Clinicopathological features and survival outcomes of pediatric mediastinal tumors: A 10-year retrospective study

Running title: Pediatric mediastinal masses: a 10-year clinicopathological study

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Abstract

Background: Primary mediastinal masses account for 3% of all chest tumors. Given their varied clinical presentations and the need for accurate diagnosis, this study investigates the clinicopathological features and survival outcomes of children with primary mediastinal masses admitted to Shahid Sadoughi Hospital, Yazd, Iran, from 2011 to 2021.

Methods: In this descriptive cross-sectional study, 17 children under 18 years with primary mediastinal masses were examined using census sampling. Data were collected via a checklist covering age, sex, tumor location, symptoms, tumor type, treatment received, and malignancy status. Prognosis and survival were tracked. Statistical analysis was performed using SPSS 22, employing Kaplan-Meier and Log-Rank tests for survival assessment.

Results: Among the 17 patients, 12 (70.6%) were girls and 5 (29.4%) boys. Five patients (29.4%) died during follow-up. Nine tumors (53%) were benign and eight (47%) malignant. Ganglioneuroma was the most frequent tumor (29.4%). Survival analysis revealed no statistically significant association between survival and surgery (P=0.222), malignancy status (P=0.158), neural origin (P=0.666), chemotherapy (P=0.057), radiotherapy (P=0.752), tumor location (P=0.661), sex (P=0.670), or age (P=0.877).

Conclusion: The study suggests that the distribution of histological types of primary mediastinal masses in children is influenced by anatomical location. However, factors such as age, sex, treatment type, and tumor location do not significantly affect survival outcomes in these patients.

Keywords: Pediatric mediastinal tumors, Clinicopathological features, Survival analysis, Histological subtypes, Iran

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Introduction

The mediastinum is the central cavity of the thorax located between the pleural cavities. The diaphragm is located at the bottom, the thoracic outlet at the top, the sternum at the front, and the vertebral bodies and paravertebral areas at the back (1). It is divided into four compartments: superior, anterior, middle, and posterior, each with a specialized structure. Consequently, masses originating from these structures are different and tend to involve specific compartments (2). Primary mediastinal masses account for 3% of all chest tumors, with an average incidence rate of 8 cases per 1 million people annually. These masses can be benign or malignant, and with respect to their primary or secondary origin, they can originate from the thymus, hematopoietic, lymphatic, germinal, neurogenic, or mesenchymal tissues (3). Mediastinal lesions have a wide histopathological and radiological spectrum, and they include any mass, benign or malignant, infectious or reactive, and can occur at any age (4). Fibromas, lipomas, and malignant tumor types may be observed in all three compartments (1, 5).

There are age-related differences in tumor biology, host characteristics, and treatment protocols for mediastinal lesions. Thymoma, neurogenic tumors, and benign cysts are the most common mediastinal lesions (60% of cases) (4). According to the Davis study (1987), out of 400 cases of mediastinal mass, the most common primary tumor was thymus neoplasm (17%), followed closely by lymphoma (16%), nerve tumor (14%), and germ cell tumor (11%) (6). In a study conducted by Whooley et al. (1999), it was found that 63.8% of tumors were in the anterior mediastinum, 22.9% in the posterior mediastinum, and 13.3% in the middle mediastinum. The most common primary tumors of the mediastinum were lymphoma, with a 21.9% frequency, followed by thymoma with 18.1% (7).

Patients may be asymptomatic and may be discovered by accident on routine chest radiography performed for another reason (3). In a study in the United States on 73 patients, 46.6% were symptomatic. The most common symptoms were chest pain, myasthenia gravis, superior vena cava obstruction, hoarseness, upper limb pain, dysphagia, and shortness of breath (8). Some masses can cause endocrine syndromes such as hypertension, hypercalcemia, thyrotoxicosis, and gynecomastia (5). Considering the occurrence of different symptoms in different types of mediastinal masses and the importance of the most accurate diagnosis, this study examines the clinicopathological characteristics and survival outcomes of primary mediastinal masses in children who were referred to Shahid Sadoughi Hospital in Yazd from 2011 to 2021.

Method

This research involved a descriptive, cross-sectional, and retrospective study. Sampling was performed through a census of all patients under 18 years old diagnosed with primary mediastinal tumors who had biopsies, with their samples sent to the pathology department of Shahid Sadoughi Hospital in Yazd between January 1, 2011, and December 31, 2021. The sample size consisted of 17 patients. The sample size consisted of 17 patients. Individuals with insufficient information, including clinical, demographic, and pathological data and those diagnosed with other types of cancers were omitted from the study. The research began after receiving permission from the Ethics Committee of the School of Medicine at Shahid Sadoughi University of Medical Sciences, which assigned the ethical code IR.SSU.MEDICINE.REC.1399.273. The files of the patients were examined and the extraction of data inclusive of age, gender, pathology reports, initial clinical symptoms, anatomical location of the tumor, type of received treatment, and contact numbers was done. Moreover, through patient records and telephone calls, clinical information was gathered, including treatment type, patient survival status, and, in case of death occurrence, the cause of

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death - specifically whether it was due to the primary mediastinal tumor (with an indicated histological type) was considered. All patients were followed up until death or the 20th of March 2021.

Estimation of Cancer-specific survival was done from the moment of diagnosis until passing because of the primary mediastinal tumor (with an indicated histological type) or the last follow-up (March 2021). Overall survival (OS) was calculated from the moment of diagnosis of the primary mediastinal tumor (with an indicated histological type) until death from any cause or the last follow-up (March 2021). Following data collection and validation, the information was put into SPSS software version 22. Percentage, mean, and standard deviation were used in descriptive analysis, while comparing frequency distributions was done using the Chi-square test, and the T-test for mean comparisons. Patient survival was evaluated using Kaplan-Meier curves, and survival comparisons between groups were analyzed using the Log-rank test. In all analyzes, a p-value of <0.05 was considered statistically considerable.

Results

This study was accomplished with the aim of investigating the clinicopathological traits and survival of primary mediastinal masses in children referred to Shahid Sadoughi Hospital, Yazd, with 17 patients with primary mediastinal tumors (PMT) from 2011 to 2021. The patients' age range was from 1 month to 16 years. Regarding the distribution rate of variables in the 17 children studied, 12 (70.6%) were girls, and 5 (29.4%) were boys. Chi-square analysis showed no significant association between gender and histological tumor types (P=0.294). Similarly, age group (≤7 years vs. >7 years) was not significantly associated with tumor types (P=0.455). Also, 8 masses (47.1%) were in the posterior mediastinum, 6 masses (35.3%) were in the middle mediastinum, and 3 masses (17.6%) were in the anterior mediastinum. Additionally, 12 of the children (70.6%) were ≤7 years old, and 5 (29.4%) were older than 7 years old. The information on the distribution frequency of the type of mass based on its location in the examination is shown in Table 1. Regarding histological types, nine tumors (53%) were benign, eight (47%) malignant, and one (6%) showed inflammatory features suggestive of infection (caseating granulomatous inflammation). Analyzing the table using the Chi-Square test showed a statistically significant difference between the frequency distribution of the type of mass according to the location of the mass in the children studied, as neurogenic tumors were only observed in the posterior mediastinum.

The results have shown that there was no statistically significant difference between the frequency distribution of the mass type according to gender, age, and initial symptoms in the children studied (p=0.294 and P=0.455, P=0.251 Chi-square test). The average survival time of children according to surgery (P=0.222), type of malignancy (P=0.158), age (0.877), gender (0.670) and radiotherapy treatment (0.752) using the Log-Rank test, shows that there is a significant relationship. No difference was found between the average survival time according to surgery and the type of malignancy in children (P-value>0.05). Also, no significant relationship was observed between the average survival time of children according to the neurological origin of the tumor and chemotherapy treatment (7.15±0.69) in the studied samples (Tables 2 and Figure 1).

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Table 1. The frequency of the type of mass according to the location

Mass type	Mass location			Total
	Posterior mediastinum (%)	Middle mediastinum (%)	Anterior mediastinum (%)	
Ganglioneuroma	5 (100)	0 (0)	0 (0)	5 (100)
Ganglioneuroblastoma	3 (100)	0 (0)	0 (0)	3 (100)
Hemangioma	0 (0)	0 (0)	2 (100)	2 (100)
Lymphoblastic lymphoma	0 (0)	1 (100)	0 (0)	1 (100)
Pleuropulmonary blastoma	0 (0)	1 (100)	0 (0)	1 (100)
Lipoblastoma	0 (0)	0 (0)	1 (100)	1 (100)
Caseating granulomatous inflammation	0 (0)	1 (100)	0 (0)	1 (100)
Rhabdomyosarcoma	0 (0)	1 (100)	0 (0)	1 (100)
Lymphoepithelial like carcinoma	0 (0)	1(100)	0 (0)	1 (100)
Lymphoblastic lymphoma	0 (0)	1(100)	0 (0)	1 (100)
Total	8 (47.1)	6 (35.3)	3 (17.6)	17 (100)
P-value	0.013			

Table 2. Survival time based on the origin (Neurogenic, non-neurogenic) of tumors in children*

Origin of tumor	Number of cases	Number of deaths	Mean survival time ±SD	P-value
Neurogenic	8	3	6.30±0.80 years	0.666
Non-neurogenic	9	2	7.46±0.95 years	
Total	17	5	7.15±0.69 years	

(The P-value of 0.666 reports no statistically significant difference between the groups.)

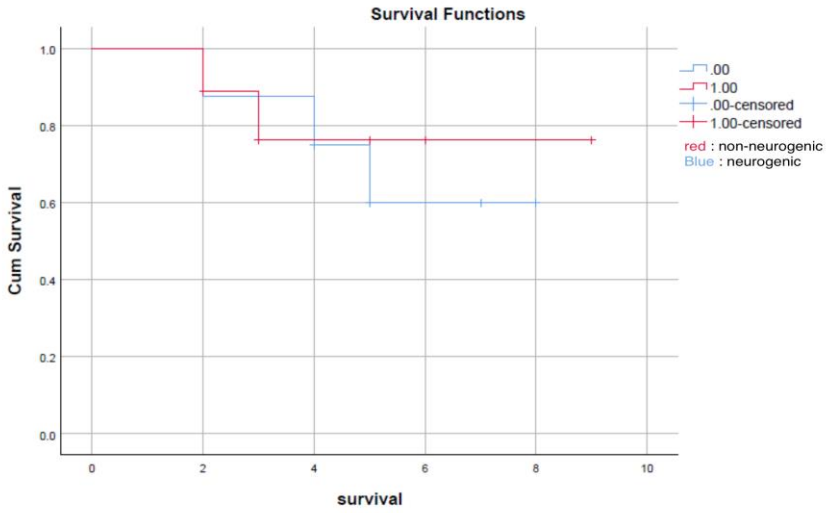

Figure 1. Kaplan-Meier survival analysis based on the origin of tumors (Neurogenic and non-neurogenic)

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Discussion

Previous studies have indicated that mediastinal tumors in adults are predominantly asymptomatic (8). For instance, the study conducted by Dalal et al. on 29 mediastinal tumors reported that the majority of patients were either asymptomatic or presented with nonspecific symptoms during diagnostic evaluations (3). Regarding the frequency distribution of symptoms observed in this study, the most frequently reported presenting symptom was cough (23.5%). A separate study reported that 41.6% of patients with mediastinal tumors were asymptomatic. However, cough, fever, and dyspnea are more commonly observed in pediatric cases than in adults. In contrast, symptoms more frequently observed in adults include chest pain or heaviness (4). A pediatric-focused study conducted by Seth et al. (2017) found nonspecific symptoms including fever, night sweats, and weight loss, and secondary symptoms such as local invasion or compression of mediastinal structures (e.g., respiratory distress and cough) to be the most common clinical manifestations (9). Additionally, research conducted by Ahmadi et al. reported that cough was the most prevalent clinical symptom (44.4%), while fever was the most common clinical sign (52.9%) (10). These findings are consistent with those observed in our current study, collectively suggesting that mediastinal tumors are more symptomatic in children than in adults. In terms of gender distribution in our current study, 70.6% of the children were female, while 29.4% were male. The findings of studies conducted on the gender distribution of patients with mediastinal masses have been inconsistent. A 2020 research study reported a predominance of women over men in terms of having mediastinal masses (2). Similarly, the study conducted by Shrivastava et al. showed a higher occurrence of mediastinal tumors in women (11), aligning with the findings of our current study, which reported a higher prevalence of mediastinal tumors in females. While Ahmadi et al.'s study on children showed an equal incidence of the disease in both genders (10), Seth's study on 58 children with mediastinal tumors revealed that 77.5% of the children were male (9). Collectively, based on the divergent results of these studies, it is evident that no specific gender preference can be assumed for mediastinal masses, irrespective of the patient population (children or adults). Regarding the age of onset of mediastinal tumors, 70.6% of the children in the current study were under 7 years old. Liu et al.'s research identified that the most predominant age group for onset is less than 10 years of age (4). In Seth's study on 58 children, the mean age for mediastinal malignancies was reported as 6.63 years (9). A separate 2007 study conducted in Iran reported that mediastinal tumors occurred across an age range of 17 days to 13 years, with the highest incidence observed in infants under 1 year of age (8). Furthermore, Ahmadi et al. documented that the highest prevalence of mediastinal tumors occurred between the ages of 5 and 10 years (38%) (10). The findings of the current study are consistent with prior research, suggesting that the highest incidence of mediastinal tumors in pediatric populations occurs in children under 10 years old.

In this study, regarding the location of the mass, 8 masses (47.1%) were located in the posterior mediastinum, 6 masses (35.3%) in the middle mediastinum, and 3 masses (17.6%) were found in the anterior mediastinum. In another study performed on 105 patients, 63.8% of the masses were in the anterior mediastinum, 22.9% in the posterior mediastinum, and 13.3% in the middle mediastinum. In line with our study, Verma et al (2020), showed that the posterior mediastinal masses were the most anatomically common location of mediastinal tumor in children, but in contrasting with our data, Ahmadi et al (2004), declare anterior mediastinal masses to be most frequent in children (10,11). All things considered, it seems that frequency of the mass location in patients with mediastinal masses were influenced by the study population; In adults, these masses are most often in the anterior mediastinum, while in children, middle mediastinum is considered

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the primary location of masses. The abundance distribution of tumor type and histological type of tumor in the present study classified 53% of the tumors as benign and 47% as malignant. Also, the most common tumors according to results were ganglioneuroma, ganglioneuroblastoma, and hemangioma with frequencies of 29.4%, 17.6%, and 11.8%, each. In the Liu et al (2017) study, the type of lesion between children and adults was compared, conducting that neurogenic tumors, germ cell tumors, mesenchymal tumors, and lymphatic lesions were more common in children compared to adults, as opposed to thymus lesions and metastatic carcinomas which showed higher rates of occurrence in adults (8). Lymphomas were shown the most common mediastinal mass (35.2%), followed by masses of neural origin in the second rank in the Ahmad et al (10) study. The survival rate of children with mediastinal masses and the affecting factors in the present study, the average survival span of children was 7.15 years, and none of the variables of age, sex, type of treatment performed, and location of the mass had an effect on the average survival of children with mediastinal masses. Choe et al (2022), showed that 76% of children with mediastinal tumors have a favorable outcome in average of 6.2 months (12). Hodgkin's lymphoma and B-cell leukemia had an 87% and 66% promising response each showing a better prognosis than T-cell leukemia and metastatic neuroblastoma with 50% favorable response. Children with superior mediastinal syndrome (SMS) had a relatively poor prognosis, and the survival rate in these patients was 67%, while the survival rate in patients without SMS was 83%. In the study by Ahmadi et al (10), the survival rate of patients was 54% in an average follow-up of 3.2 years.

Conclusion

The study findings suggest that the frequency of histological types of primary mediastinal masses in children is solely affected by anatomical location. Statistical analysis shows factors such as age, sex, type of treatment, and tumor location are not significantly impactful on the survival of children with primary mediastinal tumors.

Strengths and Limitations

Strengths: This study provides a comprehensive clinicopathological overview of primary mediastinal masses in a pediatric cohort from a single tertiary center, with long-term survival tracking using robust statistical methods (Kaplan-Meier and Log-rank tests). The census sampling ensured inclusion of all eligible cases over a 10-year period.

Limitations: The retrospective design and small sample size (n=17) limit generalizability. As a single-center study in a specific region (Yazd, Iran), findings may not reflect broader populations. Additionally, detailed molecular data were not available for all cases.

Funding Source

Not applicable.

Ethics Statement

This study was approved by the Ethics Committee of the School of Medicine at Shahid Sadoughi University of Medical Sciences, Yazd, Iran, under ethical code IR.SSU.MEDICINE.REC.1399.273.

Conflict of Interest

All authors have no conflicts of interest to disclose.

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Author Contributions

Mahlagha Zahedi, as the first author and corresponding author, designed the study, supervised data collection, performed statistical analysis, and drafted the manuscript. Sahar Abbasinia, as the second author, contributed to data collection, literature review, and manuscript preparation. All other authors participated in data interpretation and critical revision of the manuscript for intellectual content. All authors approved the final version of the manuscript.

Consent for Publication

Not applicable.

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