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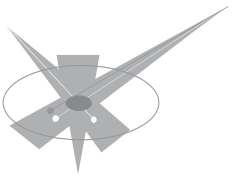

Original Paper

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Craniospinal irradiation of medulloblastoma in the supine position

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background Medulloblastoma, a primitive neuroectodermal tumour growing in the cerebellum, is one of the most sensitive childhood brain tumours to radiation therapy. The most common malignant CNS tumour of children is medulloblastoma with an overall incidence among children aged 0–19 years of 16–20% of all paediatric brain tumours. Radiotherapy is an essential method of treatment for these tumours, but surgery is the primary treatment of choice in medulloblastoma. Postoperative radiation therapy has a significant impact on local control and overall survival.

Aim Medulloblastoma is the most common malignant brain tumour of children. The tumour is sensitive to chemotherapy and radiotherapy. Radiotherapy is an essential method of treatment for these tumours, but surgery is the primary treatment of choice in medulloblastoma.

Materials/Methods Between January 1997 and March 2005 there were in this study post-operatively irradiated a total number of 33 paediatric patients aged under 15 years (median age 6.6 years) with medulloblastoma. All tumours were histologically proven and were located infratentorially in the posterior fossa. All of the patients were irradiated with a dose of 24–36Gy to the whole craniospinal axis and boost with conformal therapy restricted to the tumour bed to the total dose of 50–54Gy (30–36Gy "high risk", 24–30Gy "standard risk" group). 26 patients (78%) received chemotherapy. Patients with craniospinal irradiation were placed in the 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 1.5–1.8Gy for craniospinal axis by photon beam (6MV) of the linear accelerator.

Results The median overall survival for the whole group was 55.3 months. The median disease-free survival was 20.6 months. The overall survival rate at 5 years was 41%; 8 patients (24%) died. No relationship was found between survival and age, sex or tumour size. Endocrine deficits occurred in 30% (8 patients of the group were hypothyroid, growth retardation occurred in 7 patients).

Conclusions Results of overall and disease-free survival and side-effects of the technique of craniospinal axis irradiation in supine position are comparable with results of the technique in prone position.

Key words medulloblastoma • radiotherapy • craniospinal irradiation

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Background

Medulloblastoma, a primitive neuroectodermal tumour growing in the cerebellum, is one of the most sensitive childhood brain tumours to radiation therapy. The most common malignant CNS tumour of children is medulloblastoma with an overall incidence among children aged 0–19 years of 16–20% of all paediatric brain tumours. Radiotherapy is an essential method of treatment for these tumours, but surgery is the primary treatment of choice in medulloblastoma. Postoperative radiation therapy has a significant impact on local control and overall survival. Meta-analyses of patients with medulloblastomas irradiated postoperatively revealed prolongation of the 5-year survival rate in 60% of cases. Craniospinal irradiation 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 [1–7].

Aim

Medulloblastoma is the most common malignant brain tumour of children. The tumour is sensitive to chemotherapy and radiotherapy. Radiotherapy is an essential method of treatment for these tumours, but surgery is the primary treatment of choice in medulloblastoma.

Materials and Methods

Between January 1997 and March 2005 a total number of 33 paediatric patients aged under 15 years (median age 6.6 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 tumours were histologically proven and were located infratentorially in the posterior fossa. Detailed characteristics of the patients are shown in the table (Table 1). All of the patients were irradiated with a dose of 24–36Gy to the whole craniospinal axis and boost with conformal therapy restricted to the tumour bed to the total dose of 50–54Gy (30–36Gy "high risk", 24–30Gy "standard risk" group). 26 patients (78%) received post-operative chemotherapy.

Definition of planning target volume for craniospinal irradiation: 1. Whole brain: this volume encompasses the whole brain with 1cm safety margin. The lower limit of the frontal area must be 5mm below the frontal sinus and 1cm below the temporal lobes. A margin of 5mm is required in front of vertebra C_2. 2. Spinal axis: in the inferior limit must be included vertebrae S_{2-4}. A lateral safety margin of 5mm is required regarding the lateral process. The ICRU 50 point of the whole brain is in the centre of the target volume and of the spinal axis is in the centre of the 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 vertebrae), two opposite lateral fields ere chosen with shielding blocks of the eye bulbs; the spinal cord was irradiated with two direct posterior fields (Figure 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 (Figure 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 the supine position and fixed by a vacuum-form body immobilizer and Orfit head mask (Figure 3). Use of the vacuum-form body immobilizer caused a 1–2% decrease of applied depth dose. This irradiation technique caused a tolerable increase in the superficial skin dose with regard to the total dose applied to the planning target volume. Irradiation was performed using standard fractionation (5 fractions per week) with a single dose of 1.5–1.8Gy for craniospinal axis by photon beam (6MV) of the linear accelerator. It was

Table 1. Clinical characteristics 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%
	unknown	6.1%

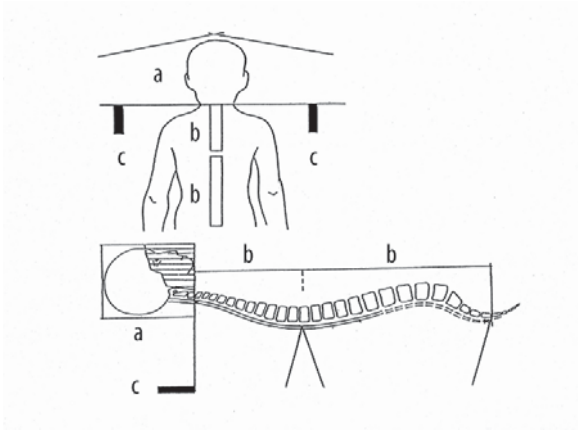

Figure 1. Modified technique of craniospinal irradiation using two opposite lateral fields (individual shielding blocks of the eye bulbs and the face part of the skull (a), and two direct fields (b), using the asymmetric jaws. Linear accelerator, X-ray, 6MV (c).

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.

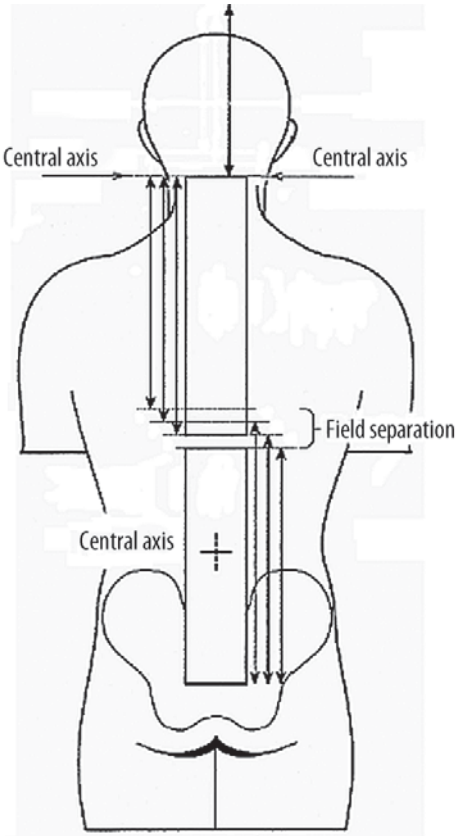

Figure 2. The radiation fields – scheme of changes of size. After reaching 33% and 66% of the planned dose, the size and the borders of the adjacent fields in the area of the spine were modified.

Figure 3. Supine position and fixed by a vacuum-form body immobilizer and Orfit head mask for patients with craniospinal irradiation.

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.

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	30% (10 patients)
Metastases without CNS	6% (2 patients)
Overall survival (median)	55.3 months
Disease-free survival (median)	20.6 months
Overall survival rate	(5 y) 41%
Dead	24% (8 patients)
Neurological symptoms	18% (6 patients)
Endocrine deficits	30% (10 patients)
hypothyreosis	24% (8 patients)
growth retardation	21% (7 patients)
deficit of growth hormone	6% (2 patients)

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 a comparative statistical test [8,9].

Results

The prescribed dose of irradiation was delivered to all patients; dose reduction was not necessary in any case. In March 2006 (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. Local relapse occurred in 3 patients (9%). Local relapse with spinal metastases was described in 10 patients (30%) and metastases without CNS in two patients (Table 2).

Radiotherapy was well tolerated. Skin reactions were mild in most patients: WHO grade I in 33 (100%) patients and grade II in 8 (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 I-II gr.), but none grade III. Leucopenia grade I was in 70%, grade II in 18%, trombocytopenia grade I in 35%, diarrhoea grade I in 47% and grade II in 23%, nausea in 36%.

The median overall survival for the whole group was 55.3 months (Figure 4). The median disease-free survival was estimated as 20.6 months. 8 patients (24%) died; these patients died of local failure. Overall survival stratified according to radiotherapy dosage on craniospinal area is better for dose 24Gy ("standard risk" group) (Figure 5). 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 the early phase of follow-up). In our study the statistical difference in survival 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 tumour size. Endocrine deficits occurred in 30% (10 patients in all: 8 patients of the group were hypothyroid, 7 patients are in growth retardation, 2 patients needed growth hormone replacement therapy, 1 patient had early puberty). The association between dose on CS (Gy) and incidence of subsequent chronic effects is shown in the table (Table 4).

Discussion

Postoperative morbidity has been significantly reduced by the introduction of microsurgical techniques. Based on previous retrospective studies, showing a rather high risk of local recurrence or cerebrospinal fluid dissemination, postoperative radiotherapy is recommended after surgical treatment of medulloblastomas [2–4].

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

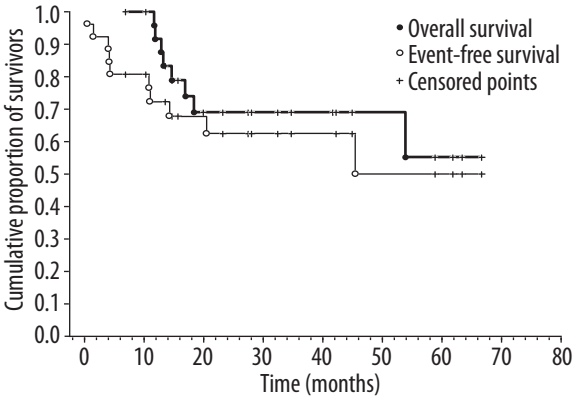

Figure 4. Kaplan-Meier curves of overall and disease-free survival (months) of 33 patients with medulloblastoma.

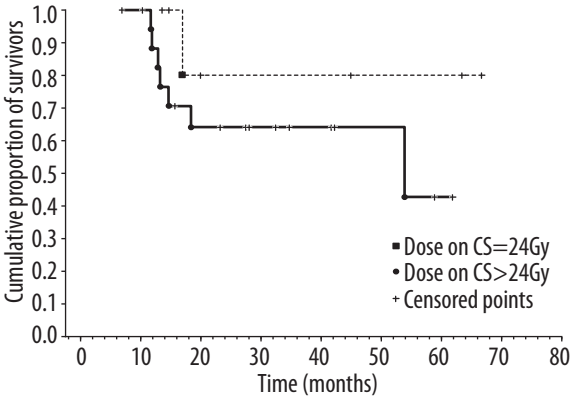

Figure 5. Overall survival stratified according to radiotherapy dosage on craniospinal area.

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

Dose on CS	Incidence of chronic effects		
	Total	According to type of effect	
		Growth problems	Hypothyreosis
24Gy	N=3 (42.9%)	N=1 (14.3%)	N=2 (28.6%)
30Gy	N=5 (45.5%)	N=4 (36.4%)	N=3 (27.3%)
36Gy	N=3 (37.5%)	N=2 (25.0%)	N=3 (12.5%)
Statistical difference1	p=0.941	p=0.568	p=0.886

* Statistical significance of differences among different dosage categories (M-L Chi-square test).

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
24Gy	N=5	N=1	N=1
30Gy	N=6	N=4	N=0
36Gy	N=2	N=5	N=1
Aggregated categories*	Complete remission	Partial remission + Progression	
24Gy	N=5 (71.4%)	N=2 (28.6%)	
>2 Gy	N=8 (44.4%)	N=10 (55.6%)	

* 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 24Gy is apparent.

was 60% as compared with 69% for those treated with reduced dose CSI [10].

The Paediatric Oncology Group (POG, 8631) and Children's Cancer Study (CCG-923) during 1986–1990 were randomized also between standard craniospinal radiotherapy to a dose of 36Gy and to a dose 23.4Gy. Event-free survival at 5 years for patients who received standard dose was 67% and 52% for patients with reduced dose [11]. In

the PNET-3 study (1992–2000) there was more intensive pre-radiotherapy chemotherapy. CSI was 35Gy. 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 [2,12].

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 [2,13,14].

Age at diagnosis is also of prognostic value. In general, the outcome of children aged over 3 years is significantly better than for 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 [15,16]. In our study differences in survival rate for patients with medulloblastoma between survival and age, sex or tumour size were not observed.

Another important factor that influences treatment results is the radicality of the surgical intervention. In their long-term study Chiu et al. reported 61% of the patients being well without relapse after complete resection, compared to only 37% of the patients surviving without symptoms of disease after partial tumour resection [17]. In our study differences for patients with complete and partial resection were not shown.

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. [18,19].

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 resultant hearing loss [20].

Patients are usually treated in the prone position, which is not as comfortable, reproducible or as easily maintained as the 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 [21–24].

The supine position provides in addition numerous advantages. For young children (less than 6–7 years of age) who require craniospinal irradiation with intubation (anaesthesia) irradiation only in the supine position is workable. Patients are more comfortable, and the treatment position is more reproducible and much better tolerated than the prone technique. The use of CT simulation significantly decreases the simulation time and also reduces daily treatment time [25].

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% [26]. In our study these treatment sequelae were not evaluated.

Growth failures are the most common form of neuroendocrinologic dysfunction as sequelae of craniospinal irradiation. Another common effect of craniospinal irradiation is hypothyroidism [27,28]. The numbers of growth failures and hypothyroidism in our study were comparable and hearing deficits were not shown.

In the study of Oyharcabal-Bourden et al. the 5-year recurrence-free survival rate of patients with all optimal quality controls of histology, radiology and radiotherapy was 71.8±10.5%. In terms of sequelae, 31% of patients required growth hormone replacement therapy and 25% required special schooling [29].

Conclusions

Irradiation of the craniospinal axis forms part of the treatment of a number of malignant diseases. Patients are usually treated in the prone position which is not as comfortable, reproducible or as

easily maintained as the supine position. Acute skin, haematological and gastrointestinal reactions were comparable with those in patients irradiated in the prone 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. These results (results of overall and disease-free survival) and side-effects ofthe technique of craniospinal axis irradiation in prone position are comparable with results of the technique in supine position.

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