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Galectin-3 in the blood serum of patients with bone tumors

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ABSTRACT

Background. Due to diversity of cancer, the functional role of galectin-3 is rather controversial; however, for many types of neoplasms, the marker acts as a tumor growth promoter.

Aim. To perform a comparative analysis of galectin-3 levels in the blood serum of healthy individuals and patients with benign, borderline, and malignant bone tumors divided into two age groups (under and over 18 years of age) based on the main clinical and morphological characteristics of the disease and prognosis.

Materials and methods. The study included 201 patients with benign, borderline (giant cell tumors, locally aggressive tumors), and malignant bone tumors and 31 healthy donors. The galectin-3 level was determined in the blood serum before treatment with Human Galectin-3 ELISA kit (R&D, USA).

Results. The level of galectin-3 in the blood serum of patients with benign and malignant bone tumors was statistically significantly higher than that in the control group of patients both under and over 18 years. In patients with borderline bone tumors, a trend toward an increase in the galectin-3 concentration compared with the controls was revealed. The ROC analysis for galectin-3 in patients with bone sarcomas showed that the area under the curve (AUC) comprised 0.795 ($p < 0.0001$) in the group of patients over 18 years and 0.868 ($p = 0.0008$) in the individuals under 18 years. For malignant bone tumors in patients over 18 years, the sensitivity of this method was 71.3%, and specificity was 71.43% (optimal cut-off level was 8.09 ng / ml; $p < 0.0001$), while in patients under 18 years, the sensitivity of the method was 80%, and specificity was 90% (optimal cut-off level was 5.49 ng / ml; $p < 0.001$). No significant associations between the serum galectin-3 level and the clinical and morphological characteristics of bone neoplasms were found both in patients under and over 18 years of age. However, it could be noted that the highest concentration of the marker was found in chordomas and at earlier stages of the disease. In patients over 18 years with chondrosarcoma and osteosarcoma, no correlation between the marker and the disease prognosis was found.

Conclusion. An increase in the galectin-3 level in the blood serum was observed in all age groups of patients with both benign and malignant bone tumors. However, the sensitivity and specificity of the method assessed by the ROC analysis do not allow to apply this marker for the diagnosis of bone tumors.

Keywords: bone tumors, galectin-3, blood serum, prognosis

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Галектин-3 в сыворотке крови больных опухолями костей

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РЕЗЮМЕ

Введение. Ввиду многогранности онкологических заболеваний функциональная роль галектина-3 достаточно противоречива, однако для многих типов новообразований маркер играет роль промотора опухолевого роста.

Цель исследования – сравнительный анализ уровней галектина-3 в сыворотке крови здоровых доноров, больных доброкачественными, пограничными и злокачественными новообразованиями костей в двух возрастных группах до и старше 18 лет с учетом основных клинико-морфологических характеристик заболевания и прогноза.

Материалы и методы. В исследование включен 201 пациент с доброкачественными, пограничными (гигантоклеточные опухоли, «локально агрессивные» опухоли), злокачественными новообразованиями костей и 31 здоровый донор. Концентрацию галектина-3 определяли в сыворотке крови до лечения наборами реактивов для прямого иммуноферментного анализа Human Galectin-3 (R&D, США).

Результаты. Показано, что содержание галектина-3 в сыворотке крови больных доброкачественными и злокачественными опухолями костей статистически значимо выше, чем в контрольной группе, как в возрасте до, так и старше 18 лет. У пациентов с пограничными опухолями костей отмечена тенденция к увеличению концентрации галектина-3 по сравнению с контролем. ROC-анализ для галектина-3 у больных саркомами костей показал, что площадь под ROC-кривой составила 0,795 ($p < 0,0001$) в группе пациентов в возрасте старше 18 лет и 0,868 ($p = 0,0008$) в группе пациентов в возрасте до 18 лет. Для злокачественных новообразований костей у больных в возрасте старше 18 лет чувствительность данного метода составила 71,3%, специфичность 71,43% (пороговый уровень 8,09 нг/мл; $p < 0,0001$), а у пациентов в возрасте младше 18 лет чувствительность этого метода составила 80%, специфичность 90% при пороговом уровне 5,49 нг/мл ($p < 0,001$). В обеих возрастных группах не найдено значимых ассоциаций содержания сывороточного галектина-3 с клинико-морфологическими характеристиками новообразований костей, однако следует отметить, что наибольшая концентрация маркера обнаружена при хордомах и на более ранних стадиях заболевания. У больных хондросаркомой и остеосаркомой старше 18 лет не выявлено связи маркера с прогнозом заболевания.

Заключение. Повышение содержания галектина-3 в сыворотке крови наблюдалось во всех возрастных группах пациентов как с доброкачественными, так и злокачественными новообразованиями костей, однако чувствительность и специфичность теста по данным ROC-анализа недостаточны для использования данного маркера для диагностики опухолей костей.

Ключевые слова: опухоли костей, галектин-3, сыворотка крови, прогноз

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Galectins are a group of galactoside-binding lectins that play specific roles both intra- and extracellularly. They trigger cytokine secretion and cellular migration, proliferation, and apoptosis. Extracellularly, galectins facilitate cell – cell interactions and interaction of cells with the extracellular matrix. Galectins bind with glycans (oligosaccharides) on the intracellular membrane surface, participating in ligation of macromolecules and formation of signaling pathways. Diverse functions of galectins have sparked the interest of researchers in unveiling their role in the pathogenesis of various diseases and pathologies.

Out of 15 galectins currently known, galectin-3 attracts special interest of researchers due to its involvement in tissue fibrosis and its potential application as a marker for cardiac failure. Galectin-3 has been found to be involved in various pathological processes, including inflammation [2], fibrosis, as well as cardiac [3, 4] and kidney [5] diseases, diabetes mellitus [6], viral infections [7], autoimmune [8] and neurodegenerative [9] diseases, and cancer [10].

The functional role of galectin-3 in the context of cancers is rather controversial, owing to their diversity. On the one hand, galectin-3 plays a role as a tumor growth promoter for many types of neoplasms. An increase in the expression of this protein is associated with proliferation and invasion of pancreatic cancer cells [11]. Galectin-3 expression, both at the mRNA and protein level, is increased in malignant liver tumors compared to normal tissues [12]. Overexpression of galectin-3 is also observed in diffuse large B-cell lymphoma and is associated with an advanced stage and a worse prognosis of this disease [13]. Increased galectin-3 expression correlates with an unfavorable prognosis in patients with nasopharyngeal carcinoma [14] and colorectal cancer [15]. Increased galectin-3 expression was also found in gastric tumors [16], and its overexpression and nuclear localization were associated with peritoneal dissemination of such tumors [17]. Galectin-3 overexpression led to the intensification of motility and invasion of lung cancer cells [18].

On the other hand, in some tumor types, galectin-3 may function as a tumor suppressor. Thus, a decrease in its expression is associated with a more malignant phenotype of breast and endometrial cancer [19]. For prostate cancer, a gradient decrease in galectin-3 expression from normal and conventionally normal tissue to tumor one was observed [20]. Suppression of the expression of this protein by siRNA reduced the migratory, invasive, and colony-forming ability of prostate cancer cells [21].

Although galectin-3 expression has been studied in the majority of solid tumors, its functional role in bone neoplasms is still unknown. An increased level of galectin-3 in the blood serum of osteosarcoma patients was reported, and its expression in the tumor was higher than in adjacent healthy tissues and correlated with disease stage and metastasis. The authors suggest that in the future, galectin-3 might become a prognostic marker for osteosarcoma [22]. It was shown that suppression of galectin-3 expression in osteosarcoma cells *in vitro* led to a decline in their metastatic potential [23]. Some authors suggest that galectin-3 may serve as a marker for the differential diagnosis of chordomas and myxoid chondrosarcomas. No data are available on the association between the levels of tissue and soluble forms of galectin-3 for other types of bone tumors.

The aim of this study was to perform a comparative analysis of galectin-3 levels in the blood serum of healthy individuals and patients with benign, borderline, and malignant bone tumors, taking into consideration the clinical and pathological characteristics of the disease and its prognosis.

MATERIALS AND METHODS

The study involved 201 patients with benign, borderline, and malignant bone tumors, 36 of whom were under 18 years old. The control group comprised 31 healthy individuals, 10 of whom were under 18 years old. All procedures involving patients and healthy individuals performed in the study complied with the standards of the Ethics Committee at N.N. Blokhin National Medical Research Center of Oncology and the Declaration of Helsinki adopted in 1964 and its further amendments or comparable ethical norms. Each study participant signed an informed consent to participate in the study. All patients underwent an examination and treatment at N.N. Blokhin National Medical Research Center of Oncology. The clinical and radiological diagnosis of the neoplasm was confirmed by the morphological examination according to the WHO histologic classification of bone tumors (2020). The main characteristics of the control and bone tumor groups are presented in Table 1–3.

Table 1

Number of patients in the study groups

Study groups	Age under 18 years	Age over 18 years
Control	10 (32.3%)	21 (67.7%)
Benign bone tumors (BBT)	11 (26.2%)	31 (73.8%)
Borderline bone tumors (BlBT)	–	19 (100%)
Malignant bone tumors (MBT)	25 (17.9%)	115 (82.1%)

Table 2

Characteristics of the bone tumor patients aged over 18 years old, *n* (%)

Parameter	Value
Age, years, *Me* (Q_{25}–Q_{75})	48 (34-57)
Sex:	
male;	61 (53.1%)
female	54 (46.9%)
Histologic tumor type:	
osteosarcoma;	35 (30.5%)
chondrosarcoma;	69 (60.0%)
chordoma;	6 (5.3%)
Ewing sarcoma	5 (4.2%)
Stage:	
I;	37 (32.2%)
II;	66 (57.4%)
III–IV	12 (10.4%)
Grade:	
G1–G2;	64 (61.6%)
G3	40 (38.4%)
Tumor size (T):	
T1;	24 (20.9%)
T2;	84 (73.1%)
T3–T4	7 (6.0%)
Nodal status:	
N0;	111 (96.6%)
N1	4 (3.4)
Distant metastasis (M):	
M0	110 (95.7%)
M1	5 (4.3%)
Type of the bone:	
spongy / flat	54 (47.0%)
tubular	61 (53.0%)
Localization:	
upper limb;	21 (18.3%)
thoracic cage / vertebral column;	9 (7.7%)
pelvis;	42 (36.6%)
lower limb	43 (37.4%)

Table 3

Characteristics of the bone tumor patients aged under 18 years old, *n* (%)

Parameter	Value
Age, years, *Me* (Q_{25}–Q_{75})	12 (9–15)
Sex:	
male;	12 (48%)
female	13 (52%)
Histologic tumor type:	
osteosarcoma;	17 (68%)
chondrosarcoma;	1 (28%)
Ewing sarcoma	7 (4%)
Stage:	
I;	–
II;	21 (84%)
III–IV	4 (16%)
Grade:	
G1–G2;	1 (32%)
G3	17 (68%)
Tumor size (T):	
T1;	–
T2;	24 (96%)
T3–T4	1 (4%)
Nodal status:	
N0;	25 (100%)
N1	–
Distant metastasis (M):	
M0	21 (84%)
M1	4 (16%)
Type of the bone:	
spongy / flat	2 (8%)
tubular	23 (92%)
Localization:	
upper limb;	–
thoracic cage / vertebral column;	2 (8%)
pelvis;	1 (4%)
lower limb	22 (88%)

The galectin-3 concentration was measured in pretreatment blood serum using the Human Galectin-3 ELISA kit (R&D, USA) in accordance with the manufacturer's guidelines and expressed in nanograms (ng) per 1 ml of serum.

The data were analyzed using GraphPad Prism 9.4. The nonparametric Mann – Whitney and Kruskal – Wallis tests were used to compare independent groups. Overall survival was assessed using the Kaplan – Meier method, and the statistical significance of differences between the curves was evaluated using the log rank test. The differences were considered statistically significant at $p < 0.05$.

RESULTS

We analyzed the levels of galectin-3 in both the control group and patients with different types of bone tumors. The median serum content of galectin-3 in healthy donors who were over 18 years of age was 6.48 ng / ml, which was significantly lower than in patients with malignant bone tumors within the corresponding age group (10.18 ng / ml; $p < 0.0001$) (Table 4).

Table 4

Galectin-3 level in patients with bone tumors based on age, ng / ml, *Me* (Q_{25}–Q_{75})

Parameter	Age ≥ 18 years	*p*	Age < 18 years	*p*
Control [1]	6.48 (3.32–8.49)	–	4.15 (3.93–5.23)	–
Benign bone tumors [2]	8.72 (6.53–11.45)	0.035 (1vs2)	7.85 (6.69–12.75)	0.001 (1vs2)
Borderline bone tumors[3]	8.88 (6.19–10.88)	0.077 (1vs3)	–	–
Malignant bone tumors[4]	10.18 (7.52–12.55)	< 0.0001 (1vs4)	7.22 (5.92–11.35)	0.002 (1vs4)

The content of galectin-3 in the blood serum of patients with benign and malignant tumors was statistically significantly higher than that in the control group both in adult patients (over 18 years old) and in patients of the younger age group (under 18 years old) (Table 4). For borderline tumors diagnosed only in adult patients, a trend toward an increase in the galectin-3 level was also noted, compared to the control group.

The information value of a galectin-3 level as a diagnostic method was analyzed by evaluating its sensitivity and specificity by the ROC analysis. The results are shown in Fig. 1.

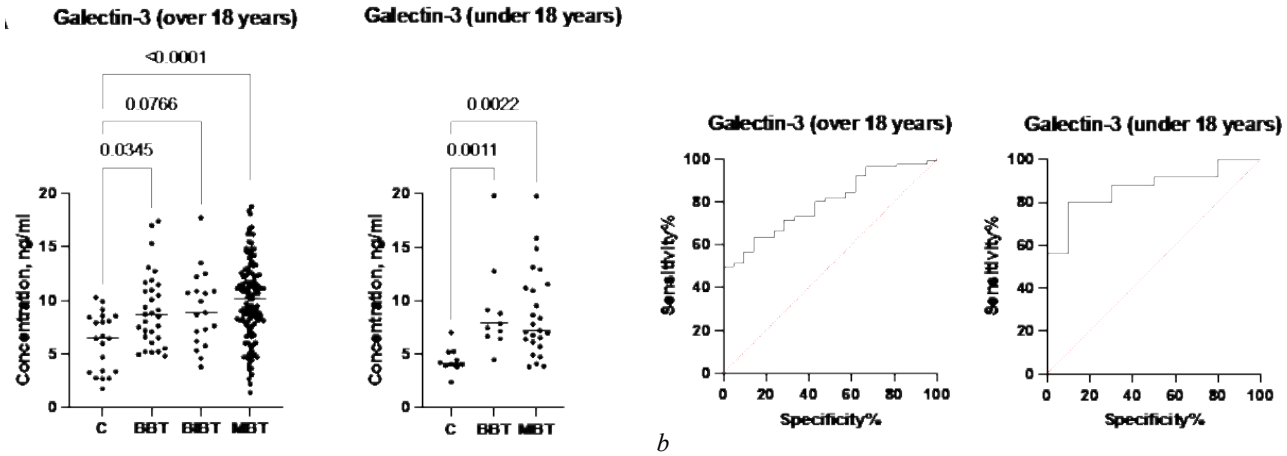

Fig. 1. Serum galectin-3 level in patients with benign, borderline, and malignant bone tumors as well as in healthy donors with regard to age: *a* – comparative analysis, *b* – ROC analysis of the diagnostic value (AUC 0.795 ($p < 0.0001$) in the group of patients over 18 years old and AUC 0.868 ($p = 0.0008$) in the group of patients under 18 years old)

For malignant bone tumors in patients over 18 years of age, the sensitivity was 71.3%, and specificity was 71.4% (the optimal cut-off level was 8.09 ng / ml; $p < 0.0001$), while in patients under 18 years old, the sensitivity of the method was 80%, and specificity was 90% (optimal cut-off level was 5.49 ng / ml; $p < 0.001$).

Next, we analyzed serum galectin-3 levels according to the main clinical and morphological characteristics of the disease for patients over 18 years of age (Table 5).

No significant associations between serum galectin-3 levels and clinical or morphological characteristics of bone neoplasms were found in the age

group of individuals over 18 years old. However, it should be noted that the highest levels of galectin-3 were detected in chordomas and at earlier stages of the disease.

At the next stage of the study, we analyzed galectin-3 levels in the blood serum of patients under 18 years of age, depending on the main clinical and morphological characteristics of the disease (Table 6). No significant associations were found between the main clinical and morphological characteristics of the disease and galectin-3 levels in the group of patients under 18 years old, as well as in the group of patients over 18 years old (Table 5, 6).

Table 5

Serum level of galectin-3 in patients with malignant bone tumors aged over 18 years depending on the clinical and morphological characteristics of the disease

Parameter	Galectin-3, ng / ml		
	Me	Q_{25}–Q_{75}	*p*
Age: – <48; – >=48	 9.15 10.66	 6.66–11.6 8.2–13.65	0.084
Sex: – male; – female	 9.21 10.93	 7.12–11.68 7.95–13.73	0.106
Histologic tumor type: – osteosarcoma (1); – chondrosarcoma (2); – chordoma (3); Ewing sarcoma (4)	 10.18 9.5 14.7 9.09	 7.00–11.81 7.49–12.34 11.64–14.62 5.88–14.32	0.06 (2vs3)
Stage: I; II; III–IV	 10.76 9.84 8.99	 7.99–13.34 6.99–11.75 6.51–12.36	>0.99
Grade: G1–G2; G3	 10.25 9.43	 8.13–12.52 6.04–11.57	0.43
Tumor size (T): T1; T2; T3–T4	 10.16 10.25 8.05	 6.67–14.34 8.03–12.19 4.74–12.41	>0.99
Nodal status: N0; N1	 10.31 7.64	 7.74–12.55 4.52–14.5	0.51
Distant metastasis (M): M0 M1	 10.25 9.28	 7.51–12.55 7.36–13.69	0.96
Type of the bone: spongy / flat tubular	 10.67 9.46	 8.18–12.75 6.69–12.31	0.28
Localization: upper limb; thoracic cage / vertebral column; pelvis; lower limb	 8.69 10.17 10.68 10.31	 4.87–12.57 8.85–15.12 7.35–12.59 8.05–12.36	>0.99

Table 6

Serum content of galectin-3 in patients with malignant bone tumors under the age of 18 years depending on the clinical and morphological characteristics of the disease

Characteristic	Galectin-3, ng / ml		
	Me	Q_{25}–Q_{75}	*p*
Age: < 12 >12	 7.07 9.67	 6.13–9.53 4.89–15.1	0.42
Sex: male; female	 9.81 6.54	 6.85–12.57 4.85–8.67	0.12
Histologic tumor type: osteosarcoma (1) chondrosarcoma (2) Ewing sarcoma (3)	 8.38 8.66 6.99	 6.06–12.32 – 4.76–7.81	 >0.99 (1vs2) 0.65 (1vs3) >0.99 (2vs3)
Stage: I (1) II (2) III–IV (3)	 – 6.99 9.92	 – 5.32–11.24 8.02–13.94	 >0.15 (2vs3)
Grade: –G1–G2 –G3	 4.11 7.52	 – 6.2–11.44	 –
Tumor size (T): T1; T2; T3–T4	 7.15 7.81	 8.81–11.44 –	 –
Nodal status: N0; N1	 7.22 –	 5.92–11.35 –	 –
Distant metastasis (M): M0 M1	 6.99 9.92	 5.32–11.24 8.02–13.94	 0.15
Type of the bone: spongy / flat tubular	 6.76 7.22	 5.7–7.81 6.13–11.52	 0.60
Localization upper limb (1) thoracic cage / vertebral column (2) pelvis (3) lower limb (4)	 – 5.92 7.81 7.80	 – 5.7–6.13 – 6.04–11.87	 >0.99 (2vs3) >0.58 (2vs4) > 0.99 (3vs4)

At the final stage of the study, we assessed the prognostic value of the galectin-3 level in the groups of patients aged over 18 years old with the most common malignant bone neoplasms, which were osteosarcoma and chondrosarcoma (Fig. 2).

The presented data show that the serum levels of galectin-3 are not a significant prognostic factor in bone sarcomas for the general group of patients with malignant bone neoplasms, as well as for two experimental groups with bone-forming (osteosarcoma) and cartilage-forming (chondrosarcoma) tumors, respectively.

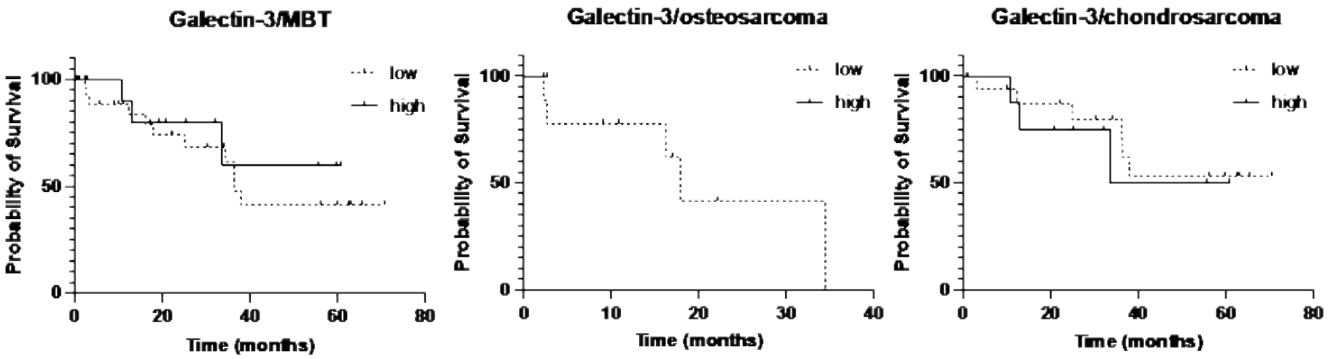

Fig. 2. Prognostic value of the galectin-3 level in three groups: in the general group of patients with malignant bone tumors, in osteosarcoma patients, and in chondrosarcoma patients over 18 years old.

DISCUSSION

A comparative study was conducted to analyze the levels of galectin-3 in the blood serum of patients with benign, borderline, and malignant bone tumors of various histologic types and healthy donors in the control group. The analysis of the data obtained revealed a statistically significant increase in the serum levels of galectin-3 in the majority of patients with bone tumors. It is worth noting that this increase was noted in both age groups (under 18 and over 18 years old) for both benign and malignant bone tumors.

However, the ROC analysis indicated that the sensitivity and specificity of the method were insufficient to use this marker for the diagnosis of bone tumors. Similar findings have been reported in the literature for other types of solid tumors [24], which suggest high sensitivity but low specificity of this biochemical diagnostic method.

In our study, we observed a trend toward an increase in the galectin-3 levels in patients over 18 years old with chordoma, while no significant differences in the galectin-3 levels were observed in other histologic types of bone tumors. In the group of patients under 18 years old, the lowest content of galectin-3 was detected in Ewing sarcoma, that contradicts the data on tissue expression of this protein, which suggests significantly higher expression of galectin-3 in Ewing sarcomas than in osteosarcomas in children [25].

Regarding the association between the galectin-3 level and other clinical and morphological characteristics of the disease, no significant regularities were found in the age group over 18 years old. In the group of patients under 18 years old, we observed a trend toward a rise in the galectin-3 levels in cases with unfavorable clinical characteristics such as advanced stage, presence of metastases, and low grade of tumor differentiation.

However, we did not find any significant prognostic value of serum galectin-3 levels both in the general group of malignant bone tumors and in primary histologic types of bone sarcomas (osteosarcoma and chondrosarcoma). It is worth noting that the prognostic value of galectin-3 is ambiguous in many tumor types, including colorectal cancer, where high levels of this protein are associated with an unfavorable prognosis [26], whereas the opposite results were reported for breast and stomach cancers [27]. Therefore, the significance of galectin-3 in bone tumors requires further investigation.

CONCLUSION

Currently, among the 15 known galectins, galectin-3 attracts the greatest interest of researchers due to its involvement in many pathological processes, including cancer. However, its functional role in malignant tumors is diverse and rather contradictory. On the one hand, it acts as a promoter of tumor growth, and on the other hand, it can function as a tumor suppressor. Our data demonstrated a significant increase in the serum galectin-3 level in patients with benign and malignant bone tumors in comparison to the control group, both in adult patients (over 18 years old) and in younger patients (under 18 years old). Although the diagnostic value of the marker in these two groups was significantly different from the controls according to the ROC analysis, the sensitivity and specificity of galectin-3 alone in patients with bone sarcomas aged < 18 years old was 80% and 90%, respectively (the optimal cut-off level in the controls was 5.49 ng / ml; $p = 0.001$). It may potentially be used as a marker in

the diagnosis of bone sarcomas in a bigger sample in the future.

However, the serum levels of galectin-3 did not differ between patients with benign, borderline, and malignant bone tumors. In addition, the highest levels of galectin-3 were detected in the serum of chordoma patients and at earlier stages of the disease. We did not observe any significant associations of galectin-3 with the main clinical and morphological characteristics of malignant tumors both in the group of patients under 18 years old and in the group of patients over 18 years old.

According to the literature, the prognostic value of galectin-3 in many tumor types is also ambiguous. In this study, the serum galectin-3 level was not a significant prognostic factor in the general group of patients with malignant bone tumors, as well as in the two most commonly revealed bone-forming (osteosarcoma) and cartilage-forming (chondrosarcoma) bone tumors, respectively. It should be noted that at this stage of research, the use of serum galectin-3 as a diagnostic marker of bone tumors has not been fully determined and requires further research.

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Kushlinskii N.E., Gershtein E.S., Yanushevich O.O., Stilidi I.S. – research topic for the study, conception and design, coordination of the study, editing of the article. Kovaleva O.V., Zybina N.N., Jurisic V. – statistical processing of the results, review of literature, drafting of the article. Prishchep P.L., Varfolomeeva S.R, Sushentsov E.A. – work with patients, treatment. Alferov A.A., Kuzmin Yu.B., Kuznetsov I.N. – acquisition of experimental data. Rogozhin D.V., Bulytcheva I.V. – morphological examination of the tumors.

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