South Russian Journal of Cancer 2022, Vol.3, No. 2, P. 22-30
https://doi.org/10.37748/2686-9039-2022-3-2-3
ORIGINAL ARTICLE

POST-RADIATION COMPLICATIONS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA WHO UNDERWENT A COURSE OF CRANIAL RADIATION

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ABSTRACT

Purpose of the study. To analyze the physical and neuropsychiatric development of pediatric patients who underwent cranial irradiation in the period from 2015 to 2020 in the radiotherapy department of the National Research Center of Oncology and to assess the risk of post-radiation complications.
Materials and methods. 17 children aged from 3 to 17 years were hospitalized under medical supervision in the department of pediatric oncology of the National Medical Research Centre for Oncology. All the children underwent a course of conformal radiation therapy totally on the brain area and the first two cervical vertebrae in the radiotherapy department of the National Medical Research Centre for Oncology. 13 patients (76.7 %) underwent radiation therapy due to the prevention of neuroleukemia with a total dose of 12 Gy (a dose per fraction was 2 Gy), 2 patients with a confirmed relapse of acute lymphoblastic leukaemia (ALL) (11.65 %), 1 patient with a confirmed diagnosis of neuroleukemia (5.8 %) and 1 patient from the high-risk group (5.8 %) – with a total dose of 18 Gy (a dose per fraction was 2 Gy). Further 75 month regular medical checkup was carried out on the basis of the Regional Children's Clinical Hospital for.
Results. None of the surviving patients showed growth retardation. Two patients (11.65 %) complained of increased fatigue, decreased concentration; one patient (5.8 %) showed unmotivated irritability and aggression during the examination. Intellectual development corresponded to age in all patients (100 %). One patient (5.8 %) experienced episodes of nausea and vomiting (grade 1 on the CTCAE scale), three patients (17.7 %) suffered from headache (grade 2 on the CTCAE scale), three patients (17.7 %) complained of fever up to 38 °C (1 degree on the CTCAE scale). Two out of 17 ALL patients died due to disease progression.
Conclusion. Taking into account the different time intervals between treatment and the moment of the study (from 9 to 75 months), cranial irradiation demonstrates relative safety for patients undergoing treatment during critical periods of development of both physical and neuropsychic spheres. However, an objective assessment of the development prospects is difficult due to the relatively short time after undergoing therapy (from 9 to 75 months) and a small sample of patients.

Keywords:
acute lymphoblastic leukemia, hemoblastoses, conformal radiation therapy, cranial irradiation, neuroleukosis, post-radiation complications

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Funding: this work was not funded.
Conflict of interest: authors report no conflict of interest.

For citation:
Rogova T. S., Sakun P. G., Voshedskii V. I., Vlasov S. G., Kozel Yu. Yu., Dmitrieva V. V., Kozyuk O. V., Aslanyan K. S., Vasileva E. V. Post-radiation complications in children with acute lymphoblastic leukemia who underwent a course of cranial radiation. South Russian Journal of Cancer. 2022; 3(2): 22-30. (In Russ.). https://doi.org/10.37748/2686-9039-2022-3-2-3

The article was submitted 28.01.2022; approved after reviewing 04.04.2022; accepted for publication 21.06.2022.

Южно-Российский онкологический журнал 2022, Т. 3, № 2, С. 22-30
https://doi.org/10.37748/2686-9039-2022-3-2-3
ОРИГИНАЛЬНАЯ СТАТЬЯ

ПОСТЛУЧЕВЫЕ ОСЛОЖНЕНИЯ У ДЕТЕЙ С ОСТРЫМ ЛИМФОБЛАСТНЫМ ЛЕЙКОЗОМ, ПРОШЕДШИХ КУРС КРАНИАЛЬНОГО ОБЛУЧЕНИЯ

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РЕЗЮМЕ

Цель исследования. Провести анализ физического и нервно-психического развития пациентов детского возраста, прошедших курс краниального облучения в период с 2015 по 2020 гг. в отделении радиотерапии ФГБУ «НМИЦ онкологии» Минздрава России и оценить риск развития постлучевых осложнений.
Материалы и методы. Под наблюдение в отделение детской онкологии ФГБУ «НМИЦ онкологии» Минздрава России было госпитализировано 17 детей в возрасте от 3 до 17 лет. Все дети прошли курс конформной лучевой терапии тотально на область головного мозга и первых двух шейных позвонков в отделении радиотерапии ФГБУ «НМИЦ онкологии» Минздрава России. 13 пациентов (76,7 %) прошли курс лучевой терапии ввиду профилактики нейролейкоза с суммарной очаговой дозой 12 Гр (разовая очаговая доза составила 2 Гр), 2 пациента с подтвержденным рецидивом острого лимфобластного лейкоза (ОЛЛ) (11,65 %), 1 пациент с подтвержденным диагнозом нейролейкоза (5,8 %) и 1 пациент из группы высокого риска (5,8 %) – с суммарной очаговой дозой 18 Гр (разовая очаговая доза составила 2 Гр). Дальнейшее диспансерное наблюдение проводилось на базе ГБУ РО «Областная детская клиническая больница» в течение 75 мес.
Результаты. Ни у одного из выживших пациентов не было выявлено задержки физического развития. У двух пациентов (11,65 %) были жалобы на повышенную утомляемость, снижение концентрации внимания; один пациент (5,8 %) проявлял немотивированные раздражительность и агрессию во время осмотра. Интеллектуальное развитие соответствовало возрасту у всех пациентов (100 %). Один пациент (5,8 %) испытывал эпизоды тошноты и рвоты (1 степень по шкале CTCAE), три пациента (17,7 %) страдали от головной боли (2 степень по шкале CTCAE), три пациента (17,7 %) предъявляли жалобы на подъем температуры тела до 38 °C (1 степень по шкале CTCAE). Из 17 пациентов с ОЛЛ погибло двое детей в связи с прогрессированием болезни.
Заключение. Учитывая разные временные промежутки между лечением и моментом проведения исследования (от 9 до 75 мес.), краниальное облучение демонстрирует относительную безопасность для пациентов, проходящих лечение в критические периоды развития как физической, так и нервно-психической сферы. Однако, объективная оценка перспективы развития затруднена ввиду относительно маленького срока после прохождения терапии (от 9 до 75 мес.) и небольшой выборки пациентов.

Ключевые слова:
острый лимфобластный лейкоз, гемобластозы, конформная лучевая терапия, краниальное облучение, нейролейкоз, постлучевые осложнения

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Финансирование: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Рогова Т. С., Сакун П. Г., Вошедский В. И., Власов С. Г., Козель Ю. Ю., Дмитриева В. В., Козюк О. В., Асланян К. С., Васильева Е. В. Постлучевые осложнения у детей с острым лимфобластным лейкозом, прошедших курс краниального облучения. Южно-Российский онкологический журнал. 2022; 3(2): 22-30. https://doi.org/10.37748/2686-9039-2022-3-2-3

Статья поступила в редакцию 28.01.2022; одобрена после рецензирования 04.04.2022; принята к публикации 21.06.2022.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a malignant disease of the hematopoietic system, consisting in the appearance of a tumor clone from cells – hematopoietic precursors of lymphoid differentiation lines [1]. ALL is the most frequent oncological disease of childhood: pathology occupies 80 % among hemoblastoses [2; 3] and 25 % of all tumors [1]. The disease occurs in 3–4 cases per 100,000 children in Russia. Over the past 10 years in the Russian Federation, the incidence of acute lymphoblastic leukemia (ALL) in children from 0 to 17 years has increased by 34 % [4], which justifies the need for regular revision of diagnostic and treatment protocols to develop safer therapy strategies while maintaining the level of therapeutic effect. One of the stages of ALL treatment is radiation therapy, in particular, cranial irradiation, but this therapy is associated with the risk of developing immediate and long-term side effects [1; 5]. ALL in children is characterized by a relatively high percentage of five-year event-free survival (> 80 %) [1; 2]. However, an integrated approach to treatment, including radiation therapy, is associated with the risk of radiation complications (pathological changes in the body, organs and tissues developing as a result of exposure to ionizing radiation [5; 6]).

Radiation therapy as one of the stages of treatment of acute lymphoblastic leukemia

Cranial irradiation (CI) is a standard component of many ALL treatment protocols. This preventive approach is aimed at destroying blast cells located in the brain that do not respond to chemotherapy. Of great importance is the coverage of the irradiation area of the entire cerebral part of the skull and necessarily the first two cervical vertebrae. Particular attention should be paid to covering the retroorbital areas, the base of the skull, as well as deep-lying areas in the area of the middle cranial fossa [1]. Cranial irradiation up to a total focal dose of 12 Gy is indicated in patients of intermediate and high risk groups as a prevention of CNS damage, the indication for increasing the total dose to 18 Gy is the detection of relapse of ALL or the diagnosis of neuroleukosis [1; 5].

Changes in bone tissue, which can manifest themselves in the interval from several months to several years, are different: from a slight short-term violation of osteoblastic function to osteonecrosis, osteomyelitis, pathological fracture. Radiation lesions of bones, as a rule, develop after 3 months or more. The clinic of radiation injuries of bones in children is diverse, so a dose of 1.5 to 10 Gy in the area of bone growth zones is sufficient to cause a temporary delay in bone growth [1].

Given the high survival rate after complex treatment, it can be assumed that irradiation of the brain in childhood with ALL may contribute to the development of secondary tumors in the long term, various types of neurological deficits, including neuropsychiatric development delay, endocrine disorders and other consequences [5; 7].

Areas of growth of skull bones

Sphenooccipital (or sphenobasilar) synchondrosis determines the shape of the skull and spine. It is formed by the posterior surface of the sphenoid bone and the basilar part of the occipital bone. This connection can be compared with two vertebrae, located in the middle part of the base of the skull. Synchondrosis persists until the age of 20–25; later it ossifies, maintaining its mobility. Kinetic dysfunction of synchondrosis generates adaptation of the state of the wedge-shaped and occipital bones, which affects the formation of the facial bones of the skull, physiological bends and the structure of the spine, which in the future may form a scoliotic deformity in a child. Dysfunction of the sphenobasilar junction changes the shape of the skull, resulting in an asymmetric face in developmental pathology [8].

During the first year of life, another growth center appears in the nasal septum – the sphenomezoethmoid. The duration of the growth zone activity is not exactly known. According to various authors, the fusion of this growth center with the center located in the main bone occurs at the age of 12 to 25 years. The cartilaginous layers between the mesoethmoidal growth center and the nearby bones of the facial and cerebral skull (frontal, lateral masses of the latticed bone) begin to ossify gradually in 2–6 years [8].

There is a definite connection between the growth of the cerebral part of the skull and the appearance of finger depressions on the inner surface of its bones, although the mechanism of their occurrence is still unclear. They are first detected at the age of 1.5–2 years in the parietal bones, then in the occipital zone and only by 7–8 years – in the frontal. Finger depressions reach their maximum severity in the puberty period, and then begin to gradually smooth out. After 15 years, the severity of these anatomical formations in various areas of the cerebral part of the skull is as follows: occipital, temporal, parietal, frontal (ratio 10:7:7:7, respectively). Some data suggest that finger indentations are more pronounced in children with delayed mental development, and their absence is an important symptom of a violation of osteogenesis processes and is usually accompanied by cortical atrophy [8].

The purpose of the study: to analyze the physical and neuropsychiatric development of children who underwent cranial irradiation in the period from

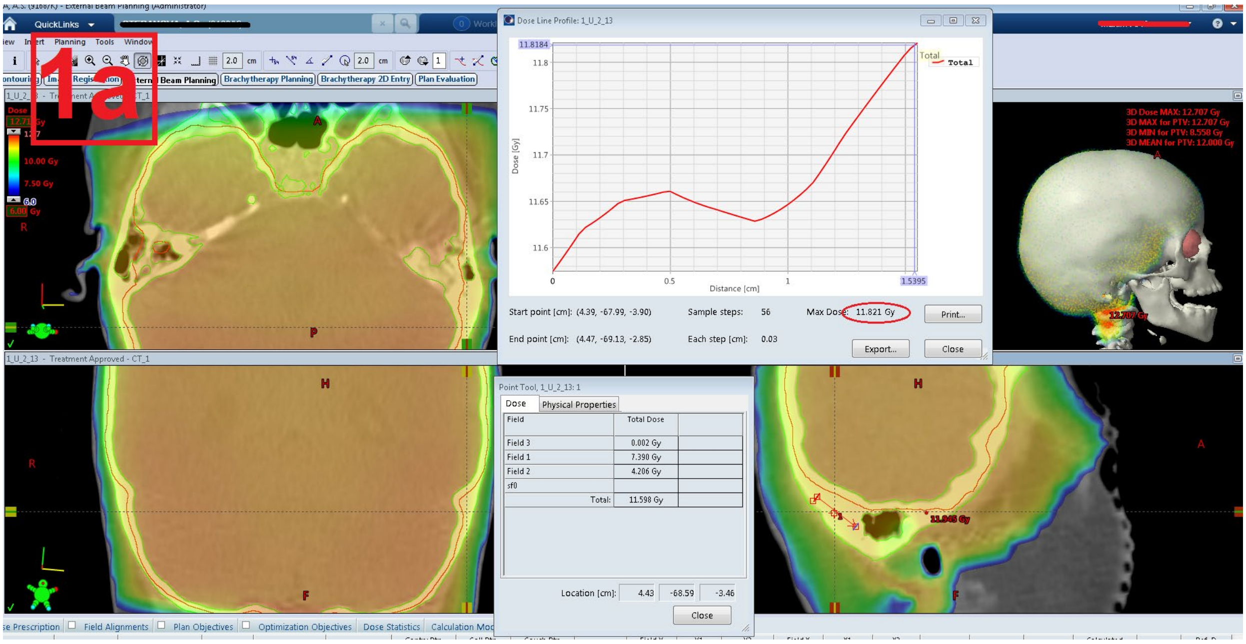

Fig. 1a. Dose load on the sphenooccipital growth zone of patient M., 4 years old. The maximum dose is 11.821 Gy.

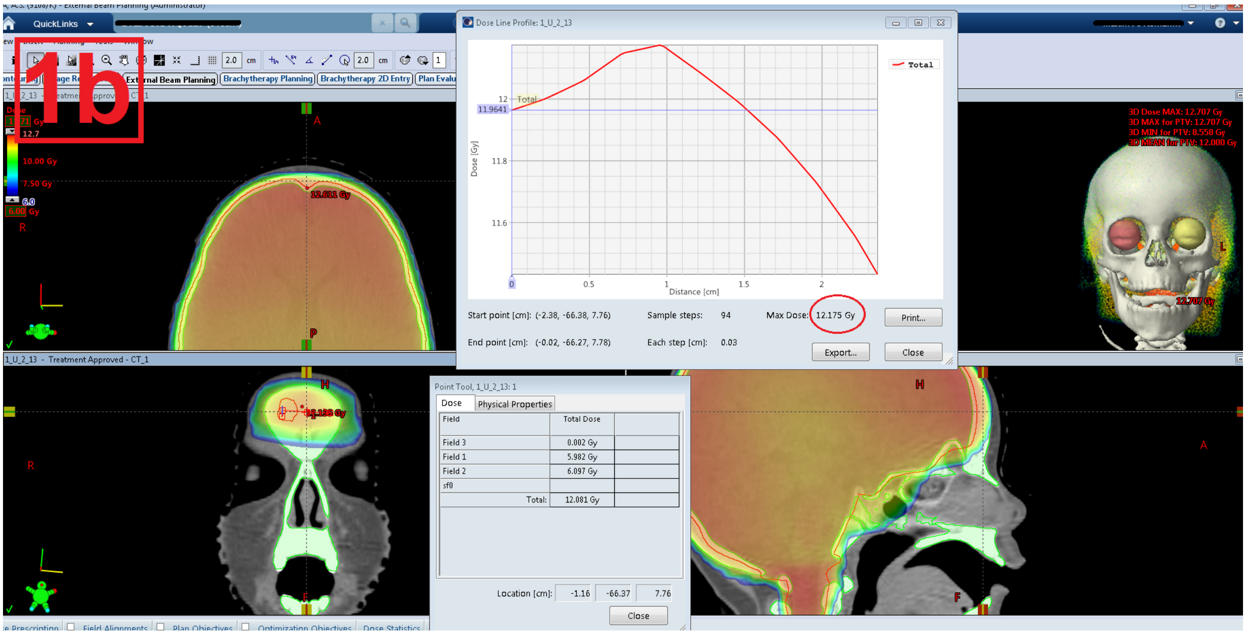

Fig. 1b. Dose load on the growth zone in the area of finger-shaped indentations of the frontal bone of patient M., 4 years old. The maximum dose is 12.175 Gy.

2015 to 2020 in the radiotherapy department of the National Medical Research Centre for Oncology and to assess the risk of post-radiation complications.

MATERIALS AND METHODS

During the period from 2015 to 2020, 17 children and adolescents aged 3 to 17 years were hospitalized under observation in the Department of Pediatric Oncology of the National Medical Research Centre for Oncology; the average age of patients was 10 years 1 month, the median age was 10 years. To conduct a course of cranial irradiation according to the protocol for the treatment of acute lymphoblastic leukemia ALL–MB-2015: 10 patients (59 %) of preschool and primary school age (3–10 years)

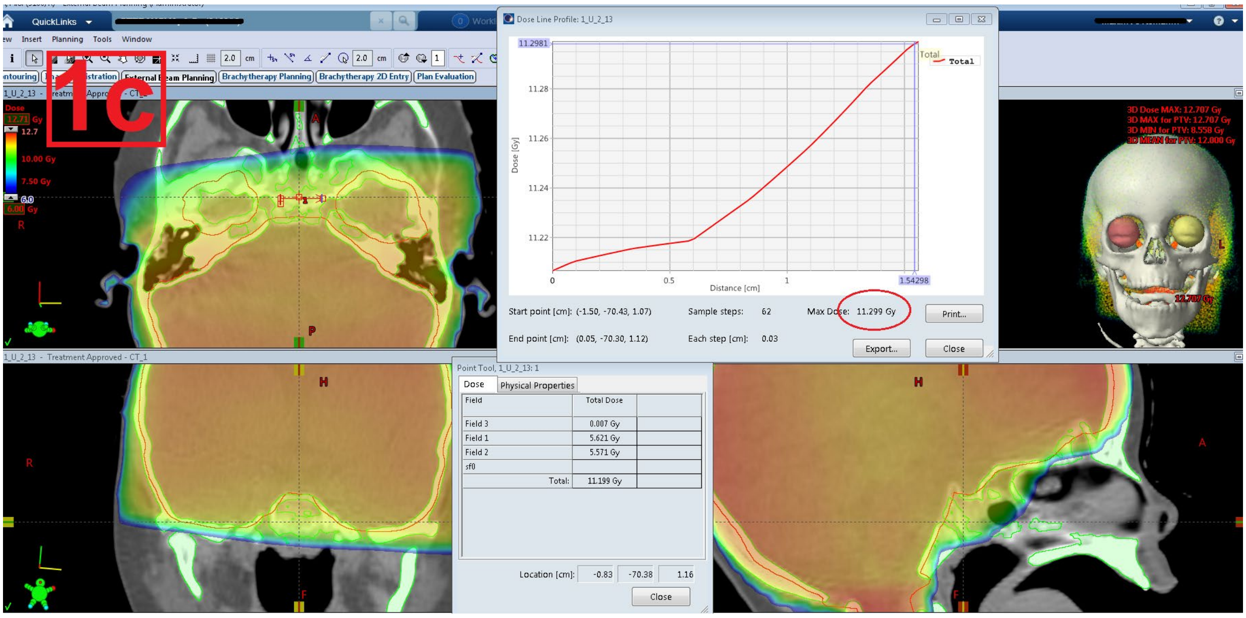

Fig. 1c. Dose load on the growth zone in the area of cartilaginous layers between the latticed and frontal bone of patient M., 4 years old. The maximum dose is 11.415 Gy.

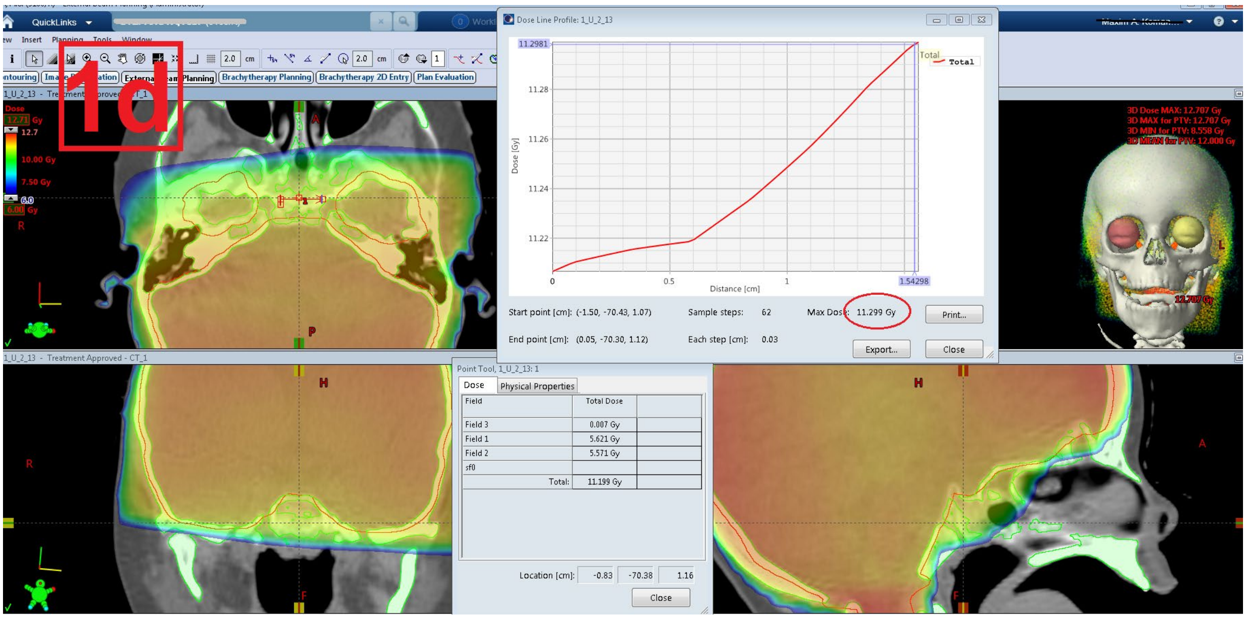

Fig. 1d. Dose load on the sphenomesoethmoidal growth zone of patient M., 4 years old. The maximum dose is 11.299 Gy.

and 7 patients (41 %) of middle and high school age (11–17 years). The ratio of boys and girls was 1:2.5, respectively. The patients underwent the stage of chemotherapy in the Department of Pediatric Oncology. The calculation and verification of the radiation therapy plan were carried out individually for each patient in the radiotherapy department. All patients underwent a course of conformal radiation therapy in the IGRT mode (Image Guided Radiation Therapy, image-controlled radiation therapy) using the Exactrac positioning system (Brainlab) totally on the brain area and the first two cervical vertebrae on the NovalisTx (Varian) device using the VMAT technique. Volumetric Modulated Arc Therapy, rotational therapy with volumetric intensity modulation) with an irradiation energy of 6 MeV and the following target coating parameters: V95 % ≥ 98 %, Dmean = 100 %, D2 % ≤ 107 % Fixation was carried out using individually manufactured devices – a thermoplastic mask with shoulders and a vacuum mattress. Subsequently, the children underwent dispensary observation on the basis of the GBU RO "Regional Children's Clinical Hospital" for 75 months. The assessment of physical development was carried out on the basis of physical examination, anthropometric parameters in accordance with the data of the WHO centile tables. The assessment of neuropsychiatric development was carried out on the basis of anamnesis collection, which includes a survey concerning the emotional-vegetative and psychomotor spheres, behavior analysis, as well as neurological examination and tests evaluating memory, thinking and attention. Adverse events were assessed on the basis of the CTCAE 5.0 toxicity scale [9].

Table 1. The ratio of the facial and cerebral parts of the skull

The ratio of the facial part of the skull to the brain	Age at the time of therapy	Age related normal values	Period after radiation therapy
2015 y. patients			
1:2	17 years	1:2	75 months
1:2	15 years	1:2	72 months
1:3	10 years	1:3	71 months
1:3	9 years	1:3	69 months
2017 y. patients			
1:3	8 years	1:3	44 months
1:4	6 years	1:4	41 months
2019 y. patients			
1:3	10 years	1:3	38 months
1:2.5	13 years	1:3	19 months
1:3	8 years	1:3	18 months
2020 y. patients			
1:2	16 years	1:2	13 months
1:2	17 years	1:2	13 months
1:3	10 years	1:3	11 months
1:4	4 years	1:4	10 months
1:4	6 years	1:4	10 months
1:5	3 years	1:5	9 months

Dose load

Of 17 patients, 13 patients (75.4 %) underwent radiation therapy with a total focal dose of 12 Gy (a single focal dose was 2 Gy), 4 patients (24.6 %) – with a total focal dose of 18 Gy (a single focal dose was 2 Gy). The indicators of dose loads on the growth zones of the skull bones were calculated: the sphenooccipital growth zone – 11.760 Gy (95 % CI 11.673–11.847), the growth zone in the area of finger–shaped depressions of the frontal bone – 11.967 Gy (95 % CI 11.835–12.098), the growth zone in the area of cartilaginous layers between the latticed and frontal bone – 11.276 Gy (95 % CI 11.199–11.354), sphenomesoethmoid growth zone – 11.276 Gy (95 % CI 11.199–11.354). An example of a dose load distribution plan is shown in Fig. 1a, 1b, 1c, 1d.

RESEARCH RESULTS AND DISCUSSION

The anamnesis data of 17 patients were analyzed, the average follow-up period after irradiation was 42 months (from 9 to 75 months). The development of early or late complications in the course of dispensary follow-up in patients was not noted. Despite the predominance of patients of preschool and primary school age groups who undergo critical periods of development, none of the surviving patients showed a delay in physical development (Table. 1, 2): the ratios of the facial and cerebral parts of the skull [8] corresponded to normal proportions in 15 (100 %) patients. The ratio of head circumference by age [7] also corresponded to the norm in 100 % of patients: the indicators of all children were between 25 and 75 percentiles.

Table 2. Distribution of head circumference (cm) by age

Distribution of head circumference (cm) by age	Age	Age related normal values (cm)	Period after radiation therapy
2015 y. patients			
55	17 year	55–57	75 months
56	15 year	54–56	72 months
53	10 year	51–54	71 months
54	9 year	50–54	69 month.
2017 y. patients			
53	8 year	50–53	44 months
51.5	6 year	50–52	41 months
2019 y. patients			
54	10 year	51–54	38 months
55	13 year	52–55	19 months
54	8 year	50–53	18 months
2020 y. patients			
56	16 year	54–56	13 months
57	17 year	55–57	13 months
55	10 year	51–54	11 months
51	4 year	49–51	10 months
53	6 year	50–52	10 months
50	3 year	48–50	9 months

Changes in the emotional-vegetative sphere were detected in two patients (11.65 %) aged 10 and 16 years, which were manifested by complaints of increased fatigue, decreased concentration of attention; in the psychomotor sphere and in behavior there were deviations in one 13-year-old patient (5.8 %), who showed unmotivated irritability and aggression during the examination. Intellectual development corresponded to the age of all patients (100 %).

Adverse events were also observed in a small part of patients. One patient aged 6 years (6.7 %) experienced episodes of nausea and vomiting (1–2 episodes (with an interval of at least 5 minutes) for 24 hours, which corresponds to 1 degree of toxicity) for two weeks a month after the end of the course of radiation therapy. Three patients (20 %) suffered from headache limiting daily activity (corresponding to grade 2 toxicity): the patient is 8 years old for three months, the patient is 10 years old for two months and the patient is 6 years old for two weeks. All three patients complained of headaches a month and a half after the course of radiation therapy. Three patients aged 6, 10 and 8 years (20 %) complained of a rise in body temperature to 38 °C (which corresponds to 1 degree of toxicity) for one and a half months. a month after the end of the course of radiation therapy. No other types of toxicity were observed in any of the patients. Of 17 patients with ALL, two children died due to the progression of the disease 4 years after undergoing radiation therapy.

CONCLUSION

The analysis of the data of the catamnesis of patients who underwent a course of radiation, taking into account the different time intervals between treatment and the moment of the study, demonstrates the relative safety of radiation therapy standards against the background of its effectiveness. Despite the fact that with ALL, patients are exposed to brain radiation during critical periods of development of both the physical and neuropsychic spheres, no significant deviations and undesirable reactions were detected. The results of these examinations and physical research methods confirm the presence of only minor and short-term changes that do not affect the quality of life of children at the moment, however, an objective assessment of the prospects for physical and neuropsychic development is difficult due to the relatively short period after therapy and a small sample of patients, as well as the absence of such studies in Russia and abroad.

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