Evaluation of late effects of postoperative radiotherapy in patients with medulloblastoma

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We aimed to evaluate long-term toxicity in children with medulloblastoma treated with postoperative radiotherapy (RT).

This study included 21 patients aged 4-16 who had been diagnosed with medulloblastoma. All of the patients in the study received postoperative craniospinal RT. Postoperative RT followed by chemotherapy was the treatment protocol. A total of 13 patients (62%) received chemotherapy concurrently with RT.

Overall survival was 50 months (range, 1-169 months) and disease-free survival was 39 months (range, 4-171 months). In the data analysis, the heights of 11 patients (91.6%) were found to be below 50% on the height curve, and 8 (66.6%) patients had weights below 50% on the weight curve. Mean sitting height was 72.58±6.33 cm, and this was statistically correlated with parameters such as LH level (p=0.037), testosterone level (p=0.020), height (p=0.002), weight (p=0.033) and age at diagnosis (p=0.002).

Radiation therapy for medulloblastoma seems to have a late toxic effect on long-term survivors. With the improving survival rate of medulloblastoma patients, RT doses should be as low as possible without sacrificing efficacy.

Key words: pediatric medulloblastoma, radiotherapy, late effects.

Medulloblastoma belongs to the primitive neuroectodermal tumor family, which includes 40% of all childhood brain tumors[1]. Postoperative radiotherapy (RT) and chemotherapy (ChT) are cornerstones of the treatment. A variety of chemotherapy regimes have been utilized before or after RT to improve the survival rate. Prior studies reported that five-year progression-free survival was 60% for the average-risk group and 50% for the high-risk group[2,3]. Despite higher survival rates, children surviving medulloblastoma are at risk for neuorologic, cognitive and endocrinologic dysfunction[3]. Because of the issue of late toxicity, there have been attempts to reduce the craniospinal radiotherapy (CSRT) dose without sacrificing control of the tumor. In our retrospective trial, we evaluated the late effects of RT in pediatric patients with medulloblastoma.

Material and Methods

Twenty-one medulloblastoma patients with a median age of 10 years (4-16 years) were treated in our department between 1995 and 2009. Fifteen (71.5%) were male and 6 (28.5%) were female. Nine patients passed away during follow-up, so endocrinologic evaluation was conducted only on the remainder of the patients (12 out of 21). The median follow-up was 37 months (4-102 months). All patients had craniospinal MRI and cerebrospinal fluid examination before initiation of RT. Disease in the patients was classified according to the Chang staging system.

We started to treat patients according to low- and high-risk criteria only after 2010. Therefore, in the present study, the median spinal dose was set at a standard 3600 cGy

(range, 3150-4450 cGy), and cranial dose with tumor boost was 5400 cGy (range, 4500-5940 cGy) with 150-180 cGy/fraction. While all of the patients received postoperative RT followed by chemotherapy (ChT), 13 patients (62%) also received concurrent ChT (vincristine). The most frequently performed adjuvant ChT protocols were vincristine and carboplatin etoposide; carboplatin etoposide-altering vincristine cyclophosphamide; and vincristine, CCNU, procarbazine and prednisolone. Patients were followed up monthly by physical examination and monitored for any recurrence. Craniospinal MRI was performed every 6 months after completing RT. Surviving patients were seen by the same pediatric endocrinologist only at the time of analysis. Penile length, testis volume, weight, height, obesity, axillary and pubic hair growth, telarche, hypothyroidism and hormone levels were evaluated and compared to standard parameters. Height, weight and penile length analyses were conducted based on the Turkish standard percentile curves. The Tanner classification was used for axillary and pubic hair growth. The effects of various parameters on treatment results were also investigated.

Independent groups were compared with each other using the Mann–Whitney U test. Pearson's chi-square/Fisher exact tests were performed to analyze the relationships among the variables. Kaplan–Meier lifetime estimates and the log rank test were used in comparing the groups. The *p*-value was set at 0.05.

Results

Subtotal resection was achieved in 12 patients (57%) and total resection was achieved in 9 patients (43%). Seventeen of 21 patients were diagnosed with classic medulloblastoma, 3 were desmoplastic and 1 was anaplastic variant. Complete and partial responses were obtained in 15 (71%) and 2 (10%) children, respectively, after postoperative RT. Response data for the rest of the patients could not be obtained. Tumor recurrence was observed in 4 patients (19.1%); all of them had to be treated with re-irradiation (1 with the Gamma Knife and 3 with external RT). A total of 9 patients (43%) were lost to follow-up. Five of them died due to the disease. Patient and treatment characteristics are displayed in Table I.

The five-year overall survival (OS) rate was 52%, and the disease-free survival (DFS) rate was 44% using the lifetime table. Sex, age at diagnosis, cerebrospinal fluid (CSF) involvement, preoperative tumor size, concurrent chemotherapy (ChT) administration, tumor stage and RT dose did not have any effect on OS or DFS. Complete response was the only statistically significant factor for both OS and DFS (p=0.012 and p=0.000, respectively). None of the patients had treatment for secondary malignancy or hematologic toxicity in the follow-up period.

In the analysis, a strong relationship was found between preoperative tumor size (<4 cm versus ≥4 cm) and advanced M stage (p=0.039). Concurrent ChT, T stage and RT dose did not

Table I. Patient and Treatment Characteristics

Characteristics	n (%)
Male	15 (71.5%)
Female	6 (28.5%)
Medulloblastoma	17 (81%)
Anaplastic	1 (4.8%)
Desmoplastic	3 (14.2%)
Subtotal resection	12 (57%)
Total resection	9 (43%)
Intracranial shunt +	17 (81%)
Intracranial shunt -	4 (19%)
Tumor size <4 cm	3 (14.2%)
Tumor size ≥4 cm	15 (71.6%)
Tumor size Unknown	3 (14.2%)
T2	8 (38%)
T3a	6 (28.5%)
T3b	3 (14.2%)
T4	4 (19.3%)
M0	14 (66.7%)
M1	4 (19.1%)
M2	0 (0%)
M3	3 (14.2%)
Complete response	15 (71%)
Stable disease	2 (10%)
Partial response	4 (9%)
Recurrence +	4 (19%)
Recurrence -	17 (81%)
Died: from disease	5 (55.5%)
from other causes	4 (44.5%)

have any influence on M stage. Also, we did not observe any impact of concurrent ChT, T stage, M stage, or tumor size on recurrence.

Late toxicity could be evaluated only in the surviving 12 patients (4 female, 8 male). Mean age of the living patients was 10 years (7-19 years) at the time of evaluation. Pubertal status was assessed clinically according to Tanner classification. Patients had their weight and height documented on standardized growth charts adapted on the basis of the Turkish standard percentile curves. The heights of 11 patients (91.6%) were below 50% on the height curve, and 8 patients (66.6%) had a weight below 50% on the weight curve. None of the male patients had gynecomastia. In the male patients, the median testis volume was 5.5 ml (range, 3-10 ml); median penile length was 5.8 cm (range, 3.5-10 cm). Seven patients (87.5%) had a penile length below 50% on the standard curve. The entire group was also analyzed for axillary and pubic hair growth, obesity and hypothyroidism (1992 WHO goiter classification) (Table II).

In the analysis, various hormone tests, whose results might be affected by RT, were evaluated. We found the median insulin-like growth factor (IGF-1) measurement to be 198 ng/ml (48-632 ng/ml); free (f) T4, 1.01 ng/dl (0.89-1.54 ng/dl); total (t) T4, 6.61 mg/dl (5.34-11.35 mg/dl); follicle stimulating hormone (FSH), 7.29 mIU/ml (1.31-37.74 mIU/ml); and luteinizing hormone (LH), 3.56 mIU/ml (0.09-8.33 mIU/ml). IGF-1 levels were low in 11 (91.6%) of the surviving patients. A significant positive correlation was seen between IGF-1 and fT4, tT4, FSH and LH levels (p=0.033, p=0.0030, p=0.001, p=0.041, respectively).

Mean sitting height was 72.58±6.33 cm; this was statistically correlated with parameters such as LH level (p=0.037), testosterone level (p=0.020), height (p=0.002), weight (p=0.033) and age at diagnosis (p=0.002).

Axillary hair growth was found to be significantly related to FSH and LH levels (p=0.031 and 0.008, respectively); pubic hair growth was found to correlate with LH level and height (p=0.012 and 0.038, respectively). We also found a significant relationship between hypothyroidism and younger age at diagnosis (p=0.040).

Discussion

The overall survival rate is known to be about 60% in pediatric medulloblastoma patients. When stratified into risk groups, this rate has been reported as 65-80% in the low-risk group, as opposed to 30-55% in the high-risk group[4,5]. A French Society of Pediatric Oncology study found 5-year OS to be 73.8% and DFS to be 64.8% in low-risk patients who received chemotherapy followed by low-dose RT[6]. Similarly, Taylor et al[5]. demonstrated that DFS outcomes were improved by preradiation chemotherapy. On the other hand, there have also been multiple studies that did not show postoperative chemotherapy before RT to have a beneficial impact on DFS[4,7, 8]. In our department, we started to treat patients according to low- and high-risk criteria only

Table II. Endocrinologic Evaluation after Postoperative RT

Characteristics		Characteristics	
Obesity +	2 (16.6%)	Gynecomastia +	0 (0%)
-	8 (66.6%)	-	8 (100%)
Axillary hair growth		Pubic hair growth	
Stage 1	5 (41.6%)	Stage 1	2 (16.6%)
Stage 2	5 (25%)	Stage 2	4 (33.3%)
Stage 3	1 (8.3%)	Stage 3	2 (16.6%)
Stage 4	2 (16.6%)	Stage 4	3 (25%)
Stage 5	1 (8.3%)	Stage 5	1 (8.3%)
Telarche		Hypothyroidism	
Stage 3	1 (25%)	Stage 1	1 (8.3%)
Stage 4	3 (75%)	Stage 2	1 (8.3%)

after 2010; thus, all of the patients in the study were treated with a standard dose of radiation. Five-year OS was 33% (median, 50 months) and DFS was 24% (median, 39 months). Our low survival rates could be related to the number of patients who died due to the disease.

Radiation has long-term effects on the hypothalamus and pituitary gland, both of which regulate hormones that are important for body functions and growth. Well-known late effects of CSRT in survivors are endocrine dysfunction, growth retardation and neurocognitive impairment. Ribi et al.[9] reported 61% of treated patients to have endocrinologic deficits, 76% to have neurological complications and 72% to have problems in school. Growth hormone (GH) and thyroid hormone deficiencies following RT were the most common disorders reported in the literature[10-13]. Growth hormone deficiency was seen especially at high radiation doses, that is, doses >18Gy[14]. On the same principle, the Pediatric Oncology Group suggested that a CSRT dose ≤24 Gy would effectively protect children from neurocognitive dysfunction[15].

Although IGF-1 and IGBF-3 levels were found to be predictive for idiopathic GH deficiency, there was no strong diagnostic value for post-radiotherapy status[16-19]. In contrast, a study by Adan et al.[14] found lower IGF levels to be related to cranial irradiation. The authors also noted that IGF-1 levels were affirmatively correlated with GH peaks, thus suggesting that IGF-1 blood concentration may be useful in monitoring residual GH secretion. In our study, we observed low IGF-1 levels in 11 (91.6%) of the surviving patients. Positive correlations were found between the levels of IGF-1 and other pituitary hormones such as LH, FSH and PL.

As a result of GH deficiencies, below-average sitting height and short stature are the most frequent physical problems noted following CSRT. It has been reported that RT administered to the spinal cord, especially at a young age, causes disproportionate growth[20,21]. Another study, by Wu et al.[22], demonstrated a substantially adverse effect of CSRT and CT on linear growth and sitting height, and suggested recombinant GH treatment as a way to partially offset this effect. In the current study, mean sitting height was 72.58±6.33 cm. The heights of 11 (92.5%) patients were below the 50th percentile on the height curve, while 8 patients (66.6%) had weights below the 50th percentile on the weight curve.

Another important dysfunction is hypothyroidism, with an 8-60% rate of occurrence after RT[10,13,23]. Even though this problem is primarily related to thyroid irradiation during treatment, hypothalamic hypothyroidism is another known issue. In a comparison of low-dose and high-dose CSRT, no differences were found in terms of thyroid dysfunction[23]. However, a clear association between hyperfractionated RT and a lower risk of thyroid toxicity has been identified and reported by some authors[13,24,25].

As a result, endocrine and growth dysfunctions occurred after CSRT, but the results did not differ by age or sex in our study. The most commonly seen late effect of treatment was short stature and decreased sitting height due to GH inhibition and spinal RT. As we stated previously, GH levels showed a statistically positive correlation with sex hormones (FSH, LH) and PL.

The main limitation of this study was that the patients generally had neither pretreatment hormone records nor examination by a pediatric endocrinologist. Since this is a very small group of patients treated with standard-dose CSRT, compared to other such groups in the literature, the results should be interpreted as a single-center study finding. With improving survival, the impact of long-term treatment-related morbidity and mortality increases; hence, RT doses should be as low as possible without sacrificing efficacy.

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