

## Article

# Mediastinal Tumor Thymoma Type B1 T4N2M1B Stage IVB with Multimodality Therapy

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**Abstract.** The incidence of thymoma increases with age, generally occurs in the 40-60s. Thymoma cases are rare at a young age. The prevalence of thymoma at a young age is very small at 0.6 – 5% of all thymoma cases. Thymoma management requires multimodality therapy depending on the stage of the thymoma, along with the development of surgery, radiotherapy and chemotherapy in the past three decades. A 21-year-old male patient with complaints of shortness of breath since 5 months before being admitted to the hospital. The patient has been diagnosed with thymoma type Mediastinum Tumor Type B1 T4N2M1B stage IVB from the results of chest X-ray investigations, chest CT scan, bronchoscopy and histopathological examination. The patient has received various therapeutic modalities including 6 cycles of chemotherapy, 30 radiotherapy and thymectomy surgery.

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## 1. Introduction

Thymoma is a type of mediastinal tumor originating from encapsulated thymic epithelial cells. Thymoma is a rare malignancy whose incidence represents 0.2-1.5% of all malignancies with an estimated incidence between 0.13 and 0.32/100,000/year. In the United States the incidence is 0.13 cases per 100,000/year. The ratio of the occurrence of thymoma in men and women in the literature stated that there was no significant difference. According to research, most of the evidence suggests

gender has no effect on disease progression, with some studies showing a slight predominance in males and other studies showing a slight predominance in females. The incidence of thymoma is very rare in the first two decades of life and increases in the age of 40-60s. The prevalence in young people is 0.6 - 5% of all cases of thymoma [1,2].

Diagnosis of thymoma is very difficult, because at first it appears without symptoms, 30% of thymoma patients do not show symptoms [18,19,20,21,22]. At first it was only found on a chest X-ray or CT scan during medical tests. Symptoms that appear only after there are effects on surrounding organs or the onset of systemic symptoms. Based on several studies, thymoma occurs in 1/3 of cases with myasthenia gravis, and local symptoms in 1/3 of cases include chest pain, neck mass and superior vena cava syndrome [2,3, 23,24,25,26,27].

Management of thymoma patients must be determined based on a definite diagnosis. The diagnosis is made using a multidisciplinary team approach by pulmonologists, radiologists, anatomic pathologists and thoracic surgeons. Thymectomy is the main choice for thymoma patients but its determination must be based on multidisciplinary discussion. Kim et al reported a multidisciplinary approach in the management of thymoma, especially in unresectable stage III-IVA patients, with a 5-year survival response rate of 95% and Yokoi et al reported a 5-year survival response of 92.9% [4,5,6].

The main therapy for thymus tumors is surgery. Complete resection is a major prognostic factor, so surgical resection is the cornerstone of therapy in patients with thymoma. Stage I thymoma is treated by surgical resection alone. Stage II thymoma is also treated with extensive thymectomy. For stage IIa, radiation therapy is not recommended, but for stage IIb, radiation therapy is recommended. Chemotherapy is not recommended for stage II. The goal of therapy in stage III is complete resection. Patients with locally expanded thymoma received neoadjuvant chemotherapy prior to resection. Postoperative radiation therapy is recommended and chemotherapy considered in cases of incomplete resection of stage III thymoma. Treatment for stage IVa thymoma is the same as for stage III. Stage IVb should be treated with intense palliative chemotherapy (cyclophosphamide, doxorubicin, cisplatin) [5].

The prognosis of thymoma depends on the staging, histopathological cell type and the resection status of the tumor. The higher the staging, the worse the prognosis, and histopathological cell types with type A thymoma have a good prognosis with 5 years survival 100% and 10 years survival 95% and type C has the worst prognosis with 5 years survival 23% [7]. Therefore, the authors are interested in bringing up a case report of a mediastinal thymoma type tumor at a young age with multimodality therapy.

## 2. Case Illustration

A 21-year-old male patient went to the ER, RSUP DR. M. Djamil with the main complaint of increasing shortness of breath since 1 day ago, shortness of breath has been felt since 5 months before being admitted to the hospital. The patient has been hospitalized several times at Dr. M. Djamil Padang and a pleural fluid puncture was performed, 3 liters of reddish fluid came out. Then a pigtail catheter was inserted with a total discharge of 2 liters of fluid. Cough since 5 months ago, comes and goes with white phlegm. History of coughing up blood, sticky sputum 4 months ago, now there is no more. The chest pain has been coming and going since 3 months ago, not radiating to the back. No fever and night sweats. Hoarse voice since 4 months ago. Decreased appetite since 5 months ago. Weight loss since 1 month ago but the patient does not know how many kg. Nausea, vomiting, and heartburn are absent.

Physical examination of the patient revealed edema on the face and both arms. On thoracic examination, static inspection was asymmetrical, left was more convex than right, left movement dynamically lagged from right, left weak palpation from right, left percussion was dim, right sonor,

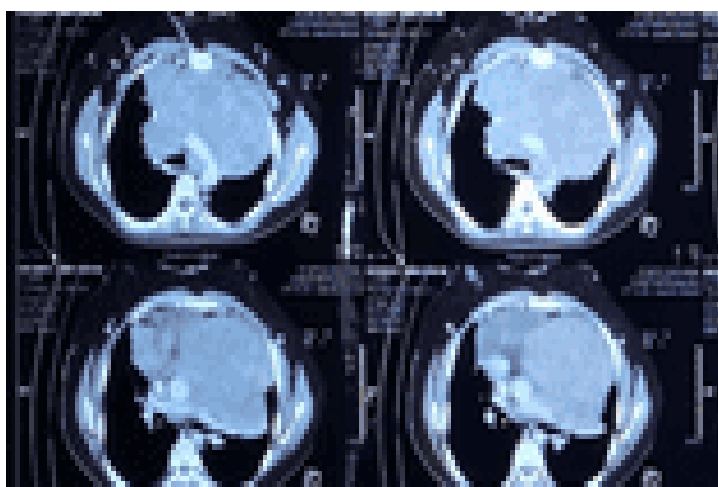
auscultation of left breath sounds weakened from RIC VII downwards, absent right breath sounds, vesicular crackles, no wheezing.

A chest X-ray examination on March 27, 2020 found a homogeneous covering with a sheathed left costophrenic angle. A pleural fluid puncture was performed, 3 liters of fluid came out and a heart pigtail catheter was inserted with a total discharge of 2 liters of serous hemorrhagic color, pleural and pericardial fluid cytology did not show malignant cells. On April 28, 2020, a chest CT scan was performed with contrast showing an inhomogeneous isodens mass in the anterior superior mediastinum, well defined, irregular edges, forming an obtuse angle with the lung parenchyma. The mass size is 19.5 x 14 x 19 cm. Mediastinal tumor impression with left pleural effusion and pericardial effusion.

A chest x-ray examination carried out on June 10, 2020 found a homogeneous covering with a sheathed left costophrenic angle. Pleural fluid puncture was performed and 1200 cc of fluid came out.



**Figure 1.** Chest X-Ray March 27, 2020



**Figure 2.** Chest CT Scan with Contrast April 28, 2020

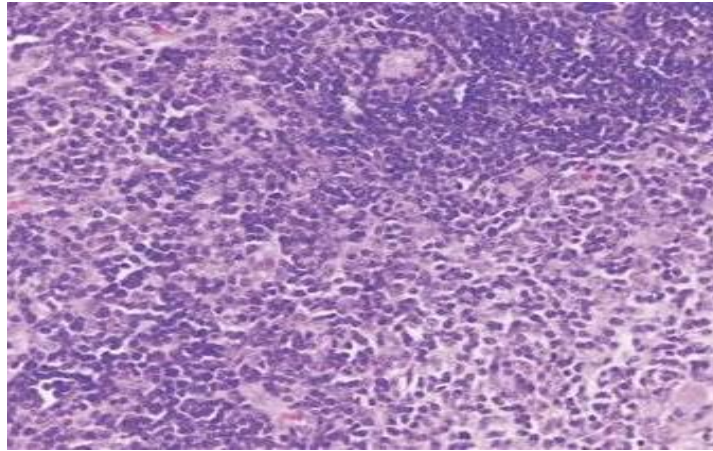


**Figure 3.** Chest X-Ray June 10, 2020

Bronchoscopy examination as shown in Figure 4 showed the impression of narrowing in the middle 1/3 of the trachea with mass propulsion from the 3 o'clock direction. The results of anatomical pathological examination of bronchial washings and post-bronchial cytology showed that there were no malignant tumor cells in the preparation. The patient was also treated with TTNA and core-biopsy with histopathological results as shown in Figure 5, which consisted mostly of lymphocytes with scattered epithelial cells and not clustered with the conclusion that it might be a thymoma. The review was carried out on June 29, 2020 because the patient was young and the results were still favorable for a thymoma.

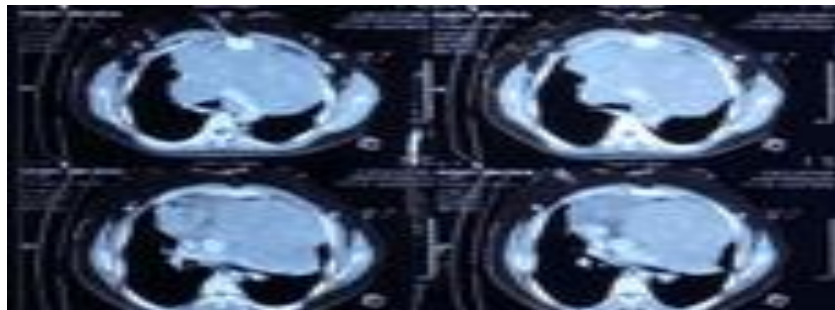


**Figure 4.** Bronchoscopy June 29, 2020

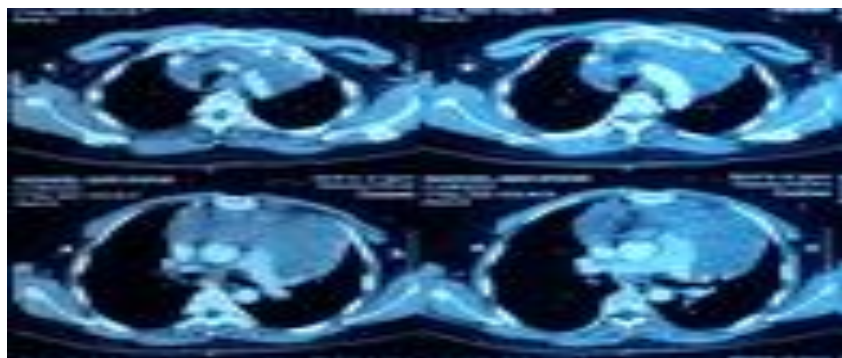


**Figure 5.** Histopathology Results Overview

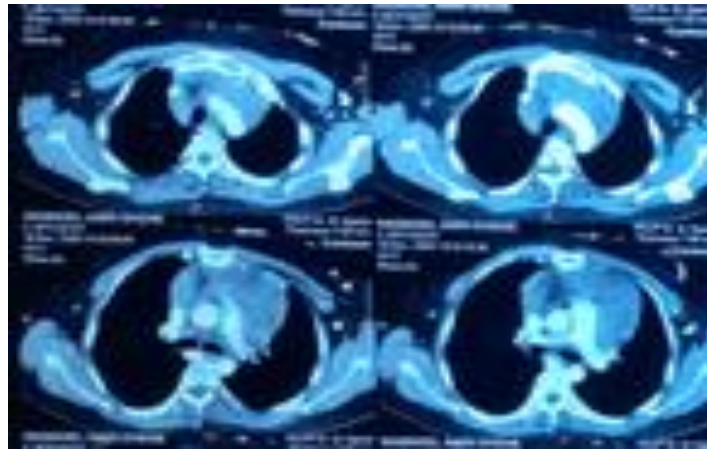
In this patient, due to the large size of the mass and close to large blood vessels, the thoracic surgery requested chemotherapy first, so a diagnostic decision was made by MDT (Multi Discipline Team) and it was concluded that sequential chemoradiotherapy was planned and continued with tumor removal. Chemotherapy started from July to November 2020 with Cisplatin, Adriamycin, and Cyclophosphamide (CAP) regimens. The 6th post-chemotherapy evaluation showed partial response (49%) where the tumor size before chemotherapy was 19.5x14x19 cm and after chemotherapy was 9.93x8.61x6.83 cm.



**Figure 6.** CT Scan of The Chest with Contrast Pre-Chemotherapy 1 size 19.5x14.3x19.2 cm

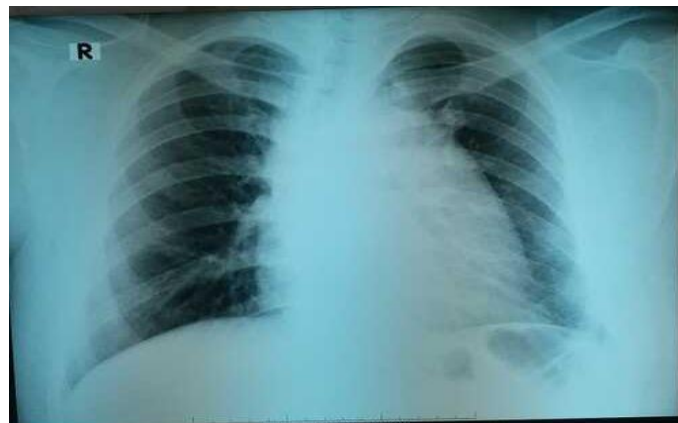


**Figure 7.** Chest CT Scan with Contrast Post-Chemotherapy 3 sizes 12.5x7,8x9,16 cm

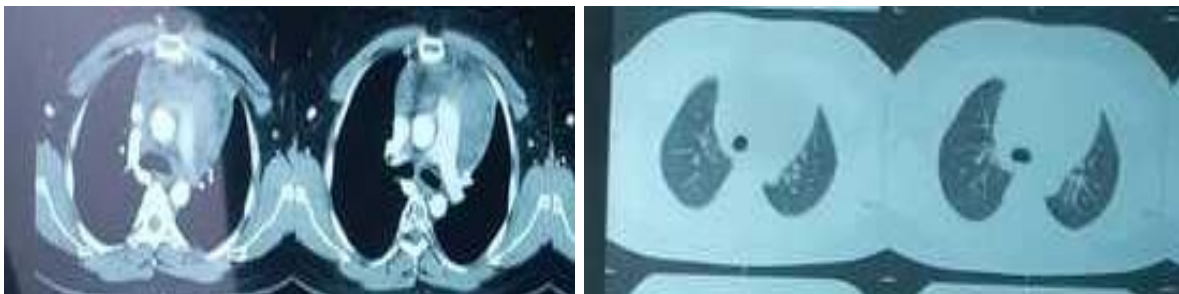


**Figure 8.** Chest CT Scan with Post-Chemotherapy Contrast 6 size 9.93x8.61x6.83 cm

The patient underwent radiotherapy for 30 cycles in December 2020. Evaluation of post-radiotherapy chest x-ray and chest CT scan with contrast was seen with a CT scan mass size of 7.9x10.6x6.61 cm.



**Figure 9.** Chest X- Ray Radiotherapy May 28, 2021



**Figure 10.** Chest CT Scan with Contrast Post-Radiotherapy June 3, 2021

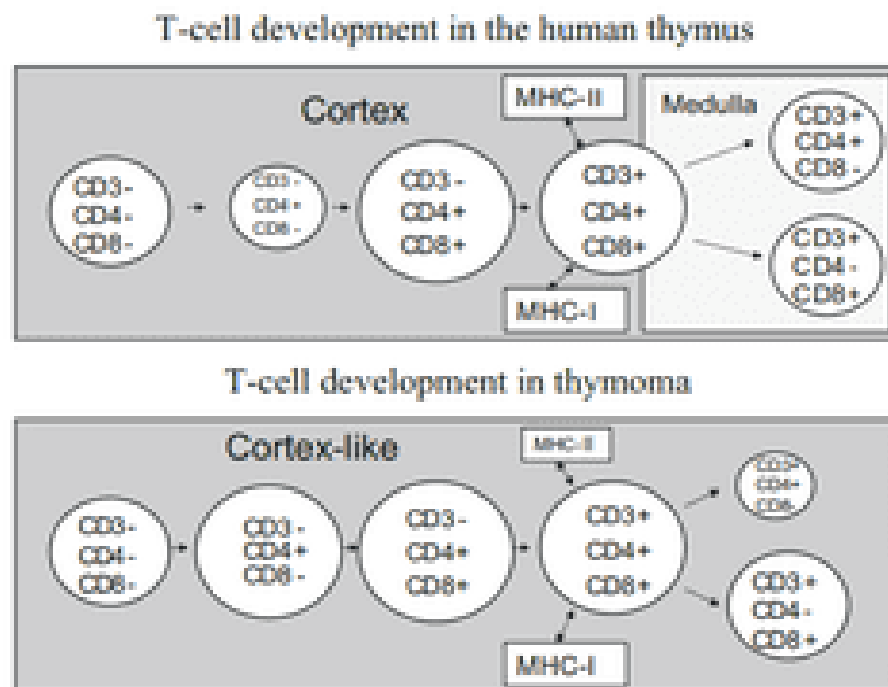
The second MDT was performed on 22 June 2021 for surgical management and it was decided to have a thymectomy. The patient underwent surgery on August 30, 2021.

### 3. Discussion

Thymoma is an epithelial neoplasm of the thymus gland. Thymoma is generally an encapsulated solid mass located in the anterior mediastinum and approximately one third of cases have necrosis, hemorrhage or a cystic component. The cystic areas in more than 40% of thymoma cases are usually mixed with a generally solid portion and very rarely are lesions that are almost completely cystic. Thymoma is a slow-growing neoplasm but may be aggressive by invading surrounding structures including the pleura and pericardium, but distant metastases are rare. In one third of cases the tumor is localized to infiltrate the capsule and surrounding tissues [8,9].

Thymoma is the most common tumor in the anterior mediastinum (50%) and 20-25% of all tumors in the mediastinum. its incidence represents 0.2-1.5% of all malignancies with an estimated incidence between 0.13 and 0.32/100,000/year. In the United States the incidence is 0.13 cases per 100,000 people/year. The incidence of thymoma increases with age, generally occurring at the age of 40-60 years with a peak incidence in the 7th decade. In older patients, almost all cases are malignant, associated with the accumulation of age-related genetic defects. Cases of thymoma in young adults are very rarely reported. This case has a very small prevalence with an incidence rate of 0.6 – 5% of all thymoma cases. This case occurred at the age of 21 years. Shivani et al reported the incidence of thymoma in a 15-year-old girl with a chief complaint of heaviness in the chest accompanied by low-grade fever, complaints of weakness, anorexia, and weight loss. The results of the chest X-ray showed widening of the mediastinum and a CT scan showed that there was a mediastinal mass about 4×4 cm in size. Gender factors have little influence on the incidence and development of thymoma. Some studies show a slight predominance in males, and others describe a slight predominance in females [1,10,11]. In this case it occurs in the male sex.

The etiology of thymic neoplasms remains unknown. There are no known risk factors for the development of thymoma or thymic carcinoma. The relationship between tobacco, alcohol or environmental factors with an increased incidence of thymoma has not been proven. There is a strong association between thymoma with myasthenia gravis and other paraneoplastic syndromes such as total red cell aplasia, polymyositis, systemic lupus erythematosus, Cushing's syndrome, and syndrome of inappropriate antidiuretic hormone secretion. Thirty to forty percent of patients with thymoma experience symptoms suggestive of myasthenia gravis. An additional 5% of patients have a paraneoplastic syndrome. The association between myasthenia gravis and CD4+ CD8+ double-positive T cells in thymoma is shown in Figure 11. Myasthenia gravis is known to be exclusively associated with thymoma that have a significant number of CD8+ CD4+ double-positive T cells, indicating that T cell development in tumors plays an important role in pathogenesis. Myasthenia gravis associated with thymoma. In this patient after being consulted to the neurology department and an EMG examination, no myasthenia gravis was found [2,12].



**Figure 11.** T-Cell Development in Normal Thymus and Thymoma [13]

Approximately 30% of thymoma patients are asymptomatic and 50%-60% of diagnosed masses are found incidentally on chest X-ray. Symptoms that may occur are usually associated with mass effects including compression and invasion of surrounding structures. Compression of the trachea, recurrent laryngeal or esophageal nerves causes coughing, shortness of breath, chest pain, respiratory infection, hoarseness or difficulty swallowing. Invasion of surrounding cardiovascular structures causes superior vena cava syndrome (SVCS) and right atrial compression can cause sudden cardiac death, but this is rare.

Systemic complaints and paraneoplastic syndromes are caused by the secretion of hormones, antibodies, and cytokines from the tumor. In this patient, SVCS occurred due to enlargement of the paratracheal lymph nodes due to a thymoma causing obstruction of blood flow in the superior vena cava. Obstruction of the superior vena cava will cause increased vascular resistance and decreased venous return. In slow and severe obstruction, significant symptoms will appear, such as shortness of breath, swelling of the face, neck, chest and upper extremities [5].

Radiologic modalities that are routinely performed in diagnosing thymoma are chest X-ray and chest CT scan. The PA position chest X-ray has a high sensitivity (77%) in diagnosing thymoma and will increase to 94% when accompanied by a lateral position. CT scan has a sensitivity of 97% in diagnosing thymoma because it has advantages in describing tumor location, tumor characteristics, involvement with surrounding organs and metastases. CT scan examination is performed using intravenous contrast medium to assess enhancement and differences with surrounding structures. The slices are 8-10 mm thick with borders ranging from the level of the thyroid gland to the level of the adrenal glands.

Radiological findings in non-invasive thymoma are lobulated round/oval masses, well-defined, generally asymmetrical and after contrast administration will produce homogeneous stinging, whereas invasive thymoma generally have irregular edges and fill both hemithorax, and exhibit heterogeneous stinging post-contrast. The tumor attenuation value before contrast administration is about 47-75 HU



and will increase to about 20 HU after contrast administration. In this patient, a CT scan was found. The chest with contrast shows an isodense inhomogeneous mass in the anterior superior mediastinum, well-defined, irregular edges, forming an obtuse angle with the lung parenchyma. The mass size was 19.5 x 14x19 cm with the impression of a mediastinal tumor with left pleural effusion and pericardial effusion, this is in accordance with the findings of CT-scan examinations in thymoma patients in general, which will be found Extensive mediastinal lymphadenopathy, pleural effusion, and pulmonary metastases are characteristic of other neoplastic processes (eg, thymic carcinoma or lung cancer) [14,16].

Another diagnostic modality for thymoma patients is Positron Emission Tomography (PET) which is useful to see whether there is invasion of other organs and extramediastinal involvement. This PET scan is more useful for staging and planning further treatment [14]. In our hospital there is no PET scan so it cannot be used in this patient. Bronchoscopy is not recommended for sampling in thymoma patients, but is done to see intrabronchial abnormalities and see whether there is lung involvement. The bronchoscopy feature of thymoma is the presence of compression stenosis. Bronchoscopy is also useful to assist the surgeon in estimating the location and extent of the procedure to be performed [15]. In this patient the result of bronchoscopy was a narrowing in the middle 1/3 of the trachea with mass propulsion from the 3 o'clock direction.

The classification of thymoma according to the World Health Organization (WHO) based on histopathology is divided into 6 subtypes, namely Type A, AB, B1, B2, B3, and C. Thymoma originates from epithelial cells and is associated with proliferation of T lymphocytes. WHO classification is based on subtypes according to cell morphology, epithelium and the number of T lymphocytes.

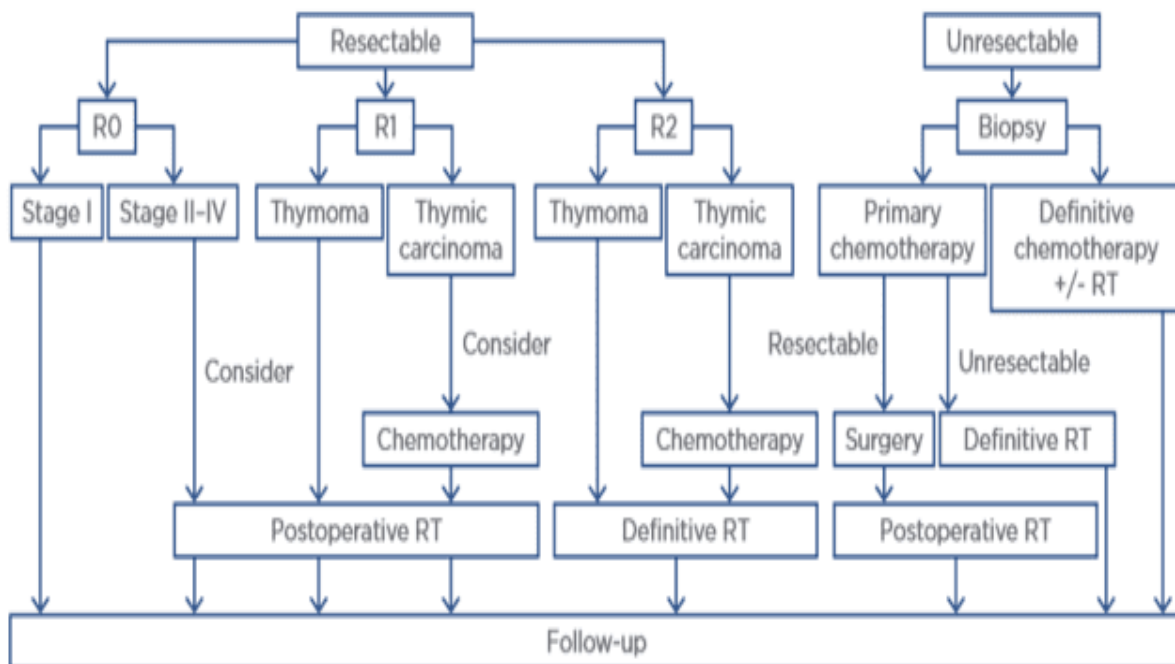
**Table 1.** Histopathological Classification of Thymoma (WHO) [12]

<b>Type A</b>	<ul style="list-style-type: none"> <li>• Consists of soft spindle cells and few scattered lymphocytes 60% of them are in stage I</li> <li>• This type tends to have a good prognosis</li> <li>• There are atypical variants that are hypercellular, have increased mitotic activity, and/or are necrotic.</li> <li>• The presence of necrosis tends to predict an advanced stage.</li> </ul>
<b>Type AB</b>	<ul style="list-style-type: none"> <li>• This type is a mixture of type A and type B1 or B2.</li> <li>• Consists of different components.</li> </ul>
<b>Type B1</b>	<ul style="list-style-type: none"> <li>• Mostly composed of lymphocytes with scattered epithelial cells, not clustered</li> <li>• There are paler medullary islets with a structure like the rare Hassall cells</li> </ul>
<b>Type B2</b>	<ul style="list-style-type: none"> <li>• It consists mostly of epithelial cells that form medullary islets and clusters</li> <li>• Atypical and may exhibit anaplastic features</li> </ul>
<b>Type B3</b>	<ul style="list-style-type: none"> <li>• Mostly composed of large polygonal cells with atypical elevations and few scattered lymphocytes</li> <li>• The prognosis is worse than for other thymoma but better than for thymic carcinoma.</li> </ul>
<b>Type C</b>	<ul style="list-style-type: none"> <li>• Tumors of the thymus (thymic carcinoma) show marked cytologic atypicals and a collection of cyto-architectural features that are no longer thymic specific, but analogous to those of carcinomas from other organs.</li> <li>• Consists of very few immature lymphocytes and is usually mixed with plasma cells.</li> </ul>

Thymoma subtypes A and AB have several distinctive growth patterns. This group has microcystic changes, storiform growth, staghorn-shaped vessels, rosettes, glandular structures, or papillary growth patterns. This group often shows a prominent infiltrate of plasma cells and myoid cells (*rhabdomyomatous thymoma*) [12].

Dilated perivascular spaces are seen in thymoma subtypes B1, B2, and B3. The perivascular space is filled with fluid plasma and may contain some lymphocytes, plasma cells, or foamy macrophages. In the center of the chamber, there are small blood vessels with hyaline walls. Neoplastic cells surround these spaces in palisade. Hassall cells are specifically seen in thymoma subtype B1. Furthermore, both thymoma subtypes B1 and B2 are rich in lymphocytes, but have some important histologic differences. Subtype B1 has areas of medullary differentiation (medullary islands) and scattered epithelial cells without clustering (<3 contiguous epithelial cells). These are often mistaken for small lymphocytic lymphomas and can be distinguished using keratin staining. Whereas in subtype B2, it has more clustered epithelial cells (> 3 adjacent epithelial cells). Subtype B3 is often confused with thymic carcinoma or metastatic SCC from elsewhere [12]. In this patient the cell type corresponds to thymoma type B1 with the appearance of mostly consisting of lymphocytes with scattered and non-clustered epithelial cells.

In cases that are difficult to determine, immunohistochemical examination is very helpful in identifying thymoma. Thymic epithelial cells were positive for keratin, epithelial membrane antigen, p63, p40, and PAX8. Thymic lymphocytes were stained with terminal deoxynucleotidyl transferase (TdT), CD1a, CD3, CD45, and CD99 [12]. In this case, immunohistochemical examination was not performed because reagents were not available at Dr. M. Djamil Hospital Padang.



**Figure 12.** Thymoma Treatment Strategy [15]

Thymoma management based on the National Comprehensive Cancer Network (NCCN) as shown in Figure 12, is divided into two, namely operable thymoma and inoperable thymoma.

### 3.1 Thymoma that Can be Operated

In patients with stage 1 and 2 thymoma, surgical resection can be performed with a good 10-year survival rate (about 90% for stage 1 and 70% for stage 2). Surgical resection should be performed with caution in patients who have been properly evaluated and resection performed by a certified thoracic surgical team. Locally advanced (unresectable) thymoma and resectable stage > II thymoma should be evaluated and discussed by a multidisciplinary team. Prior to resection, it is advisable to evaluate the signs of myasthenia gravis and control myasthenia if any signs of myasthenia gravis are found. The goal of surgery is complete excision of the lesion by total thymectomy.

Complete resection may require resection of several structures around the thymus including the pericardium, phrenic nerve, pleura, lungs, and great vessels. Bilateral phrenic nerve resection should not be performed because it will cause severe respiratory distress. During resection, the pleural surface should be evaluated for signs of pleural metastases so that the goal of complete resection is achieved. Minimally invasive procedures are not recommended due to lack of data. In patients with resection of thymoma but incomplete, adjuvant radiotherapy is recommended. Radiotherapy is performed to clean the remnants of the thymus tissue and is not recommended for lymph node radiotherapy because thymoma does not metastasize through the lymph nodes [15].

### 3.2 Thymoma that Cannot be Operated

In patients with thymoma who cannot be resected because the tumor is too large (locally advanced) or has metastasized, it is recommended to undergo radiotherapy with/without chemotherapy. In addition to radiotherapy, the NCCN also recommends chemotherapy for thymoma, especially in patients with thymoma that cannot be resected. Several studies mention that to treat the immunological complications of thymoma, it is advisable to perform thymoma resection. Thymoma resection will stop the disruption of the T cell maturation process so that disorders of the immune system will improve. Thymoma resection is the most important treatment for thymoma.

The NCCN has recommended resection of the thymoma at all stages except for locally advanced thymoma where there is extensive infiltration of the thymoma into the surrounding tissue. Delaying this resection will cause the growth of thymoma to be faster, causing a disturbance in the body's immune system which can cause impaired body functions [15]. This patient had received chemotherapy with 6 cycles of CAP regimen and continued with 30 cycles of radiotherapy. In comparison of the size of the thymoma from the CT scan of the thorax, it was found that the size was reduced but could not regress completely. This regression did not occur, because the process of impaired T cell maturation will continue to occur as long as there is still thymus tissue.

Chemotherapy and radiotherapy did not give maximum results, so a thymectomy with debulking was required. This patient had received chemotherapy with 6 cycles of CAP regimen and continued with 30 cycles of radiotherapy. In comparison of the size of the thymoma from the CT scan of the thorax, it was found that the size was reduced but could not regress completely. This regression did not occur, because the process of impaired T cell maturation will continue to occur as long as there is still thymus tissue. Chemotherapy and radiotherapy did not give maximum results, so a thymectomy with debulking was required.

Surgery can damage the anatomical structure of the lung, especially blood vessels and nerves around the tumor, making it difficult for the postoperative healing process and the possibility of achieving R0 resection is only 50-60%. Postoperative multimodality care is required for patients who experience relapse. Several studies have shown that surgery followed by other treatments can improve prognosis. However, only a small proportion of patients received postoperative care (20.4% for chemotherapy and 20.9% for radiotherapy). Surgery that did not achieve R0 resection was considered an indication for postoperative adjuvant radiotherapy. Aggressive multimodality treatment is highly

effective for unresectable localized thymoma. This multidisciplinary approach can improve patient survival rates [17]. In this patient, R0 resection was not achieved because there had been extensive infiltration of the thymoma into the surrounding tissue.

#### 4. Conclusion

The incidence of thymoma can occur at a young age although it is rare. Diagnosis and management of thymoma require a variety of therapeutic modalities including radical surgical resection, and/or postoperative adjuvant chemotherapy, and/or postoperative radiotherapy.

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