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Thymoma; clinical presentations, pathology, and prognostic factors – a surgery point of view

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Abstract

Thymomas are rare tumors that can present with a wide range of clinical characteristics. The presence of symptoms and paraneoplastic syndromes, such as myasthenia gravis, along with the histological subtype and stage of the tumor, are important factors that guide the treatment approach and prognosis for patients with thymomas. The prognosis for thymoma varies depending on several factors, including the stage and type of the tumor, as well as the presence of associated autoimmune diseases. Generally, early-stage thymomas have a better prognosis compared to advanced-stage tumors. Regular follow-up with a multidisciplinary team, including oncologists and thoracic surgeons, is essential for long-term management and surveillance of patients.

Keywords: Thymoma, outcomes, Epithelial cells, Autoimmune disease, Myasthenia gravis, Paraneoplastic syndrome, Pure red cell aplasia, Malignancy, Surgery

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Introduction

Thymoma is a type of tumor arising from the thymus's epithelial cells. The thymus is responsible for the development and maturation of T-cells, a type of white blood cell involved in immune response (1). Pathologically, thymomas are characterized by the presence of abnormal epithelial cells within the thymus. These cells form various patterns, including spindle cells, round cells, or a mixture of both. The tumor can also contain lymphocytes, which are immune cells (2). Thymomas are classified into different subtypes based on their histological appearance. The World Health Organization (WHO) classification system categorizes thymomas into five types: A, AB, B1, B2, and B3. These subtypes are based on the proportion of lymphocytes and epithelial cells present in the tumor (3). Type A thymomas have a predominantly lymphocytic composition, with few or no epithelial cells. Type AB thymomas have a mixture of lymphocytes and epithelial cells, with a predominance of lymphocytes (4). Type B1 thymoma has a variety of lymphocytes and epithelial cells, with a predominance of epithelial cells. Type B2 thymomas have a higher proportion of epithelial cells compared to lymphocytes. Type B3 thymomas have a predominantly epithelial composition, with few or no lymphocytes (2,5).

The exact molecular mechanisms underlying the development of thymoma have yet to be fully understood. However, genetic mutations are believed to play a role in the initiation and progression of thymomas. Mutations in genes such as TP53, CDKN2A, and KIT have been identified in some cases of thymoma. These mutations can disrupt normal cellular processes, leading to uncontrolled growth and division of cells (6,7). Thymomas are often associated with autoimmune diseases, such as myasthenia gravis. In these cases, it is thought that the abnormal epithelial cells in the thymoma trigger an immune response, leading to the production of autoantibodies that attack muscle cells or other tissues (8,9). Autoimmune diseases can influence thymoma's clinical presentation and prognosis (1). Diagnosis of thymoma involves a combination of imaging studies, such as chest X-rays or computerized tomography, and tissue biopsy. A biopsy is necessary to confirm the presence of abnormal cells and determine the type and stage of the tumor (10). This review study aims to provide a comprehensive understanding of the histopathological

Key point

Thymoma can be associated with paraneoplastic syndromes, including myasthenia gravis, pure red cell aplasia, hypogammaglobulinemia, dermatomyositis, and systemic lupus erythematosus. These syndromes can provide important clues for diagnosing and managing patients with thymoma. The treatment of thymoma involves a combination of surgery, radiation therapy, chemotherapy, and emerging targeted or immunotherapies. The optimal treatment approach depends on various factors and should be tailored to each patient. Ongoing research and clinical trials continue to explore new treatment strategies and improve outcomes for individuals with thymoma.

features, classification systems, and prognostic factors associated with thymoma from a surgery point of view.

Search strategy

For this review, we searched EBSCO, Scopus, PubMed, Web of Science, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords including thymoma, outcomes, epithelial cells, autoimmune disease, myasthenia gravis, Paraneoplastic syndrome, pure red cell aplasia, malignancy, surgery, chemotherapy, thymectomy, targeted therapy, prognostic factors, and radiation therapy.

Clinical characteristics of thymomas

The clinical presentations of thymoma can vary widely depending on several factors, including the size and location of the tumor and the presence of any associated autoimmune diseases (5). Several common clinical presentations can be described as follows:

Symptoms and signs

Thymomas are often asymptomatic and are discovered incidentally on imaging studies performed for other reasons. These tumors may not cause any symptoms and are often diagnosed during a regular medical examination. However, symptoms can occur due to the local mass effect of the tumor or paraneoplastic syndromes. Common symptoms include chest pain, cough, shortness of breath, and superior vena cava syndrome (11,12). Paraneoplastic syndromes associated with thymomas have myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia (13). Thymomas can occur at any age, but they are most commonly diagnosed in individuals between the ages of 40 and 60 years. They can affect both males and females, with a slight male predominance (14).

Moreover, thymomas are strongly associated with the autoimmune disease myasthenia gravis. About 30-50% of patients with thymoma also have myasthenia gravis. This disease is characterized by muscle weakness and fatigue, particularly in the muscles of the face, neck, and limbs. Symptoms may include drooping eyelids, difficulty swallowing or speaking, and weakness in the arms or legs (15). Thymectomy is often recommended for patients with thymoma and myasthenia gravis, as it can improve symptoms and disease control. Since thymomas located in the anterior mediastinum can cause symptoms related to compression or invasion of nearby structures. These symptoms may include chest pain, cough, shortness of breath and difficulty breathing, or a feeling of fullness in the chest (16,17). In addition, thymomas located in the superior mediastinum can compress the superior vena cava, a large vein that carries blood from the head, neck, and upper body to the heart. This compression can lead to a condition known as superior vena cava syndrome, which is characterized by swelling of the face, neck, and upper body, dilated veins in the chest or neck, difficulty breathing, and cough (18).

Furthermore, thymomas can produce certain substances that cause paraneoplastic syndromes, a group of symptoms that occur due to the tumor's effect on distant organs or tissues. These syndromes can include endocrine abnormalities (such as Cushing's syndrome or hypoglycemia), hematological abnormalities (such as pure red cell aplasia), or other systemic symptoms. However, the clinical presentation of thymoma can vary significantly from person to person, and some individuals may only experience symptoms once the tumor has reached an advanced stage (19). Therefore, individuals must undergo regular medical check-ups and screenings to detect thymoma at an early stage when treatment outcomes are generally more favorable.

Paraneoplastic syndromes associated with thymoma

Thymoma is a rare type of tumor arising from the thymus gland, located in the chest behind the breastbone (sternum). While thymomas are typically slow-growing and often benign, they can be associated with various paraneoplastic syndromes. Paraneoplastic syndromes are a group of disorders that occur due to substances produced by the tumor affecting distant organs or tissues (20).

One of the most common paraneoplastic syndromes associated with thymoma is myasthenia gravis. Myasthenia gravis is an autoimmune disorder characterized by muscle weakness and fatigue. It occurs when antibodies the immune system produces mistakenly attack proteins involved in nerve-muscle communication. In thymoma-associated myasthenia gravis, the tumor produces proteins that resemble those involved in nerve-muscle communication, producing autoantibodies and subsequent muscle weakness.

Another paraneoplastic syndrome seen in patients with thymoma is pure red cell aplasia. This condition is a condition characterized by a decrease in red blood cell production, leading to severe anemia. In thymoma-associated pure red cell aplasia, it is believed that the tumor produces factors that suppress red blood cell production in the bone marrow (21,22).

Other paraneoplastic syndromes associated with

thymoma included hypogammaglobulinemia, which is characterized by low levels of immunoglobulins (antibodies) in the blood, and dermatomyositis, an inflammatory muscle disease and also systemic lupus erythematosus, an autoimmune disorder affecting multiple organs (9,23).

The presence of these paraneoplastic syndromes can often aid in the diagnosis of thymoma. However, all patients with thymoma will develop these syndromes, and their presence does not necessarily indicate malignancy. Additionally, treating these syndromes often involves addressing the underlying tumor, such as surgical removal of the thymoma or chemotherapy (9,24).

Outcomes of thymoma-associated myasthenia gravis

Thymoma-associated myasthenia gravis (MG) is a rare autoimmune disorder that affects the neuromuscular junction and is associated with the presence of a thymoma. The clinical course and outcomes of thymoma-associated MG can be variable, with some patients experiencing remission and others experiencing chronic disease with significant morbidity (25,26).

Diagnosing thymoma-associated MG requires a high index of suspicion, as symptoms may initially be attributed to other causes. Diagnostic testing typically includes serologic testing for acetylcholine receptor antibodies and imaging studies to evaluate for the presence of a thymoma. Management of thymoma-associated MG involves a combination of immunosuppressive therapy and surgical resection of the thymoma. These interventions' optimal timing and sequence are still a matter of debate, and individualized treatment plans are often necessary (25,27).

Long-term outcomes of thymoma-associated MG are variable, with some patients experiencing complete remission and others experiencing chronic disease with significant morbidity. Recurrence rates after thymectomy vary depending on the stage and histologic subtype of the thymoma, with higher rates observed in patients with more advanced disease (28,29).

Classification and staging of thymoma

Thymoma is a rare type of tumor that occurs in the thymus gland, located in the chest behind the breastbone (sternum). It can be classified and staged based on various factors, including the tumor cells' appearance, the tumor's invasiveness, and the cancer's spread (5). The classification and staging systems that are commonly utilized for thymoma encompass the following:

World Health Organization (WHO) classification

The WHO classification system classifies thymomas based on the appearance and behavior of the tumor cells. It includes the following subtypes; type A, type AB, type B1, type B2, type B3, and type C. Previous studies showed type A thymomas are the least aggressive, while type C thymomas are the most aggressive form (3,30,31).

Masaoka-Koga staging system

The Masaoka-Koga system is a staging system designed explicitly for thymomas. It categorizes thymomas into five stages (32-34).

- Stage I: The tumor is limited to the thymus and has not spread to surrounding structures
- Stage II: The tumor has invaded nearby tissues or organs, but it can still be completely removed surgically
- Stage III: The tumor has spread to nearby structures, such as the lungs, heart, or large blood vessels
- Stage IVA: The tumor has spread to lymph nodes in the chest
- Stage IVB: The tumor has spread to distant organs, such as the liver or bones.

TNM staging system

The TNM (tumor, node, and metastasis) system is a general staging system conducted for various types of cancer, including thymoma. It takes into account the size of the primary tumor (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastasis (M). The TNM categories are further used to assign a stage to the thymoma (3,35,36).

Malignant thymoma

Malignant thymoma is a rare type of cancer that arises from the thymus gland. Treatment options include surgery, radiation therapy, chemotherapy, and targeted therapy. The prognosis for malignant thymoma varies depending on several factors, including the cancer stage, the type of tumor, and the patient's overall health (37,38).

Surgery is the primary treatment for malignant thymoma; complete tumor resection is associated with better outcomes. Radiation therapy may be used in combination with surgery, as a stand-alone treatment for unresectable tumors, or as adjuvant therapy to reduce the risk of recurrence. Chemotherapy may also be used in advanced cases or as neoadjuvant therapy to shrink the tumor before surgery (19,39).

Several prognostic factors have been identified that can help predict the outcome of malignant thymoma. These include the cancer stage, the tumor's histological subtype, the presence of certain genetic mutations, and the patient's age and overall health (38,40).

Patients with early-stage tumors (stage I or II) and favorable histological subtypes (such as type AB or B1) have a better prognosis than those with more advanced disease or unfavorable subtypes (such as type B3 or C). The presence of certain genetic mutations, such as mutations in the TP53 gene, may also be associated with a poorer prognosis (41,42).

Age and overall health are also important prognostic

factors. Younger patients and those with good performance status (a measure of general health and ability to carry out daily activities) tend to have better outcomes (43).

Molecular characteristics of thymomas

Molecular characterization of thymomas has provided valuable insights into the pathogenesis, classification, and potential therapeutic targets for this rare tumor.

Chromosomal alterations

Thymomas commonly exhibit chromosomal alterations, including gains and losses of genetic material. These alterations can be detected using techniques such as comparative genomic hybridization (CGH) and array-based techniques. Common chromosomal abnormalities in thymomas include gains in chromosomes 1q, 3q, 5p, 6p, 7q, 8q, and 17q, as well as losses in chromosomes 6q, 13q, 16q, and 22q (44,45).

TP53 mutations

Thymomas frequently harbor TP53 mutations associated with a more aggressive phenotype and poorer prognosis. TP53 mutations can be detected using molecular techniques such as sequencing or immunohistochemistry (46,47).

Genes associated with T-cell development

Thymomas arise from the thymic epithelial cells involved in T-cell development. Several genes involved in T-cell development have been found to be dysregulated in thymomas. For example, abnormalities in the WNT signaling pathway, including mutations in the CTNNB1 gene (encoding β-catenin), have been reported in a subset of thymomas (48,49).

Genes associated with immune regulation

Thymomas often exhibit dysregulated immune regulation, and several genes involved in immune response pathways have been implicated in thymoma development. For instance, alterations in the expression of genes involved in antigen processing and presentation, such as HLA class I and II molecules, have been reported (7,50).

Epigenetic alterations

Epigenetic modifications, including DNA methylation and histone modifications, play a crucial role in gene regulation. Thymomas have been shown to have distinct DNA methylation patterns compared to normal thymus. These epigenetic alterations can influence gene expression and contribute to the development of thymomas (51,52).

Immune checkpoint molecules

Thymomas frequently express immune checkpoint molecules, including PD-L1 and CTLA-4. This suggests that immune checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4 antibodies, could be potential therapeutic targets in thymomas (53,54).

Potential therapeutic targets

The identification of molecular alterations in thymomas has led to the exploration of targeted therapies. For example, thymomas with mutations in the KIT gene may benefit from targeted therapy with tyrosine kinase inhibitors (such as imatinib). Additionally, inhibitors of the mTOR pathway (such as everolimus) have shown promise in thymomas with mTOR pathway dysregulation (7,55).

Treatment of thymoma

The primary treatment for thymoma is surgical resection, which aims to achieve complete tumor removal whenever possible. Thymectomy is also performed in patients with myasthenia gravis to alleviate symptoms. However, the treatment of thymoma depends on several factors, including the stage of the disease, the histological subtype of the tumor, and the overall health of the patient. Other main treatment modalities for thymoma include radiation therapy and chemotherapy. A combination of these treatments may sometimes be conducted (56,57).

Surgery is the primary treatment for thymoma and involves the complete removal of the tumor and surrounding tissue. The extent of surgery depends on the stage and location of the tumor. In early-stage thymoma, a complete and any involved surrounding structures are performed. This can be conducted through various surgical approaches, including open surgery or minimally invasive techniques such as video-assisted thoracoscopic or robotic-assisted surgery. In advanced cases, more extensive surgery may be required when the tumor has invaded nearby structures or metastasizes to distant sites (56,58).

Radiation therapy may be used as an adjuvant treatment following surgery or as a primary treatment for inoperable or recurrent thymoma. It involves the use of high-energy X-rays or other forms of radiation to kill cancer cells or inhibit their growth. Radiation therapy can be delivered externally (external beam radiation therapy) or internally (brachytherapy), depending on the specific situation and treatment goals (39,59).

Since chemotherapy is typically reserved for advanced or metastatic thymoma, as well as for unresectable tumors, the most commonly used chemotherapy regimens for thymoma include cisplatin-based combinations, such as cisplatin plus etoposide or cisplatin plus doxorubicin, chemotherapy can be administered before surgery (neoadjuvant chemotherapy) to shrink the tumor and improve resectability, after surgery (adjuvant chemotherapy) to reduce the risk of recurrence, or as palliative treatment to control symptoms and prolong survival (37,60).

In recent years, targeted therapies and immunotherapies have shown promise in treating advanced thymoma. Targeted therapies, such as tyrosine kinase inhibitors (e.g., sunitinib) or mammalian target of rapamycin (mTOR) inhibitors (e.g., everolimus), can inhibit specific molecular pathways involved in tumor growth and progression. Immunotherapies, such as immune checkpoint inhibitors (e.g., pembrolizumab or nivolumab), can enhance the immune system's ability to recognize and attack cancer cells. These therapies are still being investigated in clinical trials and may be combined with standard treatments (61,62).

The treatment choice for thymoma should be individualized based on the specific characteristics of the tumor and the patient's overall health. To develop a comprehensive treatment plan, multidisciplinary collaboration among surgeons, radiation oncologists, and medical oncologists is essential. Regular follow-up and surveillance are also important to monitor for disease recurrence or progression and to manage any long-term treatment-related complications (56,63).

Focus on the surgery for the thymoma: indications and results

As mentioned above, surgery is the primary treatment for thymoma and is indicated in most cases. The specific indications for surgery depend on the disease stage and the patient's overall health. In early-stage thymoma, surgery aims to remove the tumor completely and may involve a complete thymectomy along with any involved surrounding structures. This can be achieved through various surgical approaches, including open surgery or minimally invasive techniques such as video-assisted thoracoscopic or robotic surgery (19,56).

The surgery results for thymoma are generally favorable, with high rates of complete tumor resection and long-term survival. However, the prognosis can vary depending on factors such as the stage and histological subtype of the tumor, as well as the presence of any metastasis. Early-stage thymomas generally have a better prognosis than advanced-stage tumors (56,64).

Several studies have reported high rates of complete resection (R0 resection; surgical margin is microscopically negative for residual malignancy) with surgery alone, ranging from 80% to 100%. The 5-year survival rates for completely resected thymomas range from 70% to 90%, depending on the stage and histological subtype. However, even in cases where complete resection is impossible, surgery can still provide palliative benefits and improve quality of life (30,65).

In some cases, adjuvant therapies such as radiation therapy or chemotherapy may be used after surgery to reduce the recurrence risk or treat residual disease. The decision to use adjuvant therapies is based on factors such as the stage of the disease, the presence of certain high-risk features (e.g., invasion of surrounding structures), and the patient's overall health (63,66).

Conclusion

Surgery is the mainstay of treatment for thymoma and aims to achieve complete tumor resection. The surgery results for thymoma are generally favorable, with high rates of complete resection and long-term survival. Adjuvant therapies may be conducted in certain cases to reduce the recurrence risk or treat residual disease. However, the optimal treatment approach should be individualized based on the specific characteristics of the tumor and the patient's overall health.

Authors' contribution

Conceptualization: Hamid Reza Hemmati, Mohammad Memarian.
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Funding acquisition: Hamid Reza Hemmati, Mohammad Memarian.
Investigation: Hamid Reza Hemmati.
Resources: Hamid Reza Hemmati.
Supervision: Mohammad Memarian.
Validation: Mohammad Memarian.
Visualization: Hamid Reza Hemmati.
Writing–original draft: Hamid Reza Hemmati.
Writing–review and editing: Mohammad Memarian.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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References

1. Shelly S, Agmon-Levin N, Altman A, Shoenfeld Y. Thymoma and autoimmunity. Cell Mol Immunol. 2011;8:199-202. doi: 10.1038/cmi.2010.74.
2. Suster S. Diagnosis of thymoma. J Clin Pathol. 2006;5:1238-44. doi: 10.1136/jcp.2005.031138.
3. Marx A, Chan JK, Coindre JM, Detterbeck F, Girard N, Harris NL, et al. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. J Thorac Oncol. 2015;10:1383-95. doi: 10.1097/JTO.0000000000000654.
4. Moore RR, Nagai H, Miller RA, Hardisty JF, Allison N, Shockley KR, Malarkey DE. Comparative Incidences and Biological Outcomes for Thymoma in Various Rat Strains in National Toxicology Program Studies. Toxicol Pathol. 2019;47:833-841. doi: 10.1177/0192623319863119.
5. Robinson SP, Akhondi H. Thymoma. [Updated 2022 Jul 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559291/.
6. Enkner F, Pichlhöfer B, Zaharie AT, Krunic M, Holper TM, Janik S, et al. Molecular Profiling of Thymoma and Thymic Carcinoma: Genetic Differences and Potential Novel Therapeutic Targets. Pathol Oncol Res. 2017;23:551-564. doi: 10.1007/s12253-016-0144-8.
7. Oberndorfer F, Müllauer L. Genomic alterations in thymoma-molecular pathogenesis? J Thorac Dis. 2020;12:7536-7544. doi: 10.21037/jtd.2019.12.52.

8. Marx A, Yamada Y, Simon-Keller K, Schalke B, Willcox N, Ströbel P, et al. Thymus and autoimmunity. Semin Immunopathol. 2021;43:45-64. doi: 10.1007/s00281-021-00842-3.
9. Blum TG, Misch D, Kollmeier J, Thiel S, Bauer TT. Autoimmune disorders and paraneoplastic syndromes in thymoma. J Thorac Dis. 2020;12:7571-7590. doi: 10.21037/jtd-2019-thym-10.
10. Strange CD, Ahuja J, Shroff GS, Truong MT, Marom EM. Imaging Evaluation of Thymoma and Thymic Carcinoma. Front Oncol. 2022;11:810419. doi: 10.3389/fonc.2021.810419.
11. Minervini F, Kocher GJ. When to suspect a thymoma: clinical point of view. J Thorac Dis. 2020;12:7613-7618. doi: 10.21037/jtd-2019-thym-05.
12. Bogot NR, Quint LE. Imaging of thymic disorders. Cancer Imaging. 2005;5:139-49. doi: 10.1102/1470-7330.2005.0107.
13. Denkler S, Lee DH, Schalke B. Paraneoplastic syndromes associated with thymoma beyond Myasthenia gravis: extended abstract. Mediastinum. 2022;6:18. doi: 10.21037/med-21-58.
14. Azour L, Moreira AL, Washer SL, Ko JP. Radiologic and pathologic correlation of anterior mediastinal lesions. Mediastinum. 2020;4:5. doi: 10.21037/med.2019.09.05.
15. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol. 2009;8:475-90. doi: 10.1016/S1474-4422(09)70063-8.
16. Bennett B, Rentea RM. Thymectomy. [Updated 2022 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564302/.
17. Di Crescenzo VG, Napolitano F, Panico C, Di Crescenzo RM, Zeppa P, Vatrella A, et al. Surgical approach in thymectomy: Our experience and review of the literature. Int J Surg Case Rep. 2017;39:19-24. doi: 10.1016/j.ijscr.2017.07.028.
18. Seligson MT, Surowiec SM. Superior Vena Cava Syndrome. [Updated 2022 Sep 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441981/.
19. Ruffini E, Venuta F. Management of thymic tumors: a European perspective. J Thorac Dis. 2014;6 Suppl: S228-37. doi: 10.3978/j.issn.2072-1439.2014.04.19.
20. Grosch H, Hoffmann H, Weis CA, Thomas M. Thymustumoren: Eine klinische Betrachtung [Thymus cancers: A clinical observation]. Pathologe. 2016;37:91-105; quiz 106. German. doi: 10.1007/s00292-016-0140-5.
21. Thangatorai R. Pure Red Cell Aplasia Associated With Thymoma. Cureus. 2023 3;15:e39387. doi: 10.7759/cureus.39387.
22. Lee SY, Gill A, Jung SM. Pure red cell aplasia and seronegative myasthenia gravis in association with thymoma. J Community Hosp Intern Med Perspect. 2020;10:238-241. doi: 10.1080/20009666.2020.1770019.
23. Evoli A, Lancaster E. Paraneoplastic disorders in thymoma patients. J Thorac Oncol. 2014;9:S143-7. doi: 10.1097/JTO.0000000000000300.
24. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc. 2010;8:838-54. doi: 10.4065/mcp.2010.0099.
25. Romi F. Thymoma in myasthenia gravis: from diagnosis to treatment. Autoimmune Dis. 2011;2011:474512. doi: 10.4061/2011/474512.
26. Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia Gravis: Epidemiology, Pathophysiology and Clinical Manifestations. J Clin Med. 2021;10:2235. doi: 10.3390/jcm10112235.
27. Rousseff RT. Diagnosis of Myasthenia Gravis. J Clin Med. 2021;10:1736. doi: 10.3390/jcm10081736.
28. Dharanikota A, Arjunan R, Chowdappa R, Althaf S. Survival Outcomes in Patients with Thymoma after Thymectomy in an Indian Scenario. Indian J Surg Oncol. 202;11:785-790. doi: 10.1007/s13193-020-01258-5.
29. Evoli A, Minisci C, Di Schino C, Marsili F, Punzi C, Batocchi AP, et al. Thymoma in patients with MG: characteristics and long-term outcome. Neurology. 2002;5:1844-50. doi: 10.1212/01.wnl.0000032502.89361.0c.
30. Tomaszek S, Wigle DA, Keshavjee S, Fischer S. Thymomas: review of current clinical practice. Ann Thorac Surg. 2009;8:1973-80. doi: 10.1016/j.athoracsur.2008.12.095.
31. Marx A, Chan JKC, Chalabreysse L, Dacic S, Detterbeck F, French CA, et al. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors? J Thorac Oncol. 2022;17:200-213. doi: 10.1016/j.jtho.2021.10.010.
32. Chiappetta M, Lococo F, Pogliani L, Sperduti I, Tabacco D, Bria E, et al. Masaoka-Koga and TNM Staging System in Thymic Epithelial Tumors: Prognostic Comparison and the Role of the Number of Involved Structures. Cancers (Basel). 2021;13:5254. doi: 10.3390/cancers13215254.
33. Markowiak T, Hofmann HS, Ried M. Classification and staging of thymoma. J Thorac Dis. 2020;12:7607-7612. doi: 10.21037/jtd-2019-thym-01.
34. Liang G, Gu Z, Li Y, Fu J, Shen Y, Wei Y, et al; Members of the Chinese Alliance for Research in Thymomas. Comparison of the Masaoka-Koga staging and the International Association for the Study of Lung Cancer/the International Thymic Malignancies Interest Group proposal for the TNM staging systems based on the Chinese Alliance for Research in Thymomas retrospective database. J Thorac Dis. 2016;8:727-37. doi: 10.21037/jtd.2016.03.22.
35. Rosen RD, Sapra A. TNM Classification. [Updated 2023 Feb 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553187/.
36. Smith A, Cavalli C, Harling L, Harrison-Phipps K, Routledge T, Pilling J, et al. Impact of the TNM staging system for thymoma. Mediastinum. 2021;5:32. doi: 10.21037/med-21-24.
37. Wei ML, Kang D, Gu L, Qiu M, Zhengyin L, Mu Y. Chemotherapy for thymic carcinoma and advanced thymoma in adults. Cochrane Database Syst Rev. 2013;2013:CD008588. doi: 10.1002/14651858.CD008588.pub2.
38. Alothaimeen HS, Memon MA. Treatment Outcome and Prognostic Factors of Malignant Thymoma - A Single Institution Experience. Asian Pac J Cancer Prev. 2020;21:653-661. doi: 10.31557/APJCP.2020.21.3.653.
39. Bruni A, Stefani A, Perna M, Borghetti P, Giaj Levra N, D'Angelo E, et al. The role of postoperative radiotherapy for thymomas: a multicentric retrospective evaluation from three Italian centers and review of the literature. J Thorac Dis. 202;12:7518-7530. doi: 10.21037/jtd-2019-thym-09.
40. Agrafiotis AC, Siozopoulou V, Hendriks JMH, Pauwels P, Koljenovic S, Van Schil PE. Prognostic factors and genetic markers in thymic epithelial tumors: A narrative review. Thorac Cancer. 2022;13:3242-3249. doi: 10.1111/1759-7714.14725.
41. Tateo V, Manuzzi L, Parisi C, De Giglio A, Campana D, Pantaleo MA, et al. An Overview on Molecular Characterization of Thymic Tumors: Old and New Targets for Clinical Advances. Pharmaceuticals (Basel). 2021;14:316. doi: 10.3390/ph14040316.
42. Girard N, Basse C, Schrock A, Ramkissoon S, Killian K, Ross JS. Comprehensive Genomic Profiling of 274 Thymic Epithelial Tumors Unveils Oncogenic Pathways and Predictive Biomarkers. Oncologist. 2022;27:919-929. doi: 10.1093/oncolo/oyac115.
43. Altshuler E, Mathavan A, Mathavan A, Krekora U, Mathavan M, Hones K, et al. Clinical characteristics, prognostic factors, and long-term outcomes associated with epithelial malignancies

of the thymus: A 20-year single-institution experience. Cancer Rep (Hoboken). 2023;6:e1750. doi: 10.1002/cnr2.1750.
44. Girard N, Shen R, Guo T, Zakowski MF, Heguy A, Riely GJ, et al. Comprehensive genomic analysis reveals clinically relevant molecular distinctions between thymic carcinomas and thymomas. Clin Cancer Res. 2009;15:6790-9. doi: 10.1158/1078-0432.CCR-09-0644.
45. Lee GY, Yang WI, Jeung HC, Kim SC, Seo MY, Park CH, et al. Genome-wide genetic aberrations of thymoma using cDNA microarray based comparative genomic hybridization. BMC Genomics. 2007;8:305. doi: 10.1186/1471-2164-8-305.
46. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010;2:a001008. doi: 10.1101/cshperspect.a001008.
47. Petitjean A, Achatz MI, Borresen-Dale AL, Hainaut P, Olivier M. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. Oncogene. 2007;26:2157-65. doi: 10.1038/sj.onc.1210302.
48. Inoue M, Fujii Y, Okumura M, Takeuchi Y, Shiono H, Miyoshi S, et al. Neoplastic thymic epithelial cells of human thymoma support T cell development from CD4-CD8- cells to CD4+CD8+ cells in vitro. Clin Exp Immunol. 1998;112:419-26. doi: 10.1046/j.1365-2249.1998.00606.x.
49. Vodicka P, Krskova L, Odintsov I, Krizova L, Sedlackova E, Schutzner J, et al. Expression of molecules of the Wnt pathway and of E-cadherin in the etiopathogenesis of human thymomas. Oncol Lett. 2020;19:2413-2421. doi: 10.3892/ol.2020.11343.
50. Meng FJ, Wang S, Zhang J, Yan YJ, Wang CY, Yang CR, et al. Alteration in gene expression profiles of thymoma: Genetic differences and potential novel targets. Thorac Cancer. 2019;10:1129-1135. doi: 10.1111/1759-7714.13053.
51. Handy DE, Castro R, Loscalzo J. Epigenetic modifications: basic mechanisms and role in cardiovascular disease. Circulation. 2011;123:2145-56. doi: 10.1161/CIRCULATIONAHA.110.956839.
52. Saleh R, Toor SM, Sasidharan Nair V, Elkord E. Role of Epigenetic Modifications in Inhibitory Immune Checkpoints in Cancer Development and Progression. Front Immunol. 2020 Jul 14;11:1469. doi: 10.3389/fimmu.2020.01469.
53. Zhao C, Rajan A. Immune checkpoint inhibitors for the treatment of thymic epithelial tumors: how to maximize benefit and optimize risk? Mediastinum. 2019;3:35. doi: 10.21037/med.2019.08.02.
54. Wojtukiewicz MZ, Rek MM, Karpowicz K, Górska M, Polityńska B, Wojtukiewicz AM, et al. Inhibitors of immune checkpoints-PD-1, PD-L1, CTLA-4-new opportunities for cancer patients and a new challenge for internists and general practitioners. Cancer Metastasis Rev. 2021;40:949-982. doi: 10.1007/s10555-021-09976-0.
55. Giaccone G, Rajan A, Ruijter R, Smit E, van Groeningen C, Hogendoorn PC. Imatinib mesylate in patients with WHO B3 thymomas and thymic carcinomas. J Thorac Oncol. 2009;4:1270-3. doi: 10.1097/JTO.0b013e3181b6be57.
56. Zhang Y, Lin D, Aramini B, Yang F, Chen X, Wang X, et al. Thymoma and Thymic Carcinoma: Surgical Resection and Multidisciplinary Treatment. Cancers (Basel). 2023;15:1953. doi: 10.3390/cancers15071953.
57. Zhang Z, Cui Y, Jia R, Xue L, Liang H. Myasthenia gravis in patients with thymoma affects survival rate following extended thymectomy. Oncol Lett. 2016;11:4177-4182. doi: 10.3892/ol.2016.4528.
58. Funaki S, Shintani Y, Fukui E, Kanzaki R, Kanou T, Ose N, et al. Surgical treatment strategies for invasive thymoma. J Thorac Dis. 2020;12:7619-7625. doi: 10.21037/jtd-19-3045.
59. Komaki R, Gomez DR. Radiotherapy for thymic carcinoma: adjuvant, inductive, and definitive. Front Oncol. 2014;3:330. doi: 10.3389/fonc.2013.00330.
60. Giaccone G, Ardizzoni A, Kirkpatrick A, Clerico M, Sahmoud T, van Zandwijk N. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. J Clin Oncol. 1996;14:814-20. doi: 10.1200/JCO.1996.14.3.814.
61. Lheureux S, Denoyelle C, Ohashi PS, De Bono JS, Mottaghy FM. Molecularly targeted therapies in cancer: a guide for the nuclear medicine physician. Eur J Nucl Med Mol Imaging. 2017;44:41-54. doi: 10.1007/s00259-017-3695-3.
62. Rajan A, Giaccone G. Targeted therapy for advanced thymic tumors. J Thorac Oncol. 2010;5:S361-4. doi: 10.1097/JTO.0b013e3181f21114.
63. Willmann J, Rimner A. The expanding role of radiation therapy for thymic malignancies. J Thorac Dis. 2018;10:S2555-S2564. doi: 10.21037/jtd.2018.01.154.
64. Tosi D, Damarco F, Franzi S, Mohamed S, Palleschi A, Mendogni P. Outcomes of extended surgical resections for locally advanced thymic malignancies: a narrative review. Gland Surg. 2022;11:611-621. doi: 10.21037/gs-21-642.
65. Zucali PA, De Vincenzo F, Perrino M, Digiacomo N, Cordua N, D'Antonio F, Borea F, et al. Systemic treatments for thymic tumors: a narrative review. Mediastinum. 2021;5:24. doi: 10.21037/med-21-11.
66. Süveg K, Putora PM, Joerger M, Iseli T, Fischer GF, Ammann K, et al. Radiotherapy for thymic epithelial tumours: a review. Transl Lung Cancer Res. 2021 ;10:2088-2100. doi: 10.21037/tlcr-20-458.