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MUSCULOSKELETAL SEQUELAE OF CHILDHOOD BONE SARCOMA SURVIVORS

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Background. Childhood solid tumor survivors are known to be at risk for serious musculoskeletal late effects that may result in disability, associated with multicomponent antitumor treatment.
Aims. To improve the quality of life of childhood bone sarcoma survivors.
Materials and methods. Forty-six children and adolescents (22 males, 24 females) were treated for primary bone sarcomas (follow-up, 22–216 months). Mean age at orthopedic diagnosis was 15.09 years (range, 6–23 years). Treatment consisted of neoadjuvant chemotherapy and radiotherapy of the initial tumor and metastasis left after induction and/or oncologic surgery and adjuvant chemotherapy. We used the NCI Common Terminology Criteria for Adverse Events for reporting.
Results. The most common grade of late effects observed was grade 2 (91 cases). We observed serious adverse events, that is, grade 4 (life-threatening consequences) in five cases and grade 5 (death related to adverse events) in one. A total of 32 orthopedic patients had fewer than six late effects, while 14 had more than six late effects.
Conclusions. The development of musculoskeletal sequelae is unavoidable in the majority of the survivors due to the need to use them in very aggressive treatment strategies leading to a significant increase in survival. Early diagnosis and orthopedic correction of adverse effects are necessary to ensure an acceptable quality of life and good social adaptation of patients.

Keywords: musculoskeletal; long-term adverse effects; cancer survivors; Ewing sarcoma; osteosarcoma.

АНАЛИЗ ОРТОПЕДИЧЕСКИХ ПОСЛЕДСТВИЙ МНОГОКОМПОНЕНТНОГО ЛЕЧЕНИЯ КОСТНЫХ САРКОМ У ДЕТЕЙ

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Обоснование. Выжившие после заболевания злокачественными опухолями костей дети подвержены риску возникновения ортопедических последствий, связанных с многокомпонентным противоопухолевым лечением. Раннее выявление и ортопедическая коррекция неблагоприятных последствий необходимы для обеспечения приемлемого качества жизни и хорошей социальной адаптации пациентов.
Цель — улучшение качества жизни детей, перенесших саркомы костей.
Материал и методы. Ортопедическое обследование было проведено 46 детям, жителям города Москвы — 22 (47,8 %) мальчикам и 24 (52,2 %) девочкам. Средний возраст пациентов на момент ортопедического осмотра

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составил 15,09 ± 0,65 года (от 6,0 до 23,0 года, SD = 4,42). Период наблюдения от начала лечения до 01.06.2017 составил от 22 до 216 месяцев, в среднем — 102,29 ± 7,51 месяца (SD = 50,96). Специальное противоопухолевое лечение соответствовало морфологической форме опухоли и включало полихимиотерапию, оперативное вмешательство в случае операбельности опухоли и лучевую терапию при саркоме Юинга. Степень тяжести мышечно-скелетных последствий оценивали по шкале CTCAE Version 4.0.

Результаты. У всех обследованных детей, находящихся в периоде ремиссии заболевания костными саркомами, были выявлены ортопедические последствия. У пациентов, перенесших костные саркомы, преобладала II степень тяжести ортопедических последствий — 91 (42,9 %) случай, IV степень — паралич, переломы, требующие хирургического вмешательства, и лейкемия отмечены в пяти (2,5 %) случаях. Смерть (V степень) от генерализованного фиброза соединительной ткани наступила в одном случае у ребенка с лейкемией (второй опухолью). Менее пяти последствий отмечено у 32 (69,6 %) обследованных, более пяти — у 14 (30,4 %). Среди 14 детей с наибольшим количеством последствий дети, получавшие и не получавшие лучевую терапию, распределились поровну.

Заключение. Развитие ортопедических последствий противоопухолевого лечения у детей, больных костными саркомами, неизбежно в связи с необходимостью применения у них крайне агрессивной тактики лечения, приводящей к существенному повышению выживаемости детей, в том числе с IV стадией болезни. Своевременное выявление и соответствующая коррекция последствий противоопухолевого лечения способствуют сохранению здоровья, повышению социальной адаптации и улучшению качества жизни детей — наиболее социально значимого контингента населения.

Ключевые слова: костные саркомы; противоопухолевая терапия; ортопедические последствия.

Background

Vigorous multicomponent treatment in pediatric patients leads to adverse consequences that affect the patient anatomically and physiologically. In addition, the use of chemotherapeutic agents, use of implants, and extensive resections eliminate the affected bone and surrounding soft tissues and exert damaging ionizing radiation on the tissues. Pediatric patients who survive a malignant disease are at risk of orthopedic consequences following treatment. Unfortunately, to date, the complications and long-term orthopedic effects of organ-sparing surgical treatment, and the effect of radiation therapy (RT) and surgery on the development of long-term orthopedic effects, are still poorly understood.

The development of late orthopedic effects in pediatric patients with history of malignant tumors of musculoskeletal system have not received sufficient attention and very few publications on this topic are available. In the Russian literature, there are no publications devoted to the study of the orthopedic effects of special treatment and correction methods, while abroad, recommendations have been developed for the timely identification and correction of disorders associated with the effect of integrated therapy [1], but even the modern classification of endoprosthesis replacement complications in pediatric patients [2] comprises two out of a range of orthopedic effects. In the Russian Federation, study on the orthopedic effects of antitumor treatment in pediatric patients with bone sarcomas was conducted for the first time.

This study was conducted to improve the quality of life of pediatric patients with a history of bone sarcoma by identifying the adverse orthopedic effects, the severity of orthopedic effects, and corresponding corrections.

Methods

Study design

The study group included 46 pediatric patients (residents of Moscow) who underwent anticancer treatment for bone sarcomas, from among those who underwent follow-up examinations by a pediatric oncologist in the Moscow Pediatric Oncology office of the Moscow Department of Health to identify and assess the severity of orthopedic effects of anticancer therapy. As a rule, pediatric patients in remission are under the supervision of oncologist until they reach the age of 18 years, which enables catamnesis, but does not enable to identify the consequences of musculoskeletal system, since the patients are not under the care of orthopedists in a primary care facility.

Inclusion criteria

The criterion for inclusion in the study was the presence of bone sarcoma diseases in patients and the receipt of antitumor therapy in childhood. Orthopedists examined the patients in remission.

Conditions

The study was conducted in institutions under the jurisdiction of the Department of Health of the city of Moscow, in the Moscow Pediatric Oncology office of the Moscow Department of Health, and the Priorov National Medical Research Center of Traumatology and Orthopedics.

Study duration

The follow-up period started from the date of commencement of treatment to 01.06.2017, ranging from 22 to 216 months with an average of 102.29 ± 7.51 months (SD = 50.96).

Description of medical intervention

The study included 22 boys (47.8%) and 24 girls (52.2%). The average age of the pediatric patients at the time of orthopedic examination was 15.09 ± 0.65 years (from 6.0 to 23.0 years, SD = 4.42). Thirteen pediatric patients (28.3%) from age group of 6 to 12 years, 24 patients (52.2%) from the age group of 13 to 18, and 9 patients older than age of 18 years (19.6%) were examined (Table 1).

The pediatric patients over age of 13 years visited the orthopedists more often (*n* = 33, 71.8%) due to the occurrence of adverse musculoskeletal effects. This can be explained by a growth spurt, changes in proportions, and body weight within the period of 11 to 18 years. Distribution according to the morphological form of the tumor showed that 29 patients (63.0%) had a history of Ewing sarcoma, 15 patients (32.6%) had osteosarcoma, one patient had left femoral chondrosarcoma, and one patient had recurrent malignant adamantinoma of the left fibular bone (2.2%).

Most often the tumor affected long tubular bones (*n* = 32, 69.6%). Vertebrae, including sacrum and tailbone, were affected in 4 patients (8.7%), flat bones were affected in 3 (6.5%), and other bones were affected in 5 patients (10.9%). The extraskeletal localization of bone sarcomas was registered in 2 pediatric patients (4.3%), namely Ewing sarcoma/primitive neuroectodermal tumors of the left hip soft tissues and Ewing paravertebral sarcoma/primitive neuroectodermal tumors of Th_8. The long tubular bones were affected in 51.7% of cases of Ewing sarcoma and in 100% of cases with osteosarcoma and other tumors (Table 2).

Pediatric patients with stage IIB prevailed (20 (45.5%) cases) (Table 3).

A maximum 8 cm of lesion extension on the bone was recorded in 12 pediatric patients (27.3%) and more than 8 cm was registered in 32 patients (72.7%), which determined the level of resection (Table 4).

The volume of soft-tissue component within the tumor determined the scale of soft tissues

Table 1

Distribution by age and gender of pediatric patients in remission of bone sarcomas, examined by an orthopedist

Age	Boys		Girls	
	n	%	*n*	%
6–12 years	5	22.7	8	33.3
13–18 years	12	54.5	12	50.0
19–23 years	5	22.7	4	16.7
Total	22	100.0	24	100.0

Table 2

Bone lesion depending on the morphological form of the tumor

Skeletal bones	Ewing sarcoma		Osteosarcoma		Other	
	n	%	*n*	%	*n*	%
Long tubular bones	15	51.7	15	100.0	2	100.0
Vertebrae	4	13.8	–	–	–	–
Flat bones	3	10.3	–	–	–	–
Other bones	5	17.2	–	–	–	–
Extraskeletal bones	2	6.9	–	–	–	–
Total	29	100.0	15	100.0	2	100.0

Table 3

Distribution of pediatric patients by the disease stage

Stage	TNM	*n*	%
IIA	T1N0M0	7	15.9
IIB	T2N0M0	20	45.5
III	T3N0M0	5	11.4
IVA	T1-3N0M1a	7	15.9
IVB	T1-3N1M0-1a, b T1-3N0-1M1b	5	11.4
Total		44	100.0

Table 4

Distribution of the tumor lesion extension

Extension, cm	Long tubular bones		Vertebrae		Flat bones		Other bones	
	n	%	*n*	%	*n*	%	*n*	%
Up to 8	4	12.5	3	75.0	1	33.3	4	80.0
More than 8	28	87.5	1	25.0	2	66.7	1	20.0
Total	32	100.0	4	100.0	3	100.0	5	100.0

Table 5

Characteristics of patients by amount of special treatment

Amount of special treatment	Number of patients	%
Polychemotherapy + surgery + radiation therapy	19	41.3
Polychemotherapy + surgery	22	47.8
Polychemotherapy + radiation therapy	5	10.9

Table 6

Orthopedic effects

Adverse effect	Number	%
Lymphostasis	1	2.2
Connective tissue fibrosis	1	2.2
Dislocation	2	4.3
Fracture	3	6.5
Paresis	13	28.3
Gait disorder	17	36.9
Deformities	18	39.1
Limb shortening	25	54.3
Osteoporosis	28	60.9
Scoliosis	31	67.4
Joint stiffness	31	67.4
Muscular dystrophy (scar)	42	91.3

removal. The average volume of the primary tumor was 190.28 ± 52.84 cm^3 (from 0 to 1697.3 cm^3; SD = 330.04), the soft tissue component was not detected in 9 patients (19.6%), the soft tissue component less than 100 cm^3 was registered in 17 patients (37.0%), and more than 100 cm^3 was noted in 20 patients (43.5%).

In terms of the prevalence of process, 33 pediatric patients (71.7%) had localized bone sarcomas and 13 patients (28.3%) had disseminated ones.

Special antitumor treatment corresponded to the morphological shape of the tumor and included polychemotherapy (PCT), surgery in the case of tumor resectability, and RT in Ewing sarcoma (Table 5).

Surgical treatment was performed in 41 patients (89.1%) and 21 pediatric patients (45.6%) underwent two or more surgical interventions. RT was conducted in 24 pediatric patients (52.2%).

Primary outcomes of the study

The orthopedic effects of chemoradiotherapy were registered in all patients (Table 6).

The number of adverse effects of special antitumor treatment ranged from 1 to 10 for an individual.

Outcomes registration methods

The severity of musculoskeletal effects was assessed on a CTCAE Version 4.0 scale [3] (Table 7).

Table 7

Severity of effects by CTCAE Version 4.0

Effect	Degree I	Degree II	Degree III	Degree IV
Muscular dystrophy	Mild	Moderate	Self-service restriction	The degree is not determined for this effect
Stiffness	Limiting the range of motions <25%	Limiting the range of motions >25%–50%	Limiting the range of motions >50%, contracture	The degree is not determined for this effect
Scoliosis	<20°; clinically undetectable	>20°–45°; clinically detectable when bending forward	>45°; presence of costal humpback, surgical correction is indicated	The degree is not determined for this effect
Osteoporosis	Decrease in bone density according to X-ray	Marked changes in bone tissue, fracture	Self-service restriction, inpatient treatment	The degree is not determined for this effect
Limb shortening	Minor shortening, <2 cm	Length correction is required, shortening from 2 to 5 cm	Pronounced difference in the length of the limbs, shortening > 5 cm; surgical correction is required	The degree is not determined for this effect
Deformities	Cosmetically and functionally insignificant asymmetry	Pronounced cosmetic and functional defect, which can be hidden by clothing or corrective devices	Pronounced cosmetic and functional defect, which cannot be hidden by clothing or corrective devices	The degree is not determined for this effect
Neurological disorders	Mild	Moderately pronounced	Paresis	The degree is not determined for this effect
Gait disorder	Lameness	Use of additional support	Nonambulant	The degree is not determined for this effect
Fracture	Asymptomatic, detected during examination	Non-displaced, requires immobilization	Reposition is required	Surgery in a hospital is required
Lymphostasis	5%–10% discrepancy between limbs in volume or circumference at the point of greatest visible difference	>10%–30% discrepancy between limbs in volume or circumference at the point of greatest visible difference	>30% disparity between limbs in volume	The degree is not determined for this effect

The statistical processing of data was performed using IBM SPSS 20.0 for Windows. When comparing the parametric values, the confidence of the results was assessed using a comparative paired *t*-test, and in the case of non-parametric values, it was assessed by the χ^2 Pearson test using contingency tables. The difference was considered significant at $p < 0.05$.

Results

Muscular cicatricial dystrophy was most often registered in 42 cases (91.3%). The decrease in muscle volume in the area of impact on the tumor nidus was not detected in 4 pediatric patients (8.7%). RT was performed in 24 pediatric patients (57.1%) with muscular dystrophy, while 18 pediatric patients (42.9%) did not receive radical radiotherapy.

Joint stiffness was detected in 31 pediatric patients (67.4%). In 21 pediatric patients (67.7%), joint stiffness developed after endoprosthesis replacement, and after other surgeries in 10 patients (32.3%). When comparing the difference in the volume of movements in pediatric patients who underwent endoprosthesis replacement and those who did not, no statistically significant difference was obtained, $p = 0.114$ (χ^2 Pearson). In pediatric patients with joint stiffness, RT was performed in 15 cases (48.4%), and not performed in 16 cases (51.6%).

Scoliotic deformity was noted in 31 pediatric patients (67.4%), namely less than 20° in 20 patients (64.5%), which corresponded to deformity degree I–II, from 20 to 45°in 7 cases (22.6%), and more than 45° in 4 cases (12.9%); that is, deformity degree III and IV, respectively. Eighteen out of 20 pediatric patients (90%) with deformity degree I–II had static spinal deformity, which developed due to the lower limb-length discrepancy. In 2 pediatric patients, severe contracture caused static spinal deformity. Degree III deformity was detected in 4 pediatric patients, with shortening of the limb by 5 to 8 cm, in which compensation of shortening was not performed. In 3 pediatric patients, the spinal deformity developed as a result of performing RT on the chest. Degree IV deformity was established in 4 pediatric patients who underwent RT in the spinal region. Surgical treatment was recommended to 3 pediatric patients, but it was performed in only one child with good result, while 2 pediatric patients refused the surgery. In one child, surgical treatment was not planned due to severe osteoporosis. In pediatric patients with a history of endoprosthesis replacement, scoliotic deformity of more than 45° was not revealed, unlike pediatric patients who underwent other surgical interventions on the lower limbs ($p = 0.043$) (χ^2 Pearson).

Osteoporosis, a form of cortical layer thinning, reduction of trabecularity, and architectonics of bone tissue, was radiographically detected in 28 pediatric patients (60.9%); RT was performed on 13 of these patients (46.4%). Indicators of biochemical blood analysis (protein, protein fractions, Ca, P, bone alkaline phosphatase, Ca^{2+}, creatinine and urea) and biochemical analysis of daily urine (Ca and P) were determined. The determination of urinary deoxypyridinoline (DPID), and blood parathyroid hormone, osteocalcin, β-cross-laps, and $25(OH)D_3$ was not performed during the cancer examination; therefore, these indicators were not available as screening for pediatric patients with a history of bone marrow sarcomas. In primary care facilities, pediatric patients were not examined for osteoporosis and densitometry was not performed.

The shortening of the limb (complication type VI) was noted in 25 pediatric patients (54.3%), 17 of them (68.0% of all pediatric patients with limb shortening) underwent endoprosthesis replacement and 3 patients (12.0%) had resection or extirpation of the fibula. Shortening of the limb was revealed in one patient after exarticulation of the calcaneus; in one child, it was noted after the removal of the hip soft tissue tumor. RT on the removed tumor bed and lymph-node basin was performed to 3 pediatric patients, namely on the pelvic region for two of them and on the scapula for one patient. RT was performed in 11 pediatric patients (44.0%) with limb shortening and 14 pediatric patients (56.0%) did not receive RT. Shortening of the limb ranged from 1 to 11 cm, an average of 3.74 ± 0.53 cm (SD = 2.65). Shortening of the limb less than 2 cm was recorded in 5 pediatric patients (20.0%) and limb shortening between 2 and 5 cm was registered in 13 patients (52.0%), while more than 5 cm was noted in 7 patients (28.0%).

Three out of 7 patients with a limb shortening of more than 5 cm, which developed with the growth of pediatric patients, had damage to the growth zones of the tibial bones, 3 patients had damage to the growth zones of the hip, and one had damage to the growth zones of the lower leg

and hip. In 6 cases, endoprosthesis replacement was performed, an extending endoprosthesis was used for 3 pediatric patients with fractures, and RT was performed to 2 pediatric patients. When comparing the limb lengths in pediatric patients with a history of endoprosthesis replacement and pediatric patients who underwent other surgical interventions, there was no statistically significant difference ($p = 0.484$) (χ^2 Pearson).

Musculoskeletal deformity was detected in 18 patients (39.1%), of which 10 (55.6%) had limb deformity, 5 (27.8%) had a deformity of the anterior chest wall, and 3 (16.7%) had a spinal deformity. Seven out of 10 patients with limb deformity had the phenomena of deforming osteoarthritis. Four out of 10 pediatric patients with limb axis deformity underwent endoprosthesis replacement, 4 had resection or extirpation of the fibular bone, one child had deforming ankle osteoarthritis after the exarticulation of the calcaneus, and one patient, after the removal of the hip soft tissue tumor, RT on the bed of the removed tumor, and a lymph-node basin, had a valgus deformity of the shin. Four out of 5 pediatric patients with a deformity of the chest wall underwent extirpation of the ribs with resection of the chest wall and RT, one child underwent RT on the scapular region, and 3 pediatric patients with spinal deformity underwent RT on the spine. In total, 14 pediatric patients (77.8%) with musculoskeletal deformity received RT and 4 patients (22.2%) did not.

Neurological disorder in the form of paresis was diagnosed in 13 pediatric patients (28.4%). Foot paresis was detected in 4 pediatric patients with a history of endoprosthesis replacement, in 3 pediatric patients after resection of the proximal tibial bone, and in one patient after resection of the knee joint. At the level of the distal femoral and proximal tibial bones, sciatic nerve paresis developed intraoperatively, due to which the talipes paralyticus developed, as did the indolent ischemic ulcer in the plantar surface of the foot. Hence, surgical correction was performed. Six pediatric patients underwent resection/extirpation of the fibula. Paralysis of the lower extremities occurred in one patient who underwent removal of an extradural tumor and posterior transpedicular spondylodesis D_7–D_{12} with a surgical hardware. Paresis of the bladder was noted in two pediatric patients who underwent RT to the sacral area. In patients treated with RT, paresis developed in 8 cases (61.5%), and among those who did not receive RT, it occurred in 5 cases (38.5%).

Gait disorder was recorded in 16 patients (34.8%). In 7 cases of them (43.8%), there was mild lameness, and in 9 cases (56.3%), the patients had to use additional support, as 2 pediatric patients had foot paresis and 7 pediatric patients had lower limb shortening of more than 5 cm. One patient, who underwent removal of an extradural tumor, posterior transpedicular spondylodesis D_7–D_{12} with surgical hardware, was nonambulant.

Periprosthetic bone fractures were diagnosed in three (6.5%) pediatric patients, and dislocations of the endoprosthesis head were found in two (4.1%), which led to the need for repeated surgical intervention.

The following clinical case deserves a separate description.

In 2003, a girl born on 27.03.2001, had Ewing sarcoma of the right rib XI and metastatic lung disease. Integrated treatment was performed, including polychemotherapy, rib extirpation, large-field irradiation of the lungs (cumulative dose = 12 Gy), RT per primary site (cumulative dose = 50 Gy), and high-dose therapy with peripheral stem cell (PSC) autografting. Remission was achieved. In 2007, after 33 months, a second tumor was diagnosed, namely acute myeloblastic leukemia, morphological variant M2. Four courses of polychemotherapy and allogeneic grafting of PSC were performed and resulted in remission. However, chronic graft-versus-host disease (GVHD) was noted, when generalized fibrosis of the connective tissue gradually developed. In 2015, severe muscular dystrophy was revealed in the child during the examination, as well as a deformity of the chest wall, impaired bone metabolism, joint stiffness in the upper and lower extremities, stenosing ligamentitis, flexion contractures of the finger joints, and deforming osteoarthritis of the knee and ankle joints. In 2016, the child died from chronic pneumonia with pulmonary fibrosis.

The severity of adverse effects led to the need to perform repeated endoprosthesis replacement in 8 cases. In 3 cases, surgeries were performed for periprosthetic fractures. In 2 cases, open removal of dislocations of the hip and ankle joints was performed. Two pediatric patients with foot paresis were treated with skin grafting of the anterolateral surface of tibia and corrective surgery

Table 8

Patient distribution by severity of orthopedic effects according to CTCAE Version 4.0

Effect	I	II	III	IV	Total
Muscular dystrophy	8 (19.0%)	25 (59.5%)	9 (21.4%)	–	42 (100%)
Stiffness	2 (6.5%)	16 (51.6%)	13 (41.9%)	–	31 (100%)
Scoliosis	20 (64.5%)	7 (22.6%)	4 (12.9%)	–	31 (100%)
Osteoporosis	13 (46.4%)	12 (42.9%)	3 (10.7%)	–	28 (100%)
Limb shortening	5 (20.0%)	13 (52.0%)	7 (28.0%)	–	25(100%)
Deformities	2 (11.1%)	7 (38.9%)	9 (50.0%)	–	18 (100%)
Neurological disorders	–	1 (7.7%)	11 (84.6%)	1 (7.7%)	13 (100%)
Gait disorder	7 (41.2%)	9 (52.9%)	1 (5.9%)	–	17(100%)
Fracture	–	–	–	3 (100.0%)	3 (100%)
Dislocation	–	–	2 (100%)	–	2 (100%)
Lymphostasis	–	1 (100%)	–	–	1 (100%)
Leukemia	–	–	–	1 (100%)	1 (100%)
Total	57 (26.8%)	91 (42.9%)	59 (27.8%)	5 (2.5%)	212 (100%)

Table 9

Distribution of orthopedic consequences depending on the primary site localization

Number of complications	Localization of the primary site									
	Long tubular bones		Vertebrae		Flat bones		Other bones		Extraosseous	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
1–2	4	12.5	1	25.0	–	–	–	–	–	–
3–5	17	53.1	3	75.0	2	66.7	4	80.0	1	50.0
6–8	10	31.3	–	–	1	33.3	1	20.0	–	–
9–10	1	3.1	–	–	–	–	–	–	1	50.0
Total	32	100.0	4	100.0	3	100.0	5	100.0	2	100.0

Table 10

Distribution of orthopedic effects depending on the type of treatment

Amount of special treatment	Number of patients		Total
	Less than 5	More than 5	
Polychemotherapy + surgery + radiation therapy	12 (63.2%)	7 (36.8%)	19 (100%)
Polychemotherapy + surgery	14 (66.7%)	7 (33.3%)	21 (100%)
Polychemotherapy + radiation therapy	6 (100.0)	–	6 (100.0)

for eliminating talipes paralyticus, and surgical correction of kyphoscoliosis was performed to one patient.

The orthopedic effects of degree IV (except for fractures) include life-threatening conditions, paralysis, urgent conditions, leukemia. Degree V is death due to consequences. Dislocations were classified as degree III by CTCAE Version 4.0 (Table 8).

In pediatric patients with a history of bone sarcomas, several types of orthopedic disorders were registered in various combinations, ranging from 1 to 10, with an average of 4.61 ± 0.28 (SD = 1.96) (Table 9).

By the volume of the special treatment in the past, there was no statistically significant difference between the integrated and combined treatment ($p = 0.215$) (χ^2 Pearson) (Table 10).

When analyzing the orthopedic consequences of special treatment depending on the inclusion in the program of RT, no significant differences were found, $p = 0.695$ (χ^2 Pearson).

Discussion

The present study shows that all examined pediatric patients with bone sarcomas in remission had orthopedic effects. Early detection and orthopedic intervention can help to ameliorate the development of late musculoskeletal adverse effects and prevent subsequent complications. The first mention of the gradation of long-term effects according to their severity is related to RT. In 1998, US National Cancer Institute proposed the first version of CTC (Common Toxicity Criteria) to assess the severity of long-term negative effects depending on the treatment methods used (RT, chemotherapy, surgery). The fourth version of Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 [3], is currently in use. It is known that at a younger age, high doses of RT and asymmetric or partial amount of bone tissue irradiation adversely affect the musculoskeletal system. Methotrexate and vincristine affect the muscle elasticity and strength. Laminectomy and resection of the chest wall result in spinal deformity. RT, chemotherapy, and surgical intervention affect the development of bone-muscle independently and additively [4]. The majority (77%) of the survivors, who have lived for at least 5 years with a history of Ewing sarcoma, have long-term effects. The most common long-term effects were musculoskeletal disorders (50%) and cardiac toxicity (28%). The risk of a second tumor is 5% after 10 years [5].

In a Swiss study, pediatric patients aged less than 16 years, who had lived for more than 5 years, and who were diagnosed with malignant tumors in 1976–2003 were analyzed. Restrictions of physical activity in sports and daily activities were assessed. Pediatric patients who survived after bone tumors and received RT, including treatment according to the modern protocols, suffered the most [6]. In surviving pediatric patients with a history of Ewing sarcoma, common grade II chronic side effects were generalized muscular weakness (23%) and a decrease in total range of motion (23%) [7]. According to our data, in pediatric patients who had a history of bone sarcomas in history, orthopedic effects degree II prevailed ($n = 91$, 42.9; degree IV manifested as paralysis, fractures requiring surgical intervention, and leukemia were noted in five (2.5%) cases. Death (degree V) from generalized fibrosis of connective tissue occurred in a child with leukemia (second tumor). Less than five effects were noted in 32 patients (69.6%) examined and more than five were found in 14 patients (30.4%). Among the 14 pediatric patients with the highest number of orthopedic effects, those exposed and not exposed to RT were evenly distributed. The findings suggest that some researchers overestimate the role of RT in the development of long-term musculoskeletal effects.

A decrease in bone mineral density (BMD) was noted in 48 patients surviving with high-grade osteosarcoma who were treated in accordance with the chemotherapy protocols of the German-Swiss-Austrian cooperative research group of osteosarcoma, which included high-dose methotrexate. The mean follow-up period was 16 ± 2.2 years. Ten patients were diagnosed with osteoporosis, 21 had osteopenia, and 17 were healthy according to the WHO definition; 18 patients had fractures after chemotherapy [2]. Deficiency in BMD and subsequent fractures can occur after exposure to methotrexate [8] due to the cessation of cellular activity in growth areas, reduction of the formation of calcified cartilage, and primary bone trabeculae caused by a decrease in pools of metaphyseal osteoblast cells. In a multivariate analysis, it was revealed that the risk of fractures increases among the women who survived ($p = 0.015$) the methotrexate therapy [9].

The guidelines for identifying adverse effects (Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adults, Version 4.0) in the Children's Oncology Group (COG) recommend screening for BMD deficiency among survivors who received methotrexate [5]. BMD deficiency among pediatric patients and adolescents can also be caused by vitamin D deficiency [10], low protein intake, and low physical activity [11]. Our results fully confirm the data from other studies. A decrease in BMD was noted in 60.9% of pediatric patients carrying implants and/or who received RT. Fractures on the background of osteoporosis, radiation osteonecrosis, and Looser zone of bone remodeling were noted only in 6.5% of pediatric patients. A decrease in BMD prevailed

in implant carriers. Moreover, given the inclusion of methotrexate, doxorubicin, actinomycin D, and cisplatin in modern protocols for the treatment of bone sarcomas, the influence of the latter on the development of osteopenia, as well as vitamin D deficiency and low physical activity, often with a treatment duration of more than 12 months, is not ruled out. However, a comprehensive laboratory test for osteoporosis and densitometry are not included in the treatment standards, although they should be included in the mandatory list of examinations of pediatric patients with bone sarcomas.

In this study, we noted skeletal deformities, such as spinal deformities due to the local effects on spinal column and paravertebral areas, limb-length discrepancy, especially in implant carriers, and anomalies of the chest development after extirpation of the ribs. We agree that in many cases, skeletal deformity is caused by RT leading to fibrosis of muscle tissue and asymmetric growth, but extensive resection of the tumor nidus, including chest wall resection and laminectomy, and mechanical complications of endoprosthesis replacement (types I–III by Henderson) also have a certain effect.

In vitro studies have shown that doxorubicin, actinomycin D, and cisplatin directly affect the chondrocytes of growth zones. Clinical studies using polychemotherapy have demonstrated that antimetabolites reduce bone growth and its final length [1]. Skeletal deformities include spinal deformities [12], discrepancies in the length of the limbs [13] and anomalies of the chest [14]. In many cases, skeletal deformity is caused by RT, which can stop chondrogenesis in tubular bones and vertebrae, and affect membrane ossification in flat bones (for example, skull, pelvis or ribs), which leads to hypoplasia and asymmetric growth. RT damages DNA in osteocytes and produces free hydroxyl radicals [15]. Clinical evidence suggests that RT can affect bone formation by causing a termination of chondrogenesis in the epiphyseal plate of growth, inducing absorption deficiency in calcified cartilage and bone in the metaphysis and altering diaphysial periosteal activity [16]. Spinal deformities are also common in survivors after spinal tumor [17] who received RT and/or laminectomy [18]. Scoliosis, including thoracic vertebrae, contributes to restrictive lung defects characterized by reduced total lung capacity, reduced respiratory capacity, and increased respiration rate [19]. These conditions cause an increase in energy consumption required for breathing and over time lead to fatigue of the respiratory muscle, respiratory failure, and pulmonary hypertension [20]. Kyphosis and anomalies of the chest also affect breathing, compressing the lungs, and in severe cases cause weakness in the lower limbs, increasing pressure on the nerve roots of spinal cord [21]. Rib resection is accompanied by a development of scoliotic deformity. The course of scoliosis is progressive, and the younger the patient during the resection of ribs, the more severe the progression is. The highest rate of progression is noted during the first 10 years after resection of ribs [22].

The main pathophysiology of the effect of RT with long-term adverse muscular effects is unclear. Acute irradiation inhibits mitosis of myosatellite progenitor cells [23], impairs the cell membrane permeability and fluidity of the fluid, and can result in failure of the sodium-potassium pump in neuromuscular junction [24]. In addition, post-radiation inflammation mediated by transforming growth factor-β can inhibit muscle growth [25], radiation-induced vascular, and parenchymal damage can affect muscle nutrition [26], and RT can lead to myopathy [27], all potentially contributing to muscle atrophy, fibrosis, hypoplasia, and cicatricial dystrophy [28]. Radiation fibrosis is a pathological sclerosis of fibrous tissue that can occur in response to RT. Radiation fibrosis syndrome describes many of the clinical manifestations of progressive sclerosis of fibrous tissue due to RT. Lesions caused by radiation can include "myelo-radiculo-plexo-neuromyopathy", causing muscle weakness and dysfunction as well as contributing to neuromuscular injury [29].

Joint contractures, osteoporosis, and avascular necrosis develop as late manifestations of chronic GVHD in pediatric patients with a history of PSC transplantation [30]. Pediatric patients with limb tumors are at risk of losing physical function, although many of them are well-adapted to dysfunction or loss of limbs [31]. Nevertheless, in accordance with a recent study that examined 1094 patients who survived childhood malignant tumors (CCSS) of limbs (median age was 33 years), the location of the tumor in lower limb, female gender, age, type of tumor, amputation above the knee were the risk factors [32]. According to our

data, varying degrees of limb dysfunctions after organ sparing surgeries were found in in all pediatric patients who underwent endoprosthesis replacement of large joints; therefore, early rehabilitation is important for these pediatric patients in order to restore function, master compensatory strategies or adapt to the environment, and restore maximal function [7]. The functional impairment of the limb after organ sparing surgeries was recorded in 83% of patients, and related disability was registered in 86% of cases when the activities required large knee-joint flexion angles. There were no significant differences in the degree of functional depression ($p = 0.962$) or disability ($p = 0.411$) between different types of endoprostheses [33]. The average range of motion in the hip joint in patients with a history of hip joint arthroplasty was 103°. The average range of motion in the knee joint in patients with a history of hip arthroplasty, as well as knee joint with resection of the distal femur or proximal tibia was 127, 97 and 107°, respectively. The average elongation during skeletal maturity amounted to 4.5 cm, and the average difference in length of the limb was 0.7 cm [34]. The long-term effects that affect the quality of life of patients with a history of amputations and organ sparing treatment were not significantly different [35].

Survivors of osteosarcoma or Ewing sarcoma of the lower extremity ($n = 629$) adapt well to the environment. Some of the survivors reported moderate restrictions in physical performance and quality of life, while most of them reported an absence of difficulties with social integration [36]. Obviously, not only a disease, but also its treatment can significantly impair the health in long term [37].

Pediatric patients with a history of cancer are at increased risk of developing long-term negative conditions. Drug therapy and vigorous integrated treatment in pediatric patients lead to development of consequences associated not only with the anatomical and physiological traits of the growing organism, but also with a sharp decrease in physical activity during intensive drug therapy, the toxic effect of chemotherapeutic agents, the use of implants, extensive resections and damaging effect of ionizing radiation on the tissues. Not only survival becomes of vital importance, but also the quality of life of pediatric patients who have undergone a vigorous comprehensive treatment for bone sarcomas.

Conclusion

The development of the orthopedic effects of anticancer treatment in pediatric patients with bone sarcomas is unavoidable due to the need of applying extremely vigorous treatment management in them, which leads to a significant increase in the survival rate of pediatric patients, including those with stage IV disease. An improvement on timely diagnostics and correction of the orthopedic effects of multicomponent treatment of malignant bone tumors is extremely important. Long-term follow-up of all pediatric patients who have undergone special antitumor treatment for musculoskeletal sarcomas should be performed by an orthopedist for timely detection and correction of the effects of special treatment. Early detection and appropriate correction of the effects of anticancer treatment could preserve health, increase social adaptation, and improve the quality of life of pediatric patients.

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Contribution of the authors

A.V. Petrichenko collected and processed the data, wrote the text of the article, performed the diagnostics of tumors, anticancer treatment of patients and treatment of orthopedic consequences.

E.A. Bukreeva, P.A. Romanov performed data collection and processing, wrote the text of the article.

O.A. Tiganova, N.M. Ivanova conducted anticancer treatment of patients.

A.A. Ochkurenko performed diagnostics of tumors and orthopedic consequences, writing the text and the final editing of the article.

A.I. Snetkov conducted diagnostics of tumors, orthopedic consequences and their treatment.

O.V. Kozhevnikov conducted diagnostics of orthopedic consequences and their treatment.

A.K. Morozov performed diagnostics of tumors and orthopedic consequences.

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