Genij Ortopedii. 2022. Vol. 28, no. 2. P. 241-248.

Original article

https://doi.org/10.18019/1028-4427-2022-28-2-241-248

Impact of pathological fracture on treatment of pediatric bone sarcoma

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Abstract

Introduction A pathological fracture in patients with primary bone sarcomas is a complication that requires specific management with the prognosis affecting the disease. The treatment strategy of the patients with pathological fracture remains controversial. **The aim** was to explore the effect of a pathological bone fracture on treatment of pediatric bone sarcoma. **Material and methods** The study included 141 children with bone sarcomas, residents of Moscow. A pathological fracture was observed in 17 (12.1 %) cases accompanied by osteosarcoma in 10 (58.8 %) cases and Ewing's sarcoma in 7 (41.2 %) cases. Long bones were most common location of the fracture seen in 15 (88.2 %) cases. **Results** Errors in establishing the diagnosis of bone sarcomas occurred in children with/without a fracture with no statistically significant differences ($p = 0.239$). There were no statistically significant differences in the volume of surgical interventions, functional assessment using the Musculoskeletal Tumor Society System (MSTS), and 5-year survival in children with/without a fracture ($p \geqslant 0.05$). **Discussion** Treatment of pathological fractures in children should be produced after obtaining biopsy and the histological diagnosis. The frequency of local recurrence and functional outcome does not depend on the fracture. **Conclusion** Pathological process is to be ruled out in the presence of a fracture, and adequate visualization using MRI to be followed by a biopsy in a specialized institution would be needed if a pathological focus is suspected.

Keywords: children and adolescents, pathological fracture, sarcoma, bones

For citation: Petrichenko A.V., Savlaev K.F., Shavyrin I.A., Kurdiukov B.V., Romanov P.A., Serova N.Yu., Nikishov S.O., Tiganova O.A., Kovalev D.V., Ochkurenko A.A., Morozov A.K., Ivanova N.M. Impact of pathological fracture on treatment of pediatric bone sarcoma. *Genij Ortopedii*, 2022, vol. 28, no 2, pp. 241-248. https://doi.org/10.18019/1028-4427-2022-28-2-241-248

INTRODUCTION

A pathological fracture in patients with primary bone sarcomas is a complication that requires specific management with the prognosis affecting the disease. A hematoma resulting from a fracture develops at the site of the primary bone tumor that infiltrates the adjacent joints and soft tissues with tumor cells and can stimulate the hematogenous spread of the mass and increase the risk of local recurrence. The treatment strategy of the patients with pathological fracture remains controversial since patients are treated at trauma departments with insufficient expertise of specialists providing medical care for bone sarcoma cases. There is a paucity of publications in Russian and foreign literature on the topic with the lack of standards for medical care of pathological fractures. A pathological fracture is termed as a condition that occurs under minor mechanical effect resulting from pathological changes in the bone unlike a post-traumatic fracture resulting from the simultaneous impact of excessive mechanical force. A malignant tumor cannot be ruled out with a previous injury and a trauma surgeon must identify the nature of the fracture and administer proper diagnostic procedures with a minimal suspect of a pathological process in the bone. An adequate imaging visualization including MRI and biopsy would be needed for diagnosis of a pathological fracture and a mode of bone immobilization and fixation. Biopsy and a decreased thickness of the cortex > 50 %, are risk factors for the development of fractures with malignant bone tumors [1]. Primary bone tumors are rare and constitute < 0.2 % of malignant tumors registered in the EUROCARE database [2]. The frequency of pathological fractures with diagnosed osteosarcoma and Ewing's sarcoma ranges from 5 to 10 % in children and young adults. [3]. The rare pathology can become fatal for patients due to the lack of oncological alertness among trauma surgeons and bone fixation without verified diagnosis is unacceptable to avoid extensive spread of the disease [4]. Malignant bone tumors can affect any bone in a latent manner and be provoked by trauma. Internal, external fixation or extrafocal osteosynthesis is contraindicated in a primary tumor to avoid bone and soft tissue contamination with tumor cells that can result in limb amputation or distant metastasis. The European Society for Medical Oncology recommends the use of external fixation that also contributes to pain control. Immobilization is also indicated in the risk of a pathological fracture [5]. The Mirels score can be used as a predictive instrument for fractures [6]. Another benefit with external fixation is that

the intervention suggests involvement of the biopsy and the affected areas at surgical planning of tumor removal. The therapeutic approach to a patient with bone sarcoma and a pathological fracture should primarily be aimed at eradication of tumor cells and fracture consolidation. Pathological fractures in primary sarcoma are not an absolute indication for amputation [7]. Neoadjuvant chemotherapy allows for organ-saving treatment in children. Patients should be treated according to international bone sarcoma protocols that regulate neoadjuvant chemotherapy followed by radical resection of the tumor [4]. The fracture should be stabilized with an orthosis, cast, or external fixation for chemotherapy [8]. Tumor response to chemotherapy and fracture consolidation is a favorable prognostic sign of overall survival improvement and local disease control. The impact of pathological fracture on surgical management, local recurrence and survival was evaluated in patients with high-grade, localized limb osteosarcoma (n = 484), chondrosarcoma (n = 130) and Ewing's sarcoma (n = 156). Organ-sparing treatment could be performed in 79 % of patients with a fracture compared to 84 % of patients without a fracture (p = 0.17). No differences were found in the incidence of local recurrence. A univariate analysis showed lower survival in the fracture group as compared to controls for osteosarcoma (34 % vs 58 %, p < 0.01) and chondrosarcoma (35 % vs 63 %, p = 0.04), but not for Ewing's sarcomas (75 % versus 64 %, p = 0.80). Multivariate analysis showed the fracture being a survival predictor for osteosarcoma, but not for chondrosarcoma with decisive dedifferentiated subtype. Pathological fracture can predict poorer survival in osteosarcoma but has no effect on survival in chondrosarcoma and Ewing's sarcoma. Organ-sparing treatment can be performed with adequate resection margins provided [9]. A multicenter Japanese study of 1,070 patients treated with neoadjuvant chemotherapy and surgery for localized osteosarcoma suggested that patient age, tumor location and histological response had a stronger effect on metastasis-free survival and overall survival than gender, tumor size or the presence of a pathological fracture [10]. Pathological fractures in chemotherapy-resistant primary bone sarcomas are a relative contraindication for organ-preserving operations [4].

The aim was to explore the effect of a pathological bone fracture on treatment outcomes of pediatric bone sarcoma.

MATERIAL AND METHODS

Study design

The retrospective cohort study included 141 children with confirmed diagnosis of bone sarcoma.

Eligibility Criteria

Inclusion criteria were:

– children aged 1 to 18 years with bone sarcomas;

– examinations performed according to standards;

– histological confirmation of bone sarcomas;

– the presence of a confirmed pathological fracture;

– treatment of bone sarcomas according to international standards.

Exclusion criteria:

– children aged older 18 years with the presence of bone sarcomas;

– incomplete examinations performed according to standards;

– lack of histological confirmation of bone sarcomas;

– no pathological fracture;

– treatment of bone sarcomas with no regard to international standards.

Settings

The study was conducted in specialized oncological institutions being subordinate to the Department of Health of the City of Moscow in compliance with all necessary ethical requirements.

Length of the study

The follow–up period from the beginning of treatment ranged from 1 to 252 months;, 78.31 ± 5.74 months (SD = 68.18), on average, between 1999 and 01.05.2020.

Description of medical intervention

The study included 77 (54.6 %) male and 64 (45.4 %) female patients. The average age at the time of the initial examination was 11.38 ± 0.34 years (range, 1.0 month to 17.0 years, SD = 4.00).

Ewing's sarcoma and osteosarcoma were most common diagnosed (n = 134 (95 %)) (Table 1).

Long bones (LB) were most commonly affected (n = 91 (64.5 %)) (Table 2).

The prevalence of the mass indicated to 96 (68.1 %) children with localized bone sarcomas and45 (31.9 %) with disseminated condition. Specialized treatment considering the morphological form of the tumor included polychemotherapy (PCT) using effective international and Russian protocols in case of tumor resectability, and radical surgery and radiation therapy (RT) was provided for Ewing's sarcoma.

Table 1

Distribution by morphological form of the tumor

Morphological form of the tumor	Number	%
Malignant chordoma	1	0.7
Malignant adamantioma	1	0.7
Giant cell tumor	1	0.7
Chondrosarcoma	2	1.4
Non-verified	2	1.4
Osteosarcoma	67	47.5
Ewing 's sarcoma	67	47.5
Total	141	100.0

Table 2

Location of bone sarcomas

Location	Number	%
Scapula	1	0.7
Clavicle	1	0.7
Digital phalanx	1	0.7
Ulna	1	0.7
Metacarpal bone	1	0.7
Radius	2	1.4
Calcaneus	3	2.1
Fibula	7	5.0
Humerus	11	7.8
Pelvis	12	8.5
Rib	14	9.9
Vertebrae including sacrum and coccyx	17	12.0
Tibia	27	19.1
Femur	43	30.5
Total	141	100.0

The main outcome of the study

Pathological fracture was observed in 17 (12.1 %) cases and accompanied osteosarcoma in 10 (58.8 %) cases that accounted for 14.9 % of all osteosarcoma, and Ewing's sarcoma in 7 (41.2 %) cases that accounted for 10.4 % of all Ewing's sarcomas. LBs were affected in 15 (88.2 %) cases that amounted to 16.4 % of all involved LBs (Table 3).

Table 3

Localization of pathological bone fracture

Location	Number	%
Femur	6	35.3
Tibia	4	23.5
Humerus	4	23.5
Radius	1	5.9
Ilium	1	5.9
Calcaneus	1	5.9
Total	17	100.0

Absence of initial metastases in the presence of a fracture was seen in 13 (75.5 %) children that accounted for 13.5 % of all patients with a localized process and disseminated condition was observed in 4 (23.5 %) patients that accounted for 8.9 % of all patients with disseminated involvement.

Registration of outcomes

The diagnosis of a pathological fracture was based on oncological examination and included standard radiography and RCT.

Statistical analysis

Statistical data processing was performed using the IBM SPSS 23.0 program for Windows. The $\chi 2$ Pearson test using contingency tables was employed to compare nonparametric variables. Survival was assessed with the Kaplan-Mayer method and the Log-Rank criterion. The difference was considered significant at $p < 0.05$.

RESULTS

The rare pathology that reduces the oncological alertness of primary care physicians, the lack of available MRI at the first stage affected the detection of the incidence of bone sarcomas. Unfortunately, timely diagnosis and treatment of a malignant tumor were initiated in 69 (48.9 %) patients only. Four (2.8 %) patients sought medical care in a delayed manner, 7 (5.0 %) children had a latency, 8 (5.7 %) patients were incompletely examined that led to late verification of the diagnosis and failed primary diagnosis was seen in 53 (37.6 %) cases. Errors in the diagnosis of bone sarcomas were found in children with/without a fracture without statistically significant differences with χ^2-Person of 0.239 (Table 4).

Neglected pediatric cases with/without a fracture were caused by diagnostic errors including incomplete examination seen in 10 (58.8 %) and 51 (41.1 %) cases. Bone involvement was not detected in children with a fracture due a pathological focus (n = 3) due to the lack of imaging modalities, two children underwent dynamic observation and PTL was administered for 1 child diagnosed with muscle strain. The fracture was regarded as post-traumatic in two cases and was immobilized with plaster cast and resulted from dystrophic changes in the bone in 1 case. Pathological focus was treated as osteomyelitis with a sequester in 3 cases including 1 case histologically confirmed and antibiotics prescribed. Histologically confirmed chondromyxoid fibroma was diagnosed in the 1st case.

Table 4

Causes of untimely diagnosis and treatment of bone sarcomas in children

A cause	Fracture diagnosed		No fracture diagnosed	
	n	%	n	%
Incomplete examination	2	11.8	6	4.8
Untimely reference	0	0	4	3.2
Latency	0	0	7	5.6
Errors of clinical diagnosis	2	11.8	22	17.7
Errors in imaging	4	23.5	19	15.3
Errors of histological diagnosis	2	11.8	4	3.2
Timely diagnosis	7	41.2	62	50.0
Total	17	100.0	120	100.0

There were no statistically significant differences in the frequency of initial metastasis in groups with/without a fracture with χ^2-Person of 0.429 that may be due to the absence of surgical interventions on the pathological focus and internal bone fixation. Special antitumor treatment was performed for 126 (89.4 %) children, including those with pathological fractures (n = 16 (12.7 %)) with 3 of them (2.4 %) receiving treatment and 110 (87.3 %) children have achieved remission. Antitumor treatment was not performed due to parental refusal or inadequate treatment reported in 15 (10.6 %) patients. Local tumor control was performed for 120 (95.2 %) patients: surgical treatment of primary tumor was performed for 99 (78.6 %) patients and RT was performed in 52 (41.3 %) patients including postoperative treatment (n = 31 (24.6 %)). Six (4.8 %) patients did not undergo local control: 3 children receiving induction PCT, 1 child died during induction therapy and the condition progressed to the local control stage in 2 cases. There were no statistically significant differences in the volume of surgical interventions in children with/without fracture with χ^2-Person = 0.239. Organ resecting procedures were performed with equal frequency due to continuing tumor growth with PCT performed (Table 5). Two children with pathological fractures associated with Ewing sarcoma of the left calcaneus and metastases to vertebrae, skull, pelvis, scapula, sternum and Ewing sarcoma of the left iliac bone underwent RT to the extent being equivalent to radical tumor removal.

Table 5

The volume of surgical interventions performed for primary tumor

Surgery	Fracture diagnosed		No fracture diagnosed	
	n	%	n	%
Joint replacement	10	71.4	47	55.3
Amputation	1	7.1	6	7.1
Other	3	21.4	32	37.6
Total	14	100.0	85	100.0

Resection of the left radius, transposition of the left ulna to the distal epiphysis of the left radius, resection of the right tibia with allografting and osteosynthesis (in Germany), resection of the tumor of the lower third of the left tibia with Ilizarov fixation (in China) were procedures performed for pathological fractures added to arthroplasty as a most common intervention for bone tumors (Table 6).

Table 6

Joint replacement for bone sarcomas

The joint/bone resected	Fracture diagnosed		No fracture diagnosed	
	n	%	n	%
Hip	1	10.0	4	8.2
Knee and the distal femur	3	30.0	21	42.9
Knee and proximal tibia, plasty with transferred medial crura of the gastrocnemius	2	20.0	9	18.4
The whole femur	1	10.0	5	10.2
Shoulder joint	2	20.0	5	10.2
The whole humerus	1	10.0	1	2.0
The whole tibia	–	–	1	2.0
Tibial shaft	–	–	1	2.0
Total	10	100.0	47	95.9

Four standard implants including 4 modular and 2 extendable (non-invasive and minimally invasive design)were used for patients with a pathological fracture. Function assessed with the MSTS at 12 months of arthroplasty scored 70 ± 7, SD = 23, median = 77 in children with a fracture and 69 ± 3, SD = 23, median = 77 without a fracture without statistically significant differences with χ^2-Person = 0.364. A complication developed after joint replacement in 1 patient with a pathological fracture included dislocation of the head of a total biarticulated femoral implant (mechanical type, 3A according to Henderson, 2014 [11]) and was treated with revision arthroplasty using a tailored implant for the left acetabulum, reduction of the dislocation of the head component of the left femur. 14 standard joint replacements with 13 modular and 20 expandable endoprostheses with 15 non-invasive and 5 minimally invasive designs were used for patients without fractures. Complications of joint replacement included local recurrence, type 5 according to Henderson (2014) seen in 4 (7.0 %) cases including 1 with a pathological fracture and 3 without a fracture. A local recurrence developed in 1 child with a pathological fracture who underwent transposition of the left ulna to the distal epiphysis of the left radius performed for Ewing's sarcoma.

Now 82 (58.2 %) children are alive, 59 (41.8 %) died, including 15 children who did not receive anticancer therapy (Table 7).

Table 7

The outcome of the disease in children with bone sarcomas

Outcome	Fracture diagnosed		No fracture diagnosed	
	n	%	n	%
Live without disease	9	56.3	66	60.0
Recurrence, died	6	37.5	23	20.9
Died at IMRT	–	–	1	0.9
Died on neoadjuvant chemotherapy	–	–	1	0.9
Progression	–	–	10	9.1
Died after surgery	–	–	1	0.9
Another / secondary tumor	–	–	1	0.9
Rucurrence, live	1	6.3	2	1.8
Died from other cause	–	–	1	0.9
Receiving treatment	–	–	4	3.6
Total	16	100.0	110	100.0

Assessment of the impact of a pathological fracture on the 5-year overall survival of children with bone sarcomas was based on overall survival calculated for 104 (73.8 %) patients who completed antitumor therapy in 2014 and amounted to 66.3 ± 4.6 %. No statistically significant differences were found (p Log Rank = 0.706) in the 5-year overall survival of 11 (10.6 %) children with fractures and 93 (89.4 %) children without fractures measuring 63.6 ± 14.5 % and 66.7 ± 4.6 %, respectively (Fig. 1).

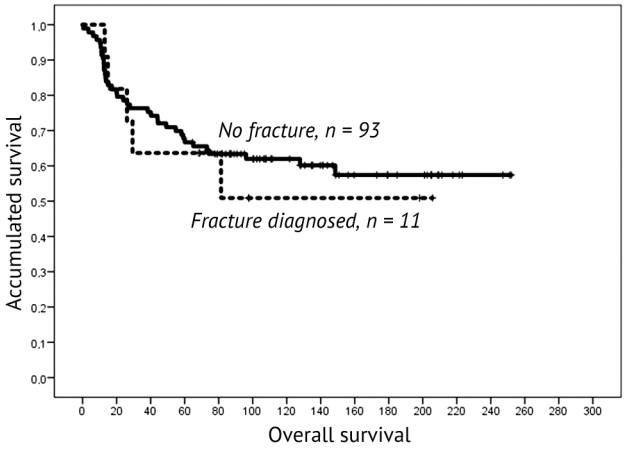

Fig. 1 Overall survival of children with bone sarcomas

A clinical instance of a 12-year-old girl G. who fell ill in early June 2014, when she developed a sore throat, an increase in body temperature up to 38.3 degrees. Her mother reported a swelling in the lower third of the left thigh after 3 days from the onset of the disease. She received antibiotics, PTL with a short-term effect. She was re-examined and physical examination and imaging showed a tumor of the lower third of the metadiaphysis of the left femur that was marginally resected together with a soft tissue component in June 2014. Histological examination revealed conventional osteogenic sarcoma, osteoblastic type. The child was referred to an oncology hospital and finally diagnosed with osteosarcoma of the left femur, stage IIB, T2N0M0, closed pathological fracture of the left femur diaphysis and angular displacement after a comprehensive examination (Fig. 2).

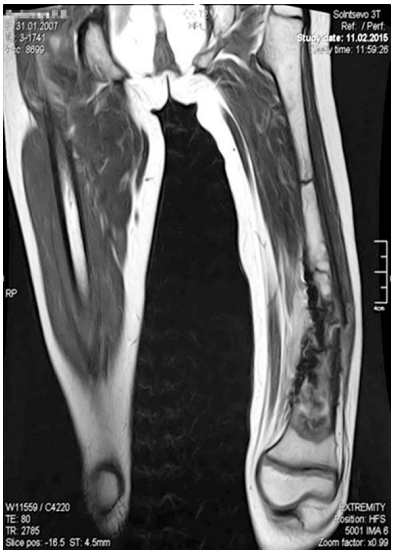

Fig. 2 Preoperative MRI of the left femur of patient G.

Combined treatment performed between August 2014 and October 2015 included program PCT with high-dose methotrexate, organ-preserving surgical treatment with total arthroplasty of the left femur using biarticular expandable endoprosthesis. The treatment resulted in a full clinical effect of drug pathomorphosis of the 4th degree, resection of R0 (Fig. 3).

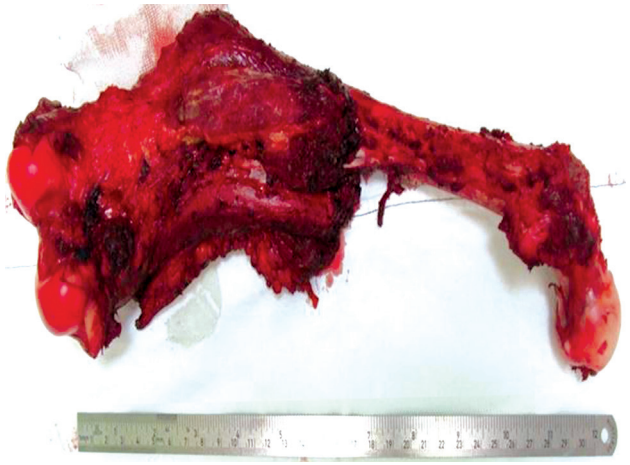

Fig. 3 Macropreparation of the left femur and the tumor resected

The patient underwent regular sessions of distraction of endoprosthesis of the left femur up to 7 cm followed by a course of rehabilitation. Clinical and radiological signs of dislocated endoprosthetic head appeared in October 2017 with greater lameness, "duck" gait and instability of the implant. Joint replacement was performed in December 2019 using a tailored implant component for the left acetabulum and dislocated endoprosthetic head of the left femur was reduced (Fig. 4).

Limb length discrepancy was 6 cm after the revision surgery with the reserve for expandable endoprosthesis of 5 cm. Comprehensive examination demonstrated complete remission maintained at the decreed time.

The clinical instance showed that intensive antitumor therapy was helpful in providing complete remission despite diagnostic errors and inadequate treatment at the first stage. Unfortunately, complications of joint replacement performed in childhood are inevitable as are the consequences of antitumor treatment.

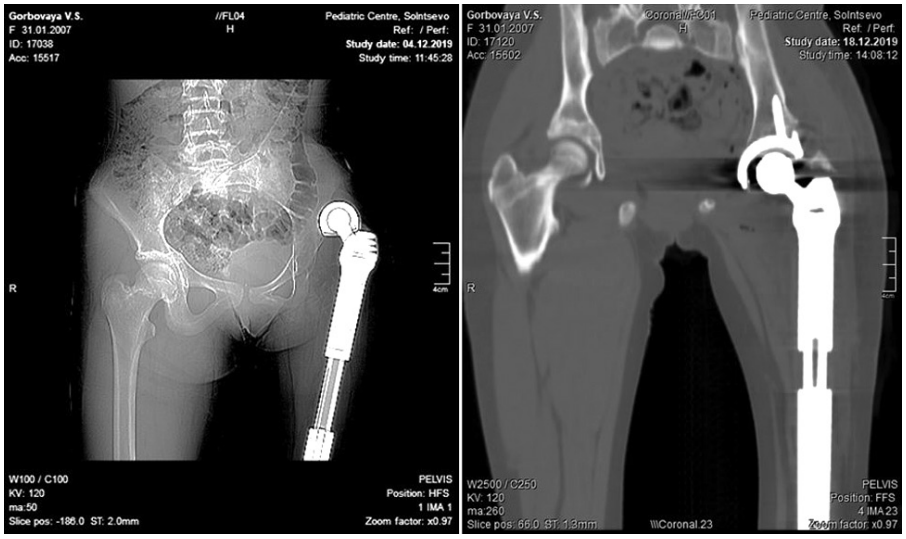

Fig. 4 Patient G. CT scan of the left hip joint before and after revision arthroplasty

DISCUSSION

Pathological fractures occur in OS patients either spontaneously or as a result of minimal trauma [12]. Pediatric pathological fractures must be treated after obtaining a biopsy and establishing a histological diagnosis [13]. We believe that each case of late treatment should be carefully analyzed in order to improve the quality of medical care provided to patients and protect medical staff from a mistake. Ruggieri et al. suggested that fractures should initially be treated with external fixation to avoid microscopic spread of the tumor [4]. Transosseous osteosynthesis with an external fixation device can be used after tumor verification if intensive chemotherapy accompanied by grade III–IV hematological toxicity is not anticipated. It should be taken into account that against the background of in patients with Ewing's sarcoma, osteosarcoma, There is a greater risk of pin tract infection and sepsis that can lead to death of osteosarcoma patients who develop neutropenia, anemia, thrombocytopenia that inevitably develop after each course of chemotherapy. Transosseous osteosynthesis with an external fixation device is commonly used for adult patients with pathological fractures due to a metastatic bone lesion or to replace post-resection defects [14–16]. Indications for the use of the method may include low-grade bone sarcomas that are not seen in children or metastatic lesion of the bones from an extraskeletal primary focus in palliative patients and it should be used with hormone therapy, treatment with bisphosphonates and monoclonal antibodies.

The patients of our series underwent immobilization of the limb using orthoses or plaster casts. Two larger studies indicated that a pathological fracture was significantly associated with an increased recurrence rate [8, 17]. However, multiple studies reported no such findings [9, 18–26]. Our results support these later studies. We found that the local recurrence rate was lower in patients with a pathological fracture than among those without fractures. Preoperative records of a patient with a pathological fracture showed that the fracture was not an indication for amputation. The cause for the amputation was progression of the tumor and neurovascular impairment. Our series and those reported by Bramer et al., Pan et al., showed no difference in overall survival between the two groups due to the fact that pathomorphosis and the effect of chemotherapy were independent predictors of outcome [9, 27]. The local recurrence rate in patients with a pathological fracture is reported to range between 10

and 26 % [9, 18, 19, 21, 28, 29]. We report a lower local recurrence in 2 (12.5 %) patients with a pathological fracture who received anticancer treatment. Our study does not support the data of other researchers comparing functional outcomes in patients with and without a pathological fracture [19, 28]. We did not find that patients with a pathological fracture had statistically significant worse functional outcomes compared with patients without a fracture. There is controversy as to whether a pathological fracture has prognostic value. Scully et al., Bramer et al., Coley et al., Ferguson et al., Lee et al., Sun et al. reported a reduction in overall survival in patients with pathological fractures due to tumor dissemination [8, 9, 18, 22 , 24, 28]. However, other investigators reported no reduction in overall survival in patients with a pathological fracture [12, 20, 23, 25, 30]. Our results are consistent with recent researches. There was no significant difference between final outcomes in patients with and without a pathological fracture. Xi et al. concluded that organ-sparing surgery could be used in patients with a pathological fracture without increasing the risk of distant metastases [20]. Our findings [31, 32] indicate to the same conclusion, but our results must be interpreted with limitations due to the small population size because of the rarity of pathological fractures in patients with bone sarcomas.

CONCLUSION

A pathological process is to be ruled out in the presence of a fracture. If a pathological focus is suspected adequate imaging including MRI to be followed by a biopsy in a specialized oncological institution is to be provided. Pathological fractures can be fixed with a plaster cast or brace/orthosis only. Internal fixation is contraindicated in the initially diagnosed process to avoid bone and soft tissue contamination with tumor cells with higher risk of local recurrence and distant metastasis. Fixation of a pathological fracture by intraosseous, extraosseous or extrafocal osteosynthesis can be used for palliative purposes, to improve the the patient's quality of life. Pathological fractures in bone sarcomas should not be considered as an absolute indication for amputation. Organ-removing interventions are performed only in case of progression of the process with use of PCT. Organ-sparing treatment for a pathological fracture demonstrate no increased risk of recurrence, either local or metastatic. The pathological fracture did not lead to the reduction in functional outcomes compared to patients without fractures.

REFERENCES

1. Canavese F., Samba A., Rousset M. Pathological fractures in children: Diagnosis and treatment options. *Orthop. Traumatol. Surg. Res*., 2016, vol. 102, no. 1 Suppl., pp. S149-S159. DOI: 10.1016/j.otsr.2015.05.010.
2. Stiller C.A., Craft A.W., Corazziari I.; EUROCARE Working Group. Survival of children with bone sarcoma in Europe since 1978: results from the EUROCARE study. *Eur. J. Cancer*, 2001, vol. 37, no. 6, pp. 760-766. DOI: 10.1016/s0959-8049(01)00004-1.
3. Papagelopoulos P.J., Mavrogenis A.F., Savvidou O.D., Benetos I.S., Galanis E.C., Soucacos P.N. Pathological fractures in primary bone sarcomas. *Injury*, 2008, vol. 39, no. 4, pp. 395-403. DOI: 10.1016/j.injury.2007.07.018.
4. Ruggieri P., Mavrogenis A.F., Casadei R., Errani C., Angelini A., Calabrò T., Pala E., Mercuri M. Protocol of surgical treatment of long bone pathological fractures. *Injury*, 2010, vol. 41, no. 11, pp. 1161-1167.
5. Casali P.G., Bielack S., Abecassis N., Aro H.T., Bauer S., Biagini R., Bonvalot S., Boukovinas I., Bovee J.V.M.G., Brennan B., Brodowicz T., Broto J.M., Brugières L., Buonadonna A., De Álava E., Dei Tos A.P., Del Muro X.G., Dileo P., Dhooge C., Eriksson M., Fagioli F., Fedenko A., Ferraresi V., Ferrari A., Ferrari S., Frezza A.M., Gaspar N., Gasperoni S., Gelderblom H., Gil T., Grignani G., Gronchi A., Haas R.L., Hassan B., Hecker-Nolting S., Hohenberger P., Issels R., Joensuu H., Jones R.L., Judson I., Jutte P., Kaal S., Kager L., Kasper B., Kopeckova K., Krákorová D.A., Ladenstein R., Le Cesne A., Lugowska I., Merimsky O., Montemurro M., Morland B., Pantaleo M.A., Piana R., Picci P., Piperno-Neumann S., Pousa A.L., Reichardt P., Robinson M.H., Rutkowski P., Safwat A.A., Schöffski P., Sleijfer S., Stacchiotti S., Strauss S.J., Sundby Hall K., Unk M., Van Coevorden F., van der Graaf W.T.A., Whelan J., Wardelmann E., Zaikova O., Blay J.Y.; ESMO Guidelines Committee, PaedCan and ERN EURACAN. Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol*., 2018, vol. 29, no. Suppl. 4, pp. iv79-iv95. DOI: 10.1093/annonc/mdy310.
6. Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. *Clin. Orthop. Relat. Res*., 1989, no. 249, pp. 256-264.
7. Haynes L., Kaste S.C., Ness K.K., Wu J., Ortega-Laureano L., Bishop M., Neel M., Rao B., Fernandez-Pineda I. Pathologic fracture in childhood and adolescent osteosarcoma: A single-institution experience. *Pediatr. Blood Cancer*, 2017, vol. 64, no. 4. DOI: 10.1002/pbc.26290.
8. Scully S.P., Ghert M.A., Zurakowski D., Thompson R.C., Gebhardt M.C. Pathologic fracture in osteosarcoma: prognostic importance and treatment implications. *J. Bone Joint Surg. Am*., 2002, vol. 84, no. 1, pp. 49-57.
9. Bramer J.A., Abudu A.A., Grimer R.J., Carter S.R., Tillman R.M. Do pathological fractures influence survival and local recurrence rate in bony sarcomas? *Eur. J. Cancer*, 2007, vol. 43, no. 13, pp. 1944-1951. DOI: 10.1016/j.ejca.2007.07.004.
10. Ogura K., Fujiwara T., Yasunaga H., Matsui H., Jeon D.G., Cho W.H., Hiraga H., Ishii T., Yonemoto T., Kamoda H., Ozaki T., Kozawa E., Nishida Y., Morioka H., Hiruma T., Kakunaga S., Ueda T., Tsuda Y., Kawano H., Kawai A. Development and external validation of nomograms predicting distant metastases and overall survival after neoadjuvant chemotherapy and surgery for patients with nonmetastatic osteosarcoma: A multi-institutional study. *Cancer*, 2015, vol. 121, no. 21, pp. 3844-3852. DOI: 10.1002/cncr.29575.
11. Henderson E.R., O'Connor M.I., Ruggieri P., Windhager R., Funovics P.T., Gibbons C.L., Guo W., Hornicek F.J., Temple H.T., Letson G.D. Classification of failure of limb salvage after reconstructive surgery for bone tumours: a modified system including biological and expandable reconstructions. *Bone Joint J*., 2014, vol. 96-B, no. 11, pp. 1436-40. DOI: 10.1302/0301-620X.96B11.34747.
12. Jaffe N., Spears R., Eftekhari F., Robertson R., Cangir A., Takaue Y., Carrasco H., Wallace S., Ayala A., Raymond K., et al. Pathologic fracture in osteosarcoma. Impact of chemotherapy on primary tumor and survival. *Cancer*, 1987, vol. 59, no. 4, pp. 701-709. DOI: 10.1002/1097-0142(19870215)59:4<701::aid-cncr2820590407>3.0.co;2-v.
13. Jackson W.F., Theologis T.N., Gibbons C.L., Mathews S., Kambouroglou G. Early management of pathological fracture in children. *Injury*, 2007, vol. 38, no. 2, pp. 194-200. DOI: 10.1016/j.injury.2006.07.040.

14. Protsenko V.V., Ilnitskii A.V., Chernyi V.S. Rezultaty osteosinteza patologicheskikh perelomov dlinnykh kostei pri metastaticheskikh opukholiakh [Results of osteosynthesis of pathological fractures of long bones in metastatic tumors]. *Travma*, 2016, vol. 17, no. 2, pp. 64-68. (in Russian)
15. Balaev P.I., Borzunov D.Yu. Chreskostnyi osteosintez v ortopedicheskoi reabilitatsii bolnykh s pervichnymi opukholiami kostei goleni [Transosseous osteosynthesis in orthopedic rehabilitation of patients with primary tumors of the leg bones]. *Zabaikalskii Meditsinskii Vestnik*, 2013, no. 2, pp. 51-58. (in Russian)
16. Balaev P.I., Borzunov D.Yu. Errors and complications in management of primary long bone tumors in the lower limbs with the Ilizarov transosseous osteosynthesis. *Genij Ortopedii*. 2018. T. 24. No 2. pp. 164-167. DOI 10.18019/1028-4427-2018-24-2-164-167.
17. Abudu A., Sferopoulos N.K., Tillman R.M., Carter S.R., Grimer R.J. The surgical treatment and outcome of pathological fractures in localised osteosarcoma. *J. Bone Joint Surg. Br*., 1996, vol. 78, no. 5, pp. 694-698.
18. Coley B.L., Pool J.L. Factors influencing the prognosis in osteogenic sarcoma. *Ann. Surg*., 1940, vol. 112, no. 6, pp. 1114-1128. DOI: 10.1097/00000658-194012000-00010.
19. Zuo D., Zheng L., Sun W., Hua Y., Cai Z. Pathologic fracture does not influence prognosis in stage IIB osteosarcoma: a case-control study. *World J. Surg. Oncol*., 2013, vol. 11, pp. 148. DOI: 10.1186/1477-7819-11-148.
20. Xie L., Guo W., Li Y., Ji T., Sun X. Pathologic fracture does not influence local recurrence and survival in high-grade extremity osteosarcoma with adequate surgical margins. *J. Surg. Oncol*., 2012, vol. 106, no. 7, pp. 820-825. DOI: 10.1002/jso.23150.
21. Natarajan M.V., Govardhan R.H., Williams S., Raja Gopal T.S. Limb salvage surgery for pathological fractures in osteosarcoma. *Int. Orthop*., 2000, vol. 24, no. 3, pp. 170-172. DOI: 10.1007/s002640000143.
22. Sun L., Li Y., Zhang J., Li H., Li B., Ye Z. Prognostic value of pathologic fracture in patients with high grade localized osteosarcoma: a systemic review and meta-analysis of cohort studies. *J. Orthop. Res*., 2015, vol. 33, no. 1, pp. 131-139. DOI: 10.1002/jor.22734.
23. Bacci G., Ferrari S., Longhi A., Donati D., Manfrini M., Giacomini S., Briccoli A., Forni C., Galletti S. Nonmetastatic osteosarcoma of the extremity with pathologic fracture at presentation: local and systemic control by amputation or limb salvage after preoperative chemotherapy. *Acta Orthop. Scand*., 2003, vol. 74, no. 4, pp. 449-454. DOI: 10.1080/00016470310017776.
24. Lee R.K., Chu W.C., Leung J.H., Cheng F.W., Li C.K. Pathologic fracture as the presenting feature in pediatric osteosarcoma. *Pediatr. Blood Cancer*, 2013, vol. 60, no. 7, pp. 1118-1121. DOI: 10.1002/pbc.24447.
25. Kim M.S., Lee S.Y., Lee T.R., Cho W.H., Song W.S., Cho S.H., Lee J.A., Yoo J.Y., Jung S.T., Jeon D.G. Prognostic effect of pathologic fracture in localized osteosarcoma: a cohort/case controlled study at a single institute. *J. Surg. Oncol*., 2009, vol. 100, no. 3, pp. 233-239. DOI: 10.1002/jso.21265.
26. Bishop M.W., Chang Y.C., Krailo M.D., Meyers P.A., Provisor A.J., Schwartz C.L., Marina N.M., Teot L.A., Gebhardt M.C., Gorlick R., Janeway K.A., Chou A.J. Assessing the prognostic significance of histologic response in osteosarcoma: a comparison of outcomes on CCG-782 and INT0133 – A report from the Children's Oncology Group Bone Tumor Committee. *Pediatr. Blood Cancer*, 2016, vol. 63, no. 10, pp. 1737-1743. DOI: 10.1002/pbc.26034.
27. Pan H.Y., Morani A., Wang W.L., Hess K.R., Paulino A.C., Ludwig J.A., Lin P.P., Daw N.C., Mahajan A. Prognostic factors and patterns of relapse in Ewing sarcoma patients treated with chemotherapy and r0 resection. *Int. J. Radiat. Oncol. Biol. Phys*., 2015, vol. 92, no. 2, pp. 349-357. DOI: 10.1016/j.ijrobp.2015.01.022.
28. Ferguson P.C., McLaughlin C.E., Griffin A.M., Bell R.S., Deheshi B.M., Wunder J.S. Clinical and functional outcomes of patients with a pathologic fracture in high-grade osteosarcoma. *J. Surg .Oncol*., 2010, vol. 102, no. 2, pp. 120-124. DOI: 10.1002/jso.21542.
29. Saraph V., Linhart W.E. Modern treatment of pathological fractures in children. *Injury*, 2005, vol. 36, no. Suppl. 1, pp. A64-A74. DOI: 10.1016/j.injury.2004.12.015.
30. Malagelada F., Tarrago L.T., Tibrewal S., Ibanez A.P., Jeyaseelan L., Alegria I.G. Pathological fracture in osteosarcoma: is it always an indication for amputation? *Ortop. Traumatol. Rehabil*., 2014, vol. 16, no. 1, pp. 67-74. DOI: 10.5604/15093492.1097490.
31. Petrichenko A.V., Bukreeva E.A., Romanov P.A., Tiganova O.A., Ivanova N.M., Ochkurenko A.A., Snetkov A.I., Kozhevnikov O.V., Morozov A.K. Analiz ortopedicheskikh posledstvii mnogokomponentnogo lecheniia kostnykh sarkom u detei [Analysis of orthopedic consequences of multicomponent treatment of bone sarcomas in children]. *Ortopediia, Travmatologiia i Vosstanovitelnaia Khirurgiia Detskogo Vozrasta*, 2019, vol. 7, no. 1, pp. 57-70. (in Russian)
32. Petrichenko A.V. *Ortopedicheskie posledstviia, oslozhneniia i rezultaty protivoopukholevogo lecheniia kostnykh sarkom u detei. Diss. dokt. med. nauk* [Orthopedic consequences, complications and results of antitumor treatment of bone sarcomas in children. Dr. med. sci. diss.]. M., 2020, 255 p. (in Russian)

The article was submitted 30.11.2020; approved after reviewing 29.07.2021; accepted for publication 26.01.2022.

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