

Long-term survival of patients treated for Hodgkin's disease in 1971–1996 depending on the clinical stage of the disease, patient's fertility after therapy and cause of death analysis

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The long-term survival in a group of 370 patients treated for Hodgkin's disease in the years 1971–1996 was retrospectively analyzed. Up to now 191 patients live, 179 patients have died.

Since the year 1978 the uniform diagnostic and therapy protocol has been used. The therapy consisted in the combination of a radiation therapy (usual dose 40 Gy) with the COPP chemotherapy (6 cycles). Since the year 1988 the alternation of the ABVD and COPP chemotherapy has been used. According to the stage of the Hodgkin's disease and the patient's age the modification of the therapy was introduced. One chemotherapy cycle was removed for each 10 years above the 50 year age of the patient. The radiation therapy was not applied to the areas of the reproductive organs in young patients to preserve their fertility.

The percentage of surviving patients for thirty years was 58.8% for Stage I and IIA,B and for Stage IIIA was 60.72%. In the group of surviving patients, we have registered 11 fathers and 34 females with up to 3 children. All together 75 children without health problems are monitored.

Keywords: Hodgkin's disease, therapy protocol, fertility, survival, causes of death

The team of authors has been engaged in Hodgkin's disease matter since the year 1971. In the year 1978 the study MORHO using the uniform diagnostic and therapy protocol was initiated on eight sites in the former Czechoslovakia [1]. In the year 1996 the team of authors was disbanded.

The aim of this study is to evaluate the long-term therapeutic results of the previous Hodgkin's disease treatment and to assess the effects of the therapy on the fertility of young patients. This study also includes the brief cause of death analysis of patients that underwent the Hodgkin's disease therapy.

Patients and methods

Altogether 370 patients were treated. The treatment was based on the combination of radiotherapy and COPP chemotherapy. Since the year 1988 the alternation of the ABVD and COPP chemotherapy has been used. We came out of the studies

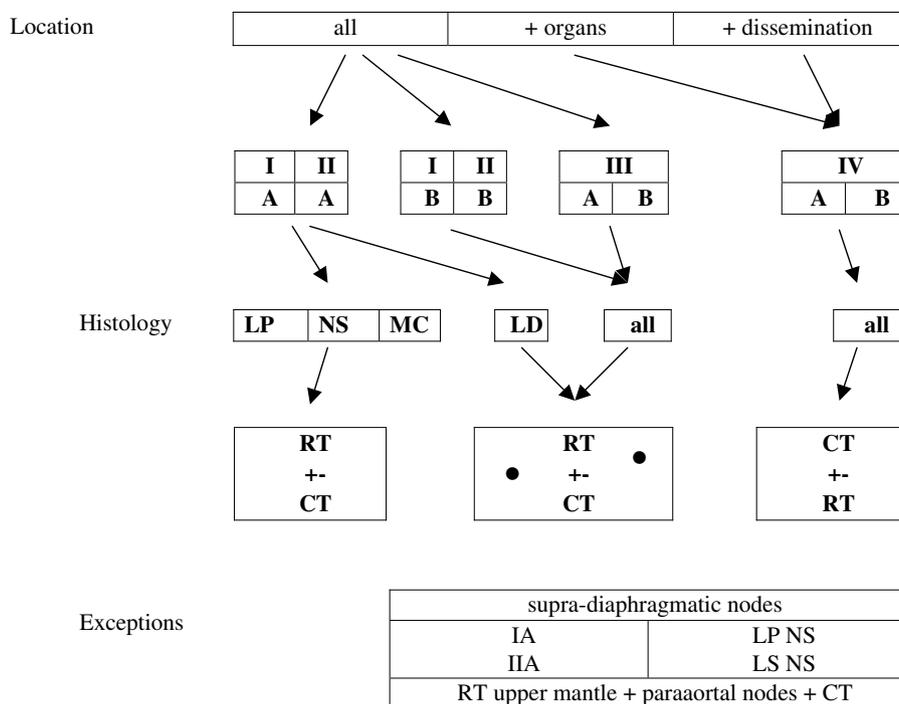
De Vita *et al* [2], Kaplan *et al* [3] and Bonnadona *et al* [4]. The therapy was modified in accordance with the clinical stage of the Hodgkin's disease, the histological type and the age of the patient. One chemotherapy cycle was removed for each 10 years above the 50 year age of the patient. For patients till 40 years of age, especially for females, the radiotherapy in the area of sub diaphragmatic nodes was applied only with a limited field covering para aortal and splenic nodes to umbilical level with the total dose not exceeding 40 Gy. We continuously published the results each 10 years [5].

The scheme of the treatment according to the protocol published in 1978 [1] is shown.

Young patients at the age of fertility that underwent the Hodgkin's disease therapy formed the group of parents in which they have been monitored after the therapy together with their born children.

Statistics. Statistical analysis was focused on the evaluation of the survival period at individual groups of patients. Classification criteria were clinical status, sex, age and the cause of death [6]. Groups of patients sorted according to the

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Scheme 1: Scheme of the treatment according to the protocol published in 1978.

mentioned factors were standardly evaluated with the Kaplan-Meier method and then on the base of their survival curves. The differences in survival curves were assessed to be significant at a 5% level with the generalised log-rank test. At the same significant level of differences in each couple of survival curves was tested with Cox-Mantel test. For the calculations the software STATISTICA 7.0 was used [7].

Results

Whole group of patients is characterized in the following Tables and Graphs.

Stage I was not assessed separately due to small number of patients, as our patients were largely in advanced Hodgkin's

Table 1: Initial group of patients.

group of patients	all	female	male	surviving	dead
number	370	172	198	191	179

Table 2: Frequency structure of the group of patients assorted according to sex and clinical stage.

Clinical stage	female	male	all	Clinical stage	female	male	all
I A	2	8	10	II A	64	46	110
I B	3	2	5	II B	25	22	47
I	5	10	15	II	89	68	157
III A	38	43	81	IV A	5	7	12
III B	20	46	66	IV B	15	24	39
III	58	89	147	IV	20	31	51

Table 3: Survival of patients according to sex and clinical stage.

Survival years	male			female		
	II	III	IV	II	III	IV
5	79.17	71.86	37.75	85.19	80.53	14.68
10	66.02	61.14	31.91	73.42	71.63	9.34
20	58.52	41.55	5.09	64.28	63.7	9.76
30	51.6	0	0	63.7	63.7	0

Table 4: Portion of the surviving patients according to clinical stage and regardless of their sex.

Survival years	II		III		IV	
	A	B	A	B	A	B
5	84.29	76.07	81.79	66.8	25.06	27.78
10	75.01	62.87	76.44	50.01	24.51	22.32
20	65.0	57.86	61.08	36.78	0	8.61
30	59.29	57.86	60.72	36.78	0	0

disease stage, mostly being sent to us from the pulmonary clinics. The patients in clinical Stage I were born in between years 1928-1950 and in the time of the Hodgkin's disease diagnosis they were from 28 to 74 years old. The period from their diagnosis up to present is in the interval of 10-39 years. The age composition and the small number of patients in this group were reflected in the survival curves.

Therefore we used the possibility of making the selection of data in groups IIA and IIB accidental. The group formed by connection with cases IA and IB built the consistent data set which satisfied the parameters for applying the method ANOVA [8]. With the plural repeating of this procedure we concluded that the survival time in between Stages IA and IB significantly differs ($p=0.0034$). Other differences in these groups accidentally made have not been significant.

This study shows that percentage of patients in Stages IIA, IIB and IIIA that survive 30 years is 59.29, 57.86 and 60.72 %, respectively. Stage IIIB patients survive 30 years in 36.78% whereas patients in Stages IVA and IVB survive 10 years in 24.51% and 23.32%, and 20 year survival for Stage IVB patients is 8.61%. Females survive longer than males. Histological type did not affect the survival time of patients; the main criterion was the clinical stage.

By the date of this study processing, 179 of the long-term-monitored patients that were treated according to the protocol MORHO have died. We have recorded 55 cases of relapse consisting of 39 males and 16 females. In 64% of relapse cases the patients were in Stage III and IV, respectively and in 78% of relapse cases the mediastinal nodes were affected. Till one year after the therapy 42% of relapse cases occurred.

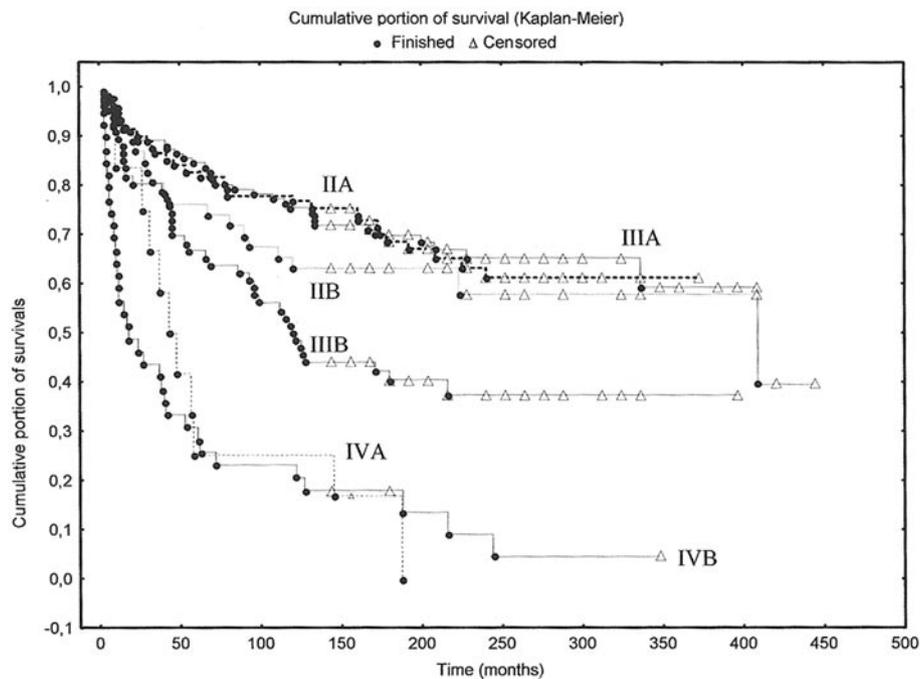


Fig. 1: Survival of patients according to clinical stages IIA – IVB.

Table 5: Results of the Cox-Mantel test comparing the survival curves according to the clinical stage and sex. Above the table main diagonal (field XXX) the p-test value is given, followed by the statistical result below it. (+ difference, - conformity).

	Male			Female		
	II	III	IV	II	III	IV
II	XXX	0.08664	0.00000	XXX	0.78605	0.00000
III	-	XXX	0.00011	-	XXX	0.00000
IV	+	+	XXX	+	+	XXX

Table 6: Statistical significance of differences in survival time in between clinical stages A and B.

	IIA	IIB	IIIA	IIIB	IVA	IVB
IIA	XXXX	0.12486	0.73134	0.00008	0.00000	0.00000
IIB	-	XXXX	0.19339	0.11910	0.00065	0.00000
IIIA	-	-	XXXX	0.00106	0.00000	0.00000
IIIB	+	-	+	XXXX	0.01210	0.00001
IVA	+	+	+	+	XXXX	0.60600

By the cause of death analysis of 179 patients we have found that 59.2% of patients died due to the original disease generalization in the period of 3-450 months after the therapy initiation, 17.1% of patients (31 patients) died of secondary tumours and 25.8% of patients (46 patients) died because of cardio-vascular and other complications. From secondary malignancies there was the most frequent incidence of bronchogenic carcinoma (8x) and NHL (Non-Hodgkin lymphoma) (4x).

In Table 7, the initial numbers of patients according to their sex and cause of death are given. The Graph 2 shows the cumulative survival of patients who died of original disease generalisation, of secondary malignancies, or of cardio-vascular and other complications, respectively. The cause of death in 59.2% of patients with HD was the generalisation of the original disease in the period of 3 months to 22 years after the therapy.

Young female patients underwent radiotherapy of lymph nodes in lower quadrant (etage) decreased on retroperitoneal area corresponding with the involved field (IF). Aim of the decreased field was not to harm reproduction capability. In the surviving group there are currently recorded 34 females

Table 7: Causes of death, G – generalisation of HD, D – secondary malignancies, J – cardio-vascular and others complications.

Cause of death	all dead patients	male	female
G	106	65	41
D	27	18	9
J	46	26	20
total	179	109	70

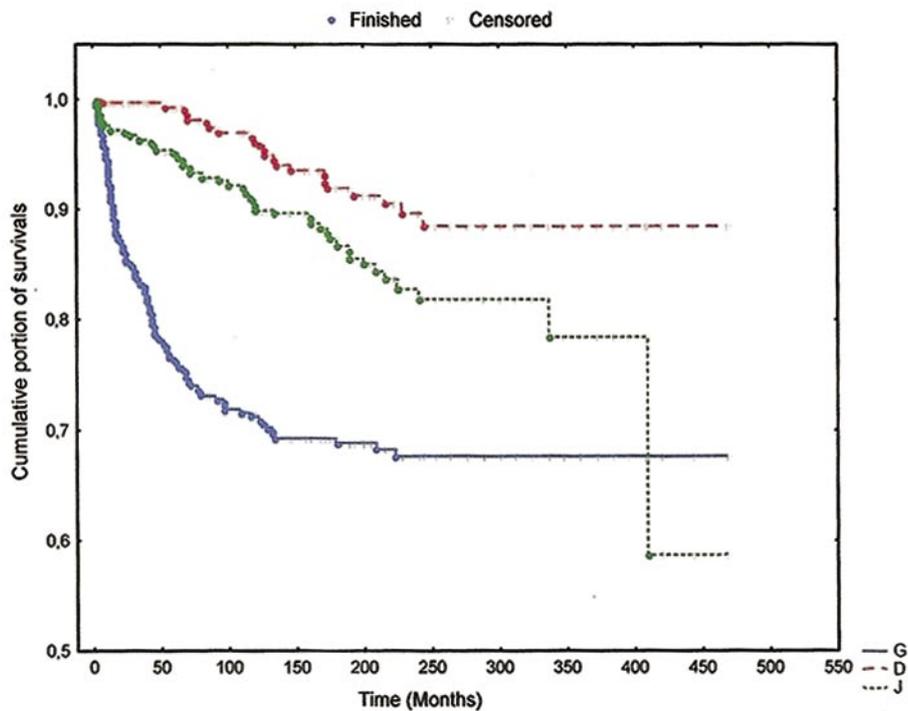
who gave a birth to one to three children and 11 males who became fathers of one and more children. All together the group includes 75 children. The offsprings born before the therapy indication was not calculated into the group of children of patients.

The age of future parents by the time of terminating their Hodgkin's disease therapy was between 10 years (therapy was applied at their child age) to 28 years. The period between the therapy termination and the birth of the child is within 42 to 263 months. 38 boys and 32 girls were born, the sex is unknown for 5 children yet. Two more female patients were pregnant during the data processing of this study.

In the group of children one case of phocomelia occurred which the geneticist did not refer to underwent therapy and allowed next pregnancy which resulted into the birth of a healthy child. Not all pregnancies, however, were successfully terminated with a birth. Seven times there was spontaneous abortion, three times miscarriage (1 dead fetus abortion, two miscarriages at the same patient after genetic investigation) and 1 child was born with Down syndrome, dying one day after birth. Next gravidity of the same patient resulted in a healthy daughter birth.

Table 8 includes characteristics of group of parents, numbers of patients and frequencies of the individual clinical stages.

In the surviving group of patients-parents, there were altogether 26 cases of original disease relapse after the primary therapy, from that 5 cases were multiple relapses. After the therapy, the CR or PR and stabilization of the Hodgkin's disease was reached. One of the fathers died of the acute myocardial infarct, while having repeated therapy of his original disease relapse in his anamnesis (8). In Table 9, the summary of the applied chemotherapy cycles is shown.



$$\chi^2 = 67,0912, p < 0,00001$$

Fig 2: Portion of the dead patients according to their cause of death.

Table 8: Characteristics of the group of parents.

clinical stage	II	III	IV			
number of patients	25	19	1			
%	55,6	42,2	2,2			
acc. to B symptoms	IIA	IIB	IIIA	IIIB	IVA	IVB
number of patients	22	3	12	7	0	1
%	48,9	6,7	26,7	15,6	0	2,2

Table 9: Summary of the applied chemotherapy cycles.

number of applied chemotherapy cycles	2	3	4	5	6	>6	chemotherapy of relapses
number of patients	2	10	3	7	22	2	7
%	4,3	21,7	6,5	15,2	47,8	4,3	15,2

Discussion

Therapy of the Hodgkin's disease according to the protocol established by the team of specialists participating on the MORHO project is comparable to the simultaneous therapy applied at different institutes abroad. It meant an outstanding development in the disease therapy in previous Czechoslovakia, especially after unification of the therapy protocol. The

treatment of Hodgkin's disease changed from mere palliation into real healing. The essential contribution of the medical team consisted in the liberalization of the medical approach to the fertility of patients. The evidence is 75 healthy children of the patients despite the complications with some pregnancies.

In conclusion, from the total number of treated patients it is evident that therapy combinations of the protocol MORHO

have enabled long term (almost 30 years) survival of patients. Obtained long-term survivals of patients with Hodgkin's disease in Stages IIA, IIB and IIIA are in accordance with similar studies. Percentage of thirty year survival of patients in Stages IIA, IIB and IIIA was 59.29, 57.86 and 60.72 %, respectively. We did not prove the effect of the histological type on the survival of the patients. The observed differences are according to the statistical analysis only accidental divergences of the patient survival. The 30 year survival of patients with Stage IIIB was 36.78%. Patients classified as a Stage IVA survived 10 years in 24.51% and as a Stage IVB in 22.32%. When the age of surviving patients was analyzed, the age group till 31 years was found reduced whereas the age group of 49-61 years in males was found increased in comparison with the age histograms of the whole group of patients. In the long term interval more females survived.

The composition of our patients group was affected due to the fact that patients were coming mostly from the pulmonary clinics having more frequent mediastinal tumors.

Cooperation of eight sites in the Czech Republic has proved to be very beneficial and has brought significant turnover towards the therapy of the Hodgkin's disease. The principle was that, it has not been any randomized study, but an introduction of approved methods to the clinical practice.

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