

# Evaluation of clinical, morphological and pathohistological characteristics of thymomas – our ten year experience

Aleksandra Lovrenski<sup>1</sup>, Dragana Tegeltija<sup>1</sup>, Ivana Jeličić<sup>2</sup>, Milorad Bijelović<sup>3</sup>, Dejan Đurić<sup>3</sup>, Milana Panjković<sup>1</sup>

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<sup>1</sup> University of Novi Sad, Faculty of Medicine, Institute for Pulmonary Diseases of Vojvodina, Department of Pathology, Sremska Kamenica, Serbia

<sup>2</sup> General Hospital, Department of Pathology, Vrbas, Serbia

<sup>3</sup> University of Novi Sad, Faculty of Medicine, Institute for Pulmonary Diseases of Vojvodina, Department of Thoracic Surgery, Sremska Kamenica, Serbia

Correspondence to:

Aleksandra Lovrenski, MD, PhD,

Assistant Professor

[aleksandra.lovrenski@mf.uns.ac.rs](mailto:aleksandra.lovrenski@mf.uns.ac.rs)

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## ABSTRACT

**Background.** Thymomas are rare neoplasms arising from tissue elements of the thymus. The objective of the study was to analyse clinical characteristics of patients with thymoma, as well as morphological and pathohistological features of neoplasms. **Methods:** Retrospectively we studied 41 medical records and pathohistological material of patients referred to the Institute for pulmonary diseases of Vojvodina between the January 2005 and December 2014.

**Results:** Patient age at presentation ranged from 19 to 77 years. A slight female preponderance was detected, with 24 (58.5%) females and 17 (41.5%) males being affected. All types of thymoma more often occurred in males, except subtype B1. Patients with type A thymoma and subtype B1 were mainly asymptomatic, while patients with subtype B2 and type AB presented with dyspnea, dysphagia, pain and cough. Myasthenia gravis often was associated with type A (40%). The most common histologic type was subtype B1. Twenty three (56%) patients had a tumor diameter between 5 and 10 cm. Five patients had malignant thymoma, and the most common types of thymoma that showed signs of capsula invasion or pleural and pericardial implants were type AB (60%) and subtype B2 (50%). Biopsies of suspected tissue were obtained through a sternotomy, video-assisted thoracoscopy surgery, and video-assisted mini thoracotomy, and after setting a diagnosis on ex tempore analysis, the lesions were removed by thymectomy or extirpation of the tumor mass. **Conclusion:** Thymomas have variable clinical presentations. Clinical outcome correlates with histological type, size and clinical stage, as well as the ability to achieve complete tumor resection.

**Key words:** Thymoma, Neoplasms

## INTRODUCTION

Thymomas are rare neoplasms arising from tissue elements of the thymus and developing in the anterior mediastinum with an annual incidence of only 0.15 cases per 100.000 person-years (1,2). They can be associated with a variety of systemic and autoimmune disorders, such as pure red cell aplasia, pancytopenia, hypogammaglobulinemia, collagen-vascular disease, and most commonly with myasthenia gravis (3-6). Although they appear in all age groups, the highest frequency of occurrence is in people over the age of 40 years. They occur in both genders equally (1). Grossly, most thymomas are sharply demarcated, pale gray, oval, lobular masses that may be a different size and weight. On cross section, one can often observe secondary changes in the form of cysts, dystrophic calcifications and hemorrhage. Mostly, they show a slow, expansive growth, but some of them invade surrounding tissues and give metastases when they have the characteristics of malignant tumors (7).

According to the current histological classification, thymomas are classified into three types: type A, type B and type AB (1,8).

Type A thymomas are constructed from the spindle-shaped epithelial cells with pale nuclei and invisible nucleoli, arranged in swirling formations and bundles. Often, at the periphery of lobule one can find microcystic and glandular formations, and sometimes pseudorosets (Figure 1). The lymphocytes are present in very small numbers.

Type B thymomas are divided into three subtypes. Subtype B1 is characterized by predominance of lymphocytes and inconspicuous epithelial component made of oval cells with small pale nuclei and prominent nucleoli (Figure 2). Subtype B2 is made of conspicuous epithelial component of oval cells with vesicular nuclei and centrally

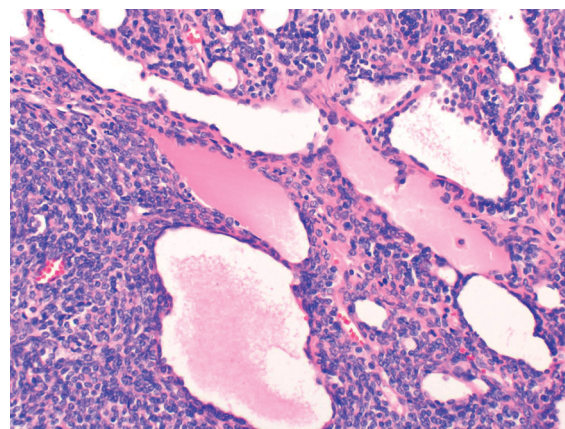


Figure 1. Thymoma type A (HE stain, magnification 20)

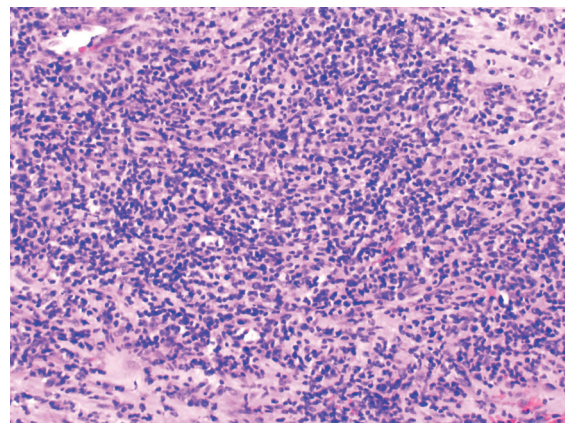


Figure 2. Thymoma subtype B1 (HE stain, magnification 20)



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placed nucleoli (Figure 3). Lymphocytic component is still abundant, but less than in the case of B1 subtype. Subtype B3 ("well-differentiated thymic carcinoma") is built of polygonal epithelial cells with mild to moderate atypia, as well as mitotic figures.

Type AB thymomas are transitional histological types of thymoma which contain the main features of thymoma type A and type B (Figure 4).

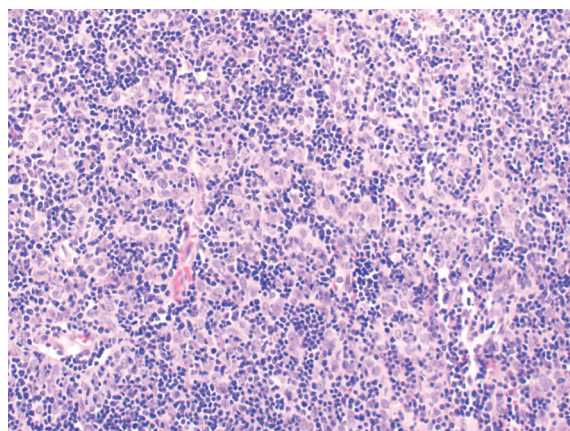


Figure 3. Thymoma subtype B2 (HE stain, magnification 20)

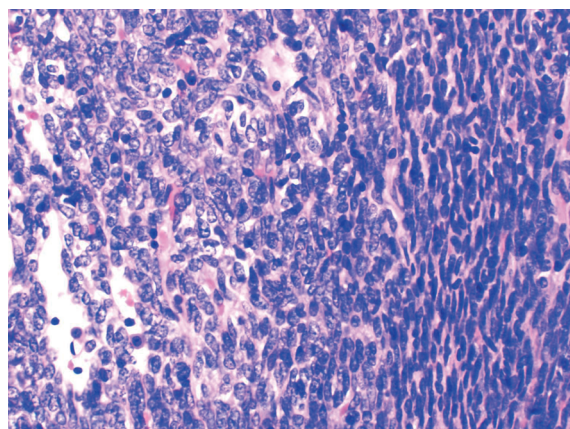


Figure 4. Thymoma type AB (HE stain, magnification 40)

Histologically, thymomas show morphological variations and they were described as: cystic thymomas (tumors with multiple cystic cavities filled with clear or hemorrhagic fluid), thymomas with a predominance of plasma cells, clear cell thymomas (tumors made of cells rich in glycogen), thymomas with pseudosarcomatous stroma (metaplastic thymomas), microscopic thymomas (size less than a 1 millimeter), sclerosing thymomas (tumor foci lined with sclerotic connective tissue) and so on (1). It is important to emphasize that each histological type of thymoma can be associated with the invasion of the capsule, pleural and pericardial implants, as well as distant metastases, therefore the term malignant thymoma is appropriate (1,8).

The setting of diagnosis is based on patient's history, clinical symptoms, objective examination, appropriate radiological diagnostic procedures and, finally, pathohistological analysis. The use of cytological, as well as immunohistochemical analysis is rarely necessary (7).

The aim of our study was to analyze the clinical characteristics of patients with pathohistologically diagnosed thymoma, as well as morphological characteristics and histological types of this neoplasm.

## MATERIAL AND METHODS

A retrospective review of The Institute for pulmonary diseases of Vojvodina database was performed from January 2005 to December 2014. Data were collected from the hospital records.

The study included 41 patients with pathohistologically diagnosed thymoma. Biopsy materials were obtained by sternotomy, video assisted thoracoscopic surgery (VATS) and video-assisted mini thoracotomy. All tissue samples, obtained with one of the above methods, were fixed in 10% neutral formalin and then embedded in paraffin, cut on microtome in 4 mm tissue slices, and then stained with routine hematoxylin-eosin (HE) method. In our study, diagnosis of the most cases of thymomas was based on pathohistological analysis of routine HE stained sections. Since cytological and immunohistochemical analyses were applied in the minority of cases they were not considered relevant for this study.

All tumors were classified according to WHO's International Histological Classification of thymic tumors as type A, AB and B (with subtypes B1, B2 and B3), based on the predominant cell type (8). Surgical and histological data were used to stage patients according to the clinical staging system devised by Masaoka and colleagues: stage I (fully encapsulated tumors), stage IIA (tumors with microscopic invasion of the capsule), stage IIB (tumors with macroscopic invasion of the capsule), stage III (tumors with macroscopic invasion of adjacent organs), stage IVA (pleural or pericardial implants) and stage IVB (tumors with hematogenous or lymphatic dissemination) (9). Collected clinical data included demographic information, such as age and sex, and presenting symptoms. Surgical data included surgical approach, procedure performed and the presence or absence of tumor invasion.

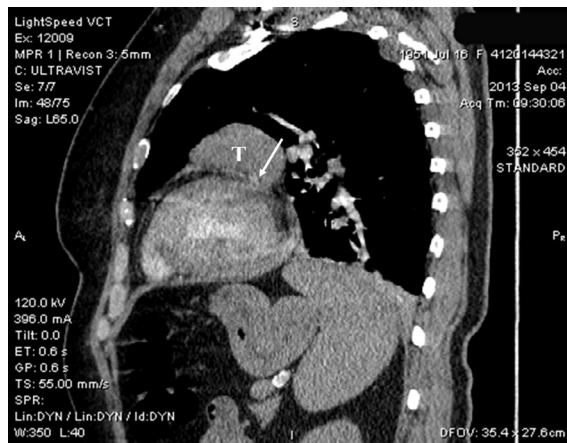
## RESULTS

Patient age ranged from 19 to 77 years (Mean = 45.6 years). A slight female preponderance was detected, with 24 (58.5%) females and 17 (41.5%) males being affected.

In one third of patients thymomas were asymptomatic (33.2%). In all asymptomatic patients the diagnosis was made as the result of an incidentally discovered mass on a chest radiograph. Among symptomatic patients, dyspnea was the most common presenting complaint (33.2% patients). Symptoms consistent with myasthenia gravis accounted for the second most frequent presentation affecting 25.9% patients. Patients also complained on cough (22.2%), had chest pain (18.6%), dysphagia (11.1%) and fatigue (7.4%). Fever was noted in 3.7% patients.

Forty patients underwent preoperative investigations. One patient died before investigations could be performed, but malignant thymoma was diagnosed on autopsy. Of the 40 patients that underwent investigations, two did not undergo surgery. In those patients surgical intervention was not attempted because of pleural and pericardial metastases diagnosed by VATS. VATS and extirpation of tumor mass were performed at 10 patients. Sternotomy with thymectomy was performed at 19 patients,

while video-assisted mini thoracotomy with extirpation of tumor was performed at 9 patients. All of the 41 chest radiographs obtained were positive for tumor mass. Computed tomography was performed in all cases; all the scans demonstrated tumor mass, and in 7 scans invasion was clearly identified (Figure 5).



**Figure 5.** Contrast-enhanced chest CT: Sagittal-plane multiplanar reconstruction showing thymoma (T) and its pericardial infiltration (arrow)

Three tumors were microscopic with multifocal involvement. In the remaining patients, tumors ranged in size from 1–16 cm in maximum dimension (Mean = 8.2 cm). In seven patients tumor diameter was from 1 - 5 cm, in 23 patients tumor diameter was from 5 - 10 cm, in 5 patients tumor diameter was from 10 - 15 cm, and one patient had a tumor with diameter over 15 cm. At two patients with Masaoka stage IVA, the size of the tumor could not be measured because only exploration and biopsy of the tumor mass without removing the tumor was performed. Disease staging by Masaoka's system was as follows: stage I, 31 (75.6%) patients; stage IIA, 2 (4.9%) patients; stage IIB, 4 (9.7%) patients; stage III, 2 (4.9%) patients; stage IVA, 2 (4.9%) patients.

Different histologic types and morphologic variation of tumors were detected. Histological type A thymoma was detected in 10 patients (24.5%), subtype B1 in 14 patients (34.1%), subtype B2 in 4 patients (9.7%), and intermediate histologic type AB in 7 patients (17.1%). Microscopic thymoma was detected in 3 patients (7.3%), and metaplastic

variation of tumor in 2 patients (4.9%). Cystic thymoma was diagnosed in only one patient (2.4%).

In relation to the histological type, all types except subtype B1 thymoma occurred more frequently in men. Patients with type A thymoma were the oldest (Mean = 59 years), whereas patients with subtype B2 were youngest, and their average age was 31 years. Patients with type A and subtype B1 thymoma were most often asymptomatic, whereas patients with subtype B2 and type AB commonly presented with dyspnea, dysphagia, chest pain and cough. Myasthenia gravis was mostly associated with thymoma in patients with thymoma type A (40%) and in patients with thymoma type AB (20%), while at the remaining types of thymomas myasthenia was not present. The most common types of thymomas that showed signs of capsular invasion or pleural and pericardial implants were type AB (60%) and subtype B2 (50%) (Table 1).

## DISCUSSION

Thymoma, a rare neoplasm arising from the epithelial cells of the thymus gland is variable in its presentation ranging from an asymptomatic incidental finding on chest radiography to signs and symptoms consistent with a local mediastinal disorder, and an unusual paraneoplastic syndrome (3-6). The majority of patients in our study (66.8%), as well as in other studies had asymptomatic disease (10). Symptoms consistent with myasthenia gravis accounted for the second most frequent presentation affecting 25.9% of our patients. Previous studies have found a higher incidence of myasthenia gravis in thymoma patients, ranging from 30%–60% (11-13). Alexiev et al. highlighted the fact that myasthenia gravis is the most common symptom in patients with subtype B2 thymoma, but our data showed that the most common type of thymoma associated with myasthenia gravis was type A (14). According to literature, in about 30-50% of patients thymomas are discovered accidentally, because patients have no symptoms. On the other hand, if symptoms occur, they are usually result of the pressure on the surrounding structures and manifest in the form of cough, pain in the mediastinum, dysphagia, hoarseness or recurrent respiratory infection (7). Also, one third of patients had symptoms of paraneoplastic syndrome: myasthenia gravis, aplasia of the red bloodline, hypogammaglobulinemia, thyroiditis, and systemic lupus erythematosus (8).

**Table 1.** Clinical and morphological characteristics of patients and tumors in relation to histological type

Histological type/subtype of the tumor	Patient's Gender	The average patient's age	Clinical symptoms	Association with myasthenia gravis	The average size of the tumor	Malignancy
A	M 60% F 40%	57.0	60% asymptomatic	40%	4.7 cm	20%
AB	M 80% F 20%	39.6	80% dyspnea, chest pain, dysphagia	20%	7.8 cm	60%
B1	F 67% M 33%	47.6	60% asymptomatic	/	7.9 cm	/
B2	M 100%	30.0	100% dyspnea, chest pain, cough	/	7.5 cm	50%

The average age of our patients was 45.6 years. Of the 41 patients, 30 were older than 40 years, which confirm the fact that the tumor predominantly occurs in people older than 40 years. This is consistent with results of Alexiev et al. in whose study the average age of patients was 46.5 years, while in research of Safieddine et al. average age ranged from 32 to 77 years (mean 55 yr) (14,15). In our study in the majority of cases (58.5%) the tumor has occurred in females compared to males (41.5%). This is consistent with study of Safieddine et al. who reported a slight female preponderance, with 38 (58%) females and 27 (42%) males being affected (15). In regard to histological type of the tumor, all types except type B1 occurred more frequently in men.

Chest radiography and CT scan of the thorax were the most commonly performed radiological methods. Computed tomography and chest radiography were performed in all cases. All scans demonstrated tumor mass, and 7 of 8 scans in patients with invasive thymomas correctly identified tumor invasion. The most common and the most preferred operative method was sternotomy, used in 50% of cases.

According to previous clinical and pathological studies, the clinical stage of the tumor (determined by the degree of encapsulation and presence of invasion or metastases), has been a more reliable prognostic indicator than pathohistological finding, with the staging system of Masaoka being the most commonly applied (9). In our study, three tumors were microscopic with multifocal involvement. In the remaining patients, tumors ranged in size from 1–16 cm in maximum dimension (Mean = 8.2 cm), and disease staging by Masaoka's system was as follows: stage I, 31 (75.6%) patients; stage IIA, 2 (4.9%) patients; stage IIB, 4 (9.7%) patients; stage III, 2 (4.9%) patients; stage IVA, 2 (4.9%) patients. According to literature data, tumors ranged in size from 1.5–16 cm in maximum dimension (Mean = 8.8 cm), and in patients having myasthenia gravis, tumor size averaged 7.8 cm. Disease staging by Masaoka's system was as follows: stage I, 23 (35%) patients; stage II, 13 (20%) patients; stage III, 19 (29%) patients; stage IV, 10 (15%) patients (14).

In our study, the most common histologic type of thymoma was subtype B1, which was diagnosed in 14 patients (34.1%), followed by types A in 10 patients (24.5%) and AB in 7 patients (17.1%). Three patients (7.3%) had microscopic thymoma, while the subtype B2 was found in 4 patients (9.7%). One patient (2.4%) had cystic thymoma, and metaplastic histologic variation of the tumor was found in 2 patients (4.9%). According to WHO, the most common histological types were subtype B2 thymoma and type AB, which are represented by the average of 20–35% each, while subtype B1 and type A were less common and represented by an average of 5–10% each (8). As noted above, each histological type of thymoma can be associated with the invasion of the capsule, pleural and pericardial implants, as well as distant metastases, and for these tumors the term malignant thymoma is appropriate (1,8). According to WHO, behavior of type A and type AB is usually benign, subtype B1 has a low malignant potential (ten-year survival is 90%), subtype B2 is a medium in malignancy, while subtype B3 is one of the well-differentiated thymic carcinomas and has the worst prognosis (8).

Of all patients included in the study, 8 (19.5%) had malignant thymoma, while the remaining 33 (80.5%) patients had benign thymoma. Three malignant tumors measured between 5 and 10 cm each, two were

between 10 and 15 cm, while one measured over 15 cm. In two patients with Masaoka stage IVA disease, tumor diameter was not available since extirpation of the tumor has not been done, (only biopsy in order to establish diagnosis). In relation to the histological type two malignant thymoma were type AB, two were type B2, two were type B1, one was type A, while one malignant tumor presented as metaplastic histologic variation.

According to the literature, there is a correlation between the incidence of infiltrative thymoma and patient's age. It was observed that the malignant thymomas more commonly affected elderly patients, which was not the case in our study (14). Eight of our patients with malignant thymoma were of different ages: the youngest patient was 30 years old, other were 35, 42, 47, 53, 56 and 59 and the oldest one was 77 years old.

The diagnosis of thymoma is not simple. Diagnostic dilemmas are diverse: hyperplastic thymus tissue, cancers (usually in relation to the subtypes B2 and B3), lymphomas (usually based on the subtype B1), solitary fibrous tumors and synovial sarcomas (compared to type A), carcinosarcomas (compared to metaplastic thymoma) and virtually all tumors of the mediastinum must be included in differential diagnosis. Also, differentiation and classification of certain histological type of thymoma is a common problem (8).

Computed tomography is the first choice technique to characterize mediastinal mass with regard to its anatomic dissemination and invasion, as well as distant metastases (16). In our hospital in tumors suspicious of thymoma, a fine-needle aspiration (FNA) has not been routinely performed, due to problematic histological differentiation between thymomas, lymphomas, and thymic hyperplasia, small volumes of obtained tissue samples, as well as possibility of seeding malignant cell during procedure (17).

Median sternotomy is the surgical approach of choice for complete surgical resection, and it is especially effective for stage I thymomas without any further treatment. Video-assisted thoracoscopic surgery with extirpation of tumor mass is effective alternative procedures for noninvasive thymomas. A complete thymectomy should always be performed if possible, because simple extirpation may result in recurrence (18,19). According to a multicenter study by Kondo and Monden (1320 patients), total resection is the most important prognostic factor for survival: the 5-year survival rate of Masaoka stages III and IV thymomas is 92.9% after total resection versus 64.4% ( $p < 0.001$ ) after subtotal resection versus 35.6% if inoperable (20). Wright and associates showed that recurrence rates after complete resection vary between 11% and 19% and correlated with stage: WHO tumor type A and AB 0%, B1 and B2 8%, B3 27% and C 50% (21). Stage of disease, histologic type, size and extent of the tumor are considered significant, independent prognostic factors on long-term disease-free survival in the majority of studies reviewed (22,23). According to the Masaoka system, fully encapsulated tumors (stage I), tumors with microscopic (stage IIA) and macroscopic invasion of the capsule (stage IIB) have a good prognosis and five-year survival rate of 100%. Tumors with macroscopic invasion of adjacent organs (stage III) have a poor prognosis although they may be resectionable, while tumors with pleural and pericardial implants (stage IVA) and tumors with hematogenous or lymphatic dissemination (stage IVB) are not resectionable and have extremely bad prognosis (9). Tumor size is an independent prognostic

factor for outcome in thymoma patients. This statement is supported by a single-center study of 179 patients by Wright and colleagues, finding a critical tumor size ( $\geq 8$  cm) to be an independent predictor for recurrence (24). The prognostic value of myasthenia gravis (MG) in thymomas is controversial in the literature. In a multicenter study, Kondo and Monden found that thymomas associated with MG seem to behave less aggressively, as thymomas associated with MG are diagnosed at an earlier stage and have lower recurrence rates, so myasthenia gravis can serve as a positive prognostic factor for the outcome of thymomas (20). In conclusion, the diagnosis of thymoma is not simple. Computed tomography is the first choice method to characterize mediastinal mass, as well as distant metastases. Median sternotomy is the surgical approach of choice for complete surgical resection. Diagnosis of the most cases of thymomas by pathologist can be done usually by analysis of routine HE stained sections, while cytological and immunohistochemical analysis can be applied in cases when pathologist has a diagnostic dilemma. Stage of disease, histologic type, size and extent of the tumor are considered significant, independent prognostic factors.

### Conflict of Interest

Authors declare no conflicts of interest

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