

## SELECTED ASPECTS OF THE EPIDEMIOLOGY OF TUMORS AND TUMOR-LIKE DISEASES OF THE SPINE AND SPINAL CORD IN CHILDREN: A 19-YEAR REGIONAL COHORT STUDY IN THE LENINGRAD REGION

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**Background.** Statistical analysis of spinal tumors in children is difficult because of its rarity and different morphology. Benign tumor and tumor-like processes are not included in modern oncology literature even though intracanal tumors have the most severe prognosis and influence on a patient's quality of life.

**Aim.** To evaluate the incidence, epidemiological structure (anatomical, sex, morphological structure), clinical characteristics, and survival of pediatric patients with tumors and tumor-like diseases of the spine and spinal cord in a single region of Russia.

**Materials and methods.** The data of 110 children with tumors and tumor-like diseases of the spine and spinal cord from the Leningrad region who received surgical treatment in Leningrad regional children's hospitals between 1998 and 2016 were included in the study. The authors evaluated the incidence, mortality, and survival rates adjusted for age, sex, morphology, and primary site of growth.

**Results.** The average annual morbidities of pediatric spinal tumors (including the spine and spinal canal) in the Leningradsaya oblast region from 1998 to 2016 were 1.93 per 100 000 pediatric patients and 0.3 per 100 000 for neuro-epithelial tumors of the spinal cord. The mortality rate was 0.2 per 100 000 pediatric patients. Spinal cord tumors of the cranio-vertebral and cervical zones as intramedullary low-malignant and extramedullary malignant metastatic spinal tumors had a negative effect on survival.

**Conclusions.** The Leningrad regional data were generally comparable with the cancer registry data of other countries. The data suggest that pediatric spinal cord patients should be treated in regional neurosurgical pediatric clinics.

**Keywords:** children; disease; tumor; neoplasm; vertebrae; spinal cord; oncology; neurosurgery; diagnostic; survivability.

## ИЗБРАННЫЕ АСПЕКТЫ ЭПИДЕМИОЛОГИИ ОПУХОЛЕЙ И ОПУХОЛЕПОДОБНЫХ ЗАБОЛЕВАНИЙ ПОЗВОНОЧНИКА И СПИННОГО МОЗГА У ДЕТЕЙ (19-летний анализ региональной когорты Ленинградской области)

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**Актуальность.** Ввиду редкости патологии при разнообразии морфологических вариантов опухолей позвоночника и позвоночного канала региональные эпидемиологические исследования на эту тему представляют несомненный интерес, так же как и их сопоставление с данными стран, ведущих соответствующие раковые регистры.

**Цель исследования:** в рамках одного субъекта РФ изучить заболеваемость, структуру (анатомическую, возрастную и морфологическую), особенности клинических проявлений, а также выживаемость больных детского возраста с опухолями и опухолеподобными образованиями позвоночника и позвоночного канала.

**Материалы и методы.** За 19-летний период в ЛОГБУЗ «ДКБ» оперированы 110 детей (жителей Ленинградской области) с опухолями и опухолеподобными новообразованиями позвоночника и спинного мозга. Определены

показатели заболеваемости, смертности, выживаемости и сопоставлены с возрастными-половыми и гистологическими особенностями и локализацией патологических образований.

**Результаты.** Заболеваемость детей с опухолями и опухолеподобными заболеваниями спинальной локализации в Ленинградской области за период 1998–2016 гг. составила 1,93 на 100 тыс. детского населения, нейроэпителиальными опухолями спинного мозга — 0,3 на 100 тыс. детского населения в год при показателе смертности 0,2 на 100 тыс. населения соответствующей возрастной группы. Достоверное отрицательное влияние на выживаемость оказывают локализация опухоли в стволе и шейном отделе спинного мозга, а также гистологические варианты опухолей — внутримозговые опухоли низкой степени злокачественности, внемозговые злокачественные опухоли, метастазы опухолей другой локализации.

**Заключение.** Несмотря на особенности ведения национальных раковых регистров, продемонстрирована сопоставимость региональных показателей Ленинградской области с данными отечественных и зарубежных исследователей. Система организации оказания нейрохирургической помощи детям в Ленинградской области позволяет вести учет и наблюдать всех пациентов с опухолями и опухолеподобными заболеваниями позвоночника и позвоночного канала на базе единого лечебного учреждения.

**Ключевые слова:** дети; болезнь; опухоли; новообразования; позвоночник; спинной мозг; онкология; нейрохирургия; диагностика; выживаемость.

## Introduction

Spine and spinal cord tumors in pediatric patients are rare, and there are few comprehensive publications on the pathology. A set of clinically reliable material on this topic will probably require many years to accumulate. The first distinctive feature of this pathology in pediatric patients is the absolute prevalence of primary spinal tumors, which is in contrast to the predominance of secondary (metastatic) tumors (>95%) in adults. The second feature of these tumors in children is their polymorphism, which hinders collection and generalization of the material because of the diversity of tumor characteristics. The third feature is the present ability to estimate the incidence of malignant tumors of pediatric patients from data collected in cancer registries and the proactive contributions of children's oncologists. However, low-grade tumors, benign tumors, and tumor-like neoplasms are not subject to such strict consideration, despite the fact that intracanal tumors are one of the most severe clinical types. The timeliness of diagnosis, the capabilities of the technical equipment of a medical institution, and the qualification of the doctors are the main factors influencing the survival and quality of life of pediatric patients with spine and spinal cord tumors [1–9].

Thus, the **aim** of this study, which was conducted within the fairly large Leningrad Region, was to comprehensively evaluate the problem of tumors in childhood by analyzing the disease epidemiology, clinical and neurological symptoms, histological structure, localization of tumors and tumor-like formations of the spinal canal as well as factors associated with patient survival.

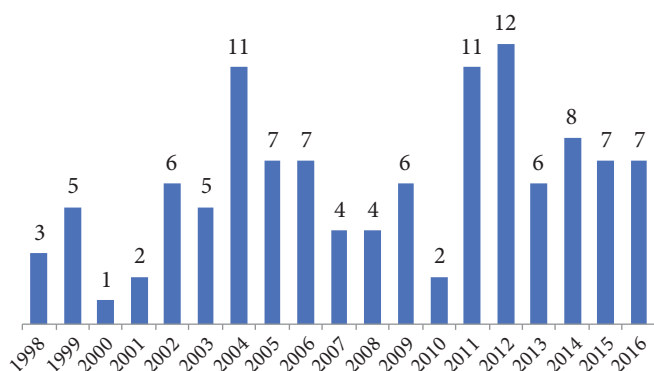
## Materials and methods

This was a retrospective single-center cohort study. We examined the medical documentation (medical records, surgical records, morphologists' conclusions) as well as data on the catamnesis of 110 children who were residents of the Leningrad Region and had undergone surgery for tumors and tumor-like diseases of the spine and spinal canal in the Leningrad Regional State Budget Health Institution Children's Clinical Hospital. The patients ranged in age from 20 days to 18 years (inclusive) who were treated during the period from 1998 to 2016. For statistical data processing, the open software environment R was used.

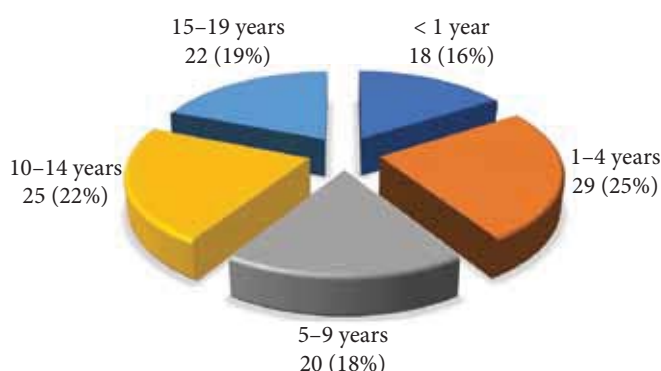
## Results and discussion

The system of organization of neurosurgical care for children in the Leningrad Region enables maintaining records and monitoring of all patients with tumors and tumor-like diseases of the spine and spinal canal in the Leningrad Children's Regional Hospital. For 19 years, we monitored 110 pediatric patients who underwent 114 surgical interventions for neoplasms of the spine and spinal canal, with the number of interventions ranging from 1 to 12 per year (Fig. 1).

The average incidence of children <18 years old with spinal neoplasms in the Leningrad Region during the study period was 1.93 per 100,000 children per year, including 0.3 per 100,000 of primary intracerebral (neuroepithelial) tumors and 0.75 per 100,000 children per year of malignant tumors of the spinal canal and spinal cord.



**Fig. 1.** Dynamics of the number of surgical interventions performed in the Leningrad Regional State Healthcare Institution Children's Clinical Hospital in pediatric patients with tumors and tumor-like diseases from 1998 to 2016



**Fig. 2.** Age distribution of the patients who underwent surgery

When comparing the incidence rate of pediatric patients with primary intracerebral tumors of the spinal cord with the rates of these patients in similar regional (St. Petersburg) and foreign (Germany, USA) countries, both their similarities and differences of the pathology according to age are striking (Table 1).

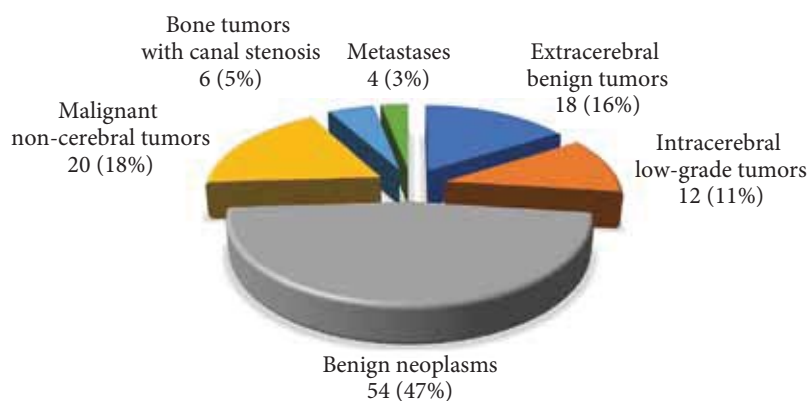
The age distribution of patients requiring surgical treatment shows significant increase of tumors in children aged <5 years (41%) and similar rates in subsequent 5-year periods (Fig. 2).

The overall sex distribution of patients (Table 2) was relatively uniform, but among children <1 year, 5-9 years, and 15-18 years, boys

Incidences of spinal cord tumors in pediatric patients

Table 1

Region	Incidence per 100,000 children	Age category (years)	Data source	Comments
Leningrad Region (1998-2016)	0.3	0-18 inclusive	Author's research	Neuroepithelial tumors: Low-grade astrocytoma — 10 Low-grade ependymoma — 3
USA	0.26	0-19	Central registry of brain tumors (cBTRuS)	Neuroepithelial tumors
Germany	0.26	0-15	German Cancer Register (GccR)	Neuroepithelial tumors
St. Petersburg (1989-1999)	0.15	0-14	Thesis of M.D. Vladovskaya	Benign and malignant intramedullary tumors (except mts and tumors that have spread from neighboring locations)



**Fig. 3.** Histological structure of the operated tumors

Table 2

Distribution of patients according to age and sex

Age groups	Boys	Girls	Total	%
<1 year	12	6	18	16
1–4 years	9	20	29	25
5–9 years	12	8	20	18
10–14 years	14	11	25	22
15–18 years	14	8	22	19
Total	61	53	114	100
	54%	46%	100%	

predominated, whereas in the 1–4-year age group, girls predominated. However, the sex composition of different age groups of the Leningrad Region population was not evaluated, which meant that we were unable to reliably determine the age and sex structure of the pathology.

Considering the location of the tumor relative to the lumen of the spinal canal, 2 groups were formed: 108 (95%) patients had tumors exhibiting intracanal spread, and 6 (5%) patients had bone tumors that caused spinal stenosis due to expansive intravertebral growth. In the spinal cord, intramedullary and extramedullary tumors were noted in 47 (41%) and 6 (59%) cases). The structures of the operated neoplasms exhibited quite diverse morphology that was classified into 6 groups according to the localization and degree of malignancy (Figure 3).

After the surgical stage, the relevant categories of patients received treatment from oncologists–hematologists. In addition, 1 patient was diagnosed as having acute myeloid leukemia associated with therapy (bone marrow transplantation was performed for the patient). In another patient, the development of cholesteatoma was preceded by multiple lumbar punctures that he received for acute lymphoblastic leukemia. In some patients, benign tumors and tumor-like formations of the spinal canal were accompanied by defects in their development.

**1. Metastases of malignant tumors of extra-spinal localization.** Four patients (3%) had intramedullary metastases: 1 case of metastasis of the germ cell tumor of the pineal region, 1 case of a teratomatous rhabdoid tumor, and 2 cases of medulloblastoma metastasis.

**2. Benign intracanal neoplasms.** This group consisted of 54 (47%) patients, 14 with arachnoid

and epidermoid cysts, 5 with cholesteatomas, and 35 with lipomas, including 1 in combination with diastematomyelia and 2 in combination with meningoradiculocoele. The fact common to patients with these tumors (lipoma is a mesenchymal non-meningothelial tumor, ICD-O code 8850/0) and tumor-like formations is that the specific treatment of such patients is limited to surgical intervention and does not require further treatment by an oncologist.

**3. Bone tumors of the spine with spinal stenosis.** As noted above, this group consisted of 6 (5%) patients, including 3 with Langerhans cell histiocytosis and 3 with fibrous dysplasia of the spine. These patients did not have an intracanal tumor spread, but because of deformation of bone structures, local stenosis of the spinal canal was generated, and compression of the spinal cord or its roots developed.

**4. Intracerebral (intramedullary) low-degree tumors.** This group included 12 (11%) patients with neuroepithelial low-grade tumors: 10 patients in which astrocytoma (grades I–II) was verified, and 2 patients in which low-grade ependymoma was noted. It should be noted that the term “intracerebral” largely indicates the origin of the tumor (from the substance of the spinal cord) rather than its formal localization. According to ICD-O, ependymomas of low malignancy are not benign and can have both code 9391/3 (malignant tumors) and 9394/1 (malignancy is not specified). The coding of a low-grade astrocytoma (9421/3, 9420/3, 9410/3) confirms their malignant nature, which is based on the following 2 criteria: 1) the tumor develops in a space in which the vital and functionally significant structures are densely located and 2) there is a probability of their transformation

into high-grade tumors. These patients require monitoring by an oncologist regardless of the radical degree of the surgery. In the case of continued growth or a significant residual volume of the tumor after surgery, radiation therapy, and/or chemotherapy may be performed.

**5. Extracerebral malignant tumors.** Out of the 20 (18%) patients with malignant extramedullary intracranial tumors, 1 patient had verified non-Hodgkin's lymphoma, 6 patients had neuroblastoma of the paravertebral ganglia or adrenal gland with invasion of the vertebral canal, 3 patients had primitive neuroectodermal tumor, sarcoma (not specified) was noted in 7 patients, and teratoblastoma (malignant teratoma of immature teratoma grade III) was noted in 3 patients. In all patients, the tumor had spread to the spinal canal and was located in the spinal cord in 3 of them. The treatment of these patients necessarily included conservative antitumor treatment (chemotherapy +/- radiotherapy); therefore, the program of their treatment should be planned in cooperation with the children's oncologists.

**6. Extracerebral intracanal benign tumors.** The group comprised 18 (16%) patients. In 3 patients, hemangioblastoma (ICD-O code 9161/1) was diagnosed, and despite intramedullary localization, the tumor did not originate from the brain tissue and is a tumor of the meninges of unknown genesis. Other morphological variants were represented by mature teratoma (9080/0) in 4 patients, neurinoma in 1, ganglioneuroma in 2, neurofibroma (9540/0) in 6, angiofibroma in 1, and meningioma (9539/0) in 1. Patients of this group require postoperative follow-up by an oncologist. Relapses of the disease in this group are extremely rare, but transformation into malignant tumors is possible.

When comparing age and morphological aspects of neoplasms (Figure 4), certain differences were revealed.

Thus, in children <1-year old, "benign neoplasms" accounted for 67% of the total number (12 of 18 cases), including dermoid cysts (4 cases) and lipomas (8 cases). "Malignant extracerebral tumors" were represented by neuroblastoma (2 cases) and malignant teratoma (1 case). Three patients underwent surgery for an extracerebral benign tumor, which was a mature teratoma. The group of children from 1 to 4 years was characterized by an increase in the incidence of neoplasms of the spi-

nal cord and spinal canal. The number of malignant tumors (6 cases) increased twice as much as those in the group of children <1 year, which included 3 cases of neuroblastoma, 1 case of teratoblastoma, 1 case of primitive neuroectodermal tumor, and 1 case of metastasis of the teratomatous rhabdoid tumor. "Benign neoplasms" (17 cases) accounted for 12 cases of lipoma, 2 cases of dermoid cyst, 1 case of cholesteatoma, and 1 case of arachnoid cyst. "Extracerebral benign tumors" were represented by ganglioneuroma, ganglioneurofibroma, mature teratoma, meningioma, and neurofibroma, which were noted as 1 case of each morphological variant. Intracerebral low-degree astrocytoma was diagnosed in a child of 4 years.

In the age group of children from 5 to 9 years, the number of intramedullary tumors was sharply increased (5 cases), including low-grade astrocytomas (4 cases), and low-grade ependymoma (1 case). "Benign and non-neoplastic formations" were represented by lipoma (5 patients), cholesteatoma (3 cases), and spinal canal cyst (1 case). Additionally, 1 patient had a bone tumor that was a histiocytoma, which causes spinal stenosis. In this age group, the level of malignant tumors was high: neuroblastoma (1 case), teratoblastoma (1 case), and sarcomas (Ewing's sarcoma, chondrosarcoma) (3 cases) were observed for the first time.

Among children from 10 to 14 years, "extracerebral benign tumors" (6 cases) were represented by neurofibroma (3 cases), hemangioblastoma (2 cases), and neurinoma (1 case). Practically the same level of neuroepithelial low-degree tumors (4 cases of astrocytoma) were observed. Three patients were operated for metastases in the spinal cord of malignant tumors of other localization (gonadoblastoma of the pineal region and medulloblastoma), 1 case of non-Hodgkin's B-cell lymphoma with spinal cord injury (primary presentation), and 1 case of the sacrum sarcoma that had spread into the spinal canal were also identified. Three patients had bone tumors with canal stenosis: histiocytosis (1 case) and fibrous dysplasia (2 cases).

In the older age group (15-19 years) "benign neoplasms" were diagnosed in 9 patients (4 lipomas, 1 cholesteatoma, 4 spinal canal cysts), low-grade neuroepithelial (intracerebral) tumors (astrocytoma and ependymoma) were diagnosed in 2 cases, intracerebral and "extracerebral benign tumors" (2 cases of neurofibroma, 1 case of hemangioblastoma,

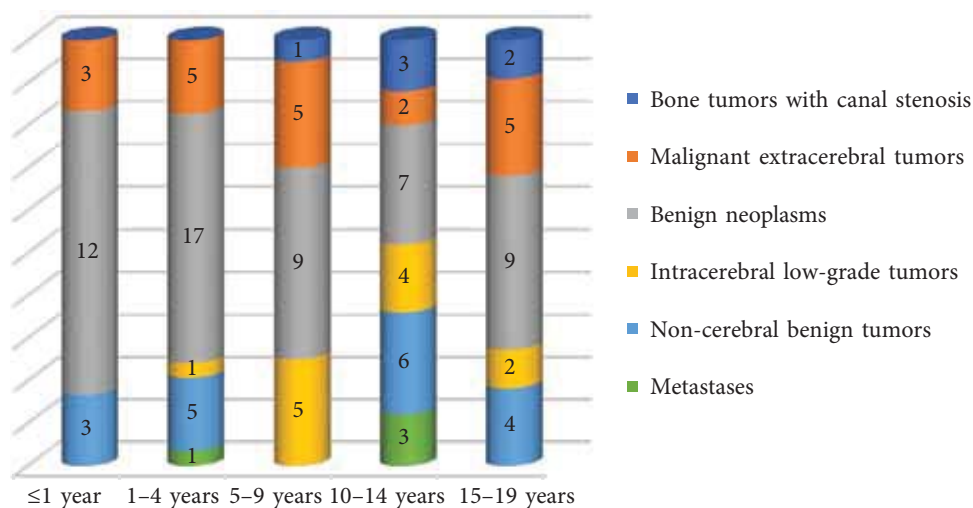


Fig. 4. Special aspects of the distribution of patients by age and morphological group of tumors

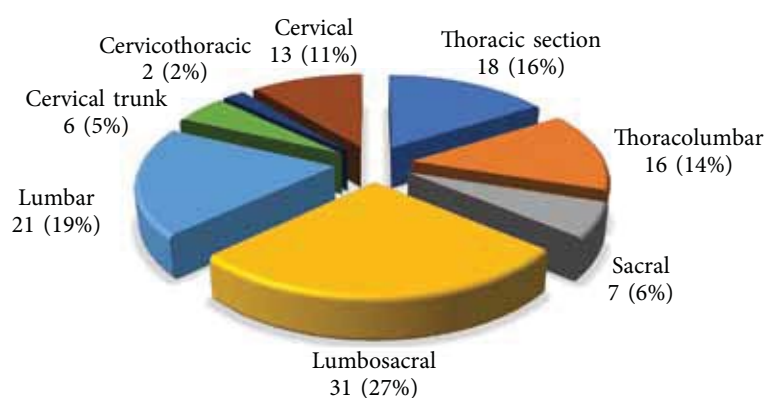


Fig. 5. Distribution of surgical interventions depending on the localization (level) of the neoplasm

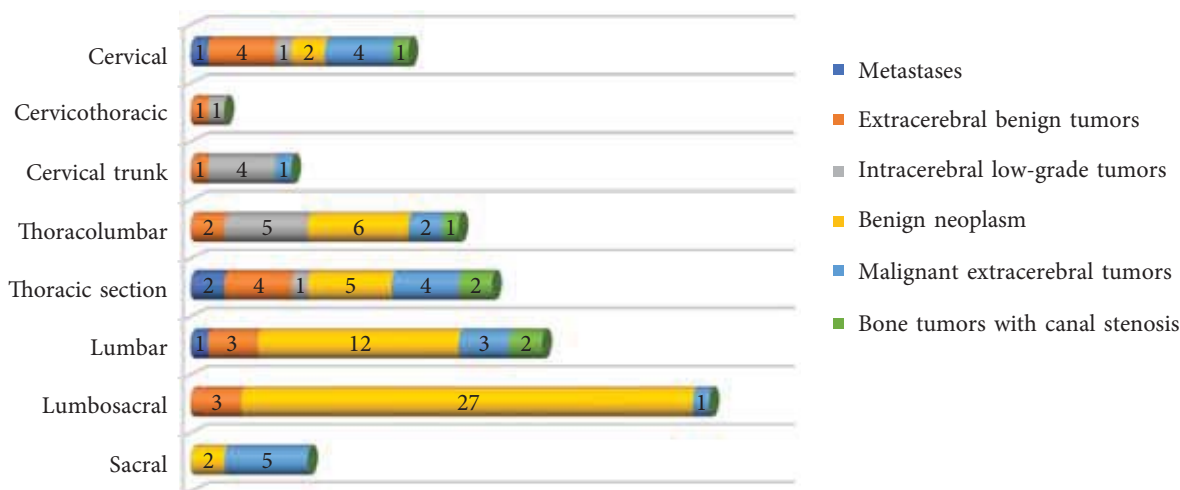


Fig. 6. Level and histological structure of the neoplasms

1 case of angiofibroma) were diagnosed in 4 cases. In addition, there were 5 cases of “malignant extracerebral tumors” (2 cases of peripheral neuroectodermal tumor and 3 of sarcomas) as well as 3 cases of bone tumors with canal stenosis.

The distribution of patients according to the location of the neoplasm is shown in Figure 5, and

a comparison with their morphological variants is shown in Figure 6.

As can be seen from the diagrams, malignant neoplasms were found in all parts of the spine, and the sacrum was more often affected by malignant processes. The greatest specific weight of benign formations was noted in the lumbosacral localization.

Table 3

Distribution of mortality causes according to localization and histological tumor\* group

Histology/localization	Sacral (7)	Lumbar (21)	Thoracic (18)	Cervical (13)	Cervical trunk (6)	Total of the deceased	Share of the deceased, %
Metastases (4)		1	1	1		3	75
Intracerebral low-grade tumors (12)					3	3	25
Benign neoplasm (54)				1		1	1.9
Extracerebral high-grade tumors (17)	4	1	1	2	1	9	52.9
Total	4	2	2	4	4	16	14
Share of the deceased from the total number of patients in this category, %	57	9.5	11	30.8	66.7	14	

Примечание: \* the total number of patients with this characteristic in the cohort is indicated in parentheses.

When analyzing the catamnesis, it was established by September 1, 2017 that out of 110 patients, 16 (14%) died of progression of the tumor process, and 94 (86%) were alive. Thus, according to the regional cohort of the Leningrad Region, the mortality from this type of pathology was 0.2 per 100,000 children per year. The distribution of the deceased according to the level of lesion and the morphological variant of the tumor is presented in Table 3.

The deceased were distributed according to age as follows: <1 year (early lethality), 1 child;

1 to 4 years, 5 children; 5 to 9 years, 3; 10 to 14 years, 4; and 15 to 19 years, 1 adolescent. The cumulative survival rate at the median follow-up of 81 months was 84.6% (Figure 7), 1 patient was lost to observation (with a high probability of the event). There were no significant differences in the survival rates of patients according to sex, age, or localization of the neoplasm with respect to the spinal cord (intra- or extramedullary). The survival rates for patients with tumor location are shown in the Kaplan–Meier curve (Figure 8) and in Table 4.

Table 4

Survival rates of patients according to level of tumor lesion

Localization	Cumulative survival rate, %	Median follow-up, months
Cervical trunk	33.3	69.5
Cervical section	64.8	36
Cervicothoracic	100	130.5
Thoracic	85.6	114
Lumbar	95	117
Lumbosacral	100	70
Sacral	50	56.5

Table 5

Survival of patients with different morphological variants of tumors

Histological group	Cumulative survival rate, %	Median follow-up, months.
Intracerebral low-grade tumors	61.4	100
Benign neoplasms	100	73.5
Extracerebral benign tumors	98.1	136
Bone tumors with canal stenosis	100	139
Malignant extracerebral tumors	54.6	38
Metastasis of tumors of other localization	25	44.5

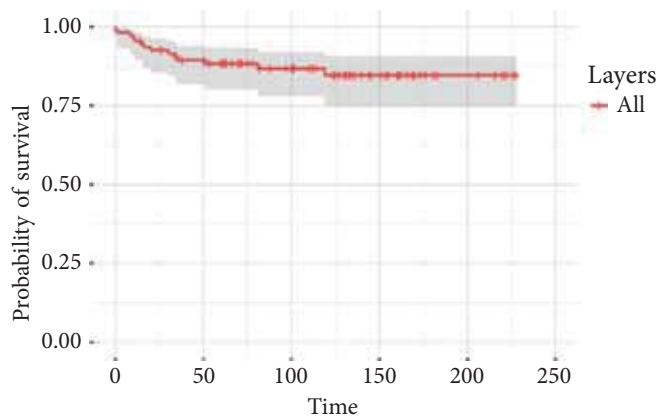


Fig. 7. Total cumulative survival rate

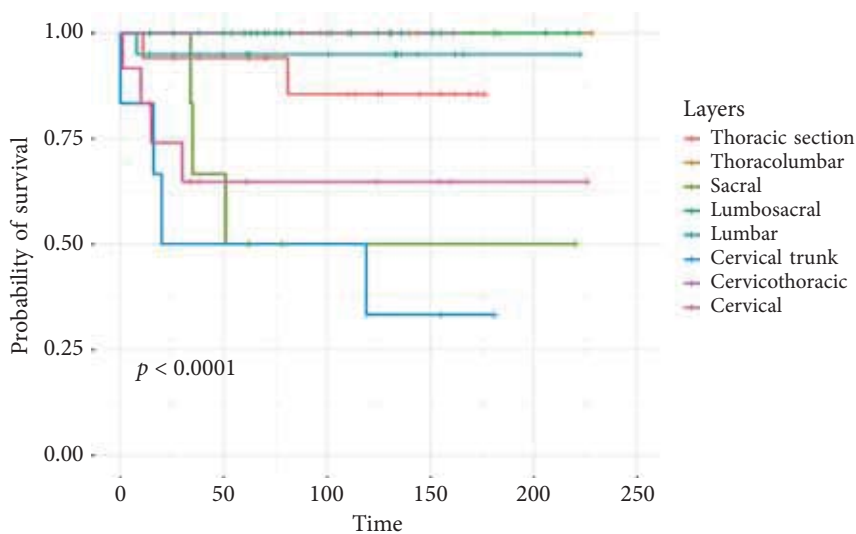


Fig. 8. Cumulative survival rates of patients with tumors of the spinal canal according to tumor location

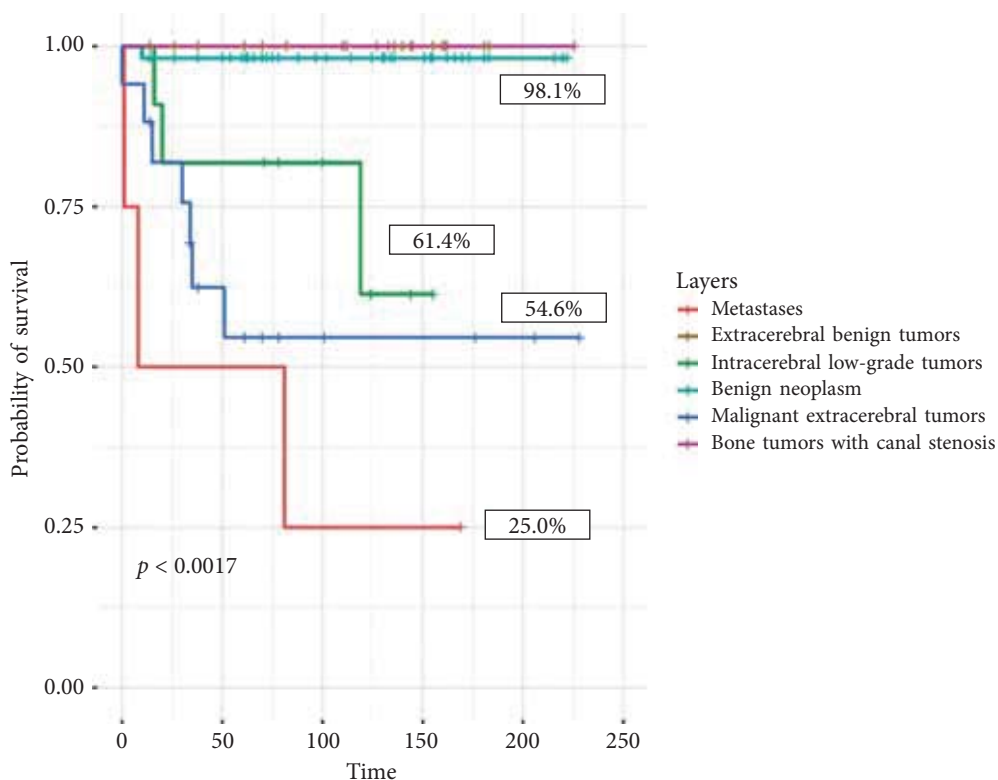


Fig. 9. Cumulative survival rates of patients with different histological variants of the spinal canal tumor



In the pairwise comparison of the groups, the following prognostic relationships were statistically proved: the best prognosis for survival was for patients with tumors of the cervicothoracic, thoracic, and lumbosacral localization, and the worst prognosis was for patients with tumors of sacral localization as well as lesions at the level of the cervical trunk and cervical region. The survival parameters according to the morphological variant of the tumor are shown in Figure 9 and in Table 5.

## Conclusion

1. The morbidity rate of pediatric patients with spinal tumors and tumor-like diseases in the Leningrad Region for the period 1998–2016 was 1.93 per 100,000 children per year, and the rate for those with neuroepithelial tumors of the spinal cord was 0.3 per 100,000 children per year, which are comparable to epidemiological data for the United States and St. Petersburg. The incidence of malignant tumors of the spinal canal was 0.75 per 100,000 children per year.
2. Among the patients who underwent surgery, the mortality rate was 14% and was 0.2 per 100,000 for the corresponding age group population. The data from the epidemiological analysis showed that there were 3 prognostic groups with statistically significant differences in survival:
  - Patients with metastases of extravertebral tumors had the worst prognosis
  - Patients with intracerebral low-grade tumors (61.4%) and malignant extracerebral tumors (54.6%) did not show significant differences in survival rate
  - Patients with bone tumors with canal stenosis and benign intra- and extracerebral neoplasms had the best prognosis.
3. The survival rate of patients with spinal tumors with a median follow-up of 81 months was 86%, and the cumulative survival rate was 84.6%. The sex and age of the patients as well as the location of the tumor with respect to the spinal cord did not have a significant effect on survival rate.
4. The survival rates of the patients decreased for patients with tumors located at the level of the trunk and the cervical section of the spinal cord and of the patients with certain histological

variants, such as intracerebral low-degree tumors, extracerebral malignant tumors, and tumor metastases of other localization.

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The authors declare no conflicts of interest related to this manuscript.

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