Longterm treatment results of childhood medulloblastoma by craniospinal irradiation in supine position

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Medulloblastoma, a primitive neuroectodermal tumor growing in cerebellum, is one of the most sensitive to radiation therapy childhood brain tumors. The radiotherapy is an essential method of treatment for these tumours, but the surgery is the primary treatment of choice in medulloblastoma. I this study between January 1997 and March 2005 were post-operative irradiated a total number of 33 pediatric patients aged under 15 years (median age 8.7 years) with medulloblastoma. All tumors were histologically proved and were localizated infratentorially in the posterior fossa. All of the patients were irradiated with a dose of 24-36 Gy to the whole craniospinal axis and boost with conformal therapy restricted to the tumor bed to the total dose of 50-54 Gy (30-36 Gy "high risk", 24-30 Gy "standard risk" group). Chemotherapy received 26 patients (78%). Patients with craniospinal irradiation were placed in supine position and fixed by a vacuum-form body immobilizer and head mask. Irradiation was performed using standard fractionation (5 fractions per week) with a single dose of 1.5-1.8 Gy for craniospinal axis by photon beam (6 MV) of the linear accelerator. The median overall survival for the whole group was 55.3 months. The median of disease-free survival was 20.6 months, 8 patients (24%) died. In our study the statistical difference in survival rate between standard and high-risk patients with medulloblastoma was not shown. No relationship was found between survival and age, sex or tumor size. Endocrine deficits occurred in 45% (8 patients of the group were hypothyroid, 6 patients needed growth hormone replacement therapy, 1 patient had early puberty). This results (results of overall and disease-free survival) and side-effects of technique of craniospinal axis irradiation in supine position are comparable with results of technique in prone position. Further evaluation of the effectiveness of our therapy is not feasible due to the small number of patients.

Key words: medulloblastoma, radiotherapy, craniospinal irradiation

The most common malignant CNS tumor in childhood is medulloblastoma with an overall incidence among children aged 0-19 years of 16-20% of all pediatric brain tumors. Medulloblastoma, a primitive neuroectodermal tumor growing in cerebellum, is one of the most sensitive to radiation therapy of all childhood brain tumors. The radiotherapy is an essential method of treatment for these tumors, but the surgery is the primary treatment choice. The using of the combination of treatment modalities is prefered in the treatment of medulloblastomas, ependymomas and gliomas. Postoperative radiation therapy has significant impact on the local control and the overall survival. In general, postoperative radiotherapy has been reported to improve the outcome. Meta-analyses of patients with medulloblastomas irradiated postoperatively revealed prolongation of the 5-year survival rate in 60% cases. Radiotherapy is a very effective treatment for medulloblastoma, but it also damages the surrounding disease-free brain. Craniospinal irradiation (CSI) is necessary in the treatment of medulloblastoma, although it results in significant long-term sequelae, particularly in young children. The impact of technical quality of radiation therapy on survival was recently considered [1,2,3].

Patients and methods

Between January 1997 and March 2005 a total number of 33 pediatric patients aged under 15 years (median age 8.7 years) with medulloblastoma were irradiated in the Department of Radiation Oncology, Masaryk Memorial Cancer Institute in Brno. Surgical resection was performed in all patients. All tumors were histologically proved and were localizated infratentorially in the posterior fossa. Detailed characteristics

of the patients are shown in table (Table 1). All of the patients were irradiated with a dose of 24-36 Gy to the whole craniospinal axis and boost with conformal therapy restricted to the tumor bed to the total dose of 50-54 Gy (30-36 Gy "high risk", 24-30 Gy "standard risk" group). In cases with residual tumor a total irradiation dose up to 54-56 Gy was delivered. Postoperative chemotherapy received 26 patients (78%).

Definition of planning target volume for craniospinal irradiation 1) whole brain: this volume encompass the whole brain with 1 cm safety margin. The lower limit of the frontal area must be 5 mm below the frontal sinus and 1 cm below the temporal lobes. The margin of 5 mm are required in front of vertebra C_2. 2) spinal axis: in the inferior limit must includevertebra S_{2-4}. The lateral safety margin of 5 mm is required regarding lateral process. ICRU 50 point of whole brain is in centre of the target volume and of spinal axis is in centre of medullar cord. Treatment planning was based on a series of about 30-40 consecutive CT slices. The use of three-dimensional treatment planning is a standard therapeutic method.

In whole brain and cervical spine irradiation (with the caudal border between C_3-C_4 vertebras), two opposite lateral fields were chosen with shielding blocks of the eye bulbs; the spinal cord was irradiated with two direct posterior fields (Fig. 1). After reaching 33% and 66% of the planned dose, the size and the borders of the adjacent fields in the area of the spine were modified (Fig. 2). It was necessary to include the whole vertebral volumes in the irradiated volume in order to diminish the risk of postirradiation scoliosis of the spine. Patients were placed in supine position and fixed by a vacuum-form body immobilizer and ORFIT head mask. The use of the vacuum-form body immobilizer caused the 1-2% decrease of applied depth dose. This irradiation technique caused a tolerable increase of the superficial skin dose with regard to the total dose applied to the planning target volume. Irradiation

Table 1. Clinical charakteristics of children with medulloblastoma.

Gender	male	66.7%
	female	33.3%
Age	median	8.7 years
	mean	8.8 years
Children under 3 years		15.2%
Extent of resection	total	42.4%
	subtotal	39.4%
	less than subtotal	18.2%
Chang T	T1	3.0%
	T2	9.1%
	T3a	39.4%
	T3b	30.3%
	T4	18.2%
Chang M	M0	69.7%
	M1-3	30.3%
Histological subtype	"classic"	69.7%
	desmoplastic	18.2%
	large cell	6.1%
	unknow	6.1%

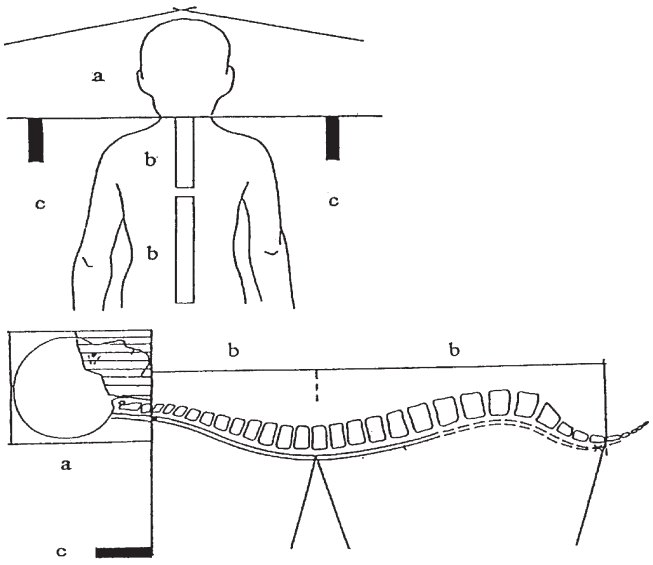


Figure 1. Modified technique of craniospinal irradiation with the use of two opposite lateral fields (individual shielding blocks of the eye bulbs and the face part of the skull (a), and two direct fields (b), with the use of the asymmetric jaws. Linear accelerator, X-ray, 6 MV (c).

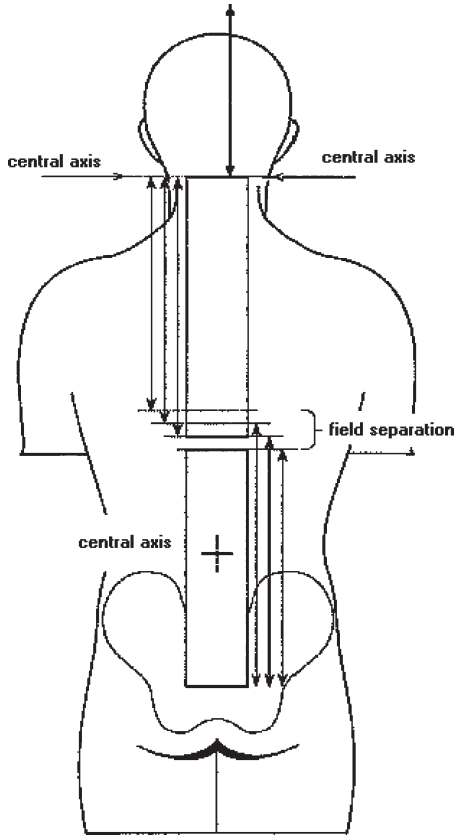
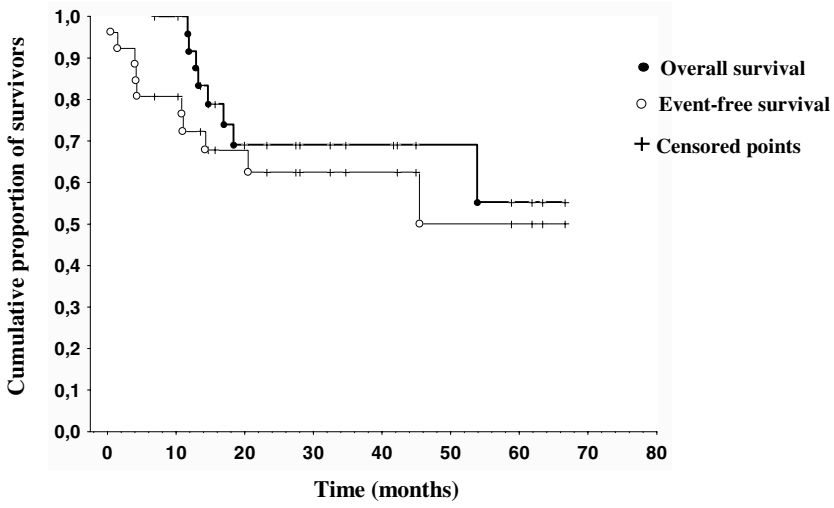


Figure 2. The radiation fields – scheme of the changes of the size. After reaching 33% and 66% of the planned dose, the size and the borders of the adjacent fields in the area of the spine were modified.



Slampa -FIGURE 3

Figure 3. Kaplan-Meier curves of overall and disease-free survival (months) of 33 patients with medulloblastoma.

was performed using standard fractionation (5 fractions per week) with a single dose of 1.5-1.8 Gy for craniospinal axis by photon beam (6 MV) of the linear accelerator. It was necessary to determine exactly the position of the child on the treatment table with the help of laser beams and the optical pointer of the irradiation device.

A value $\alpha<0.05$ was taken as a universal indicative limit for statistical significance in all analyses. Standard descriptive statistics were used to express differences among subgroups of cases, namely robust statistics like median and MIN/MAX values. Standard univariate statistical techniques were used to test differences between chosen subgroups of patients: M-L chi-square test for binary or ordinal categorical variables and Kruskal-Wallis rank test continuous scales. Kaplan-Meier product-limit method was applied to describe survival rates and to discriminate them among two or more subgroups. Peto-Prentice generalized log-rank test was used as comparative statistical test [4,5].

Results

Prescribed dose of irradiation was delivered to all patients; dose reduction was unnecessary in any case. In March 2005 (date of evaluation) 17 out of 33 patients (51,5%) remain without any sign of disease, one patient has local relapse. Six patients (18%) present significant neurological symptoms. The local relapse occurred in 3 patients (9%). The local relapse with spinal metastases were described in 5 patients (15%) and metastases outside of CNS in two patients. (Table 2).

Radiotherapy was well tolerated. Skin reactions were mild in most patients: WHO grade 1 in 33 (100%) patients and grade 8 in two (24%) patients (in areas of ears). Within three months after the completion of radiotherapy these reactions disappeared. The gastrointestinal and haematological toxicities were mild to moderate in all patients (WHO 1-2 gr.), but none grade 3. Leucopenia grade I was in 70%, grade II 18%, trombocytopenia grade I in 35%, diarrhoe grade I 47% and grade II 23%, nausea in 36%.

The median overall survival for the whole group was 55.3 months. The median of disease-free survival was estimated as 20.6 months (Fig. 3), 8 patients (24%) died. These patients died of local failure. Graphical comparison of event free survival and overall survival specifically showed prolonged overall survival in the region of early risk events (early relapses and/or progression that occur in early phase of follow-up). In our study the statistical difference in survival

Table 2. Results of treatment in children with medulloblastoma (33 patients).

without sign of disease	51.5% (17 patients)
local relapse	9% (3 patients)
local relapse + spinal metastases	15% (5 patients)
metastases outside of CNS	6% (2 patients)
overall survival (median)	55.3 months
disease-free survival (median)	20.6 months
dead	24% (8 patients)
neurological symptoms	18% (6 patients)
endocrine deficits	45% (15 patients)
hypothyroidism	24% (8 patients)
deficit of growth hormone	18% (6 patients)
early puberty	3% (1 patient)

Table 3. Association between dose on CS (Gy) and therapeutic response.

Dose on CS	Categories of therapeutic response		
Primary data			
	Complete remission	*Partial remission*	*Progression*
24 Gy	N = 5	N = 1	N = 1
30 Gy	N = 6	N = 4	N = 0
36 Gy	N = 2	N = 5	N = 1
Aggregated categories[1]			
	Complete remission	*Partial remission + Progression*	
24 Gy	N = 5 (71.4 %)	N = 2 (28.6 %)	
> 24 Gy	N = 8 (44.4 %)	N = 10 (55.6 %)	

[1] Data were aggregated in order to document most visible asymmetry in the reached categories of therapeutic response. Although not exactly statistically significant (p = 0.221; M-L Chi-square test), the accumulation of CR category after dosage of 24 Gy is apparent.

rate between standard and high-risk patients with medulloblastoma and association between dose on CS (Gy) and therapeutic response was not shown (Table 3). No relationship was found between survival and age, sex or tumor size. Endocrine deficits occurred in 45%, 8 patients of the group were hypothyroid, 6 patients needed growth hormone replacement therapy, 1 patient had early puberty (Table 4).

Table 4. Association between dose on CS (Gy) and incidence of subsequent chronic effects.

Dose on CS	Incidence of chronic effects		
		According to type of the effect	
	Total	*Growth problems*	*Hypothyreosis*
24 Gy	N = 3 (42.9 %)	N = 1 (14.3 %)	N = 2 (28.6 %)
30 Gy	N = 5 (45.5 %)	N = 4 (36.4 %)	N = 3 (27.3 %)
36 Gy	N = 3 (37.5 %)	N = 2 (25.0 %)	N = 1 (12.5 %)
Statistical difference[1]	p = 0.941	p = 0.568	p = 0.672

[1] Statistical significance of differences among different dosage categories (M-L Chi-square test)

Discussion

Until recently, the standard care for patients with average disease risk consisted of postoperative radiotherapy to a dose to the craniospinal axis of 35-36 Gy followed by a boost to the entire posterior fossa to a total dose of 54-55 Gy. In multi-institution studies, such treatment results in long-term event-free survival were in aproximately 60-65% of patients [1,3,7]. Two cooperative groups tested the efficacy of reduced-dose in radiotherapy with average risk medulloblastoma. In SIOP II study with a double randomization were eligible patients with all stages and were randomized between standard dose (35 Gy) and reduced dose (25 Gy) for craniospinal irradiation. Overall, event-free survival at 5 years for patients who received standard dose CSI with or without chemotherapy was 60% as compared with 69% for those treated with reduced dose CSI [6].

The Pediatric Oncology Group (POG, 8631) and Children´s Cancer Study (CCG-923) at 1986-1990 years were randomized also between to standard craniospinal radiotherapy and a dose of 36 Gy and a dose of 23.4 Gy. Event-free survival at 5 years for patients who received standard dose was 67% and 52% for patients with reduced dose [7]. In PNET-3 study (1992-2000) is more intensive pre-radiotherapy chemotherapy. The CSI was 35 Gy. At 3 years, event-free survival for patients treated with radiotherapy alone was 64.2% as compared with 78.7% for patients treated with pre-radiotherapy chemotherapy [1,8].

For patients with high stage disease a randomized phase III study in Europe and North America has been used of pre-radiotherapy chemotherapy. In CCG-921 trial that opened in 1986 were randomized and the significant survival advantage was in the group that received post-radiotherapy chemotherapy (63% vs. 45%) [9]. In the German study (HIT´91) was compared pre- and post-radiotherapy chemotherapy. Pre-radiotherapy chemotherapy was highly effective, yielding a complete response in 56.5% and a partial response in 17.4% of patients with residual tumor [10]. In our study differences for patients with pre- and post-radiotherapy chemotherapy were not evaluated.

Overall ten-year survival rates in series that include patients with all stages of disease are approximately 40-50%. Factors that correlate with outcome include the presence or absence of cerebrospinal fluid seeding at diagnosis, the completeness of surgical resection, and age at diagnosis [1,11,12].

The age at diagnosis is also of prognostic value. In general, the outcome of children aged over 3 years is significantly better compared to younger patients. Children younger than 3 years have markedly poorer outcomes. Younger children more commonly present with metastatic disease and they do not commonly receive conventional doses of craniospinal radiotherapy [13,14]. In our study the difference in survival rate for patients with medulloblastoma between survival and age, sex or tumor size was not observed.

The risk of chronic postirradiation changes can be diminished by hyperfractionated radiotherapy (twice a day at a lower dose), but this method of irradiation has not been routinely used so far. Hyperfractionated irradiation, however, increases the risk of severe acute and subacute changes in the brain tissue (haemorrhages, necroses). Hyperfractionated radiation has not been shown to hold any benefit over conventionally fractionated radiation [15,16].

Intensity modulated radiation therapy (IMRT) is a modern conformal technique that employs energy beams shaped by dynamic multi-leaf collimators to deliver radiation to a tightly defined area, with the goal of reducing normal tissue radiation exposure. One of the main benefits of IMRT use in therapy of medulloblastoma is avoidance of cochlear irradiation and the resulting hearing loss [17].

Patients are usually treated in prone position which is not as comfortable, reproducible, or as easily maintained as supine position. To minimize anaesthesia-related risks, irradiation in supine position would be preferable to standard prone position. Treatment in supine position would be more comfortable for adult patients as well [18,19,20,21].

The cognitive deficits induced by cranial irradiation are delayed in onset, then progressive over 3 to 5 years and vary with neuro-developmental status, radiation dose and volume. Endocrine deficits occurred in 61%, neurological complications in 72%, and significant school problems in 72%. All patients had significant deficits in neurocognitive functioning: attention and processing speed was impaired in 79%, learning and memory in 88%, language in 56%, visual perception in 50%, and executive functions in 64% [22]. In our study this treatment sequelae was not evaluated.

Growth failures is the most common form of neuro-endocrinologic dysfunction as a sequelae of craniospinal

irradiation. Another common effect of craniospinal irradiation's hypothyroidism [23,24]. Number of growth failures and hypothyroidism in our study were comparable and hearing deficits were not shown.

In the study of the 5-year recurrence-free survival rate of patients with all optimal quality controls of histology, radiology, and radiotherapy Oyharcabal-Bourden et al. [25] was induced in 71.8%+/-10.5%. In terms of sequelae, 31% of patients required growth hormone replacement therapy and 25% required special schooling.

In conlusion the irradiation of the craniospinal axis is a part of the treatment of a number of malignant diseases. Patients are usually treated in prone position which is not as comfortable, reproductable, or as easily maintained as supine position. Acute skin, haematological and gastrointestinal reactions were comparable with those in patients irradiated in prone position. To minimize anaesthezia related risks irradiation in supine position would be preferable to standard prone position. Treatment in supine position would be more comfortable for adult patients as well. This results (results of overall and disease-free survival) and side-effects of technique of craniospinal axis irradiation in prone position are comparable with results of technique in supine position. Further evaluation of the effectiveness of our therapy is not feasible due to the small number of patients.

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