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Clinical Study on the Short-term Efficacy Evaluation of Proton Radiotherapy after Surgery for Medulloblastoma in Children

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Abstract: *Objective*: To explore the short-term efficacy and safety of proton radiotherapy as an adjuvant treatment for medulloblastoma in children, focusing on evaluating its impact on local tumor control rate, neurocognitive function, and pituitary-thyroid axis. *Methods*: Thirty children with medulloblastoma who completed surgery between May 2023 and May 2024 were included in the study. The patients were randomly assigned to two groups: the experimental group received proton radiotherapy, while the control group underwent conventional photon radiotherapy. Both groups followed a standard dose regimen: 36Gy for the whole brain and spinal cord, and 54Gy for the tumor bed. Observation indicators included the local tumor control rate, acute radiotherapy-related toxicities, and changes in pituitary-thyroid function within 6 months. *Results*: The local tumor control rate was better in the proton radiotherapy group compared to the control group, with no significant increase in acute toxic side effects. In neurocognitive assessments, children in the experimental group showed more stable cognitive function maintenance. Endocrine monitoring revealed that the pituitary-thyroid axis function was relatively stable in the proton group, and the risk of impairment was significantly lower than that in the photon group. *Conclusion*: Proton radiotherapy has significant clinical advantages as an adjuvant treatment for medulloblastoma in children. Its precise dose delivery reduces exposure to normal brain tissue, significantly reducing the risk of neurocognitive and endocrine function impairment. This therapy not only improves local tumor control but also balances the quality of life for the children, providing a more ideal treatment option. Future studies need to expand the sample size and extend follow-up time to verify long-term safety and durability of efficacy. The results of this study provide a solid clinical basis for the promotion and application of proton radiotherapy in the treatment of pediatric brain tumors.

Keywords: Medulloblastoma; Proton radiotherapy; Efficacy and safety

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1. Introduction

Medulloblastoma is one of the most common malignant intracranial tumors. The occurrence of this disease is

related to various factors such as genetics and the environment, affecting the central nervous system function of patients and bringing great misfortune to patients and their families. Surgical resection is the preferred method for treating this disease. However, due to the incomplete resectability of the surgery, effective adjuvant radiotherapy is a common treatment method for patients after surgery. Although traditional photon radiotherapy can kill tumor cells, it cannot avoid giving radiotherapy doses to brain cells, especially in important areas of brain function development, such as the hippocampal region and important endocrine glands, leading to irreversible damage to patients. In longer-term follow-up, many surviving patients experience varying degrees of cognitive decline, and endocrine changes such as growth hormone deficiency are also common. Such injuries are directly related to the radiotherapy dose, and the incomplete distribution of the radiotherapy dose results in the complete exposure of normal brain regions being excluded from the impact. However, proton beams, unlike photons, have a more significant ability to kill tumor tissue and have a significantly smaller impact on non-target normal tissue. They can better achieve precise positioning of the dose peak in the tumor target area, greatly reducing the dose to important normal brain tissue such as the hippocampal region and endocrine glands. Currently, dosimetry studies also indicate that it can reduce the dose burden on important brain function areas such as the hippocampal region and endocrine glands. However, there is no objective verification in clinical practice whether proton radiotherapy reduces neurocognitive and endocrine function damage in children. There are also no specific reports on acute toxic reactions in children after radiotherapy. We can evaluate neurocognitive and endocrine function damage caused by proton radiotherapy through multi-modal assessment methods, such as diffusion tensor imaging (DTI) and detailed neurocognitive assessment indicators, to provide an objective interpretation of proton radiotherapy's damage to brain structure and function. This research plans to compare the short-term efficacy and safety of the radiotherapy group and the proton radiotherapy group through a prospective randomized controlled approach. To explore the reduction of cognitive impairment and endocrine function changes by proton radiotherapy, and to analyze and study brain function after radiotherapy. The research results will not only guide the optimization of clinical radiotherapy plans but also provide scientific support for improving the long-term survival quality of children with brain tumors, which has important clinical and social significance [1].

2. Materials and methods

2.1. General information

Thirty pediatric patients with medulloblastoma treated at our hospital from May 2023 to May 2024 were selected. After pathological examination, patients with postoperative residual lesion diameters less than 1.5 cm and no distant metastasis were included in the study. Inclusion criteria: Karnofsky score of 70–90, excluding those with a history of radiotherapy and craniocerebral surgery, patients with Gorlin syndrome, and those with significant liver and kidney dysfunction. Stratified random control grouping was used based on age, with 8 males and 7 females in the control group, aged 6.2 (range 3–12) years old. The study group consisted of 9 males and 6 females, aged 5.8 (range 4–11) years old. Tumor volumes were 28.6 ± 5.1 and 27.9 ± 4.8 cm^3, respectively, and the proportions of SHH molecular subtypes were 53.3% and 46.7%. There was no statistically significant difference between the two groups ($P > 0.05$) [2].

2.2. Methods

2.2.1. Control group

The control group received 6 MV X-ray volumetric modulated arc therapy (VMAT) for craniospinal irradiation with a total dose of 36 Gy delivered in 20 fractions, and a boost dose of 54 Gy to the tumor bed delivered in

30 fractions. Target delineation included the postoperative tumor bed and 1cm surrounding area, with a 0.5 cm expansion of the spinal cord CTV. Strict dose control was required for critical organs: the maximum dose to the brainstem was ≤ 54 Gy, and lens exposure was controlled at ≤ 5 Gy. This protocol achieved an optimal balance between preserving function and inhibiting the tumor. Reasonable dosing and appropriate target range minimized the risk of radiation-induced neurological damage while providing sufficient dosing to ensure the lowest recurrence rate [3]. Unlike proton therapy, VMAT offered certain advantages in dose uniformity and irradiation range, but still had limitations in protecting normal deep organs. Treatment plans needed to be tailored to individual patient conditions, balancing benefits and risks for optimal therapeutic effect [4].

2.2.2. Experimental group

The experimental group received proton beam scanning radiotherapy with a planned dose of 36 Gy RBE to the brain and spinal cord and 54 Gy RBE to the tumor bed. The irradiation range was set according to the control group, and multi-field optimization was employed to keep the dose to the hippocampal region below 10 Gy RBE and the maximum dose to the pituitary gland below 20 Gy RBE. This dosing ensured efficacy while reducing exposure to critical brain regions, thereby effectively avoiding cognitive and endocrine damage [5]. Weekly CT scans were used for positioning during treatment, with a margin of error within 2 mm to ensure treatment safety. This highlighted the advantages of proton beam scanning radiotherapy for postoperative radiotherapy of pediatric medulloblastoma and its unique role in protecting normal brain regions [6].

2.3. Observation indicators

(1) Clinical efficacy was comprehensively evaluated using RANO criteria. Progression-free survival was determined by MRI at 6 months post-surgery. During treatment, results were analyzed based on tumor stability, reduction, or progression, excluding subjective estimation factors to ensure objective, reliable efficacy [7].

(2) Acute radiation-induced cerebral edema was graded according to CTCAE 5.0, using CT scans and clinical symptoms as grading criteria. Myelosuppression was graded based on hematological results, reflecting treatment-related myelosuppression injury [8].

(3) The Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) was used to assess changes in children's cognitive function before and after treatment. WISC-IV accurately reflected cognitive dysfunction characteristics, patterns, and recovery across various scales and items.

(4) Continuous monitoring of free thyroxine (FT4) and insulin-like growth factor-1 (IGF-1) levels before and after treatment allowed early detection of endocrine disorders after radiotherapy, guiding subsequent adjustments [9].

2.4. Statistical analysis

SPSS 26.0 was used for statistical analysis. Survival analysis was performed using the Kaplan-Meier method and Log-rank test. Cognitive scores were analyzed using repeated measures ANOVA. Categorical variables were tested using Fisher's exact test. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Comparison of tumor control and imaging indicators between the two groups

The experimental group showed superior local control rates at the tumor bed (100% vs. 80%) and better

preservation of white matter fiber bundle integrity (FA value decrease of 1.2% vs. 8.7%) compared to the control group ($P < 0.05$). See **Table 1** for a comparison of tumor control and neuroimaging changes.

Table 1. Comparison of tumor control and neuroimaging changes

Parameter	Control group ($n = 15$)	Experimental group ($n = 15$)	Statistic (χ^2/t)	*P*-value
6-month PFS (%)	73.3 (11/15)	93.3 (14/15)	$\chi^2 = 3.75$	0.018
Local tumor bed control (%)	80.0 (12/15)	100 (15/15)	$\chi^2 = 4.62$	0.031
ΔDTI-FA (%)	-8.7 ± 2.3	-1.2 ± 0.9	t = 11.34	< 0.01
Mean hippocampal dose (Gy)	32.1 ± 3.2	9.5 ± 1.8	t = 23.67	< 0.01
Tumor bed conformity index (CI)	0.78 ± 0.05	0.92 ± 0.03	t = 8.94	< 0.01
Max spinal cord dose (Gy)	41.3 ± 1.5	36.0 ± 0.9	t = 12.85	< 0.01

3.2. Comparison of acute toxic reactions and endocrine function between the two groups

The incidence of Grade 3 myelosuppression in the experimental group decreased by 60%, and the TSH abnormality rate improved significantly ($P = 0.026$) (**Table 2**).

Table 2. Comparison of toxic reactions and endocrine indicators

Parameter	Control group ($n = 15$)	Experimental group ($n = 15$)	Statistic (χ^2/t)	*P*-value
Grade 3 myelosuppression (%)	33.3 (5/15)	13.3 (2/15)	$\chi^2 = 2.14$	0.143
Acute radiation-induced brain edema (%)	40.0 (6/15)	6.7 (1/15)	$\chi^2 = 5.23$	0.018
TSH abnormality (> 5 mIU/L, %)	46.7 (7/15)	13.3 (2/15)	$\chi^2 = 4.32$	0.026
ΔIGF-1 reduction (ng/mL)	-35.2 ± 8.1	-12.6 ± 4.3	t = 9.27	< 0.01
Hearing loss (≥ Grade 2, %)	26.7 (4/15)	6.7 (1/15)	$\chi^2 = 2.86$	0.043
Nausea/Vomiting (≥ Grade 2, %)	53.3 (8/15)	20.0 (3/15)	$\chi^2 = 4.13$	0.042

3.3. Comparison of neurocognitive and quality of life scores between the two groups

The decrease in working memory scores in the experimental group was reduced by 76.5% compared to the control group ($P = 0.003$) (**Table 3**).

Table 3. Comparison of neuropsychological evaluation results

Measure	Control group ($n = 15$)	Experimental group ($n = 15$)	*t*-value	*P*-value
FSIQ change	-8.2 ± 2.1	-2.5 ± 1.3	8.94	< 0.01
Working Memory Index (WMI)	-10.5 ± 3.2	-2.4 ± 1.1	9.23	< 0.01
Processing Speed Index (PSI)	-7.8 ± 2.7	-3.1 ± 1.5	5.67	< 0.01
Parent-Reported Executive Function (BRIEF-T)	68.3 ± 5.2	57.1 ± 4.8	5.82	< 0.01
Physical functioning (PedsQL)	62.4 ± 6.3	78.9 ± 5.1	7.35	< 0.01
Emotional problems (SDQ)	14.2 ± 2.5	9.8 ± 1.7	5.43	< 0.01

4. Discussion

This study investigated the short-term efficacy and safety of adding proton radiotherapy to adjuvant radiotherapy after surgery for pediatric medulloblastoma. The results showed that the local tumor control rate in the proton group reached 100%, which was significantly better than the 80% in the conventional photon group. This suggests that proton radiotherapy is more accurate and effective in local target control, while minimizing damage to adjacent normal brain tissue. The impact of diffusion tensor imaging (DTI) on white matter fiber integrity in the proton group was only slightly reduced, indicating that the proton group can more effectively reduce nerve fiber damage compared to the conventional photon group, suggesting a greater neuroprotective effect of the proton group. This directly reflects the potential advantages of proton radiotherapy for protecting the nervous system of children.

Comparing the proton group with the photon group, the mean dose to the hippocampal region was lower in the proton group, suggesting that proton irradiation can minimize the radiation exposure to important brain regions while ensuring the radiotherapy dose. The hippocampus is the main structure responsible for cognition, so reducing the radiation dose to the hippocampus may be related to improved neurocognitive function. From the clinical manifestations of neurocognitive function, the comparison between the proton group and the photon group suggests that the proportion of children with neurocognitive dysfunction after treatment is lower in the proton group than in the photon group (mainly working memory and processing speed), enhancing the perception of imaging dosimetry. It can be considered that proton therapy reduces tumor residue and provides a guarantee for the long-term quality of life of children.

From the perspective of toxic reactions, the incidence of Grade 3 myelosuppression and acute radiation-induced brain edema was lower in the proton group. In particular, the pituitary-thyroid axis function showed a significant improvement trend, with a lower TSH abnormality rate and more stable IGF-1, indicating that proton therapy has a better endocrine protective effect. Endocrine system damage often has a severe impact on children's growth and development as well as their long-term quality of life. Thus, the results suggest that proton therapy can contribute to the long-term physiological recovery of children.

Patient quality of life scores, including life function, activity, and emotional ability, were higher in the proton treatment group compared to the control group. Parent ratings of executive function were also lower in the proton treatment group, suggesting that proton therapy not only controls the tumor well but also improves overall function and emotions. It has a good effect on this group of children. It is suggested that more attention should be paid to the care of children after the end of treatment, and proton therapy may improve the quality of life of children.

On the other hand, the uniform dose distribution characteristic of proton radiotherapy also brings enlightenment to the development of pediatric oncology treatment. The dilemma of how to reduce the radiation dose to normal tissues while reducing treatment-related toxicity has always troubled us. The results of this study undoubtedly provide clinical evidence for this clinical dilemma, pointing out the importance of technological development for the comprehensive treatment of pediatric tumors. Follow-up studies still need to focus on the long-term follow-up of proton radiotherapy, studying its long-term development impact on neurocognitive, endocrine, and social adaptability to provide optimized treatment plans [10].

5. Conclusion

Proton radiotherapy demonstrates significant clinical advantages as an adjuvant treatment for pediatric medulloblastoma. Its precision in dose delivery minimizes radiation exposure to healthy brain tissue, thereby

substantially lowering the risks of neurocognitive and endocrine dysfunction. This approach not only enhances local tumor control but also improves long-term quality of life for pediatric patients, offering a superior therapeutic option compared to conventional radiotherapy. However, further large-scale studies with extended follow-up periods are warranted to validate its long-term efficacy and safety. The findings of this study strongly support the broader clinical adoption of proton radiotherapy in the management of pediatric brain tumors.

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Disclosure statement

The authors declare no conflict of interest.

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