ORIGINAL ARTICLES

UDC: 616.438-006
https://doi.org/10.2298/VSP180103056S

Clinicopathological retrospective analysis of thymoma in Serbia: A single center experience

Kliničkopatološka retrospektivna analiza timoma u Srbiji: iskustvo jednog centra

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Abstract

Background/Aim. Thymoma is the most common mediastinal tumor. The treatment procedures are based on the results from the research of retrospective studies because they are not frequent tumors. The aim of this work was to define common clinical features, therapeutic aspects, survival and recurrence free survival. **Methods**. This study was performed in the Clinic for Pulmonology, Clinical Centre of Serbia, Belgrade from January 1993 to December 2013. We analyzed 62 patients with histopathologically proven thymoma. The results were obtaind from medical history, physical exam, chest X-ray and/or computed tomography and operational findings or diagnostic procedure reports. Thymomas were clasiffied according to the World Health Organization classifying system, based on histopathological findings, and staged according to the Masaoka-Koga staging system. **Results.** There were more female (54.8%) patients. Patients were mostly in the seventh decade of life. One third (29%) of the patients were asymptomatic. Cough was the dominant symptom. Myasthenia gravis was the most common paraneoplastic syndrome (12.9%). Solitary tumor was the most common in our patients (61.3%), as well as the tumors larger than 5 cm (52.5%), and noninvasive thymomas (52.5%). The majority of patients (40%) were in the stage I of the disease. The operative approach was conducted in most of the patients (88.7%). A statistically significant difference in survival was in women, patients with solitary tumor, non-invasive thymomas, patients in the stage I of the disease, and those who were operated. The dimension of the tumor mass approached the conventional level of significance. **Conclusion.** In patients with thymomas, statistically significant survival rate predictors are gender, presence of solitary tumor mass, tumor invasiveness, clinical stage and surgical treatment of the disease.

Key words:
thymoma; diagnosis; neoplasm staging; treatment outcome; survival; serbia.

Apstrakt

Uvod/Cilj. Timomi su retke bolesti, ali najčešći tumori medijastinuma. Terapijski vodiči su zasnovani na rezultatima analiza retrospektivnih studija. Cilj ove studije je bio da se definišu osnovne kliničke karakteristike obolelih od timoma, terapijski aspekti, preživljavanje i pojava relapsa bolesti. **Metode.** Ovom retrospektivnom studijom analizirana su 62 bolesnika sa patohistološki verifikovanim timomom u Klinici za plućne bolesti Kliničkog centra Srbije u Beogradu, u periodu od januara 1993. do decembra 2013. Popunjavani su upitnici koji su obuhvatali podatke iz istorije bolesti, fizički pregled bolesnika, nalaze radiografije i/ili kompjuterizovane tomografije grudnog koša, operativne liste i/ili patohistološke nalaze biopsija. Analizirani su klinička slika, terapijski aspekti, preživljavanje i pojava relapsa bolesti. Timomi su klasifikovani prema patohistološkoj klasifikaciji Svetske zdravstvene organizacije i prema Masaoka-Koga sistemu. **Rezultati.** Više je bilo obolelih žena (54,8%). Najveći broj bolesnika je bio u sedmoj deceniji života

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(32,3%). Skoro trećina bolesnika je bila asimptomatska (29%), a ostali su imali bar jedan simptom, najčešće kašalj. Najčešći paraneoplastički sindrom bila je miastenija gravis (12,9%). Najčešće je konstatovano prisustvo solitarne promene u grudnom košu (61,3%), tumora većeg od 5 cm (52,5%) i neinvazivnih timoma (52,5%). Većina bolesnika je bila u I stadijumu bolesti (40%), a najčešći terapijski pristup operacija (88,7%). Statistički značajna razlika u preživljavanju konstatovana je kod žena, bolesnika koji su imali solitarni tumor, neinvazivni timom, I stadijum bolesti i bolesnika kojima je učinjena operacija. Dimenzija tumora je bila blizu granice konvencionalnog nivoa značajnosti. **Zaključak**. Statistički značajni prediktori preživljavanja kod obolelih od timoma su pol, diseminovanost bolesti, invazivnost tumora, klinički stadijum bolesti i operativno lečenje.

Ključne reči:
timom; dijagnoza; neoplazme, određivanje stadijuma, lečenje, ishod; preživljavanje; srbija.

Introduction

Thymomas are not so common mediastinal tumors. They are developing from epithelial thymic cells and present 0.2–1.5% of all malignancies [1]. On one hand they are very rare, but on the other hand they present 20% of all mediastinal masses and up to 50% of all anterior mediastinal masses [2]. Average incidence of thymomas is 0.15 per 100,000 persons/year. The disease is usually developed locally but metastases are most often found on the pleura, pericardium, or diaphragm [3, 4]. The World Health Organization (WHO) classifies thymmomas on the basis of histopathological (HP) findings which differ thymomas from thymic carcinomas. This classification was made in 1999 and updated in 2003. Thymomas are subdivided into five main types (called A, AB, B1, B2, B3) and a few less frequent other types based upon the morphology of the epithelial tumor cells and on the proportion of the non-tumoral lymphocytic component, which may indicate an aggressiveness of the tumor. The greatest probability of a good outcome has the type A, and decreases going to the type B3 [5, 6]. Staging of thymomas is based on the Masaoka-Koga system (1994) which was adapted in 2011 by the International Thymic Malignancy Interest Group (ITMIG) [7]. Clinical presentation of thymomas can be asymptomatic, with the symptoms of local spread of the tumor and within paraneoplastic syndromes. Autoimmunity is a very frequent clinical feature [8], especially myasthenia gravis (MG) which is present in 30% of patients, but also other autoimmune diseases can be seen [9–12]. Treatment options for this patients are: operational approach, radiotherapy (RT), chemotherapy and the best supportive care (BSC), and/or combinations of these regimens [13] depending on the disease location, thymoma stage, general condition of a patient, as well as a presence of comorbidities.

Here we retrospectively analyzed the clinical presentation and overall survival in patients with histologically confirmed thymoma diagnosed during an 20-year period in our institution.

Methods

This retrospective study was performed in the Clinic for Pulmonology, Clinical Centre of Serbia, Belgrade from January 1993 to December 2013. We analyzed 62 patients who were hospitalized and treated in our hospital. All the cases with thymoma were confirmed by the histopathological (HP) analysis of the tissue obtained during surgery or by fine needle aspiration biopsy (FNAB). Thymomas were classified according to the WHO histopathological classification and staged on the basis of the Masaoka-Koga staging system. The results were obtained from medical history, physical exam, chest X-ray and/or computed tomography, and operational findinga or reports of a diagnostic procedure with HP proof of thymoma. We analyzed potential influence of gender, age and smoking on thymoma and whether they affect the survival rate in thymoma patients. We also analyzed the incidence of paraneoplastic disorders, paying particular attention to myasthenia gravis, comorbidities in thymoma patients and the presence of certain symptoms and their duration before establishing the diagnosis. The overall survival rate was analyzed in relation to the tumor size, tumor spread and invasiveness of the disease, its clinical stage and HP findings as well as to the therapy approaches, i.e. whether tumor was treated by surgical methods, especially if the radical operation or incomplete resection (palliative surgical approach) was done, or it was treated by other methods of treatment when surgical approaches could not be carried out. We also studied thymoma recurrence in patients who had complete surgical resection in relation to the possible influence of smoking, clinical stage of the disease and HP findings.

Results were presented as count (percent), mean ± standard deviation (SD) or median, depending on data type. Log rank test was performed to assess significant predictors of survival rate. Survival rate was presented using medians or means with confidence intervals (CI) if appropriate. Due to a small sample size, Cox regression was performed using the Forward method. Also, due to large difference between arithmetic means and medians, some results were presented as medians without confidence interval and medians were taken for calculating survival rate. All data were analyzed using SPSS 20.0 (IBM corp.) statistical software. All p values less than 0.05 were considered significant.

The Institutional Ethics Committee approved the study.

Results

The study included 34 (54.8%) women and 28 (45.2%) men, with the proportion of 1.2 : 1. The average age was 55.7 ± 13.0 years (ranging from 21 to 75 years). The highest percentage of patents was in their seventies, 20 (32.3%), and the next group were the patients in their sixties, 17 (27.4%). The basic characteristics of the patients are shown in Table

1. The clinical presentation of thymomas varied. Nearly one third (29%) of the patients had no symptoms and rest of the patients had minimum symptoms (Figure 1): the dominant one was cough in 24 (38.7 %) of the patients followed by general weakness and chest pain, in 22 (35.5%) of the patients each. Polyneuropathia as paraneoplastic syndrome was present in 1 (1.6%) patient, while myasthenia gravis was present in 8 (12.9%) of the patients, 5 (62.5%) of whom were women. The duration of symptoms prior to diagnosis of thymoma varied from 1 month to more than one year.

Table 1
Basic characteristics of 62 patients with thymoma

Characteristics	Values
Gender (male/female), n (%)	28 (45.2) / 34 (54.8)
Age (years), mean ± SD	55.7 ± 13.0
Smoking habits, n (%)	36 (58.1)
Symptoms, n (%)	44 (71)
Symptom duration (n = 44), n (%)	
1 month	12 (26.7)
6 months	21 (46.7)
1+ year	11 (25)
Paraneoplastic disorders, n (%)	9 (14.5)
Comorbidities, n (%)	30 (48.4)

n (%) – number (percentage) of patients; SD – standard deviation.

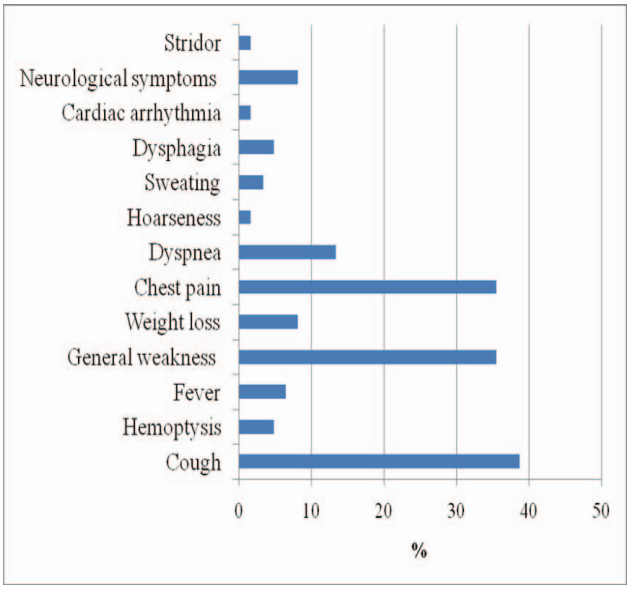

Fig. 1 – Symptoms distribution in 62 patients with thymoma.

The majority of the patients (nearly half, or 46.7%) had symptoms with a duration of 6 months, while a duration of one month and a duration of more than one year were approximately the same: 12 (26.7%) and 11 (25%) patients, respectively. Comorbidities were recorded in nearly half of the patients, 30 (48.4%), mainly in women, 21 (70%). The most common comorbidity was arterial hypertension in 13 (43.3%) of the patients, 4 (13.3%) of the patients had hyperplasia of the thyroid gland. Two patients (6.6%) experienced following diseases: bronchiectasis, angina pectoris, and cardiac arrhythmia. Other diseases (such as degenerative spinal diseases and alcoholism) were in individual cases. Secondary malignancies were present in 4 (13.3%) of the patients, and all were previously cured by a radical operational approach. A solitary finding was more frequent radiographic presentation in our patients (61.3%), while atypical lesions (21%) and metastatic process (17.7%) were less present (Table 2).

Table 2
Clinical characteristics of 62 patients with thymoma

Clinical characteristics	n (%)*
Radiographic finding	
solitary	38 (61.3)
atypical	13 (21)
metastatic	11 (17.7)
Tumor size (cm)	
> 5	36 (58.1)
< 5 m	26 (41.9)
Tumor invasiveness	
non-invasive	32 (52.5)
invasive in fatty tissue	11 (18)
metastatic	18 (29.5)
Masaoka-Koga stage	
I	29 (46.5)
II (IIA and IIB)	17 (27.4)
III	5 (8.1)
IV (IVA and IVB)	11 (17.7)
Diagnosis approach	
invasive	8 (12.9)
OP	54 (87.1)
WHO histology type	
A	16 (25.8)
AB	16 (25.8)
B1	18 (29)
B2	4 (6.5)
B3	8 (12.9)
Operation (n=55)	
radical/complete resection	50 (90.9)
palliative/incomplete resection	5 (10.1)
Therapy	
operation	55(90.9)
other treatments	16 (25.8)
Death (n = 61)	25 (40.9)

***Results are presented as number (n) and percentage (%) of patients. WHO – World Health Organization.**

Massive tumors, larger than 5 cm, verified by radiographic findings or /and during surgery, were the most commonly present in 58.1% of the patients. Noninvasive thymomas were the most common (in 52.5% of the patients). A majority of the patients were in the stage I of the disease (46.5%), while 27.4% were in the stage II, 8.1% in the stage III and 17.7% in the stage IV. The analysis of HP findings showed that most frequently present was the type B1 (in 29% of the patients), followed by the type A and type AB, and they were equally presented, each in 25.8% of the patients, followed by the type B3 and type B2, in 12.9 and 6.5% of the

patients, respectively. For the largest number of patients, the diagnosis, that is the HP verification of the process, was established during the operation itself (87.1%), and for other patients (12.9%) diagnosis was established using invasive diagnostic procedures, fine needle aspiration biopsy (FNAB) in all patients except the one who underwent mediastinotomy with tumor biopsy. The treatment in most cases (88.7%) was carried out by surgical approach, while radical operation (RO) was carried out in much greater number of patients compared to a incomplete resection (palliative surgery), in 90.9 and 10.1% f the patients, respectively. Therapeutic treatment modalities that were applied to others, non-operated patients, included the use of chemotherapy, radiotherapy (RT) and BSC equally in every two patients (3.2%), except BSC which was applied in 3 (4.8%) of the patients. Death was recorded in 40.9% of the patients, out of whom 3 (12%) died in the first week after the surgery was performed, as a complication of the surgery. The survival rates of our patients are presented in Table 3. As of December 2013, the median overall survival in patients with thymoma was 204 months (95% CI: 116.7–291.3). The 1-, 2-, 5- and 10-year survival rates of patients with thymoma were 85.2, 75.3, 69.9 and 62.8%, respectively. The 1-, and 10-year survival rates were the best in patients in the stage I, the AB HP finding followed by the type A. For patients who were operated on, the 5- and 10-year survival rates were 85.5%, 75.7% and 67.8%, respectively, and in those who were not operated on, the 1-year survival rate was 83%, but only one of them (12.5%) had a 10-year survival rate (Table 3).

Table 3
Survival rate (%) of 62 patients with thymoma according to stage, histopathological (HP) findings and operation

Parameters	1 year	5 year	10 year
All stages	58.2	69.9	62.8
stage I	92.9	92.9	92.9
stage II	94.1	70.6	48.1
stage III	40.0	40.0	40.0
stage IV	72.7	27.3	27.3
HP findings			
type A	86.7	73.3	65.2
type B1	77.8	60.0	60.0
type B2	75.0	75.0	75.0
type B3	87.5	50.0	50.0
type AB	93.7	87.5	72.2
Operation			
yes	85.5	75.7	67.8
no	83.0	16.6	12.5

The comparison of median survival according different patients' characteristics is presented in Table 4. Statistically significantly longer survival was found in women, 240 months (95% CI: 10.8–376.1) compared to men, 108 (95% CI: 0–226.5) (p = 0.036). Patients who had a solitary tumor in the chest had longer survival compared with atypical presentations of the tumor and the metastatic disease (p = 0.015). Patients with non-invasive thymomas had a statistically significant better survival than patients with invasive tumor in fat tissue and metastatic tumors (p = 0.003). The best survival had patients at the stage I of the disease compared to the patients in the stages II, III and IV, as well as the operated patients (p = 0.002). Longer survival was noticed in the patients under the age of 55 (240 months). There were no statistically significant difference when we compared two age groups (p = 0.231), smoking habits (p = 0,246), the presence of myasthenia gravis (p = 0,679), tumor size (p = 0,074), HP findings according to the WHO clasifficiation (p = 0,694) and the extent of resection (p = 0.215) (Table 4).

Table 4
Survival of 62 patients with thymoma, according to the different characteristics

Characteristics	Survival (months), median (95% CI)	p value
Overall survival	204 (116.7–291.3)	
Gender		
male	108 (0–226.5)	0.036
female	240 (10.8–376.1)	
Age		
≤ 55	240 (no CI)	0.231
> 55	168 (88.2–247.8)	
Smoker		
no	204 (125.3–282.7)	0.246
yes	240 (19.3–460.7)	
Myasthenia gravis		
no	240 (71.4–408.6)	0.679
yes	204 (no CI)	
Radiographic finding		
solitary	204 (no CI)	
atypical	168 (64.8–271.2)	0.015
metastatic	17 (0–58.8)	
Tumor size		
> 5 cm	108 (0–240.9)	0.074
< 5 cm	204 (134.5–273.4)	
Tumor Invasiveness		
non-invasive	204 (no CI)	
invasive in fatty tissue	108 (49.3–166.7)	0.003
metastatic	21 (4.7–37.6)	
Masaoka-Koga stage		
I	214.6 (172.1–257.1)*	
II (IIA and IIB)	108 (no CI)	0.001
III	12 (0.191–23.8)	
IV (IVA and IVB)	21 (10.2–31.8)	
WHO histology type		
A	117.8 (81.8–153.9)*	
B (B1, B2, B3)	204 (0–494.6)	0.694
AB	168 (no CI)	
Operation		
no	17 (4.9–29.0)	0.002
yes	204 (124.4–281.5)	
Extent of resection (n=55)		
radical/complete/resection	204 (125.7–282.2)	0.215
palliative/incomplete/resection	54 (0–118.6)	

WHO – World Health Organization.
***Mean (95% confidence interval) instead of median (95% confidence interval).**

Eight (16.0%) of the radically operated patients experienced a recurrence (relapse) of the disease. Seven patients died while one (12.5%) female patient is still alive. She was

in the stage II, with the type A thymoma, smoker. The treatment was continued by chemotherapy and RT, with 10-year survival rate. In other patients, recurrence free survival was 6 months in 4 (50.0%) of the patients, two of whom were in the stage III, both had the type B1 thymoma. All were smokers except one patient, with the 1-year survival rate despite chemotherapy and RT treatment after relapse of the disease. One patient had a relapse after one year, he was a smoker with the preoperative stage II, the type B3 thymoma. The operation was carried out again as well as chemotherapy and RT, with the 5-year survival rate. Two patients had a relapse of the disease after five years. The relapse of the disease occurred in two patients after 5 years, one patient was a smoker with the preoperative stage III, the type B3 thymoma and the 10-year survival rate, while the other patient was a nonsmoker, with the initial stage II of the disease, and the type A thymoma, with the 5-year survival rate. Significant predictors of survival according to the Cox regression analysis are presented in Table 5. Gender and clinical stage were significant predictor of longer survival.

Table 5
Significant predictors of survival, according to the Cox regression analysis

Predictors of survival	*p* value	HR (95% CI)
Gender (male)	0.004	4.129 (1.114–12.025)
Clinical stage		
I	0.002	1 – ref. category
II	0.029	3.709 (1.114–12.025)
III	0.002	14.971 (2.787–80.416)
IV	0.001	7.253 (2.293–22.946)

HR – hazard ratio; CI – confidence interval.

Discussion

According to published data, thymomas are heterogeneous group of infrequent thoracic tumors, with evidence of annual incidence from 1.3 to 3.2 per million [14]. The thymoma incidence is probably related to genetic risk factors because they are more common in Blacks and Asians/Pacific Islanders than in Whites and Hispanic [15]. There is little information about thymoma in the region of the Balkans including our country and Southern Europe too. Thymoma is the most common in the middle age and seventies patients, while in children and young adults it is very rare [16, 17]. Our study is one of the largest about thymoma cases in the Southeast Europe, and so far no similar studies have been conducted in the region. We found that there were more female than male patients (gender ratio 1.2 : 1) with thymoma, mostly in the seventies, but approximately the same number of patients was in the sixth decade of life too, about 30% each, which is confirmed by papers from different regions [5, 14], but there were studies with different findings. Weis et al. [18] gave the results of the study which was focused on 4,221 thymomas diagnosed between 1983 and 2012 with WHO histotype information from the ITMIG database presented with the aim to recognize the most important clinical features and to improve the options for treatment, due to rarity of the disease and lack of information from single centers. According to those results, gender factor is not important (49% male and 51% female patients). The type A and AB patients were much older than type B1-3 patients. Concerning symptoms before the diagnosis in our study, nearly half of the patients (46,7%), came for an examination in the period of the first 6 months from the appearance of symptoms, while the duration of symptoms of one month and more than one year were approximately similar, 26.7 and 25% respectively. Quick establishing diagnosis is most probably due to obvious clinical symptoms which showed the existence of the tumor. Almost one third of the patients in our study were asymptomatic. Coughing dominated in more than one third of patients, followed by general weakness and chest pain in 35.5% of patients, while a small number of patients (4.8%) had dysphagia, and only one patient had both stridor and hoarseness, indicating that in most of the patients the disease was not in an advanced stage. Other complaints included nonspecific symptoms such as weight loss, fever, sweating, as well as hemoptysis and cardiac arrhythmia. Our experience is consistent with literature data. Chest pain, cough and dyspnoea are frequent symptoms of local compression on mediastinal structures, as well as hoarseness due to pressure on recurrent laryngeal nerve or phrenic nerve palsy, and superior vena cava obstruction may be present too. Presentation with pericardial or pleural effusions, as a sign of metastatic disease, is indicative of a poor prognosis. Our research does not differ from the analysis of the other centers in which it has been stated that one third to one half of patients are incidentally diagnosed because they are asymptomatic and one third presents with local symptoms [8]. In 40% of patients there is paraneoplastic syndrome, such as systemic and neurologic syndromes [19, 20]. Above mentioned syndromes myasthenia gravis (MG) is well studied due to its frequency (it appears in 30-50% of patients). On the other hand 10–15% of MG patients are diagnosed with thymoma. Five percent of thymoma patients with MG can have several paraneoplastic syndromes [19]. In contrast, MG was less frequently observed among our patients (12.9%). MG was more frequent among women, and only one patient of them had polyneuropathy. Neurological symptoms existed in just over half of our patients with paraneoplastic syndrome. Comorbidities were recorded in half (48.4%) of the patients, and mainly in women (70%). The most common was arterial hypertension (43.3% of the patients), and it cannot be characterized as a predisponing disease or condition. Other chronic illnesses, such as hyperplasia of the thyroid gland, angina pectoris, and cardiac arrhythmia, were observed in fewer cases, while degenerative spinal diseases and alcoholism were represented in even smaller numbers. Diseases that represent a risk factor for the occurrence of malignant lung disease were present in two patients (6.6%) who had chronic obstructive disease. Secondary malignancies were found in 4 (13.3%) of the patients in our study; these patients had previously been cured of breast cancer, carcinoma of the urinary bladder, skin cancer and uterine cancer. Some studies [21] conducted in single centers have shown that thymoma patients are under a high risk for

cancer (lung, thyroid, prostate, lymphomas, sarcomas and leukemias etc), probably because of genetic risk factors or immune disorders. Besides, environmental risk factors, as well as therapy for thymoma (chemo/radiotherapy) are responsible for occurrence of the disease [22, 23]. The influence of smoking history, secondary malignancies, particularly those caused by viruses as Epstein-Barr Virus (EBV) on the occurrence of thymoma have not been clearly proven jet [24]. In our study, FNAB was performed as the invasive diagnostic procedure in a certain proportion of the patients (12.9%). That was a small number of patients who could not be operated due to extensive disease or because of the presence of comorbidities that represented a risk factor for the operation, which is in line with the literature data [7]. In order to establish diagnosis of thymic tumors clinical, radiologic and HP examinations are necessary. Computed tomography (CT) scan is used if the disease is suspect and to check up the patients during the treatment regimens [25]. Magnetic resonance imaging (MRI) is very useful in preoperative preparation in order to detect possible infiltration of the heart and great vessels [26]. Position emission tomography (PET) scan is used to differ benign from malignant lesions. Cytohistological diagnosis by biopsy is performed only if the tumor is unresectable [27, 28]. Radiographic findings in our research showed that solitary tumors in the chest were more frequent, in two-thirds (61.3%) of the patients. Massive tumors larger than 5 cm were the most commonly present, occurring in more than half of the patients (58.1%). On the contrary, atypical lesions and metastatic process were significantly less present (21% and 17.7% of the patients, respectively). All the patients had pathological findings on radiography. Sometimes it is impossible to detect the disease by X ray due to small size of the tumor localized in the anterior mediastinum, which cannot be visualized. This is the reason why the diagnosis is often established lately, hence radical operation (RO) cannot be implemented on time. Fukui et al. [29] proved that the size of the tumor is one of the crucial prognostic factors in the prediction of better survival. In our analysis it was noted that the noninvasive thymomas were the most common, in half (52.5%) of the patients, while the invasive process in the fatty tissue was observed in 18%, and metastatic disease in 29.5% of the patients. Recent researches proved rising occurrence of metastases in the United States. For example, 17 cases were diagnosed in 1973, while in 2008, 90 cases were registered in the Survellance, Epidemiology and End Results Program (SEER) database. Kaufman and Flores [30] discovered that male population is more susceptible to the disease. This is explained by Engels and Pfeiffer [15] who demonstrated the influence of an occupational exposure. Authors reported the presence of pleural and/or pericardial metastasis in 6.8% of all thymoma cases. Stage of the disease is one of the the main prognostic factors in thymoma patients, as an indicator of operability that represents a therapeutic approach with the highest probability of healing. Kaufman and Flores [30] described that the ability to do radical operation for early stage disease is almost 100%, while in the third and fourth stages of the disease, the radical operation rate fluctuated considerably, depending on the tumor location and degree of invasion, as well as the difference in the strategic approaches to radical operation treatment of the medical centers [30]. Our analysis showed that a majority of the patients, nearly one half, were in the stage I, while a remarkable variability in the proportion of stages, as specified by the Masaoka-Koga staging system, was noticed in the stages II, III and IV. Di Crescenzo et al. [31] have found that roughly 40% of thymomas are discovered while they are in the stage, while 25% are in the stages II and III, 10% at the stage IVa and 1–2% at the stage IVb. Invasion into the mediastinal tissue (in the stages II and III) occurs in 50% of thymomas. Pleural invasion is the most widespread, followed by pulmonary and pericardial invasion. About 30% of these cases involve the innominate vein or superior vena cava and 20% involve the phrenic nerve. Our analysis of HP findings showed that the most frequently present was the the type B1, followed by type A and type AB (equally represented in nearly a third of the patients), and finally the types B3 and B2 were least represented. Margaritora et al. [32] performed an analysis of 317 patients with thymomas, but some of them had a thymic carcinoma too, and discovered that the type B2 tumors were the most often noticed (in 57.5% of the cases), followed by the type B1 (19.2% of the cases) and finally the type AB (9.5% of the cases). Weis at al [18] in multicentre analysis proposed that difference was due to geography; the rate of occurrence of the type A thymoma is roughly the same in Europe as in the United States (15% and 14%, respectively), but markedly lower in Asia (6%). Thymomas of the type AB occur more often in Asia than in Europe or the United States (27%, 23% and 18%, respectively). The frequency of the type B2 thymomas is comparable in Europe (31%) and the United States (32%), but considerably lower in Asia (20%). Type B3 thymomas are found more often in Asia than in Europe or the United States (32%, 15% and 16%, respectively). However, the type B1 thymoma (16–20%) does not appear to vary drastically among different geographic regions. In patients with the type AB when compared to thymomas of the type B1 to B3 (38% of the type B3 thymomas were in the stage III). The median overall survival (OS) (Table 3) in patients with thymoma was 204 months. Overall, almost two thirds of patients with thymoma had 10- years survival rate, and most of these patients were in the stage I, as expected by literature data. Patients in the stage I had the best survival rate in all of these categories (1-,2-,5-,10-years survival) as compared to other stages of the disease, which is in accordance with other center studies. Statistically significantly longer survival was found in women compared to men. There was no statistically significant difference in survival in relation to age, but longer survival was observed in patients under the age of 55. There was no statistically significant difference in survival in smokers compared to non-smokers. There is no precise data in the literature about smoking habits [33]. The presence of MG was not statistically significant in survival, but patients without MG had a better survival rate in comparison with those who had MG. Our results did not show an important connection between immunological disorders and secondary malignancies and survival, but some researches have shown that the types A and AB thymomas have a low association with

MG, whereas the types B1 and B2 are more likely to be associated with MG, and thus may contribute to prognosis. Okumura et al. [34] claimed that the type A thymomas and the type C carcinomas were not found in cases with MG, while the types AB, B1, B2, and B3 were found in 6.8%, 40%, 55.6%, and 10% of the cases, respectively. In previously published studies, the impact of MG on the prognosis for thymoma is disputed. Initial studies seemed to indicate that the presence of MG signalled a poor prognosis. The latest publications appear to show that existence of MG may either not have an effect on the prognosis, or that these thymoma patients might have a more favorable prognosis [35]. The results of a study carried out by Wang et al. [36] suggest that MG has a positive impact on the long-term outcomes of thymoma. Filosso et al. [37] pointed to a link between MG and the early Masaoka stage (Table 6).

Table 6

Staging of thymic epithelial tumors: Masaoka-Koga-based staging system [38, 39], International Thymic Malignancy Interest Group refinements [40] and overall survival and recurrence-free survival (range) [41]

Masaoka-Koga, 1994		International Thymic Malignancy Interest Group, 2011	10-year overall survival	10-year cumulative incidence of recurrence	
				Thymoma	Thymic carcinoma
Stage I	Grossly and microscopically completely encapsulated tumour	– Invasion into but not through the capsule – In the absence of capsule, absence of invasion into surrounding tissues	84% (81–86%)		
Stage IIA	Microscopic transcapsular invasion	– Microscopic transcapsular invasion (< 3 mm)	83% (79–87%)	8% (7–8%)	25% (22–29%)
Stage IIB	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through the mediastinal pleura or pericardium	– Gross extension into normal thymus or perithymic fat surrounding the tumour (microscopically confirmed) – Adherence to pleura or pericardium, with microscopic confirmation of perithymic invasion			
Stage III	Macroscopic invasion into neighbor organ (i.e. pericardium, great vessel or lung)	– Microscopic invasion of the mediastinal pleura (either partial or penetrating the elastin layer) – Microscopic invasion of the pericardium (either partial in the fibrous layer or penetrating through to the serosal layer) – Microscopically confirmed direct penetration into the outer elastin layer of the visceral pleura or into the lung parenchyma – Invasion into the phrenic or vagus nerves (microscopically confirmed) – Invasion into or penetration through major vascular structures (microscopically confirmed) – Adherence (i.e. fibrous attachment) of lung or adjacent organs only if there is mediastinal pleural or pericardial invasion (microscopically confirmed)	70% (64–75%)	29% (27–31%)	59% (44–76%)
Stage IVA	Pleural or pericardial metastasis	– Microscopically confirmed separate nodules in the visceral or parietal pleural, pericardial or epicardial surfaces	42% (26–58%)	71% (34–100%)	76% (58–100%)
Stage IVB	Lymphogenous or haematogenous metastasis	– Lymphogenous or haematogenous metastasis	53% (32–73%)	57% (24–90%)	54% (37–67%)

Information rewritten: Girard et al. [7].

Symptoms of MG help to detect the disease early, and that is way that the prognosis is better. A statistically significant difference in survival was in patients who had a solitary tumor in the chest in our study, compared to atypical presentations of thymomas and the metastatic disease, and in our analysis, the impact of tumor size was not of statistical significance to survival. But dimension of the tumor mass was approaching the conventional level of significance. This analysis did not differ from those earlier reported in the literature. Patients in our study with non-invasive thymomas had a statistically significant better survival than those with invasive ones in the fat tissue and metastatic tumors. Patients in the stage I had the best survival rate and the difference was statistically significant compared to patients in the stages II, III, and IV. It was confirmed by our work that the Masaoka-Koga stage is the best prognostic predictor of survival [38–42]. Correlation between the WHO classification and stage at diagnosis can best explain clinical features and prognostic factors of thymoma [6, 43, 44]. There was no statistically significant difference in survival in our study in relation to HP findings, although longer survival was registered in patients with the type B thymoma versus the type AB and type A of the tumor. Although it is still debatable, it has been concluded that the stage of the disease is better predictor of its outcome, in spite of the fact that many authors, including Carillo et al. [45] underline that HP findings can also predict the survival rate: starting from the type A to B3, prognostic factors are getting worse. Patients with the early stage of the disease are good candidates for radical operation, but this also depends on patient`s general condition and the presence of potential comorbidities. As for treatment, in the group of patients analyzed in our Clinic, the most common was the operative approach (88.7% of the patients), with the majority of the patients (90.9%) completely operated, while 10.1% of the patients had incomplete resection. In nonoperated patients, other treatment modalities were applied: in 3.2% of the patients, chemotherapy and RT were administered, and 4.8% of the patients received BSC. Thymomas are rare tumors, so that for a long time there were no recommendations or guidelines for the treatment of these diseases, which is an explanation for the small amount of applied neoadjuvant/adjuvant chemotherapy and/or RT, as well as our patient series was analyzed for a period of 20 years since 1993. A statistically significant difference in survival was in patients who were operated compared to those who were not operated in our research, but there were no statistically significant differences in relation to whether the operation was radical compared to palliative one. However, survival was longer in radical operated patients and the results are in agreement with studies conducted in other centers. Sixteen percent of the radically operated patients experience relapse, of whom one woman is still alive. She was initially in the stage II, with the HP type A. Chemotherapy and RT continued after the relapse of the disease and she has 10-year survival rate. In other patients, recurrence free survival was from 6 months in 4 patients to 5 years, with a survival time of 240 months. The survival rate after radical operation for thymoma is great. In the most comprehensive retrospective researches of thymectomy for thymoma, 92% of patients had radical operation. The survival rate at both 5 and 10 years for the stage I thymoma was 100%. Patients in the stage II of the disease had very similar 5-year and 10-year survival rates of 98%. However, the stage III patients exhibited a much lower survival rate compared to the stage I and II patients, with 5-year survival rate of 89% and 10-year survival rate of 78%. Patients in the stage IV manifested similar tendencies, approximately 5-year survival rate of 71% and 10-year survival rates of 47%. This shows that even patients with extensive disease can rich long-term survival rate that are not common in other malignancies [30]. If radical operation cannot be accomplished at the time of surgery (either initially or after neoadjuvant chemotherapy), patients should undergo maximum debulking procedure followed by postoperative chemotherapy/RT [46]. The operational approach has another important role: even in unresectable cases, explorative thoracotomy is recommended for establishing the diagnosis of thymoma, in terms to precisely define diagnosis and prevent the disease dissemination due to invasive diagnostic procedures such as fine needle aspiration biopsy. Due to the fact that usually the nature of this tumor is not aggressive in majority of the cases, even for the patients who were operated, the prolonged follow-up is advisable. The authors are consistent in this statement. Locoregional recurrence is the most frequent one [47–49] but it can often be seen (≤ 92.0%) on the pleura [50, 51]. Weis et al. [18] noticed that the progression of free survival is better in the early stages and in the types A and AB (recurrence rates, 1–2%) compared to the types B1 to B3 thymomas (2–7%). Whenever a relapse occurs, it is advised to retry the operation, followed by adjuvant therapy as RT or chemiotherapy or both, depending on the stage of the disease [52]. Our study analyzed a small heterogeneous group of patients whose age ranges from 21 to 61 years, which had diverse smoking habits. They differed in relation to the presence of comorbidity. All the HP findings and clinical stages of the disease were manifested in these patients. Given this small group of respondents, based on these findings, a general conclusion cannot be drawn about the predisposing factors on the onset of the disease relapse. However, according to conducted multicenter examinations, we can conclude that radicality of the operation, early stage of the disease and A-AB HP findings are the aspects that can influence on better survival [38, 41, 42]. The chemotherapeutic approach in this chemosensitive tumor is quite complex. It can be applied in non-operable patients with the extensive disease or with comorbidities which prevent surgical approach, alone or combined with RT. In patients who are primarily nonoperable, chemotherapy can decrease the disease and thus a patient can become operable. In postoperative approach, chemothetrapy is administrated as adjuvant treatment together or without RT with the intention of preventing recurrence of the disease. Platinum-based regimens are recommended. Some researchers give advantage to anthracycline-based regimens, and carboplatin/paclitaxel options in B3/C thymoma [53]. The patients with the advanced stage of the disease have benefits from postoperative RT (PORT) [54]. Although, findings are contradictory such as those of Boothe et al. [55] who found that pa-

tients with thymic carcinoma and the type A and AB thymomas have better results. When a patient is not considered to be operative, RT is suggested along with chemotherapy [56], where multidisciplinary approach is needed. As thymoma patients have long-term good prognosis, lung parenchyma and heart have to be protected during RT. Recently, there has been an expansion of knowledge related to the molecular biology of thymoma, and this has led both, to the discovery of numerous significant mutations and to the consideration of therapeutic options related to thymoma genetics [57], as it is called personalized medicine. One of the most encouraging and recent treatment strategies, so-called checkpoint blockade, has been shown to block immunosuppression by using inhibitors against particular checkpoint receptors. There are a number of reports of favorable systemic responses to immunotherapy treatment [58]. If multiple studies justify the application of molecular therapy and immunotherapy in patients with thymomas, and these drugs are included in the treatment of these patients, it is likely that longer survival will be achieved with improving the quality of life of the patients, since the therapy is better tolerated and has less adverse effects. Final concluion, according to our results, cannot be made because we had a small and very heterogeneous group of patients with thymoma over a long, two-decade time interval in which treatment approaches were changed and supplemented, until finally guidelines for treating thymoma were established, what is confirmed by other researches as well. Based upon data from retrospective series, treatment guidelines have been declared by the European Society for Medical Oncology (ESMO) [7], National Comprehensive Cancer Network (NCCN), and by the Cancer Care Ontario program [28]. The European Society of Thoracic Surgeons (ESTS) Thymic Group, the Japanese Association for Research in Thymus (JART), the ITMIG and the International Association for the Study of Lung Cancer (IASLC) played a major role in developing of the 8th edition of the tumor-node-metastasis (TNM) classification of thoracic malignancies (Table 7), which has been officially accepted by the Union of the International Cancer Control (UICC) and American Joint Committee of Cancer (AJCC) and globally implemented in 2017, but the AJCC has delayed its implementation until 2018 [59]. The new TNM staging (Table 7) may help to formalize resectability criteria [60].

The retrospective nature is one of the factors which influences the results of our research. In order to make important conclusions, which would improve the treatment of the thymoma patients, it is necessary to conduct the study in the countries of the region, ie the Balkans, as a multicentre study, and with cooperation with worldwide countries and thus to integrate all findings. Further projects should intensify genomic explorations and establish data base for these patients.

Table 7

Proposed Tumour-Node-Metastasis staging (the International Association for the Study of Lung Cancer Prognostic Factors Committee-International Thymic Malignancy Interest Group) [58] and corresponding Masaoka-Koga stage

Tumour stage		**Descriptors**
T1	T1a	Encapsulated or unencapsulated, with or without extension into the mediastinal fat
	T1b	Extension into the mediastinal pleura
T2		Direct invasion of the pericardium (partial or full-thickness)
T3		Direct invasion of the lung, the brachiocephalic vein, the superior vena cava, the chest wall, the phrenic nerve and/or hilar (extrapericardial) pulmonary vessels
T4		Direct invasion of the aorta, arch vessels, the main pulmonary artery, the myocardium, the trachea or the oesophagus
Node		
N0		N0 No nodal involvement
N1		N1 Anterior (perithymic) nodes (IASLC levels 1, 3a, 6 and/or supradiaphragmatic/inferior phrenic/pericardial)
N2		N2 Deep intrathoracic or cervical nodes (IASLC levels 2, 4, 5, 7, 10 and/or internal mammary nodes)
Metastasis		
M0		No metastatic pleural, pericardial or distant sites
M1	M1a	Separate pleural or pericardial nodule(s)
	M1b	Pulmonary intraparenchymal nodule or distant organ metastasis
Stage grouping		**Corresponding Masaoka-Koga stage**
I	T1N0M0	I, IIA, IIB, III
II	T2N0M0	III
IIIA	T3N0M0	III
IIIB	T4N0M0	III
IVA	T any N0,1 M0,1a	IVA, IVB
IVB	T any N0-2 M0-1b	IVB

Information rewritten: Girard et al. [7].

Conclusion

Predictive factors of better survival in patients with thymoma in our study are early stage of the disease, non-invasive thymoma, younger age and operative treatment approaches. There is a need for further analysis of the dimension of the tumor mass as a predictive factor. Timely detection of the disease with providing a timely therapy will prolong the overall survival of these patients, prolong the recurrence free survival and increase the number of cures.

Acknowledgements

This work was supported by the Ministry of Education, Science and Technological Development of the republic of Serbia, Contract No. 175046, 2011–2016.

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Received on January 3, 2018.
Revised on March 11, 2018.
Accepted on March 26, 2018.
Online First April, 2018.