish the efficacy of the combined modality treatment (CMT) including curative extended field radiotherapy (EFRT) and chemotherapy (CHT) by examining the long-term outcome in Hodgkin's disease (HD) patients at the Sofia University Hospital "Queen Giovanna-ISUL", with particular focus on second primary malignancy (SPM), and to establish independent factors correlated with treatment outcome. ***Methods and Materials:*** Between 1982 and 2007, 170 patients with HD with median age of 12 years (range 3–40), (68 females, 102 males), were included in this retrospective study. The clinical stage (CS) distribution was CS I in 1 patient (0.6%), CS II in 86 (50.5%), CS III in 77 (45.3%) and CS IV in 6 (3.5%) patients. Histologic subtypes included lymphocyte predominance 7.6%, mixed cellularity 47.1%, nodular sclerosis 42.9% and lymphocyte depletion 0.6%. B symptoms were observed in 57.6% of the patients, hepatosplenomegaly – in 30.6%, anemia – in 27.1% and elevated serum lactat dehydrogenase (LDH) – in 41.2%. The overall treatment consisted of both EFRT and CHT. In 115 patients (67%) supradiaphragmatic irradiation of lymphatic nodes was carried out, in 3 (2%) patients subdiaphragmatic irradiation was performed and in 52 (31%) – irradiation of the supra- and infra-diaphragmatic lymph nodes basically by subtotal 35 (20.6%), and total lymphoid irradiation – in 4 (2.4%) patients. The daily dose was 1.5–2 Gy, the total dose for EFRT was 20–40 Gy. From the analyzed 170 patients 150 were assessable for long-term outcome and 120 for SPM analyses. ***Results:*** Follow-up extended from a minimum of 0,3 years to maximum 25,7 years, with a median observation time 12 years. The 5-, 10-, 15-, and 25-year overall survival (OS) in the whole group was 93% : 86% : 82% : 82%, respectively. A tendency for better survival was found for patients with age ≤ 15 than for those with > 15 years, with 5-, 10-, and 15- year OS of 95% : 87% : 84% vs 84% : 84% : 56%, p = 0.09. There was a trend for better survival in males compared with females with 5-, 10- and 15-year OS of 96% : 93% : 91% vs 88% : 73% : 65%, p = 0.001. The OS difference between CS IIB and IIIA turned out to be significant in favor of the patients in CS IIIA with 5- and 10-year OS of 89% : 76% vs 95% : 90%, respectively, p = 0.03. The following factors were analyzed for their prognostic influence: age, gender, stage, histologic subtype at first diagnosis, sites of involvement, number of involved lymph node areas, B symptoms, hepatosplenomegaly, anemia, elevated serum LDH, daily dose, total dose, boost and technique used in EFRT. In univariate analysis, independent risk factors were gender (p < 0.001), stage (IIB : IIIA) (p = 0.03), mediastinal involvement (p = 0.03), daily dose (p = 0.01) and total dose (p = 0.02). In multivariate analysis, independent risk factors age ≤ 15 years (p < 0.001), male gender (p = 0.005), daily dose ≤ 1.5 Gy (p = 0.009), and total dose 26–30 Gy (p = 0.048) were found to positively affect OS. We investigated a prognostic model, identifying groups of HD patients with particularly responsive disease, combining prognostic factors as age ≤ 15 years (p = 0.001), male gender (p = 0.011), and total dose 26–30 Gy (p = 0.012). In the observed 25-year period SPM development was not established in any of the 120 patients subjected to follow-up. ***Conclusion:*** The performed first Bulgarian study on CMT including EFRT and CHT exhibited a certain therapeutic potential in the treatment of HD patients, expressed in the achievement of high long term outcome and low SPM frequency.

Key words

combined modality treatment – chemotherapy – extensive field radiotherapy – Hodgkin's disease

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Souhrn

Východiska: Stanovit účinnost kombinované léčby zahrnující léčebnou radioterapii s rozšířeným polem (extended field radiotherapy – EFRT) a chemoterapii (CHT) přezkoumáním dlouhodobých výsledků pacientů s Hodgkinovou chorobou v sofijské univerzitní nemocnici „Queen Giovanna-SUL", se zaměřením zejména na sekundární primární malignitu (SPM), a stanovit nezávislé faktory korelující s výsledkem léčby**.** ***Materiál a metody:*** V období 1982 až 2007 bylo do této retrospektivní studie zařazeno 170 pacientů s Hodgkinovou chorobou se středním (medián) věkem 12 let (rozmezí 3–40 let, 68 žen, 102 mužů). Rozložení klinických studií bylo následující: klinická studie I u 1 pacienta (0,6 %), klinická studie II u 86 pacientů (50,5 %), klinická studie III u 77 pacientů (45,3 %) a klinická studie IV u 6 pacientů (3,5 %). Histologické podtypy zahrnovaly typ s převahou lymfocytů 7,6 %, typ se smíšenou buněčností 47,1 %, typ nodulárně sklerotický 42,9 % a typ s lymfocytární deplecí 0,6 %. Symptomy B byly pozorovány u 57,6 % pacientů, hepatosplenomegalie u 30,6 %, anémie u 27,1 % a zvýšená laktátdehydrogenáza v séru (LDH) u 41,2 %. Celková léčba zahrnovala jak EFRT, tak CHT. U 115 pacientů (67 %) bylo provedeno supradiafragmatické ozařování lymfatických uzlin, u 3 pacientů (2 %) bylo provedeno subdiafragmatické ozařování a u 52 pacientů (31 %) bylo provedeno ozařování supra- a infradiafragmatických lymfatických uzlin (35 pacientů – 20,6 %) a celkové lymfatické ozařování (4 pacienti – 2,4 %). Denní dávka byla 1,5–2 Gy, celková dávka pro EFRT byla 20–40 Gy. Z analyzovaných 170 pacientů byly u 150 posouzeny dlouhodobé výsledky a u 120 provedena analýza SPM**.** ***Výsledky:*** Doba sledování byla od 0,3 let do maximálně 25,7 let, s mediánem doby pozorování 12 let. Celková doba přežití po dobu 5, 10, 15 a 25 let v celé skupině byla 93 % : 86 % : 82 % : 82 %. Sklon k lepšímu přežití byl zjištěn u pacientů s věkem ≤ 15 let v porovnání s pacienty ve věku > 15 let, s celkovou dobou přežití 5, 10 a 15 let 95 % : 87 % : 84 % vs 84 % : 84 % : 56 %, p = 0,09. Byl zjištěn trend lepší doby přežití u mužů v porovnání s ženami s celkovou dobou přežití 5, 10 a 15 let (96 % : 93 % : 91 % vs 88 % : 73 % : 65 %, p = 0,001). Rozdíl celkové doby přežití mezi klinickou fází IIB a IIIA byl významný ve prospěch pacientů v klinické fázi IIIA s celkovou dobou přežití 5 a 10 let (89 % : 76 % vs 95 % : 90 %, p = 0,03). Byl zkoumán prognostický vliv následujících faktorů: věk, pohlaví, studie, histologický podtyp při první diagnóze, místa postižení, počet zasažených lymfatických uzlin, symptomy B, hepatosplenomegalie, anémie, zvýšená LDH v séru, denní dávka, celková dávka, posilovací dávka a technika použitá při EFRT. V univariantní analýze byly nezávislými rizikovými faktory pohlaví (p < 0,001), studie (IIB : IIIA) (p = 0,03), mediastinální postižení (p = 0,03), denní dávka (p = 0,01) a celková dávka (p = 0,02). V multivariantní analýze byly nezávislými rizikovými faktory věk ≤ 15 let (p < 0,001), mužské pohlaví (p = 0,005), denní dávka ≤ 1,5 Gy (p = 0,009) a celková dávka 26–30 Gy (p = 0,048), u kterých bylo zjištěno, že pozitivně ovlivňují celkovou dobu přežití. Zkoumali jsme prognostický model identifikující skupiny pacientů s Hodgkinovou chorobou s obzvlášť citlivou variantou a zkombinovali prognostické faktory jako věk ≤ 15 let (p = 0,001), mužské pohlaví (p = 0,011) a celková dávka 26–30 Gy (p = 0,012). Během pozorovaného 25letého období nebyl stanoven rozvoj SPM u žádného ze 120 pacientů zařazených do sledování**.** ***Závěr:*** První provedená bulharská studie kombinované léčby zahrnující EFRT a CHT prokázala určitý potenciál při léčbě pacientů s Hodgkinovou chorobou vyjádřený dosažením dlouhodobých výsledků a nízké četnosti SPM.

Klíčová slova

kombinovaná léčba – chemoterapie – radioterapie s rozšířeným polem – Hodgkinova choroba

Introduction

Hodgkin's disease (HD) has been a successful model for the development of effective treatment programs. The increasing cure rates in this disease represent one of the most significant advances of modern oncohaematology. The achieved progress is an example for the fundamental dependence of clinical practice on scientific investigations that have brought to improvements in staging techniques, use of new markers for risk assessment, patient stratification in single risk groups, implementation of highly effective chemotherapeutic schemes, launching the so-called "target" therapy with using monoclonal antibodies (rituximab, alemtuzumab), proteazome inhibitors (bortezomib), modern radiotherapy (RT) and supportive measures.

The crude incidence and mortality of HD in the European Union and Bulgaria do not differ substantially (2.2/ /100 000/year vs 2.0/100 000/year and 0.7/100 000/year vs 1.0/100 000/year) [1–2]. The annual incidence in Bulgaria is about 150 new cases, which corresponds approximately to the frequency in Europe [1–2].

The susceptibility to contiguous spread of lymphoproliferative diseases represents an important and well known problem in oncological practice. The possibility of control on it is of crucial significance in the determination of a given therapeutic strategy. Following the world trends as early as in 1979 a routine implementation of extended field RT (EFRT) as a sole or as a part of combined modality treatment (CMT) of HD was launched in the Sofia University Hospital.

The objective of the present analysis is to establish the efficacy of CMT, including curative EFRT and chemotherapy (CHT), expressed by the achieved long-term outcome in HD patients, with particular focus on second primary malignancy (SPM), and to establish independent factors correlated with the treatment outcome.

Methods and materials

Patient characteristics

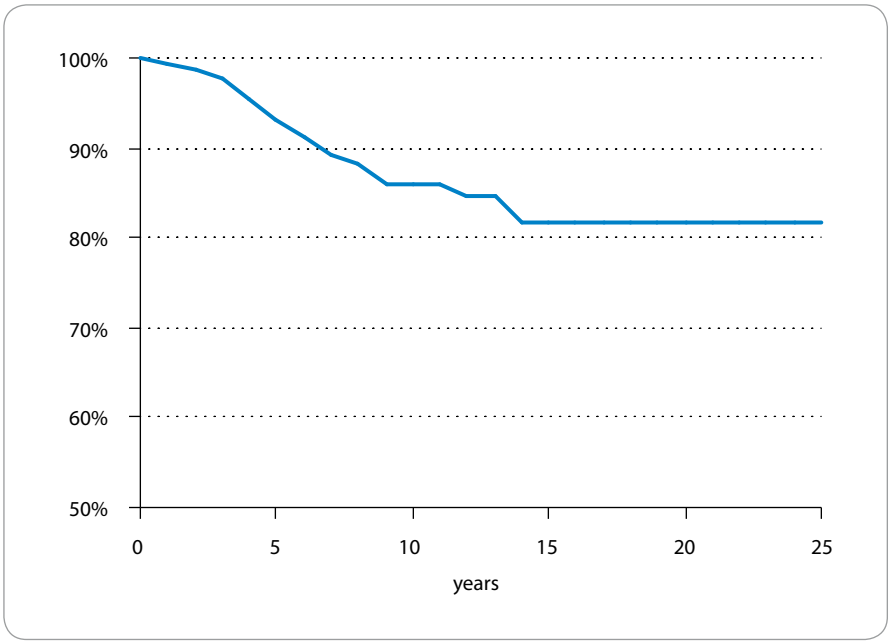
From 1982 through 2007, 170 HD patients were treated with EFRT and CHT at the Radiotherapy and Hematology Department of the Medical University of Sofia. Data for the patients were obtained from tumor registry, operative notes, pathology, RT chart reviews, and CT flow sheets. For the patients with lethal outcome, information about the exact date of death was taken from the National Cancer Registry (NCR), from the system of the Oncological dispensaries and the Unified System for Civil Registration and Administrative Services to Population (USCRASP). The information for SPM development was also taken from NCR. Of the 170 patients, 150 patients were informative for the analysis of the long-term outcome and 120 for the analysis of the SPM development.

There were 102 males (60%) and 68 females (40%). The mean and median age of all patients is 12 years (range, 3 to 40). The patients of up to 20-years of age

represent 97.1%. The predominating group consists of children of the age from 10 to 15 years – 74 (43.5%). Stage by Ann Arbor criteria is I in 1 patient (0.6%), II in 86 (50.5%), III in 47 (45.3%), and IV in 6 (3.5%). In summary, 31 (18.2%) have early-stage disease, 139 (81.8%) – advanced-stage disease at first diagnosis. Of all cases 13 patients (7.6%) have been classified as lymphocyte predominance, 80 (47.1%) as mixed cellularity, 73 (42.9%) as nodular sclerosis, 1 (0.6%) as lymphocyte depletion, and 3 (1.8%) are not specified. The most involved are cervical lymph nodes – 140 patients (82.4%), followed by mediastinal involvement in 139 patients (81.8%). A considerable part of the patients 88 (52%) have 2, and 50 (29%) patients have 3 or more involved lymph node areas. B symptoms are observed in 98 (57.6%) patients, hepatosplenomegaly – in 52 (30.6%), anemia – in 46 (27.1%) and elevated serum lactate dehydrogenase (LDH) – in 70 patients (41.2%).

Treatment was planned by a multidisciplinary team of cancer specialists. All the 170 patients received CMT including CHT and EFRT. The basic CHT schemes that have found application during the 25-year observation period are MOPP (mechlorethamine, vincristine, procarbazine, prednisone), ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), COPP (cyclophosphamide, vincristine, procarbazine, prednisone), MOPP/ABV hybrid regimes, COPP/ABVD, BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone).

EFRT by a 60 Co unit was carried out for all patients. In 115 patients (67%) EFRT of supradiaphragmatic lymph nodes was delivered, in 48 (28.2%) – with adjacent fields and in 67 (39.4%) – with mantle technique. In 3 (2%) patients EFRT of infradiaphragmatic lymph nodes and in 52 (31%) – EFRT of the supra- and infradiaphragmatic lymph nodes was delivered, in 35 (20.6%) with subtotal and in 4 (2.4%) with total lymphoid irradiation. The daily dose was 1.5–2 Gy, the most frequently applied being 1.5 Gy (52%). The realized total dose was 20–40 Gy, mainly 21–25 Gy (54%). A boost in certain lymph node formations was necessary for a considerable number of the patients with total dose from the EFRT and local RT varied also from 20 to 40 Gy, predominantly 31–35 Gy (44%).



Graph 1. Actuarial OS for 150 patients with HD.

Demographics and disease characteristics were summarized using descriptive statistics. The assessment of the achieved therapeutic results was made on the basis of overall survival (OS) analysis of the 150 patients with HD, which was satisfactory for the necessary number of observed cases in order to reach reliability of results. It was not possible to obtain data about the clinical status of 20 patients despite of our efforts to contact NCR, the regional dispensaries and USCRASP. For our regret, only 120 patients could be analyzed for SPM development and fifty patients were excluded from the final analysis due to lack of data.

OS, measured from the date of entry into the treatment protocol until death of any cause, was estimated according to the life table method. Prognostic factors for OS were assessed by univariate life table analysis and by multivariate Cox regression analysis, which results are listed in Tab. 2,3. The following factors were analyzed for their prognostic influence: age, gender, stage, histologic subtype, sites of involvement, number of involved lymph node areas, B symptoms, hepatosplenomegaly, anemia, elevated serum LDH, daily dose, total dose, boost and technique used in EFRT. No adjustment was made for multiple comparisons; all p values were two-sided. Removal and entry levels of significance were 0.1 and 0.05, respectively. In multivariate analysis, independent risk factors age ≤ 15 years ($p < 0.001$), male gender ($p = 0.005$), daily dose ≤ 1.5 Gy ($p = 0.009$), and total dose 26–30 Gy ($p = 0.048$) were found to positively affect OS. After analyzing the prognostic factors, we investigated a prognostic model combining relevant prognostic factors as age, gender and total dose. OS was the primary end point for assessment of the model. The objective was to identify groups of HD patients with particularly aggressive or responsive disease, based on characteristics available at the time of diagnosis and treatment given. All statistical analyses were performed using SPSS 13.1. Standard Version Copyright SPSS Inc.

Results

The main demographic and clinical features of the patients and the characteristics of the treatment given are reported in Tab. 1. The median fol-

Tab. 1. Demographic, clinical and treatment characteristics of patients with HD.

Characteristic	Number of patients N	(%)
patients	170	**100**
gender		
male	102	60
female	68	40
age, years		
median	12	
range	3-40	
stage c		
I	1	0.6
II	86	50.5
III	77	45.3
IV	6	3.5
histology		
lymphocyte predominance	13	7.6
mixed cellularity	80	47.1
nodular sclerosis	73	42.9
lymphocyte depletion	1	0.6
unclear	3	1.8
nodal involvement		
cervical involvement	140	82.4
mediastinal involvement	139	81.8
number of involved lymph node areas		
(+2)	88	52
(+3)	50	29
B symptoms		
present	98	57.6
absent	72	42.4
hepatosplenomegaly		
present	52	30.6
absent	118	69.4
anemia		
(males < 12.0 g/dl; females < 10.5 g/dl)	46	27.1
present	124	72.9
absent		
LDH ≥ 1× normal		
present	70	41.2
absent	100	58.8
type EFRT		
supradiaphr. EFRT	115	67.6
infradiaphr. EFRT	3	1.8
supra-infradiaphr. EFRT	52	30.6
daily dose		
≤ 1.5 Gy	76	52
1.6–2.0 Gy	74	48
total dose		
≤ 20 Gy	22	12.9
21–25 Gy	92	54.1
26–30 Gy	33	19.4
> 30 Gy	23	13.5

LDH – lactat dehydrogenase; c – data derived from both pathologically and clinically staged patients

low-up is 12 years for the whole series. Graph 1 shows life table curves for OS of 150 patients with HD with 5-, 10-, 15- and 25-year OS of 93% : 86% : 82% : 82%, respectively.

Life table curves for OS by **age** (≤ 15 years of age; > 15 years of age) as **patient-related characteristic** are shown in Graph 2. In the lower age group the median survival time is 25 years, while for the group of older patients (> 15 years of age) the median survival time is 16 years, i.e. the observation period for this group is considerably shorter. The 5-, 10-, and 15-year OS in both groups is as follows: 95% : 87% : 84% vs 84% : 84% : 56%, p = 0.09. With respect to the longer observation period 20- and 25-year OS is established only for the younger age group. Comparisons between the two categories using the log-rank test fail to reveal any significant differences in OS, although there is a trend for better survival in patients with ≤ 15 years of age compared to > 15 years of age.

When splitting the patients in two new groups – ≤ 12- and > 12-years of age, due to their relatively uniform distribution – 73 and 77 patients in each of them, the significantly better 5- and 10-year OS rates for the younger age groups are exhibited again, the proportions being 95% : 91% vs 91% : 81%, although these differences are not statistically significant (p = 0.17).

Life table curves for OS by **gender** are shown in Graph 3. There is a trend for better 5-, 10-, 15-, 20- and 25-year OS in males compared to females (96% : 93% : 91% : 91% : 91% vs 88% : 73% : 65% : 65% : 65%), statistically significant – p = 0.001. Women have 4.073 higher risk for lethal outcome than man (95% CI – 1.544–10.746), statistically significant (p < 0.01).

In general outline the established OS is correlated with the **clinical stage** as **disease-related characteristic** (CS) of HD. In our study the risk of lethal outcome is significantly higher (up to 6 times) for the patients with CS IIB compared to these with IIA but the difference does not reach statistical significance, p = 0.09. The difference in OS turns out to be statistically significant (p = 0.03) only between CS IIB and IIIA in favor

of the patients with CS IIIA, the ratio between 5- and 10-year OS being 89% : 76% vs 95% : 90%, respectively.

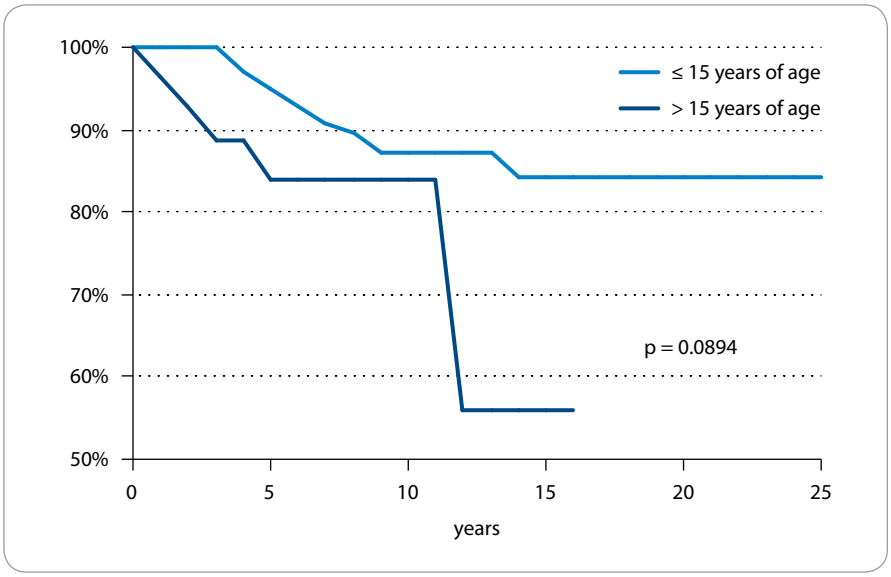
The achieved OS rates for the patients with **hystologic subtype** lymphocyte predominant are better compared with these with mixed cellularity and nodular sclerosis with 5-, 10-, and 15-year OS, 92% : 92% : 92% vs 90% : 84% : 79% vs 97% : 87% : 81%, respectively, but the difference also does not reach statistical significance (p = 0.45).

The impact of the **involved lymph node area** has been also subjected to analysis. However, due to the small number of patients in the single groups, we have focused our attention only on the **mediastinal involvement** and established statistically significant better results in the patients without mediastinal involvement. The proportions of the 5-, 10, and 15-year OS in the patients with and without mediastinal involvement are 91% : 83% : 78% vs 100% : 95% : 95%, respectively, p = 0.04.

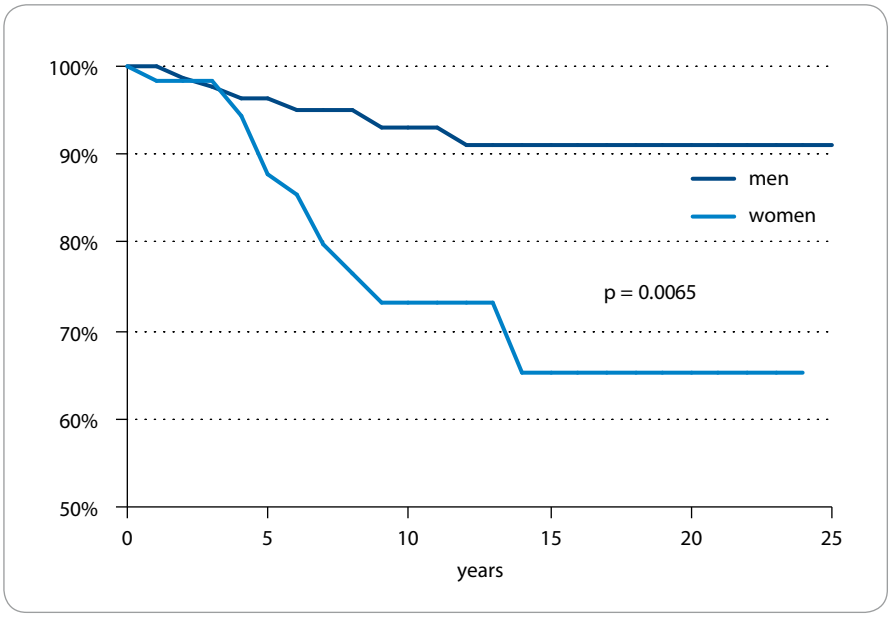
In our study we have separated the patients in two groups, with 1 and with ≥ 4 **number involved lymph node areas** and a better 5- and 10-year OS is established for the patients with 1 involved lymph node area, 94% : 94% vs 93% : 85%, although no statistically significant difference is found between the two groups (p = 0.67).

According to the impact of the **B symptoms** we have established better OS in the patients "without" B symptomatic but the differences between the two groups are again statistically insignificant (p = 0.19). The same is also true for the impact of the developed **hepatosplenomegaly**, the availability of **anemia** and of elevated **serum LDH** on OS, and for this reason we do not present the results here. Obviously, the parameters determining the biological characteristics of HD have not managed to exert their prognostic impact on our clinical material.

From the **treatment-related characteristics**, we have analyzed the impact of the **daily dose in EFRT** on the therapeutic results, and statistically significant differences are established between the achieved 5-, 10, and 15-years OS for daily dose ≤ 1.5 Gy and 1.6–2.0 Gy, in favor of the smaller dose (p = 0.01), 96% : 93% : 89% vs 90% : 74% : 66%, respectively (Graph 4). The risk of lethal outcome for the bigger dose is 3.709 times higher (95.0% CI – 1.396–9.855).



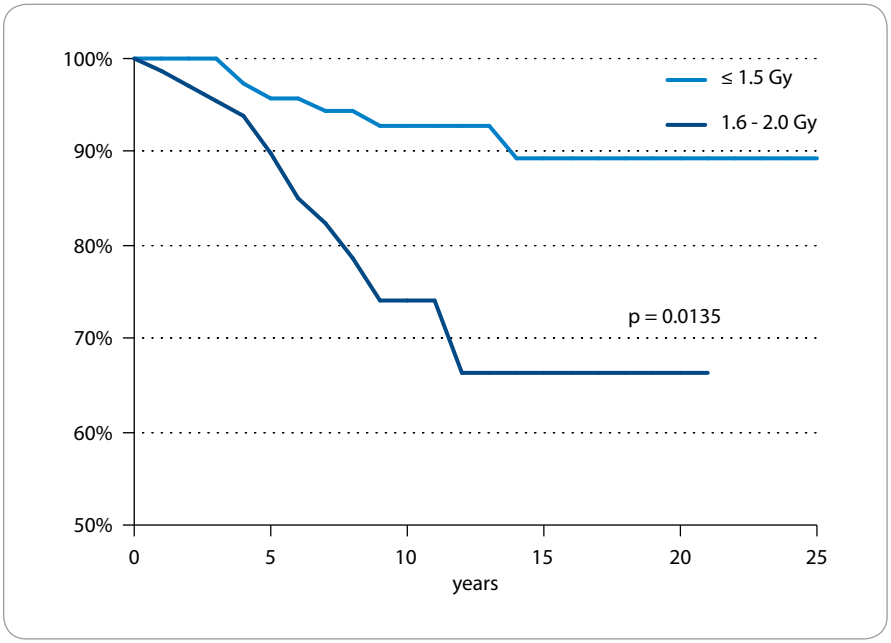
Graph 2. Actuarial OS for 150 patients with HD by age (< 15 years of age; > 15 years of age).



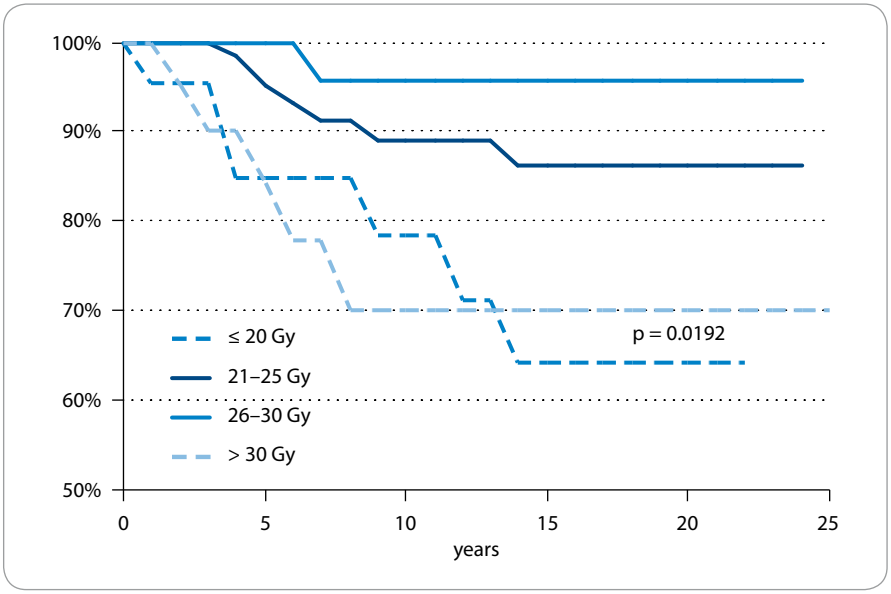
Graph 3. Actuarial OS for 150 patients with HD by gender.

According to the magnitude of the **total dose in EFRT** we have established statistically significant differences between the 4 distinguished groups (≤ 20 Gy, 21–25 Gy, 26–30 Gy, > 30 Gy), (p = 0.019) (Graph 5). It is proved that the realization of the dose of 26–30 Gy leads to the best therapeutic results, i.e. the factor is protective.

The addition of a **boost to the performed EFRT** has not lead to a significant difference in the achieved 5- and 10-year OS, the results between the patients "with" and "without" boost being 93% : 85% vs 93% : 89%, respectively, p = 0.51. The **total dose** from the consecutively realized **EFRT and local RT**, divided respectively by the total dose ≤ 30 and 31–40 Gy, with achieved 5- and 10-year OS of 89% : 84% vs 95% : 86%, respectively, does not reach statistically significant differences too (p = 0.53).



Graph 4. Actuarial OS for 150 patients with HD by daily dose (≤ 1.5 Gy; 1.6–2.0 Gy).



Graph 5. Actuarial OS for 150 patients with HD by total dose in EFRT (≤ 20Gy, 21–25 Gy, 26–30 Gy, > 30 Gy).

In univariate analysis, independent risk factors are gender ($p < 0.001$), CS (IIB : IIIA) ($p = 0.03$), mediastinal involvement ($p = 0.03$), daily dose ($p = 0.01$) and total dose ($p = 0.02$). For the multivariate analysis performed using a Cox proportional hazards regression model, we have established that the independent risk factors age ≤ 15 years ($p < 0.001$), male gender ($p = 0.005$), daily dose ≤ 1.5 Gy ($p = 0.009$), and total dose 26–30 Gy ($p = 0.048$) are found to positively affect OS (Tab. 2). After analyzing the prognostic factors, we investigate a prognostic model, with OS as the primary end point, combining relevant prognostic factors as age ≤ 15 years ($p = 0.001$), male gender ($p = 0.011$), and total dose 26–30 Gy ($p = 0.012$) which appear to be protective factors (Tab. 3). The objective is to identify groups of HD patients with particularly responsive disease, based on the characteristics available at the time of diagnosis and treatment given.

We have not established SPM development during the 25-year observation period in any of the 120 HD patients who were followed-up by us and by means of NCR.

Discussion

The treatment of malignant lymphomas has improved dramatically. After the successful implementing of EFRT in the treatment of HD by Kaplan and Rosenberg in 1966, it has been acknowledged to be a standard therapeutic approach for a long historic period. Decades on end treatment strategies maximized the use of EFRT because historically it was considered the only curative method and less toxic than MOPP. Subsequently IFRT has been applied in RT practice still more intensively. The lessons from this period should not be limited to the awareness of the late toxic effects but the high effectiveness of EFRT as a sole or a part of combined treatment should also be recognized.

Regardless of the rather diverse opinions and statements concerning the applied involved and extended RT techniques in HD, during the last years some authors consider that EFRT leads to better OS and disease-free survival (DFS) compared to IFRT. This finding was validated in a metaanalysis conducted by Specht et al [3]. This study was based on combined data from almost 1974 patients with early-stage HD obtained from eight randomized trials. In comparing treatment with more versus less extensive RT, it was found that more extensive RT significantly reduced the risk of failure at 0 to 4, 5 to 9, and 10 or more years. There was a trend toward fewer HD deaths in the more extensive RT arm, although the difference was not statistically significant. Moreover, there was a slightly higher risk of death of causes other than HD with more extensive RT, although it was not significant.

However, it is an indisputable fact that CMT offers optimal treatment in HD. This is confirmed by the conducted metaanalysis combining 12 trials including 16 66 early-stage HD patients, on CHT plus RT compared with RT alone [3]. The results demonstrated that CMT significantly reduced the risk of failure by 53%

Tab. 2. Results of the multivariate analysis.

Characteristic	B	SE	Wald	df	OR	Hazard Ratio 95% CI	p-value
age > 15	0.136	0.038	12.453	1	1.45	1.062–1.235	**< 0.001**
gender (female)	1.404	0.435	8.048	1	4.073	1.544–10. 746	**0.005**
daily dose ≤ 1.5 Gy 1.6–2.0 Gy	1.311	0.499	6.910	3	3.709	1.396–9.855	**0.009**
total dose ≤ 20 Gy			7.906	3			**0.048**
21–25 Gy	–1.103	0.551	3.930	1	0.332	0.111–0.988	**0.047**
26-30 Gy	–2.164	1.081	4.008	1	0.115	0.014–0.956	**0.045**
> 30 Gy	–0.029	0.607	0.002	1	0.971	0.296–3.191	0.962

at 10 years from approximately one-third to approximately one-sixth. The absolute benefit appeared greatest in years 0 to 4, with significantly fewer recurrences also in years 5 to 9. This highly significant reduction in failure translated into only a borderline significant improvement in OS at 10 years.

Years on end the principal objective of RT in HD is to treat involved and contiguous lymph nodes to a dose associated with a high likelihood of tumor eradication [4]. The control on the contiguous spread of disease by application of extensive RT combined with CHT was determinative in our therapeutic strategy.

According to a number of clinical studies on the therapeutic potential of CMT including EFRT or IFRT and CHT in children with HD, the 10-year OS for the early stages varies from 85% to 97%, and for the advanced stages – from 70% to 90% [5–10]. The therapeutic results achieved by us for a quarter of a century provided comparable 5-, 10-, and 25-years OS relative to contemporary published modality regimens, for stage II–IV HD patients, 93% : 86% : 82%, respectively.

Advances in the treatment of HD have diminished the importance of prognostic factors. Yet, they are more important for defining therapy than in predicting outcome as well as, defining risk groups for patient stratification, and providing insight into the disease process e. g., natural history, biology.

Tab. 3. Prognostic model in patients with Hodgkin's disease.

Characteristic	Pc2	df	p-value
age	10.286	1	**0.001**
gender	6.509	1	**0.011**
total doses			
26–30 Gy	10.962	3	**0.012**

According to a number of clinical studies **age** appears to be a significant prognostic factor in HD. Although extremely rare, the cases with children younger than 4 years with HD are for example with exceptionally good prognosis [11]. According to the retrospective review at the Stanford University Medical Center 5- and 10-years OS in children at the age of up to 10 years of age, for adolescent 11–16 years of age and for adults with HD, is 94% : 92% vs 93% : 86% vs 84% : 73%, respectively [12]. Five- and 10-years OS for children ≤ 12 and > 12 years of age from our study 95% : 91% vs 91% : 81%, p = 0.17 correlate with those cited in reference literature.

Large series report a slightly worse outcome for men than for women [13]. An analysis, performed between 1969 and 1987 found that female **gender** was correlated with inferior DFS [14]. Klimm et al conducted a detailed analysis of 4 626 HD patients, of all prognostic risk groups, who were enrolled onto the multicenter studies HD4 to HD9 of the German Hodgkin Study Group [15]. The authors established that acute CHT-related hematotoxicity in women, especially more severe leucopenia are related with fewer relapses and deaths, leading to significantly better freedom from treatment failure (FFTF). In our study, without analyzing the hematological toxicity of the conducted CMT, we established the opposite – 4 times higher risk of lethal outcome for female gender, which turned out to be statistically significant.

Stage has a critical role in the selection of treatment. It determines the 90–95% probability for curing in the early-stage disease compared to the maximum 65–70% in the advanced disease stages [16–17]. In our study the risk of lethal outcome is significantly (up to 6 times) higher in the patients in the CS IIB compared to these in CS IIA but the difference does not reach statistical significance, p = 0.09. We have proved statistically significant difference only between CS IIB and IIIA – p = 0.03, in favor of the more advanced stage patients. The explanation of a similar result may be found in the problems

of the exact staging of the disease through the decades, especially with respect to the abdominal lymphnode and organ involvement and the ensuing from this possibility of certain sub-staging of patients and respective inadequate treatment in part of them. On the other hand, obviously the presence or absence of B symptoms may be also important as well as the difference in the conducted EFRT under the condition that no difference exists between the conducted CHT in patients with CS II and III of HD.

The analysis of **histologic subtypes** for the period 1968–2001 [12] carried out in the Stanford University on 2 116 patients with HD is also of special interest. It emphasizes the prevalence of the unfavorable histologic types and their more aggressive behaviour. As early as in the 90-ies of the past century it was assumed that histologic subtype was relevant, at least among adults [18]. It is known that the patients with lymphocyte predominant have radically different OS and DFS [19]. Nodular sclerosis is related to the more unfavorable prognosis but not according to all studies [20]. However, the last analysis of the United Kingdom Children's Cancer Study Group (UKCCSC) on 331 children with HD does not confirm the prognostic value of the histologic variant [21]. In our study we have established prevalence of the unfavorable histologic subtypes (90,6%), but we are not able to confirm any correlation of the histologic variant and the therapeutic outcome in HD.

The **disease bulk** is important, especially in the mediastinum. The availability of large mediastinal adenopathy determines the highest risk of relapse both after conducting independent RT and CMT [22–24]. The recent DAL-HD-90 trial, in which bulk disease did not influence survival, represents a special interest [25]. The possibility of realizing salvage CHT and higher RT doses in patients with large lymphnode or persisting after CHT formations has gradually changed the prognostic importance of this factor. In our study statistically significant better results were established for the patients without mediastinal involvement ($p = 0.04$).

It is considered that patients with a multitude (most often more than 3) clinically involved lymphnode formations have usually worse OS and RFS [26–28]. We have also established, although statistically insignificant, better results in the patients with fewer involved lymph node areas.

Systemic symptoms reflect biologic aggressiveness and confer a worse prognosis for HD [29–31]. In our material the patients "with" B symptomatics are with worse OS compared to those "without" similar symptoms, but the difference does not reach statistical significance. The presence of hepatosplenomegaly, as well as a number of laboratory tests as the levels of erythrocyte sedimentation rate (ESR), serum ferritin, hemoglobin level, serum albumin, LDH and serum CD8 antigen levels have been reported to predict a worse outcome [17,31–32]. In our study, OS for the patients "with" and "without" data for **hepatosplenomegaly**, **anemia** and **elevated LDH** do not differ significantly.

According to the available literature the problem of the **optimal daily dose** is not an issue of high scientific interest. In our study we established statistically better therapeutic results for a daily dose ≤ 1.5 Gy than for 1.6–2.0 Gy, $p = 0.01$. The lower daily dose found application in the younger age group. The higher dose was applied for the older patients, who in that case most often were in the puberty age, which was principally considered to be a higher risk one and with unfavorable prognosis. We accept the fact that the lower dose has a certain therapeutic potential in HD in child age. However, we consider that not only the treatment carried out, but also the biological characteristic of the disease in certain age groups are determinative for the final therapeutic result. The **optimal total dose** of RT in the complex approach to HD is not established. According to the early clinical studies 40 Gy are accepted as necessary for achieving 98% local tumor control [33]. In the last reanalysis of the dose dependence in HD there is no evidence for higher response when realizing doses above 32.5 Gy [34]. There are recent data from a randomized trial by the German Hodgkin Lymphoma Group (GHLG), in which patients (adults) with CS I and IIIA disease received 20, 30, or 40 Gy to nonbulky or uninvolved sites following 4 months of CHT. With these constraints, no difference has been observed for various doses [35]. Two German trials GHSC HD1 and HD5 also show that the realization of 40, 30 or 20 Gy EFRT after COPP/ABVD does not lead to statistically significant difference in OS and DFS [36–37]. In the analysis of 150 patients with HD, treated with CMT in our center, the total dose of 26–30 Gy exerted significant positive effect on the therapeutic results.

On the basis of the performed univariate analysis the gender, the mediastinal involvement, the daily and total dose magnitude have statistically significant effect on the achieved therapeutic results in 150 patients with HD. On the grounds of multivariate analysis we demonstrate that age, gender and total dose, can be used to construct a prognostic factor model that distinguishes patients with different degree of prognosis and different OS.

Adverse treatment consequences, including the development of second malignancies, appear to be more prevalent in patients with HD as compared to those with any other malignancies [38]. According to Ng AK et al after a period of 15 and 20 years increased risk is established in such patients of 2.3% and 4% per person per year and the cumulative risk is 15% [39]. It is accepted that RT leads mainly to secondary solid tumor development. They are manifested with a frequency of 5.8% after the 12th year – usually for a latent period from 9.5 to 12 years [40]. In a recently published metaanalysis, an IFRT versus EFRT (19 trials, 3 221 patients), there was no significant difference in secondary malignancy risk ($p = 0.28$) although more breast cancers occurred with EFRT ($p = 0.04$) [41]. In the investigated by us 120 patients with HD for cancerogenesis after delivered EFRT and CHT, no cases with SPM were established.

We support the standpoint of Cellai et al that the growing amount of data acquired on SPM after HD does not imply, by itself, simply "more reasons for less RT" [42]. The treatment should not be

reduced to such an extent that the general effectiveness would be compromised. In future the joint efforts of the multidisciplinary teams should be focused on searching optimal therapeutic approaches with minimal toxicity and late relapse, ensuring good quality of life and resocialization of millions of patients with malignant diseases.

Conclusion

The performed for the first time Bulgarian study on EFRT shows a certain therapeutic potential in the treatment of HD, expressed in the achieved high long-term outcome and low SPM frequency.

Age, mediastinal involvement, daily and total dose magnitude exert significant impact on the achieved therapeutic results in patients with HD.

On the basis of the multivariate analysis carried out, a prognostic model has been developed, which determines the risk of lethal outcome in patients with HD. The younger age, male gender and realization of a total dose of 26–30 Gy, appear to be protective factors.

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