Radiation Therapy in the Treatment of Brain Tumors in Children

Davlatov B.N.,	Andijan State Medical Institute.
Mirzayuldashev N.Yu,	Andijan State Medical Institute.
Isakov B.M.,	Andijan State Medical Institute.
Isakov K.B.	Andijan State Medical Institute.

ABSTRACT

Up to 95% of cases of tumors of the central nervous system (CNS) in children are brain tumors. The treatment tactics are determined by their histological variant. If possible, tumors are removed (surgical resection); an important method of treatment in children older than 3 years is radiation therapy; in young children, chemotherapy plays an important role in the treatment of CNS tumors, which allows you to postpone radiation therapy or reduce its dose, and in some cases exclude it altogether. Tumors of the central nervous system (CNS) in children occupy the 2nd place in frequency in the structure of malignant neoplasms of childhood and the 1st place among solid tumors. According to the registers, they account for about 20% of all malignant neoplasms of childhood and are mainly represented by brain tumors (OGM).

Keywords: CNS, surgical resection

Introduction

The frequency of CNS neoplasms in children from 0 to 19 years is 3.5–4.0 per 100 thousand children; about 1000-1200 new cases of OGM are registered annually in Uzbekistan [1, 2]. CNS tumors in children are a large heterogeneous group of neoplasms, the variety of histological variants of which depends on the age of the patient. In children under 15 years of age, embryonic tumors and astrocytomas of varying degrees of differentiation predominate, other variants are rare. In the adolescent group, there is a decrease in the frequency of embryonic tumors typical of children, and the number of neoplasms that occur in adult patients increases. In 70% of cases in children, CNS tumors are represented by infratentorial localization, supratentorial tumors are detected in 30% of patients [2, 4]. Among the malignant tumors of the central nervous system in children, medulloblastoma (MB) takes the first place, followed by malignant gliomas (glioblastoma multiforme – MGB – and anaplastic astrocytoma – AA) and anaplastic ependymoma; piloid astrocytoma and craniopharyngioma predominate among tumors of low malignancy. Approximately 45% of patients with malignant OGM at the initial diagnosis reveal metastasis to other parts of the central nervous system; more often it happens with MB [1, 3-5]. When diagnosing tumors of the central nervous system, magnetic resonance imaging (MRI) and computed tomography (CT) with contrast enhancement (CU) are necessarily performed. In rare cases, with embryonic tumors of the central nervous system, there is extraneural metastasis, mainly to the bone marrow (about 5%) and bones (2%), which may be accompanied by a decrease in the level of hemoglobin, platelets and leukocytes in the general blood test. Diagnosis of extraneural metastases is carried out by examining the bone marrow and scanning the bone skeleton with technetium [6,7]. The tactics of treatment of CNS

tumors is determined by the histological variant of the tumor. An important principle of the treatment of CNS tumors is a multidisciplinary approach involving neurosurgeons, radiation therapists, oncologists, chemotherapists, morphologists.

Material and methods.

The first stage of treatment of CNS tumors is surgical resection of the tumor, the purpose of which is the maximum removal of the tumor, clarification of the histological variant and reduction of neurological symptoms. In the last 20 years, most patients with CNS tumors have received surgical treatment. If it is impossible to remove the tumor, a tumor biopsy is performed and its histological variant is clarified. The exception is patients with diffuse tumors of the brain stem, for whom surgical intervention in any variant is associated with serious consequences. Tumor biopsy in patients with a brain stem tumor is advisable with an atypical radiological picture [5, 7, 8]. Today, radiation therapy (LT) is a very important method of treating CNS tumors radiation therapy is a very important method of treating CNS tumors in children. The existing concepts of irradiation make it possible to choose the right amount of LT individually for each child. The standard of LT of brain tumors in children is 3 D-conformal irradiation. New research has made a significant contribution to minimizing the effects of LT. In the near future, an increase in the use of proton irradiation in pediatrics for CNS tumors is expected, since the high conformality of this type of LT theoretically does not cause long-term consequences and does not increase the risk of secondary tumors. Craniospinal tomotherapy can be a good alternative to conventional irradiation techniques and is therefore an object of research [8-10].

Results.

At the beginning of the last century, total CNS irradiation was the fundamental standard of treatment for all CNS tumors, regardless of the histological variant. Now there are 3 different types of CNS irradiation: 1) craniospinal irradiation (CSR); 2) cranial irradiation; 3) local irradiation (irradiation of the tumor bed). Today, CSR is used only in some variants of CNS tumors associated with a significant risk of leptomeningeal dissemination, as well as in the detection of tumor metastasis in the CNS [10-12]. Local irradiation is most often used in the treatment of CNS tumors in children. In principle, this type of LT includes irradiation of the tumor (or the postoperative bed) and additionally a safe area that insures against the potential spread of the tumor. The limits of irradiation depend on the histological structure of the tumor and the volume of surgical treatment. This concept is typical for tumors with a low risk of leptomeningeal spread or situations where systemic chemotherapy is likely to successfully prevent tumor metastasis in the central nervous system [11-13]. In recent decades, the percentage of children cured of CNS tumors has increased significantly, the 5-year survival rate is 60-70%. Therefore, the main interest today is the quality of life after treatment. Unfortunately, any child with a CNS tumor has a risk of developing side effects that depend on the dose and volume of LT, as well as the age of the patient during treatment. Possible side effects of LT include: developmental abnormalities, neurological disorders, hearing impairment, growth retardation, pituitary and thyroid gland dysfunction, psychosocial problems, as well as an increasing number of cases of secondary tumors [10-12]. In this regard, it is obvious that the treatment strategy should be chosen in such a way as to postpone or reduce the radiation dose, as well as to limit the volume of LT, especially if we are talking about young patients [12].

Conclusions.

Meningoblastoma is the most common tumor in childhood. In some countries, MB is better known as a subtentorial primitive neuroectodermal tumor (PNEO). MB often spreads through the cerebrospinal spaces, up to 45% of patients with primary diagnosis have an M+ stage [2, 19]. For many years, MB was treated only with CSR [12]. In the last decade, it has been found that PCT and local irradiation are sufficient treatment for children younger than 3 years with the classic MB variant and M0 stage. In patients younger than 3 years with the

desmoplastic variant of MB, the use of PCTs alone without irradiation makes it possible to achieve relapse-free survival in 95% of cases [22]. Long-term relapse-free survival in MB patients younger than 3 years with metastases is possible only in 30-40% of cases [14, 16, 23]. In children over 3 years of age, standard treatment still includes CSR at a dose of 24-36 Gy with additional booster irradiation of the tumor bed (up to 54-55 Gy) and PCT [10, 11, 15, 20, 21]. In patients older than 3 years, the average dose of PCT after tumor resection and CSR with parallel CT allows 70% of MB patients to achieve long–term survival - general (OS) and without progression (PFS); (Fig. 2-4). Unfavorable prognosis factors are: stages M2 and M3, anaplastic/large-cell variant MB, the presence of amplification of the MYCC gene [10, 11, 15, 18, 21]. Malignant gliomas – HR (AA and glioblastoma multiforme– MGB) are characterized by an extremely unfavorable prognosis [2, 23]. Despite the progress in the treatment of neuro-oncological diseases, the median survival of patients with MGB, according to various authors, does not exceed 10-14 months, in patients with AA, life expectancy reaches 2-3 years [12-19]. These tumors are associated with a high frequency of relapses after initial treatment and are one of the main causes of mortality in patients with malignant neoplasms. The reason for the unfavorable prognosis in HR is primarily diffuse invasion of tumor cells into the surrounding brain tissue, which limits the effectiveness of surgical removal of the neoplasm. In addition, AA and MGB are significantly more radio- and chemoresistance compared to other CNS tumors [17]. The modern therapeutic strategy of AA and MGB is based on surgical removal of the tumor to the maximum extent, followed by local LT and the use of CT.

Literature

1. Kühl J., Doz F., Taylor R. Embryonic tumors // Walker DA, Perilongo G, Punt JAG, Taylor RE, eds / Brain and spinal Tumors of childhood – Arnold, 2004 – p. 314-330. lecture 12'2011 27
2. Kaatsch P., Spix C., Michaelis J. 20 Years German Childhood Cancer registry. Annual report 1999. Mainz: Institute for Medical Statistics and Documentation of the University. 2000: www.kinderkrebsregister.de.
3. Matsko D.E., Korshunov A.G. Atlas of tumors of the central nervous system. – St. Petersburg, 1998. – pp. 76-80.
4. Kleihues P. World Health Organization classification of tumors. In Kleihues P, Cauance WK, eds. / Pathology and genetics of the tumors of the central nervous system – Lyon, France: International Agency for Research on Cancer Press, 2000. – pp. 208-241.
5. Stewart J. Chemotherapy of central nervous system tumours in infants // Child's Nerv Syst.– 1999; 15: 592–612.
6. Blaney S., Kun L., Hunter J. et al. Tumors of central nervous system // Pizzo PA, Poplack DG, eds. Principles and Practices of Pediatric oncology. 5th ed. – Philadelphia, PA – Lippincott Williams-Wilkins, 2006. – pp. 786-864.
7. Kun L. Brain tumors in infants and young children. U.S.A., ASCO // J. Clin. Oncol. – 1999: 574–578.
8. Clerico A., Cappelli C., Schiavetti A. Adjuvant chemotherapy in medulloblastoma patients: single institution experience. SIOP-ASPH/O MEETING. – Canada, Monreal, 13–18 Sept, 1999. – Abstract. – P: 32, 204.
9. Biegel J., Janss A., Raffel C. et al. Prognostic significance of chromosome 17p deletions in childhood primitive neuroectodermal tumors (medulloblastomas) of the central nervous system // Clin. Cancer. Res. – 1997; 3: 473–478.
10. Gajjar A. Recent advances in therapy for medulloblastoma. U.S.A., ASCO // J. Clin. Oncol., 1999; 579–586.
11. Gold D., Packer R., Cohen B. et al. Treatment strategies for medulloblastoma and primitive neuroectodermal tumors // Neurosurg Focus. – 1999; 2: Article 1.
12. Kalapurakal J., Goldman S., Hsieh Y. Long term results of hyper fractionated craniospinal radiation in

medulloblastoma. SIOP-ASPH/O MEETING. – Canada, Monreal, 13–18 Sept, 1999. – Abstract. – P: 52, 208.
13. Walker D., Perilongo G., Punt J. et al. Brain and spinal Tumors of childhood // Arnold – 2004: 519.
14. Kuhl J., Muller H., Berthold F. et al. Preradiation chemotherapy of children and young adults with malignant brain tumors: results of the German Pilot trial HIT'88/89 // Klin. Padiatr. – 1998; 210 (4): 227–233.
15. Packer R., Sutton L., Elterman R. et al. Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU and vincristine chemotherapy // J. Neurosurg. – 1994; 81: 690–698.
16. Rutkowski S., Bode U., Denlein F. et al. Treatment of early childhood medulloblastoma // N. Eng. J. Med. – 2005; 352: 978–986.
17. Balis F. Concepts and physiological underpinnings of intrathecal chemotherapy. SIOP Abstract Book, 40 th Congress of the SIOP. – Berlin, Germany, October 2–6, 2008. – S.063, p.13
18. Yang H., Nam D., Wang K. et al. Supratentorial primitive neuroectodermal
19. tumor in children: clinical features, treatment outcome and prognostic factors //
20. Childs. Nerv. Syst. – 1999; 15: 377–383.
21. McNeil D., Cote T., Clegg L. Incidence and trends pediatric malignancies medulloblastoma/primitive neuroectodermal tumor: Surveillance Epidemiology and Results // Med. Pediatr. Oncol. – 2002; 39 (3): 190–194.
22. Timmermann B., Kortmann R., Kühl J. et al. Role of Radiotherapy in Supratentorial Primitive Neuroectodermal Tumor in Young Children: Results of the German HIT-SKK87 and HIT-SKK92 Trials // J. Clin. Oncol. – 2006; 24: 1554–1560.
23. Gold D., Packer R., Cohen B. et al. Treatment strategies for medulloblastoma and primitive neuroectodermal tumors // Neurosurg Focus – 1999; 2: Article 1.22.von Bueren A., von Hoff K., Pietsch T. et al. Treatment of young children with localized
24. medulloblastoma by chemotherapy alone: results of the prospective, multicenter trial HIT 2000 confirming the prognostic impact of histology // Neuro Oncol. – 2011; 13 (6): 669–679.
25. Kuhl J., Bode U., Deinlein F. et al. Cure of infants with medulloblastoma (M0/
26. M1-stage) by postoperative chemotherapy only. SIOP-ASPH/O MEETING. – Canada, Monreal, 13–18 Sept, 1999. – Abstract, O-107, 169.
27. Kuhl J., Gnekow A., Havers W. et al. Primary chemotherapy after surgery and delayed irradiation in children under three years of age with medulloblastoma - pilot trial of the German Pediatric Brain Tumor Study Group. Protocol HIT-91, 1991.
28. Norden A., Drappatz J., Wen P. Novel anti-angiogenic therapies for malignant gliomas // Lancet Neurol. – 2008; 7 (12): 1152–1160.