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Original Research Article

Retrospective analysis of mediastinal tumors in childhood

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ABSTRACT

Background: The aim of this study was to determine etiologic distribution, epidemiologic properties, treatment, clinical course and late effects of the treatment of the patients diagnosed with mediastinal tumor.
Methods: Patients under 18 years old diagnosed with mediastinal tumors between January 1990 and June 2011 at the 19 Mayis university department of child oncology were examined retrospectively.
Results: There were 50 (61%) males, 32 (39%) females with mediastinal tumor. Median age at diagnosis was 9.28 years (30 days-17.4 years). Most common symptoms were respiratory distress (29.2%) and cough (23.1%). Sixty eight cases (82.9%) were malignant. Two cases died before diagnosis. Thirty seven cases (45.1%) were located in anterior followed by 16 (19.5%) in middle and 23 (28%) in posterior mediastinum. Most common malignant tumors were lymphomas (n=46, 67.6%), followed by sarcomas (n=12, 17.6%), neural crest tumors (n=8, 11.8%) and germ cell tumors (n=2, 2.9%). Thirteen cases had vena cava superior syndrome and 4 cases had signs of spinal cord compression at the time of diagnosis. Forty eight cases (58.5%) were alive and symptom free on follow-up (mean 39.5 months, 3-139 months), and 22 (26.8%) were died. Sixteen cases (23.5%) had late effects. Overall survival for all malignant tumors were 60.5±7.8%.
Conclusions: Mediastinal tumors should be considered in children with acute progressive respiratory distress and cough. Early diagnosis is still most important factor for prognosis.

Keywords: Mediastinal tumor, Childhood, Follow-up

INTRODUCTION

Childhood cancers have become important chronic diseases that occur during innocent and cheerful childhood. The cause of these cancers is largely unknown and generally not preventable. The term "childhood cancer" is used to refer to cancer that occurs in children before the age of 18.[1] Cancers seen in this age group cover 0.5% to 4.6% of all cancers. The overall incidence rates of these cancers in the world vary between 50 and 200 per million.[2] More than 300,000 children are diagnosed with cancer every year around the world, and a child dies of cancer every three minutes. The most common cancer types in children aged 0-14 years are leukemias (3/4), brain and other central nervous system tumors and lymphomas.[3] Cancer of the breast, lung, colon or rectum, which is usually seen in adults, is very rare in children. While the number of children with cancer is much less than the global incidence of adult cancers, the number of lives saved is significantly higher, with survival rates on average reaching 84% in high-income countries.[4]

Today, 70% of childhood cancers can be cured with multidisciplinary approach, because of the advances in diagnosis and treatment.[5-6] Considering this high rate of success in treatment and the life expectancy of children, the importance of early diagnosis and effective treatment increases.

Most of the masses seen in the thorax in childhood are located in the mediastinum. Primary tumors of the lung are rare in children, and metastatic lesions of many tumors can be detected in the lung parenchyma. About

40% of the masses detected in the mediastinum are malignant.[7]

The mediastinum is anatomically divided into 3 regions as anterior, middle and posterior mediastinum. Localization is of great importance in the differential diagnosis of kits. While lymphomas are most common in the anterior and middle mediastinum, neuroblastomas (NBL) are seen in the posterior mediastinum. Neuroblastoma is the most common tumor detected in the mediastinum from the neonatal period to the age of 3 years. Lymphomas are most common after the age of 3.[8]

Mediastinal masses compress the adjacent large vessels and airways, resulting in clinical findings, therefore the severity of symptoms is directly proportional to the size of the mass. While small masses are asymptomatic and can be detected incidentally, large masses may present with oncological emergencies such as airway obstruction and superior vena cava syndrome (VCSS).

The aim of this study is to determine the epidemiological, clinical and laboratory characteristics, treatment and results, and late complications of patients with primary mediastinal tumor diagnosed in Ondokuz Mayıs university, department of pediatric oncology between January 1990 and June 2011.

METHOD

In our study, the files of 82 patients with mediastinal tumors from 950 patients diagnosed in Ondokuz Mayıs university, department of pediatrics, department of pediatric oncology between January 1990 and June 2011 were retrospectively reviewed. The medical information of the patients was obtained from the pediatric oncology follow-up and archive files.

Patients' age, gender, province of residence, first application dates and complaints on admission, duration of complaints, physical examination findings, anatomical localization of the mass, treatment initiation dates, laboratory values at the time of admission (White blood cell, hemoglobulin, platelet count, sedimentation rate, LDH, cytomegalovirus) (CMV), EBV, hepatitis serologies), late complications (thyroid dysfunction, nephropathy, growth and development retardation, etc.) and current status of the patients were recorded. World health organization (WHO) ICD-O-3 codes were used for morphological descriptions.

The patients were examined in five groups, 0-<1, 1-4, 5-9, 10-14, 15-18, according to the age groups at which they were diagnosed.

The duration and doses of chemotherapy and radiotherapy of the patients were examined. Follow-up times and late complications that occurred during follow-up were evaluated.

Statistical analysis

Data were analyzed with SPSS 21.0 for Windows (SPSS Inc.). Numerical data are given as mean ± standard deviation. Chi-square test was used to compare numerical data. Parametric data were compared with student T, non-parametric data with Mann-Whitney U test. Survival analysis was performed according to Kaplan-Meier survival analysis, and survival comparison was made with log-rank analysis. The statistical significance limit was accepted as $p<0.05$.

RESULTS

Five (61%) of 82 cases were male. The mean age of the cases at the time of admission was 9.28±4.93 years. There were 7 cases (8.5%) under the age of one, 4 of them (57.1%) were girls. There were 10 cases (12.2%) between the ages of 1-4, 17 cases (20.7%) between the ages of 5-9, 30 cases (36.6%) between the ages of 10-14, and 18 cases (22%) between the ages of 15-18 years (Figure 1).

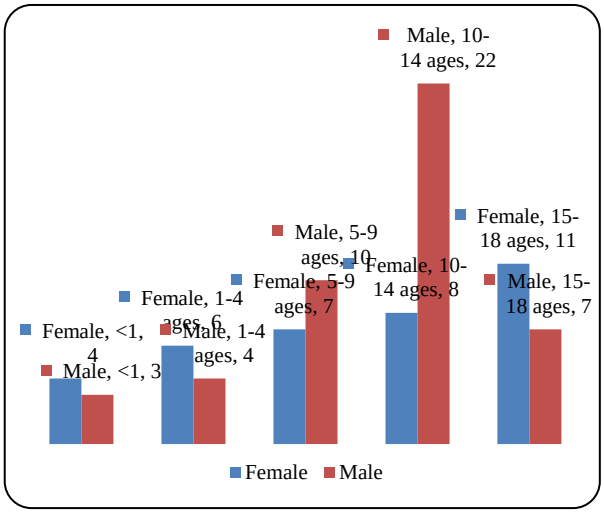

Figure 1: Distribution of cases by age and gender.

The most common complaint at presentation was respiratory distress with 29.2% (n=24). In 3 cases, the mass was detected incidentally during routine control, and they had no complaints.

Of 68 cases with malignant mass, 6 (8.8%) had a history of cancer in their relatives.

When organomegaly was evaluated in the physical examination, isolated hepatomegaly was found in 17.1% (n=14) of the cases, isolated splenomegaly in 1.2% (n=1) and hepatosplenomegaly in 35.4% (n=29). No organomegaly was found in the physical examination of 38 patients (46.3%). Pathological lymphadenopathy was present in any of the cervical, inguinal, axillary, and supraclavicular regions in 59.8% of the cases (n=49).

Pathological lymphadenopathy was present in 86.4% (n=38) of 44 patients with organomegaly.

Biopsy was performed in 73.2% of the patients and total excision of the mass was performed in 24.4% for histopathological diagnosis. Of the patients who underwent mass excision, 40% were malignant and 50% were benign. Two patients died intraoperatively without diagnosis. The diagnosis was made in 1 patient by studying cytology and flow from the thoraco-synthesis material, and no invasive procedure was performed in 1 patient with thymus hyperplasia. Biopsy was performed in 11 patients, the existing mass was reduced by chemotherapy and it was operated.

The mean time between the patient's admission and surgery was 24.4±19.2 days (shortest 8 days, longest 72 days) for benign masses and 55.1±59.6 days (shortest 2 days, longest 174 days) for malignant masses.

Patient diagnoses were made according to the WHO ICD-O-3 classification. 82.9% (n=68) of the cases were evaluated as malignant and 14.6% (n=12) as benign. 2.4% (n=2) of the cases died intraoperatively without being diagnosed.

When the mass localizations of the cases were evaluated, 45.1% were found in the anterior mediastinum, 19.5% in the middle mediastinum, and 28% in the posterior mediastinum (Figure 2).

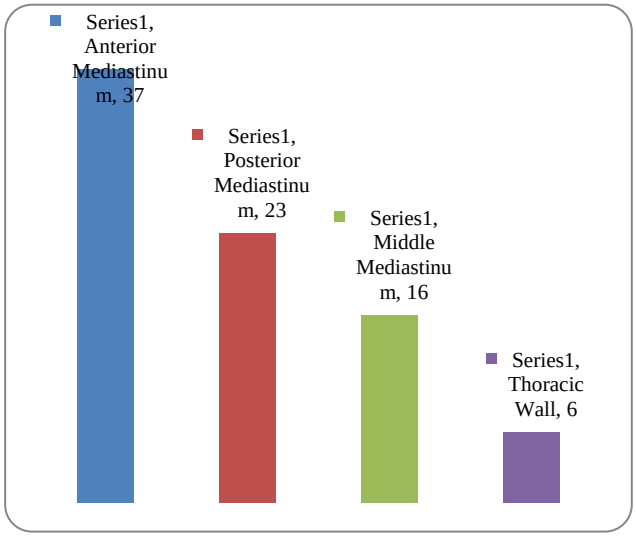

Figure 2: Distribution of cases according to mass localization.

The most common mass detected in the anterior mediastinum was lymphomas (75.7% non-Hodgkin lymphoma, 24.3% Hodgkin lymphoma). The most common cause of mass detected in the middle mediastinum was again lymphomas, 81.3% Hodgkin lymphoma, 18.7% non-Hodgkin lymphoma) neuroblastomas were most common in the posterior mediastinum (56.5%).

The most common malignant masses were lymphomas with 67.6%. Hodgkin's and non-Hodgkin's lymphomas were found equally in lymphoma cases. Sarcomas were 17.6%, neural crest-derived tumors 11.8%, germ cell tumors 2.9%.

Table 1: Distribution of benign cases according to their pathologies.

Pathology	N	Percentage (%)
Ganglioneuroma	5	41.7
Inflammatory myofibroblastic tumor	3	25.1
schwannoma	1	8.3
Thymus hyperplasia	1	8.3
hamartoma	1	8.3
Mucous adenoma	1	8.3
Total	12	100

Table 2: Distribution of malignant cases according to WHO ICD-O-3 diagnosis codes.

Diagnosis	N	Percentage (%)
Lymphomas and reticuloendothelial system neoplasms	46	64.8
Sarcomas	12	17.6
Tumors of neural crest origin	8	11.3
Germ cell tumors	2	2.8
Total	68	100

Table 3: Distribution of malignant cases according to WHO ICD-O-3 subtypes.

Pathology	N	Percentages (%)
Hodgkin lymphoma	22	32.4
Non-Hodgkin lymphoma	22	32.4
Neuroblastoma	6	8.8
Pyrimitive neuroectodermal tumor	4	5.9
Ewing	3	4.4
Angiosarcoma	3	4.4
Langerhans cell histiocytosis	2	2.9
Ganglioneuroblastoma	2	2.9
chondrosarcoma	1	1.5
seminoma	1	1.5
Endodermal sinus Tm	1	1.5
Rhabdomyosarcoma	1	1.5
Total	68	100

Nodular sclerosing type was found most frequently with 40.9% among Hodgkin lymphomas. Although the male-female distribution was 2/1 in the nodular sclerosing type, it was equal for all types.

Table 4: Distribution of Hodgkin lymphomas by subtypes and gender.

Subtype	Male		Female		Total	
	N	%	N	%	N	%
Nodular sclerosing	3	33.3	6	66.7	9	40.9
Mixed cellular	3	50.	3	50	6	27.3
Poor of lymphocytes	4	80	1	20	5	22.7
Uncertain	1	50	1	50	2	9.1
Total	11	50	11	50	22	100

When the stages of the cases were evaluated, the most common 3rd stage cases were found. B symptoms were present in 72.7% of the patients.

Table 5: Distribution of Hodgkin lymphomas by stage and gender.

Stage	Male		Female		Total	
	N	%	N	%	N	%
Stage 2A	1	50	1	50	2	9.1
Stage 2B	0	0	2	100	2	9.1
Stage 3A	2	66.7	1	33.3	3	13.6
Stage 3D	5	55.6	4	44.4	9	40.9
Stage 4A	1	100	0	0	1	4.5
Stage 4B	2	40	3	60	5	22.7
Total	11	50	11	50	22	100

T-cell lymphoblastic lymphomas were the most common non-Hodgkin lymphomas (57.9%). The female to male ratio was 1/2.1.

Table 6: Distribution of non-Hodgkin lymphomas by subtypes and gender.

Subtype	Male		Female		Total	
	N	%	N	%	N	%
T cell lymphoblastic	7	63.6	4	36.4	11	50
Uncertain	1	33.3	2	66.6	3	13.6
Anaplastic large cell	1	50	1	50	2	9.1
Burkitt lymphoma	2	100	0	0	2	9.1
T cell	2	100	0	0	2	9.1
Common large B-cell	1	100	0	0	1	4.5
Precursor T cell	1	100	0	0	1	4.5
Total	15	68.1	7	31.9	22	100

The mean haemoglobin value in malignant cases was found to be 10.5±1.9 g/dl. The mean white blood cell count was 10635±5685/mm^3, and the mean platelet count was 377720±160090/mm^3. LDH levels were measured in 92.6% (n=63) of the cases. The mean LDH value was found to be 653±389 U/L. When evaluated according to histological types, mean LDH values were found to be 524 U/L in Hodgkin lymphomas, 793 U/L in non-Hodgkin lymphomas, and 722 U/L in neuroblastomas.

The sedimentation value was measured in 63 cases (92.6%), and the mean value was 55±33 mm/hr. When evaluated according to histological types, the sedimentation values were 68.9 in Hodgkin lymphomas, 59.7 in non-Hodgkin lymphomas, and 40.4 in neuroblastomas.

Uric acid was measured in 48 patients (70.5%). The mean was found to be 3.9±1.8 mg/dl.

EBV and CMV serology were evaluated in 63.2% of the cases. EBV IgG was positive in 4.7%, CMV IgG in 9.3%, and both CMV and EBV IgG in 55.8% of the cases. No CMV IgM positivity was detected. Only 2 cases were positive for EBV IgM. EBV IgG was positive in one of these cases and negative in the other. EBV IgG was positive in 78.6% of Hodgkin lymphoma cases and 66.7% of non-Hodgkin lymphoma cases.

When the complete blood counts of the benign patients were evaluated, the mean haemoglobin was found to be 11.7±1.3 g/dl. The mean white blood cell values were determined as 8862±1583 / mm^3. The mean platelet values were found to be 356416±127435/mm^3.

LDH value was measured in 83.3% of the cases. The mean LDH value was found to be 376±146 U/L.

Sedimentation value was measured in all cases. The mean was 17.5±13.7 mm/hr.

Serological examination was performed in 3 (25%) cases. EBV IgG (+) was detected in 1 case, and both EBV and CMV IgG (+) were detected in 1 case. Both patients had negative IgMs.

When the laboratory values of malignant and benign cases were compared, a slight statistical difference was found in the haemoglobin value and a significant statistical difference in the LDH and sedimentation values. No statistical difference was found in terms of mortality rates in cases with a sedimentation value above and below 20 mm/hr at the time of diagnosis. Again, there was no difference in mortality rates of cases with LDH values above and below 500 U/L at the time of diagnosis (p=0.77) (Table 7).

Chemotherapy was started in 94.1% of the cases with malignant histological diagnosis. The mean time elapsed between the admission dates of the cases and the initiation of chemotherapy was 18.6 days. When evaluated according to the diagnoses, the mean duration was found to be 21.9 days in Hodgkin lymphomas, 12.3 days in non-Hodgkin lymphomas, and 18.5 days in neuroblastomas.

Table 7: Comparison of laboratory findings of malignant and benign cases.

Laboratory results	Malign	Benign	P
Haemoglobin (gm/dl)	10.5±1.9	11.7±1.3	0.049
WBC (/mm^3)	10635±5685	8862±1583	0.261
Plt (/mm^3)	377720± 160090	356417± 127435	0.694
LDH (U/L)	653±389	376±146	0.007
Sedimentation (MM/hr)	55±33	17.5±13.7	0.00

LDH: Lactate dehydrogenase, WBC: White blood cell, Plt: Platelet

When the results of 82 cases were evaluated in the long-term follow-up, while 46 cases (58.5%) were disease-free, 10 cases (12.2%) were still treated, 1 case (neuroblastoma) could not go into remission despite treatment, 1 case with Hodgkin lymphoma underwent bone marrow transplantation. The 22 of our cases (26.8%) died.

The mean follow-up period of the patients was 39.5±31.3 months. According to Kaplan-Meier analysis of all malignant cases, the survival rate was 60.5±7.8%. According to disease groups, survival rate was 79.1±6.8% in lymphoma and reticuloendothelial system tumors (NHL 69.6%±10.4, HL 88.2±8%), 83.3±15.2% in neural crest tumors, 50±35% in germ cell tumors 9.4±8.9% in sarcomas. Five-year survival was 62±8.8% in all cases, 78.1±8.7% in lymphomas (HL 91.7%±8%, NHL 55.6±16.6%). When groups were evaluated in log-rank analysis, no statistical significance was found in survival between lymphomas and neural crest tumors ($p>0.05$). The survival rates of neural crest tumors and lymphomas were better than those of sarcoma and germ cell tumors ($p<0.05$). In addition, the survival rates of lymphoma subgroups for HLs were significantly better than for NHLs ($p<0.05$).

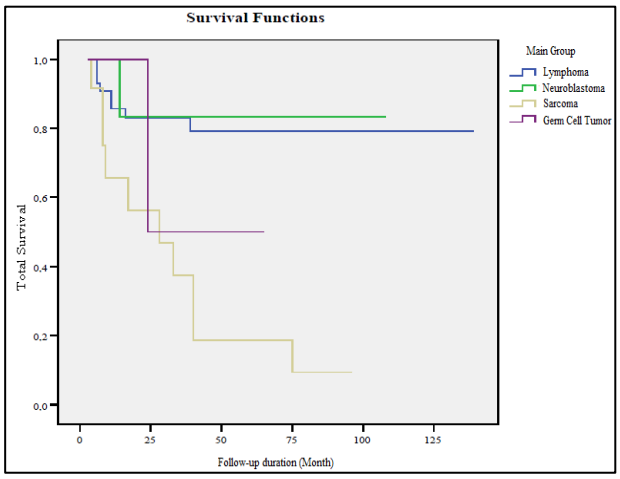

Figure 3: Overall survival rates according to the pathologies of the cases.

DISCUSSION

In recent years, significant progress has been made in terms of diagnosis and treatment of childhood cancers. Despite all these advances, cancer has high mortality rates. The most important factor affecting the prognosis is still early diagnosis. In our study, the files of primary mediastinal tumor cases in childhood were reviewed retrospectively. Patients' age at admission, physical examination and laboratory findings at admission, imaging and pathological diagnostic procedures, oncological emergencies at the time of admission, treatments, and follow-up periods were evaluated. Survival analyzes were performed.

Among 950 oncology patients diagnosed in our clinic, 82 patients with primary mediastinal tumor were detected (8.6%). In the literature, there was not enough data on the ratio of primary mediastinal tumors to all cancers in childhood. It was determined that only 22 (0.02%) of 110,284 adult and pediatric patients were pediatric patients with primary mediastinal tumors.

In our study, the mean age at diagnosis was 9.28. Compared with the data in the literature, Mutlu et al found as 9.5, Temes et al found as 11, Sairanen et al found as 8.6, Tansel et al found as 8, Freud et al found as 5.6 and Lam et al found as 4 in their researches.[9-14] Gender distribution, 60% male-40% female in the Mutlu et al study, 65% male-35% female in Tansel et al study, 59% male-41% female in Temes et al study, 59% male-41% female in Lam et al study.[9-,10,12,14] A slight male dominance was present in all studies reviewed in literature. Gender distribution in our study consistent with the literature and found to be 61% male and 39% female.

In our study, hepatolomegaly was found in 17% of the cases at the time of admission, and hepatosplenomegaly was found in 35% of the cases. When the literature was examined, there were no adequate reports about organomegaly of the patients at the time of admission. In the study of Tansel et al it was stated that hepatosplenomegaly was not a common finding.[12]

In the study of Mutlu et al 47% of the masses were anterior, 19% medium, 11% anterior and middle, 23% posterior mediastinum, in the study of Sairanen et al 37.7% anterior, 15.6% medium, 46.6%.[9,11] In our study, 45% of the masses were detected in the anterior mediastinum, 19% in the middle, and 28% in the posterior mediastinum. We think that the biggest factor in these differences between studies is the incidence of tumors in the geographical region where the studies were conducted and the average age of the patients included in the study. In the study of Mutlu et al which is very close to our study in terms of geography and age group, the distribution of the masses is largely similar to our study.[9] Since lymphomas are seen less frequently in developed countries, the rate of mass detection in the anterior mediastinum is lower in studies compared to countries

where lymphoma is more common. Since the frequency of neuroblastoma is higher in studies with more cases under 4 years of age, the rate of tumor detection in the posterior mediastinum is higher than in studies with more cases over 4 years of age. In addition, the most common histopathological types depending on localizations were found both in our study and in the literature as lymphomas in the anterior and middle mediastinum and neuroblastomas in the posterior mediastinum.[9-16]

In our study, 83% of 82 cases had malignant histology. When the studies in the literature were evaluated, the cases were reported to be 92.5% benign-7.5% benign in the study of Mutlu et al 65% benign-35% malignant in the study of Tansel et al 52% benign-48% malignant distribution in the study of Sairanen et al.[9,11,12] The reason for the higher rate of malignancy in our study compared to the literature is that cases with benign pathologies were not referred to our clinic and since almost all of these studies in the literature were published by surgical clinics, it also included cases that were operated in these centers but were not referred to oncology clinics because their histopathology was benign.

In our study, when evaluated according to the distribution of malignant cases in the mediastinum, 64% were found to have lymphomas, 18% were sarcomas, 16% were tumors of neural crest origin, and 3% were germ cell tumors. In the study of Sairanen et al neural crest-derived tumors were 38%, in the study of Takeda et al 46% of tumors of neural origin, germ cell tumors of 18%, in the study of Tansel et al 25%, tumors of neural crest origin, 13% of germ cell tumors, in study of Mutlu et al lymphoma 80%, neuroblastoma detected in 12%.[9,12,15]

When laboratory values were examined, statistical differences were found between malignant and benign cases in haemoglobin, LDH and sedimentation values. In our study, the mean LDH values of malignant cases were found to be 653 U/L for all malignant cases and 376 U/L for benign cases. LDH levels increase in malignant tumors as a result of rapid turnover-induced anaerobic metabolism and shift to glycolysis.[17] It has been shown in the literature that it is a prognostic factor for leukemia and lymphomas, and is correlated with the number of blasts in leukemia and the size of the mass in lymphomas.[18-19] In the study of Kornberg et al mean LDH values were reported as 402 U/L in HL and 313 U/L in NHL, and laboratory normal reference ranges were given as 100-500 U/L in this study.[18] In our study, the mean LDH values were 524 U/L in HL and 793 U/L in NHL. Sedimentation values were found to be 55 mm/hr for malignant tumors and 17 mm/hr for benign masses. Mutlu et al in their study, divided the cases into 2 groups with a sedimentation value of less than or equal to 20 mm/hr, and reported that the sedimentation rate was above 20 mm/hr in 63% of cases with HL and 55% of cases with NHL.[9] There was no significant effect on mortality rates when the sedimentation value was 20 mm/hr and LDH over 500 U/L at the time of diagnosis.

The 53% of our malignant cases were followed up without disease. The 15% are still receiving treatment. The 29% of our patients died. Autologous bone marrow transplantation was performed in 1 case. In the study of Sairenan et al 62.3% of the patients and in the study of Mutlu et al 64.1% were alive without disease.[9,11] 18% of our cases followed up with lymphoma and 16% of our cases followed up with neural crest tumor died.

When the survival rates were evaluated, the results were very close to the literature. The survival rate in all malignant cases was 60.5%. According to the disease groups, it was found to be 79.1% in lymphoma and reticuloendothelial system tumors (NHL 69.6%, HL 88.2%) and 83.3% in tumors of neural crest origin. When 5-year survival was evaluated, it was determined as 62±8.8% in all cases and 78.1±8.7% in lymphomas (HL 91.7%±8, NHL 55.6±16.6%). In the study of Mutlu et al the survival rate was 46% in NHL, 89% in HL, 61% in all cases, 40% in NHL, 74% in HL, 67% in neural crest tumors, 25% in germ cell tumors in the study of Temes et al was detected.[9] Although a statistically significant difference was found in survival rates between HL and NHL in our study, no statistical significance was found in the study of Temes et al.[10] In our study, the survival rates of sarcomas and germ cell tumors were statistically significantly lower than those of lymphoma and neural crest tumors.

CONCLUSION

In conclusion, a detailed history should be taken and physical examination should be done, complete blood count, CRP, LDH, sedimentation values should be checked, direct radiographs should be taken and mediastinum should be evaluated in children presenting with sudden onset and progressive respiratory distress, cough, and facial swelling complaints.

With the data obtained in our study, it was aimed to provide data on the epidemiology of mediastinal tumors in our region, to lay the groundwork for future studies, and to increase the early and accurate diagnosis of pediatric patients with mediastinal masses.

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