China Anti-Cancer Association Guidelines for the diagnosis, treatment, and follow-up of thymic epithelial tumors (2023)

Wentao Fang[1], Zhentao Yu[2], Chun Chen[3], Gang Chen[4], Keneng Chen[5], Jianhua Fu[6], Yongtao Han[7], Xiaolong Fu[8], Jie Wang[9], Teng Mao[1], Zhitao Gu[1], Ning Xu[1]

[1]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Department of Thoracic Surgery, National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital and Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China; [3]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou, China; [4]Department of Pathology, Zhongshan Hospital, Fudan University, Shanghai, China; [5]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing, China; [6]Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China; [7]Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu, China; [8]Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [9]State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Contributions: (I) Conception and design: W Fang, Z Yu, T Mao, Z Gu; (II) Administrative support: W Fang, Z Yu, X Fu; (III) Provision of study materials or patients: W Fang, Z Yu, C Chen, G Chen, K Chen, J Fu, Y Han, X Fu, J Wang; (IV) Collection and assembly of data: T Mao, Z Gu, N Xu; (V) Data analysis and interpretation: W Fang, Z Yu, K Chen, T Mao, Z Gu, N Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Wentao Fang, MD. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, 241 West Huaihai Road, Shanghai 200030, China. Email: vwtfang@hotmail.com.

Background: Thymic epithelial tumors (TETs) are a relatively rare type of thoracic tumors with higher incidence in Asians. The diagnosis and treatment pattern has long been based mainly on clinical experience and expert consensus. In recent years, with an increasing number of TETs detected in physical examinations, there is an urgent need to develop the guidelines that apply to the Chinese population. Thus, we intend to develop a holistic integrative guideline for TETs.

Methods: Under the leadership of the Chinese Anti-Cancer Association (CACA) Mediastinal Tumor Committee, a multidisciplinary guideline development group was established. Systemic literature review and two rounds of questionnaires regarding key clinical issues were carried out. The grading of recommendations assessment, development and evaluation (GRADE) approach was used to rate the quality of evidence and the strength of recommendations.

Results: The CACA guideline provides recommendations for the clinical differential diagnosis of anterior mediastinal lesions, management of asymptomatic small anterior mediastinal nodules, pathological classification and staging systems of TETs, as well as principles of surgery, neoadjuvant and adjuvant therapies, systemic therapies for advanced TETs, and follow-up strategies after surgical resection.

Conclusions: This guideline provides holistic integrative management strategies for TETs and would be a useful tool for clinicians on decision-making.

Keywords: Thymic epithelial tumor (TET); guideline; holistic; integrative

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Epidemiology

Common types of mediastinal lesions

Mediastinal lesions may be tumors [e.g., thymoma (TM), thymic carcinoma (TC), neuroendocrine thymic tumor (NETT), malignant lymphomas, germ cell tumors, thymic lipoma, extra-thoracic metastatic tumor] or non-neoplastic diseases (e.g., intrathoracic goiter, thymic cyst, and aortic aneurysm). Many mediastinal lesions are benign, especially those found in asymptomatic patients. On the other hand, patients with symptoms usually have malignant mediastinal lesions. All patients with mediastinal lesions should be evaluated to determine the possible histological type and extent of invasion prior to treatment. Before treatment, it is important to differentiate thymic epithelial tumors (TETs) from other diseases (e.g., lung metastases, lymphomas, goiter, and germ cell tumors) because these diseases are treated differently. Most metastatic mediastinal masses are from primary lung cancer (e.g., non-small cell lung cancer). However, approximately 50% of primary tumors in the anterior mediastinum are TETs in adults.

TET, especially TM, usually develops slowly, while the symptoms of lymphoma or malignant germ cell tumor develop rapidly. Lymphomas typically present as a systemic disease but may also present as primary anterior mediastinal lesions [e.g., nodular sclerosis Hodgkin's lymphoma and non-Hodgkin's lymphoma (e.g., primary mediastinal large B-cell lymphoma and T lymphoblastic lymphoma)]. Patients usually have lymphadenopathy accompanied by elevated serum lactate dehydrogenase (LDH). However, thymic extranodal marginal zone lymphoma of mucosal-associated lymphoid tissue (MALT lymphoma) is a type of clinically indolent non-Hodgkin lymphoma. Systemic "B symptoms" (i.e., fevers, night sweats, weight loss) are uncommon (1). Many patients with MALT lymphoma have a history of autoimmune disease (e.g., Sjögren's syndrome, systemic lupus erythematosus, or relapsing polychondritis, Hashimoto's thyroiditis) (2). Extragonadal germ cell tumors are rare and may also occur in the mediastinum.

Epidemiological characteristics of TETs

TETs originate from the thymus, including TMs, TCs and NETTs.

TETs were previously considered a rare type of tumors, with an incidence of 0.30/100,000 depending on the Surveillance, Epidemiology, and End Results (SEER) database (3). However, in recent years, with the popularization of chest computed tomography (CT) screening for lung cancer, an increasing number of TETs have been detected in physical examinations, and the incidence may exceed 100 times higher than previously thought (4-6).

TMs usually occur in patients between 40 and 70 years old and rarely in children or teenagers. The etiology of TMs is unknown. Alcohol, smoking and ionizing radiation do not seem to be risk factors for TMs. The higher incidence of TMs among African Americans and Asia-Pacific islanders suggests a possible genetic factor. Some patients have no symptoms, but others may have chest pain, cough, dyspnea or superior vena cava syndrome. Approximately 30–50% of patients with TMs are complicated with myasthenia gravis, followed by pure red blood cell aplastic anemia, hypogammaglobulinemia, dermatomyositis, etc. The symptoms suggestive of myasthenia gravis include ptosis, diplopia, salivation, difficulty climbing upstairs, hoarseness and/or dyspnea. For all patients suspected of myasthenia gravis, it is recommended to measure the level of serum anti-acetylcholine receptor antibodies to determine the occurrence of myasthenia gravis to avoid respiratory failure during the perioperative period. If myasthenia gravis is combined, preoperative evaluation and treatment by a neurologist are recommended.

TCs are rare, aggressive tumors that have higher risk of metastasis to regional lymph nodes and extra-thoracic locations than TMs; thus, the prognosis of TCs is worse than that of TMs. The survival rate of TCs varies by the stage (stage I–II: 91%; stage III–IV: 31%) and resectability (7). TCs can be differentiated from TMs due to different histological morphology, immunohistochemical and genetic characteristics. However, TCs should be differentiated from metastases of extrathymic tumors. They have similar histological features, but some immunohistochemical markers can be used for differential diagnosis.

Notably, the clinical course of TCs is different from that of TMs. Paraneoplastic syndromes (including myasthenia gravis) are very rare in patients with TCs. If the diagnosis of myasthenia gravis is established, the pathological diagnosis of TC should be reassessed. The patient may actually have a TM.

NETT, with an incidence of 0.18/1,000,000 (8), is a subtype of TET that is rarer than TM and TC, accounting for 2–5% of all TETs. According to the SEER database, the average age of patients with NETTs is 55 years old, which is more common in men (8). It was reported that approximately 25% of patients with thymic carcinoid tumors have a family history of type I multiple neuroendocrine tumors (MEN1), and 17% to 30% of adults have paraneoplastic syndromes

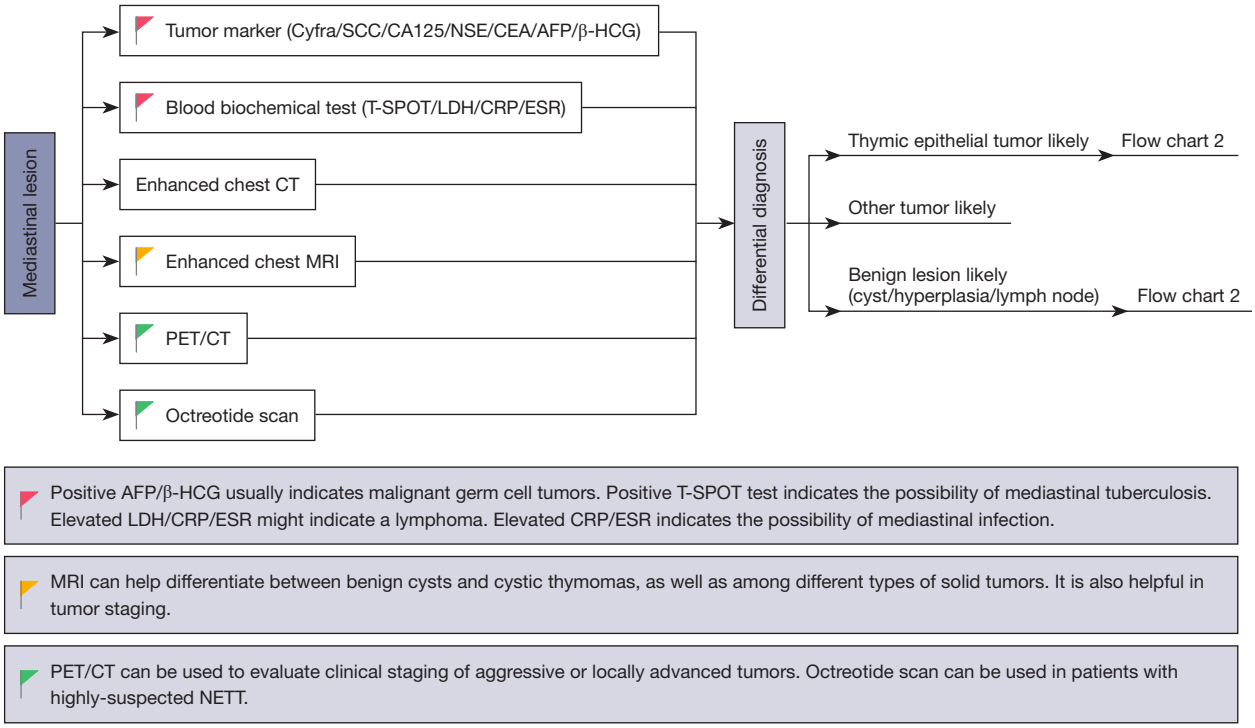

Figure 1 Differential diagnosis of mediastinal lesions. SCC, squamous cell carcinoma antigen; NSE, neuron-specific enolase; CEA, carcino-embryonic antigen; AFP, alpha-fetoprotein; β-HCG, β-human chorionic gonadotropin; T-SPOT, T-cell spot test; LDH, lactate dehydrogenase; CRP, C-reaction protein; ESR, erythrocyte sedimentation rate; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; NETT, neuroendocrine thymic tumor.

(e.g., Cushing syndrome). NETTs have a higher degree of malignancy and are more likely to have lymph node and distant metastasis than TCs.

Prevention and screening of mediastinal lesions

Recommendation (1B): CT screening for TETs is not recommended at present. *Recommendation (1B)*: For small anterior mediastinal nodules detected on physical examination or by accident, magnetic resonance imaging (MRI) is recommended for differential diagnosis (*Figure 1*). If benign lesions (thymic cyst, thymic hyperplasia, small lymph node) are considered, follow-up by CT or MRI is recommended in 3–6 months and then every 1–2 years. Nontherapeutic surgery should be avoided for asymptomatic benign lesions. In patients with small anterior mediastinal lesions ≤3 cm, upfront surgery is recommended when high-grade TETs (type B2/B3 TM, TC, NETT) are suspected, but when low-grade TMs (type A/AB/B1) are suspected, either upfront surgery or close follow-up can be applied (*Figure 2*).

At present, there is no data available for the prevention of mediastinal lesions.

There is no evidence suggesting that low-dose CT screening can improve the prognosis of patients with TMs and TCs. Considering the low incidence of TETs, low-dose CT screening for TETs is not recommended at present. However, for patients diagnosed with autoimmune diseases (e.g., myasthenia gravis) and MEN1 diseases (9), targeted screening for TETs should be performed with chest CT.

The current Guidelines from National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) do not have relative recommendations for managing accidentally detected asymptomatic anterior mediastinal nodules (usually considered to be ≤3 cm in diameter). According to a study of 419 patients with asymptomatic small anterior mediastinal nodules (10), the majority of these lesions (65.6%) were benign cysts that remained stable during follow-up. Incorporating MRI with CT scans is helpful for differential diagnosis. Follow-up is suitable and safe for benign lesions, such as thymic cysts, thymic hyperplasia, and small lymph nodes. High-grade

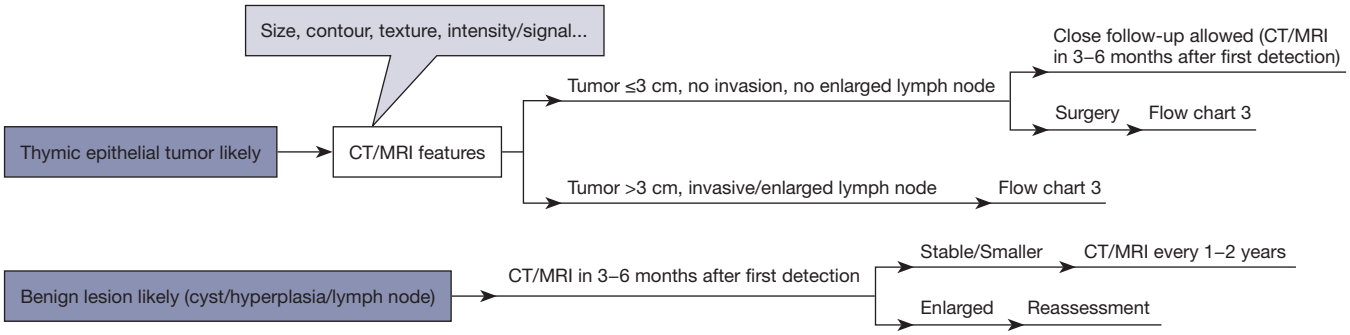

Figure 2 Follow-up strategy of incidentally detected asymptomatic mediastinal lesions. CT, computed tomography; MRI, magnetic resonance imaging.

TETs (type B2/B3 TM, TC, NETT) need upfront surgery. In low-grade TMs (type A/AB/B1), these small nodules are usually well-demarcated, and the median tumor doubling time can be longer than one year. Thus, repeating CT/MRI 6 months after the first detection seems safe in patients with low-grade lesions.

Diagnosis and staging

Clinical differential diagnosis of mediastinal lesions

Recommendation (1B): The examinations for the clinical differential diagnosis of mediastinal lesions include blood biochemical tests, enhanced chest CT and MRI (*Figure 1*). Enhanced chest MRI is recommended to differentiate between mediastinal cystic and solid lesions, cystic and necrotic areas in solid lesions, septa and soft-tissue areas in cystic lesions, and TM and thymic hyperplasia/insufficient degeneration. Positron emission tomography/computed tomography (PET/CT) is used to detect the existence of recurrence or metastasis for invasive or aggressive tumors, as well as to assist in clinical staging and assess the therapeutic effect. Octreotide scan is preferable for highly suspected NETTs and screen for the potential treatment of somatostatin analogs (SSAs) for patients with NETTs.

Blood biochemical test

It has been reported that there is a low rate of elevated tumor markers in TETs. However, elevated serum cytokeratin 19 fragment (Cyfra 21-1) before surgery may suggest tumors in an advanced stage or with more aggressive behavior (11), thus indicating a higher risk of recurrence after resection. In addition, elevation of serum CA125 may be related to pleural effusion (11). Negative alpha-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) can generally exclude malignant germ cell tumors. Significant elevation of LDH indicates the possibility of lymphoma (12). A positive T-SPOT test indicates the possibility of mediastinal tuberculosis. Significant elevation of C-reaction protein (CRP) and erythrocyte sedimentation rate (ESR) indicates the possibility of mediastinal infection. Significant elevation of angiotensin-converting enzyme (ACE) indicates the possibility of sarcoidosis. For patients with suspected autoimmune diseases, specific antibodies should be tested. For patients with suspected paraneoplastic syndrome, hormonal workup should be done and guided by the presence of symptoms of the excess hormone (9).

Chest X-ray

In adults, the thymus is usually invisible on chest radiographs. Only when the size of a TET is large can it be detected on anteroposterior chest radiography, which generally shows a mass projecting to one side of the mediastinum. The tumor may also obscure the left or right heart border, and calcification in the tumor can also be seen on chest radiographs. On lateral radiographs, the tumor can present as an opacity posterior to the sternum and anterior to the aortic arch, main pulmonary artery, and heart. Other signs can also indicate the extent of tumor invasion, e.g., diaphragm elevation, pleural effusion, and pleural thickening. In general, chest radiographs are of limited value in the differential diagnosis and clinical staging of mediastinal lesions, and more effective imaging studies should be recommended.

Enhanced chest CT

The following features of mediastinal lesions should be considered on enhanced chest CT: localization; size; contours; texture (cystic, solid, or part-solid); density

(with or without cystic change, necrosis, calcification, fatty tissue, and bleeding); the degree of enhancement (if any); the relationship between the mass and neighboring structures (invasion or not); with or without enlargement of mediastinal lymph nodes; with or without the occurrence of metastasis to the pleura, lung, bones, etc.

On CT scans, a TM usually presents as a round or oval mass with a clear boundary in the thymus, without lymphadenopathy. Aggressive TETs, such as TCs or NETTs, should be suspected when heterogeneous anterior mediastinal tumors are accompanied by local invasion, lymphadenopathy, and pleural effusion.

A lymphoma usually appears as a slightly enhanced soft tissue mass on CT, which usually surrounds and may even invade vessels. There might be enlargement of internal mammary lymph nodes that fuse with the tumor and enlargement of lymph nodes in the mediastinum, neck, axilla or other areas. In addition, when the combination of the above imaging features and typical "B" symptoms takes place in a young patient, a biopsy can usually confirm the diagnosis of lymphoma.

Retrosternal goiters and teratomas can be easily diagnosed using CT.

Among malignant germ cell tumors, seminomas are more common in young men. They present as homogeneously enhanced soft tissue masses on CT, although areas of cystic change or necrosis can be seen. Mixed germ cell tumors are heterogeneously enhanced masses with ill-defined areas of low attenuation secondary to necrosis, hemorrhage, or cystic change. Hematogenous metastasis is more likely to occur in these tumors.

Shen *et al.* studied the usefulness of CT features in accurate tumor staging before surgery (13). The results showed that the clinical staging of TET could be accurately evaluated with CT features, including tumor shape, contour, enhancement pattern, with or without invasion of adjacent structures, and presence of pleural or pericardial effusion or intrapulmonary metastasis.

However, there are limitations in the differential diagnosis of anterior mediastinal lesions by CT scan. This is mainly due to the difficulty in discriminating between benign cysts and tumors with cystic areas (e.g., cystic TM and MALT lymphoma). On CT scans, benign cysts are usually homogeneous, round or oval lesions with clear and smooth borders and water attenuation. In circumstances where cysts have high attenuation or appear as multilocular cystic lesions or with inflamed and thickened cystic walls, diagnosis by CT alone is difficult, and chest MRI is needed for further differentiation.

Enhanced chest MRI

For masses with high attenuation on CT scan, MRI is superior to CT in differentiating between mediastinal cystic and solid lesions, cystic and necrotic areas in solid lesions, and septa and soft tissue areas in cystic lesions (14). Dynamic contrast-enhanced images and curves can well detect cysts with high attenuation on CT as well as cysts with high signal intensity on T1-weighted images. An irregularly thickened and enhanced cyst wall is useful for differentiating cystic TETs from benign cysts. In addition, it is helpful for choosing a biopsy area when solid areas and cystic or necrotic areas inside the tumors can be demonstrated clearly.

The change in the signal intensity on dynamic contrast-enhanced images and curves can accurately evaluate the change in tumor cell viability after adjuvant/neoadjuvant therapy, which is superior to CT scan.

Chemical shift imaging of MRI can detect microscopic fatty tissue inside lesions through the phenomenon of reduced signal intensity in the opposed phase, which will not occur in TMs. Thus, it can be used to differentiate TMs from thymic hyperplasia or insufficient degeneration. In addition, this phenomenon does not occur in lymphomas.

On T2-weighted images, great vessels present low signal intensity due to the flow void effect, while mediastinal fat presents high signal intensity. Combined with enhanced MRI and CT, it is helpful to evaluate whether the tumor has invaded the vascular wall.

PET/CT

PET/CT is helpful in detecting the occurrence of metastasis to lymph nodes, lungs, pleura, or distant areas, but it is not recommended as a routine examination for thymic tumors. It can be used to evaluate the clinical staging of aggressive or advanced tumors and identify suspected recurrence and metastasis. PET/CT can also be used to evaluate tumor response to radiotherapy, chemotherapy, or other treatments.

Octreotide scan

Octreotide scans may help in the differential diagnosis of patients with highly suspected NETTs. In addition, for patients diagnosed with NETT, it can be used to evaluate whether they are suitable for the treatment of SSAs.

Pathological diagnosis of TET

The present guidelines follow the recommendations of

the World Health Organization (WHO) Classification for tumors of the thymus (15). The main points of diagnosis are as follows.

TM

TMs are mainly classified into type A (including an atypical variant), AB, and B (separated into B1, B2 and B3) TMs by histology and immunohistochemistry (the morphology and atypia of neoplastic epithelial cells, the percentage of immature T cells, and so on).

Type A TMs usually contain mild spindle or oval tumor cells with few or no immature lymphocytes. In recent years, the concept of atypical type A TM has been proposed, characterized by a certain degree of atypical features, including hypercellularity, increased mitosis, and focal necrosis. Clinically they sometimes present with pulmonary metastases, which is extremely rare in typical type A TMs. However, due to the rarity of atypical type A TMs, their prognosis remains to be explored.

Type AB TMs usually consist of a component dominated by spindle cells (type A-like) with few lymphocytes and a lymphocyte-rich (type B-like) component. The ratio of the two components varies greatly among different patients.

Type B1 TMs are histologically similar to the normal thymus, where epithelial cells are scattered on the background of massive immature lymphocytes. The neoplastic epithelial cells are similar to the cortical epithelial cells. Medullary differentiation areas always exist.

Type B2 TMs consist of polygonal neoplastic epithelial cells intermingled with abundant immature T cells. Neoplastic epithelial cells are usually clustered, and the density of these cells is higher than that in type B1 TMs or normal thymus. Medullary differentiation areas could exist or not.

Type B3 TMs are mainly composed of mild to moderate atypical polygonal neoplastic epithelial cells arranged in sheets, with scarcity or absence of immature T cells.

Immunohistochemistry showed that immature lymphocytes express TDT, CD1a, and CD99, while neoplastic epithelial cells could express epithelial markers such as CK, CK19, and P63 but not CK20.

In addition, there are three rare types of TMs. Micronodular TM with lymphoid stroma is composed of multifocal, mild, spindle or oval cells surrounded by lymphoid stroma. A metaplastic TM is a biphasic tumor composed of solid areas of epithelial cells in a background of mild spindle cells. Lipofibroadenomas are similar to fibroadenomas of the breast.

TC and NETT

The diagnostic criteria of TC and NETT are similar to those of the corresponding tumors in other parts of the human body.

The most common type of TC is thymic squamous cell carcinoma. Positive CD5 and/or CD117 by immunohistochemistry usually indicate that squamous cell carcinoma originates from the thymus.

Micronodular TC with lymphoid hyperplasia is a new subtype of thymic squamous cell carcinoma with 'non-organotypic' lymphoid stroma that otherwise mimics micronodular TM with lymphoid stroma.

Lymphoepithelioma-like carcinomas, which resemble nasopharyngeal carcinomas in histology, are considered to be undifferentiated or poorly differentiated, with significant infiltration of lymphocytes and plasmocytes. Tumor cells are positive for Epstein-Barr virus in a significant number of cases.

Primary thymic adenocarcinomas are rare. Invasion or metastasis from adenocarcinomas elsewhere should be excluded before diagnosis.

A nuclear protein of the testis (NUT) carcinoma is a poorly differentiated tumor characterized by rearrangement of the *NUT* gene.

Undifferentiated carcinoma is an exclusionary diagnosis. Its histology and immunohistochemistry do not show the specific characteristics of TCs.

Basaloid carcinoma, mucoepidermoid carcinoma, clear cell carcinoma, sarcomatoid carcinoma, adenosquamous carcinoma, and TC NOS (not otherwise specific) occasionally occur.

The diagnostic criteria of subtypes of NETTs are similar to those of the lung. Differential diagnosis is generally not difficult.

Biopsy

Recommendation (1A): Biopsy is not recommended for a possible TET that can be resected upfront. Core-needle biopsy is recommended for tumors that cannot be resected upfront or might need non-surgical treatment. In circumstances where a core-needle biopsy cannot be performed (e.g., blocked by the sternum or lung tissue), biopsy via surgery, endobronchial ultrasonography (E-BUS), or mediastinoscope is suitable. However, in order to avoid tumor seeding into the pleural cavity which would impact the prognosis, biopsy via a trans-pleural approach is not routinely recommended for tumors without pleural metastasis.

For the pathological diagnosis of TETs using biopsy acquired samples, it is recommended to rule out the possibility of germ cell tumors and lymphomas first because

they are also common in the mediastinum. The next step is to differentiate between NETTs and TMs or TCs. Last, it is best to differentiate between TMs and TCs. However, this may not always be feasible due to the limited volume of samples and the complicated histologic features. Further subtyping of a TM is also encouraged. For the purpose of accurate diagnosis, patients' clinical information, including but not limited to gender, age, imaging features, tumor markers, and other relative test results, is also important.

Pathological report

Key points that should be demonstrated in a pathological report of surgical specimens are as follows. Further details can be found in the Thymic Epithelial Tumors Histopathology Reporting Guide (3rd edition) developed by International Collaboration on Cancer Reporting (ICCR) (16).

- Specimens submitted, including but not limited to the partial or total thymus, the primary tumor, co-resected tissues, lymph nodes, and/or metastatic lesions;
- Macroscopic findings of the specimens including the size, color, texture, with or without a capsule;
- Microscopic findings including the pathological subtype, invaded structures, status of resection margins, lymph node involvement, and pathological reaction to previous treatment;
- Results of immunohistochemical markers used for differential diagnosis.

Clinicopathologic staging of TETs

For decades, the Masaoka-Koga staging system (17) has been the most widely accepted staging system for thymic malignancies. In recent years, a new stage classification was proposed by the International Thymic Malignancies Interest Group (ITMIG) and the International Association for the Study of Lung Cancer (IASLC), which then formed the Union for International Cancer Control (UICC) TNM staging system (8th edition) for thymic malignancies (18). The current Chinese Anti-Cancer Association (CACA) guidelines recommend using the TNM staging system. Combined usage of the Masaoka-Koga staging system is allowed.

Treatment

Surgical treatment

The optimal treatment strategy for a TET patient should be proposed by a multidisciplinary team consisting of at least a thoracic surgeon, a radiologist, a pathologist, a medical oncologist, and a radiation oncologist. Whether a tumor can be resected completely is critical and should be evaluated by thoracic surgeons with experience in this field. The main principles of surgery are demonstrated in *Table 1*.

Surgical indication

Recommendation (*Figure 3*):

(I) Upfront surgery is recommended for resectable TETs (1A).

(II) For locally advanced tumors (staged in T3–4), re-evaluation for surgery after neoadjuvant therapy is recommended (1B).

(III) For patients with pleural dissemination or limited intrapulmonary metastases, upfront resection of the primary tumor and metastatic lesions or surgery after neoadjuvant therapy is recommended, depending on the resectability of the primary tumors (2C).

(IV) For patients with mediastinal or pleural recurrence, surgical resection is an option and should be determined by a multidisciplinary team (1C).

Completeness of resection is one of the most important prognostic factors for TETs (19,20). For patients who can tolerate it, surgery is recommended for all resectable TETs. Therefore, it is very important to accurately assess the extent of tumor invasion before surgery. Shen *et al.* retrospectively analyzed the correlation between CT features and clinical staging or resectability among 138 TET patients receiving surgery (13). The results showed that the clinical staging of TETs could be evaluated via CT features, including tumor shape, contour, enhancement pattern, with or without invasion of adjacent structures, pleural or pericardial effusion, and intrapulmonary metastases. The absence of invasion of the great arteries on CT suggests the possibility of complete resection of a TET. Furthermore, chest MRI is more helpful in determining whether a tumor has invaded the vascular wall.

Common sites of recurrence for TETs, especially TMs, are the pleural cavity and primary tumor bed. A retrospective study based on the Japanese Association of the Research on the Thymus (JART) database analyzed the clinical characteristics of 405 patients with recurrent TETs (21). The results showed that 56.3% were in Masaoka stage I–III, and 25.9% were in stage IVa, suggesting that most recurrent tumors could still be resected. Of the 405 patients, 162

Table 1 Principles of surgery and radiotherapy and commonly used chemotherapy regimens for thymic epithelial tumors

Principles of surgery	
(I)	Surgical resection should be performed after evaluation of the possibility of complete resection by thoracic surgeons and radiologists. Locally advanced tumors require cooperative treatment by a multidisciplinary team
(II)	When a resectable thymic tumor is highly suspected based on clinical and radiological characteristics, surgical biopsy should be avoided considering the chance of iatrogenic pleural dissemination
(III)	Before surgery, the signs and symptoms of myasthenia gravis should be evaluated and medically controlled
(IV)	Goal of surgery is complete excision of the lesion with total thymectomy and complete resection of invaded tissues. Complete resection may require the removal of neighboring tissues, including the pericardium, phrenic nerve, pleura, lung, and even great vessels. Bilateral phrenic nerve resection should be avoided due to severe respiratory complications
(V)	Surgical clips can be placed in areas with suspicious margins or residual lesions to help guide accurate postoperative radiotherapy
(VI)	During surgery, exploration for the existence of pleural metastases should be performed. If feasible, resection of pleural metastases is recommended to achieve gross complete resection
(VII)	Minimally invasive surgery is recommended for early-stage (UICC stage I or Masaoka-Koga stage I–II) tumors. In large clinical centers with mature techniques, minimally invasive surgery could be applied to UICC stage II–IIIa tumors
(VIII)	Dissection of anterior mediastinal (N1) lymph nodes is recommended as a routine procedure, as N1 nodes are within the scope of total thymectomy. For tumors staged in T3 and above or those with high-grade histology (highly suspected or biopsy confirmed type B3 TM, TC, and NETT), further sampling of at least ipsilateral N2 lymph nodes is recommended. Bilateral N2 lymph node dissection is unnecessary, except for highly suspected NETTs with notable bilateral N2 nodes enlargement
Principles of radiotherapy	
(I)	A CT-based treatment plan prior to radiotherapy is highly recommended. Timely communication with the surgeon is helpful to determine the target volume
(II)	For postoperative radiotherapy, the recommended radiation dose is 45–50 Gy for clean or close margins and 54 Gy for microscopically positive margins. For patients with unresectable tumors or with gross residual lesions, the recommended dose is 60–70 Gy (1.8–2 Gy/fx)
(III)	The clinical target volume for postoperative radiotherapy should include the entire thymus, surgical clips, and potential residual lesions. The planning target volume should consider target motion and daily setup errors
(IV)	At least a three-dimensional conformal technique should be adopted in radiotherapy to minimize the damage to surrounding normal tissues (e.g., heart, lung, esophagus, spinal cord). IMRT can further improve the dose distribution and reduce the irradiation dose of normal tissues. Proton therapy has better dosimetry thus favorable local control and toxicity than IMRT, and can be used in appropriate situations
(V)	Given that patients with thymic tumors are relatively young and have long-term survival, it is recommended to minimize the dose volumes to normal tissues
Commonly used chemotherapy regimens	
(I)	CAP regimen: cisplatin 50 mg/m^2 IV d1; doxorubicin 50 mg/m^2 IV d1; cyclophosphamide 500 mg/m^2 IV d1, every 3 weeks
(II)	TC regimen: carboplatin AUC 6; paclitaxel 200 mg/m^2, every 3 weeks
(III)	PE regimen: cisplatin 60 mg/m^2 IV d1; etoposide 120 mg/m^2/day IV d1–3, every three weeks
(IV)	ADOC regimen: cisplatin 50 mg/m^2 IV d1; doxorubicin 40 mg/m^2 IV d1; vincristine 0.6 mg/m^2 IV d3; cyclophosphamide 700 mg/m^2 IV d4, every 3 weeks
(V)	Etoposide/ifosfamide/cisplatin regimen: etoposide 75 mg/m^2 d1–4; ifosfamide 1.2 g/m^2 d1–4; cisplatin 20 mg/m^2 d1–4, every 3 weeks

UICC, Union for International Cancer Control; TM, thymoma; TC, thymic carcinoma; NETT, neuroendocrine thymic tumor; CT, computed tomography; IMRT, intensity-modulated radiation therapy; AUC, area under the curve.

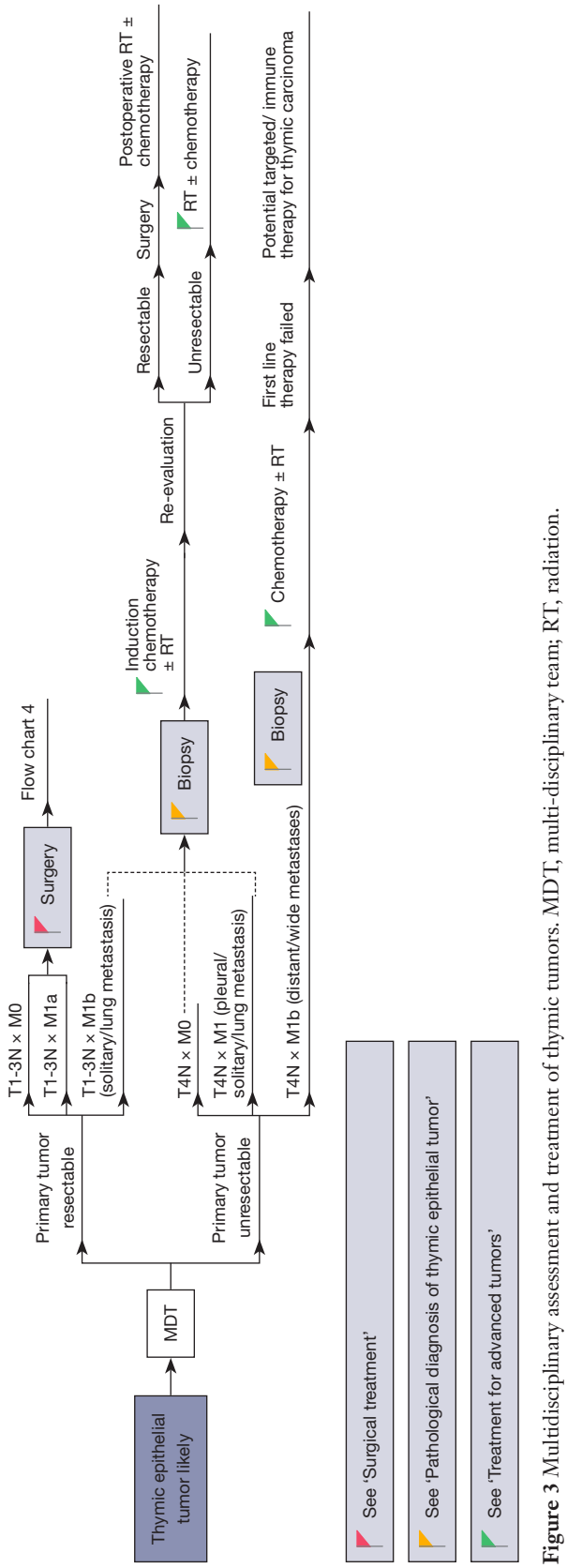

Figure 3 Multidisciplinary assessment and treatment of thymic tumors. MDT, multi-disciplinary team; RT, radiation.

received surgery, and the rate of R0/1 resection reached 72%. The survival results showed that the 10-year overall survival (OS) was significantly higher in patients receiving surgery than in patients receiving other therapies (68.2% *vs.* 25.4%, P<0.001).

Extent of resection

Recommendation: For patients without myasthenia gravis, the goal of surgery is complete excision of the lesion with total thymectomy and complete resection of invaded tissues (1B). For patients with myasthenia gravis, further extended thymectomy (total thymectomy with resection of adjacent bilateral mediastinal pleura and fatty tissue within the mediastinum, peri-pericardium areas, and aortopulmonary window) is recommended (1C).

Total thymectomy via median sternotomy is the conventional surgical procedure for patients with thymic tumors. Removing the thymus in patients with early-stage tumors that can be completely resected is not technically difficult. In addition, the thymus loses its immune function in adults, so thymectomy theoretically will not cause a functional loss in these patients.

With the development of minimally invasive techniques, the opinion of total thymectomy has been challenged. According to a study of 1,047 patients with Masaoka-Koga stage I/II TETs based on the database of Chinese Alliance of Research for Thymomas (ChART) (22), nearly 1/4 of patients received partial thymectomy. In contrast, almost all patients with sternotomy received total thymectomy. However, the proportions of total and partial thymectomy were comparable in patients receiving minimally invasive surgery. Multivariate analysis showed that the 10-year OS was similar between patients who underwent total and partial thymectomy (90.9% *vs.* 89.4%, P=0.732). Although the recurrence rates after partial and total thymectomy were similar (3.2% *vs.* 1.4%, P=0.259) among patients with Masaoka-Koga stage I tumors, there were significantly more recurrent events in patients receiving partial thymectomy than in those with total thymectomy in patients with Masaok-Koga stage II diseases (14.5% *vs.* 2.9%, P=0.001). Given that it is difficult to discriminate Makaoka-Koga stage I (encapsulated) and stage II (microscopic infiltration of capsule or mediastinal fatty tissue) tumors through preoperative imaging or intraoperative exploration, as well as the possibility of multiple lesions within the mediastinum, total thymectomy, either via an open or minimally invasive procedure, is recommended to ensure the efficacy of surgical resection based on the anatomic resection principle

as well as oncological principles.

Surgical approach

Recommendation (1A): On the premise of following oncological principles and ensuring the safety of operation, surgeons can choose conventional median sternotomy or minimally invasive surgery depending on different situations. Minimally invasive surgery is recommended for early-stage (UICC stage I or Masaoka-Koga stage I–II) tumors. In large clinical centers with mature techniques, minimally invasive surgery could be tried on UICC stage II–IIIa tumors as long as surgical and oncological principles are guaranteed.

The conventional approach is median sternotomy, which allows exposure of the mediastinum and both thoracic cavities and evaluation of gross capsular invasion, infiltration of the thymus and mediastinum fatty tissue, peri-tumor pleural adhesion, and involvement of surrounding structures.

Minimally invasive surgery is mainly applied to early-stage tumors. Gu *et al.* analyzed 1,087 patients of UICC stage I (Masaoka stage I/II) TETs in the ChART database (23). The results showed that after the median follow-up of 26 months for the video-assisted thoracoscopic surgery (VATS) group and 36 months for the open group, there was no significant difference in 5-year OS (85.7% *vs.* 93.1%, P=0.539), disease-free survival (DFS) (92.5% *vs.* 91.9%, P=0.773), cumulative incidence of recurrence (CIR) (7.1% *vs.* 5.8%, P=0.522), or the improvement rate of myasthenia gravis between the two groups (83.3% *vs.* 88.2%, P=0.589). This suggests that minimally invasive surgery can achieve similar long-term effects to open surgery. Another retrospective study in Japan compared the oncologic outcomes of VATS with those of sternotomy in 2,835 patients with TMs (24). The 5-year OS in VATS-treated patients reached 97.9%, similar to that in sternotomy-treated patients (P=0.74).

Technically, it is not difficult to resect a UICC stage II–IIIa tumor with limited invasion of the pericardium or adjacent lung tissues and achieve comparable completeness of resection via minimally invasive surgery. Gu *et al.* reported the perioperative and survival results of MIT (minimal invasive thymectomy) compared to MST (median sternotomy thymectomy) in patients with UICC stage T2–3 TETs (25). After propensity score matching, the MIT group had considerably less blood loss (P<0.001), fewer postoperative complications (P=0.048), a shorter duration of chest drainage (P<0.001), and a shorter hospitalization duration (P<0.001) than the MST group. The 5-year freedom from recurrence rate was comparable between the two groups (78.2% *vs.* 78.5%, P=0.942).

With the development of minimally invasive techniques, it is possible to obtain complete resection for patients with recurrent or metastatic tumors and those with previously advanced tumors but downstaged after induction therapy, apart from patients with UICC stage IIIa tumors with limited invasion. For patients who probably need multimodality treatment, minimally invasive surgery is superior in less surgical trauma and faster functional recovery so that patients can better tolerate adjuvant therapy to achieve desired oncological outcomes.

There is still no consensus on the specific diameter of TETs suitable for minimally invasive surgery. Previously, a tumor over 5 cm was considered a "large" tumor in most studies, and it is safe and feasible to perform minimally invasive surgery for TETs ≤5 cm (26). However, with the improvement of surgical techniques, it has been reported that the main reason for conversion in minimally invasive surgery for tumors over 5 cm is the invasion of great vessels. In addition, for tumors over 5 cm, minimally invasive surgery could achieve oncological results similar to those of open surgery (24). Therefore, compared to the extent of tumor invasion, tumor size is not a major factor affecting the choice of surgical approach. It should be noted that due to the limited space in the mediastinum, it is more difficult to perform minimally invasive surgery when the tumor becomes large. There would also be increased risks of pleural dissemination in this situation. Surgeons should strictly adhere to oncological principles during surgery. Conversion to open surgery should be carried out if complete resection is difficult or there is a risk of tumor spillage.

In addition, the surgical approach is not affected by the histological type, which is difficult to confirm before surgery for most early-stage tumors. Although the retrospective studies of ITMIG (27) and JART (28) did not include TCs, the study of the ChART (29) database showed that early-stage TC was not a contraindication of minimally invasive surgery as long as complete resection could be obtained.

Lymph node dissection

Recommendation (1B): Dissection of anterior mediastinal (N1) lymph nodes is recommended as a routine procedure, as N1 nodes are within the scope of total thymectomy. For tumors staged in T3 and above or those with high-grade histology (highly suspected or biopsy confirmed type B3 TM, TC, and NETT), further sampling of at least ipsilateral N2

lymph nodes is recommended. Bilateral N2 lymph node dissection is unnecessary, except for highly suspected NETTs with notable bilateral N2 nodes enlargement.

Lymph node metastasis is believed to be rare in TETs; thus, lymph node dissection is rarely carried out in conventional surgeries.

In recent years, the issue of lymph node metastasis has gained increasing attention. In the widely used Masaoka-Koga staging system, lymph node metastasis is grouped into stage IVb, together with distant metastasis. However, in the 8th edition of UICC staging, the node (N) category is divided into three tiers (N0–2) depending on the presence of nodal involvement in different anatomical regions. Recent studies have shown that the incidence of lymph node metastasis varies depending on the histological type and the extent of tumor invasion. A study of 1,320 patients from the JART database (30) found that the overall incidence of lymph node metastasis was only 5.9%. There were 1.8% of TMs, 27% of TCs, and 28% of thymic carcinoids accompanied by lymph node metastasis. Two studies based on the SEER database (31,32) included patients with surgical removal of at least one lymph node. The results showed that the incidence of lymph node metastasis was 13.3% in TMs, 33.5% in TCs, and 62.3% in NETTs.

According to the results of a retrospective study from the ChART database (33), among 2,421 patients in 20 hospitals, lymph node metastasis was rarely seen in TMs (only 0.5%) but occurred in 7.9% of TCs and 16.7% of NETTs. Moreover, lymph node metastasis was closely related to the prognosis of TETs.

Further prospective observational study from ChART (34) showed that lymph node involvement in thymic malignancies is more common than previously recognized. Through intentional lymph node sampling or systemic dissection, lymph node metastasis was seen in 2.1% of patients with TMs, 25% of TCs, and 50% of NETTs. N2 node dissection, along with higher-grade tumor histology and advanced T category, were found to be associated with increased nodal-positive rate. Thus, TETs were further divided into a low-risk group (type A-B2 TMs staged in T1–2) and a high-risk group with higher-grade histology (type B3 TM, TC, and NETT) or stage T3 and above for nodal metastasis. Intentional lymph node dissection could increase the detection rate of nodal involvement and improve the accuracy of staging and the completeness of resection. Theoretically, when total thymectomy is performed as recommended above, N1 nodes, located in the anterior mediastinum, would have already been dissected together. Considering that N2 involvement was usually on the ipsilateral side of tumor extension according to the ChART study, as well as that bilateral N2 node dissection would not be feasible via minimally invasive surgery with a unilateral approach, it is recommended that ipsilateral N2 nodes should at least be sampled for patients in the high-risk group.

Specimen handling

After resection, complete retrieval of the specimen should be done carefully to prevent specimen disruption. For minimally invasive surgery, the specimen should always be extracted in a retrieving bag (35). It is encouraged to handle the resected specimens as follows (36).

- Orienting the unfurled specimen on a mediastinal board or diagram is encouraged.
- Mark co-resected structures (mediastinal pleura, lung tissue, pericardium, phrenic nerve, blood vessels, etc.).
- Mark areas of concern, for example, margins of resection.
- Record the location of lymph nodes removed during operation.
- Provide the patient's medical history, especially previous therapies and comorbidities, on the pathological examination application form and communicate with the pathologist promptly.

Adjuvant therapy

TM

Recommendation (1C): After complete resection, adjuvant therapy is not recommended for TMs in UICC stage I and type A/AB/B1 TMs in stage II–IIIa. Adjuvant radiotherapy or follow-up is alternative for type B2/3 TMs in UICC stage II–IIIa. Adjuvant radiotherapy is recommended for TMs with incomplete (R1/2) resection. Adjuvant chemotherapy is recommended for tumors with lymph node metastasis (*Figure 4*, *Table 1*).

A retrospective analysis based on the ChART database (37) involving 1,546 patients with Masaoka-Koga stage I–III TETs showed that adjuvant radiotherapy could improve OS and DFS for patients with R1/2 resection.

A retrospective analysis using the ITMIG data (38) from 1,263 patients with completely resected Masaoka stage II–III TMs showed that the 10-year OS was higher in patients with postoperative radiotherapy than those without (86% *vs.* 79%, P=0.002). Furthermore, for stage III type B TMs,

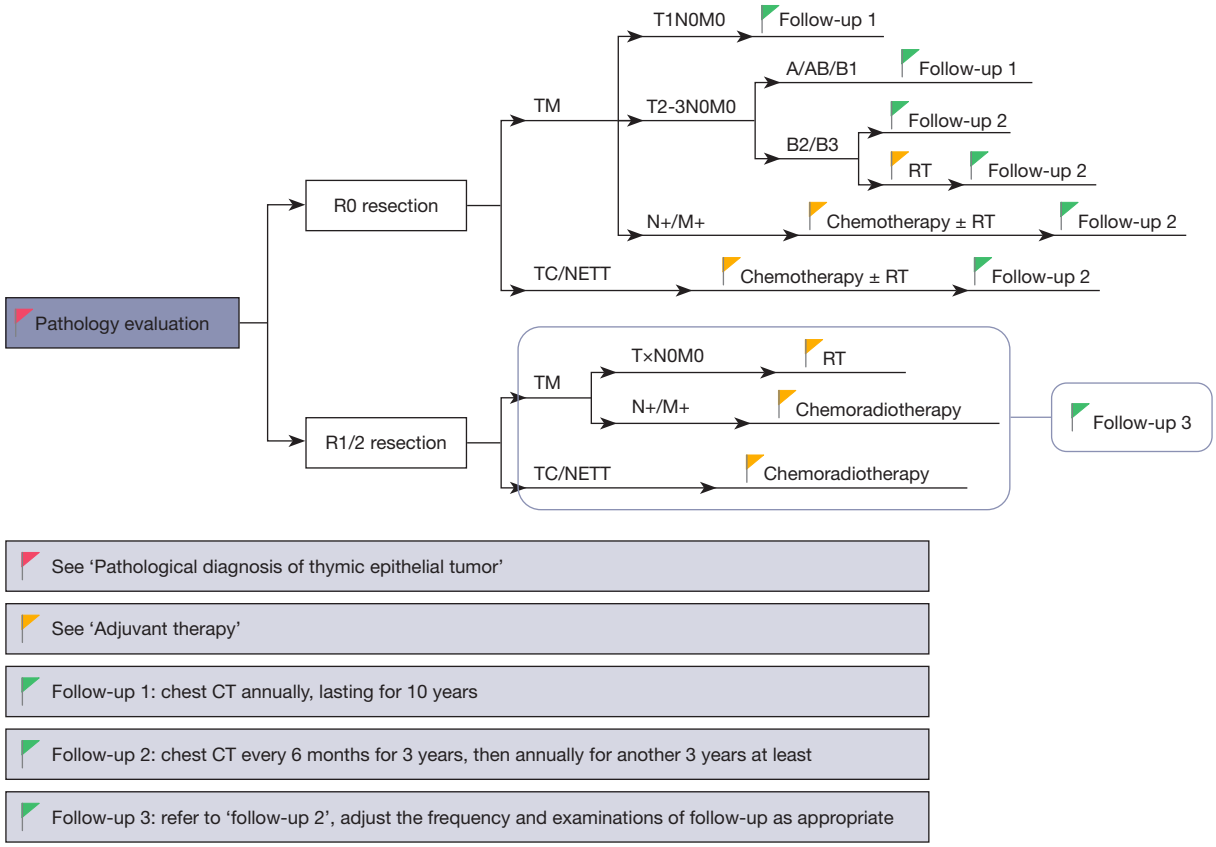

Figure 4 Postoperative treatment and follow-up of thymic tumors. TM, thymoma; TC, thymic carcinoma; NETT, neuroendocrine thymic tumor; RT, radiation; CT, computed tomography.

postoperative radiotherapy could also significantly improve OS. However, the results from the JART database (39) showed that postoperative radiotherapy might be beneficial only in stage III TCs in terms of recurrence-free survival (RFS) but not OS. It could not improve RFS or OS for patients with Masaoka stage II TETs or stage II TCs.

In the NCCN Guidelines (2021. V1) (40), adjuvant radiotherapy is not recommended for completely resected (R0) Masaoka-Koga stage I TMs. Adjuvant radiotherapy can be considered for TMs with capsular invasion after an R0 resection. Postoperative radiotherapy is recommended for Masaoka-Koga stage III (invasion of adjacent structures) TMs because of the higher risk of recurrence.

However, depending on the recurrence predictive model based on the ChART database (41), patients with stage T1 TMs or stage T2–3 type A, AB, and B1 TMs (low-risk group) had a significantly lower incidence of recurrence than those with stage T2–3 type B2, B3 TMs and all TCs and NETTs (high-risk group) (2.7% *vs.* 20.1%, P<0.001).

Based on the above literature, adjuvant therapy is not recommended for patients with UICC stage I TMs and stage II–IIIa type A/AB/B1 TMs after an R0 resection. Adjuvant radiotherapy or follow-up can be considered in patients with UICC stage II–III A type B2/3 TMs.

For adjuvant chemotherapy, a retrospective study based on the ChART database included 739 patients with Masaoka-Koga stage III/IV TETs (42). Among patients with stage IV TMs, there was no difference in 5-year OS for patients with or without adjuvant chemotherapy (76.1% *vs.* 85.7%, P=0.862). However, for patients with stage III TMs, patients with adjuvant chemotherapy had worse 5-year OS than those without (88.1% *vs.* 92.1%, P<0.001). Moreover, among patients with completely resected TMs, the 5-year OS was significantly lower for patients with chemotherapy than those without (67.2% *vs.* 92.8%, P=0.001). Therefore, adjuvant chemotherapy is not recommended for patients with TMs. However, systemic therapy is still recommended for patients with lymph node metastasis (although lymph

node metastasis is rare in TMs).

TC and NETT

Recommendation (1C): For completely resected TCs and NETTs, adjuvant chemotherapy with or without radiotherapy is recommended. For TCs and NETTs with an incomplete (R1/2) resection, adjuvant chemoradiotherapy is recommended (*Figure 4*, *Table 1*).

A retrospective study from Shanghai Chest Hospital included 116 patients with completely resected TCs (43). The results showed that adjuvant chemotherapy significantly improved the 5-year RFS for patients with Masaoka stage II tumors (84% *vs.* 66.6%, P=0.035) and the 5-year OS for patients with stage III tumors (84.6% *vs.* 63.7%, P=0.036).

A retrospective study based on the JART database included 1,265 patients with Masaoka stage II–III TETs (39). Data showed that postoperative radiotherapy was associated with better RFS [hazard ratio (HR) 0.48, 95% confidence interval (CI): 0.30–0.78, P=0.003] but not OS for stage III TC patients. Another meta-analysis of 592 patients of completely resected Masaoka stage II–III TETs showed that postoperative radiotherapy could not reduce the recurrence rate (44).

According to the recurrence predictive model proposed by ChART (41), patients with TCs and NETTs had a higher risk of recurrence, especially distant metastasis. Therefore, adjuvant chemotherapy with or without radiotherapy is recommended for completely resected TCs and NETTs.

Treatment for advanced tumors

Neoadjuvant therapy

Recommendation (1B): For locally advanced TETs, neoadjuvant chemotherapy or chemoradiotherapy is recommended, followed by a re-evaluation of surgical indications. Postoperative radiotherapy or chemoradiotherapy is recommended depending on the resection margins and pathological assessment. Definitive radiotherapy or chemoradiotherapy is recommended if the tumor is deemed unresectable after induction therapy (*Figure 3*). First-line chemotherapy regimens for TMs, TCs, and NETTs are CAP or TC, TC, and PE regimens, respectively (*Table 1*).

Recommendation (2C): For patients with pleural dissemination or intrapulmonary metastases, induction followed by surgery is an option.

Induction therapy followed by surgery might be effective for potentially resectable TETs (45-51).

A recent cohort study showed a similar 5-year OS for patients receiving induction chemotherapy followed by surgery to those receiving surgery alone (77.4% *vs.* 76.7%, P=0.596) (46).

To date, there have been two phase II clinical trials (51,52) studying the efficacy of induction chemotherapy. The objective response rate (ORR) reached 62% and 77%, respectively, with a high incidence of adverse events. The rate of pathological complete response (PCR) was 14% and 9%, and the rate of R0 resection was 43% and 73%, respectively. However, considering that both studies only accrued TMs and had a high proportion of low-grade subtypes, the actual efficacy of induction chemotherapy for high-grade TETs, especially for TCs, is unclear. According to the results of clinical trials in non-surgical patients, TCs respond poorly to chemotherapy (53,54).

According to a phase II clinical trial of neoadjuvant concurrent chemoradiotherapy for locally advanced high-grade TETs (type B2/B3 TM, TC, NETT) at Shanghai Chest Hospital, the ORR was 48.5% with tolerated toxicities. The rate of R0 resection was 82.6% for patients receiving surgery, and the rate of PCR reached 17.4%. The 5-year OS rates for TM and TC patients were 81.8% and 54.2%, respectively.

A previous phase II trial (55) from North America and Europe reported a 47.6% response rate and a 71% 5-year OS for locally advanced TETs after neoadjuvant concurrent chemoradiation followed by surgery.

Systemic therapy

Recommendation: Definitive chemoradiotherapy is recommended for unresectable advanced TETs (*Figure 3*) (1B). Surgery remains an option for patients with recurrent locally advanced lesions, solitary metastasis, or ipsilateral pleural metastasis (2C).

TM

Given different metastatic scenarios, it is sometimes difficult to specify radiation doses for metastatic lesions. Stereotactic body radiation therapy (SBRT) is an appropriate option for focal metastases, while conventional fractionation is suitable for larger metastatic lesions. In palliative treatment, typical palliative doses of 8 Gy/fx, 20 Gy/5 fxs or 30 Gy/10 fxs can be used, depending on the target. Even for metastatic TMs, due to their slow growth, highly conformal techniques might be suitable for lesions of limited size. It could be helpful to improve local control by increasing radiation doses. On the other hand, multiple radiotherapies for recurring metastatic lesions might increase the risk of radiation-induced lung injury.

Currently, the recommended first-line chemotherapy regimens for TMs are platinum-based regimens (CAP or TC) (56-59). The response rates of the CAP regimen for TMs are approximately 44% (60). Non-anthracycline regimens [e.g., cisplatin/etoposide (± ifosfamide), carboplatin/paclitaxel] are alternative for patients who cannot tolerate more aggressive regimens.

Second-line regimens for TMs include pemetrexed, everolimus, paclitaxel, octreotide [long-acting release (LAR)] with or without prednisolone, gemcitabine with or without capecitabine, 5-FU, etoposide, and ifosfamide (59,61-69). However, these drugs have not been assessed in randomized phase III trials. For TMs, response rates of subsequent systemic therapy range from 15% to 39% (60). A study of pemetrexed in the treatment of TM patients (n=16) reported 2 patients with complete response (CR) and 5 patients with partial response (PR) (70). Based on clinical trial data, capecitabine might be an effective addition to a single gemcitabine regimen (61,68). Among 22 TM patients treated with gemcitabine/capecitabine, 3 patients achieved CR, and 5 achieved PR. Octreotide may be an option for TM patients with a positive octreotide scan or symptoms of carcinoid syndrome. Pembrolizumab is not recommended for TM patients due to concerns about severe immune-related events. It was reported that 71.4% of TM patients receiving pembrolizumab had grade 3 or higher immune-related adverse events (71). Sunitinib is not recommended due to the scarcity of c-Kit mutations in TMs (72,73).

TC

TCs respond poorly to chemotherapy. Carboplatin/paclitaxel (TC) regimen is recommended as the first-line therapy for its highest reported response rate in clinical trials for TCs (53,54,74-82). Clinical data suggest that CAP and cisplatin/adriamycin/vincristine/cyclophosphamide (ADOC) regimens are also effective but more toxic (60,80).

There are limited data about second-line therapy for TCs. Alternative options include sunitinib, pemetrexed, everolimus, paclitaxel, octreotide (LAR) with or without prednisone, gemcitabine with or without capecitabine, 5-FU, etoposide, ifosfamide, and pembrolizumab (7,70,83). Response rates range from 4% to 21%. Sunitinib may be effective in patients with c-Kit mutations, but such mutations are rare in TCs (<10%) (64,72,84-88). S-1 (oral fluorouracil) seems to be effective for patients with TCs (89,90).

Pembrolizumab might be an effective second-line therapy for TC patients. According to the two trials of immunotherapy for thymic tumors, 19.2% and 22.5% of patients with TCs responded after receiving pembrolizumab (71,91). The incidence of severe immune-related adverse events was 15.4% and 15%, respectively. Capecitabine/gemcitabine is also suitable for TCs in the second-line setting (61,68). Three out of 8 patients with TCs had PR after receiving the gemcitabine/capecitabine regimen. In addition, the response rate of immune checkpoint inhibitors (ICIs) in combination of chemotherapy was reported to be 44.4% for advanced TCs, higher than that of ICIs monotherapy (17.4%) (92). The combination of ICIs and anti-angiogenesis drugs also has been explored in TCs (93). However, the efficacy and safety of combined therapies are in need for further study.

NETT

Patients with NETTs, especially the more aggressive subtypes, are more likely to have local invasion, lymph node metastasis and distant metastasis. Although SSAs were reported to be effective for neuroendocrine tumors (94), only 2 and 4 patients received SSAs before and after surgery, respectively. Given the limited efficacy of conventional chemotherapy and radiotherapy in treating NETTs, other agents, such as SSAs, should be explored, as well as mammalian target of rapamycin (mTOR) inhibitors (95) and multitarget drugs targeting vascular endothelial growth factor receptors (96) that have been tried in other neuroendocrine tumors.

Rehabilitation

The postoperative management of TET patients was similar to that of other patients undergoing thoracic surgery. In recent years, with the development of enhanced recovery after surgery (ERAS), recovery after thoracic surgery has gradually gained increasing attention. As current clinical evidence only focuses on recovery after lung surgery, the Clinical Practice Guidelines for ERAS in China (2021 Edition) (97) proposed by the Chinese Medical Association and the Guidelines for Enhanced Recovery After Lung Surgery (98) proposed by the European Society of Thoracic Surgeons (ESTS) can be referred to for enhanced recovery after thymic surgery.

It should be noted that for patients with myasthenia gravis, clinicians should pay attention to worsening symptoms or even myasthenia crisis. If so, clinicians should adjust medication promptly, strengthen monitoring, and apply for a consultation with a neurologist when needed.

Follow-up

Recommendation (1B): For patients in the low-risk group

Table 2 Levels of evidence and grades of recommendation adapted from the GRADE system (102)

Categories	Definition
Levels of evidence	
High (A)	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate (B)	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low (C)	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low (D)	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect
Grades of recommendation	
Level 1 (strong)	The panel is highly confident that the desirable consequences of an intervention outweigh its undesirable consequences. We believe that all or almost all informed people would make the recommended choice for or against an intervention
Level 2 (weak)	The panel is less confident that the desirable consequences of an intervention outweigh its undesirable consequences. We believe that most informed people would choose the recommended course of action, but a substantial number would not

Used with permission from Elsevier. GRADE, grading of recommendations assessment, development and evaluation.

(stage T1 TMs, stage T2/T3 type A/AB/B1 TMs), follow-up annually for 10 years is recommended. For patients in the high-risk group (stage T2/T3 type B2/B3 TMs, all TCs and NETTs), follow-up is recommended every six months for three years and then annually for another 3 years at least (*Figure 4*).

Liu *et al.* (41) analyzed 907 patients with completely resected TETs based on the ChART database. The results showed that the recurrence rate in patients with stage T1 TMs and T2/T3 type A/AB/B1 TMs (low-risk group) was significantly lower than that in patients with stage T2/T3 type B2/B3 TMs and T1-T3 TCs and NETTs (high-risk group) (2.7% *vs.* 20.1%, P<0.001). In the low-risk group, the majority of recurrences occurred in the tumor bed and pleural cavity (88.9%). In the high-risk group, there were more patients with distant metastasis (40.7%) and pleural dissemination (25.9%), which mostly (55.2%) occurred within 3 years after surgery. Only one case of recurrence in the high-risk group occurred over 6 years after surgery, but local recurrence still could be seen 10 years after surgery in the low-risk group.

In addition, for patients who receive adjuvant therapies or suffer from advanced tumors, the frequency of follow-up and type of examination should be adjusted accordingly.

TM patients have an increased risk of developing second malignancies (99-101). Since there is no consensus on screening, routine physical examination is still important.

Methodology

A multidisciplinary guideline development group was established among members of the CACA Mediastinal Tumor Committee. Systemic literature review and two rounds of questionnaires regarding key clinical issues were carried out. The grading of recommendations assessment, development and evaluation (GRADE) approach was used to rate the quality of evidence and the strength of recommendations (*Table 2*) (102). We present this article in accordance with the RIGHT reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-54/rc).

Conclusions

These CACA guidelines focus on the clinical differential diagnosis of anterior mediastinal lesions, management of asymptomatic small anterior mediastinal nodules, pathological classification and staging systems of TETs, as well as principles of surgery, neoadjuvant and adjuvant therapies, systemic therapies for advanced TETs, and follow-up strategies after surgical resection. Due to the rarity of TETs and limited high-level evidence, there are

still many controversies remaining and future researches are encouraged to solve these questions.

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Footnote

Reporting Checklist: The authors have completed the RIGHT reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-23-54/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Review Article

Surgical access to the mediastinum—*all roads lead to Rome*: a literature review

Nora Mayer^, Peter Kestenholz^, Fabrizio Minervini^

Division of Thoracic Surgery, Lucerne Cantonal Hospital, Luzern, Switzerland

Contributions: (I) Conception and design: F Minervini, N Mayer; (II) Administrative support: P Kestenholz; (III) Provision of study materials or patients: N Mayer; (IV) Collection and assembly of data: N Mayer, F Minervini; (V) Data analysis and interpretation: N Mayer, F Minervini; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Fabrizio Minervini, MD, PhD, FEBTS, MBA. Division of Thoracic Surgery, Lucerne Cantonal Hospital, Spitalstrasse 16, 6000 Luzern, Switzerland. Email: fabrizio minervini@hotmail.com.

Background and Objective: The mediastinum is a complex, heterogeneous area, which leads vertically across the thoracic cavity between the bilateral mediastinal pleurae, connecting the head and neck region with the thoracic cavity. Different classifications have been published to differentiate between the so-called mediastinal compartments while the most used classification surely is the 4-compartments Gray`s classification, dividing it into the superior, anterior, middle and posterior mediastinum. Mediastinal abnormalities include infections (mediastinitis) and solid or cystic mediastinal masses. These masses can be divided into benign and malignant lesions originating from mediastinal structures/organs or represent manifestations of metastatic disease, often metastatic non-small cell lung cancer (NSCLC). This review aims to explore the different mediastinal pathologies along with indications and surgical approaches.

Methods: We performed literature research in PubMed, MEDLINE, Embase, CENTRAL, and CINAHL databases. Only papers written in English were included.

Key Content and Findings: Depending on the indication for surgical intervention and the localization of the pathology, surgical approach may differ immensely. Mediastinal staging of lung cancer, primary lesions of the mediastinum, mediastinitis and traumatic mediastinal injuries display the most frequent indications for mediastinal surgery. Surgical approaches trend towards minimally invasive, video- or robotic-assisted techniques and are becoming increasingly refined to adapt to the special characteristics of the mediastinum. However, certain indications still require open access for best possible mediastinal exposure or oncological reasons.

Conclusions: To guide optimal surgical approach selection to the mediastinum, the following overview will present all published surgical approaches to the mediastinum and discuss their practical relevance and indications aiming to help surgeons in the management of patients with mediastinal pathologies who should undergo surgery.

Keywords: Mediastinum; mediastinal pathologies; surgical access; minimally invasive; mediastinal staging

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^ ORCID: Nora Mayer, 0000-0001-7412-8224; Peter Kestenholz, 0000-0002-0419-3685; Fabrizio Minervini, 0000-0003-3595-7307.

Introduction

The mediastinum is divided into specific compartments, most commonly referred to as the superior, anterior, middle and posterior mediastinum (1-3). It contains fundamentally important vascular and non-vascular structures as well as organs and furthermore, it connects the head and neck region with the thoracic cavity. The currently accepted radiological standard of mediastinal compartments was developed by the International Thymic Malignancy Interest Group (ITMIG) based on computed tomography (CT)-images. It defines the different compartments bordered by specific anatomic structures (4) (*Table 1*).

Mediastinal lesions can be of benign or malignant nature originating from the respective mediastinal structures or be metastatic manifestations of distant disease.

Primary tumours in the anterior mediastinum account for more than half of all mediastinal masses in adults comprising malignant and benign lesions (5). Malignant lesions consist of thymoma, lymphoma and teratoma whilst benign lesions include thymic cysts, lymphangioma and intrathoracic goitre (6). A further quarter of the mediastinal abnormalities can be found in either the middle or the posterior mediastinum respectively (7). There, the lesions comprise neurogenic tumours lymphoma and mediastinal cysts (8,9).

Clinical characterization plus radiological findings in CT may be sufficient for definitive diagnosis, however, in other cases, further imaging like magnetic resonance imaging (MRI), fluorodeoxyglucose-positron emission tomography-CT (FDG-PET-CT) or histological confirmation (often immunohistochemistry) may become necessary to delineate the origin of mediastinal abnormalities (7). To choose the optimal treatment, histological diagnosis sometimes is mandatory if the imaging cannot predict a diagnosis with a high degree of certainty. A biopsy indication however has to be evaluated carefully and the biopsy technique highly depends on the localization of the lesion and surrounding structures, the experience of the respective physician as well as the most expected nature of the lesion. Metastatic seeding of the lesion through biopsy procedures needs to be avoided.

Various interventional biopsy options including CT-guided percutaneous biopsy, endobronchial ultrasound-guided transbronchial fine needle aspiration (EBUS-TBNA) and endoscopic ultrasound fine-needle aspiration (EUS-FNA) exist. For the posterior mediastinum, EUS-FNA is safe and provides an excellent diagnostic yield with a sensitivity of more than 90% and a specificity of 100% (10,11). Concerning mediastinal staging in lung cancer patients, EBUS-TBNA and EUS-FNA are currently playing an increasing role as a minimally invasive alternative, reducing the need for mediastinoscopy (12). However, if clinical suspicion of mediastinal lymph node (LN) metastases remains, cervical mediastinoscopy in the experienced hand is still recommended (13).

Surgery, like cervical mediastinoscopy mentioned above, may be required in cases of failed interventional mediastinal staging (technical, localization, insufficient tissue amount for molecular analysis, inconclusive histopathological result). The chosen surgical approach depends on different factors including the localisation of the pathology as well as the surgical indication. Biopsy/staging techniques include mediastinoscopy, Chamberlain/McNeill procedure, video-assisted mediastinoscopic lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA).

Furthermore, surgery remains the standard for removal of mediastinal masses, with transsternal open resection having been the gold standard for many years. However, minimally invasive surgical techniques such as video- and robotic-assisted thoracic surgery (VATS/RATS) are gaining ground if not already longing to replace open surgery in certain fields (8,14).

The aim of our publication was to describe all the available surgical accesses and emphasize their indications

Table 1 Boundaries and contents of the 4-compartment mediastinal scheme

Mediastinal compartment	Boundaries	Content
Superior	Thoracic inlet to a line from the sternal angle to T4	Aorta, great vessels, trachea, upper 3rd of the oesophagus, upper thymus
Anterior	Pericardium, sternal body	Mediastinal fat and thymus
Middle	Pericardium to pericardium	Pericardium, heart, carina, lymph nodes
Posterior	Dorsal pericardium to anterior surface of T4–T12	Oesophagus, thoracic aorta, azygos vein, thoracic duct

Table 2 Methods and specification of underlying database research

Items	Specification
Date of search	Search performed between 19th of November and 6th of December 2023
Databases searched	PubMed/MEDLINE/Embase/CENTRAL/CINAHL
Search terms used	(mediastinum OR mediastinal) AND (access OR approach OR surgery OR resection OR "surgical resection" OR "tumour resection") OR (mediastinoscopy)
	(mediastinal OR mediastinum) AND (tumour OR pathology OR mass OR "tumour mass" OR neoplasia)
	(RATS OR "robotic-assisted" OR robotic OR "video-assisted" OR VATS OR "minimally invasive" AND surgery) AND (thymectomy OR "resection of thymus" OR thymoma)
Timeframe	Not specified
Inclusion and exclusion criteria	Inclusion criteria:
	❖ Studies including mediastinal tumor resection were included
	❖ All surgical approaches (open/video/robotic-assisted thoracoscopic surgery)
	Exclusion criteria:
	❖ Commentaries and case reports
	❖ Language other than English
	❖ Full text unavailable
Selection process	Initially, records were screened by title and abstract and then duplicate studies were identified and removed using ZOTERO
	For the second stage of screening, we performed full text review of all eligible studies from the title and abstract screening. Both stages were performed by two authors (F.M., N.M.)

RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracic surgery.

and practical implementation as well as informing about current evolutions to provide guidance for decision-making in choosing the most appropriate surgical approach to the mediastinum. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-71/rc).

Methods

We performed a literature search in PubMed, MEDLINE, Embase, CENTRAL, and CINAHL databases to identify relevant publications for the assessed topic of accesses/approaches to the mediastinum for mediastinal pathologies (*Table 2*).

The searches for the main review were conducted as: (mediastinum OR mediastinal) AND (access OR approach OR surgery OR resection OR "surgical resection" OR "tumour resection") OR (mediastinoscopy).

The more specific research for certain sections of the review was done with the following additions: (mediastinal OR mediastinum) AND (tumour OR pathology OR mass OR "tumour mass" OR neoplasia).

(RATS OR "robotic-assisted" OR robotic OR "video-assisted" OR VATS OR "minimally invasive" AND surgery) AND (thymectomy OR "resection of thymus" OR thymoma).

All citations returned from the above searches were exported into a ZOTERO library. Duplications were removed and abstracts were reviewed by two authors (N.M., F.M.) for potential inclusion in the manuscript.

Further searches were conducted without using Boolean operators.

We included all the studies where surgery-related mediastinal pathologies were reported. Only publications in English language were included. We were focussing on the most recent publications to enhance the importance of our review, however, publications including first descriptions of rare access techniques were included.

Due to the narrative design of the review, a certain

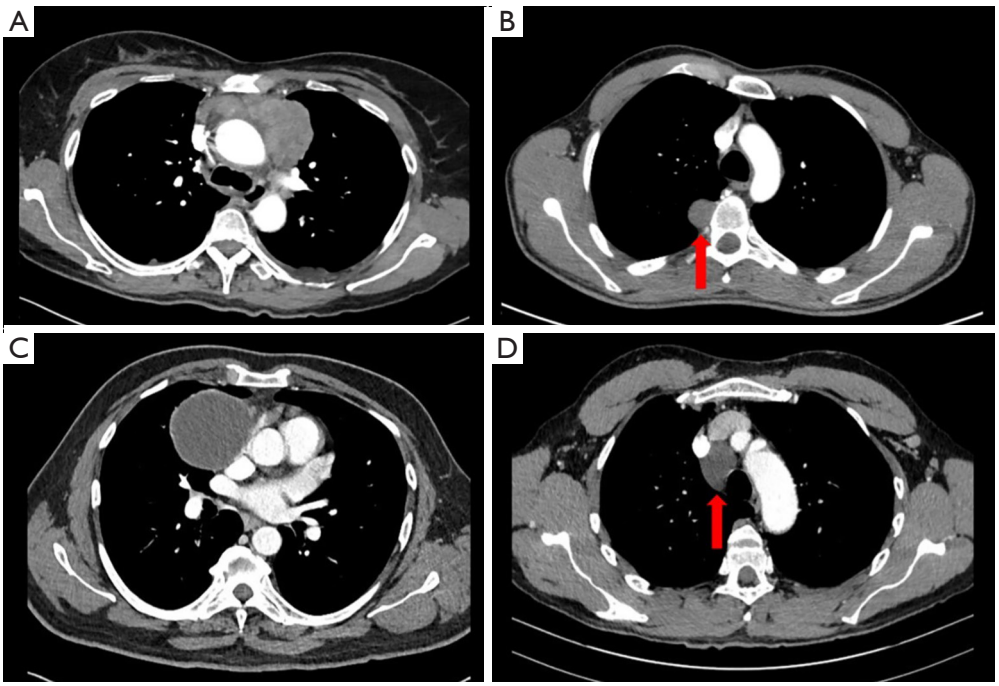

Figure 1 Pathologies of the mediastinum. (A) Thoracic CT showing a thymoma type B3 in the anterior mediastinal compartment, (B) CT showing a neurogenic tumor in the posterior mediastinum (arrow), (C) CT-scan showing a pericardial cyst in the antero-medial compartment of the mediastinum as well as (D) showing at CT-scan with a bronchogenic cyst (arrow) in the middle compartment of the mediastinum. CT, computed tomography.

subjectivity in choice of studies included is likely. Patients' consents were obtained for publication of the images and saved in their electronic charts.

Pathologies of the mediastinum

Mediastinal lesions/tumours

Anterior mediastinum

Thymoma is by far the most common tumour of the anterior mediastinum (9). Open extended thymectomy via sternotomy remains the gold standard, particularly for advanced-stage tumours. There is however significant evidence now available for the use of minimally invasive approaches for early-stage thymomas (15). Teratoma, lymphoma and thyroid or other endocrine masses are less common differential diagnoses of anterior mediastinal masses (5,16). Growth of lymphoma or lymphadenopathy may occur in all three compartments of the mediastinum (17) (*Figure 1A*).

Posterior mediastinum

Neurogenic tumours (mainly benign peripheral nerve sheath neoplasms like schwannoma and neurofibroma) most commonly occur in the posterior mediastinum (17) (*Figure 1B*).

Middle mediastinum

Lymphoma and mediastinal cysts (predominantly bronchogenic and enteric as well as pericardial cysts) are the most common tumours of the middle mediastinum (17) (*Figure 1C,1D*).

Mediastinitis

Mediastinitis is a life-threatening condition mainly secondary to oropharyngeal abscesses, neck infections or oesophageal leak either descending into the mediastinum via the cervical fascial planes or directly penetrating the intrathoracic mediastinum with a mortality of up to 40%. Early diagnosis and optimal immediate therapeutic approach, often including surgical drainage of the mediastinum, are crucial for patient survival (18).

Traumatic mediastinal injuries

Traumatic mediastinal injuries must be divided into blunt

and penetrating injuries according to their injury mechanism. Blunt thoracic trauma occurs in up to 60% of polytraumatized patients and results in about 25% mortality (19). Due to the suspected high mortality caused by injury of major mediastinal structures in blunt thoracic trauma in the preclinical setting as well, the exact incidence of mediastinal injuries remains uncertain (20,21).

Indications for mediastinal surgery

Indications for mediastinal surgery include (I) tissue sampling and staging, (II) surgical drainage of mediastinal infection/abscess (mediastinitis), (III) resection of mediastinal pathologies for diagnostic and therapeutic reasons, especially when they are symptomatic, and traumatic mediastinal injuries (20,22).

Sampling and staging

Surgical access to the mediastinum may be necessary for tissue sampling or mediastinal staging. Open and/or video-assisted surgical access is available. Mediastinoscopy, one of the most common approaches is often indicated in mediastinal LN staging in non-small cell lung cancer (NSCLC) patients.

Surgical resection

Several surgical approaches to the mediastinum with a tendency towards minimally invasive techniques, currently favouring robotic-assisted techniques, have been described before (23). Minimally invasive approach for surgical resection of mediastinal masses, for example the well-studied minimally-invasive thymectomy is associated with improved surgical results and fewer complications compared to transsternal open thymectomy, without any substantial changes in myasthenia gravis (MG) complete rates of remission (8).

Surgical drainage of mediastinal infection/mediastinitis

Necrotizing mediastinitis has high mortality rates of around 25% to 40% and mainly arises from head-and-neck abscesses (descending necrotizing mediastinitis) or develops after oesophageal perforation (iatrogenic, spontaneous) (24,25). Aggressive surgical drainage and debridement of the mediastinum as well as of accompanying pleural effusion and empyema in combination with broad-spectrum or targeted antibiotic treatment and elimination of the primary source has shown to drastically reduce mortality (26). Both open and minimally invasive approaches of all kinds have been described (26-29). As published series are rather small and surgical accesses are very heterogenous, there are no clear guidelines as to which access can be considered superior but there is still a tendency to open approach due to the aggressivity and fatality of the disease (30).

Traumatic mediastinal injuries

Due to suspected high mortality of traumatic injuries of major structures of the mediastinum in blunt thoracic trauma, the exact incidence of mediastinal injuries remains uncertain (20,21). Mortality rates after resuscitation thoracotomy for penetrating trauma are reported from 15% to 35%, while those with blunt thoracic trauma only yielded in successful resuscitation in about 2% (31,32).

A left anterolateral thoracotomy is recommended in hemodynamically instable patients with blunt chest trauma aiming to control avoidable causes of death (haemothorax, pneumothorax, hemopericardium) and providing access to mediastinal structures (33,34). To gain access to the contralateral hemithorax if necessary, a right-sided thoracotomy and/or extension to a clamshell incision may follow (34,35).

In hemodynamically stable individuals with suspicion of cardiac injury, median sternotomy is the most suitable approach to expose the heart and thoracic cavity bilaterally (36). VATS may provide diagnostic and therapeutic value in hemodynamically stable patients with localized, penetrating thoracic trauma (21,37).

Surgical access to the mediastinum

The various surgical accesses to the mediastinum can be divided into open and minimally invasive approaches and further categorized in accordance with the respective targeted compartment of the mediastinum, the size of the targeted mass and the relation to adjacent structures. As surgery of mediastinal pathologies can be very challenging, open surgical techniques may be combined with minimally invasive ones to improve the effectiveness and outcome. To help understand the various access modalities, we have either added an illustration taken in our institution or for less commonly applied techniques have highlighted significant illustrated reference.

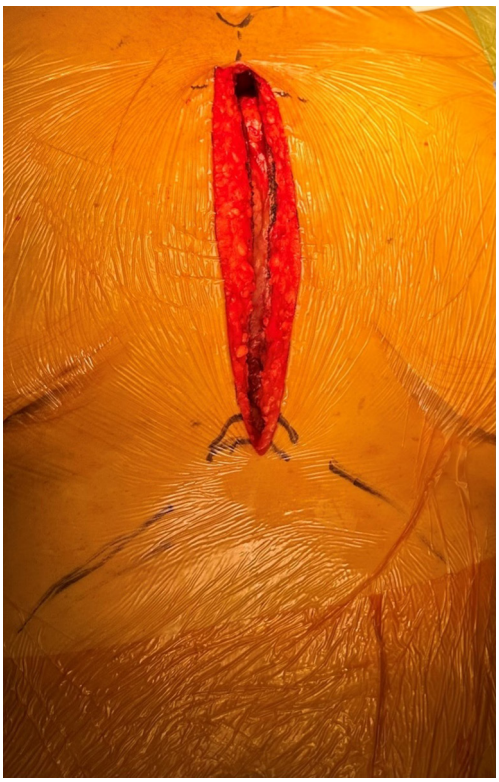

Figure 2 Median sternotomy incision in a 57-year-old female. The sternal notch and xiphoid process as well as the ventral rib cage are inked to the skin foil as landmarks.

Open accesses

Median sternotomy

Median sternotomy is the most common access for cardiac bypass surgery and remains a very common open thoracic approach for mediastinal, bilateral pulmonary or lower trachea and main stem bronchus surgery (38). The sternotomy technique is well established, and the technical details were presented many times before (*Figure 2*). Crucial steps are the strict sternal midline preparation and performing the osteotomy during apnoea in order to avoid injuries of the underlying structures like pericardium, pleura, innominate vein and brachiocephalic artery. A proper sternal closure to prevent instability and infection is as important as performing a proper sternotomy to reduce morbidity (39). Because of its midline location, the postoperative pain associated with sternotomy is less than for intercostal incisions like performed in thoracotomy.

Partial upper sternotomy

Partial sternotomy is an appropriate approach for thyroid surgery with reachable retrosternal extension and for limited additional access to the anterosuperior mediastinum (40,41). However, a full median sternotomy as described above should be performed in cases of proven or expected malignancy, extension into the posterior mediastinum and extension to the aortic arch. For the partial upper sternotomy, a 10–12 cm mid-sternal incision is followed by a division of the sternum in a J-form manner from the sternal notch to the right 4th intercostal space. A spreader is inserted to grant access. A valuable illustration of a partial upper sternotomy (in aortic valve surgery) can be found in the publication of Gillinov *et al.* (42). As for full median sternotomy, cautious closure of the partial sternotomy is crucial to avoid long-term morbidity. In addition to a cosmetic benefit, the incidence of sternal wound infection can be reduced by helping maintain part of the sternum, hence keeping the rigidity of the chest wall.

Trapdoor incision (anterior cervico-sterno-thoracotomy)

The trapdoor incision gives access to the superior mediastinum and thoracic inlet. A partial J-type sternotomy in the 2nd or 3rd intercostal space is combined with the supraclavicular extension of a standard sternotomy. The major necessary addition to complete the trapdoor incision is the extension of the inferior lateral arm of the incision through the pectoralis major muscle. The internal mammary vessels need to be ligated when entering the chest. A rib-spreading retractor is elevating the "trapdoor". Large anterior mediastinal masses, such as thymomas and germ cell tumours can be accessed through the trapdoor, hence this approach is often used in paediatrics (43,44). Christison-Lagay *et al.* showed a clear illustration of the trapdoor-incision and the respective surrounding anatomical structures in their work from 2014 (43).

(Hemi-) Clamshell

The Hemi-clamshell incision is defined as a partial sternotomy with antero-lateral thoracotomy. As compared to the afore-mentioned, seldom used trapdoor incision, it provides additional exposure of the mediastinum in its middle and lower compartments. The transverse intercostal incision connecting to the sternal incision is positioned in the 4th or 5th intercostal space. Postoperative analgetic requirements have shown to be similar to those after different approaches (45). The patient is positioned supine. An L-shaped skin incision is done, followed by entering the chest through the intercostal space after ligating the internal mammary pedicle. Afterwards, median sternal

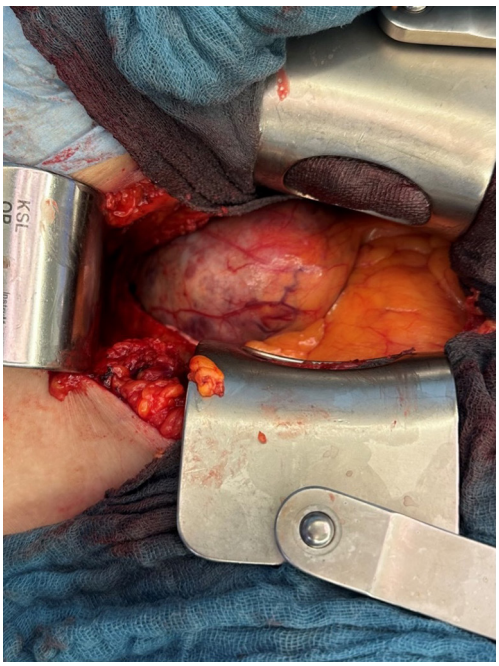

Figure 3 Right antero-lateral thoracotomy in a 60-year-old female with visible biopsy proven large type B1 thymoma surrounded by pericardial fatty tissue in the anterior mediastinum.

incision followed by the J-formed incision of the respective half of the sternum is done. Sternal wires and pericostal non-resorbable sutures serve for closure. Bains *et al.* nicely demonstrate sketches of both the hemi-clamshell and clamshell incision as well as the exposure of relevant structures with these two approaches in their publication from 1994 (46).

Thoracotomy (postero-lateral, antero-lateral)

Postero-lateral

The postero-lateral thoracotomy is one of the most used incisions in thoracic surgery providing access to the lung, hilum, middle and posterior mediastinum, endothoracic trachea and oesophagus. The patient is positioned in lateral decubitus position. The skin incision runs along the fifth or sixth intercostal space starting from the anterior axillary line (AAL) with a slight curve around the tip of the scapula. The M. latissimus dorsi is opened with electrocautery. the anterior portion of the M. trapezius and rhomboid muscles can be divided posteriorly. The M. serratus anterior muscle is usually spared and retracted. To identify the appropriate intercostal space, the hand is passed towards the first rib by developing a plane beneath the scapula. To make access to the chest cavity easier, a rib resection or partial rib resection can be done according to the surgeon's preference followed by the opening of the endothoracic fascia and parietal pleura along the upper border of the rib to avoid injury of the neurovascular bundle. A retractor is then placed and opened gently to avoid rib fractures. For closure of the intercostal spaces after the procedure, a loop or interrupted stitches can be applied. Standard wound closure of all layers is performed (47). Muscle-sparing postero-lateral thoracotomy has been described as well, but has not prevailed (48).

Antero-lateral

The antero-lateral thoracotomy provides good access to the anterior mediastinum (*Figure 3*). The skin incision runs from the 4th or 5th intercostal space from parasternal until the AAL. It can be easily extended to become a Hemi-Clamshell incision. The pectoral muscle in direction of the fibres followed by division of the intercostal muscles and parietal pleura to enter the chest (49,50).

Anterior mediastinotomy

Anterior mediastinotomy, also known as Chamberlain- or McNeill-procedure, is an open procedure done under general anesthesia that allows for dissection of the aortopulmonary LNs (51,52). This technique is very effective in biopsying the anterior mediastinal, the periaortic, the aortopulmonary LNs, or the lung. The chest is entered via a restrictive incision in the 2nd parasternal intercostal space on the left. The Chamberlain-procedure has mainly been abandoned nowadays but has its main indication in aorto-pulmonary (AP)-window (paraaortic/subaortic LN station 5/6) involvement in NSCLC, unreachable in mediastinoscopy and EBUS-TBNA (53). Ginsberg showed a recommendable sketch of the access in their publication of mediastinal accesses from 1987 (54).

Mediastinoscopy

Mediastinoscopy through a 2–3 cm transverse cervical incision (Kocher-incision) provides access to the pre-tracheal, paratracheal, and anterior sub-carinal LNs (55-57). One has to differentiate between video-assisted (VAM) and conventional mediastinoscopy (CM) without video-support (58). The VAM is considered the standard as compared to CM nowadays. After the Kocher-incision, the video-mediastinoscope is inserted (with closed spatula) after opening of the pretracheal fascia, identification of the anatomical landmarks (bifurcation, both main bronchi and the left recurrent nerve) is necessary to avoid injuries.

Mediastinal dissection continues with spatulas open. LN-stations 2, 3, 4, 7, 10 and 11 can be accessed bilaterally. Of note, mediastinoscopy has a high sensitivity (>80%) and specificity (100%) in the staging of lung cancer (55). One rare but potentially fatal complication of mediastinoscopy is bleeding from one of the great vessels in close proximity to the operating field. However, even when Eric Carlens published his experience on his first 100 cases back in 1959, no bleeding complication occurred (59). As of today, the rate of complications and mortality remains minimal (56,60).

Extended cervical mediastinoscopy

This extended cervical mediastinoscopy approach published and apparently to our knowledge best visualized by Ginsberg in 1987 helps to reach the subaortic and preaortic station 5 and 6 LNs through a conventional Kocher-incision in addition to the aforementioned investigated pre-tracheal, paratracheal, and anterior sub-carinal LNs. The video-mediastinoscope is advanced over the aortic arch between the innominate artery and the left common carotid artery. In case of failure of this approach in staging of left upper lobe tumours, an additional anterior mediastinotomy through a second incision can follow to complete staging (54). Ginsberg concluded in their original work, that "In expert hands, invasive mediastinal exploration has very low morbidity and mortality". Nevertheless, we advocate for critically evaluating any other less invasive modality to reduce potentially fatal injury of neighbouring arteries along the way of this access.

Video-assisted, mediastinoscopic lymphadenectomy (VAMLA)

VAMLA has shown to be safe and represents one of the two best staging methods in terms of accuracy in mediastinal staging of NSCLC. Like TEMLA, it can serve as preresectional lymphadenectomy prior to VATS (61,62). After starting VAMLA like a mediastinoscopy described above, the subcarinal nodes are extracted *en bloc*. In this way, the oesophagus and the mediastinal pleura can be exposed and right para-oesophageal nodes as well as hilar N1-nodes can be carefully harvested. *En bloc* resection of the pre-tracheal, right paratracheal and right tracheobronchial compartments is done afterwards.

TEMLA

TEMLA, developed by Zieliński *et al.*, is performed through a 5–8-cm transverse cervical incision in the neck and enables the complete removal of all mediastinal nodal stations except for station 9 and station 4L nodes (63). TEMLA is an open procedure performed partly with mediastinoscopy-assisted and video-assisted techniques and includes elevation of the sternal manubrium with a retractor as well as bilateral visualization of the laryngeal recurrent and vagus nerves. It can serve as a preresectional lymphadenectomy in VATS cases like the before described VAMLA.

Minimally invasive video-assisted techniques

VATS

VATS is a suitable access for both mediastinal staging and resection of mediastinal masses mainly in the middle and posterior, as well as accessible lesions in the anterior mediastinum. Right VATS provides access to LN stations 10R, 4R, 7, 8R and 9R. On the left side, LN station 10L, 4L, 5, 6, 7, 8L and 9L can be reached. Station 4L cannot be explored in right VATS due to its difficult access. VATS can be performed uniportally or with a multi-port-approach, while the single port technique is increasing worldwide. Double lumen endobronchial tube insertion for selective ventilation is done before placing the patient in a lateral decubitus position or slightly one side lifted supine position, is recommended. In addition to selective ventilation, CO_2 gas insufflation for further collapsing the lung can be applied in selected patients. A 0° or 30° video-telescopic camera via a two-to-three port access plus a potential subxyphoideal access for better visualization and retrieval of the specimen have shown to be successfully used in thoracic surgery practice.

Subxiphoid

For a uniportal subxiphoid approach, the patients can be positioned supine or in slightly half sided 45° lifted supine position. A 2–3 cm transverse or vertical skin incision is made 1–2 cm below the xiphoid. A vacuum multi-port system with the possibility of CO_2 insufflation with two to three ports is inserted. In a multiport approach, a second or third intercostal 5 mm incision can be added (64).

RATS

Since the first RATS thymectomy reported by Yoshino *et al.* in 2001, RATS has shown to have clear benefits in technically demanding anatomical regions like the mediastinum whilst in addition showing better outcomes in postoperative quality of life (QoL), pain, length of stay (LOS) with equal results regarding MG compared to open approach (65,66). RATS can be performed through

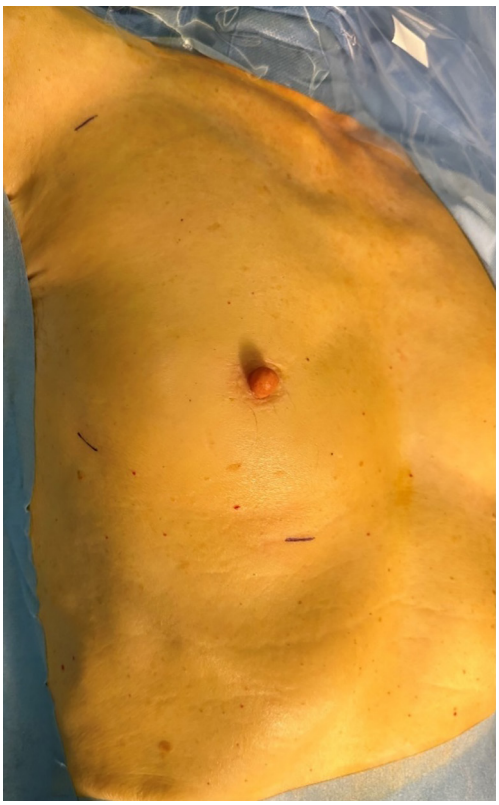

Figure 4 Three-port right sided RATS access for thymectomy in a 57-year-old female patient with thymoma. RATS, robotic-assisted thoracic surgery.

three port incisions (thoracoscope, two robotic arms) under CO_2 insufflation, double lumen intubation and intercostal blockades (*Figure 4*). The phrenic nerves can be visualized on both sides and spared. Being provided with a robotic surgery console,-technical benefits like an increased range of motion in a stable operation field with excellent camera stability and improved 3D-visualization, a superior mediastinal dissection can be achieved (67). Advanced thoracic surgeons in this rapidly evolving robotic field like Diego Gonzalez-Rivas have started doing RATS thymectomies through a 4 cm uniportal subxiphoideal longitudinal incision (with the cartilaginous xiphoid process excised), initially on cadavers in 2018 followed by Park *et al.* in the clinical setting (performed in 2018/2019) and published in 2020 (68,69). A single, 2.5 cm cannula accessible for an articulating 3D camera and three fully articulating instruments with seven degrees of freedom were used (70). A hybrid subxiphoid VATS/RATS approach (3-ports in total) described as trans-subxiphoid robotic thymectomy was found equally minimal-invasive as single-port VATS thymectomy by Suda *et al.* in 2016 (71).

Combination of minimally invasive and open access

VATS-assisted anterior mediastinotomy

VATS-supported anterior mediastinotomy has shown to be another upcoming technique for removal of anterior mediastinal masses (72). Under general anaesthesia, a single port is inserted in the AAL in the 5th intercostal space, and a 0°–30°-degree thoracoscope is introduced into the chest. A parasternal 2–3 cm transverse incision is made over the second or third intercostal space under thoracoscopic guidance. The surgeon may benefit from dual visual control through a spreader directly and indirectly from below using the thoracoscope (73,74). A clear self-made illustration of this technique is available in the publication of Hunt *et al.* (73).

Transcervical VATS procedure

A transcervical approach with a silicon rubber cup to apply pneumomediastinum and the insertion of multiple ports for thoracoscopic instruments was used in the series of Tsuboi *et al.* in 2018 for resecting a parathyroid adenoma in the superior mediastinum (75). This access can rather be considered experimental than being an established access and is best illustrated in the original publication mentioned above.

Discussion

Fortunately, an already comfortably wide range of surgical approaches to the mediastinum, which is still further developing and evolving, is available at our disposal. While there are well established guidelines for common pathologies (e.g., median sternotomy as the gold standard in malign/suspected malignant tumours, thymomas of certain size and tumours invading surrounding anterior mediastinal structures), it requires certain experience to choose the most appropriate mediastinal access for more complex cases, to successfully achieve the desired outcome. The choice of access primarily depends on the indication, which may either be sampling/biopsy or surgical resection as well as the localization and extent of the anomaly.

In our opinion, patient selection criteria tend to take a back seat in connection with mediastinal pathologies, apart from exceptions such as geriatric patients, who should preferably be treated as minimally invasive as possible where indication allows, to minimize morbidity and

mortality. To mention in addition, obesity has shown to be a contraindication for subxiphoid accesses due to difficult subcutaneous tunnel creation and instrument angulation (69). Selection criteria such as (I) sepsis, hemodynamics, and onset of infection in mediastinitis, (II) trauma mechanism (blunt *vs.* penetrating) and hemodynamics in thoracic trauma or (III) the expertise of the surgical team should be prioritized and outweigh patient selection criteria by far. Oncological indications should be mandatorily discussed in a multidisciplinary team (MDT) meeting prior to surgical intervention.

The aim of our publication was to describe all the available surgical accesses and emphasize their indications as well as their practical implementation to inform about current clinical practice in this rapidly evolving field trending towards minimally invasive approaches and ultimately help to guide decision-making in finding the most appropriate access to mediastinal abnormalities. In general, we ought to take into consideration, that the best compromise between the least invasive method and maximal benefit should guide our decision on which access to choose. However, as certain minimally invasive methods are not suitable for being extended, e.g., in the event of bleeding in subxiphoid or mediastinoscopy approach, the surgeon should always have an alternative emergency access in mind and drape the patient accordingly in theatres (69,76).

In terms of sampling and staging procedures, one should appreciate that interventional access like EBUS- and EUS-TBNA have become a valuable alternative to video-mediastinoscopy for diagnosing and staging the mediastinum (77). However, in times of immunohistochemistry, thorough molecular analysis requires more tissue than often provided by the aforementioned, especially in suspected lymphatic disease. In these cases, surgical biopsy is of high importance to achieve tissue diagnosis. In the special field of mediastinal staging in NSCLC, the combination of EBUS-TBNA and mediastinoscopy has proven to be more accurate in mediastinal staging than just one option alone and video-mediastinoscopy shall not be omitted in persistent clinical suspicion of mediastinal metastatic spread. For sampling reasons, mediastinoscopy represents a recommendable option for anterior mediastinal masses, while VATS has been suitable for middle and posterior mediastinal biopsies with beneficial perioperative outcomes (78).

If surgical R0-resection of a mediastinal mass is required, nowadays, most pathologies allow minimally invasive approach (VATS/RATS). The personal surgeon's preference and availability of equipment play a major role in decision-making. The minimally invasive accesses to the mediastinum have shown to lead to less blood loss, post-operative pain and reduced need for analgesia, allow quicker recovery, shorter LOS in hospital and intensive care unit, and lower perioperative morbidity (9,79). Equivalence in oncologic outcome as compared to open approach (e.g., in terms of minimally invasive thymectomy) has recently been published (80). Comparing outcomes between RATS and VATS, Haruki *et al.* could retrospectively show in 2021 that more LNs could be dissected with RATS compared to VATS, especially in bilateral hilar and superior mediastinal regions in lymphadenectomy in NSCLC surgery (81). RATS was described to provide better visualization, manoeuvrability, deep perception and lower risk of bleeding complications, yet being technically superior to VATS and safe (82-84). However, some known disadvantages of RATS are the lack of tactile feedback for the surgeon as well as the acquisition and maintenance cost (84).

A major limitation of minimally invasive accesses for resection of mediastinal masses is the technical restriction when invasion of relevant surrounding anatomic structures by large tumours is present. To avoid incomplete resection, open access remains the recommended approach. Removal of even average size mediastinal lesions through small keyhole access may be challenging too. Overcoming this challenge, either an additional incision (like a minimal cervicotomy or an inframammary incision) or the extension of one of the existing incisions were proposed (82,84). Median sternotomy remains the gold standard in malign as well as suspected malignant tumours as well as thymomas of certain size and tumours invading surrounding structures in the anterior mediastinum, while antero-lateral thoracotomy is superior for resection of lesions in the middle and posterior mediastinum (85,86). Again, there is no standard open access carved in stone for any known mediastinal pathology and anatomical relations of the lesion and related important structures and their best visualization should be taken into consideration. Benign mediastinal tumours, however, can primarily be approached via VATS or RATS access (78). Tumours in the middle compartment of the mediastinum or tumours of exceptional great extend benefit from exposure via hemi-clamshell approach. When compared to minimally invasive techniques, open accesses are associated with more postoperative pain, higher morbidity and longer LOS with slower return to active life (78,87). Partial and full median sternotomy, however, showed less postoperative pain and quicker recovery than thoracotomy.

Concerning mediastinitis, overall patient perioperative outcome mainly depends on rapid diagnosis and immediate targeted treatment as well as on the underlying pathology. Nevertheless, the outcome associated with the respective surgical modality should as well be taken into consideration. In lack of consensus regarding modality-comparing studies, individual experience and knowledge about approach-associated outcomes shall guide decision-making (28). VATS has been leading to lower morbidity (29), however, the risk of undertreatment, resulting in poor outcomes, should prevent us from choosing minimal-invasive access in mediastinitis, especially as the morbidity caused by thoracotomy is usually minimal. Minimally invasive techniques should certainly be avoided in advanced stages of the disease and unstable/septic patients.

Critically reviewing rarely applied open accesses (e.g., parasternal/anterior mediastinotomy or the Chamberlain-procedure), which have basically vanished from everyday surgical practice being replaced by VATS/RATS, we must reflect on whether these accesses shall still be considered mandatory in surgical training logbooks. As already done by some colleagues in case series, it might be worth combining a minimally invasive approach with an open approach to improve accessibility, the field of vision and the removability of the resected lesion (73,75).

There is a noticeable trend to reduce invasiveness of mediastinal approaches even further to e.g., subcostal or subxiphoid uniportal VATS/RATS (68,70,88,89) almost certainly being followed by a race for more appealing economics, reduction in operating time and postoperative pain, increase in non-intubated cases with shorter LOS and ultimately, at least in terms of elective surgery, a potential complete displacement of open accesses (90). For now, further economic analysis comparing VATS/RATS is still wanted e.g., as claimed by O'sullivan *et al.* in 2019. Non-debatable, however, is that minimally invasive accesses are clearly superior in blood loss, LOS and postoperative pain (14,91). Even more crucial is a thorough decision-making in selecting the most appropriate approach to the mediastinum.

Limitations

Our review has certain limitations. To start with, even though our aim was to give a detailed overview on accesses to the mediastinum, the accesses are described in detail but not displayed in step-by-step graphics with the intention not to turn this review in a book chapter. As some of the described accesses are rather rare and not applied regularly (e.g., the Chamberlain or the Ginsberg procedure), imagination of these approaches without precise visualization for the unexperienced (thoracic) surgeon may be difficult. Furthermore, our review fails to provide structured indication guidelines for certain accesses as per lack of significant evidence due to only rare cases being published or due to more recent advantages in accesses which need further prospective trials to prove superiority to established accesses (e.g., in comparing RATS and VATS for early-stage thymoma) (14).

Conclusions

The complex mediastinal anatomy and the variety of mediastinal pathologies require different surgical approaches to the respective mediastinal compartment. While there is a wide selection of surgical accesses and certain guidelines available, often, individual choice of access depends on surgical expertise and available equipment.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Patients' consents were obtained for publication of the images and saved in their electronic charts.

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Review Article

Relevance of robotic surgery for thymoma: a narrative review

Masahiro Miyajima, Atsushi Watanabe

Department of Thoracic Surgery, Sapporo Medical University, Sapporo, Japan

Contributions: (I) Conception and design: Both authors; (II) Administrative support: A Watanabe; (III) Provision of study materials or patients: M Miyajima; (IV) Collection and assembly of data: M Miyajima; (V) Data analysis and interpretation: M Miyajima; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Atsushi Watanabe, MD, PhD. Department of Thoracic Surgery, Sapporo Medical University, Chuo-Ku S1 W16, Sapporo 060-8543, Japan. Email: atsushiw@sapmed.ac.jp.

Background and Objective: Thymectomy with median sternotomy is the gold standard for thymoma and myasthenia gravis, although minimally invasive procedures such as robot-assisted surgery have recently become more common. However, the superiority of these approaches has not been established, and they are infrequently recommended for localized lesions. The International Thymic Malignancies Interest Group warned that despite the perceived reduction in length of hospital stay and pain, the benefits of these approaches compared to the open approach have not been fully substantiated and that prospective collaborative data collection is critical in defining the value of these techniques. Whether thymectomy is necessary for stage I thymomas in the absence of myasthenia gravis or anti-acetylcholine receptor antibodies is also unclear. This study reviews and discusses the literature on this subject.

Methods: A narrative review was conducted using PubMed and Scopus databases. Original research articles comparing robotic to video-assisted thoracic surgery or to open thymectomy for thymomas were included. A comparison of partial resection and total thymectomy (thymothymectomy) for thymomas was also conducted.

Key Content and Findings: Perioperative outcomes such as blood loss, operative duration, complications, and length of hospital stay were better for robot-assisted resection of early-stage thymomas than for open thymoma surgery. It would be premature to consider partial resection as an appropriate treatment option for thymomas.

Conclusions: Robotic thymothymectomy is safe with effective and promising long-term results and oncological and surgical outcomes in patients with thymoma. Robotic thymectomy can become the standard procedure in patients with early-stage thymomas.

Keywords: Robotic surgery; thymoma; da Vinci; thymectomy

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Introduction

Background

Thymomas are rare neoplasms that exhibit a wide range of behaviors, from indolent to fatal (1). However, several unanswered questions require further research. Thymectomy is the standard procedure for thymoma treatment and an important component of multidisciplinary treatment for myasthenia gravis. Although there are several approaches to thymectomy, including minimally invasive approaches, median sternotomy remains the golden standard (2). However, in recent years, treatment methods have changed significantly with the widespread use of minimally invasive approaches. The advent of robot-assisted surgery has led to several innovations. Since Yoshino *et al.* first performed robotic surgery for thymoma in 2001, various approaches to robotic surgery have been developed (3). Although the use of video-assisted thoracic surgery (VATS) or robot-assisted

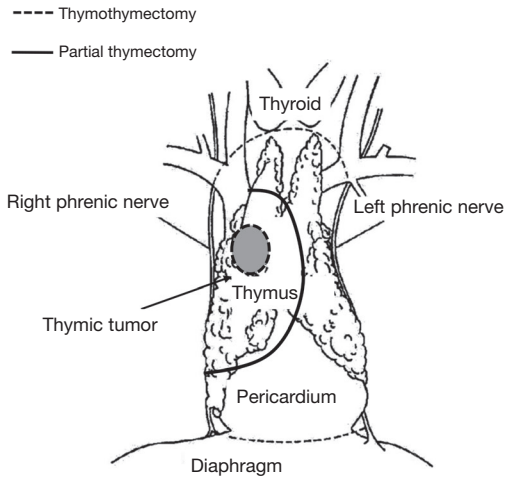

Figure 1 Extent of resection. Partial thymectomy removes a portion of the thymus gland with a margin from the tumor (solid line); thymothymectomy removes the same area as a total thymectomy (dotted line).

thoracic surgery (RATS) has increased in recent years, its superiority over conventional open thoracic surgery has not been established, and it is infrequently recommended as an approach for localized lesions (4-6). It is unclear whether thymectomy is necessary for stage I thymomas without symptoms of myasthenia gravis or the presence of anti-acetylcholine receptor antibodies. Although the extent of resection is not of considerable concern with sternotomy, the difficulty of complete dissection has led to a debate that should be resolved as minimally invasive approaches become more popular: whether thymectomy is necessary for localized thymomas or localized resection is sufficient (*Figure 1*). No coherent reports on this subject have been reported and no definite conclusions have been drawn. Therefore, we review and discuss the literature on this subject.

The curative treatment for thymic epithelial tumors is surgical resection. If thymic epithelial tumors are suspected on imaging and complete resection is possible, surgical treatment is performed without pathological biopsy. The principal surgical technique is thymectomy through median sternotomy. In particular, patients with myasthenia gravis are indicated for extended thymectomy, wherein the fatty tissue below the thyroid gland in the anterior cervical region is resected.

Rationale and knowledge gap

The thoracoscopic approach to stage I–II thymomas is an acceptable technique according to the Japanese guidelines, though the level of evidence is low (4-8). The Japanese guidelines have provided the same level of recommendation as for thoracoscopic surgery. However, minimally invasive surgery is not routinely recommended in the National Comprehensive Cancer Network guidelines because of the lack of long-term results and evidence (9-13).

Objective

The use of robotic surgery for thymomas has increased in recent years. We outline the protocol for robotic surgery for thymoma, and review the literature to clarify the suitability of the robotic surgical approach and the extent of resection that should be performed. In addition, we also consider whether thymectomy is necessary or partial resection is sufficient in cases of localized thymoma. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-37/rc).

Methods

Literature search strategy

Thymectomy-specific publication searches were conducted using PubMed and Scopus databases to find relevant publications for this clinical evaluation (*Table 1*). Publication searches were conducted as listed: (robot[All Fields] OR robot assist[All Fields] OR robotic[All Fields] OR da vinci[All Fields] AND "surgery"[all fields] AND "thymoma"[all fields]).

All citations returned from the above searches were exported into an EndNote library. Duplications were removed and titles and abstracts were reviewed by two authors (M.M., A.W.) for inclusion in the library.

Review

Surgery

For reference, we outline the protocol of thymoma surgery used in our department. Since 2018, we have been performing robotic surgery for thymomas using the da Vinci Xi Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA) in our department (14). The patient's position is shown in *Figure 2*. The robotic 8 mm port was placed between the second and eighth intercostal spaces, according to the patient's physique. Four robotic arms were placed

Table 1 The search strategy summary

Items	Specification
Date of search	January 1st, 2023 and August 31st, 2023
Databases and other sources searched	PubMed, Scopus
Search terms used	MeSH: (robot[All Fields] OR robot assist[All Fields] OR robotic[All Fields] OR da vinci[All Fields] AND "surgery"[all fields] AND "thymoma"[all fields])
Timeframe	From January 2010 to August 2023
Inclusion criteria and exclusion criteria	Inclusion: original articles, review. Exclusion: case report, abstract of meeting
Selection process	M.M. and A.W. conducted the selection. Consensus of all authors was obtained

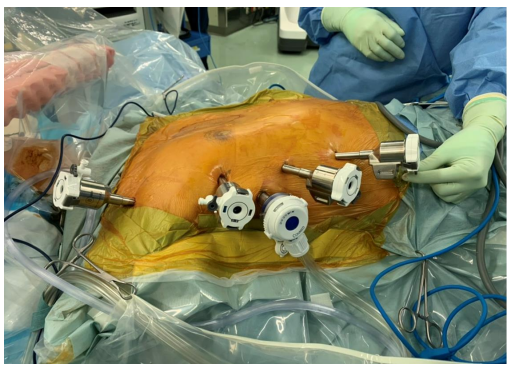

Figure 2 Port placements. Robotic 8-mm ports were placed in the second, fourth, sixth and seventh intercostal space. Then, an assistant port with a 12-mm air seal port placed in the sixth intercostal space.

(*Figure 2*). Fenestrated bipolar forceps, an 8-mm endoscope, Maryland-type bipolar forceps, and Vessel Sealer Extend (Intuitive Surgical Inc.) were used. The port placed at the sixth intercostal space was used as an assistant port with a 12-mm air-seal port (Medical Leaders Inc., Tokyo, Japan). The intraoperative thoracic carbon dioxide insufflation pressure was set at 8–10 mmHg. The thymus with the thymoma was removed through a 30 mm or larger assistant port or extended port incision. In our department, we performed median sternotomy for tumors larger than 5 cm. However, as we became more proficient with this technique, we expanded its use to include larger tumors.

Comparison of RATS, VATS, and open surgery

Historically, prudence has been required while using minimally invasive approaches to thymic tumors because of the risk of damaging the tumor capsule, which may increase the risk of local recurrence (13,15,16). With the application of minimally invasive surgeries for thymomas, the International Thymic Malignancies Interest Group (ITMIG) proposed several standard policies in 2011. "To ensure an adequate margin of safety, thymomas should be resected with the surrounding normal thymus and fat". Intact thymic tissue and perithymic fat should be used for tumor grasping and traction in a "no touch" technique that avoids the risk of capsular rupture (17). It should be noted that capsular rupture makes analysis by the pathologist difficult, so to avoid the risk of rupture, the utility incision must be adapted so that the capsule does not rupture in the extraction bag when the specimen is removed. ITMIG warned that despite the perceived reduction in length of hospital stay and pain, the benefits of these approaches in comparison to those of the open approach have not been fully substantiated, and that prospective collaborative data collection is critical in defining the value of these techniques.

Recently, the number of reports on robot-assisted surgery has increased. Perioperative outcomes with robot-assisted surgery are better than with open or thoracoscopic approaches while comparable outcomes to those with thoracoscopic approaches have been reported (16,18-24) (*Tables 2,3*). Regarding long-term prognosis, the 5-year overall survival did not differ significantly between thoracoscopic and open approaches, although both groups included stage III or higher cases (21,22). Only Yang *et al.* found the 5-year overall survival difference in minimally invasive cardiothoracic surgery (MICS) *vs.* open (90.7 *vs.* 86.9 months, P=0.04), but this difference was lost after propensity score matching (PSM) (89.4 *vs.* 81.6 months, P=0.2) (22). However, long-term outcomes beyond 10 years remain unclear. Furthermore, open thoracotomy has been compared with thoracoscopic surgery, including robot-

Table 2 Study characteristics of thymothymectomy according to robotic, thoracoscopic and open approaches

Author	Study year	Study design	Duration	Study arm	Sample size	Approach	Age (years)†	Thymoma stage	Follow-up interval†
Balduyck (20)	2011	PC	2004–2008	R	14	Rt or Lt multiport	49 [18–63]	A: 1, B1: 2, B2: 1, AB: 1	34 mo
				O	22	Median sternotomy	56 [23–84]	A: 1, B1: 2, B2: 5, B3: 1, AB: 3	50 mo
Burt (18)	2017	ITMIGDB	1997–2012	R	146	NA	56 [15–85]	MICS I: 199, II: 186, III: 27, IV: 12	NA
				VATS	315	NA	NA	NA	NA
				O	2,053	Sternotomy/ thoracotomy	54 [8–88]	I: 669, II: 654, III: 344, IV: 130	NA
Qian (19)	2017	RC	2009–2014	R	51	Rt or Lt, 3-port	49±13	I: 19, IIA: 21, IIB: 21	421±469 d
				VATS	35	Rt or Lt, 3-port	50±13	I: 10, IIA: 14, IIB: 11	701±382 d
				O	37	Median sternotomy	47±14	I: 10, IIA: 12, IIB: 15	818±592 d
Ye (16)	2013	RC	2009–2012	R	21	Rt or Lt, 3-port	53±8	I: 21	17 [6–48] mo
				VATS	25	Rt or Lt, 3-port	53±5	I: 25	25 [6–48] mo
Marulli (24)	2018	RCC-PSM	1982–2017	R	41	Rt or Lt, multiport	58±11	I: 8, II: 33	28 [18–61] mo
				O	41	Mediansternotomy	58±10	I: 9, II: 32	88 [62–116] mo
Yang (22)	2020	NCDB	2010–2014	R	176	NA	59.6±12.7	I-IIa: 203: Iib:77, III: 37	35.9 [24.9–52.2] mo
				VATS	141	NA	NA	NA	40.7 [27.3–56.8] mo
				O	906	Sternotomy/ thoracotomy	57.4±14.1	I-Iia: 432, Iib: 196, III: 278	NA
Yang (22) PSM	2020	NCDB-PSM	2010–2014	MICS	185	NA	61.6±10.4	I-Iia: 110, Iib: 49, III: 26	36.4 [25.8–55.4] mo
				O	185	Sternotomy/ thoracotomy	62.6±11.1	I-Iia: 116: Iib: 40, III: 29	35.9 [25.4–50.5] mo
Kamel (23)	2019	NCDB	2010–2014	R	300	NA	63 [54–72]	4.5 (range, 3.1–6.3) cm	NA
				VATS	280	NA	62 [53–70]	5.0 (range, 3.5–7.8) cm	NA
Kamel (23) PSM 1	2019	NCDB-PSM	2010–2014	R	197	NA	62	5.0 cm	NA
				VATS	197	Sternotomy/ thoracotomy	62	5.3 cm	NA
Kamel (23) PSM 2	2019	NCDB-PSM	2010–2014	R	272	NA	61	5.1 cm	NA
				O	272	NA	61	5.1 cm	NA

†, data are presented as mean ± standard deviation or mean [range]. Yang matched: age, sex, race, Charlson-Deyo comorbidity score, regional education levels, tumor size, insurance type, histology, stage, year of diagnosis, distance from facility, and facility type. Kamel matched: age, gender, Charlson comorbidity index, induction therapy, tumor size and tumor extension. PC, prospective study; R, robotic; O, open approach; Rt, right; Lt, left; mo, months; ITMIGDB, International Thymic Malignancy Interest Group Database; NA, not applicable (not reported); VATS, video-assisted thoracic surgery; MICS, minimally invasive cardiothoracic surgery; RC, retrospective cohort; d, days; PSM, propensity score matching; RCC-PSM, retrospective case control study using PSM; NCDB, National Cancer Database; NCDB-PSM, NCDB study using PSM.

assisted surgery, using PSM adjusted for confounding factors, but significant differences in short-term prognosis, long-term prognosis, or perioperative outcomes have not been reported, despite significant differences in length of hospital stay (18,21,23).

Perioperative outcomes such as blood loss, operative duration, respiratory complications, and postoperative length of hospital stay were better for thoracoscopy-assisted resection of stage I–II thymic epithelial tumors than for open thoracic surgery (4,5,9). However, there was no significant difference in the R0 resection rate, which was approximately 80% with both techniques (7,8).

Table 3 Outcomes of robotic thymectomy by other approaches

Author	Study arm	Sample size	Operative time (min)†	P value	Blood loss (mL)†	P value	In-hospital duration (days)†	P value	Conversion rate (%)	P value	5-year overall survival (%)	P value	Mortality (in-hospital or 30-day, %)	P value	R0 resection (%)	P value
Balduyck (20)	R	14	224.2±66.5	NS	NA	–	9.6±3.9	NS	7.1	–	NA	–	0	NS	NA	–
	O	22	243.8±55.5	–	NA	–	11.8±5.7	–	NA	–	NA	–	0	–	NA	–
Burt (18)	O	146	NA	–	NA	–	NA	–	0	–	NA	–	0	NS	92	0.2
	VATS	315	NA	–	NA	–	NA	–	NA	–	NA	–	0	–	86	–
		2,053	NA	–	NA	–	NA	–	NA	–	NA	–	–	–	NA	–
Qian (19)	O	51	71.2±39.8	–	77.5±69.5	–	4.3±1.1	<0.001	0	–	NA	–	0	NS	NA	–
	VATS	35	88.5±37.6	–	246±316.5	v	6.6±1.4	–	NA	–	NA	–	0	–	NA	–
		37	NA	–	NA	–	NA	–	NA	–	NA	–	–	–	NA	–
Ye (16)	R	21	97±38	–	61.3±21.9	<0.01	3.7±1.1	<0.01	0	–	NA	–	NA	–	NA	–
	O	25	214.5±35.4	–	466.1±91.4	–	11.6±10.4	–	NA	–	NA	–	NA	–	NA	–
Marulli (24)	R	41	132.5 [115–170]	<0.001	NA	–	3 [3–4]	<0.01	3.5	–	NA	–	0	NS	100	NS
	O	41	115 [90–137]	–	NA	–	6 [5–7]	–	NA	–	NA	–	0	–	100	–
Yang (22)	MICS	317	NA	–	NA	–	NA	–	NA	–	90.7	0.04	NA	–	NA	–
	O	906	NA	–	NA	–	NA	–	NA	–	86.9	–	NA	–	NA	–
Yang (22) PSM	MICS	185	NA	–	NA	–	3 [2–4]	<0.001	19	–	89.4	0.2	<10	NS	76.2	0.84
	O	185	NA	–	NA	–	4 [3–5]	–	NA	–	81.6	–	<10	–	69.7	–
Kamel (23) PSM 1	R	197	NA	–	NA	–	4±5	0.76	23	0.031	93	0.571	1	NS	50	0.47
	VATS	197	NA	–	NA	–	4±5	–	11	–	94	–	2	–	57	–
Kamel (23) PSM 2	R	272	NA	–	NA	–	4±8	0.057	NA	–	91	0.094	1	NS	32	0.13
	O	272	NA	–	NA	–	5±7	–	NA	–	80	–	2	–	47	–

†, data are presented as mean ± standard deviation or mean [range]. R, robotic; O, open approach; NS, not significant; NA, not applicable (not reported); VATS, video-assisted thoracic surgery; MICS, minimally invasive cardiothoracic surgery; PSM, propensity score matching.

Our previous study revealed that RATS offers the advantage of improved postoperative quality of life according to nursing care systems compared with VATS (14). We found no significant differences in pain between patients with either of the two techniques, at the first and second follow-up visits, although RATS involved the use of more ports and intercostal space access than VATS (14). Şehitogullari *et al.* reported no significant differences in postoperative pain between patients with RATS and VATS (25). Kamel *et al.* found the differences in conversion rates in VATS and RATS (23% *vs.* 11%, P=0.031) (23).

However, many other references report no or little difference. This may be due to differences in facility criteria for conversion.

In recent years, the RATS approach has been used in patients with large thymomas. However, data are scarce. In the existing literature, most investigators warn against the routine use of RATS for thymomas larger than 4 cm (26). How far can the surgeons push the limits of robot-assisted surgery?

Kneuertz *et al.* performed the single institution retrospective study to compare the safety and feasibility of RATS (n=20) and open approach (n=34) for thymoma larger than 4 cm using the PSM (27). They demonstrated that robotic assisted thymectomy is a safe and effective approach even for patients with large thymomas, which can be performed in similar radical fashion and with a high rate of complete resection compared with the traditional open procedure (complication rate: 15% *vs.* 24%, P=0.45; R0: 90% *vs.* 85%, P=0.62).

Bongiolatti *et al.* retrospectively reviewed 106 thymectomies from 2010 to 2020, creating two groups based on the surgical approach (open or RATS) and size (28). Kaplan-Meier and Cox regression were used to estimate and identify risk factors of oncological outcomes. To perform a well-balanced analysis, a PSM analysis was conducted for large thymomas. They performed 54 RATS thymectomies and 46.3% (n=24) were large thymomas (larger than 5 cm). All patients had a complete resection. The median and the overall survival rate for larger tumor were similar between RATS and open (109 *vs.* 67 months, 92% *vs.* 83%, P=0.95).

Extent of resection for thymoma surgery

Because of the need for complete resection and the high incidence of myasthenia gravis, thymoma treatment is usually total thymectomy or complete tumor resection. However, in recent years, improvements in minimally invasive thoracic surgery (video- or robot-assisted) have encouraged thoracic surgeons to treat smaller thymomas by performing partial resections rather than resecting the entire thymus gland and thymoma (29-33) (*Tables 4-6*).

In 2016, three articles based on a large national thymus database reported the results of a comparative analysis between partial thymectomy and thymothymectomy. Narm *et al.* used data from the Korean Association for Research on the Thymus Registry. They did not report a significant difference in the recurrence rate of thymoma (29). PSM analysis was performed on data pertaining to 141 patients selected from each group. The 5- and 10-year recurrence-free rates in the partial thymectomy group were 96.3% and 89.7%, respectively, whereas those in the thymothymectomy group were 97.0% and 85.0%, respectively (P=0.86).

In contrast, an analysis of The Japanese Association for Research on the Thymus (JART) database, a prospective study conducted by the Japanese Thymus Study Group (30), and the Chinese Alliance for Research in Thymoma reported a higher recurrence rate in the partial resection group (31). In the JART study, 276 pairs of patients with stage I (T1N0M0) thymomas were compared using PSM. The 5-year overall survival rate was 97.3% in the partial thymectomy group and 96.9% in the thymothymectomy group (P=0.487); hence, local recurrence in the partial thymectomy group was more frequent than in the thymothymectomy group (2.2% *vs.* 0.4%, P=0.0613). The Chinese Alliance for Research in Thymomas enrolled patients with stage I and II thymomas. They reported similar 10-year overall survival between the two groups (90.9% after thymothymectomy and 89.4% after partial thymectomy, P=0.732). Overall, the recurrence rates were 3.1% after thymothymectomy and 5.4% after partial thymectomy, with no significant difference between the two groups (P=0.149). However, this study had some limitations. In the case of partial thymectomy, the possibility of incomplete resection was high, particularly in patients with stage II disease (2.9% *vs.* 14.5%) (31).

In 2021, Guerrera *et al.* published a study comparing short- and long-term outcomes of partial thymectomy and thymothymectomy in patients with non-myasthenia gravis stage I thymoma using the European Society of Thoracic Surgeons Thymic Database. The 5-year overall survival (55% *vs.* 89%) and 5-year disease-free survival (79% *vs.* 96%) of patients who underwent partial thymectomies were worse than those of patients who underwent thymothymectomies (32). This result suggests that we cannot perform partial resection for thymoma with

Table 4 Study characteristics of partial thymectomy and thymothymectomy for thymoma

Author	Study year	Study design	Duration (year)	Study arm	Sample size, open	Age (years), mean ± SD	Diagnosis	Thymoma stage	Follow-up interval [range], mo
Narm (29)	2016	RC	2000–2013	Limited	295	49±13	Masaoka-Koga	I: 161, IIA: 70, IIB: 64	48 [0.3–189]
				Total	467	52±12	Masaoka-Koga	I: 241, IIA: 147, IIB: 79	50 [0.2–178]
Narm (29) PSM	2016	RCC-PSM	2000–2013	Limited	141	50±14	Masaoka-Koga	I: 80, IIA: 34, IIB: 27	48 [0.3–189]
				Total	141	50±12	Masaoka-Koga	I: 88, IIA: 28, IIB: 25	50 [0.2–178]
Nakagawa (30)	2016	RC	1991–2010	Limited	289	61.1±13.2	Masaoka	I: 174, II: 115	NA
				Total	997	57.0±13.2	Masaoka	I: 479, II: 518	NA
Nakagawa (30) PSM	2016	RCC-PSM	1991–2010	Limited	276	60.6±13.2	Masaoka	I: 161, II: 115	48
				Total	276	61.0±11.9	Masaoka	I: 158, II: 118	59
Gu (31)	2016	RC	1994–2012	Limited	251	52.3±11.9	Masaoka	I: 178, II: 73	38
				Total	796	50.9±12.2	Masaoka	I: 523, II: 273	38
Guerrera (32)	2021	RC	1994–2012	Limited	30	65.9±10.8	Masaoka	T1a: 26, T1b: 4	37 [17–72]
				Total	441	60.9±13.0	Masaoka	T1a: 388, T1b: 53	37 [17–72]
Guerrera (32) PSM	2021	RCC-PSM	1994–2012	Limited	30	65.9±10.8	Masaoka	T1a: 26, T1b: 4	37 [17–72]
				Total	90	65.0±11.3	Masaoka	T1a: 79, T1b: 11	NA
Yano (33)	2017	PC	2007–2011	Limited	36	61±12	Masaoka	I: 22, II: 14	63.1

Narm matched: age, sex, surgical approach, tumor size, WHO histology type, Masaoka-Koga stage, and adjuvant radiotherapy. Nakagawa matched: age, sex, tumor size, WHO histologic subtype, Masaoka stage, and adjuvant radiotherapy. Guerrera matched: age, gender, cardiac comorbidity, other comorbidities, thymoma size, surgical approach, WHO histology and pathological TNM. SD, standard deviation; mo, months; RC, retrospective cohort; PSM, propensity score matching; RCC-PSM, retrospective case control study using PSM; NA, not applicable (not reported); PC, prospective cohort; WHO, World Health Organization.

impunity. Future prospective randomized studies are needed to evaluate the extent of resection in early-stage thymoma surgery.

In 2017, Yano *et al.* evaluated the efficacy of partial or subtotal thymectomy for early-stage thymoma in the prospective study (33). Thirty-three out of 36 patients underwent partial resection of the thymus and all patients remained recurrence-free with the mean follow-up of 63 months. According to the authors, preserving the thymus could benefit the rest of one's life as an immunological supplement against future diseases. Some surgeons believe that thymomas behave docilely and complete resection is not required. Choe *et al.* performed a retrospective study of 72 patients who underwent resection of thymic epithelial tumors with *de novo* metastasis to the pleura or pericardium (34). Patients with negative or microscopically positive R0 or R1 resection margins were compared with those with grossly positive margins (R2). The overall survival was 11.8 *vs.* 5.5 years, respectively. In the present study, incomplete resection was identified as a major negative predictive factor for overall survival. Therefore, it would be premature to consider partial thymectomy as an appropriate treatment for thymoma.

Drawbacks of robotic surgery

Robotic surgery has several limitations including the high cost, lack of tactile sensation, annual maintenance costs, and expensive disposable robotic equipment. However, some of these limitations can be countered by the interdisciplinary use of robots (35). The interference of surgical instruments in the narrow mediastinum, which was a problem with VATS, has been eliminated with RATS, coupled with the expansion of the surgical field by CO_2 insufflation. Furthermore, in recent years, robots with tactile senses have been developed and proven to be effective, yet robots currently in widespread use do not have antennae (36). It should also be noted that it can take time to respond to unexpected injuries or bleeding from the innominate vein.

Table 5 Outcomes of partial thymectomy and thymothymectomy for thymoma

Author	Study arm	Sample size	Operative time (min), mean [range]	P value	Blood loss (mL), mean [range]	P value	Complication rate (%)	P value	In-hospital duration (days)	P value	MICS rate (%)	P value
Narm (29)	Limited	295	NA	–	NA	–	NA	–	NA	–	VATS: 71.9; sternotomy: 17.3; *others: 10.8	<0.01
	Total	467	NA	–	NA	–	NA	–	NA	–	VATS: 18.2; sternotomy: 73.2; *others 8.6	–
Narm (29) PSM	Limited	141	110 [72–136]	<0.01	50 [0–200]	<0.01	7	0.55	5	0.95	VATS: 51.1; sternotomy: 34.0; *others: 14.9	0.44
	Total	141	133 [112–165]	–	150 [35–300]	–	5	–	5	–	VATS: 53.9; sternotomy: 33.3; *others: 12.8	–
Nakagawa (30) PSM	Limited	276	NA	–	NA	–	12	0.0397	NA	–	NA	–
	Total	276	NA	–	NA	–	23	–	NA	–	NA	–
Gu (31)	Limited	251	NA	–	NA	–	NA	–	NA	–	VATS: 22.8; thoracotomy: 68; sternotomy: 9.2	<0.001
	Total	796	NA	–	NA	–	NA	–	NA	–	VATS: 27.6; thoracotomy: 9.8; sternotomy: 62.6	–
Guerrera (32)	Limited	30	NA	–	NA	–	62	0.079	NA	–	MICS: 70	<0.001
	Total	441	NA	–	NA	–	4	–	NA	–	MICS: 25.4	–
Guerrera (32) PSM	Limited	30	NA	–	NA	–	NA	–	NA	–	MICS: 70	0.91
	Total	90	NA	–	NA	–	NA	–	NA	–	MICS: 71	–
Yano (33)	Limited	36	NA	–	NA	–	NA	–	NA	–	VATS: 29, sternotomy: 5, thoracotomy: 2	–

*others = missing data. MICS, minimally invasive cardiothoracic surgery; NA, not applicable (not reported); VATS, video-assisted thoracic surgery; PSM, propensity score matching.

Drawbacks of partial thymectomy

Some studies claim that partial thymectomy has a lower complication rate, less operative time and less blood loss. However, consideration should be given to the increased likelihood of incomplete resection with limited resection of the thymus, especially in stage II, as shown in a study by the ChaRT study (2.9% *vs.* 14.5%) (31). In addition, partial resection of the thymus could not secure the safe anatomic margins and eventually could lead to leave behind multifocal thymic epithelial tumors (37,38). The final stage is established on the pathological examination of the specimen, sometimes the diagnosis is corrected compared to preoperative imaging. We should keep in mind these drawbacks when considering the partial thymectomy for thymoma. Furthermore, it is important to note that performing partial resection does not allow node removal following the 2015 ITMIG recommendations (39).

Limitations

Our narrative review has some limitations. First, considering the advances in RATS technology, we basically excluded an article published before 2010. This may have resulted in selection bias. Furthermore, there is still a lack of sufficient long-term outcome data to analyze the survival rates of RATS and Open approaches for early-stage thymoma.

Conclusions

Robotic thymectomy is a proven procedure performed

Table 6 Long-term outcomes of partial thymectomy and thymothymectomy for thymoma

Author	Study arm	5-year DFS	P value	10-year DFS	P value	5-year OS	P value	10-year OS	P value	Mortality (%)	P value	R0 (%)	P value	Recurrence rate (%)	P value
Narm (29)	Limited	NA	–	NA	–	NA	–	NA	–	NA	–	NA	–	11	0.1
	Total	NA	–	NA	–	NA	–	NA	–	NA	–	NA	–	19	–
Narm (29) PSM	Limited	96.3%	0.86	89.7%	0.86	94.1%	0.82	86.8%	0.82	17	0.65	96.5	0.76	7	>0.99
	Total	97%	–	85%	–	96.9%	–	86.0%	–	23	–	95.7	–	5	–
Nakagawa (30) PSM	Limited	93.8%	0.588	NA	–	97.3%	0.487	NA	–	1	NS	97.8	0.142	11	0.102
	Total	94.9%	–	NA	–	96.9%	–	NA	–	1	–	99.3	–	5	–
Gu (31)	Limited	NA	–	NA	–	NA	–	89.4%	0.732	1	NS	98.4	0.267	Stage I: 1.4; stage II: 14.5	Stage I: 0.259
	Total	NA	–	NA	–	NA	–	90.9%	–	1	–	98.7	–	Stage I: 3.1; stage II; 2.9	Stage II: 0.001
Guerrera (32)	Limited	79%	<0.001	NA	–	55%	0.002	NA	–	2	0.23	94.6	0.83	NA	–
	Total	96%	–	NA	–	89%	–	NA	–	12	–	93.7	–	NA	–
Guerrera (32) PSM	Limited	79%	0.025	NA	–	49%	0.144	NA	–	NA	–	NA	–	NA	–
	Total	98%	–	NA	–	80%	–	NA	–	NA	–	NA	–	NA	–
Yano (33)	Limited	94.1%	–	NA	–	94.1%	–	NA	–	2	–	NA	–	0	–

DFS, disease free survival; OS, overall survival; NA, not applicable (not reported); PSM, propensity score matching; NS, not significant.

at many centers. Current data indicate that it is safe with effective and promising long-term results and oncological and surgical outcomes in patients with thymoma. Future prospective randomized studies are needed to evaluate its superiority over the standard thoracoscopic techniques. Robotic thymectomy can become the standard procedure in patients with early-stage thymomas. Furthermore, it is premature to consider partial thymectomy as an appropriate treatment for thymomas.

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Review Article

Proposal for a standardized methodology for performing endobronchial ultrasound-guided mediastinal cryobiopsy: a four-step approach

Miguel Angel Ariza Prota[1]^, Javier Pérez Pallarés[2], Emanuela Barisione[3], Sammy Onyancha[4], Nadia Corcione[5], Hector Enrique Torres Rivas[6], Luis Fernández Fernández[6], Marta García Clemente[1], Francisco Julián López González[1]

[1]Division of Respiratory Medicine, Interventional Pulmonology Unit, Hospital Universitario Central de Asturias, Oviedo, Spain; [2]Division of Respiratory Medicine, Interventional Pulmonology Unit, Hospital Universitario Santa Lucía, Murcia, Spain; [3]Division of Respiratory Medicine, Interventional Pulmonology Unit, IRCCS Policlinico San Martino Hospital, Genoa, Italy; [4]Division of Respiratory Medicine, Interventional Pulmonology Unit, St. Elisabeth Hospital, Frankfurt, Germany; [5]Division of Respiratory Medicine, Interventional Pulmonology Unit, Azienda Ospedaliera Di Rilievo Nazionale Antonio Cardarelli, Naples, Italy; [6]Division of Pathology, Hospital Universitario Central de Asturias, Oviedo, Spain

Contributions: (I) Conception and design: All authors; (II) Administrative support: M García Clemente, FJ López González; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: MA Ariza Prota, J Pérez Pallarés, E Barisione, S Onyancha; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Miguel Angel Ariza Prota, MD. Division of Respiratory Medicine, Interventional Pulmonology Unit, Hospital Universitario Central de Asturias, Avenida de Roma, S/N, 33011 Oviedo, Asturias, Spain. Email: arizamiguel@hotmail.com.

Abstract: Endobronchial ultrasound (EBUS)-guided mediastinal cryobiopsy is a novel technique that increases the accuracy of diagnosing most pathologies that affect the mediastinum. Although EBUS-guided transbronchial needle aspiration (EBUS-TBNA) is the first choice in the diagnosis of mediastinal pathology, mediastinal cryobiopsy offers a larger and higher quality biopsy with minimal artifacts and no crushing when compared to conventional cytological samples obtained through EBUS-TBNA. It is particularly valuable in pathologies where EBUS-TBNA has diagnostic limitations, such as lymphoproliferative diseases, benign granulomatous conditions like sarcoidosis and silicosis, some rare infectious processes, metastases from rare non-pulmonary tumors, and in advanced stages of non-small cell lung cancer (NSCLC) where immunohistochemistry and molecular analysis are essential for personalized treatment. Therefore, mediastinal cryobiopsy seems to play a crucial role in these challenging scenarios. However, there is ongoing debate in the field of interventional pulmonology regarding the best approach for obtaining a mediastinal cryobiopsy. Some interventional pulmonologists use a high-frequency needle knife to create an incision in the tracheobronchial wall adjacent to the mediastinal lesion before inserting the cryoprobe, while others use a needle to create a pathway to the target area. There are also variations in the use of endoscopic or ultrasound imaging for guidance. In this article, we aim to review the current literature on different methods of performing mediastinal cryobiopsy and share our own clinical experience and methodology in a systematic way for its implementation in a safe, fast, and effective way.

Keywords: Mediastinal cryobiopsy; endobronchial ultrasound (EBUS); Cryo-EBUS; mediastinal lesions; Ariza-Pallarés method

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^ ORCID: 0000-0001-7183-2646.

Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the preferred method for examining mediastinal and hilar lesions (1). However, inadequate biopsy samples can impact its effectiveness and lower its diagnostic accuracy for certain conditions such as lymphoproliferative and granulomatous disorders (2). In such cases, additional diagnostic procedures like re-biopsies or mediastinoscopy may be necessary, especially when there is a high likelihood of malignancy. It is important to note that there are potential complications associated with both intra and post-operative procedures of video-assisted mediastinoscopy (VAM) and video-assisted mediastinoscopic lymphadenectomy (VAMLA). These complications, including wound infection, mediastinal hematoma and seroma, mediastinitis, pleural effusion, pneumothorax, chylothorax, and left-sided recurrent nerve paralysis, occur in approximately 5–8% of cases (3). In recent years, it has become increasingly important to accurately characterize tissue samples for the treatment of thoracic malignancies, particularly in cases of non-small cell lung cancer (NSCLC). While EBUS-TBNA is effective in diagnosing primary lung cancers, it may not always provide enough tissue for a definitive diagnosis of uncommon tumors, some benign mediastinal conditions or when immunohistochemical and molecular analyses are required. In such cases, a histopathological evaluation and assessment of the surrounding tissue structure is often necessary (4,5). Therefore, mediastinal cryobiopsy seems to play a crucial role in these challenging scenarios. However, there is ongoing debate in the field of interventional pulmonology regarding the best approach for obtaining a mediastinal cryobiopsy. Some interventional pulmonologists use a high-frequency needle knife to create an incision in the tracheobronchial wall adjacent to the mediastinal lesion before inserting the cryoprobe, while others use a needle to create a pathway to the target area. There are also variations in the use of endoscopic or ultrasound imaging for guidance.

In this article, we aim to review the current literature on different methods of performing mediastinal cryobiopsy and share our own clinical experience and methodology in a systematic way for its implementation in a safe, fast, and effective way.

Literature review

Botana-Rial *et al.* conducted a systematic review of 555 patients, concluding that genetic studies and immunohistochemical determination of programmed death-ligand 1 (PD-L1) were feasible in almost all (97%) of the samples obtained by Cryo-EBUS, while this was only possible in 79% of those obtained by EBUS-TBNA (6). In 2020, Zhang *et al.* reported the first case of transbronchial mediastinal cryobiopsy (TMC) (7). They described a young male with a mediastinal mass of more than 4 cm who was diagnosed with seminoma. The procedure was performed under local anesthesia and conscious sedation with intravenous midazolam. It involved four passes of TBNA using a 22-gauge needle (Olympus NA-201SX-4022; Olympus, Tokyo, Japan), followed by the insertion of a high-frequency needle knife (Olympus KD-31C-1; Olympus) through the EBUS scope into the airway wall near the location of needle aspiration. After applying cautery, the needle knife was inserted into the mediastinal lesion and then withdrawn. Next, a 1.1 mm cryoprobe (Erbe 20402-401; Erbe, Tübingen, Germany) was inserted into the target area and cooled for 15 seconds before being extracted. Two cryobiopsies were obtained in total. In 2021, Gonuguntla *et al.* published a case series on four patients who underwent mediastinal cryobiopsy in lymph nodes greater than 1 cm (8). The procedure was carried out as follows: all four patients underwent EBUS-TBNA under general anesthesia with laryngeal mask airway. Initially, a 19-gauge needle was used for puncture, followed by the insertion of a 1.1 mm cryoprobe (Erbe 20402-401; Erbe) into the working channel of the EBUS bronchoscope. The cryoprobe was then guided under endoscopic vision to the puncture site and cooled down for 3 seconds before being removed, resulting in one cryobiopsy for one patient and two for the others.

In 2021, Zhang *et al.* published a randomized trial involving 197 patients who underwent TMC in lymph nodes greater than 1 cm (9). In their study, all patients underwent four TBNAs and three cryobiopsies. The team again used a high-frequency needle knife to create an incision in the tracheobronchial wall before introducing the cryoprobe into the lesion. The probe was cooled down for 7 seconds. The most common adverse event reported was minor bleeding, which resolved without intervention. Additionally, there were two cases of pneumothorax and one case of pneumomediastinum, both of which resolved spontaneously without the need for drainage. Genova *et al.* presented a series of five patients who underwent both EBUS-TBNA and TMC for diagnostic and staging purposes (10). Patients with mediastinal lymph nodes with greater diameter ≥2 cm were included. The procedure

was carried out under deep sedation using propofol and midazolam. Once suitable lymph nodes were identified through EBUS, the operator performed TBNA with 19-gauge needle at the targeted stations of interest (3 samplings for each station). Afterwards, the puncture hole left by the needle was located through endoscopic vision, and the cryoprobe was inserted into de lymph node. The probe was cooled for 4 seconds, and no major complications were reported.

In 2022, Ariza-Prota *et al.* published a case series of four patients who underwent mediastinal cryobiopsy (11). The study included patients with mediastinal lymph nodes greater than 1 cm. The procedures were performed under conscious sedation using midazolam and fentanyl. Once the targeted lymph node station was identified, the operator conducted four TBNAs with 22-gauge cytological needle (SonoTip EBUS Pro Flex GUS-45-18-022; Medi-Globe, Rohrdorf, Germany). Following the TBNA puncture, a 1.1 mm cryoprobe (Erbe 20402-401) was inserted into the working channel of the EBUS bronchoscope (EB19-J10U; Pentax Medical) and gently advanced towards the puncture site. The cryoprobe was then introduced gently through the previous puncture site created by the needle. The EBUS image confirmed the cryoprobe's correct placement within the lymph node. After cooling the cryoprobe for 3 seconds, it was retracted with the bronchoscope along with the frozen biopsy tissue attached to its tip.

In 2023, Fan *et al.* conducted an open-label, randomized trial at three hospital sites in Europe and Asia to evaluate the safety and added value of combining TMC with standard EBUS-TBNA for diagnosing mediastinal diseases (12). Eligible participants had at least one mediastinal lesion measuring 1 cm or longer in the short axis that required diagnostic bronchoscopy. A total of 271 patients were randomly assigned in a 1:1 ratio to either the combined group, which received both EBUS-TBNA and TMC, or the control group, which received EBUS-TBNA alone. They used a high-frequency needle knife to create an incision in the tracheobronchial wall before introducing the cryoprobe into the lesion. The study found that adding cryobiopsy to standard sampling significantly increased the overall diagnostic yield for mediastinal lesions, with 126 out of 136 participants (93%) in the combined group and 109 out of 135 participants (81%) in the control group achieving successful diagnoses. Subgroup analyses also showed that the combined approach was more sensitive than standard needle aspiration for benign disorders (94% *vs.* 67%), and it improved the suitability of tissue samples for molecular and immunological analyses of NSCLC. The incidence of adverse events related to the biopsy procedure did not differ between the two trial groups. Their trial concluded that the addition of mediastinal cryobiopsy to standard EBUS-TBNA resulted in a significant improvement in diagnostic yield for mediastinal lesions, with a good safety profile.

In 2023, Ariza-Prota *et al.* published a prospective study of 50 patients who underwent EBUS-TBNA and TMC using a 22-gauge needle (SonoTip TopGain GUB-42-18-022; Medi-Globe) (13). The authors aimed to simplify the procedure and introduce the Ariza-Pallarés method for its implementation. This was the first time that the mediastinal cryobiopsy procedure was described as completely ultrasound-guided. Patients with mediastinal lesions >1 cm were recruited in the study. All procedures were performed under conscious sedation with midazolam and fentanyl, and with a short oral biter. After identifying the suitable lymph node station with EBUS, three passes of TBNAs were performed. During the last puncture, a "tunnel" was created using the unique crown-cut tip of this needle. The 1.1 mm cryoprobe was then inserted under ultrasound guidance, without the need for endoscopic vision. By focusing only on the ultrasound imaging, the authors were able to identify the trace left by the TBNA puncture and the broken capsule of the lymph node. The position of the cryoprobe within the lymph node was confirmed with the EBUS image. The cryoprobe was cooled down for 4 seconds and retracted with the EBUS scope, with the frozen biopsy tissue attached to its tip. The cryobiopsy site was immediately examined and no complications were reported. The authors state that in numerous cases, the site from the previous puncture could not be located using endoscopic vision. However, with the use of ultrasound imaging, the trace left by the needle inside the lesion and the broken capsule could be identified in all cases, making the process simpler and reproducible in all lymph node stations. All patients received post-procedural chest radiographs or pleural echography to confirm that a pneumothorax had not been produced and the patient was discharged 2 h after verifying that there had been no complications. Follow-up was conducted on all patients at 24 h via phone call and 2 weeks after the procedure to check that there were no delayed complications.

When to do it? Possible indications

(I) Suspected lymphoproliferative disorders (both for *de novo* diagnosis and for recurrence /relapse diagnosis);
(II) Suspicion of benign granulomatous processes (sarcoidosis, silicosis, rare mediastinal infections and

ganglionar tuberculosis);
(III) Metastases from other non-pulmonary or infrequent tumors (seminoma, thymoma, thymic carcinoma, etc.);
(IV) Non-diagnostic EBUS-TBNA;
(V) Necrotic lymph nodes/lesions;
(VI) NSCLC stages III–IV (immunohistochemical and molecular analysis);
(VII) Restaging the mediastinum after induction chemotherapy and/or radiotherapy for locally advanced NSCLC.

After careful analysis, these are the possible indications that our group determined for considering performing a mediastinal cryobiopsy. It should be noted that these indications are not set in stone and may differ based on the resources of each interventional pulmonology unit, including technology, EBUS-TBNA diagnostic yield, expert cytopathologists, rapid on-site evaluation (ROSE), etc. Therefore, it is crucial to take these individual factors into account when determining the optimal utilization of Cryo-EBUS and delivering top-quality care to your patients. One scenario where Cryo-EBUS is particularly advantageous is in restaging the mediastinum after receiving chemotherapy and/or radiotherapy for locally advanced NSCLC. In these cases, the lymph nodes can become necrotic or stiff, making it challenging to obtain a viable sample through traditional TBNA methods for immunohistochemical and molecular testing. However, since incorporating Cryo-EBUS into our diagnostic approach, we have observed a significant increase in our diagnostic yield from 62% to 94%. Each case should be approached individually as every situation is unique. Regarding the risk of mediastinitis, there is limited data directly linking the procedure to this rare complication. When a necrotic lymph node or lesion is accessible by EBUS, we always opt for TBNA, and we see no reason for this to be any different for Cryo-EBUS. However, if our suspicion is a cystic lesion, we do not perform EBUS-TBNA, and therefore would not perform a mediastinal cryobiopsy in that scenario. One crucial factor to consider is the presence of ROSE, which allows for real-time assessment of sample quality. If ROSE indicates that the sample is too necrotic for accurate immunohistochemical and molecular analysis, or contains very few viable cells, we have seen excellent results with mediastinal cryobiopsy.

When not to do it?

The contraindications of a Cryo-EBUS are the same as for EBUS-TBNA in our experience.

(I) Current or recent myocardial ischemia;
(II) Severe hypoxemia;
(III) Hemodynamic instability;
(IV) Severe pulmonary hypertension;
(V) Poorly controlled heart failure;
(VI) Chronic obstructive pulmonary disease (COPD)/asthma exacerbation;
(VII) Life-threatening dysrhythmias;
(VIII) Patient on anticoagulation/dual antiplatelet therapy;
(IX) Clotting abnormalities;
(X) Intolerance to sedation/anesthesia;
(XI) Vascular image patterns of grade III–IV on the ultrasound (14):
  (i) Grade 0: no blood flow or small amounts of flow;
  (ii) Grade I: a few main vessels running toward the center of the lymph node from the hilum;
  (iii) Grade II: a few punctiform or rod-shaped flow signals, a few small vessels found as a long strip of a curve;
  (iv) Grade III: rich flow, more than four vessels found with different diameters and twist or helical flow signal;
  (v) Grade IV [bronchial artery (BA) inflow sign]: the blood flow from the BA toward the lymph node that was visualized as blue signals on EBUS color Doppler-mode image.

Four-step technique

The Ariza-Pallarés method outlines four crucial steps for effectively performing a mediastinal cryobiopsy, applicable to both the transbronchial (EBUS) and transesophageal [endoscopic ultrasound with bronchoscope (EUS-B)] approaches (15).

Step 1: the planning (select the best place, choose it wisely)

It is crucial to thoroughly evaluate the chest computed tomography (CT) scan or fluorodeoxyglucose positron emission tomography (FDG-PET) to determine the complexity of the procedure. Factors such as location, size, and vascularity of the lesion or lymph node must be taken in consideration to determine the feasibility of the technique. If the planning reveals that the EBUS-TBNA procedure will be challenging, it is likely that the cryobiopsy will also

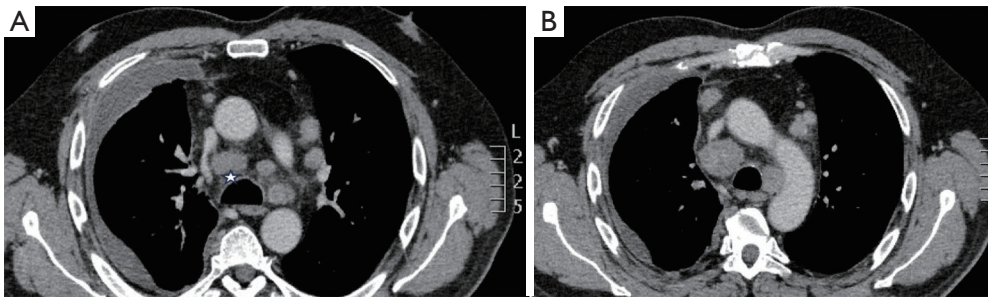


Figure 1 Thorax CT from different levels for the same patient. (A) Asterisk showing the space between 4R station and the tracheobronchial wall. (B) CT showing how the space between the 4R station and the right paratracheal wall decreases as we move down the trachea. CT, computed tomography.

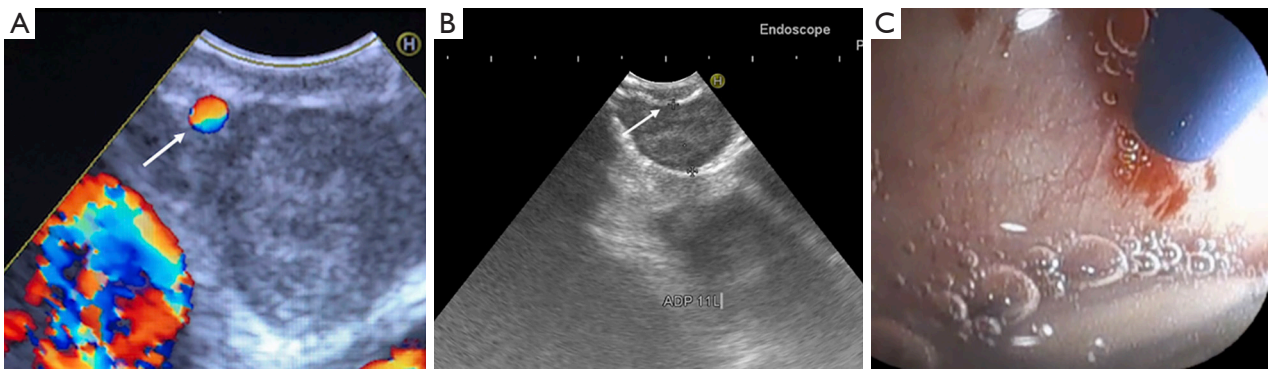


Figure 2 Lymph node stations and Doppler-mode on the ultrasound image. (A) Arrow showing a vessel in the proximal zone of the lymph node. (B) Arrow showing the location with the thinnest mucosa and lymph node capsule. (C) Needle sheath avoiding cartilage before performing the puncture. ADP, adenopathy.

be. However, if the needle is inserted successfully into the lymph node, the 1.1 mm cryoprobe can also be inserted. The initial step in the planning process is to determine whether the lymph node or lesion is in contact with the tracheobronchial wall, regardless of the station. If there is no contact and the space between them is more than 1 cm (*Figure 1A*), the closest space on the ultrasound image should be chosen for the first TBNA. Here, we present different CT levels from the same patient, showing how the space between the 4R station and the right paratracheal wall decreases as we move down the trachea (*Figure 1B*), this is a crucial aspect to consider then in the ultrasound imaging, suggesting that the nearer the lesion is to the TBNA entry point, the simpler the procedure will be. Based on our experience, mediastinal cryobiopsy can be performed in all lymph node stations. We have ranked the lymph node stations accessibility from easiest to most challenging as follows: 11L, 11Ri, 7, 11Rs, 4R, 2L, 2R, 10R, 10L, 3p, and 4L.

Step 2: the puncture (the first puncture will guide the rest of the process)

Based on our experience, we recommend that this procedure be performed by two operators. While a high skill bronchoscopist in EBUS-TBNA may be able to perform the technique after mastering the learning curve, we can ensure that having two operators makes the process easier, quicker, and safer. Sedation was performed with midazolam (0.07 mg·kg^{-1}) and fentanyl citrate (0.5–2 µg·kg^{-1}), starting with boluses of 1–3 mg of midazolam and 0.1 µg of fentanyl citrate. Sedation was maintained with intermittent boluses of 1.2 mg midazolam and 0.1 µg fentanyl citrate according to the clinical judgment of the pulmonologist. When viewing the ultrasound image, it is important to always use the Doppler mode to avoid any vessels (*Figure 2A*), carefully

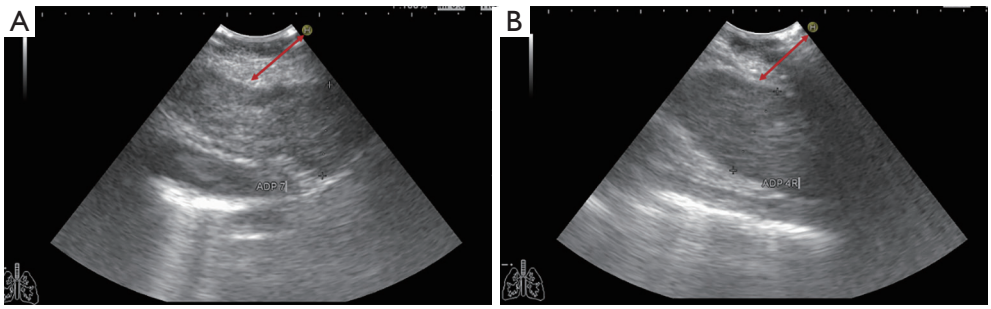


Figure 3 Distance between the mucosa and the lymph node capsule. (A) Arrow showing significant distance between the TBNA entry point and the lymph node capsule in station 7. (B) Arrow showing the distance between the TBNA entry point and the lymph node capsule in station 4R. ADP, adenopathy; TBNA, transbronchial needle aspiration.

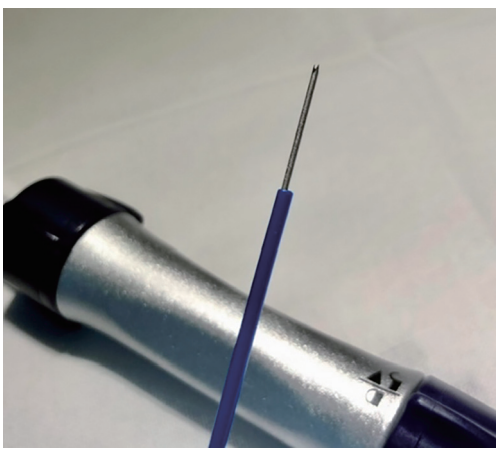


Figure 4 22-gauge SonoTip TopGain crown cut tip needle.

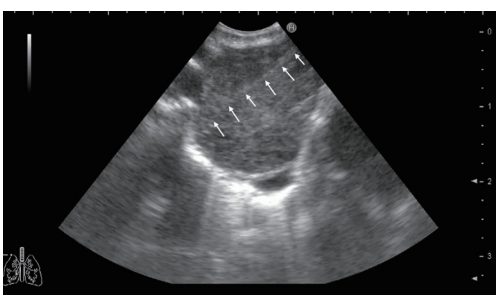


Figure 5 Arrows on the ultrasound image showing the trace left by the TBNA needle inside the lymph node. TBNA, transbronchial needle aspiration.

choose the location with the thinnest mucosa and lymph node capsule (*Figure 2B*), and steer clear of any cartilages before performing the TBNA (*Figure 2C*). The use of Doppler is essential in this procedure. Here we show a significant distance between the TBNA entry point and the lymph node capsule. This distance is due to the enlarged mucosa and cartilage, which should be avoided during the procedure (*Figure 3A,3B*).

Should we use suction during this step? As with all EBUS-TBNA procedures, we rely on the ultrasound features of the lymph node/lesion and its vascularization in Doppler mode to make this decision. If we observe grade 2 or higher vascularization, suction is typically not used. The use of suction and the specific characteristics of the 22-gauge 3-point needle tip with crown cut (*Figure 4*), also aid in creating a more distinct trace mark within the lesion, which will serve as a guide for the tunneling step and insertion of the cryoprobe. How many passes are typically performed during the puncture step? This step involves a conventional EBUS-TBNA. Our standard practice is to make 8–12 passes during each TBNA, which is also applicable in this step.

Step 3: "the tunnel"

Once the first TBNA has been performed in the optimal location, we will proceed with the second TBNA while implementing tunneling techniques. First, we must locate the trace left by the TBNA in the lymph node from the previous puncture. To identify this trace, the EBUS operator must be in the same position and angle as the first TBNA, carefully scanning for a subtle line or small white dots within the lymph node. This trace will guide us in making the second TBNA and creating a "tunnel" (*Figure 5*). Once the trace is localized, we can move on to the second TBNA. During the tunneling process, we do not use aspiration as it may cause further trauma or bleeding in the proximal area of the lymph node. Tunneling involves

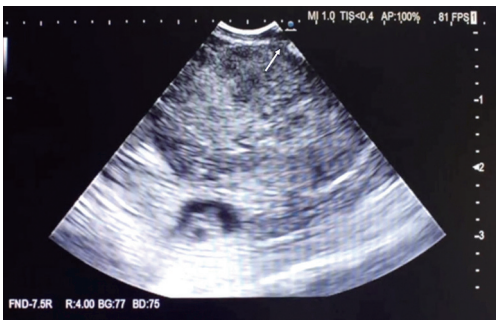


Figure 6 Arrow pointing at the broken lymph node capsule.

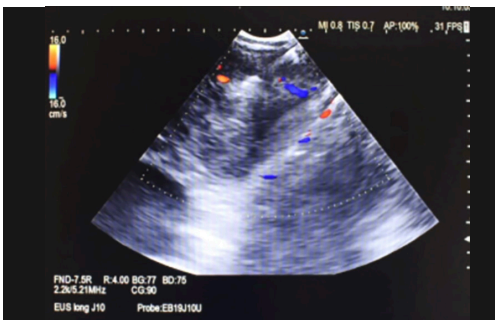


Figure 7 Doppler mode to ensure that the 1.1 mm cryoprobe path is free of vessels.

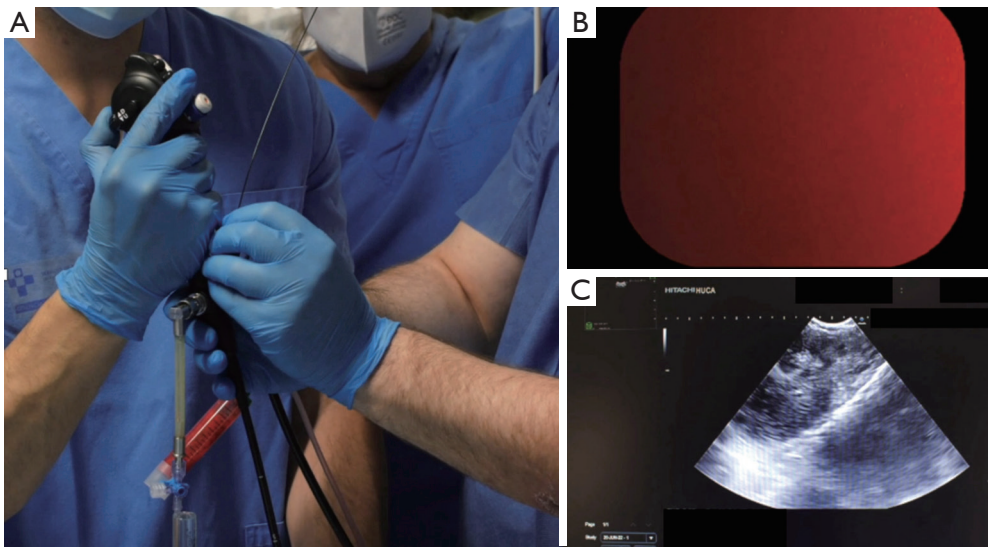


Figure 8 Introduction of the cryoprobe. (A) 1.1 mm cryoprobe being introduced gently into the working channel of the EBUS bronchoscope. (B) No endoscopic vision for letting us locate the previous puncture site. (C) Ultrasound image showing the needle trace inside the lymph node. EBUS, endobronchial ultrasound.

creating a pathway through the mucosa, submucosa, and capsule of the lymph node to allow for easy insertion of the cryoprobe. If the trace is not clearly visible, we can identify the broken capsule by observing a discontinuity and loss of echogenicity in the usually homogenous and hyperechoic lymph node capsule (*Figure 6*). To create the "tunnel", we will first perform 8–12 conventional TBNA passes without aspiration, then shorten the needle length by 1 cm to focus on the proximal part of the lymph node. This TBNA sample is also sent for further analysis. When the needle can easily enter and exit the proximal area without resistance, we can confirm that the capsule has been successfully broken and we can proceed to step 4.

Step 4: the cryobiopsy

Now that the "tunnel" has been made, the next step is to obtain the cryobiopsy sample. This is an ultrasound-guided procedure, and it is crucial to identify the broken capsule and the trace from the previous TBNA, as shown in step 3. The EBUS operator must be in the same position and angle as when performing the second TBNA. The Doppler mode should be used again to ensure that there are no vessels in the cryoprobe's path (*Figure 7*). Once the needle trace and the broken capsule are identified, the 1.1 mm cryoprobe is introduced into the working channel of the EBUS bronchoscope (*Figure 8A*). There is no need to visually locate the puncture site since this is an ultrasound-

guided procedure. In this case, it would have been impossible to do so because the puncture site is not visible (*Figure 8B*). The needle trace can be seen inside the lymph node (*Figure 8C*). Using ultrasound imaging and Doppler mode, the cryoprobe is gently advanced into the lymph node to confirm its correct position (*Figure 9*). As for where to take the cryobiopsy samples, we recommend performing three cryobiopsies per station, one distally, one medially, and one more proximal to the capsule (*Figure 10A-10C*). This allows to obtain samples from different areas of the lymph node. The "fanning" technique can also be performed by adjusting the lever of the EBUS scope to access different zones of the lesion (16). During this process, it is advisable to hold the cryoprobe firmly with the fourth and fifth fingers, and once it is fixed, put the lever of the EBUS scope in a neutral position and press the pedal for 3–5 seconds, and then retracted with the EBUS scope and the frozen biopsy tissue attached to the tip of the probe. The pedal should be pressed until the sample is secured outside the airway (*Figure 11*). After retrieving the cryobiopsy in saline and fixed formalin (*Figure 12*), the cryobiopsy site should be examined. Key points in this step: (I) lever of the EBUS bronchoscope in neutral position before taking the scope out with the cryobiopsy sample; (II) always keep the tip of the cryoprobe image on the ultrasound; and (III) keep the pedal close to your foot and keep it pressed until the sample is secured (*Video 1*).

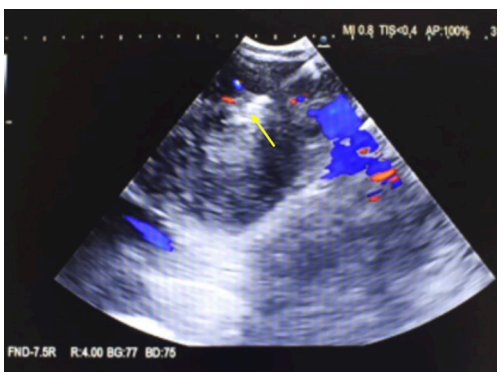


Figure 9 Arrow in the ultrasound image and Doppler mode pointing the tip of the cryoprobe in the correct and desired position.

Conclusions

The Ariza-Pallarés method for performing EBUS-guided mediastinal cryobiopsy is a minimally invasive, feasible, and safe technique that can be performed in a bronchoscopy suite under moderate sedation by a highly experienced interventional pulmonologist in performing EBUS. This novel approach has shown to have a significantly higher diagnostic yield compared to EBUS-TBNA, particularly in the diagnosis of lymphoproliferative disorders, non-pulmonary uncommon tumors, and NSCLC that require further molecular and immunohistochemical testing. We have applied this method using various types of TBNA needles, each of different diameters (19- and 22-gauge) and characteristics (standard needle tip and 3-point needle tip). It is worth noting that the 22-gauge crown cut tip needle only requires a single TBNA to create the "tunnel", while other conventional needles may require between three and four TBNA's before the 1.1 mm cryoprobe can be inserted in the desired target. This can significantly prolong the procedure, increase the need for sedation, and potentially increase the risk of complications. Regarding mediastinal cryobiopsy and its potential complications, our experience has shown that we have not encountered any cases of pneumothorax, pneumomediastinum, mediastinitis, or major bleeding. We believe that the complications associated with this technique are no different from those of EBUS-TBNA. However, in studies where pneumomediastinum

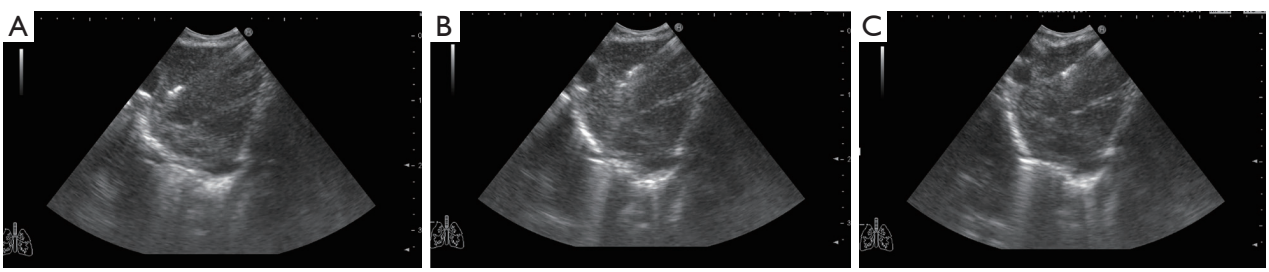


Figure 10 Ultrasound image of the cryoprobe. (A) Ultrasound image confirms the cryoprobe tip positioned distally within the lymph node. (B) Cryoprobe's tip located in the lymph node's medial area. (C) Cryoprobe's tip positioned in the proximal zone of the lymph node.

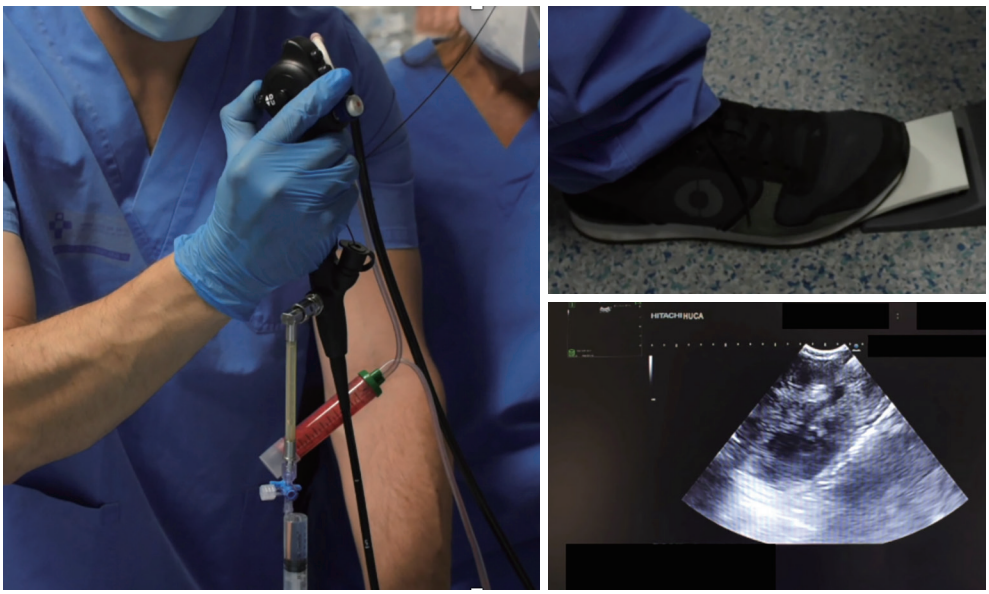


Figure 11 The Cryoprobe firmly grasped with the fourth and fifth fingers, once fixed, the lever of the EBUS scope should be in neutral position. The pedal needs to be pressed for 3–5 seconds until the sample is secured outside the airway. EBUS, endobronchial ultrasound.

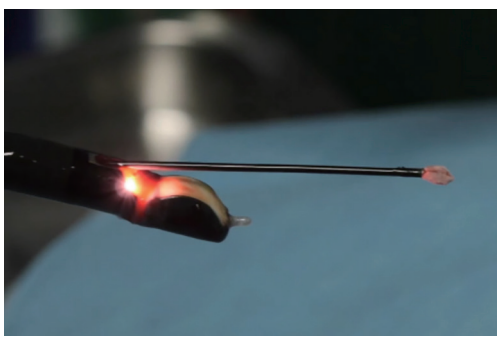
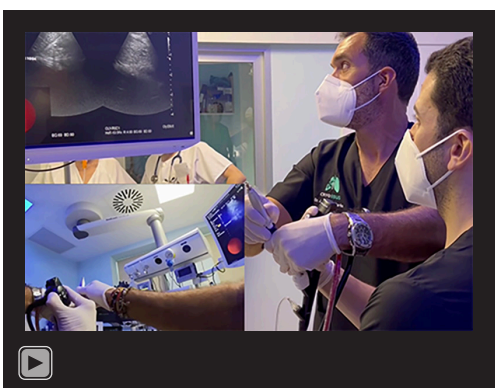


Figure 12 Cryobiopsy attached to the tip of the 1.1 mm cryoprobe.



Video 1 Steps 2 (transbronchial needle aspiration), 3 (tunneling), and 4 (cryobiopsy) of the Ariza-Pallarés method. This video is published with the participants' consent.

and pneumothorax have been reported (9,12), the cryoprobe was frozen for more than 6 seconds. It is important to mention that the sample size does not increase after freezing for more than 6 seconds. Additionally, it should be noted that the proximal part of the cryoprobe begins to freeze at this point. This issue is crucial, as freezing for more than 6 seconds can result in obtaining samples not only from the lymph node, but also from the pleura and mucosa, which may contribute to the reported complications in previous studies. Therefore, we recommend freezing for 3–5 seconds, which we believe is both safe and sufficient to obtain high-quality samples for accurate diagnosis. A crucial aspect to consider is the learning curve associated with this technique. Based on our experience, we highly recommend performing a minimum of 30 procedures within a 3-month timeframe and obtaining samples from different lymph node stations rather than solely on one. This approach will greatly aid in mastering the learning curve. The Ariza-Pallarés method demonstrates that the use of a high-frequency needle knife is not necessary for performing mediastinal cryobiopsy; we have eliminated this step of the process by directly introducing the 1.1 mm cryoprobe under ultrasound guidance, therefore, simplifying the

procedure and making it more accessible and reproducible. Our objective is to share the Ariza-Pallarés method, so that numerous interventional pulmonology colleagues can employ this technique efficiently and safely in their daily clinical practice. Standardization of the methodology for conducting mediastinal cryobiopsy is crucial for future published trials to be easily comparable.

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Footnote

Peer Review File: Available at https://med.amegroups.com/article/view/10.21037/med-23-65/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-23-65/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All clinical procedures described in this study were performed in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this article and accompanying images and video. A copy of the written consent is available for review by the editorial office of this journal.

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Review Article

Physiological and pathological roles of the thymus and value of thymectomy in myasthenia gravis: a narrative review

Waqar Waheed[1]^, Agnes Bacopulos[1], Muhannad Seyam[1]^, Hannah Kooperkamp[2], Maryam Moin[3], Tariq Malik[4], Rup Tandan[1]

[1]Department of Neurological Sciences, University of Vermont Robert D. Larner, MD College of Medicine and University of Vermont Medical Center, Burlington, VT, USA; [2]Division of Thoracic and Cardiac Surgery, University of Vermont Robert D. Larner, MD College of Medicine and University of Vermont Medical Center, Burlington, VT, USA; [3]Department of Neurology, University of Illinois College of Medicine, Peoria, IL, USA; [4]Department of Anesthesiology, Chicago Medical School at Rosalind Franklin University of Medicine and Science, Chicago, IL, USA

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Correspondence to: Waqar Waheed, MD. Department of Neurological Sciences, University of Vermont Robert D. Larner, MD College of Medicine and University of Vermont Medical Center, 89 South Williams Street, Burlington, VT 05401, USA. Email: waqar.waheed@uvmhealth.org.

Background and Objective: Myasthenia gravis (MG) is a well-elucidated autoimmune disorder affecting the neuromuscular junction. Given the relationship between MG and thymic pathologies, with T cell and antibody-mediated pathogenesis, surgical (i.e., thymectomy) and non-surgical approaches remain a mainstay of management of the disease. This review seeks to outline the involvement of the thymus in the development of lymphocytes leading to MG.

Methods: Different databases were searched exploring the role of thymectomy in treatment and outcomes in various MG patient subpopulations, including in ocular versus generalized disease, different age groups, and antibody status.

Key Content and Findings: Overall, the findings of multiple studies and reviews provide evidence to support the efficacy and long-term success of thymectomy in the management of MG; outcomes have included remission status, symptom severity, and need for adjunctive therapy. However, the heterogeneity in the MG population suggests that there are multiple factors that may confound the results of thymectomy and still need further examination. Separately, other autoimmune diseases develop following thymectomy, and further research is required to elucidate this susceptibility. Finally, our review will discuss the different surgical approaches for thymectomy, including their advantages, limitations, and perioperative complications.

Conclusions: Overall, in light of the known pathogenesis and association of the thymus with MG, thymectomy remains an extremely effective approach for long-term management and improved clinical outcomes.

Keywords: Myasthenia gravis (MG); T cell development; thymic pathologies; thymectomy

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^ ORCID: Waqar Waheed, 0000-0003-3049-5430; Muhannad Seyam, 0000-0003-4405-7036.

Introduction

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction (NMJ), with prevalence rates for acetylcholine receptor (AChR) MG and muscle-specific kinase (MuSK) MG ranging from 70 to 163 per million, and 1.9 to 2.9 per million, respectively. Although MG can occur at any age, there is a bimodal distribution in terms of age and gender predominance, with an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decades (male predominance) (1). The defining feature of MG is fatigable skeletal muscle weakness that primarily affects the ocular muscles, with a 2-year risk of progression to generalized weakness. Up to 20% of AChR+ MG patients develop myasthenic crises due to the involvement of the respiratory and bulbar muscles. The diagnosis is confirmed by the presence of known serum autoantibodies, characteristic findings on electrophysiological testing (single-fiber electromyography and repetitive nerve stimulation), and improvement of symptoms following the administration of acetylcholinesterase inhibitors or following the cold pack test (2).

Although MG is linked to a variety of thymic pathologies, there is scarcity of literature addressing its pathogenesis in relation to the various thymus abnormalities. Since the initial pivotal trial showed that thymectomy improves outcomes in non-thymomatous AChR+ MG patients (3), there have been numerous published studies to support this, which will be subsequently discussed in the "*Evidence supporting role of thymectomy in MG*" section. In this review, we examine the role of the thymus in T lymphocyte development and its significance in the pathophysiology of MG; review data supporting the relevance of thymectomy in MG; and address the practical management in relation to thymectomy. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-43/rc).

Methods

For this narrative review, we used the following keywords to search the Cochrane Central Register of Controlled Trials, EMBASE, LILACS, and PubMed from January 1900 to July 2023: "thymectomy", "myasthenia gravis", "non-thymomatous and thymomatous myasthenia gravis", "pathogenesis", "myasthenic crisis", "perioperative management", and "remission". See *Table 1* for search strategy summary.

T cell development during life

The body's immune system is akin to the defense system of a country. Comparable to well-trained soldiers, T cells in the immune system go through several stages during their development, maturation, and differentiation.

Origin of lymphoid cells and their early development and migration to the thymus (Figure 1)

The formation of the blastocyst from the zygote, created during the process of sperm and egg fertilization, marks the beginning of the origin of lymphoid cells. The inner cellular mass of the blastocyst is the source of totipotential stem cells, which are capable of self-renewal and differentiation into cells of all tissue lineages, i.e., developing into an entire organism. These include hematopoietic pluripotent stem cells that originate in the yolk sac, fetal liver, and bone marrow that differentiate into multipotent lymphoid progenitor cells (LPCs) and myeloid progenitor cells (MPCs) responsible for adaptive immunity, and innate immunity, respectively. B cell precursor-producing LPC remain in the bone marrow for continued development, whereas T cell precursors proceed to the thymus for maturation. T cells derive their name from the thymus. By 9 weeks of gestation, T cell progenitors are visible in the thymus in humans, and by 24 weeks, mature T cells are seen in the peripheral lymphoid organs.

Settlement in secondary lymphoid organs (Figure 1)

The thymus and bone marrow constitute the primary lymphoid structures responsible for the initial generation of T and B cells, respectively. Following their maturation, T cells leave the thymus and circulate through the blood to subsequently settle and segregate into distinct domains in secondary lymphoid tissues. These include lymph nodes, spleen, tonsils, and the aggregations of lymphoid tissue located in the gastrointestinal and respiratory tracts. On the other hand, tertiary lymphoid organs form in response to inflammatory, infectious, autoimmune, and neoplastic events (discussed in section "*Pathophysiology of MG*").

T cell activation and differentiation

Upon stimulation by an antigen that is presented by antigen-presenting cells (APCs) in secondary lymphoid organs, T cells enlarge and undergo rapid proliferation. Activated lymphocytes exit into the lymph to return to the

Table 1 Search strategy summary

Items	Specification
Date of search	July 1st–November 21st, 2023
Databases and other sources searched	Cochrane Central Register of Controlled Trials, EMBASE, LILACS, and PubMed
Search terms used	"thymectomy", "myasthenia gravis", "non-thymomatous and thymomatous myasthenia gravis", "pathogenesis", "myasthenic crisis", "perioperative management", and "remission"
Timeframe	Between January 1900 and July 2023
Inclusion and exclusion criteria	Inclusion: (I) English speaking articles; (II) article types: retrospective, prospective, randomized control trial, case-series, original research, meta-analyses, systematic review
	Exclusion: (I) non-English speaking articles; (II) articles with incomplete or irrelevant data
Selection process	W.W. conducted the literature search. All authors subsequently discussed and agreed on the literature selection

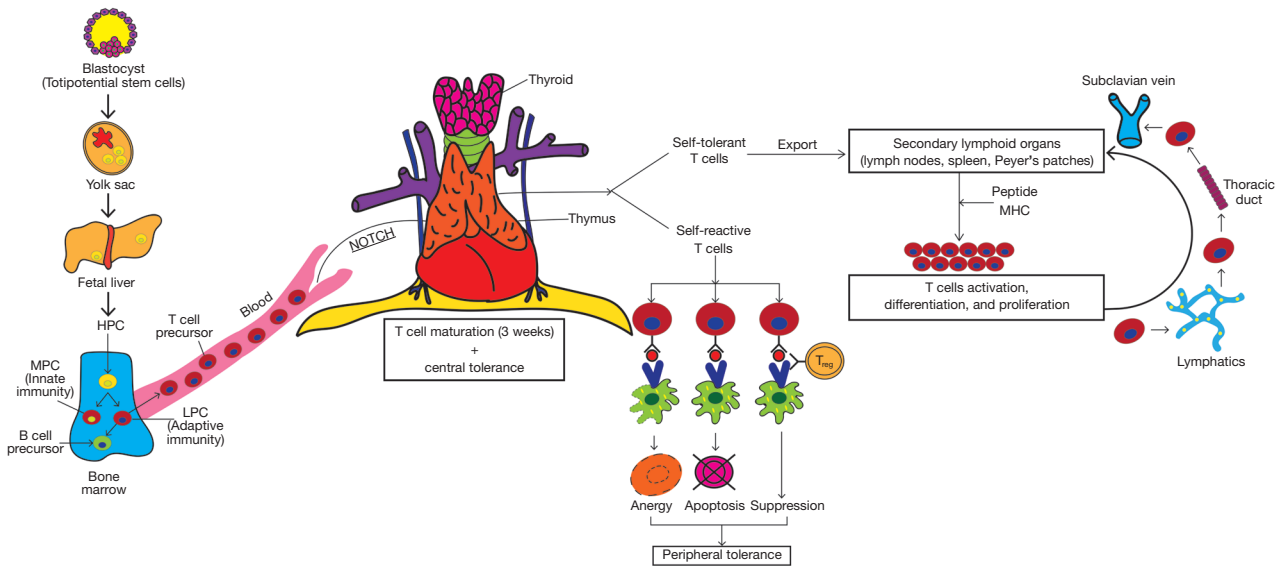

Figure 1 Journey of T cells. Hematopoietic pluripotent stem cells originating in the yolk sac, fetal liver, or bone marrow differentiate into T cell precursor-producing LPCs, which move to thymus for antigen independent T cells maturation. Naive T cells then migrate to secondary lymphoid organs for antigen dependent differentiation and activation. They then leave into the lymph and return to the blood via the thoracic duct. HPC, hemopoietic precursor cell; MPC, myeloid progenitor cell; LPC, lymphoid progenitor cell; MHC, major histocompatibility complex; Treg, regulatory T cell.

blood via the subclavian vein through the thoracic duct (4-6).

Thymus

Location

The thymus is a training school for T cells; it possesses a particular role within the lymphoid system and differs from other lymphoid structures both in structure and functionality. It is located within the superior mediastinum behind the sternum, above the heart, and extends up into the neck for a short distance.

Evolution of thymic weight

The thymus is relatively large at birth (weighs around 15 grams), and reaches its maximal size and weight of

35 to 40 grams at puberty. Thereafter, it regresses and is practically reduced to a vestige and largely replaced by fat (weighs 5 grams at age 70 years). This is reflected functionally by a reduction in thymopoiesis, which begins to decline after puberty and is minimal in most individuals >40 years of age (7).

Main cell types within the thymus

The main cell types found in the thymus are cortical and medullary thymic epithelial cells (TECs) which provide the milieu for T cell development; developing T cells called thymocytes; professional APCs that include macrophages and dendritic cells; and myoid cells. In contrast to TEC that display unfolded AChR, myoid cells are the only known cells, aside from skeletal muscle, to express AChR in its native folded form. Myoid cells also express additional important target autoantigens, such as ryanodine receptors (RYRs) and titin. Myoid cells also help in the development of tolerance by transferring muscle self-antigens to dendritic cells for cross-presentation to T cells because they are major histocompatibility complex (MHC)-II-negative. Under physiological circumstances, B cells are almost non-existent in the thymus (8).

Histology

The thymus is an encapsulated bilobed primary lymphoid organ in which each lobe is divided into multiple small lobules by trabecular connective tissue. The different regions within each lobule include subcapsular cortical, cortical, corticomedullary junction, and medulla. While epithelial cells are more noticeable in the less cellular medulla, the cortex is hypercellular and filled with developing T lymphocytes.

T cell maturation in the thymus (*Figure 2*)

T cell maturation occurs in the thymus and involves collaboration between thymocytes, TECs, and other stromal cells such as dendritic cells and myoid cells (9,10).

Thymic progenitor cells

T cell precursor-producing LPC enter the thymus through the circulation, passing through high endothelial venules (HEVs) located close to the corticomedullary junction, before moving to the outer cortex. These precursors sense cues in the thymus microenvironment that are capable of activating notch one receptor. Notch signaling induces a gene expression program that differentiates T cell precursor LPC into thymic progenitor cells. This represents the first stage in the development of T cells. Notch signaling is crucial for not only early commitment to the T cell lineage, but together with other factors also regulates subsequent steps in T cell development (11).

T cell receptor (TCR) development

Thymic progenitors within the thymus go through several stages of maturation that are distinguishable by the expression of several cell surface markers. The development of a working TCR is a crucial stage in T cell maturation. Ultimately, each mature T cell has a distinct TCR that responds to a random pattern, enabling the immune system to distinguish a variety of pathogens. The majority of cells in the thymus give rise to TCRs, which possess α and β chains termed αβ T cells; however, approximately 5% bear the γ and δ TCR and are γδ T cells.

Checkpoint no. 1: TCR β-chain selection for TCR diversity

The earliest developing thymocytes lack expression of the co-receptors CD4 and CD8 and are thus termed double negative (DN) cells. There are four DN stages (DN1–DN4) distinguishable by expression of cell surface markers, CD44 and CD25.

A pivotal checkpoint in mammalian α/β T cell development, termed beta selection, occurs at the DN3 stage. At this stage, the T cells upregulate the recombination activating genes (RAGs) RAG1 and RAG2 and test variable (V)/diversity (D)/joining (J) segments rearrangement of their TCR beta genes. The diversity of TCR, and their capacity to engage with a wide variety of peptides, are both the result of this rearrangement.

The primary goal of β selection is to test whether thymocytes express the functional TCR β chain. This is accomplished not by rearranging the TCR α chain, but by pairing it with a surrogate alpha chain called pre-T cell receptor alpha (pTα), to produce pre-TCR. The pre-TCR tests the functionality of the recombined candidate β chain by undergoing antigen-independent activation and signal transduction. Successful engagement of signaling results in arrest of further rearrangement of β chain loci, DN cell proliferation, and further differentiation by up-regulation and expression of CD4 and CD8, these cells are termed double positive (DP) cells. Cells that do not undergo beta-

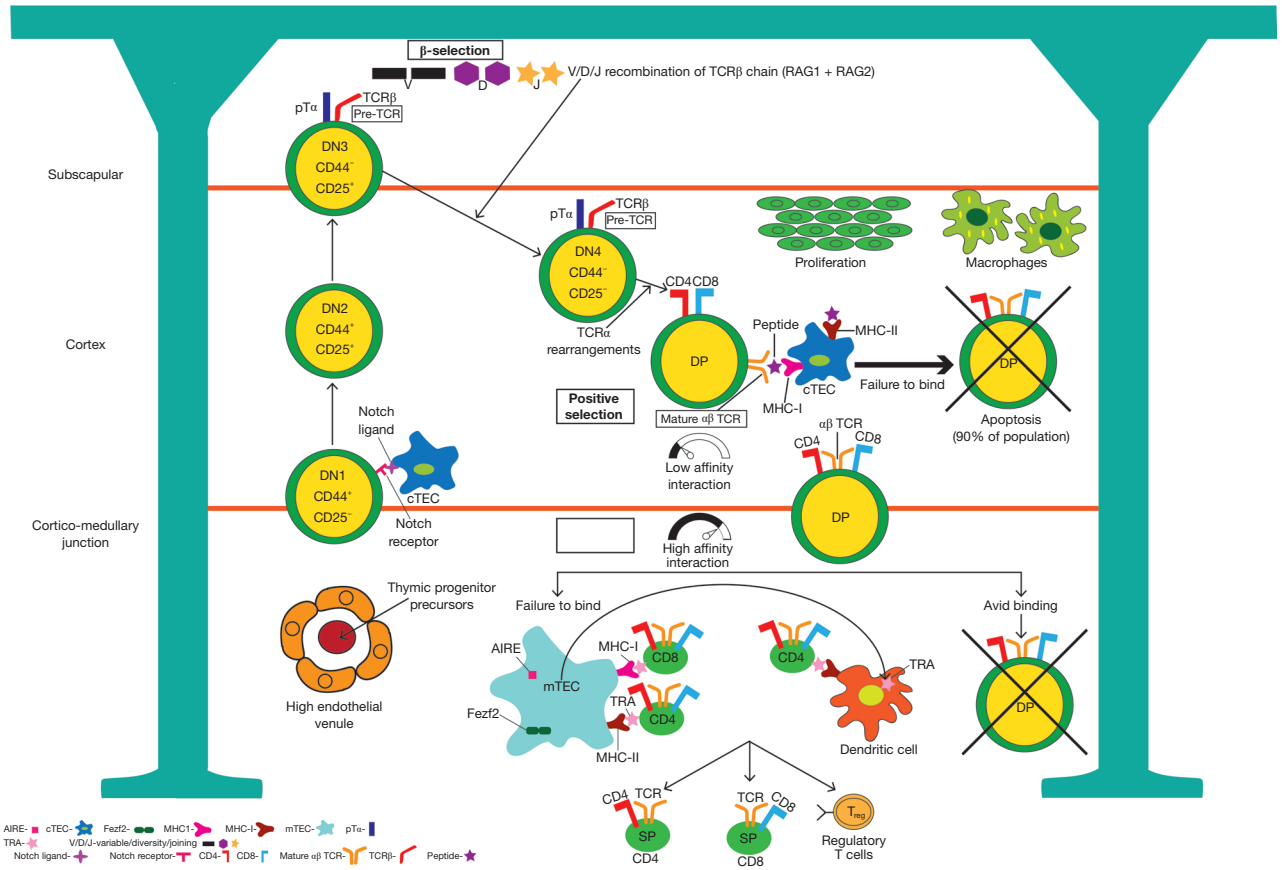

Figure 2 T cell development in thymus. Thymic progenitors within the thymus undergo different maturation phases that can be identified by the expression of several cell surface markers. After receiving Notch signaling from cTEC at the corticomedullary junction, DN thymocytes migrate outward in the thymic cortex. Positive selection occurs as DP thymocytes migrate back to the cortico-medullary interface and interact with MHC expressed on cTECs. Thymocytes that have been positively chosen move into the medulla. SP thymocytes are subjected to negative selection within the medulla by being evaluated for reactivity to tissue-restricted self-antigens expressed by mTECs or dendritic cells. Mature T cells leave the thymus through blood or lymph. pTα, pre-T cell receptor alpha; TCR, T cell receptor; V/D/J, variable/diversity/joining; RAG, recombination activating gene; DN, double negative; DP, double positive; cTEC, cortical thymic epithelial cells; MHC, major histocompatibility complex; AIRE, autoimmune regulator; mTEC, medullary thymic epithelial cell; Fezf2, forebrain embryonic zinc finger-like protein 2; TRA, tissue-restricted self-antigen; SP, single-positive; Treg, regulatory T cell.

selection die by apoptosis.

DP cells rearrange their TCR-α chain loci to produce a mature αβ-TCR. Subsequently, DP thymocytes test the functionality of the recombined α chain during two additional checkpoints of positive and negative selection to achieve signaling maturity.

Checkpoint no. 2: positive selection to promote development of foreign reactive T cells

Positive selection occurs in the cortex and determines whether V/J recombination of α chain pairs with β chain to produce a TCR that recognizes self-MHC, termed MHC restriction. TCR must bind to self-antigen-MHC expressed on cortical TECs with moderate affinity (confirming the ability to recognize self-MHC), but without a strong reaction to self-peptide. Only thymocytes that engage successfully with MHC will receive a vital "survival signal" and be able to respond to foreign antigens in a self-MHC-restricted manner. Thymocytes that do not react with MHC, representing 90% of the developing thymocytes, die from neglect.

Checkpoint no. 3: negative selection to eliminate self-reactive T cells

Thymocytes that survive positive selection are subjected to the final checkpoint of negative selection, which occurs in the thymic medulla and is supported by medullary TECs (mTECs) and dendritic cells. The purpose of negative selection is to remove TCR clones that recognize self-antigens, and constitutes the basis for central tolerance to prevent autoimmunity. Negative selection results from high-affinity interaction between developing T cells and self-peptides presented on MHC antigens (i.e., TCR recognizes self-peptide as well as MHC), compared to low-affinity interaction with self-peptide in positive selection. Negative selection is regulated by the transcription factor, autoimmune regulator (AIRE), which is expressed in the thymic medulla and controls the intrathymic expression of self-antigens. AIRE is down regulated by estrogen and upregulated by testosterone, possibly explaining the sex difference in the prevalence of young-onset MG. A new and crucial transcription factor in the negative selection process has recently been identified as the forebrain embryonic zinc finger-like protein 2 (Fezf2). Fezf2 regulates a large number of tissue-restricted antigens (TRAs); it is specifically expressed in mTECs and suppresses the initiation of an autoimmune response. With only limited overlap, Fezf2 and AIRE control the expression of various TRAs (12). Most autoreactive T cells are eliminated by apoptosis, but some differentiate into regulatory T cells (Tregs)—a process termed agonist selection.

Single positive T cells and thymic output

After negative selection, down-regulation of either co-receptors results in naive CD4 or CD8 single positive cells that leave the thymus and circulate in the periphery.

Peripheral tolerance (Figure 1)

T lymphocytes generated in the thymus are trained to be selective for a specific foreign antigen; self-reactive T cells are eliminated in the thymus via central tolerance. Self-reactive T cells that circumvent central tolerance are suppressed in the periphery (process termed peripheral tolerance) by several possible mechanisms: apoptosis, anergy (functional non-responsiveness due to lack of the co-stimulatory signal B7 on APCs), or by the action of Tregs, a subset of $CD4^+$ cells that are outsourced from the thymus gland.

Pathophysiology of MG

MG is an antibody-mediated disease with T cell driven immune pathogenesis and involves intricate interactions between $CD4^+$ T cells and B cells. Depending on the type of the underlying antibody present, the pathogenic mechanisms are further separated. Serum antibodies against the nicotinic AChR occur in 85% of patients, whereas antibodies against MuSK are found in 6% of patients. Seronegative MG accounts for less than 10% of patients, and refers to those who may have autoantibodies that are undetected by routine diagnostic tests for AChR and MuSK antibodies. Additional antibodies in this seronegative group, discovered utilizing cell-based assays, include those against low density lipoprotein receptor-related protein 4 (LRP4), agrin, collagen Q, titin, RYR, contactin, heat shock protein-70, matrix metalloproteinases, and voltage-gated potassium channel (Kv1.4); however, the pathogenic significance of these latter antibodies is still unknown (13).

Pathologic abnormalities in MG thymus

Heterogeneous findings in MG thymus include normal gland, thymic lymphocytic hyperplasia (TLH), thymic involution (atrophy), and thymoma.

TLH

While B cells are essentially nonexistent in the thymus under healthy conditions, the presence of B cell infiltrates defines TLH. Some of these infiltrates organize into germinal centers (GCs), which combined with other cells, most notably follicular dendritic cells, create lymphoid follicles, that are localized in the medulla or the perivascular areas. TLH is associated with numerous autoimmune diseases, including multiple sclerosis and Graves' disease. The GCs in the MG thymus differ from lymphoid follicles in peripheral lymphatic organs in several ways, including in their proximity to myoid cells that express AChR and their association with lymphangiogenesis and angioneogenesis (14). The GC number and serially measured AChR antibody levels show a positive association, indicating that the thymus is a source of anti-AChR antibodies. Furthermore, the finding that 80% of patients with TLH and GCs are young females, explains why young-onset MG (before age 40–50 years) is predominantly a female disease, while late-onset MG (LOMG) is frequently a male disease and is linked with thymic atrophy or thymoma. As mentioned above, the down-regulation of AIRE by estrogen may explain the sex

Table 2 Thymic pathologies associated with MG antibodies

MG type	Thymic follicular hyperplasia	Normal or atrophic thymus	Thymoma
AChR-MG	40%	50%	10%
MuSK-MG	Single cases	>95%	Single cases
LRP4-MG	30%	>70%	–
Seronegative-MG	+	+	Single cases

+, can be associated with either thymic follicular hyperplasia or normal/atrophic thymus. MG, myasthenia gravis; AChR, acetylcholine receptor; MuSK, muscle-specific kinase; LRP4, low density lipoprotein receptor-related protein 4.

difference in young-onset MG (15).

Abnormal diffuse enlargement of the thymus (besides its association with TLH) occurs in true thymic hyperplasia, which relates to an enlarged but normally organized thymus. True thymic hyperplasia is a reversible disorder that arises from physiological stresses such as chemotherapy, corticosteroid use, irradiation, or thermal burns, and is unrelated to autoimmune diseases (16).

Thymoma

Thymomas are slow-growing, locally invasive epithelial tumors consisting of transformed epithelial cells surrounded by maturing polyclonal T cells (17). Thymoma-associated MG (particularly type B2) accounts for around 15–20% of all MG patients; such cases are almost always AChR antibody positive and can be associated with other autoimmune and paraneoplastic syndromes [e.g., stiff person syndrome, neuromyelitis optica (NMO), Isaacs' syndrome]. Thymomatous MG occurs mainly in individuals >50 years of age; about 25% of individuals with thymoma have subclinical MG, which is defined as AChR antibody positive status but without symptoms (18).

Differentiating the underlying cause of an enlarged thymus is facilitated by its imaging features. Diffuse enlargement and a triangular shape of the gland suggest hyperplasia, whereas focal enlargement and a rounded shape indicate thymoma. Thymic hyperplasia and thymoma can additionally be distinguished using chemical shift (which detects microscopic fatty infiltration found in normal thymus and thymic hyperplasia) and diffusion-weighted sequences used in magnetic resonance imaging (MRI); restricted diffusion and a high chemical shift ratio favor thymic neoplasm over thymic hyperplasia (19,20).

Thymic involution/atrophy

From 10–20% of AChR+ MG cases, usually seen in patients over 40 years of age, have an atrophic thymus that consists predominantly of adipose tissue and calcifications. Although the amount of adipose tissue and epithelial space in an atrophic thymus is very similar to that seen in age-matched controls, the remaining islands of medullary parenchyma have a high density of infiltrating B cells, which in some cases form GCs, and show marked follicular hyperplasia; the disease in such cases, particularly in some elderly individuals, responds favorably to thymectomy (14,21).

MG, antibodies, and thymus gland (Table 2)

The thymus is implicated in the etiology of MG in individuals with AChR autoantibodies, but its role in seronegative patients and those with MuSK and other antibodies is yet unknown. The thymus of individuals with MuSK+ MG shows only minor histological changes, and the organ often matches that of age-matched controls. Seronegative patients, in varying percentages have hyperplastic changes (22,23). A large epidemiological study found that the LRP4-MG thymi were diverse, and that only 32% of patients had thymic abnormalities (24).

Pathophysiology of TLH related MG (Figure 3)

The central role of the chronic expression of interferon beta (IFN-β): MG, a thymic-restricted interferonopathy

Interferons type I (IFN-I) are major cytokines that are transiently produced in response to viral infections. However, the IFN-I particularly with the IFN-β signature is detectable in the MG thymus, even long after disease onset, suggesting an inadequate resolution of inflammation (25). Unlike other autoimmune disorders, such as systemic lupus erythematosus and dermatomyositis, that are characterized by the chronic overexpression of IFN-I in peripheral blood and target tissues, the IFN-I signature is specifically detected in the thymus, suggesting that MG could represent a thymus restricted interferonopathy (26).

To avoid chronic IFN-I production, the IFN-I signaling is tightly controlled by different retro control mechanisms,

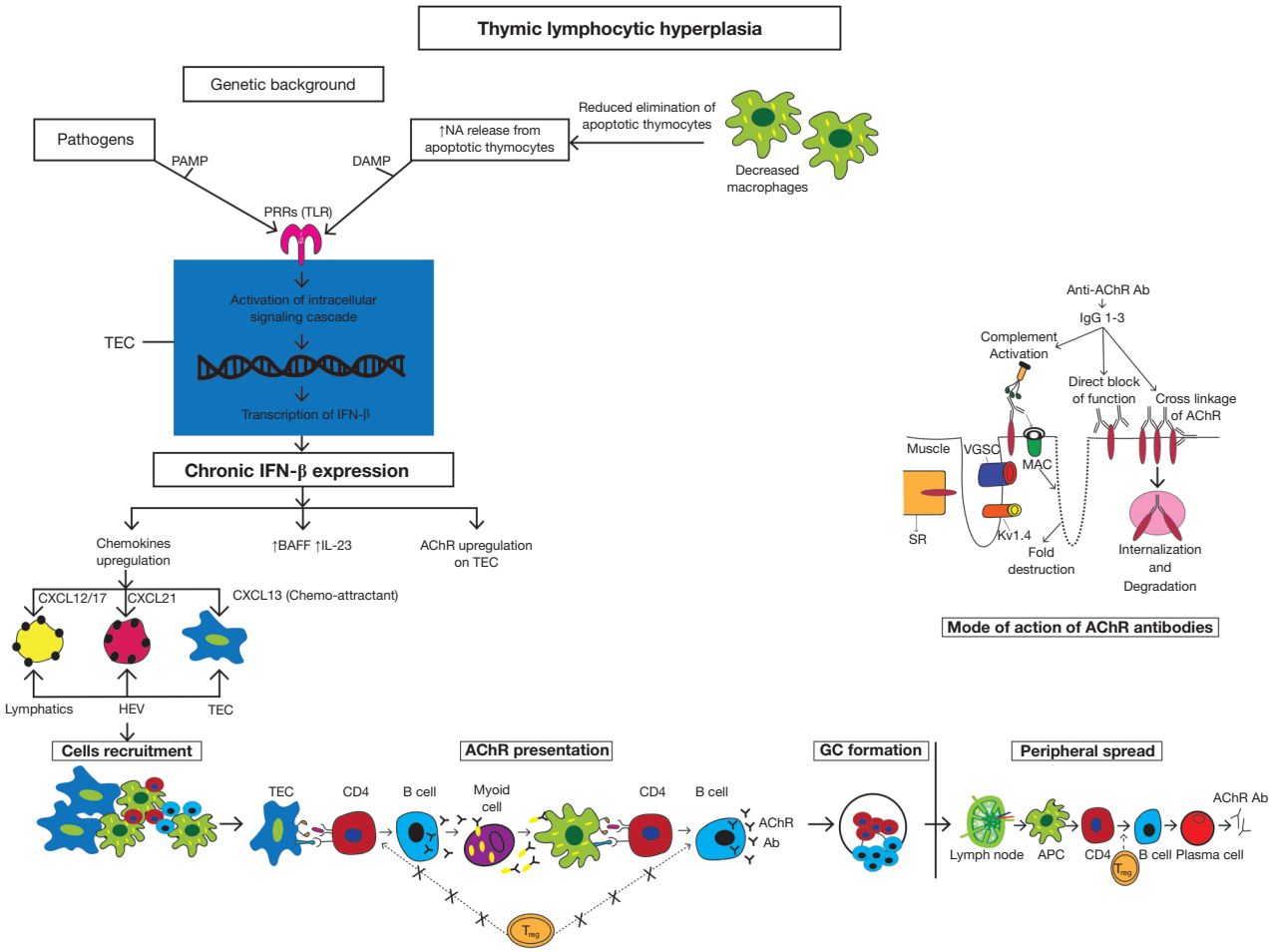

Figure 3 Pathogenesis of thymic lymphocytic hyperplasia related MG. Excessive NAs released from necrotic cells, exacerbated by impaired macrophage clearance in the thymus, as well as infections via TLRs on thymic epithelial cells, result in chronic over-expression of IFN-β. IFN-β upregulation is the primary orchestrator of thymic alterations: sensitization to AChR by selectively expressing α-AChR expression in TECs; promotes the expression of CXCL13 and CCL21 in the thymus, two chemokines involved in germinal center formation; causes BAFF overexpression; promotes the growth of pathogenic Th17 cells in the thymus. These modifications transform the thymus into a tertiary lymphoid organ with germinal center formation and the production of anti-AChR antibodies, resulting in neuromuscular junction failure. The autoimmune process triggered by the thymus can also disseminate to the periphery, explaining why disease activity persists even after thymectomy. PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; PRRs, pattern recognition receptors; TLR, toll-like receptor; NA, nucleic acid; TEC, thymic epithelial cell; IFN-β, interferon beta; BAFF, B-cell activating factor; IL-23, interleukin 23; CXCL, chemokine family of ligands; HEV, high endothelial venule; AChR, acetylcholine receptor; Treg, regulatory T cell; GC, germinal center; APC, antigen presenting cell; IgG, immunoglobulin; VGSC, voltage-gated sodium channels; SR, sarcoplasmic reticulum; Kv1.4, voltage-gated potassium channel subfamily A member 4; MAC, membrane attack complex; MG, myasthenia gravis.

that include modulation by micro RNAs (miRNAs). miRNAs regulate post-transcriptional gene expression and are potent modulators of protein expression. Specific miRNAs are implicated in the MG thymic pathogenesis. MIR-146, which is engaged in retro-control of IFN-I signaling, is downregulated in the MG thymus; this deficiency may lead to prolonged innate immunological activation and inflammation (27,28).

The triggering factor

The inciting event leading to immune activation in MG

could be: (I) an infection: the thymus is a common target organ in infectious diseases. Even though no clear link with a pathogenic infection is yet established, there is evidence identified of certain infections including Epstein-Barr, polio, and West Nile viruses in MG thymi (29-31). (II) Endogenous nucleic acids (NAs) released from necrotic cells, including thymocytes, can induce IFN-β expression in the thymus. Thymocyte apoptosis not only occurs during thymocyte development (where about 95% of thymocytes are eliminated), but is also induced by acute stress. Under physiological circumstances, thymic homeostasis is maintained by removal of apoptotic cells by phagocytes, such as macrophages, through a process called efferocytosis. A decreased number of macrophages is seen in the thymus of patients with AChR+ MG. As a result, apoptotic thymocytes would be insufficiently eliminated, and progress to a secondary necrotic stage, release intracellular materials such as NAs, and promote the production of IFN-β in the thymus (32).

Activation of innate immune signaling pathways

Pathogen-associated molecular patterns (PAMPs) from pathogenic infections, and damage-associated molecular patterns (DAMPs) linked with the release of endogenous molecules such as NAs from injured or dying cells, are recognized by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). Such receptors are widely expressed on APCs, and partially on non-professional immune cells such as epithelial cells (33,34), and may thus become activated.

Aberrant activation of TLR pathways in the MG thymus activates intracellular signaling cascades, leading to the transcription of IFN-I subtypes. In AChR+ MG, a persistent IFN-I signature, particularly overexpression of IFN-β, seems to be the main orchestrator of changes seen in the thymus (25).

Formation of GCs in thymic follicular hyperplasia

GCs often occur in secondary lymphoid organs that produce B cells, such as lymph nodes. They are responsible for generating the humoral immune response that results in the production of antibodies and lasting memory B cells. The thymus does not contain GCs under healthy conditions; TLH is defined by their existence. These findings not only confirm the occurrence of thymic inflammation, but also suggest that the function of the thymus has changed from a repository for T cell maturation to one of the establishment of an adaptive immune response, making it a tertiary lymphoid tissue (35).

Steps involved in the generation of GCs

The following series of events is hypothesized in the development of tertiary lymphoid structures in the thymus of MG patients:

(I) Cellular recruitment

IFN-β induces the upregulation of non-functional unfolded AChR and chemokine family of ligands (CXCL). The latter includes upregulation of the chemoattractant CXCL13, particularly for B lymphocytes on TEC; and promotion of neogenesis of the lymphatic endothelial vessels by CXCL 21 and HEV by CXCL 12 and 17 in the thymus of MG patients, which favor the recruitment of peripheral cells (36). IFN-β also induces the overexpression of B-cell activating factor (BAFF; the pro-survival cytokine for B cells) (37) and induces pro-inflammatory cytokines such as interleukin (IL)-23, favoring the differentiation of naive T-cells into pro-inflammatory T helper (Th) 17 cells that produce IL-17 (38). Functional defects in Treg cells, which maintain immune homeostasis and self-tolerance and prevent autoimmune disease, are identified in MG (39). The combination of neogenesis and chemoattractant upregulation provides an extensive vascular network and an ideal inflammatory environment for peripheral APCs, B cells, and T cells to find their niche in the thymus.

(II) Sensitization to AChR and GC formation

The sensitization to the AChR involves a two-step model: (I) upon re-entry of AChR-reactive T cells from the blood to the thymus, the effector T cells get 'primed' by hyperplastic mTECs expressing MHC and non-functional, unfolded AChR subunits, leading to the production of low-affinity early AChR antibodies. (II) These early antibodies attack thymic myoid cells which express intact, folded AChRs. Due to the lack of MHC-II molecules, myoid cells are unable to present to T lymphocytes; instead, they activate complement and induce the release of AChR antibody complexes for processing by nearby APCs. Activated APCs then cross-present autoantigen-peptides to AChR-specific autoreactive CD4 T cells and B cells, which then organize into GCs, leading to the production of high-affinity late AChR antibodies and subsequent epitope diversification (40).

Altogether, these observations indicate that in a predisposing background [human leukocyte antigen (HLA) D-related genotype, sex hormones, vitamin D level, etc.], after the initial innate immune response is activated by either infection(s) or the release of NAs from necrotic thymocytes, TLR activation results in the persistent production of IFN-I by TECs. This provides a pro-

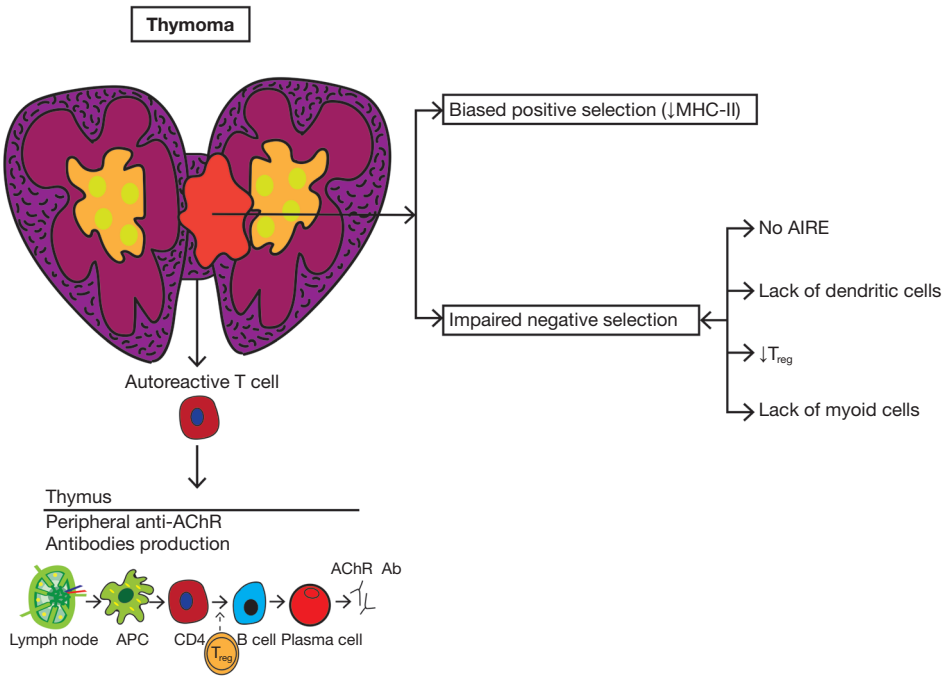

Figure 4 Pathogenesis of thymoma related MG. The absence of thymic architecture in thymoma, which is required for T-cell maturation and development, contributes to the formation of self-reactive T helper cells via biased positive selection and impaired negative selection. After being appropriately activated, self-reactive T helper cells results in the generation of autoantibodies against native AChR outside of the thymoma. MHC, major histocompatibility complex; AIRE, autoimmune regulator; Treg, regulatory T cell; AChR, acetylcholine receptor; APC, antigen presenting cell; MG, myasthenia gravis.

inflammatory environment for the induction of subsequent adaptive immune response, suggesting that IFN-I serves as an interface between innate and adaptive immunity.

Peripheral spread of thymus-initiated autoimmune process

The autoimmune process that began in the thymus later extends to the peripheral secondary lymphoid organs. This explains the ongoing disease activity detected even after thymectomy, which is likely mediated by autoantibody-producing B cells that have emigrated from the thymus, functionally defective Treg cells, and AChR antibodies produced at extra-thymic sites such as bone marrow and lymph nodes (41).

Mode of action of AChR-specific autoantibodies

AChR antibodies belong to the immunoglobulin (IgG)1 and IgG3 subclasses. They mediate tissue damage at the NMJ by multiple mechanisms: (I) antibody binding to AChRs leads to focal NMJ endplate lysis through complement activation and membrane attack complex formation; (II) cross-linking of adjacent AChRs by antibody leads to their internalization and degradation; and (III) further disruption of neuromuscular function is caused by antibody directly blocking the acetylcholine binding site (13).

Pathophysiology of thymoma-related MG (Figure 4)

Thymomas are closely associated with several immunological illnesses, including MG, because they lose thymic architecture that is necessary for T cell maturation and development. The following pathogenetic theories are proposed for thymoma-associated MG (8):

Biased positive selection

Neoplastic epithelial cells express epitopes of AChR subunits and titin, however MHC class II expression is low or absent in the neoplastic TECs, which is crucial for the T lymphocytes' positive selection. The TCR repertoire is altered by the reduced expression of MHC class II on

neoplastic epithelial cells. This results in the positive selection of Th cells with a stronger affinity for self-MHC-II molecules that should have been deleted, resulting in the subsequent emergence of T cell-dependent autoimmunity.

Impaired negative selection

Due to the lack of mature medullary structure required for negative selection, the self-reactive Th cells survive or are pre-primed *in-situ* by their target autoantigens. These factors include: (I) the absence of AIRE, which controls the expression of tissue-specific self-antigens; (II) lack of dendritic cells; (III) dysregulation of the master gene, forkhead box protein 3 (FoxP3). The FoxP3 gene is essential for Treg function; the latter keeps autoreactive effector T cells in check, thus affecting both central and peripheral tolerance; and (IV) lack of myoid cell-derived AChRs and titin, which are important for tolerogenic cross-presentation by APCs.

Peripheral anti-AChR antibody production

After evading central and peripheral tolerance, autoreactive mature Th cells enter the circulation, and after appropriate activation, stimulate the B cell response. Most often, this results in the generation of autoantibodies against native AChR outside of the thymoma. Only a small percentage of thymomas have intratumor lymphatic follicular hyperplasia and GCs. These ectopic GCs contribute to the local immune response and induction of antibody production against tumor-associated or self-antigens, thus increasing the risk of developing MG (42).

MG exacerbation post-thymectomy

The export of T cells from the thymus occurs years before a thymoma is diagnosed. Long-lived T cells may perpetuate anti-AChR antibody production at any time in the periphery (43). These data explain why some thymomatous MG patients after thymectomy may experience significantly higher mortality, lower remission rates, and less improvement than those who undergo thymectomy for nonthymomatous MG (44).

Pathophysiology of LOMG (Figure 5)

It has been hypothesized that age-related thymic involution contributes to immunosenescence (insufficiency) and inflammaging (overreaction), leading to the development of MG (45).

Immunosenescence

Immunosenescence is the term for age-related disruption in structural architecture and the functional components of the innate and adaptive immune systems. Immunosenescence causes thymic involution, which lowers the number of naive T cells while boosting the peripheral oligo-clonal growth of memory T cells. These events may lead to a decreased diversity in the overall TCR repertoire, leading to immunosenescence (immune insufficiency) (46).

Inflammaging

The current paradigm states that thymocytes are prone to negative selection if they express a TCR with a high affinity for self-peptides shown by MHC-II on mTECs. Age-related mTEC deficiencies include decreased AIRE and MHC-II expression. These factors reduce the ability to express the self-peptide-MHC-II ligand, which then modifies the intensity of TCR signaling (47,48).

Strong signaling, which results in negative selection and self-reactive elimination, swings either to weak signaling which releases self-reactive thymocytes, or to an intermediate level of signaling which supports the development of Treg cells. Normal Tregs suppress self-reactivity; however, aged Treg cells are unable to do so because of the loss of Treg TCR diversity (49).

The result of these changes is the generation of self-reactive T cells from an atrophic, myoid cell-deficient and AIRE-negative thymus, which upon activation in the periphery leads to the generation of pathogenic AChR antibodies and LOMG. After initiation, LOMG may become self-perpetuating due to stimulatory AChR/autoantibody complexes in muscle-draining lymph nodes, which may explain why thymectomy is ineffective in LOMG. Rarely, TLH can occur in older MG patients; in such cases, thymectomy can still be effective (21).

Evidence supporting role of thymectomy in MG

Thymomatous MG

Thymomas can spread locally and to distant sites, potentially causing compression in areas like the bronchi, lungs, or superior vena cava, leading to symptoms like superior vena cava syndrome. Therefore, regardless of whether the MG is ocular or generalized, thymectomy is indicated for definite tumor management. Thymomatous MG requires close observation and rigorous postoperative MG management since it is often more severe and responds less effectively to

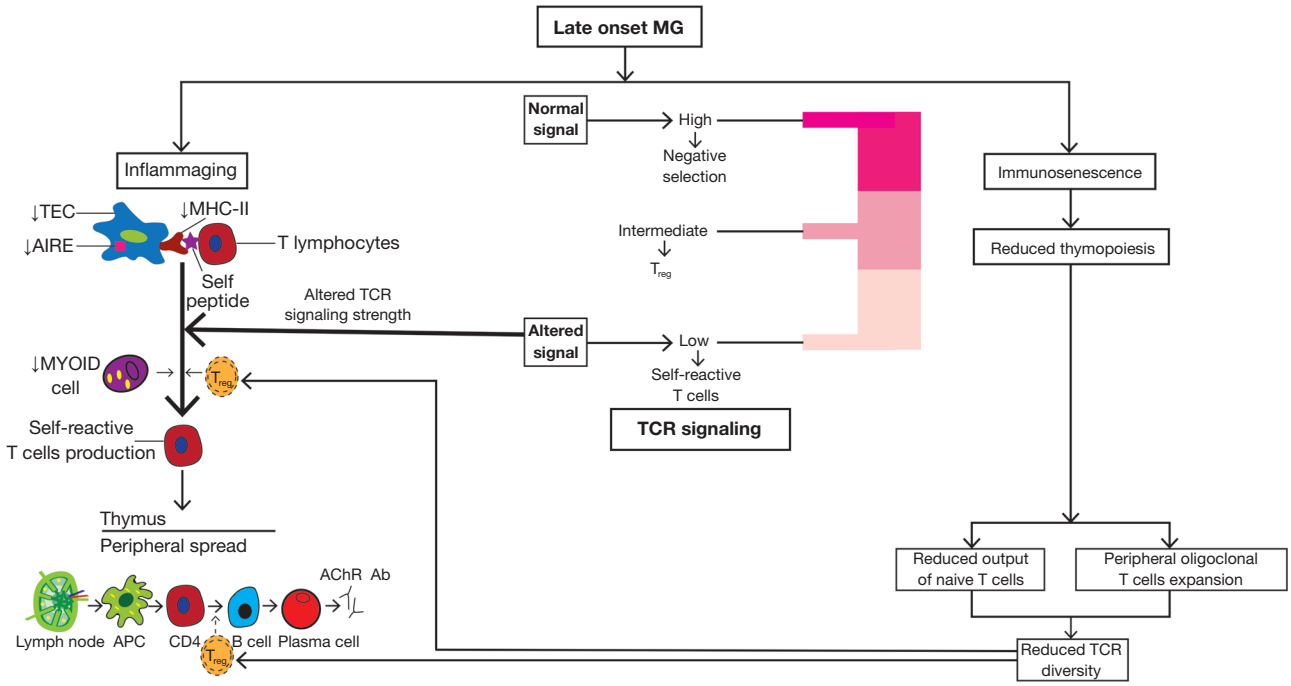

Figure 5 Pathogenesis of thymic Atrophy related MG. Inflammaging (because to defective negative selection and imbalanced generation of Treg TCR repertoire) and immunosenescence (due to diminished thymopoiesis and the proliferation of oligo-clonal T cells) both contribute to an increase in self-reactive T cells. These self-reactive T cells upon activation in the periphery leads to the generation of pathogenic AChR antibodies and late onset MG. MG, myasthenia gravis; TEC, thymic epithelial cell; MHC, major histocompatibility complex; AIRE, autoimmune regulator; Treg, regulatory T cell; TCR, T cell receptor; AChR, acetylcholine receptor; APC, antigen presenting cell.

thymectomy (please see section "*Pathophysiology of thymoma-related MG*" for details) (42-44).

Non-thymomatous MG

According to international consensus guidelines, thymectomy is advised for generalized nonthymomatous AChR+ MG patients aged 18 to 50 years in order to improve disease control and minimize immunotherapy needs while also reducing exacerbations and hospitalizations (50). This recommendation is supported by the following lines of evidence:

Randomized MGTX (Thymectomy Trial in Non-Thymomatous MG Patients) trial

The landmark MGTX multicenter, randomized trial demonstrated the superiority of prednisone and thymectomy, versus prednisone alone at 3-year follow-up; this observation was also supported by its 2-year extension study (total of 5-year follow-up) (3,51). The study compared various outcomes in these groups, including level of weakness and other symptoms related to MG, hospitalizations for exacerbations, and requirement for additional immunosuppression: within these and additional outcome measures, the thymectomy group demonstrated superiority. Further, these findings persisted at longer-term follow-up, though data were somewhat limited due to attrition of patient numbers.

Meta-analysis and systematic review

Various meta-analyses also support the conclusion that thymectomy is associated with improvement and even remission status in MG. One review, that included 22 retrospective studies, found the likelihood of achieving remission much higher among the surgical group compared to the conservative treatment alone group [odds ratio (OR) for improvement 2.44, 95% confidence interval (CI): 1.91–3.12] (52). These findings were further corroborated by a separate meta-analysis (53); however, these conclusions were somewhat limited due to multiple confounding factors,

observational study limitations, and heterogeneous methods among the included studies.

Evaluation of different predictors as well as short-term and long-term clinical response following thymectomy

A retrospective, single-center study (54) investigating short-term and sustained clinical response following thymectomy found that 72% of patients initially responded, but only half had a sustained clinical response on long-term follow-up at a median of 89.5 months. Thus, 28% of patients, therefore, never showed a sustained clinical response. Since a greater reduction in AChR levels was associated with a higher likelihood of achieving an initial clinical response, it has been suggested that AChR could represent a favorable prognostic marker. However, this study did not find any predictive value of sex, age at onset, disease subtype (thymomatous *vs.* non-thymomatous), thymus histology, delay to surgery after disease onset, surgical approach, and immunosuppressive treatment before surgery for reaching a sustained clinical response.

Conclusions from thymectomy studies

The following conclusions are drawn from these studies:

The advantage of thymectomy plus prednisone over prednisone alone suggests that in addition to the reduction of GCs with prednisone, thymectomy also eliminates molecules and cells that may contribute to disease pathogenesis (55,56).

Thymectomy may not be a curative procedure for MG, and the benefit may not last. This is due to the peripheral expansion of the autoimmune process from the thymus to the peripheral secondary lymphoid organs, which contributes to ongoing disease activity even after thymus removal and necessitates long-term immunosuppressive medications, possibly in a lower dose.

- The work by Rath *et al.* and other studies (54,57) show the effectiveness of minimally invasive, particularly robotic thymectomy, as compared to the extended trans-sternal method used in the MGTX trial to achieve removal of the entire thymus.
- The fact that clinical and demographic factors cannot accurately predict outcomes after thymectomy suggests that further investigation into miRNAs, particularly miR-150-5p, and the use of specific MRI techniques, could be employed as objective indicators for mechanism-based tailored treatment (see section "*Pathologic abnormalities in MG thymus*" for details) (58).

Thymectomy in sub-populations of MG

Ocular MG (OMG)

Thymectomy is recommended in thymoma-associated OMG patients; however, its role in non-thymomatous OMG remains controversial due to a lack of prospective trials.

Case series and meta-analysis

Remission rate

A number of case studies and meta-analyses have demonstrated that the remission rate of 57% to 71% over more than 5 years after thymectomy in OMG and generalized MG (gMG) is comparable (59,60).

Reduction in progression to gMG

No patients in two series of 96 total patients, and only 1 in a series of 61 patients, developed gMG after thymectomy (60-62). This suggests that thymectomy may delay the development of gMG, as the projected generalization rate throughout this time period was 50%. However, the significance of these findings is limited by the heterogeneity among trials.

Additional factors

- Histology: thymomatous MG patients with pathology revealing subtype B2/B3 thymoma had a higher risk of conversion to gMG compared to those with AB/B1 subtype or hyperplasia (63).
- Age and race: complete remission was higher in children and subjects from Western countries, than in adults and in the Asian population with OMG (64).

Recommendation

Thymectomy is not currently recommended as first-line treatment for OMG, but it may be offered in AChR+ non-thymomatous OMG patients, not responding to immunosuppressive medications or acetylcholinesterase inhibitors, or in those who have contraindications to taking immunosuppressive medications or who are unable to tolerate them (50).

Age—elderly/juvenile MG patients

Adults beyond the age of 50 years

There is limited data on the role of thymectomy in elderly patients. The MGTX trial allowed patients to participate up to the age of 65 years; however, the median age of the thymectomy arm was 32 years (range, 18 to 63 years), and neither arm had many patients above the age of 50 years (3).

In general, thymic atrophy is more prevalent in older

persons. This results in the generation of self-reactive T cells and the production of self-perpetuating pathogenic AChR antibodies outside the thymus, thus explaining the relative lack of effectiveness of thymectomy in LOMG (see section "*Pathophysiology of LOMG*") (45-49).

A single-centre, retrospective study involving 43 MG patients older than 60 years at onset, who underwent robotic thymectomy, identified thymic atrophy to be the most prevalent pathology (seen in 86%). However, thymectomy in this study seemed to be safe (1 perioperative death due to aortic dissection) and effective as 20% had a good outcome, which was defined as minimal disease manifestations or better, and with a statistically significant steroid-sparing effect (65).

Although there is no set age limit for thymectomy, most experts advise against surgery for most patients >60 years of age, based on a concern that the risks of thymectomy outweigh the potential benefits at this age. Others, however, disagree and advocate a customized strategy based on each patient's risk and benefit analysis, believing that older age is not always an excluding factor.

Juvenile MG

Juvenile MG involves the same pathophysiology as adult-onset disease. Thymectomy is a widely accepted option for peripubertal and postpubertal children with AChR+ gMG. In a review of various studies that included 588 patients, thymectomy was associated with improvement in clinical status and reduced need for medical therapy in 77% of patients. Within this group >12 years of age, increased likelihood for remission and more favorable outcomes were seen in those who underwent surgery within 1 year of onset of symptoms (66). These findings were also seen in previous reviews (67), suggesting a role for earlier intervention with thymectomy.

Antibody status: AChR, MuSK and seronegative MG

To-date there are a few studies that have examined outcomes related to antibody status in MG; however, some trends are evident (63,66-70). One study of OMG patients found a significant positive association between AChR –ve (AChR negative) MG status and complete remission following thymectomy (63). In contrast, when examining juvenile MG patients, Heng *et al*. (68) found an improved response in children with AChR+ MG, whereas Tracy *et al.* (67) did not find a significant difference.

MuSK+ MG patients, who often present with significant bulbar and facial involvement, remain difficult for long-term management given their often challenging and treatment-resistant clinical course (69,70). Assessment of outcomes in these patients following thymectomy remains mixed and additional data are needed. Most MuSK+ MG patients often have normal thymus histology, although a few show thymic hyperplasia (71). Analyses in a review examining the relationship between MuSK antibody and MG status found lack of improvement in clinical outcomes following thymectomy for MuSK+ patients; further, there was no difference in the need for immunosuppressive agents between the surgical and non-surgical groups (71,72). However, a study examining a small subset of MuSK+ patients in Thailand found favorable responses to thymectomy in several patients, including complete remission in three of seven and the ability to decrease immunosuppressant amount in four (72). Interestingly, the complete response appeared following a longer interval (up to 3 years), suggesting longer follow-ups are needed. Similarly, a separate retrospective study examining various treatment options reported favorable response at 3 years to thymectomy in 39% of the MuSK+ cohort, though notably most of these patients were also on immunosuppressants (71).

Despite the fact that thymectomy is an option for those with seronegative MG, including those with LRP4 antibodies, there are little data to support its use in this group. This is in large part because seronegative MG patients were ineligible for the MGTX trial, and in general make up a small proportion (6% to 12%) of all MG patients.

Risk of other autoimmune disorders post thymectomy

There is a wealth of evidence suggesting a relationship between MG and increased risk for developing other autoimmune diseases. While thymectomy has become a standard treatment in MG, there is also growing evidence of an increased rate of autoimmunity following this procedure (73). Although removal of the thymus can decrease Th cell populations and activity, it may lead to increased T cell suppressor activity, thus upsetting the T cell homeostasis (73).

In a study by Lin *et al.* (73) that examined the emergence of autoimmune diseases post-thymectomy, the incidence of any autoimmune disease was 2.68 times higher in the post-thymectomy group (MG and non-MG) compared to the non-thymectomy group. The hazard ratio for any autoimmune disease was 2.65 in the post-thymectomy

Table 3 Perioperative management

Preoperative
• Continue baseline myasthenia-related drug management to optimize disease control
• Risk stratify postop respiratory failure
• Minimize sedation
• Optimize lung function and comorbidities
• Rule out cardiac dysfunction
• Large substernal thymoma—evaluate for airway/cardiac collapse
• Minimize steroid dose as able
• Consider IVIg *vs.* plasmapheresis in the weeks prior to planned resection
Intraoperative
• Mechanical ventilation (with lung isolation if thoracoscopic approach)
• Minimize muscle relaxant use
• Sugammadex to reverse muscle relaxants
Postoperative
• Adequate pain control
• Avoid sedative/opioids
• Pulmonary toilet with breathing exercises/incentive spirometry
• Aggressive treatment with medication/IVIg/plasmapheresis if disease worsens
• Consider stress dose steroids depending on preoperative dose
• Avoid medications that can exacerbate MG (magnesium, beta blockers etc.)
• Review clinically for need for resumption of anticholinesterase drugs

IVIg, intravenous immune globulin; MG, myasthenia gravis.

group, after adjustment for age and sex; this finding remained after analyzing for organ-specific and systemic autoimmune diseases (73). Similarly, a single center cohort study from Beijing observed a higher occurrence of autoimmune diseases in MG patients post-thymectomy (4.3%) compared to those without thymectomy (1.98%); however, this difference could have been confounded by a higher proportion of females in the thymectomy group (74). There have also been case reports on patients with MG following thymectomy who develop NMO, another autoimmune disorder, though more work is needed to clarify this relationship (75).

Thymectomy: perioperative management

The reported rates of myasthenic crisis after surgeries, notably thymectomy, range from 2% to 25% in various series (76). To prevent this potentially fatal complication, MG patients undergoing thymectomy are best managed by a multidisciplinary team comprising the surgeon, anesthesiologist, and neurologist, with a presurgical customized plan to formulate management during the preoperative, intraoperative, and postoperative phases (*Table 3*).

Preoperative

Thymectomy in MG is an elective procedure, typically advised within the first three years of the diagnosis. It is advisable that MG symptoms are optimally controlled such that patients have minimal to no respiratory or bulbar manifestations (minimal disease defined per MG Foundation of America disease severity grading) (50). In real practice, this can be quite difficult to achieve given treatment resistance and disease severity, and at times, patients undergo the procedure despite ongoing symptoms in an effort to curtail disease activity. Since MG patients can be quite sensitive to the discontinuation of their medications, the use of symptomatic anticholinesterase medication (e.g., pyridostigmine) and immunotherapy should be continued through the perioperative period. It is also important to recognize that anticholinesterase drugs may not only alter the response to both depolarizing and nondepolarizing neuromuscular blocking agents (NMBAs), but also that NMBA reversal may be unpredictable or insufficient if sugammadex is not used for NMBA reversal. While corticosteroids may help with disease-induced muscle weakness, it is likely advantageous to taper the steroids to as low a dose as possible as the clinical condition allows to reduce the likelihood of postoperative infections and problems with wound healing.

Intravenous immune globulin (IVIg) or plasmapheresis should be used in patients with mild persistent residual respiratory or bulbar dysfunction. To ensure that the benefits of the fast therapy peak and last during the perioperative phase, these treatments should finish one week before surgery. This gives the coagulation factors eliminated by the exchange in the event of plasmapheresis

Table 4 Patient related factors predisposing to respiratory failure

Factors	OR (95% CI)
History of myasthenic crisis	4.13 (3.08, 5.54)
Bulbar symptoms	3.71 (2.54, 5.42)
Osserman stage (IIB + III + IV)	11.15 (6.88, 18.08)
Pyridostigmine dose (>750 mg/day)	3.53 (2.47, 5.03)
Elevated serum acetylcholine receptor antibody level	8.74 (3.31, 23.08)
Decreased vital capacity	5.71 (3.11, 10.48)
Coexisting disease	33.78 (10.57, 107.96)
Disease duration (>2 years)	5.94 (1.12, 31.48)

OR, odds ratio; CI, confidence interval.

Table 5 Surgical factors predisposing to respiratory failure

Factors	OR (95% CI)
Open *vs.* minimally invasive	5.88 (2.06, 16.80)
Blood loss (>1,000 mL)	15.03 (3.50, 64.50)

OR, odds ratio; CI, confidence interval.

Table 6 Scoring system to predict respiratory failure after surgery

Variables	Points
Osserman stage	
Stage I–IIA	0
Stage IIB	1
Stage III–IV	3
Duration of myasthenia gravis (years)	
<1	0
1–2	1
>2	2
Lung resection	
No	0
Yes	2.5
BMI (kg/m^2)	
<28	0
≥28	1

Total points (range, 0.0–8.5). BMI, body mass index.

time to recover.

Based on a variety of preoperative characteristics, patients should be risk stratified for the likelihood of the occurrence of postoperative respiratory failure and hence to anticipate the need for intensive care unit (ICU) care post-surgery (*Table 4*) (77).

Intraoperative (Table 3)

A range of techniques, including inhalation agents and intravenous anesthetics, is utilized for inducing and maintaining anesthesia for MG patients. The main objectives are to avoid anesthetic medications that can have lingering effects on the respiratory and bulbar muscles, and thus to facilitate a quick recovery after surgery. This is accomplished by maintaining body temperature, avoiding long-acting sedatives including opioids, and minimizing the use of non-depolarizing muscle relaxants. The lingering effects of anesthesia are best reversed with use of sugammadex and a twitch monitor, with the aim of shortening recovery time.

When using a thoracoscopic approach, mechanical ventilation uses a lung isolation technique with advanced airway devices like a double-lumen endotracheal tube or a bronchial blocker. Only ventilating the non-operative side during the procedure will ensure the lung is out of the field for the procedure. Since the lungs are not in the operating field during procedures requiring sternotomy, lung isolation is not required.

Surgical factors predisposing to respiratory failure must also be assessed (*Table 5*) (77).

Postoperative (Table 3)

Appropriate postoperative management includes pulmonary toilet and utilization of optimal pain management using multimodal analgesia that minimizes the use of opioids and sedation, as weak and ineffective cough can risk respiratory compromise and infection. Following extubation, patients need vigilant monitoring, early continuous positive airway pressure therapy, or IVIg or plasma exchange treatment to prevent reintubation.

Leuzzi *et al.* have proposed a simplified scoring system to predict respiratory failure after thymectomy in MG patients (*Table 6*). A score of <2.5 has less than a 10% chance of

respiratory failure and need for ICU admission, versus more than a 50% chance if the score is >4 (78).

Surgical methods

The goal of thymectomy in MG is to remove the thymus and as much of the surrounding mediastinal and cervical fat, which contains varying levels of ectopic thymic tissue, without endangering the recurrent laryngeal, left vagus and phrenic nerves (79).

There are four major methods for surgical approaches to thymectomy: open transsternal, transcervical, combined transcervical-transsternal, and minimally invasive (video- or robot-assisted) (80-82).

For many years, transsternal thymectomy (which was employed in the MGTX trial) has been the acknowledged standard surgical technique. It permits a thorough examination of the anterior superior mediastinum and the total removal of all thymic tissue and related fat. Since the MGTX trial, less invasive thymectomy techniques have become more common. Comparing non-randomized trials, these techniques produce outcomes that are comparable to those after aggressive surgeries. These less invasive methods have shorter recovery and hospitalization times, lower morbidity, and seem to be just as successful as open thymectomy. A recent systematic review (which included patients with thymomas, mediastinal masses, and thymectomies for MG) compared robot-assisted thoracic surgery (RATS) *vs.* video-assisted thoracoscopic surgery (VATS) *vs.* open thymectomy and found no significant differences between VATS and RATS approaches. RATS compared to an open approach had fewer complications and shorter length of stay in the hospital (83).

The thoracoscopic approach may be unilateral (right or left), bilateral thoracoscopic, or sub-xiphoid. With regard to unilateral thoracoscopic thymectomy there is no consensus as to which side (right *vs.* left) is more likely to achieve total thymectomy (84). Some have advocated for a subxiphoid thoracoscopic approach rather than right or unilateral thoracoscopic approach, with less pain and higher rates of total thymectomy noted, though this approach is not widely employed (85,86).

A key distinction between VATS and RATS, is that the former involves the surgeon holding the tools, while the latter allows the surgeon to operate the unique wristed instruments directly from a console, managing every aspect of their movement with a greater degree of freedom instead of having to handle "straight stick" instruments directly. The number and size of the incisions are usually similar when comparing VATS and RATS approaches. While there are no randomized trials comparing RATS *vs.* VATS approaches for thymectomy, one retrospective cohort study did show greater rates of remission with a 42-month follow-up after robotic resection (39.25% *vs.* 20.3%, P=0.01) with similar operative time (87). Another more recent retrospective cohort study showed RATS technique was an independent predictor of remission, with a trend toward greater remission after RATS *vs.* VATS (26% *vs.* 18%, P=0.06) (88). *Table* 7 provides a comparison of the pros and cons of these techniques.

Conclusions

The thymus is crucial for the development and maturation of T cells and the establishment of central tolerance. Different thymic pathologies including TLH, thymoma and thymic atrophy, use diverse pathways to contribute to the development and maintenance of autoimmunity in MG. A deeper understanding of these pathophysiological processes will not only shed more light on the role of thymectomy with specific pathologies, but will also explain why the prognosis is different with various thymic pathologies.

Minimally invasive thymectomy is now increasingly utilized for both non-thymomatous and thymomatous MG. The effectiveness and long-term outcomes of thymectomy in children, geriatric patients, and in those with ocular, MuSK+, and seronegative MG must be determined by

Table 7 Approaches in thymectomy

Factors	Transsternal	Extended cervical	Minimally invasive
Use	Standard approach	1st described surgical approach—extended approach by Cooper (introduced in 1988) most commonly used cervical approach	Increasingly utilized
Surgical access	Standard median sternotomy (midline chest incision from 2 cm below the sternal notch to the xiphoid process)	Transverse curvilinear incision made 2 cm above the sternal notch between the sternocleidomastoid muscles	VATS *vs.* RATS—access via 3–4 small ports (may be left, right, bilateral, or subxiphoid approach)
Major advantage	Excellent exposure of the anterior mediastinum and thymus	No significant advantage—often used by surgeons trained in this technique. Less pain associated with recovery	Minimally invasive, general advantages of video-assisted/robotic-assisted surgery
Limitations	Extended restrictions to allow for healing of sternum	Controversial and not widely accepted due to lack of familiarity, inadequate thymus exposure, and concern for incomplete resection. More limited visualization of the gland	Requires careful patient selection. Requires tolerance of single lung ventilation, can have difficulty visualizing contralateral phrenic nerve Increased cost with robotic
Indication	Large tumors and tumors invading adjacent structures	Limited to treatment of nonthymomatous myasthenia gravis	Stage I to II thymomas, thymic carcinomas <5 cm, nonthymomatous myasthenia gravis—increasing experience with larger tumors
Conversion rate	–	0–19% to transsternal approach—some may require sternotomy to control bleeding	0–7% to transsternal approach
Perioperative course	Longer hospitalization, postoperative pain from sternotomy, complications related sternotomy including infections and mediastinitis, rare perioperative death	Brief hospitalization (often 1 night or even none), operative major complication rate <1%	Shorter hospitalization, lower operative blood loss, decreased postoperative pain, rare perioperative death
Complications	Pulmonary: respiratory failure and prolonged intubation often associated with patients with myasthenia gravis—otherwise pleural effusion, pneumonia, atelectasis, pneumothorax		
	Nerve injury: phrenic nerve (<1% with transsternal approach, 7% with VATS, extremely rare though possible with RATS—leading to diaphragmatic dysfunction); left recurrent laryngeal nerve (with dissection of the aorticopulmonary window leading to vocal cord paralysis)		
	Infection/mediastinitis: overall rare—mediastinitis is more likely with sternotomy		

VATS, robot-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

randomized controlled studies.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work have been investigated and resolved.

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Review Article

Surgical treatment of thymic epithelial tumors: a narrative review

Apostolos C. Agrafiotis[1,2]^, Lawek Berzenji[1], Stien Koyen[1], Dries Vermeulen[1], Rachel Winthagen[1], Jeroen M. H. Hendriks[1,3], Paul E. Van Schil[1,3]

[1]Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Edegem, Belgium; [2]Department of Thoracic and Vascular Surgery, Wallonie Picarde Hospital Center (Centre Hospitalier de Wallonie Picarde—CHwapi), Tournai, Belgium; [3]Antwerp Surgical Training, Anatomy and Research Centre (ASTARC), University of Antwerp, Wilrijk, Belgium

Contributions: (I) Conception and design: AC Agrafiotis, JMH Hendriks, PE Van Schil; (II) Administrative support: S Koyen, D Vermeulen, R Winthagen; (III) Provision of study materials or patients: AC Agrafiotis, L Berzenji; (IV) Collection and assembly of data: AC Agrafiotis, L Berzenji, S Koyen, D Vermeulen, R Winthagen; (V) Data analysis and interpretation: AC Agrafiotis, L Berzenji, S Koyen, D Vermeulen, R Winthagen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Apostolos C. Agrafiotis, MD. Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Drie Eikenstraat 655, B-2650 Edegem (Antwerp), Belgium; Department of Thoracic and Vascular Surgery, Wallonie Picarde Hospital Center (Centre Hospitalier de Wallonie Picarde—CHwapi), Tournai, Belgium. Email: apostolos.agrafiotis@gmail.com.

Background and Objective: Thymic epithelial tumors (TETs) are scarce neoplasms of the prevascular mediastinum. Included in this diverse category of lesions are thymomas and thymic carcinomas (TCs). Surgery is the mainstay of treatment of tumors that are deemed resectable. However, up till now, optimal surgical access has been a subject of debate. The advent of new techniques, such as video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS), challenged the median sternotomy which was traditionally considered the access of choice. This review aims to demonstrate the current evidence concerning the surgical treatment of TET and to enlighten other controversial issues about surgery.

Methods: PubMed research was conducted using the terms [surgery] AND [thymic epithelial tumors] OR [thymomas] and [surgical treatment] AND [thymic epithelial tumors] OR [thymomas]. Papers concerning pediatric cases and non-English literature papers were excluded. Individual case reports were also excluded.

Key Content and Findings: Minimally invasive surgical techniques (MIST) such as VATS and RATS are increasingly applied in early-stage TET. Although numerous published studies have demonstrated better perioperative outcomes in early-stage TET, long-term follow-up data are still required to demonstrate the oncological equivalent of MIST to open surgery. Resection of stage III TET is more challenging. Thymectomy can be expanded en bloc to include the major vascular structures, lung, pleura, phrenic, or vagus nerve in these individuals. There is no agreement on the ideal surgical access and traditionally these patients underwent open sternotomy, sometimes combined with a thoracic access. Evidence concerning the treatment of stage IVA disease is mainly derived from retrospective case series which are highly heterogeneous in terms of the number of enrolled patients, histology, degree of pleural involvement, and timing of presentation.

Conclusions: New techniques in the field of minimally invasive surgery are gaining acceptance for early-stage TET but longer follow-up periods are warranted to prove their oncological outcomes. On the contrary, these techniques should be used cautiously in case of locally advanced tumors. Surgeons must not forget that the main objective is the complete resection of the lesion, which is one major predictive factor for increased survival.

Keywords: Thymoma; thymic carcinoma (TC); robotic surgery; thoracoscopic surgery

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^ ORCID: 0000-0002-7525-2080.

Introduction

Thymic epithelial tumors (TETs) are scarce neoplasms of the anterior (prevascular) mediastinum (1). Included in this diverse category of lesions are thymomas and thymic carcinomas (TCs). Thymomas have in general an indolent course and until recently, they were considered to be benign lesions (2). On the contrary, TC are more aggressive tumors that tend more frequently to invade adjacent organs and metastasize (2,3). Consequently, TC have a worse prognosis than thymomas (2). Many staging classification systems have been suggested and put into practice. The most popular staging system is that developed by Masaoka in 1981 and modified by Koga in 1994 (4-6). The World Health Organization (WHO) histological classification (1999) was accepted on a global scale. The revised WHO classification in 2015 classified these tumors as A, AB, B1, B2, and B3 thymomas and TC (7,8). The Masaoka-Koga stage classification and the WHO histological classification, however, are not directly correlated (4-9). The International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancies Interest Group (ITMIG) created a new tumor-node-metastasis (TNM) staging system in 2014 (9). Consequently, thymic malignancies were matched to other solid tumors using a TNM method.

Surgery is the mainstay of treatment of tumors that are deemed to be resectable. Indeed, many studies have shown that one of the major predictive factors of survival is the completeness of resection (10). However, up till now, optimal surgical access has been a subject of debate. The rarity and histological heterogeneity of TET preclude the conduction of large-scale randomized trials and this problem is also applicable to the choice of surgical technique. The available body of evidence is mainly derived from retrospective series and thus robust recommendations are difficult to define. The advent of new techniques, especially in the field of minimally invasive surgery, such as video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS), challenged the median sternotomy which was traditionally during decades considered the access of choice for the resection of TET (11). Nowadays, still many surgeons consider median sternotomy to be the preferred surgical approach. Transcervical or subxiphoid access has also been proposed as an alternative to the trans-sternal and intercostal techniques, involving sometimes sternal lifting (12). This review aims to demonstrate the current evidence concerning the surgical treatment of TET by providing an appraisal according to the stage of the lesions and to enlighten other controversial issues about surgery. For demonstrative and educational reasons, two perioperative photos and one photo of an operative specimen of three different cases operated in the University Hospital of Antwerp are provided in the main text, without elements that could reveal the identity of the patients. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-44/rc).

Methods

The current recommendations on the quality assessment of narrative review articles were followed in the elaboration of this review (13). Research from PubMed was done with the terms [surgery] AND [thymic epithelial tumors] OR [thymomas] and [surgical treatment] AND [thymic epithelial tumors] OR [thymomas]. Papers concerning pediatric cases and non-English literature papers were excluded. Individual case reports were also excluded. Papers were chosen based on relevance because the current study is not a systematic review. The majority of studies were retrospective case series and consequently, papers with higher levels of evidence have not been identified. The references of selected papers were sought to find other pertinent articles. The search strategy is demonstrated in *Table 1*.

An overview of the surgical treatment of TET

The surgical treatment of TET is presented for each stage according to the Masaoka-Koga staging system. The treatment of recurrent disease, the extent of lymphadenectomy, the place of salvage surgery and the extent of resection (total versus limited thymectomy or thymomectomy) are the subjects of separate analysis.

The histological heterogeneity of TET inevitably creates inhomogeneous studies in terms of WHO histological classification and the Masaoka-Koga clinical stage. In addition, patients with thymomatous myasthenia gravis (MG) are added to the population. This innate heterogeneity is aggravated by the difference in definitions, because by using the term “thymectomy”, the extent of resection is sometimes considerably variable. Toker *et al.* provided definitions to standardize surgical practice and research (12). These definitions have been endorsed by ITMIG members. More specifically, a complete

Table 1 The search strategy summary

Items	Specification
Date of search	01/09/2023
Databases and other sources searched	PubMed
Search terms used	[surgery] AND [thymic epithelial tumors] OR [thymomas] and [surgical treatment] AND [thymic epithelial tumors] OR [thymomas]
Timeframe	No date restriction
Inclusion and exclusion criteria	Inclusion: all types of studies
	Exclusion: papers concerning pediatric cases and non-English literature papers were excluded. Individual case reports were also excluded
Selection process	The literature research and selection process were conducted independently by four of the authors (L.B., S.K., D.V., R.W.)
	Any discrepancies were resolved after a discussion between the researchers, if no consensus was obtained, the opinion of the designers of the study (A.C.A., J.M.H.H., P.E.V.S.) was sought

thymectomy (complete removal of the thymic gland) is advised for patients without MG, and an extended thymectomy (removal of the contiguous right and left mediastinal pleura, mediastinal and pericardiophrenic fatty tissues, and dissection of the aorto-pulmonary window in addition to a complete thymectomy) is advised for patients with MG (12). Therefore, unless it is in the context of a clinical trial, surgical resection of anything less than a complete thymectomy is seen to be unsuitable at this time. Onuki *et al.* and Bae *et al.* used the term "limited thymectomy", described as the removal of the thymoma (thymomectomy) along with the fatty tissue and surrounding tissue, leaving behind residual thymic tissue (14,15). Even if encouraging results in terms of recurrence are presented, however, these should be interpreted cautiously because long follow-up periods are warranted in order to draw robust conclusions. The indolent course of TET renders mandatory the establishment of longer follow-up programs. For all these reasons, limited thymectomy is highly debated.

The anatomic position of the thymus in the anterior (prevascular) mediastinum reasonably led the thoracic surgical community to consider median sternotomy as the optimal surgical access that could provide easy and complete resection of thymic lesions (11). Thymectomy may also be performed by cervicotomy and thoracotomy but there are concerns raised about the completeness of resection that can be achieved. Median sternotomy remains the primary surgical method for resectable lesions (stage I, II, and selected stage III cases), according to the European Society of Medical Oncology (ESMO) recommendations on thymic tumors (grade IV, level A) (16). Nevertheless, minimally invasive techniques are considered to be an alternative for assumed stages I and II, according to the ESMO guidelines, if local technical expertise exists.

Stage I and II

Minimally invasive surgical techniques (MIST) such as VATS and RATS are increasingly applied in early-stage TET (17-20). There are many papers, mainly retrospective series, that provide excellent complete resection rates in favor of MIST. There are also studies comparing these techniques with open sternotomy, however, the absence of randomized controlled trials must be underlined. In order to compare MIST and open surgery in TET, Friedant *et al.* conducted a systematic review and meta-analysis of the relevant literature (21). Individuals in the MIST group had smaller tumors and were expected to be in stage I/II than individuals in the open surgery group (95% *vs.* 78%). Patients in the MIST group had less blood loss during surgery, but there were no significant differences in the length of the procedure, or the incidence of pulmonary, cardiac, or other complications. Patients in the MIST group had shorter lengths of stay. When only patients with Masaoka stage I and stage II thymic malignancies were examined, neither the rate of R0 resection nor the total recurrence rate differed (21). In the systematic review of Hess *et al.*, the tumors removed by open surgery were

larger than the ones in the MIST group (22). Decreased intraoperative blood loss, faster removal of the chest tube, and shorter hospital stay were all related to MIST resection. The two groups did not vary in terms of surgical complications or thymoma recurrence (22).

As for the size, traditionally MIST were considered to be indicated only for smaller tumors (23). Tumor size is a significant consideration when considering a VATS thymectomy (24). Originally set at 3 cm, the cutoff was later raised to 5 cm (25). According to Kimura and colleagues, patients were most frequently found to have tumor capsule damage during VATS in case of thymomas 5 cm in diameter or larger (26). However, numerous researchers concur that VATS thymectomy is theoretically possible for thymomas with a diameter of up to 5 cm (27). Girard and colleagues commented that large tumors were not candidates for VATS treatment due to the technical challenge of managing the tumor intraoperatively (28). According to some reports, thymoma invasion into the great veins and pericardium is a more important factor in determining the indications for VATS thymectomy than tumor size itself (29). Agatsuma *et al.* conclude that there is indeed no agreement on the largest tumor size that can be removed through VATS thymectomy, however, larger thymomas should still get cautious consideration to prevent capsule damage (30). MIST have been reported to be successful in the removal of bigger tumors when combined with enhanced technology resources and robotic resection (31). Therefore, it appears from the available data that tumor dimension does not always preclude MIST as long as the fundamentals of TET resection are upheld. (avoidance of capsule rupture and complete resection) (31).

In terms of postoperative morbidity, loco-regional recurrence rates, overall and recurrence-free survival, MIST are comparable to open surgery. Furthermore, MIST are linked to a shorter hospital stay and less intraoperative blood loss. Gu *et al.* studied patients who were included in the ChART (Chinese Alliance for Research in Thymomas) database in order to compare VATS with open surgery for stage I TET (32). It was a propensity score-matched study with 110 patients in each group (after matching). Their analysis showed no significant difference in overall survival (OS), disease-free survival (DFS), cumulative incidence of recurrence, and improvement of MG between the two groups. However, it has to be taken into consideration that the median follow-up was 26 and 36 months for VATS and open surgery, respectively. In conclusion, according to the Guideline Committee of the Japan Lung Cancer Society (JLCS) for Thymic Tumors, for clinical stage I–II TET, thoracoscopic resection may be considered, although there is insufficient scientific evidence (grade C1) (33).

A retrospective study using data derived from 32 Japanese institutions, compared VATS and sternotomy for the surgical treatment of Masaoka I and II stage thymomas (30). Using propensity scores, the study evaluated postoperative complications, positive surgical margins, location of recurrence, and survival in 140 patients who underwent VATS and 140 patients who underwent sternotomy. There was no statistically significant difference in the recurrence rate, the recurrence-free survival, and OS rates between groups. According to the authors, the risk of pleural spreading is not increased with VATS thymectomy.

The advent of RATS has revolutionized surgical resection of TET mainly because of the better visualization of the anterior mediastinal compartment (especially in distal areas such as the superior thymic horns) offering better and more precise dissection (34,35). These advantages demonstrate that RATS can overcome the limitations of VATS. A meta-analysis published in 2017 compared RATS and VATS for TET. More particularly, surgical outcomes, operative time, length of stay, intra-operative blood loss, conversion to sternotomy, and postoperative complications were investigated (36). Five articles were included and a total of 450 patients were analyzed (169 by RATS and 281 by VATS). The quantitative analysis revealed no significant differences between the RATS and VATS. There were no significant differences in terms of conversion rates, operative time, and length of hospitalization. There was a slightly higher blood loss in the RATS group. Another meta-analysis included 350 patients (182 and 168 patients treated by RATS and VATS thymectomy, respectively). In terms of conversion to open surgery, hospital stay time, or postoperative pneumonia, there was no statistically significant difference. The RATS thymectomy group had a longer operative time (37). A third study included a total of 489 patients, of whom 215 underwent RATS and 274 open surgery. Patients undergoing RATS spent less time in the hospital than patients treated by open surgery. The differences in pleural drainage days, intraoperative blood loss, and postoperative complications were not significant between the two groups (38). Soder *et al.* conducted a propensity-score matching analysis of two groups of patients, operated by RATS or open procedures (39). RATS was associated with decreased operative time, complications, chest tube duration, and length of stay. The completeness of resection was similar between the two groups. OS was

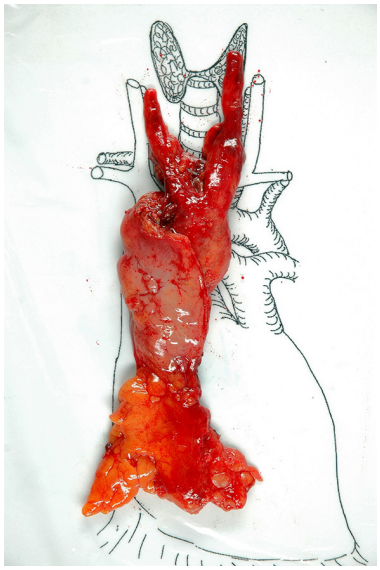

Figure 1 Operative specimen of a small thymic carcinoma removed by robotic-assisted thoracoscopic surgery.

85.3% in the open surgery group and 96.8% in the RATS group (the median OS was not reached in the two groups), however, it has to be mentioned that the median follow-up was significantly shorter in the RATS group.

Consequently, RATS seems a valid alternative for open surgery in terms of perioperative outcomes but longer follow-up is needed in order to support the oncological outcomes. Another issue that has to be taken into account is the high cost of the robotic platform that hinders its widespread use. On the other hand, studies comparing different techniques do not always provide a cost analysis. *Figure 1* shows the operative specimen of a small TC removed by RATS in our institution.

Li *et al.* conducted a propensity score-matching study comparing VATS and RATS (60 patients in each group) (40). The majority of tumors were stage I and II. Progression-free survival (PFS) was longer in the RATS group but not statistically significant. The surgical time in the RATS group was significantly shorter than that in the VATS group. However, there were no significant differences in postoperative complications, duration of chest tube insertion, the median volume of drainage (in the first 24 hours), or postoperative hospital stay (40).

A retrospective study from the Netherlands concluded that RATS is a safe and feasible procedure for patients with thymomatous MG (41). More particularly, the majority of myasthenic patients with a thymoma presented remission, mostly within 12 to 24 months after surgery. There was no discernible variation in the results between myasthenic and non-myasthenic patients. (41).

The entry point into the thorax is also a matter of debate in both RATS and VATS. Right-sided, left-sided, or bilateral access is applied by different groups without a consensus about the optimal strategy. Valid arguments exist to support the choice of each surgical access depending on the surgeon's and center's experience.

Subxiphoid access seems to overcome this problem by providing a surgical view equivalent to a sternotomy with visualization of both phrenic nerves and a good exposure of the upper poles of the thymus. Many groups reported excellent results (42-44), and the addition of sternal elevation further improves surgical view (44). Suda *et al.* evaluated thymectomies performed either through a single subxiphoid incision or via trans-subxiphoid RATS (43). The operative time was significantly shorter in the single-port group compared to the robotic group (135±48 and 204±40 min, respectively). The amount of blood lost during surgery, the length of the hospital stay following the procedure, and the time spent using oral analgesics afterward did not significantly differ between the groups. There were no intraoperative complications (43). Even though RATS could be applied through a subxiphoid incision, this technique is not widely adopted and thus more evidence is necessary. Song *et al.* evaluated the treatment efficacy of thymectomy for stage I and II TET performed using a subxiphoid thoracoscopic technique with a double elevation of the sternum compared to intercostal uniportal VATS (45). They gauged the degree of resection by measuring the length of the removed thymic tissues. Significantly larger specimens were resected through a subxiphoid VATS approach compared to the intercostal VATS group. No significant differences were found in the hospitalization cost, incidence of complications, or 3-year DFS between the two groups (45). The authors concluded that in comparison to intercostal VATS, the subxiphoid approach with double elevation of the sternum demonstrates the possibility for a more thorough clearing of thymic tissue (45).

There are numerous reports of the oncologic reliability of VATS thymectomy for Masaoka stage I and II tumors in terms of the oncologic outcome (46). According to Jurado and colleagues, there was no difference in 5-year recurrence-free survival (RFS) and recurrence rates between patients receiving VATS treatment and those receiving open sternotomy (47). When compared to sternotomy, VATS yielded a better 5-year OS, but the 5-year RFS did

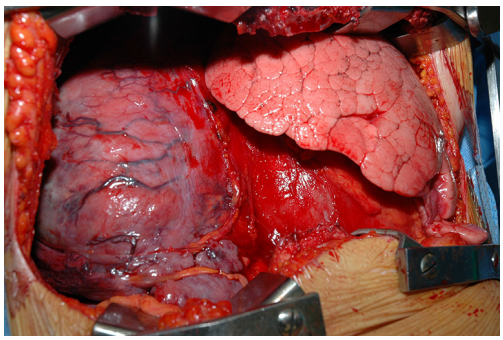

Figure 2 Intraoperative photo of a large thymoma B2 operated by clamshell incision.

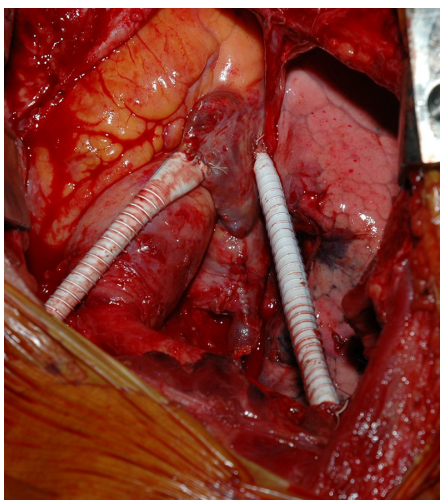

Figure 3 Intraoperative photo of another case of B2 thymoma operated by sternotomy with venous reconstruction with two ringed polytetrafluoroethylene grafts.

not change between the groups, according to Sakamaki and colleagues' research (48).

However, it is unclear whether VATS thymectomy for MG has the same operative outcomes as median sternotomy due to the lack of randomized prospective clinical research.

However, the adoption of VATS thymectomy has been hindered, particularly for large tumors, due to oncological concerns of the thoracoscopic excision associated with the potential manipulation of the tumor and consequent pleural seeding, as well as the limited working space (39).

In conclusion, median sternotomy remains the surgical access of choice for TET in the absence of large-scale randomized controlled trials (49).

Although numerous published studies have demonstrated better perioperative outcomes, long-term follow-up data are still required to demonstrate the oncological equivalent of MIST to open surgery. It has to be mentioned that in the case of histologically proven TC, the preferred surgical approach for some groups is open surgery, even for stage II lesions (50).

Stage III

Resection of stage III TET is more challenging (51). Thymectomy can be expanded *en bloc* in these individuals to include the major vascular structures, lung, pleura, phrenic, or vagus nerve (20,52). Upfront surgery is not always feasible and for that reason, multimodality protocols are applied in these cases (53,54). When surgery is performed as the first intention treatment in stage III TET, the completeness of resection is almost sub-optimal and highly variable (40–90%) according to the different series (55). Induction therapy can in fact result in tumor downstaging and render complete resection possible in case of tumors that were initially considered to be unresectable (16,55). Combined resection of involved adjacent organs is recommended, if feasible, to achieve a complete resection (33). Incomplete resection rates are increased compared to stages I and II (56).

It has been debatable how to operate on stage III TET. There is no agreement on the ideal surgical access and traditionally these patients underwent open sternotomy, sometimes combined with a thoracic access (55). In fact, in cases of involvement of posterior mediastinal structures, an extension of the incision is necessary, in the form of hemi-clamshell or clamshell incision (57). *Figure 2* shows the case of a large thymoma B2 operated by clamshell incision and *Figure 3* is another case of B2 thymoma operated by sternotomy with venous reconstruction with two ringed PTFE grafts; both cases were operated in our institution.

The study conducted by Chen *et al.* investigated the feasibility of MIST for the resection of stage III TET (58). The study included 26 individuals who underwent surgery for Masaoka stage III thymic malignancies by VATS (subxiphoid VATS and two cases of subxiphoid combined right-sided VATS) and open sternotomy. Significantly larger tumors were resected by sternotomy. Lesions more commonly affected the phrenic nerve and superior vena cava in the same group of patients. The factors that hampered successful VATS excision were determined to be the size of the tumor (>6 cm) and the involvement of the phrenic nerve and superior vena cava. The authors conclude that

in selected cases of Masaoka stage III thymic malignancies (a thymic tumor of less than 6 cm, though invading the innominate vein, pericardium, and part of the lung), MIST are acceptable (58). However, the efficiency of the VATS resection was questioned throughout the short-term follow-up period, and more research into MIST long-term oncological outcomes is required. Yokota *et al.* operated on patients with TC. MIST were performed for stage III unless a vascular invasion necessitating a reconstruction was encountered (59).

A multicenter study enrolled 134 patients who underwent RATS resection of TET (60). Whenever stage III and IV disease were encountered during surgery, a conversion to open surgery (sternotomy or thoracotomy) was performed. In case of involvement of the pericardium, the phrenic nerve, and the parietal pleura the resection was still performed by RATS. According to the authors, despite being theoretically possible, extended resections ought to be seen as experimental surgery and only used in a very small number of cancer cases. Kang *et al.* expand the indications for robotic thymectomy in stage III TET, by including cases of lung, mediastinum, and innominate vein invasions, whereas robotic thymectomy is deemed contraindicated in cases of chest wall and great vascular invasion (61).

Stage IVA

De novo stage IVA thymomas, which account for around 7% of all thymomas, present 5- and 10-year survival rates of 59% and 36%, respectively. Even while stage I to stage III thymoma relapse rates are generally low, more than half of these do so in the pleural space, and are associated with a poor prognosis (62,63). Evidence concerning the treatment of stage IVA disease is mainly derived from retrospective case series which are highly heterogeneous in terms of the number of enrolled patients, histology, degree of pleural involvement, and timing of presentation (de novo disease versus relapse) (64). The degree of pleural involvement may extend from a solitary deposit, a more extensive spread manageable by extrapleural resection, to a bulky disease not amenable to surgical resection. Patients with fewer pleural implants, representing a lower disease burden, have a better OS (52,65-67).

There are different techniques described in the case of pleural involvement, ranging from debulking surgery to extrapleural pneumonectomy (EPP) (64). Since no single surgical strategy has invariably been shown to improve survival compared to the others, many support choosing the surgical treatment in a tailored fashion according to specific factors related to the patient and the extent of the disease (64). A multimodal treatment plan is routinely adopted (16,53,68).

Case reports and case series described the initial experience of cytoreductive surgery combined with hyperthermic intrapleural chemotherapy (69-72). Yu *et al.* presented a small case series of 4 patients who underwent cytoreductive therapy combined with hyperthermic intrapleural chemotherapy (two patients with *de novo* stage IV and two patients with recurrent disease). Patients were followed up for 1–4 years. One elderly patient died of heart failure one year after surgery, whereas the remaining three patients presented no local recurrence or distant metastases (73). Belcher *et al.* retrospectively analyzed six patients who underwent cytoreductive therapy and received intraoperative hyperthermic pleural irrigation, after induction chemotherapy (74). The median follow-up was 18.8 months and 4 out of 6 patients were alive with no evidence of recurrent disease. For stage IV disease with pleural metastasis, robotic thymectomy can be performed in selective patients with oligometastatic disease (61). Yellin *et al.* evaluated surgical resection combined with heated pleural chemoperfusion as a treatment for *de novo* stage IVA thymoma and TC and for thymoma with pleural relapse (62). The goal of surgery was to completely remove any mediastinal involvement and completely remove any pleural disease. The chest wall pleura was the primary target of the partial pleurectomy. When necessary, diaphragmatic implants with partial muscle thickness were removed. Lung involvement was treated by wedge resection. A lung-sparing strategy was applied by this group. Five-, 10-, and 15-year OS were 81%, 73%, 58% for *de novo* stage IVA thymoma, 67%, 56%, 28% for thymoma with pleural relapse, and 0%, 0%, 0% for TC. Five- and 10-year PFS was 61%, 43% for *de novo* stage IVA thymoma, and 48%, 18% for thymoma with pleural relapse. The authors conclude that even though this strategy is acceptable in the case of thymoma with pleural spread, the results in the case of stage IVA TC are disappointing (62). There is an ongoing debate between pleurectomy and EPP. This choice is most of the time guided by the degree of lung involvement. The proponents of EPP underline its improved local control, nevertheless, patient selection is crucial in order to identify those who can tolerate major surgery (75-80). On the other hand, proponents of pleurectomy put forward its lung-sparing advantage and its more acceptable morbidity-mortality (76). In fact, the median PFS of 12 patients with pleural recurrence of thymoma who underwent extended

pleurectomy and decortication combined with hyperthermic intrathoracic chemoperfusion was 72.2 months (81).

The benefit of debulking still remains controversial (82,83). Debulking has been favored by some groups in cases of untreatable disease. Patients who underwent subtotal resection had better OS than those who underwent no resection at all, according to a large review by Kondo *et al.*, although this may be partially attributed to selection bias in the patients enrolled in the intervention arm (31,64,84).

Lymphadenectomy

The new IASLC/ITMIG TNM staging system in order to standardize surgical practice and communication between specialists, defined the N factor as follows: N0 No nodal involvement, N1 Anterior (perithymic) nodes, and N2 Deep intrathoracic or cervical nodes (9,85,86). The distinction between the N1 and N2 nodes supports the theory that the involvement of deep lymph nodes (N2) rather than lymph nodes near the thymus (N1) indicates a more advanced or aggressive disease (87).

In a Japanese study of 1,320 resected thymic tumors, lymph node invasion was observed in 2% of thymomas, including 1% of stage I cases, and 6% of stage III cases, and was primarily found in the anterior mediastinum (84). TC are more likely to have nodal invasion because they occur more frequently in extrathoracic sites (in 30% of cases), other intrathoracic areas (in 35% of cases), and the anterior mediastinum (in 70% of cases) (87,88). A retrospective analysis of a Chinese database including 1,617 patients demonstrated that the frequency of nodal invasion was 2.2% and resulted in worse OS. Nodal involvement was found in only seven of 1,310 (0.5%) patients with thymoma, whereas in patients with TC and neuroendocrine thymic tumors (NETTs), it was 7.9 and 16.7%, respectively (89). According to Fang *et al.*, patients with thymomas had a rate of lymph node metastasis of 2.1%, those with TC a rate of 25%, and those with NETTs a rate of 50%. The authors also identified TC, NETTs, advanced clinical stages, N2 nodal dissection, and histological WHO classification B3 as predictors of nodal involvement. As a result, they advise adding ipsilateral N2 nodes to the lymph node dissection recommendation in these circumstances (90). However, bilateral nodal dissection is typically not required apart from cases of NETTs that are associated with a high prevalence of considerable nodal disease.

According to the current recommendations, the resection of all thymomas with invasion of the surrounding structures (> T2, stage II or higher) should be associated with the routine removal of the anterior mediastinal nodes and the low anterior cervical nodes (N1 stations) routinely. Typically, the specimen is removed along with the perithymic nodes. In the event of stage III/IV thymomas, systematic sampling of the deep regional nodes is strongly advised. In the case of TC and NETTs a thorough nodal dissection of all N1 and N2 regions is warranted (16,86,91,92).

Recurrent disease

Re-resection of relapsing thymomas is an approved choice when a complete resection appears to be possible because it has been shown to improve long-term patient survival in various studies (33,93,94).

One of the mainstays of treatment for recurrent disease is a new surgical resection. Studies have demonstrated that patients who had their recurrent disease surgically removed had much better results than those who had received adjuvant therapy (66,67,95). Mizuno *et al.*, extracted 420 patients who presented a recurrent TET after resection (incidence of recurrence 14.8%) from a national Japanese database (96). Among them, 162 patients were treated surgically, and 243 were treated non-surgically. The most frequent metastatic site was the pleura (54.1%), followed by the lungs (21%). Female sex, Masaoka I–II stage, non-TC histology, absence of preoperative treatment, and longer recurrent-free interval were significantly favorable factors for survival in the surgery group. In multivariate analysis, non-TC histology and longer recurrence-free interval were recognized to be independent prognostic factors. The survival of the surgery group was significantly better compared to the non-surgery group, with 5- and 10-year survival rates of 82.7% and 68.2%, respectively, in the surgery group and 43.5% and 25.4%, respectively, in the non-surgery group (96). Okumura *et al.*, evaluated 67 patients with tumor recurrence. Among them, 22 patients underwent re-resection. The 10-year survival rate was 70% for patients who underwent a re-resection, and 35% for those who did not (93).

Salvage surgery

Salvage surgery is defined as the surgical resection of persistent or recurring tumors following local treatments with curative intent or after the administration of exclusive chemotherapy for voluminous lesions. There are no documented indications for salvage surgery in TET. Even

if this strategy could result in acceptable rates of morbi-mortality, it should be reserved in selected cases after multidisciplinary discussion and approval (57,97).

Total thymectomy vs. thymomectomy

In the case of TET, the current guidelines advocate an en-bloc resection of the tumor with the thymus gland (thymo-thymomectomy) (12,16). This recommendation is based on the theory that in the long-term follow-up, a total thymectomy would decrease the likelihood of recurrence. However, there are studies that challenge this attitude by proposing a resection of the tumor only (thymomectomy) without the necessity of removal of the entire gland in stage I and II TET without the presence of MG (14,98,99). On the other hand, a study from the ChART compared the local recurrence rate in patients with Masaoka stage I and II who underwent thymomectomy alone and thymomectomy plus total thymectomy (100). They observed a significantly higher local recurrence rate in patients with Masaoka Stage II who received thymomectomy alone. The authors draw the conclusion that, in light of their findings, total thymectomy should be performed in conjunction with tumor excision in cases of early-stage thymomas where thymomectomy alone is a suboptimal technique. A major drawback of limited resection is the difficulty of defining an adequate surgical margin while removing only the tumor, especially in the case of stage II lesions. Another limitation of the studies suggesting thymomectomy alone is the relatively short follow-up and for that reason, the results should be interpreted cautiously. In conclusion, in the absence of well-designed and adequately powered prospective studies, total thymectomy remains the treatment of choice, according to the current recommendations. Even if there are concerns about the increase in all-cause mortality and the risk of cancer in patients who underwent a thymectomy, leaving *in situ* residual thymic tissue in case of thymoma and certainly in case of TC, cannot be recommended (101). The risk of recurrence is not negligible and on the other hand, multifocal thymomas have been described. Moreover, the increase in cancer risk after thymectomy is an observation, it is not clear whether cancer development is a consequence of the thymus removal or the result of a deficient baseline immune system.

Conclusions

The rarity and histological heterogeneity of TET preclude the conduction of well-designed sufficiently powered randomized controlled trials. For that reason, the current evidence about their surgical treatment is mainly derived from retrospective case series. New techniques in the field of minimally invasive surgery are gaining acceptance for early-stage TET but longer follow-up periods are warranted in order to prove their oncological outcomes. On the contrary, these techniques should be used cautiously in case of locally advanced tumors. Surgeons must not forget that the main objective is complete resection of the lesion, which is one major predictive factor for increased survival. Surgeons are invited to adopt the new classification systems and the correct definitions in order to facilitate communication between specialists and the interpretation of the results presented in the literature. The establishment of nationwide and international databases could enhance the available data and the uniformization of the nomenclature.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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Review Article

Update on thymic epithelial tumors: a narrative review

Luis Cabezón-Gutiérrez[1,2]^, Vilma Pacheco-Barcia[1], Fátima Carrasco-Valero[3], Magda Palka-Kotlowska[1], Sara Custodio-Cabello[1], Parham Khosravi-Shahi[4]

[1]Medical Oncology, Torrejón University Hospital, Madrid, Spain; [2]Faculty of Medicine, Francisco de Vitoria University, Madrid, Spain; [3]Internal Medicine, Torrejón University Hospital, Madrid, Spain; [4]Medical Oncology, Gregorio Marañón University Hospital, Madrid, Spain

Contributions: (I) Conception and design: L Cabezón-Gutiérrez, V Pacheco-Barcia; (II) Administrative support: L Cabezón-Gutiérrez, V Pacheco-Barcia, M Palka-Kotlowska; (III) Provision of study materials or patients: L Cabezón-Gutiérrez, F Carrasco-Valero; (IV) Collection and assembly of data: L Cabezón-Gutiérrez, V Pacheco-Barcia, F Carrasco-Valero; (V) Data analysis and interpretation: L Cabezón-Gutiérrez, V Pacheco-Barcia, S Custodio-Cabello; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Luis Cabezón-Gutiérrez, MD, PhD. Medical Oncology, Torrejón University Hospital, Calle Mateo Inurria N°1, Madrid, Spain; Faculty of Medicine, Francisco de Vitoria University, Ctra. Pozuelo-Majadahonda KM 1.800, 28223 Pozuelo de Alarcón, Madrid, Spain. Email: lcabezon@torrejonsalud.com.

Background and Objective: Thymoma, thymic carcinoma and thymic neuroendocrine tumors originate from the epithelial cells of the thymus and account for the thymic epithelial tumors (TETs). Although TETs are uncommon, they are the most frequent tumor type in the anterior mediastinum. Multidisciplinary approach is essential for their correct management. The aim of the present review is to summarize the update management for TETs.

Methods: For this review, we searched in Excerpta Medica database (EMBASE) and MEDLINE until 6 September 2023. The terms used in the search included thymoma, thymic carcinoma, thymic epithelial tumors, management, immunotherapy, multiple tyrosine kinases inhibitors.

Key Content and Findings: The therapeutic approach is based on histology and tumor stage and may involve surgery with or without neoadjuvant or adjuvant treatment. In the metastatic setting, platinum-based chemotherapy is the standard of care and patients who do not respond to first-line treatment have limited treatment options mainly because of the poor efficacy shown in subsequent lines of therapy.

Conclusions: Future research should focus on identifying predictive biomarkers for patients with TETs, and should implement multicenter collaborations and appropriate clinical trials tailored for rare tumor types. Immune check point inhibitors, mammalian target of rapamycin (mTOR) and antiangiogenic multikinase inhibitors have also been studied in this clinical setting.

Keywords: Thymoma; thymic carcinoma; thymic epithelial tumors (TETs); thymic neuroendocrine tumors and management

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Introduction

Thymic epithelial tumors (TETs) include thymomas, thymic carcinomas, and neuroendocrine tumors of the thymus (NETTs). Although their incidence is low, they are the most common tumors of the anterior mediastinum (1).

The most common subgroup of TET is thymoma, which represents almost 50%, followed by thymic carcinoma (14–22%) and NETTs (2–5%) (1).

^ ORCID: 0000-0002-3468-3626.

Table 1 The search strategy summary

Items	Specification
Date of search	6th September 2023
Databases and other sources searched	MEDLINE, EMBASE
Search terms used	Keywords: thymoma, thymic carcinoma, thymic neuroendocrine tumors, thymic epithelial tumors (TET), TET management, TET immunotherapy, TET multiple tyrosine kinases inhibitors
Timeframe	January 1, 1950 to September 6, 2023
Inclusion and exclusion criteria	Inclusion: (I) English and Spanish language; (II) case reports, case series, retrospective cohort series, prospective studies; (III) focusing on subtopics of histology and diagnosis
	Exclusion: extra-thoracic tumors
Selection process	L.C.G., V.P.B. and F.C.V. selected literature, all authors chose those for inclusion

Epidemiologically, even though the distribution by age is quite similar, there is a slightly higher incidence in patients over 50 years of age (2), with the mean age at diagnosis being 50–60 years. The incidence by gender is similar, prevailing in men. The frequency of metastasis at diagnosis is higher in thymic carcinoma and NETTs than in thymomas (2), due to their more aggressive behavior with a greater tendency to disseminate systemically (1,3). Risk of developing a secondary malignancy is increased in this population, especially patients with thymomas. This is possibly due to treatments for their primary malignancy which includes radiotherapy (2).

In terms of survival, thymoma has an overall 5-year survival of approximately 78% (1). Thymic carcinomas and NETTs, as they are more aggressive entities with worse prognosis, the 5-year survival is 30% and 23%, respectively (1-4). No differences in prognosis have been observed between men and women in TETs (2). It has been observed that prognosis may be affected by histology, stage and the presence or absence of paraneoplastic syndromes (1).

This review aims to summarize the existing literature regarding the management for TETs. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-47/rc).

Methods

For this review, we searched EMBASE and MEDLINE until 6 September 2023. The search strategy is described in *Table 1*. The terms used in the search included thymoma, thymic carcinoma, thymic epithelial tumors, management, immunotherapy, multiple tyrosine kinases inhibitors. One of the main methodological limitations that we found when conducting the literature search and in the preparation of this manuscript is the lack of randomized clinical trials in this type of rare tumors. Many of the articles included are older, reviews or retrospective case series.

Clinical and diagnostic

For the diagnostic management, we must consider the clinical presentation and the findings in the diagnostic tests, being of special interest the radiological and histopathological findings (1).

Concerning the clinical presentation, about 33% of patients with thymic tumors are asymptomatic at the time of diagnosis. In those patients who are symptomatic, 40% present with symptoms related to intrathoracic mass compression (chest pain, cough, hoarseness, superior vena cava syndrome or dyspnea), 30% present with neurological symptoms and 30% present with systemic symptoms (weight loss, night sweats or fever), which make them difficult to differentiate from lymphoma (2).

In thymic carcinomas, the usual clinical presentation is as described above, with no more frequent associations with other entities (5). However, in NETTs, in addition to the symptoms described, 50% are functionally active and can be associated with endocrinopathies, with up to 40% presenting associated Cushing's syndrome, or less frequently, multiple endocrine neoplasia (MEN) I in 19 to 25% (3). The association of MEN type IIA with NETT is an unusual presentation, known in a few cases, and considered a variant of Sipple's syndrome (described as incomplete Sipple's syndrome) (6,7).

The most frequent thymoma's association is myasthenia

gravis (1), present in up to 82% (8), in contrast to non-thymoma TETs, where the association with myasthenia gravis is exceedingly rare (9).

Preoperative diagnosis of these thymic masses can be complex, but currently, imaging tests are available to assist in this process (10).

Despite the fact that chest radiography is used for the initial study to confirm the presence of a thymic mass (1), the most useful and frequently used diagnostic test is contrast enhanced computed tomography (CT). CT scans provide information on clinical tumor local stage with an evaluation of the organs and structures adjacent to it (1). It also provides information on the presence of pleural parietal deposits (also called "droplet metastases"), as well as on the density characteristics of the thymic neoplasm. The identification of areas whose density is different from thymoma, such as hemorrhage, calcification or necrosis, provides relevant information for staging-for instance, the presence of calcifications suggesting B1, B2, and B3 types of thymoma (2).

Thymomas frequently appear as well-defined rounded masses located anterior to the great vessels and heart. In contrast, thymic carcinoma is characterized by irregular margins and associated lymph nodes (2). In the case of NETTs, a lobulated thymic mass with heterogeneous enhancement and central areas of decreased attenuation secondary to areas of necrosis or hemorrhage are observed (3).

Magnetic resonance imaging (MRI) is usually reserved for cases where iodinated contrasts cannot be administered or to examine for the presence of cystic lesions or areas of local invasion (1,2). Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT may be considered for thymic carcinoma, given the high metabolism of this tumor, for the detection of occult metastases (1) or to characterize lesions suspicious for recurrence (5).

NETTs exhibit an overexpression of somatostatin receptors (SSTRs) on their cell membrane. Imaging techniques targeting SSTRs, such as 68Ga-DOTATOC/DOTATATE-PET, are employed to identify hormonally active tumors of this nature and devise suitable therapeutic strategies. This holds significance as the verification of receptor affinity through diagnostic imaging serves as a crucial determinant of the potential for peptide receptor radionuclide therapy (PRRT). PRRT, involving the use of receptor agonists or antagonists within the context of a theranostic approach, has gained widespread acceptance as an effective treatment modality for neuroendocrine neoplasms (NENs) since its introduction (11). While 68Ga, a positron emitter radionuclide, is exclusively utilized for diagnostic imaging, 90Yttrium-DOTA octreotide and 177-Lutetium DOTA octreotide are the most commonly employed regimens for PRRT (12).

Pathology

At the histological level, moderate atypicality with little associated mitosis and immature T-cell lymphocytes can be observed in thymoma. Vascular invasion and necrosis are usually absent. In contrast to thymomas, the histology of thymic carcinomas is characterized by marked atypicality, frequent mitosis, mature T- and B-cells and vascular invasion and necrosis. Immunohistochemically, thymoma is c-KIT (CD117) negative whereas in thymic carcinoma, in 60–80% of cases, epithelial cells are c-KIT positive, with frequent CD5-associated expression (13).

NETTs differ from the two previously described entities by the presence of elongated tumor cells, pleomorphic nuclei and arrangement in small, rosette-like acinar structures. Immunohistochemically, they are characterized by positivity for markers such as cytokeratin, Leu-7, synaptophysin and cytoplasmic chromogranin stain. Among the latter markers, TTF-1 positivity is noteworthy (3).

It is necessary to compare the histopathological differences among these tumor types, as they contribute to the postoperative diagnosis. This is imperative in scenarios where clinical presentation and imaging findings are merely suggestive (2).

Table 2 describes the histological classification for thymoma and *Table 3*, the histological classification for thymic carcinoma (1,14). NETTs are histologically classified into three categories: low grade (well differentiated), intermediate grade (moderately undifferentiated) and high grade (poorly differentiated) with well-differentiated (WD) carcinomas being the most frequent (3).

Despite the fact that there are relatively few studies on tumor mutational burden (TMB) in TETs, it is necessary to elucidate its role in this type of tumors. TMB stands as an indirect indicator of the ability and extent of tumors to produce new antigens, which is correlated to the suitability for immunotherapy (15).

Some of the most mutated genes in TETs are *GTF2I*, *HRAS*, *TTN* and *TP53*. GTF2I has been described as the predominant mutation in TETs, particularly in the case of the comparatively indolent type A and AB thymomas. However, its incidence is notably infrequent in the more aggressive types B and C. Patients with GTF2I mutations exhibit a more favorable prognosis, potentially attributable

Table 2 Histological classification for thymoma according to the World Health Organization (14)

Histological subtypes of thymoma	Obligatory criteria	Optional criteria
Subtype A	Occurrence of bland, spindle shaped epithelial cells	Polygonal epithelial cells CD20+
	Paucity or absence of immature T cells	Epithelial cells
Atypical subtype A variant	Criteria of type A with comedo-type tumor necrosis	
	Elevated mitotic count, nuclear crowding	
Subtype AB	Occurrence of bland, spindle shaped epithelial cells	
	Profusion of immature T cells	
Subtype B		
Subtype B1	Thymus-like architecture and cytology	Hassall's corpuscles
	Profusion of immature T cells with areas of medullary differentiation	Perivascular spaces
	Paucity of polygonal or dendritic epithelia cells without clustering	
Subtype B2	Elevated numbers of single or clustered polygonal or dendritic epithelial cells intermingled	Criteria of type B1
	Profusion of immature T cells	Medullary islands
Subtype B3	Sheets of polygonal slightly to moderately atypical epithelial cells	Hassall's corpuscles
	Absent or rare intercellular bridges	Perivascular spaces
	Paucity or absence of intermingled T cells	
Micronodular thymoma (MNT) with lymphoid stroma	Nodules of bland spindle or oval epithelial cells surrounded by an epithelial cell-free lymphoid stroma	Lymphoid follicles
		Monoclonal B cells and/or plasma cells
Metaplastic thymoma	Biphasic tumor formed of solid areas of epithelial cells in a background of bland-looking spindle cells	Pleomorphism of epithelial cells
	Absence of immature T cells	Actin, keratin, or EMA-positive spindle cells
Other subtypes		
Microscopic thymoma	Occurrence of bland, spindle shaped epithelial cells	–
Sclerosing thymoma	Paucity or absence of immature T cells	
Lipofibroadenoma		

EMA, epithelial membrane antigen.

to their prevalence in relatively less aggressive subtypes (16). Comparing to thymomas, the incidence of GTF2I is decreased in thymic carcinomas (16).

Differential diagnosis and staging

The differential diagnosis of these tumors should be made primarily with: (I) lymphomas (both Hodgkin's and non-Hodgkin's), the most common, (II) extragonadal germ cell tumors and (III) metastatic carcinomas that may involve the mediastinum (1). In order to provide a differential diagnosis, the patient's age, sex, clinical features and CT images should be considered (1,2).

One of the main differential diagnoses for TETs is lymphoma, however patients presenting with lymphoma tend to be younger compared to those with TET. They usually have constitutional symptoms, different from parathymic syndromes, such as night sweats, fever, weight loss and malaise. In contrast to TET, the physical examination of a patient with lymphoma may reveal lymphadenopathy.

There are several staging systems for this group of tumors; however, the most commonly used are the TNM

Table 3 Histological classification for thymic carcinoma according to the World Health Organization (14)

Histological subtypes of thymic carcinoma:
Adenocarcinoma
Adenocarcinoma, NOS
Low grade papillary adenocarcinoma
Thymic carcinoma with adenoid cystic carcinoma-like features
Adenocarcinoma, enteric-type
Squamous carcinoma
Squamous cell carcinoma, NOS
Basaloid carcinoma
Lymphoepithelial carcinoma
Adenosquamous carcinoma
Salivary gland-like carcinoma
Mucoepidermoid carcinoma
Clear cell carcinoma
Sarcomatoid carcinoma
Carcinosarcoma
Carcinoma undifferentiated, NOS
Thymic carcinoma, NOS
NUT carcinomas

NOS, not otherwise specified; NUT, nuclear protein in testis.

8th edition and the Masaoka-Koga staging system. *Tables 4–6* describe these systems, respectively (1,2).

In the most recent 2021 classification of thymic tumors by the World Health Organization (WHO), NETTs are categorized into three groups (17): low-grade typical carcinoids (TC), intermediate-grade atypical carcinoids (ACs), and two high-grade malignancies—specifically, large cell neuroendocrine carcinomas (LCNEC) and small cell carcinomas (SCC).

Localized disease

Surgical approach of thymoma and thymic carcinoma

Surgery is the main treatment strategy of patients diagnosed with thymoma and thymic carcinoma (18) and a complete surgical resection (R0) is a prognostic factor for recurrence and survival in these patients (19,20). Survival may differ according to the resection margins: complete R0 resection has an excellent prognosis, microscopic R1 has shown a 64% 10-year survival compared with macroscopic R2 that has shown a 36% 10-year survival (21-26). The best surgical approach is debatable and both an open surgery or a minimally invasive surgery could be performed on a case-by-case basis. For an open surgery, a median sternotomy can allow an extensive evaluation of mediastinal structures and surgical manipulation as well (4). If structures of the posterior mediastinum or the pulmonary hilar are infiltrated, a horizontal incision would be a better option (4).

Minimally invasive surgery could be considered for patients with early clinical stages (I-II) if a complete resection is feasible, taking into account that long-term data of the benefits of minimally invasive surgery compared to open surgery are lacking (27,28). Depending on the surgical approach, minimally invasive surgery could be divided in different categories: (I) unilateral transthoracic video-assisted thoracic surgery (VATS) thymectomy; (II) conventional subxiphoid VATS thymectomy; (III) transcervical VATS thymectomy; (IV) subxiphoid VATS thymectomy with double elevation of sternum. Open surgery has been compared with VATS thymectomy and robotic VATS (R-VATS) thymectomy and has been shown to have acceptable oncological outcomes and less perioperative complications (29,30). However, it should be taking into consideration that resecability is the first evaluation that should be performed in patients with localized disease and it is mainly based on the expertise of the surgeon (4). A thymectomy which includes the resection of the thymic tumor, residual thymus and perithymic fat is recommended (31). Furthermore, the resection of pleura, pericardium, phrenic nerve, lung and major vessels that are close to the thymus may be required as well.

Lymphadenectomy in thymic tumors is controversial and there the data on the prognostic significance is lacking. Systematic lymphadenectomy is recommended in stage II or higher, WHO histology B2/3, C, tumors >6 cm and NETTs (32). N1 could be resected with the total thymectomy but, N2 with the station R 2/4 and L 5/6 depend usually on the suspicious intraoperative findings (4). After curative therapy, if there is persistent or recurrent disease, salve surgery could be performed but the oncological outcomes are not well defined (33).

Thymoma

Resectable disease

Thymomas are classified as type A, type AB, type B1/B2/B3

Table 4 TNM 8th edition staging system for TETs (1)

Primary tumor (T)
TX: primary tumor cannot be assessed
T0: no evidence of primary tumor
T1: tumor encapsulated or extending into the mediastinal fat. It can involve the mediastinal pleura
• T1a: tumor with no mediastinal pleura involvement
• T1b: tumor with direct invasion of mediastinal pleura
T2: tumor with direct invasion of the pericardium (either partial or full thickness)
T3: tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins
T4: tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessel, intrapericardial pulmonary artery, myocardium, trachea, esophagus
Regional lymph nodes (N)
NX: regional lymph nodes cannot be assessed
N0: no regional lymph node metastasis
N1: metastasis in anterior (perithymic) lymph nodes
N2: metastasis in deep intrathoracic or cervical lymph nodes
Distant metastasis (M)
M0: no pleural, pericardial or distant metastasis
M1: pleural, pericardial, or distant metastasis
• M1a: separate pleural or pericardial nodule(s)
• M1b: pulmonary intraparenchymal nodule or distant organ metastasis

TETs, thymic epithelial tumors.

Table 5 AJCC prognostic groups (1)

Stage	T	N	M
Stage I	T1a, b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N0-N1	M1a
	Any T	N2	M0–M1a
Stage IVB	Any T	Any N	M1b

AJCC, American Joint Committee on Cancer.

in the WHO fifth edition which includes gene mutations and gene fusions (17). The Masaoka-Koga staging has been associated with survival and is based on the extension of the tumor (34). The prognostic relevance of molecular changes in thymomas has been recently highlighted as a distinctive feature and may allow future targeted treatments (35).

The symptoms and underlying autoimmune diseases that are diagnosed in patients with thymoma can have an impact in the workup required for diagnosis and in the treatment strategy. Myasthenia gravis can be present in up to 50% of patients with thymoma (36) and require an evaluation and treatment by a neurologist before a surgery can be performed

Table 6 Modified Masaoka clinical staging system for thymoma (1)

Masaoka stage	Diagnostic criteria
Stage I	Macroscopically and microscopically completely encapsulated
Stage II	(A) Microscopic transcapsular invasion
	(B) Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organs (for example: lung, great vessels or pericardium)
	(A) Without invasion of great vessels
	(B) With invasion of great vessels
Stage IV	(A) Pleural or pericardial dissemination
	(B) Lymphogenous or hematogenous metastasis

Table 7 Postoperative radiotherapy in the adjuvant setting of thymomas, depending on margin status

Thymoma	Resection margins	Radiotherapy
Resected thymoma	Clear/close margins	45–50 Gy
	Microscopically positive resection margins	54 Gy (48,49)
	Gross residual disease	60–70 Gy (1.8–2 Gy/fraction per day) (50,51)
Resected thymoma with capsular invasion	R0	Can be considered
Incompletely resected thymomas	–	Recommended (52-58)

because these patients have an increased surgical risk and could require a specific treatment prior to the intervention (37-39). Patients with a strong suspicion of having a resectable thymoma do not require a surgical biopsy nor a transpleural approached biopsy because there could be tumor seeding when the tumor capsule is ruptured (40).

Thymomas can invade local structures like pleura and lung but it is unlikely to spread to extrathoracic sites or lymph nodes (41,42). For patients with resected tumors the most important prognostic factor is the complete resection rate that depend on the adhesion to other structures (43): stage I and II have 10-year OS of 90% and 70%, respectively (40,44). Patients with tumors invading structures that can be resected or those patients with encapsulated tumors should be evaluated for surgery as the standard approach of resectable thymomas (45,46). A total resection of the thymus and a lymph node dissection is the most common surgical approach in patients with early stage without myasthenia gravis (47).

After surgery, clinicians should evaluate the benefit of postoperative radiotherapy (PORT) depending on the stage of thymoma and resection margins, these recommendations are summarized in *Tables 7,8*. Thymomas don't usually metastasize to regional lymph nodes, therefore, extensive elective nodal radiation is not a recommendation (41-48). On the contrary, postoperative adjuvant chemotherapy has not demonstrated a benefit in the adjuvant setting (59,60).

The surveillance of patients with resected thymomas should be done with a chest CT scan every 6 months during the first 2 years followed by an annual chest CT scan for a total of 10 years (61).

Potentially resectable disease

Patients with locally advanced thymomas where a complete resection is not feasible, may benefit from induction chemotherapy, surgery and PORT (62-69). *Table 9* summarizes studies with a multidisciplinary approach of unresectable malignant thymomas. The preferred chemotherapy regimen for thymoma as first-line combination is the CAP regimen: cisplatin, doxorubicin, cyclophosphamide administered every 3 weeks with response rates of approximately 44% (55,70-72). However, a recent cohort study did not report differences between

Table 8 Postoperative radiotherapy in the adjuvant setting of thymomas, depending on tumor stage

Thymoma	Resection margins	Radiotherapy
Stage I		
No capsular invasion	R0	Not recommended (53,57,58)
Invasion of mediastinal fat or pleura	R0	Can be considered
Microscopic or grossly positive surgical margins	R1/R2	Can be considered
Stage II		May not benefit but can be considered
Stage III thymoma	Macroscopic invasion into neighboring organs	Recommended

upfront surgery alone versus induction chemotherapy followed by surgery (76.7% *vs.* 77.4%, respectively, P=0.596) (63). For patients with oligometastastic disease that are diagnosed with solitary metastasis or ipsilateral pleural metastases two therapeutic approaches can be considered: (I) upfront surgery alone; (II) induction chemotherapy followed by surgery for patients with resectable disease (36,37).

Neoadjuvant chemotherapy may be useful for achieving a complete R0 resection. Previous studies have reported response rates that range from 77–100% and an average R0 resection rate of 72%. One of the main controversies is that the data to recommend a multimodality approach with neoadjuvant therapy is based on small studies that could not be representative (73).

Thymic carcinoma

Resectable disease

Thymic carcinomas are infrequent tumors that harbor a worse prognosis than thymomas and can metastasize to lymph nodes and other organs (74-76). The main differences between thymomas and thymic carcinomas are based on histologic grounds because thymic carcinomas show malignant features as well as different genetic and immunohistochemical features (17,75). The standard of care of patients with resectable tumors at diagnosis is surgery. If a patient is resectable and undergoes resection the 5-year OS is 50–75% and survival rates vary according to stage: (I) stages 1 and 2: 91%; (II) stages 3 and 4: 31% (77).

As previously reported for thymomas, for most patients with thymic carcinomas the mainstay of surgery is a total resection of the thymus and a lymph node dissection (35). Tumor stage and the invasion of other structures can alter the possibility of performing a complete resection (47). In order to achieve an R0 resection, surgeons with specialized training may need to perform surgery over the pericardium and the adjacent lung parenchyma with the main goal of achieving negative margins that can impact long-term survival (47,78).

Thymic carcinomas have a higher risk of recurrence and adjuvant PORT is recommended in order to achieve local control (77). Therefore, after surgery, clinicians should evaluate the benefit of PORT depending on the stage of thymic carcinoma and the resection margins obtained: recommendations on PORT are summarized in *Table 10*. The benefit of PORT in thymoma and thymic neoplasms has been observed in retrospective data and is summarized in *Table 11*.

Thymic carcinomas with positive margins or residual disease may benefit of PORT supplemented with adjuvant chemotherapy with carboplatin and paclitaxel (84). Adjuvant chemoradiotherapy could be an option for patients with thymic carcinoma and macroscopic residual disease after surgery (84).

Potentially resectable disease

Thymic carcinomas that invade phrenic nerve(s), innominate vein or heart/great vessels are usually not suitable for upfront surgery because it is difficult to achieve an R0 resection, thus, a multimodal approach incorporating induction chemotherapy and postoperative RT is recommended (85). Prior to the start of induction chemotherapy, a diagnostic biopsy is recommended (84). An extensive evaluation on the risk of iatrogenic phrenic nerve injury should be performed prior to surgery because it can impair respiratory function.

Multimodality therapy approach based on previous studies of unresectable malignant thymomas, summarized in *Table 10*:

Table 9 Studies with a multidisciplinary approach of unresectable malignant thymomas

Author	Type of study	Year	Country/region	N	Treatment strategy	Response rates and survival outcomes
Kanzaki *et al.* (65)	Retrospective	2019	Japan	29	Preoperative CT or chemoradiotherapy + surgery	37% PR 5-year OS: 100% 10-year OS: 87%
Park *et al.* (63)	Retrospective	2019	Korea	110	Induction CT + surgery	Response rates not reported 5-year OS: 77.4% *vs.* 76.7% for surgery alone
Ruffini *et al.* (64)	Retrospective	2019	Europe and United States	484	Induction CT + surgery + PORT	Overall response rate: 10.8% Note: thymic carcinoma and neuroendocrine thymic tumors included
Hassan *et al.* (69)	Prospective	2009	Saudi Arabia	9	Induction CT (×3 cycles) + surgery + PORT + consolidation CT (×3 cycles)	77% major responses: 11% CR 4-year OS: 77%
Wright *et al.* (67)	Retrospective	2008	United States	10	Induction CT (×2 cycles) + concurrent radiotherapy followed by surgery + postoperative CT if high risk	60% stable disease, 40% PR 5-year OS 69%
Kim *et al.* (68)	Phase II	2004	United States	22	Induction CT (×3 cycles) + surgery + PORT + consolidation CT (×3 cycles)	77% major responses: 14% CR 5-year OS: 95% 7-year OS 79%

CT, chemotherapy; PR, partial response; OS, overall survival; PORT, postoperative radiotherapy; CR, complete response.

Table 10 Postoperative radiation in the adjuvant setting of thymic carcinomas

Thymic carcinoma	Resection margins	Radiotherapy
Resected thymic carcinoma	Clear/close margins	45–50 Gy
	Microscopically positive resection margins	54 Gy
	Gross residual disease	60–70 Gy (1.8–2 Gy/fraction per day)
Resected thymic carcinoma with capsular invasion	R0	Can be considered
Stage I	R0	Not recommended

(I) Induction chemotherapy based on combination regimens, with resecability rates that range from 36–69% (57,68,86) followed by complete surgery and adjuvant radiotherapy/chemotherapy has been shown to prolong free survival (55). The recommendation of chemotherapy regimen is the same as unresectable disease: cyclophosphamide/doxorubicin and cisplatin repeated every 3 weeks.

(II) Reevaluate with imaging techniques if surgery is feasible. Patients who require a pleurectomy or extrapleural pneumonectomy because of the extent of disease should be discussed since the evidence of prolonged disease survival after performing an aggressive surgical approach is controversial (84).

(III) If an R0 resection is not possible it should be discussed if a maximum debulking followed by adjuvant RT (PORT) can be performed (84). Patients with residual disease may benefit from adjuvant chemotherapy and PORT.

Recurrent disease

Patients who have a localized recurrent disease require an assessment of a radical approach of surgery and the

Table 11 Retrospective data on PORT for thymic neoplasms

Study	Year	Country	N	Stage (Masaoka)	Thymic neoplasm	Survival outcomes
Jackson *et al.* (79)	2017	United States	4,000	Any stage	Thymoma	↑OS (HR 0.72, 95% CI: 0.59–0.87), not significant, for stage IIB o III or positive margins
						No benefit of PORT in stage I or IIA
					Thymic carcinoma	↑OS (HR 0.79, 95% CI: 0.64–0.97), not significant
Boothe *et al.* (80)	2016	United States	1,156	II and III	Thymic malignancies	↑5-year OS after PORT (83% *vs.* 79%, P=0.03)
Rimner *et al.* (81)	2016	Global	1,263	II or III	Thymoma	↑5-year OS (95% *vs.* 90%)
						↑10-year OS (86% *vs.* 79%)
Lim *et al.* (82)	2015	United States	529	IIB, III or IV	Thymoma	↑OS rate (76% *vs.* 66%)
						↑RFS at 7-year (91% *vs.* 81%)
						Benefit limited to stage III or IV
Omasa *et al.* (83)	2015	Japan	1,265	II or III	Thymoma and thymic carcinoma	↑RFS in thymic carcinoma
						No benefit in OS
						No benefit of PORT for thymoma
Forquer *et al.* (56)	2010	United States	901	I–III	Thymoma and thymic carcinoma	PORT had no benefit in surgically resected stage I
						↑5-year OS by adding PORT (76% *vs.* 66% for surgery alone, P=0.01) for stage II–III
Utsumi *et al.* (58)	2009	Japan	324	I–IV	Thymoma	10-year OS in stage I and II with surgery alone: 100%
						No benefit of PORT in stage I and II

↑, increase. PORT, postoperative radiotherapy; OS, overall survival; HR, hazard ratio; CI, confidence interval; RFS, relapse-free survival.

consideration of PORT or chemotherapy (87-89). If an R0 resection is not feasible, the resection of resectable disease and radiotherapy for the non-resectable disease can be discussed (90). If the patient has metastastic widespread disease then the treatment approach should be palliative (84).

NETTs

NETTs are usually diagnosed in a more advanced stage compared to thymic carcinomas and are larger in size (91,92). In functional lesions, locally advanced invasive tumors or fast-growing mediastinal lesions a histological confirmation is recommended prior to the surgical approach (93). The resection should include invaded mediastinal structures to achieve an R0 resection. In advanced tumors where there is an invasion of great vessels, pleural deposits or lung invasion, a posterolateral thoracotomy combined with sternotomy could be performed (93).

NETTs harbor an aggressive behaviour and have a poor prognosis even when an R0 resection has been achieved. If a recurrence occurs, an extensive surgical approach should be considered at the multidisciplinary meeting and an adjuvant radiotherapy has been shown to be effective in this subgroup of patients (94-96).

Unresectable/advanced disease

Thymoma and thymic carcinoma

Unresectable disease is that which presents with extensive pleural and/or pericardial metastases, unreconstructable great vessel, heart, or tracheal involvement or otherwise technically unresectable disease, including those with distant metastases.

Treatments are individualized according to the symptoms, extent of disease, and performance status. A multidisciplinary team should evaluate on a case-by-case basis the best therapeutic approach for patients with TETs. Debulking surgery may also provide benefit to select

patients with initially unresectable disease, so continued involvement of a multidisciplinary team, including a thoracic surgeon, is important.

Patients with locally advanced, unresectable disease (TNM stage IIIB or Masaoka-Koga stage IVB), thymoma, or thymic carcinoma should be treated with concurrent chemoradiotherapy (cisplatin and etoposide) when feasible. Extrapolating from treatment paradigms for locally advanced lung cancer, radiotherapy doses of 60 Gy are appropriate (5). In this setting, chemoradiotherapy can offer long-term survival benefit and control the symptoms of the disease (97).

In select patients with initially unresectable disease, it is appropriate to evaluate for debulking surgery, as this approach may improve survival outcomes (97).

First line

Chemotherapy is the primary palliative treatment modality for patients with more widespread disease (1). Up to six cycles of platinum-anthracycline based regimens as CAP (cyclophosphamide, doxorubicin, cisplatin), cisplatin and etoposide and carboplatin and paclitaxel are the chemotherapy regimens that have shown efficacy in this setting (1). Six first-line chemotherapy regimens are recommended, with the carboplatin-paclitaxel combination being the preferred regimen (84). In advanced thymoma, a pooled analysis of 10 prospective and 5 retrospective studies indicated that anthracycline-based and platinum chemotherapy was superior to platinum without anthracycline in overall response rate (ORR 69.4% *vs.* 37.8%) and cisplatin-based chemotherapy was superior to carboplatin-based chemotherapy (ORR 53.6% *vs.* 32.8%) (72).

Although several regimens are acceptable, cyclophosphamide, doxorubicin, and cisplatin (CAP) and cisplatin and etoposide (PE) have been used successfully for thymomas or thymic carcinomas. Data suggest that the CAP and ADOC regimens could be effective for thymic carcinomas, but they are more toxic than carboplatin/paclitaxel (98,99). The combination of carboplatin and paclitaxel is also used extensively, especially in patients with thymic carcinoma, while the CAP regimen is preferred in patients with thymoma (84). *Table 12* summarizes the different chemotherapy regimens (100-104).

Subsequent therapy

There are no further recognized standard lines of treatment for patients with TETs who progress on initial chemotherapy. Despite them, many patients are candidates to receive a second line. None of the agents studied in this context has been assessed in randomized phase 3 trials.

Pemetrexed, everolimus, octreotide [long-acting release (LAR)] with or without prednisone, paclitaxel, 5-fluorouracil (5-FU), gemcitabine with or without capecitabine, sunitinib, ifosfamide and etoposide are second-line chemotherapy options for thymomas (105-116).

Pemetrexed, 5-FU, sunitinib, everolimus, paclitaxel, lenvatinib, gemcitabine with or without capecitabine, ifosfamide and pembrolizumab are second-line chemotherapy options for thymic carcinomas (99,105,109,117-122). *Table 13* summarizes the different chemotherapy regimens.

Although immunotherapy studies have shown efficacy in patients with advanced thymoma, we do not offer immunotherapy, as high rates of immune-related adverse events (irAEs) have been reported in these patients (121,122). In clinical trials, pembrolizumab demonstrated durable responses in patients with thymic carcinoma, which may be more pronounced those whose tumors express programmed death-ligand 1 (PD-L1) (121-123). These patients should be carefully monitored for possible severe irAEs, including myocarditis, myasthenia gravis, and hepatitis. There are no randomized trials directly comparing immunotherapy with other subsequent-line regimens, such as chemotherapy.

The elevated incidence of irAEs in TETs patients that receive immune checkpoint inhibitors warrant additional biomarker studies to identify patients who can benefit the most from immunotherapy and could present less irAEs (122). In this context, immunologic biomarkers for the early identification and prediction identification of irAEs are currently being investigated (124,125). Biomarkers like immune gene expression, IL-17 or peripheral eosinophil counts have been associated with the development of irAEs in solid tumors (124).

Sunitinib or lenvatinib are multiple tyrosine kinases inhibitors, including vascular endothelial growth factor (VEGF) and c-KIT, are an appropriate option in patients with thymic carcinomas refractory to initial chemotherapy, based on data from phase II trials and retrospective studies (109,110,120).

There is no clear role for nivolumab or avelumab in patients with relapsed thymic carcinoma, as clinical trials evaluating these agents showed limited activity and significant toxicity (126,127). Similarly, everolimus is

Table 12 Chemotherapy regimens in unresectable/advanced TETs

Name	Study	Patient population	Dose	Efficacy
PE	Giaccone *et al.* (100)	16 patients with advanced thymoma	Cisplatin (60 mg/m^2 IV day 1) and etoposide (120 mg/m^2 IV days 1 to 3), repeated every three weeks	ORR: 56% CR: 31% PFS: 2.2 years OS: 4.3 years
CAP	Loehrer *et al.* (101)	29 patients with metastatic or progressive thymoma	Cyclophosphamide (500 mg/m^2 IV day 1), doxorubicin (50 mg/m^2 IV day 1), and cisplatin (50 mg/m^2 IV day 1), repeated every three weeks	ORR: 50% CR: 10% OS: 38 months
CAP with prednisone	Kim *et al.* (68)	22 patients with locally advanced unresectable thymoma	Cyclophosphamide (500 mg/m^2 IV day 1), doxorubicin (20 mg/m^2/day as a continuous infusion, days 1 to 3), cisplatin (30 mg/m^2 IV day 1 to 3) and prednisone (100 mg/day on days 1 to 5), repeated every three weeks	ORR: 77% CR: 14%.
ADOC	Fornasiero *et al.* (102)	37 patients with locally advanced invasive thymoma	Cisplatin (50 mg/m^2 IV day 1), doxorubicin (40 mg/m^2 IV day 1), vincristine (0.6 mg/m^2 IV day 3), and cyclophosphamide (700 mg/m^2 IV day 4), repeated every three weeks	ORR: 92% CR: 43% OS: 15 months
CP	Lemma *et al.* (103)	44 patients with advanced previously untreated thymoma (21) and thymic carcinoma (23)	Carboplatin (area under the curve 6) and paclitaxel (225 mg/m^2 IV) every three weeks	Thymoma: ORR: 43% CR: 14% OS: NR Thymic carcinoma: ORR: 22% CR: 0% OS: 20 months
VIP	Loehrer *et al.* (104)	34 patients with advanced previously untreated thymoma and thymic carcinoma	Etoposide (75 mg/m^2 IV days 1 to 4), ifosfamide (1.2 g/m^2 IV on days 1 to 4), and cisplatin (20 mg/m^2 IV days 1 to 4), repeated every three weeks	Only 28 patients were evaluable ORR: 32% CR: 0% OS: 32 months

TETs, thymic epithelial tumors; IV, intravenous; ORR, overall response rate; CR, complete response; PFS, progression free survival; OS, overall survival; NR, not reached.

not routinely used due to severe toxicity (pneumonitis), despite initial studies that suggest some efficacy in relapsed thymoma and thymic carcinoma (128).

Later-line options for treatment-refractory thymomas and thymic carcinomas include etoposide, ifosfamide, pemetrexed, octreotide, fluorouracil, S-1, gemcitabine plus capecitabine and paclitaxel.

Arunachalam *et al.* performed a meta-analysis focused on the efficacy and safety of subsequent treatments for advanced thymic carcinoma after failure of first-line platinum-based chemotherapy (123). From the nineteen trials identified in the systemic literature review, three trials with one or two TC patients were removed to reduce publication bias. The pooled ORRs in patients receiving S-1 (46 patients), sunitinib (46 patients), or pembrolizumab (66 patients) were 28%, 24%, and 21%, respectively. Pembrolizumab obtained an extended duration of response with a pooled median OS of 23.8 months [95% confidence

Table 13 Systemic treatments in pretreated advanced thymic epithelial tumors

Study	Patient population	Phase	Dose	Efficacy
Palmieri *et al.* (106)	N=30: 22 thymoma, 8 thymic carcinoma	II	Capecitabine (650 mg/m^2 twice daily on days 1–14) and gemcitabine IV (1,000 mg/m^2 on days 1 and 8 every 3 weeks)	ORR: 40% PFS: 11 months OS: NR
Bluthgen *et al.* (107)	N=20: 5 thymoma, 15 thymic carcinoma	Retrospective study	Oral etoposide 25 mg three times daily for 3 weeks, followed by 1 week off (4-week cycle)	Thymoma: ORR: 20% SD: 80% PFS: 21 months OS: 99 months Thymic carcinoma: ORR: 13% SD: 33% PFS: 4 months OS: 13 months
Zucali *et al.* (108)	N=51: 32 thymoma, 19 thymic carcinoma	II	Everolimus 10 mg/day continuous	Thymoma: ORR: 9% SD: 85% PFS: 16.6 months OS: NR Thymic carcinoma: ORR: 16% SD: 58% PFS: 5.6 months OS: 14.7 months
Thomas *et al.* (109)	N=41: 16 thymoma, 25 thymic carcinoma	II	Sunitinib 50 mg orally once a day, in 6-week cycles (i.e., 4 weeks of treatment followed by 2 weeks without treatment)	Thymoma: ORR: 6% SD: 75% PFS: 8.5 months OS: 15.5 months Thymic carcinoma: ORR: 26% SD: 65% PFS: 7.2 months OS: NR
Antonarelli *et al.* (110)	N=20: 8 thymoma, 12 thymic carcinoma	Retrospective study	Sunitinib 37.5 mg/day continuous daily dosing	–

Table 13 (*continued*)

Table 13 (*continued*)

Study	Patient population	Phase	Dose	Efficacy
Gbolahan *et al.* (111)	N=27: 16 thymoma, 11 thymic carcinoma	II	Pemetrexed, 500 mg/m^2 IV every 3 weeks	Thymoma: ORR: 27% PFS: 12.1 months OS: 46.4 months Thymic carcinoma: ORR: 9% PFS: 2.9 months OS: 9.8 months
Loehrer *et al.* (114)	N=38: 32 thymoma, 5 thymic carcinoma, 1 thymic carcinoid	II	Octreotide in a dose of 0.5 mg subcutaneously 3 times a day, for a maximum of 1 year. Patients with stable disease at the end of two cycles, receive prednisone at a dose of 0.6 mg/kg per day	ORR: 30% SD: 37% Octreotide: PFS: 2 months Octreotide plus prednisone: PFS: 9.2 months Thymoma: PFS: 8.8 months OS: NR Thymic carcinoma: PFS: 4.5 months OS: 23.4 months
Highley *et al.* (116)	N=15: 15 thymoma [only 7 patients received prior treatment (one chemotherapy)]	Retrospective study	Ifosfamide 1.5 g/m^2 on days 1 to 5	ORR: 46% CR: 38% Estimated survival rate 5 years 57%
Conforti *et al.* (117)	N=18: 5 thymoma, 12 thymic carcinoma, 1 mixed histology	Multicentric, prospective study	Ifosfamide (1 g/m^2/day) and sodium-2-mercaptoethanesulfonate (1 g/m^2/day), as continuous infusion, via a portable pumps for 14 consecutive days. Treatment was administered every 4 weeks	ORR: 28% SD: 39% PFS: 5.4 months
Sato *et al.* (120)	N=42: 42 thymic carcinoma	II	Lenvatinib 24 mg orally once daily in 4-week cycles	ORR: 38% SD: 57% PFS: 9.3 months OS: NR
Giaccone *et al.* (121)	N=40: 40 thymic carcinoma	II	Pembrolizumab 200 mg every 3 weeks for up to 2 years	ORR: 23% SD: 53% PFS: 4.2 months OS: 24.9 months

Table 13 (*continued*)

Table 13 (*continued*)

Study	Patient population	Phase	Dose	Efficacy
Cho *et al.* (122)	N=33: 7 thymoma, 26 thymic carcinoma	II	Pembrolizumab 200 mg every 3 weeks	Thymoma: ORR: 29% SD: 71% PFS: 6.1 months Duration of response: NR Thymic carcinoma: ORR: 19% SD: 54% PFS: 6.1 months Duration of response: 9.7 months

IV, intravenous; ORR, overall response rate; PFS, progression free survival; OS, overall survival; NR, not reached; SD, stable disease; CR, complete response.

interval (CI): 12, not reached]. Patients who had received lenvatinib, sunitinib, capecitabine + gemcitabine, S-1, everolimus or pembrolizumab reported a median PFS of at least five months. S-1 or pembrolizumab trials reported a median OS of at least 20 months; this endpoint was not reached in trials evaluating lenvatinib, regorafenib, or sunitinib. Therefore, the study found limited treatment options upon relapse, and there is a need for further investigations into novel therapeutics and well-powered clinical trials to better inform on optimal treatments.

NETTs

Approximately 80% to 90% of WD thoracic NETTs express SSTRs on their cell surface, that bind with high affinity somatostatin analogs (SSAs) lanreotide autogel and octreotide LAR (2). SSAs should probably be chosen first line for patients with relatively low-volume, relatively asymptomatic, SSTR-positive disease (129-131).

There are other several systemic treatment options: everolimus, temozolomide-based chemotherapy, and peptide receptor radioligand therapy using a radiolabeled SSA such as lutetium Lu-177 dotatate (^{177}Lu-dotatate).

Beyond SSAs, there are no data for selecting or sequencing these treatments except that ^{177}Lu-dotatate is limited to SSTR-expressing tumors. Even in those tumors, there is no real basis for choosing ^{177}Lu-dotatate over everolimus, or viceversa, as the second-line treatment. Most of the data on the effectiveness of these drugs is extrapolated from thoracic, gastroenteropancreatic or intestinal neuroendocrine tumors, with only data available from retrospective studies of patients with NETTs. *Table 14* summarizes the different treatment options in G1/G2 advanced/metastatic NETTs.

Patients with intermediate to poorly-differentiated tumors respond to platinum-based chemotherapy regimens (135,139). In particular, treatment of poorly-differentiated NETTs with platinum-based regimens, such as carboplatin and etoposide, as per treatment guidelines for poorly-differentiated NETs at other sites.

New combinations of SSAs and other investigational drugs are therefore warranted, with the aim to improve clinical outcomes, while maintaining a good tolerability profile.

New therapeutics options

Immunotherapy administered alone or in combination with other agents is currently under study in several trials including patients with advanced B3 thymoma and thymic carcinoma which relapsed after at least one line of platinum-based chemotherapy. One of the main lines of research is the combination of antiangiogenic agents with chemotherapy or immunotherapy. *Table 15* summarizes the

Table 14 summarizes the different treatment options in G1/G2 advanced/metastatic NETTs

Name	Study	Patient population	Dose	Efficacy
Octreotide LAR	Rinke *et al.* (130)	85 gastroenteropancreatic neuroendocrine tumors patients	Octreotide LAR 30 mg intramuscularly in monthly intervals until tumor progression or death *vs.* placebo	SD: 66.7% *vs.* 37.2%; P=0.0079 PFS: 4.3 and 6 months, HR =0.34; (95% CI: 0.20 to 0.59; P=0.000072) OS: HR =0.81 (95% CI: 0.30 to 2.18)
Extended-release aqueous-gel formulation of lanreotide	Caplin *et al.* (131)	204 patients with advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor-positive neuroendocrine tumors of grade 1 or 2 and documented disease-progression status	Extended-release aqueous-gel formulation of lanreotide at a dose of 120 mg or placebo once every 28 days for 96 weeks	SD: NR PFS: HR =0.47; 95% CI: 0.30 to 0.73 OS: no differences
Everolimus	Yao *et al.* (132)	302 patients with advanced, progressive, well-differentiated, non-functional neuroendocrine tumors of lung or gastrointestinal origin	Randomly assigned in a 2:1 ratio to receive everolimus 10 mg per day orally or identical placebo, both with supportive care	SD: 81% in the everolimus arm *vs.* 64% in the placebo arm PFS: 11.0 *vs.* 3.9 months in the placebo group. HR =048 (95% CI: 0.35–0.67, P<0.00001) OS: HR 0.64 (95% CI 0.40–1.05), one-sided P=0.037
Everolimus	Lang *et al.* (133)	4 patients with progressing NETTs (two well-differentiated atypical carcinoids and two atypical carcinoids with large cell characteristics)	Everolimus 10 mg/day until progression disease	SD interval in all patients and mean PFS of 20.8 months PFS interval was longer in well differentiated tumors (24 and 42 months, respectively) compared with large cell differentiation (7 and 10 months) OS: NR
Temozolomide	Ekeblad *et al.* (134)	36 patients with advanced and pretreated neuroendocrine tumor (1 gastric, 7 thymic and 13 bronchial carcinoids, 12 pancreatic endocrine tumors, 1 paraganglioma, 1 neuroendocrine foregut, and 1 neuroendocrine cecal cancer)	Temozolomide 200 mg/m^2 for 5 days every 4 weeks	SD: 53% and 14% of ORR (in 7 NETTs, SD in 71% and 0% ORR) PFS: 7 months (95% CI: 3–10) OS: NR
Temozolomide	Crona *et al.* (135)	28 patients with NETTs, of which 8 received temozolomide	NR temozolomide dose	SD: 75% and ORR 12.5% PFS: median PFS of 20.5 months OS: NR

Table 14 (*continued*)

Table 14 (*continued*)

Name	Study	Patient population	Dose	Efficacy
Capecitabine plus temozolomide	Saranga-Perry *et al.* (136)	3 patients with progressive NETTs	Patient 1: capecitabine (700 mg/m^2 b.i.d. days 1–14 every 28 days) and temozolomide (170 mg/m^2 days 10–14) every 28 days Patient 2: capecitabine (600 mg/m^2 b.i.d. days 1–14 every 28 days) and temozolomide (190 mg/m^2 days 10–14 every 28 days) Patient 3: capecitabine (750 mg/m^2 b.i.d. days 1–14 every 28 days) and temozolomide (180 mg/m^2 days 10–14 every 28 days)	SD 67% and ORR 33%
Radiolabeled somatostatin analog ^{177}Lu-dotatate	Strosberg *et al.* (137)	229 patients with advanced midgut NETs, high level of expression of somatostatin receptors	^{177}Lu-Dotatate at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide LAR administered intramuscularly at a dose of 30 mg) or octreotide LAR alone administered intramuscularly at a dose of 60 mg every 4 weeks	ORR: 18% *vs.* 3%; P<0.001 PFS: not reached in the ^{177}Lu-Dotatate group and was 8.4 months (95% CI: 5.8 to 9.1) in the control group (HR 0.21; 95% CI: 0.13 to 0.33; P<0.001) OS: HR 0.40; P=0.004
Radiolabeled somatostatin analog ^{177}Lu-dotatate	van Essen *et al.* (138)	Nine patients with bronchial, five with gastric and two with thymic carcinoids were treated. All patients had metastasised disease	^{177}Lu-Dotatate at a dose of 7.4 GBq, injected in 30 min. The interval between treatments was 6–10 weeks. Patients were treated up to an intended cumulative dose of 22.2–29.6 GBq	SD of two patients with NETTs was 50%

NETTs, neuroendocrine tumors of the thymus; LAR, long acting release; SD, stable disease; PFS, progression free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; ORR, overall response rate; NR, not reported.

main ongoing clinical trials in patients with advanced TETs.

Conclusions

TETs are rare and heterogeneous tumors that arise in the anterior mediastinum. Thymomas may be an incidental diagnosis discovered at chest imaging, and patients may present with symptoms due to the presence of a mass in the thorax or to a paraneoplastic phenomenon such as myasthenia gravis. The management of TETS requires a multidisciplinary approach (pathologists, medical oncologists, radiation oncologists and thoracic surgeons). Complete surgical resection is the initial treatment approach for all patients when preoperative evaluation suggests that a complete resection will be feasible and there are no medical contraindications to surgery. For patients with resected disease, the approach to postoperative radiation therapy is based on stage. In case of potentially resectable disease the recommendation is initial treatment with neoadjuvant chemotherapy and local treatment depending on the response.

In unresectable disease, RT alone, chemotherapy, or the combination is appropriate for patients in whom surgery is not technically feasible or is contraindicated, and may be of curative potential. Platinum-based chemotherapy is the treatment of choice in case of metastatic disease. However, patients with metastatic TETs have limited treatment options beyond platinum-based chemotherapy, due to the poor effectiveness showed by several other agents administered in subsequent lines of therapy. New therapies have been explored in this clinical setting such as the antiangiogenic multikinase inhibitors, mammalian target of

Table 15 Ongoing clinical trials in patients with TETs (140)

Study	ClinicalTrials.gov identifier	Phase	Patient population	Drug	Primary end point
Pembrolizumab in treating participants with unresectable T or TC	NCT03295227	I	Unresectable T or TC	Pembrolizumab	Safety
Combination of pembrolizumab and lenvatinib in pre-treated TC patients (PECATI)	NCT04710628	II	Advanced B3 T and TC relapsed after at least one line of P-ChT	Pembrolizumab, lenvatinib	PFS
Pembrolizumab and sunitinib malate in treating participants with refractory metastatic or unresectable TC	NCT03463460	II	Advanced TC relapsed after at least one line of P-ChT	Pembrolizumab, sunitinib	ORR
A Phase II, neo-adjuvant pembrolizumab, docetaxel, cisplatin therapy followed by surgery and pembrolizumab consolidation therapy in locally advanced thymic epithelial tumor (TET)	NCT03858582	II	Locally advanced TET	Pembrolizumab, docetaxel, cisplatin	Major pathologic response rate
Chemotherapy combined with pembrolizumab in treating patients with T and TC	NCT04554524	IV	First line in locally advanced or metastatic invasive T and TC that cannot be removed by surgery	Carbo-paclitaxel/ nab-paclitaxel combined with pembrolizumab	ORR
A pilot study to investigate the safety and clinical activity of avelumab in T and TC after progression on platinum-based chemotherapy	NCT03076554	II	Advanced T and TC relapsed after at least one line of P-ChT	Avelumab	Safety ORR
Nivolumab in patients with type B3 T and TC (NIVOTHYM)	NCT03134118	II	Advanced B3 T and TC relapsed after at least one line of P-ChT	Nivolumab	PFS
Trial of sunitinib in patients with type B3 T or TC in second and further lines (STYLE)	NCT03449173	II	Advanced B3 T and TC relapsed after at least one line of P-ChT	Sunitinib	ORR
Carboplatin and paclitaxel with or without ramucirumab in treating patients with locally advanced, recurrent or metastatic TC	NCT03694002	II	Advanced TC with no anti-cancer therapy for locally advanced or metastatic disease	Carboplatin, paclitaxel, ramucirumab	PFS
Ramucirumab and carbo-paclitaxel for untreated thymic carcinoma/B3 thymoma with carcinoma (RELEVENT)	NCT03921671	II	Chemotherapy-naïve patients with thymic carcinoma or B3 thymoma with areas of carcinoma	Carboplatin, paclitaxel, ramucirumab	ORR
A study of KC1036 in patients with advanced TC	NCT05683886	II	Advanced recurrent, unresectable and/or metastatic T	KC1036	ORR
A study of KN046 in patients with TC who failed ICIs	NCT04925947	II	Advanced TC relapsed after P-ChT and at least one line of ICIs	KN046	ORR
KN046 in subjects with TC	NCT04469725	II	Advanced TC relapsed after at least one line of P-ChT	KN046	ORR

Table 15 (*continued*)

Table 15 (*continued*)

Study	ClinicalTrials.gov identifier	Phase	Patient population	Drug	Primary end point
Bintrafusp alfa (M7824) in subjects with T and TC	NCT04417660	II	Advanced T and TC relapsed after at least one line of P-ChT	Bintrafusp alfa (M7824)	ORR
PT-112 in subjects with T and TC	NCT05104736	II	Advanced T and TC relapsed after at least one line of P-ChT	PT-112	ORR
Atezolizumab in previously-treated patients with advanced TC	NCT04321330	II	Advanced TC who failed prior systemic therapy	Atezolizumab	ORR
ChT plus cetuximab followed by surgical resection in patients with locally advanced or recurrent T or TC	NCT01025089	II	Clinical Masaoka stage II–IVa T and TC	Cetuximab, cisplatin, doxorubicin, and cyclophosphamide	Major pathologic response rate
Nivolumab in combination with vorolanib in patients with refractory thoracic tumors	NCT03583086	I/II	Non-small cell lung cancer naïve to ICIs non-small cell lung cancer who have progressed on ICIs small cell lung cancer (who have progressed on platinum-based chemotherapy), and TC	Oral vorolanib plus infusional nivolumab	Adverse events ORR

TETs, thymic epithelial tumors; T, thymoma; TC, thymic carcinoma; P-ChT, platinum-based chemotherapy; ICIs, immune checkpoint inhibitors; PFS, progression-free survival; ORR, overall response rate.

rapamycin (mTOR) inhibitor, ICIs and their combinations.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-23-47/coif). L.C.G. reports he received payment for presentations of Roche, Astra Zeneca, Brystol Myers Squibb, Merck Serono, Ipsen Pharma, Grunenthal, Kyowa Kirin, Pfizer and Eisai and received support for attending meetings from Roche, Merck, Eli Lilly, Bristol-Myers Squibb and Nutricia. V.P.B. reports she received a grant as an award from Merck and FSEOM, payment for presentations of Merck, Eli Lilly, Eisai and Pierre Fabre and received support for attending meetings from Roche, Eli Lilly, Bristol-Myers Squibb, Merck, Amgen, Merck Sharp and Dhome, and Nutricia. V.P.B. also reports she participated in an advisory board from advanced accelerator applications, a Novartis company. The other authors have no conflicts of interest to declare.

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Review Article

Perioperative strategies and management of giant anterior mediastinal tumors: a narrative review

Kengo Tani^, Daisuke Kimura, Tsubasa Matsuo, Takahiro Sasaki, Shuta Kimura, Chisaki Muto, Masahito Minakawa

Department of Thoracic and Cardiovascular Surgery, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori, Japan

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Correspondence to: Kengo Tani, MD. Department of Thoracic and Cardiovascular Surgery, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036-8562, Japan. Email: tani-kengo@hirosaki-u.ac.jp.

Background and Objective: Giant anterior mediastinal tumors sometimes may cause circulatory collapse and respiratory failure, known as mediastinal mass syndrome (MMS). The prediction and prevention of MMS is challenging. The aim of this study is to summarize the evaluation methods for MMS and formulate treatment strategies for giant anterior mediastinal tumors.

Methods: We performed a thorough analysis of recent international literature on giant anterior mediastinal tumors (>10 cm in diameter) and MMS published in the PubMed database. The search spanned the duration of the preceding 10 years from August 19, 2023, and only studies published in English were included.

Key Content and Findings: Mature teratomas and liposarcomas are the most common giant anterior mediastinal tumors and MMS develops most frequently in case of malignant lymphomas. Here, we propose a new treatment strategy for giant anterior mediastinal tumors. Based on imaging findings, giant anterior mediastinal tumors can be classified as cystic or solid and further blood investigation data are useful for a definitive diagnosis. When malignant lymphoma or malignant germ cell tumor is highly suspected, the first choice of treatment is not surgery but chemotherapy and radiotherapy. Moreover, image-guided drainage may be effective if giant cystic anterior tumors develop into MMS. The risk classification of MMS is important for treating giant anterior mediastinal tumors. If the MMS risk classification is 'unsafe' or 'uncertain', the intraoperative management deserves special attention. The surgical approach should however be based on tumor localization and invasion of surrounding tissues. Multidisciplinary team coordination is indispensable in the treatment of giant anterior mediastinal tumors.

Conclusions: When giant anterior mediastinal tumors are encountered, it is important to follow the appropriate treatment strategy, focusing on the development of MMS based on imaging findings and symptoms.

Keywords: Giant; huge; anterior mediastinal tumor; anterior mediastinal mass; mediastinal mass syndrome (MMS)

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^ ORCID: 0000-0003-3218-3895.

Introduction

Background

Giant anterior mediastinal tumors may cause severe hemodynamic and respiratory decompensation due to mass effects (1-11). Since mediastinal space is narrow, giant anterior mediastinal tumors are susceptible to mechanical compression or infiltration of the surrounding organs (4). The circulatory collapse and respiratory failure related to the compression are known as mediastinal mass syndrome (MMS), which may occur during biopsy or surgery, even in the absence of any symptoms, owing to the supine position and the use of sedatives and muscle relaxants (1-8,10,11). MMS is a life-threatening condition that can occur not only during anesthesia but also at any time in patients with large mediastinal tumors (2,6,7,10). Therefore, multidisciplinary peri-operative management strategies are required.

Rationale and knowledge gap

No specific guidelines have been established for the management of patients undergoing surgery for giant anterior mediastinal masses. Anterior mediastinal tumors represent a diverse group of diseases, and their treatment varies depending on their diagnosis (5). A comprehensive preoperative assessment based on the differential diagnosis and risk evaluation for MMS is required.

Objective

This study aimed to summarize the evaluation methods for anterior giant mediastinal tumors and safe perioperative management strategies. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-40/rc).

Methods

A literature review was conducted on August 19, 2023 by searching the PubMed database for the search terms (((giant) OR (huge)) AND (anterior) AND ((mediastinal) OR (mediastinum)) AND ((tumor) OR (mass))) and (mediastinal mass syndrome). Studies published over the past 10 years were selected for the analysis. Only studies published in English were included in this analysis. We also searched the references of the articles identified using this search strategy and selected those that were adjudged relevant. In this review, ((giant) OR (huge)) was defined as tumors >10 cm in diameter, with some selected from older references in the case of landmark papers or secondarily referenced in studies of interest (*Table 1*).

Table 1 Summary of the search strategy

Items	Specification
Date of search	August 19th, 2023
Databases and other sources searched	PubMed
Search terms used	(((giant) OR (huge)) AND (anterior) AND ((mediastinal) OR (mediastinum)) AND ((tumor) OR (mass)))
	(mediastinal mass syndrome)
Timeframe	2013–2023
Inclusion and exclusion criteria	Inclusion criteria: all types of articles available in full text in English [(giant) or (huge) are defined as a tumor larger than 10 cm in diameter, with some select older references in the case of landmark papers or if secondarily referenced in studies of interest]
	Exclusion criteria: as for case reports, tumors less than 10 cm in diameter or not listed
Selection process	The records were first screened for title or abstract by three independent reviewers (K.T., D.K. and T.M.), and subsequently screened for full text. Then, the articles were evaluated collectively by all authors. Debate over article selection was resolved with consensus

Search findings

Giant anterior mediastinal tumors

A literature search of studies published over the past decade revealed that mature teratomas (12-29) were the most common large anterior mediastinal tumors, exceeding 10 cm in diameter. Some mature teratomas can grow rapidly and it has been estimated that approximately 15% of patients requires a resection extended to other structures (e.g., lobectomy, pericardiectomy) for complete tumor resection (4). Liposarcomas (30-40) were the second most common. Other tumors included thymomas (41-47), thymolipomas (48-52), thymic neuroendocrine tumors (NET) (53-56), malignant germ cell tumors (GCT) (57), and malignant lymphomas (58).

MMS

MMS is an acute hemodynamic and/or respiratory decompensation that occurs because of mechanical compression caused by mediastinal tumors (1-11). MMS can be aggravated by the induction of anesthesia or positional changes during surgery. However, it can occur at any stage of anesthesia (2,6,7,10). Asymptomatic patients can also develop MMS.

Hemodynamic decompensation occurs when an anterior mediastinal tumor compresses the heart and great vessels [superior vena cava (SVC) and pulmonary artery (PA)]. The induction of general anesthesia results in decreased venous return, which reduces right ventricular filling and causes low cardiac output (1,7). In the context of respiratory failure, supine positioning and positive pressure ventilation contribute to compression of the heart and great vessels, resulting in acute circulatory collapse (1,6,7). Compression of the SVC reduces the venous return of the upper half of the body (1,7). Therefore, edema of the face and upper extremities may occur (1,7,8). Furthermore, coughing, wheezing, dyspnea, and dysphagia are symptoms of pharyngeal and laryngeal edema (1). Cerebral edema causes headaches and disorders of consciousness. These conditions are referred to as SVC syndromes (1,6-8). PA compression may impair pulmonary perfusion, cause hypoxemia, acute right ventricular failure, and cardiac arrest.

Respiratory failure is caused by the mechanical compression of the trachea and/or main bronchus by a tumor. Induction of general anesthesia aggravates critical respiratory conditions (1,6,7,11). The use of sedatives or muscle relaxants causes a decrease in the respiratory muscle tone and elevation of the diaphragm (1,6,7,11). The position of the tumor changes, thereby increasing the risk of mechanical airway obstruction. Furthermore, loss of spontaneous breathing during controlled ventilation promotes the onset of respiratory complications (1,2,6,7). Positive pressure ventilation increases pleural pressure and strengthens the compression of mediastinal structures (1,6,7). The supine position during anesthesia induction also increases compression of the mediastinal structures because of the gravitational effect. This posture also causes a reduction in the transverse diameter of the thorax and cephalad displacement of the diaphragm, which increases the intrathoracic pressure, thereby promoting airway compression and impairing ventilation (7,59).

Tan *et al.* (2) reviewed 85 patients from 77 case reports. They reported that 48 (56.5%) patients had anterior mediastinal tumors with larger diameters than tumors of the superior, middle, and posterior mediastinum. MMS also occurred in 39 of 85 patients (45.9%), 25 of whom had anterior mediastinal tumors. Of the 39 patients who developed MMS, lymphomas were the most common, accounting for 15 (38.5%), suggesting that lymphomas may grow at a faster rate depending on the histologic type and that respiratory and circulatory compensations often do not occur in time.

Risk classification of MMS

Coordination of a multidisciplinary team (thoracic surgeons, anesthesiologists, respiratory medicine physicians, oncologists, radiologists, pathologists, cardiovascular surgeons, and clinical engineers) is indispensable for the management of giant anterior mediastinal tumors (3,5,7).

First, the presence of symptoms is identified. Preoperative orthopnea and upper body edema are high-risk factors for anesthesia-related complications in children (8). Orthopnea: P=0.033, odds ratio (OR) 5.31, 95% confidence interval (CI): 1.15–24.56, upper body edema: P=0.035, OR 8.00, 95% CI: 1.16–55.07 (8). Other symptoms included chest distress, dyspnea, swelling, tachycardia, cyanosis, and stridor (*Table 2*) (2,6). Symptomatic patients are generally at a higher risk of MMS (1-3,5-8,10). The prediction of perioperative complications were the occurrence of cardiorespiratory signs and symptoms at presentation (OR 6.2, 95% CI: 1.2–31.5) (10). It is also important to identify the 'rescue position', the position at which the symptoms are alleviated (1,2,5-8).

Risk classification were based on symptoms,

Table 2 Risk classification of mediastinal mass syndrome [adapted from Tan *et al.* (2) under the terms of the CC-BY license]

Risk classification	Signs and symptoms	Imaging examination findings
Safe	No	No
Unsafe	Yes: chest distress, dyspnea, swelling, tachycardia, cyanosis, orthopnea, stridor, SVC syndrome	Yes: tracheobronchial CSA <50% or compressed heart/vessel
Uncertain	Yes	No/NA
	No	Yes

SVC, superior vena cava; CSA, cross-sectional area; NA, not available.

tracheobronchial compression, and heart/great vessel compression (*Table 2*) (1-3,5-7,10). Tracheal cross-sectional area (CSA) is an indicator of tracheal stenosis. A >50% reduction in normal CSA has been reported to increase the risk of perioperative respiratory complications (1-3,6-8,10) even in asymptomatic patients (3).

Differential diagnosis and preoperative management

Imaging study

Computed tomography (CT) can be used to confirm the location and size of a tumor and its relationship with the trachea, bronchi, heart, and great vessels (4-7). The evaluation of airway stenosis is also important. Contrast-enhanced CT allows for the differentiation of vascular abnormalities, evaluation of intratumoral necrosis, compression of the great vessels, and intravenous thrombus (1,60). Magnetic resonance imaging (MRI) is inferior to CT in terms of its spatial resolution but superior in qualitative evaluation. This provides valuable insight into the differential evaluation of solid and cystic lesions (60). MRI is a sensitive technique for differentiating soft tissues and delineating their boundaries. CT and MRI findings can predict the differential diagnoses (60). Solid masses included thymic epithelial tumors, thymic NETs, malignant lymphomas, GCTs, thymic hyperplasia, and thymolipomas. Cystic masses include thymic cysts, pericardial cysts, mature cystic teratomas, substernal goiters, ectopic parathyroid cysts, and neurogenic tumors (60). Positron emission tomography (PET)-CT is effective in differentiating benign and malignant thymic epithelial tumors because of differences in the maximum standardized uptake value (SUV) (61,62). However, it is not an appropriate tool for providing additional anatomical information (4).

Blood investigation data

Differential diagnoses can be made based on the blood investigation data. Patients positive for anti-acetylcholine receptor antibodies demonstrate an increased probability of thymoma even when they do not have myasthenia gravis (63). Levels of soluble interleukin-2 receptor (sIL-2R) are elevated in malignant lymphomas (63). If either alpha-fetoprotein (AFP) or beta-human chorionic gonadotropin (β-HCG) levels are elevated, the diagnosis of yolk sac tumor or choriocarcinoma, respectively, can be made, and a biopsy is not necessary (63,64). Malignant nonseminomatous germ cell tumor (NSGCT) can be diagnosed by abnormally high levels of AFP and β-HCG without waiting for biopsy or other pathology results, and chemotherapy can be initiated immediately in such cases (64).

Physiological function tests

Echocardiography can be used to evaluate the status of compression of the heart and great vessels, cardiac function, and the presence of pericardial effusion (2, 5, 10). Pulmonary function tests have been reported to have low sensitivity in predicting intraoperative respiratory complications (1). However, they can also be used to predict the risk of postoperative respiratory complications. Béchard *et al.* demonstrated that a peak expiratory flow rate (PEFR) of <40% was associated with a >10-fold increase in the risk of postoperative respiratory complications (P=0.010, OR =12.8, 95% CI: 1.5–47.1) (10). Bronchoscopy can also be used to evaluate the airway stenosis. The rescue position can be ascertained by changing the patient's position (5).

Biopsy

Biopsy is of paramount importance because the treatment

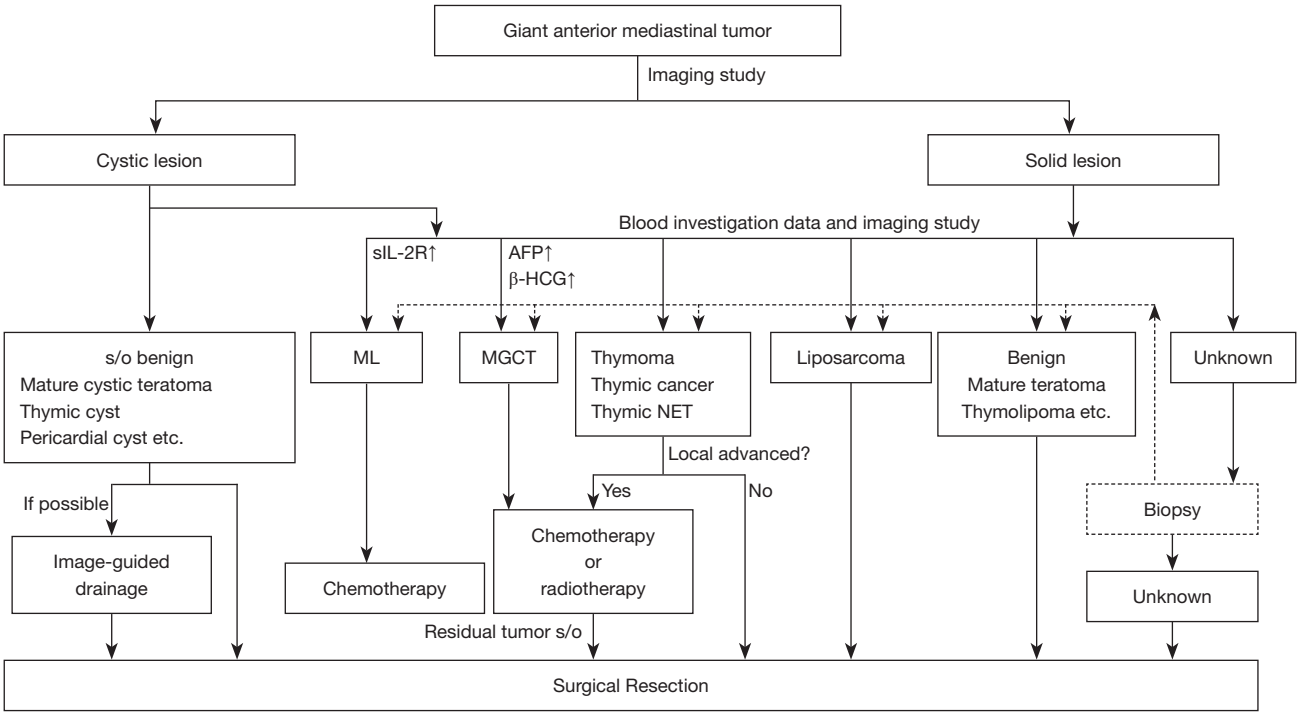

Figure 1 Differential diagnoses and preoperative management of giant anterior mediastinal tumor. sIL-2R, soluble interleukin-2 receptor; AFP, alpha-fetoprotein; β-HCG, beta-human chorionic gonadotropin; s/o, suspect of; ML, malignant lymphoma; MGCT, malignant germ cell tumor; NET, neuroendocrine tumor.

varies depending on the pathological diagnosis (*Figure 1*). Biopsy techniques include ultrasound-guided endoscopic biopsy, percutaneous image-guided needle biopsy, parasternal anterior mediastinotomy, cervical mediastinoscopy, video-assisted thoracoscopic surgery (VATS), and open surgery (4,63). However, for giant tumors, biopsy under general anesthesia increases the risk of MMS (9,11). If the MMS risk classification is 'unsafe' or 'uncertain', biopsy in a comfortable position with local anesthesia is preferred. Cytopathological evaluation of pleural effusions or biopsies of palpable lymph nodes on the body surface may provide a definitive diagnosis (6,65). Early initiation of chemotherapy after a definitive diagnosis is important to improve the survival of patients with malignant lymphoma (4,58). Among malignant GCT, seminomas respond to chemotherapy and radiotherapy (64). NSGCT are treated with chemotherapy, followed by surgical resection of residual tumors (57). If the imaging findings are those of a cystic lesion and there is no elevation in the levels of tumor markers, although cancer antigen-125 (CA-125) may be elevated in the presence of inflammation (20), a mature cystic teratoma is more likely to be diagnosed. Image-guided drainage results in tumor shrinkage reduces the risk of MMS (12,19,24,28). If thymoma is strongly suspected and resectable, a penetrating biopsy of the pleura should be avoided because of its potential for dissemination (66). Preoperative chemotherapy or radiotherapy is indicated for complete resection of locally advanced thymomas (4,41,43,44,46,67).

Intraoperative management

If the MMS risk classification is 'unsafe' or 'uncertain', intraoperative management deserves special attention as follows (2).

Rescue position

It is important to determine the patient's comfortable position or 'rescue position'. The Fowler's position (elevated upper body) is reportedly effective in patients with SVC syndrome (7). Lateral decubitus (59) and prone (68) positions are also useful. A positional change in the contralateral direction in which the tumor weight is

applied (e.g., left lateral decubitus position if the trachea is compressed mainly from the left thoracic cavity on CT images) is usually selected. However, if the patient is placed in a prone position, it is difficult to establish extracorporeal membrane oxygenation (ECMO). Leaving patients in 'rescue position' as long as possible during any induction for anesthesia is important.

Airway management

If the tracheal carina or main bronchus is compressed, the intubation tube is advanced beyond the stenosis to ventilate the distal airway. The double-lumen tube allows for intubation beyond the distal airway stenosis and provides good surgical vision during tumor resection by providing isolated lung ventilation (5). Intubation beyond the distal portion of the stenosis is expected to be difficult in malignant cases because the tumors are generally firm. In these cases, the use of a rigid bronchoscope should be considered. In cases with airway emergency, temporary endotracheal stenting is effective after establishment of veno-venous ECMO (VV-ECMO) under local anesthesia (58,69).

ECMO

Indications for ECMO are cardiac support, respiratory support or a combination of both (70). Veno-arterial ECMO (VA-ECMO) is preferred in patients at high risk of respiratory and hemodynamic collapse. VV-ECMO should be used in patients with isolated respiratory symptoms and airway compression (1). If respiratory and/or circulatory distress is obvious in adults, a sheath should be placed on the femoral artery and vein (depending on the type of ECMO setup chosen), so that ECMO can be introduced promptly before the induction of general anesthesia (1-3,5-7). Clinical engineers should be available in the operating room for the whole duration of surgery with a primed ECMO machine (1,7). Furthermore, ECMO should be on standby in asymptomatic patients with highly compressed trachea, main bronchus, heart, and great vessels. In infants, it is difficult to administer ECMO under local anesthesia. Ramanathan *et al.* (3) advocated that the following cases should be considered a 'high-risk' group: (I) acute SVC syndrome, (II) PA or right ventricular outflow tract (RVOT) obstruction, (III) > 50% airway compression, and (IV) cardiac or great vessel involvement/invasion with possible need for cardiac or vascular excision or reconstruction.

Induction of anesthesia

In cases of SVC compression or obstruction, intravenous access routes should be secured in the lower extremities (femoral vein) (1,5-7,10). The administered drug cannot be reliably perfused in SVC syndrome, and there is a risk of further increase in the central venous pressure. The use of short-acting medications is important to maintain normal muscle tone and adequate spontaneous breathing (1,2,5,7). Therefore, careful attention should be paid to the use of sedatives and muscle relaxants in these patients. Ideally, airway management should be performed while the patient is awake and maintains spontaneous breathing (7,56). Erdös *et al.* (7) delineated the following 12 rules for perioperative anesthesia management of MMS in adults: (I) interdisciplinary team consultation; (II) possibility of irradiation/chemotherapy; (III) clinical/radiological findings; (IV) MMS-risk classification; (V) availability of adequate number of staff; (VI) no premedication; (VII) transportation with anesthesiologist; (VIII) intravenous access in the lower extremity; (IX) pulse oximetry to the right arm; (X) artery catheter/central venous access; (XI) flexible operating table. 'comfortable' position; (XII) alternative airway/circulation options (e.g., cannulation of femoral vessels).

MMS occurrence

In the event of occurrence of MMS, the patient should be repositioned to the 'rescue position' by moving the operating table. During respiratory decompensation, the intubation tube should be advanced beyond the obstruction area to ventilate the distal airway section or a rigid bronchoscope should be inserted. Inotropes and hyperosmolar solutions must be administered to prevent circulatory collapse. If there is no improvement, ECMO should be established, and emergency thoracotomy should be performed quickly to release the mechanical compression of the tumor.

Figure 2 shows a flowchart of the perioperative management and strategies for giant anterior mediastinal tumors (2,3,5).

Surgical approach

A surgical approach is essential to reach and resect the

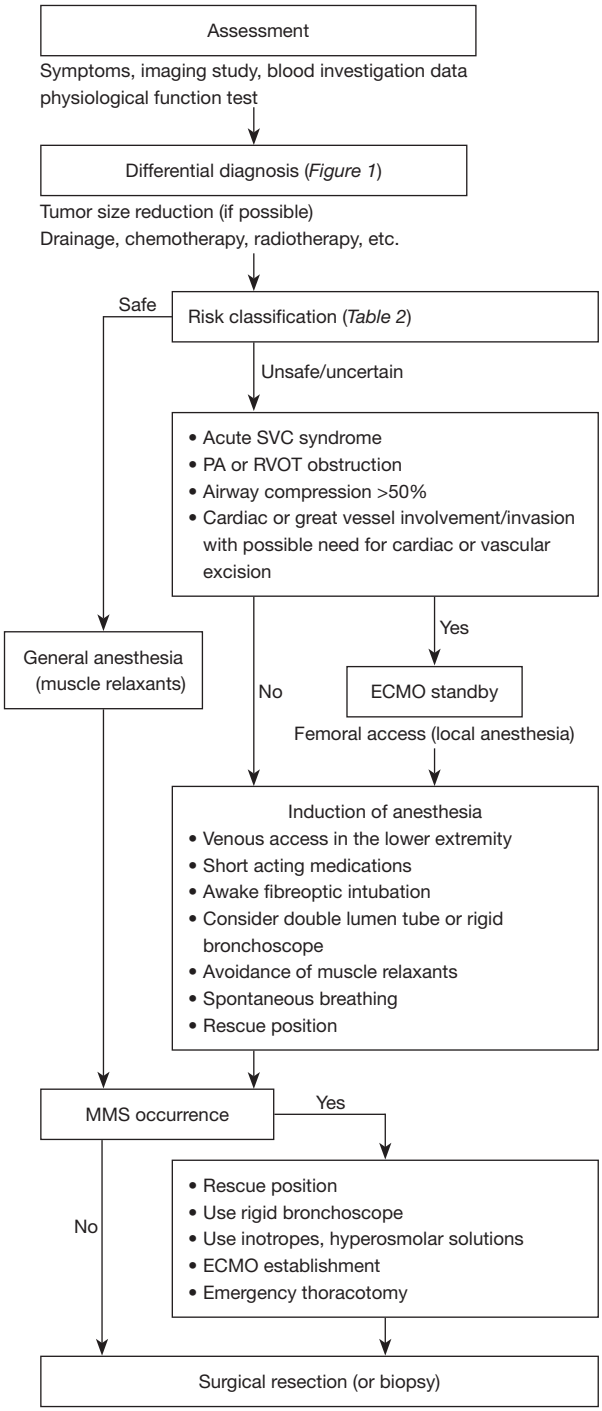

Figure 2 Flowchart depicting the perioperative management and strategies for giant anterior mediastinal tumor. Reprinted/adapted with permission from Ramanathan *et al.* (3) and Li *et al.* (5), and under the terms of the CC-BY license for Tan *et al.* (2). SVC, superior vena cava; PA, pulmonary artery; RVOT, right ventricular outflow tract; ECMO, extracorporeal membrane oxygenation; MMS, mediastinal mass syndrome.

tumor properly. Median sternotomy is a commonly used approach for mediastinal tumor resection (4). It allows better exposure of the superior and anterior mediastinal lesions. However, it is not suitable for tumors extending into the thoracic cavity because of poor access to the hilum or posterior thorax (47).

Lateral thoracotomy was considered when the tumor was unevenly distributed to the right or left. Lateral thoracotomy combined with median full sternotomy (20,25,27,39) and upper partial sternotomy combined with lateral thoracotomy [hemi-clamshell thoracotomy (47)] are effective for achieving good surgical vision.

Clamshell thoracotomy (13,30,32,37,38,40,44), although highly invasive, involves a large transverse incision that allows access to the bilateral pleural lumen. Sometimes, a longitudinal sternal incision is added to clamshell thoracotomy (40,44). The addition of an upper partial sternotomy provides a good view of the superior mediastinum, while the addition of a lower partial sternotomy is useful for the resection of tumors situated on the diaphragm.

VATS has also been used in some cases (16,26,29,45). However, this approach requires the use of advanced techniques. VATS may be effective in a limited number of giant anterior mediastinal tumors.

Postoperative management

Cases classified as 'unsafe' or 'uncertain' according to the risk classification should be managed postoperatively in the intensive care unit. Early extubation reduces the risk of postoperative complications. Therefore, adequate pain management is recommended. Epidural anesthesia was effective. However, it is difficult to use this technique in patients at a risk of hypotension or coagulopathy. Systemic heparinization is necessary in cases of ECMO and cardiopulmonary bypass; however, the risk of hematoma with epidural catheters remains controversial. An erector spinae plane block (1) or thoracic paravertebral block may be an effective alternative to epidural anesthesia.

Strengths and limitations

This article describes the differential diagnosis of giant anterior mediastinal tumors and the corresponding strategies based on the MMS risk classification. However, as mediastinal tumors are rare, this review does not encompass all entities.

Conclusions

When encountering a giant anterior mediastinal tumor, the degree of symptoms should be checked, and the status of the airway and heart/great vessel compression should be confirmed using imaging studies. Risk assessments of MMS and differential diagnoses should be performed simultaneously. Depending on the differential diagnosis, tumor reduction following surgery is effective. Biopsy and surgery must be carefully planned and multidisciplinary team coordination is essential.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-23-40/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-23-40/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Review Article

Thymectomy for juvenile myasthenia gravis: a narrative review

Michela Carter^, Sara Ungerleider, Seth D. Goldstein

Division of Pediatric Surgery, Department of Surgery, Northwestern University Feinberg School of Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

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Correspondence to: Michela Carter, MD. Division of Pediatric Surgery, Department of Surgery, Northwestern University Feinberg School of Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Avenue, Chicago, IL 60611, USA. Email: micarter@luriechildrens.org.

Background and Objective: Thymectomy as a management strategy for juvenile myasthenia gravis (JMG) has been increasingly adopted with the advent of minimally invasive surgical techniques. This review evaluates existing evidence regarding the surgical management of JMG, including the benefits of surgical compared to medical therapy, important considerations when evaluating surgical candidacy and determining optimal timing of intervention. In addition, we provide an overview of the open, thoracoscopic and robotic surgical approaches available for thymectomy and compare the existing data to characterize optimal surgical management.

Methods: A thorough literature review was conducted for full length research articles, including systematic reviews, retrospective cohort studies and case series, published between January 2000 and July 2023 regarding open, thoracoscopic or robotic thymectomy for management of JMG. Reference lists of the identified articles were manually searched for additional studies. Evidence was summarized in a narrative fashion with the incorporation of the authors' knowledge gained through clinical experience.

Key Content and Findings: Although data specific to JMG are limited to small retrospective cohort studies, available evidence supports equal to greater disease control following thymectomy versus pharmacologic management. Furthermore, outcomes may be optimized when surgery is performed earlier in the disease course, particularly for patients who are post-pubertal with generalized or severe disease and those necessitating high-dose steroid administration thereby limiting its metabolic and growth inhibitory effects. Open transsternal resection is the historic gold-standard; however, as surgeons become more comfortable with thoracoscopic and robotic-assisted thymectomy, an increasing proportion of patients are expected to undergo thymectomy. At present, the data available is unable to support conclusions regarding which surgical approach is superior; however, minimally invasive approaches may be non-inferior while offering superior cosmesis and decreased morbidity.

Conclusions: Higher-level investigation through the use of multi-institutional databases and randomized prospective trials is warranted in order to understand which child warrants thymectomy, at what point in their disease course and their development, and which surgical approach will optimize postoperative outcomes.

Keywords: Myasthenia gravis (MG); thymectomy; thoracoscopy; robotic surgical procedures; pediatrics

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^ ORCID: 0000-0003-3704-1351.

Introduction

Myasthenia gravis (MG), an incumbering autoimmune disease with prevalence of 150–200 cases per million people, is a result of antibodies directed against antigens located at the postsynaptic endplate of the neuromuscular junction (1). When present, antibodies most commonly target the acetylcholine receptor; therefore, the neurotransmitter is out-competed impeding motor nerve to skeletal muscle impulse resulting in weakness and fatigability (1-3). Juvenile MG (JMG), defined as symptom onset prior to 18 years old, accounts for 15% of patients with MG (4). JMG is most often limited to oculomotor symptoms (e.g., ptosis, diplopia and ophthalmoplegia); however, this may be accompanied with or progress to generalized muscle weakness, involving the bulbar, facial, limb and respiratory muscles. While those with pure ocular-type JMG more often have pre-pubertal onset, those with post-pubertal onset are more likely to have generalized disease (5).

The thymus is rich with anti-acetylcholine receptor (anti-AChR) antibody-promoting antigens; therefore, making it the target of surgical management (6). While ocular JMG can often be controlled medically, through an astute combination of cholinesterase inhibitors, corticosteroids and/or immunomodulators, those with generalized or medically-refractory JMG may warrant thymectomy (2,7). However, much of the evidence directing the management of JMG is a result of the extrapolation of data from adult MG studies (8-18). Even still, the only prospective randomized evidence regarding the efficacy of surgical management in adults is limited to the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX) which demonstrated superior outcomes following open transsternal thymectomy when compared to pharmacotherapy for generalized non-thymomatous seropositive MG (19-21). However, caution should be taken when applying adult studies to JMG as there are significant differences in the demographics of and prognosis for these diseases (5,22). Despite this, thymectomy as a management strategy for JMG has become generally accepted, and attention is pivoting to attempt to understand which child warrants intervention, when surgery should take place and by which approach.

The objective of this review is to evaluate the existing evidence regarding the surgical management of JMG, including the benefits of surgical versus medical management and important considerations to make when determining surgical candidacy and timing of intervention. In addition, we provide an overview of the approaches available to perform thymectomy for JMG and compare existing data to characterize its optimal surgical management. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-41/rc).

Methods

The search strategy is outlined in *Table 1*. A thorough literature review was conducted using the PubMed database in July of 2023. A free text search was performed with the following search terms: ("thymectomy") AND ("juvenile" OR "children" OR "pediatric") AND ("myasthenia gravis"). Full length research articles in English, including systematic reviews, retrospective cohort studies and case series, published between January 2000 and July 2023 regarding open, thoracoscopic or robotic thymectomy for management of JMG were included. In addition, reference lists of the identified articles were manually searched for additional studies. Case studies, editorials and commentaries were excluded as well as those with content or study population extending beyond the surgical management of JMG. Article selection is visualized in *Figure 1*.

Surgical *vs.* medical management

There are no prospective studies which compare complete stable remission (CSR), disease improvement, or change in medication requirement for thymectomy relative to medical management for JMG, such as the MGTX trial did for MG; however, we identified four retrospective studies (*Table 2*) and two systematic reviews (*Table 3*) which evaluate thymectomy and compare it to medical management for JMG. Available data consist of small and heterogeneous populations limiting cohort comparisons; however, patients who undergo thymectomy have less postoperative corticosteroid and cholinesterase inhibitor use in addition to comparable if not higher rates of CSR (4,23,26). Furthermore, thymectomy has been shown to decrease the number of days spent intubated, in the intensive care unit and hospitalized (23). An analysis of the KID database demonstrated between 2003 and 2012 there was stability in the number of thymectomies performed in children for JMG (27). However, data estimating the number of pediatric thymectomies performed before and after the publication of the MGTX trial in 2016 is not available at present.

Table 1 The search strategy summary

Items	Specification
Date of search	July 24, 2023
Databases and other sources searched	PubMed
Search terms used	Free text search including the terms: ("thymectomy") AND ("juvenile" OR "children" OR "pediatric") AND ("myasthenia gravis")
Timeframe	Jan 2000 to Jul 2023
Inclusion and exclusion criteria	Inclusion: full length research articles written in the English language regarding open, thoracoscopic or robotic thymectomy for pediatric/juvenile myasthenia gravis Exclusion: case reports, commentaries/editorials, articles purposed to evaluate medical or anesthetic management of juvenile myasthenia gravis, cohort contained patients undergoing thymectomy for disease other than juvenile myasthenia gravis
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Article selection was collectively performed by M.C. and S.U.
Any additional considerations, if applicable	Reference lists for relevant articles were manually searched for additional studies

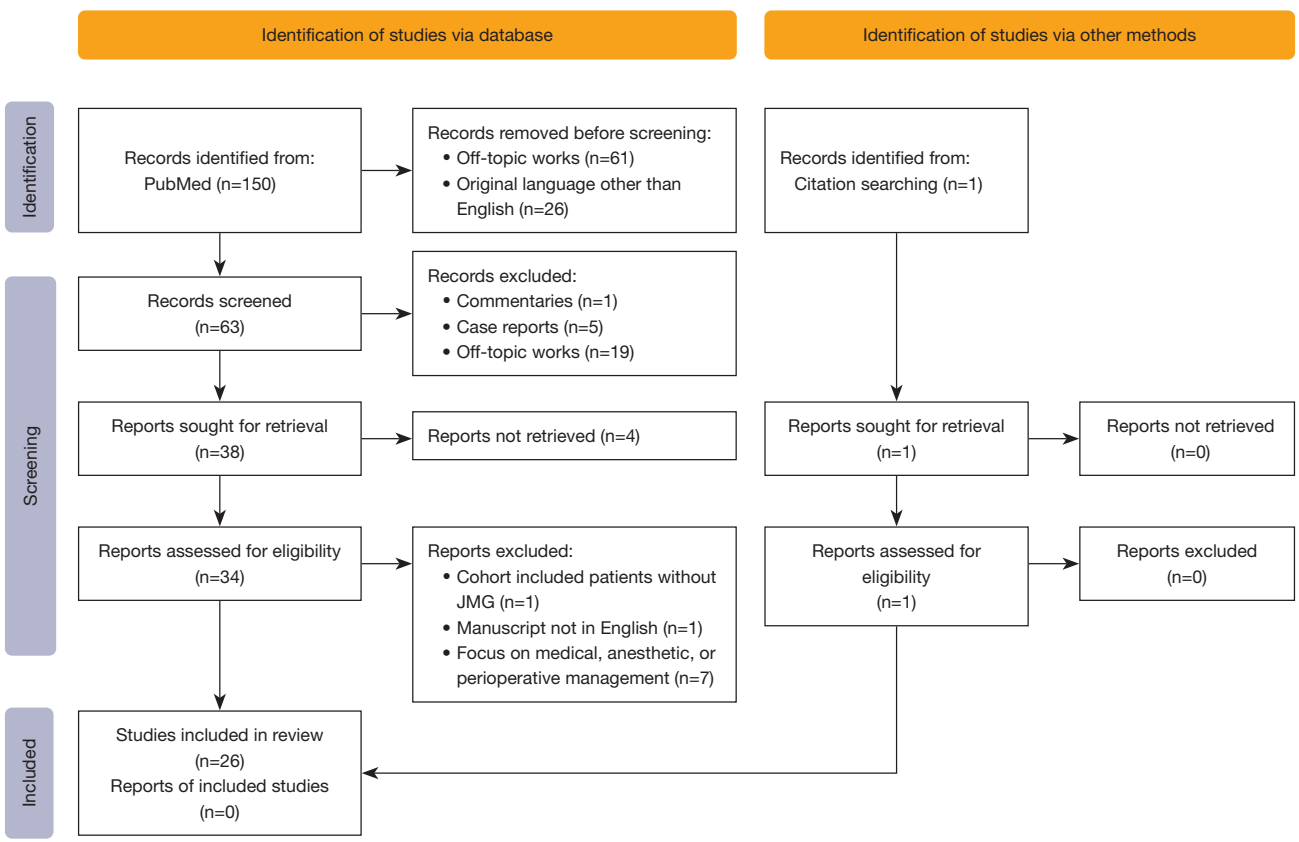

Figure 1 Flow chart demonstrating article selection for evaluating thymectomy for management of juvenile myasthenia gravis. JMG, juvenile myasthenia gravis.

Table 2 Retrospective studies comparing surgical and medical management for juvenile myasthenia gravis

Authors, year published	Surgical approach [n]	Mean [range] age at thymectomy	Mean [range] disease duration prior to thymectomy	Key findings
Tracy *et al.* (23), 2009	Thymectomy, unspecified [13] *vs.* non-surgical [32]	10 years 10 months [17 months–18 years 7 months]	9.2 months [17 days–2 years 9 months]	(I) 62% improvement, 31% CSR (II) Mean time from onset to surgery longer in those who did not improve (397 *vs.* 198 days) (III) Thymectomy resulted in a reduction in days intubated, in the intensive care unit, and in the hospital
Wang *et al.* (24), 2013	Thymectomy, unspecified [52] *vs.* non-surgical [24]	NR	NR	(I) No significant association between thymectomy and delayed bone age and height based on chronological age (II) Delayed bone age and height retardation in JMG thought to be related to past cumulative prednisone intake and age at disease onset might be a factor
Popperud *et al.* (25), 2021	Thymectomy, unspecified [32] *vs.* non-surgical [15]	17 [2–33] years	21 [9–31] months	(I) Patients who undergo thymectomy have evidence of premature immunosenescence not related to age at surgery (II) No clinical consequence of premature immunosenescence demonstrated at last follow-up {median [IQR] 12 [7–26] years}
Li *et al.* (4), 2022	Robotic [47] *vs.* non-surgical [20]	NR	16 [7–25] months	(I) Patients who underwent robotic thymectomy had a significantly shorter disease duration, greater preoperative steroid use and larger proportion were anti-AChR+ (II) Median [IQR] follow-up 47 [30–94] months (III) Robotic thymectomy cohort had higher proportion as well as significantly higher 5-year cumulative probability of CSR (IV) Robotic thymectomy cohort experienced a reduction in daily dose of cholinesterase inhibitors and corticosteroids while the non-surgical group did not (V) 19.1% postoperative complication rate

anti-AChR+, anti-acetylcholine receptor antibody positive; CSR, complete stable remission; IQR, interquartile range; JMG, juvenile myasthenia gravis; NR, not reported.

Surgical candidacy

While thymoma is rare in children, affecting just over 2% of children with JMG, thymomatous JMG is always surgical (22,28-30). As such, after diagnosis of JMG, either magnetic resonance imaging or computed tomography is performed to evaluate for the presence of thymic enlargement or thymoma (31). When imaging suggests non-thymomatous disease, there is lack of consensus regarding the indications for surgical management. This is perpetuated by a lack of standardized classification system between existing pediatric studies. Likewise, available evidence regarding the role of thymectomy for patients with ocular *vs.* generalized disease, pre- *vs.* post-pubertal age at surgery, and seropositive *vs.* seronegative antibody status remain insufficient (26).

The first categorization system developed, the Osserman Score, was introduced in 1958 (32). Ranging from Class I to IV based on symptom severity and progression, Class I involves only the ocular muscles while Classes II-IV represent progressive and increasing severity of generalized muscle involvement (32). Hans Oosterhuis published his scoring system in the 1980s after observing more than

Table 3 Systematic reviews evaluating outcomes following thymectomy for juvenile myasthenia gravis

Authors, year published	Years included	Number of articles	Key findings
Madenci *et al.* (26), 2017	2000–2016	16	(I) 488/1,131 (43%) underwent thymectomy
			(II) Preoperative severity: 50% Osserman stage I, 30% stage II, 14% stage III, 6% stage IV
			(III) Approach: 82% transsternal, 17% thoracoscopic, 1% transcervical
			(IV) 77% had post-operative improvement, 29% CSR
			(V) Postoperative complications were rare (range, 0–30%), most common pneumonia/atelectasis and mechanical ventilation
			(VI) 0.2% cause-specific mortalities
			(VII) 3 studies compared surgical and non-operative management, 1 reported trend toward higher CSR with thymectomy, 1 reported thymectomy to be protective against the development of generalized symptoms, 1 reported similar CSR rates
			(VIII) 4 studies compared open to thoracoscopic thymectomy, 3 concluded thoracoscopic to be non-inferior in terms of reduction in disease severity, 1 noted incomplete resection with thoracoscopic; thoracoscopic was associated with less blood loss, shorter length of stay, lower to similar complication rate
			(IX) Studies were entirely retrospective, power limited and with heterogeneous populations
Ng and Hartley (22), 2021	1997–2020	17	(I) 588 patients underwent thymectomy
			(II) 77% improvement, 40% CSR
			(III) Overall, surgical outcomes may be associated with early intervention, post-pubertal intervention, AChR+, more severe disease, presence of thymic hyperplasia
			(IV) 6 studies compared open and thoracoscopic thymectomy, overall report similar clinical outcomes with reduced length of stay and improved cosmesis with thoracoscopic
			(V) Pathology: 62% hyperplasia, 24% normal, 2% thymoma
			(VI) Mixed results regarding seropositivity, 1 found improved outcomes while 1 found no difference
			(VII) Studies limited by retrospective nature, variable follow-up times, lack of control groups and statistical power

CSR, complete stable remission; AChR+, anti-acetylcholine receptor antibody positive.

400 patients with MG. Scores of 1–4 represent increasing degree of disability while 0 represents complete remission and 5 mechanical ventilatory dependence (33). In 2000, the Myasthenia Gravis Foundation of America (MGFA) published the Quantitative MG Score (QMG) intended as the first objective system based on a patient's strength when performing specified actions (34). This system was utilized in the MGTX trial; however, it has not been adopted widely by pediatric studies which continued to use the Osserman or Oosterhuis classifications for grading preoperative disease severity (22). However, the QMG was modified for pediatric patients by eliminating the grip strength test and incorporating a straw for bulbar strength evaluation to create the first JMG-specific scoring system that is both more developmentally appropriate and less impacted by a child's cooperability (35).

Despite this heterogeneity, most JMG cohorts are described as to whether disease is pure ocular or with generalized involvement. Although pure ocular disease is more common, nearly two-thirds of children who undergo thymectomy have generalized JMG (30). In addition, there is a trend in some studies toward greater response to thymectomy for those with generalized and/or more severe disease than those with pure ocular type (22). However, this was not found across all studies (22,36,37).

Approximately 80% and 3.5% of JMG patients have anti-AChR and anti-muscle specific tyrosine kinase (anti-MuSK) antibodies, respectively (22,30). Overall, data regarding

the influence of seropositivity in response to surgery is insufficient (26). The presence of anti-AChR antibodies has been shown to correlate with greater surgical response; therefore, anti-AChR seropositivity often contributes to the determination to pursue thymectomy (22,38). However, some patients who are anti-AChR negative respond to thymectomy; therefore, the role of surgery remains ambiguous for those with anti-MuSK antibodies or who are seronegative (22,39).

Still, there remains significant controversy surrounding the appropriate age and timing from symptom onset to thymectomy. Delaying thymectomy affords a chance for spontaneous remission, an event which occurs as often as 20–29% of the time in children (40). Furthermore, the thymus is critical in the growth and development of a child's immune system; therefore, many argue that surgery should be postponed due to concern that removing the thymus while the immune system is still in development will have negative consequences later in life (22,41-43). As such, a study performed by Popperud *et al.* confirmed that thymectomy for JMG performed at median (range) age at thymectomy of 17 [2–33] years can lead to premature immunosenescence, including a reduced number of B cells, naive cytotoxic T cells and helper T cells and increased memory T cells at median (interquartile range) 12 [7–26] years after thymectomy was performed. However, these findings were not related to age at thymectomy nor with any discernible clinical consequence (25). However, it is necessary to mention a 2023 case-control study in adults with MG who are five years or more post-thymectomy found thymectomized patients have not only decreased production of CD4+ and CD8+ lymphocytes and higher levels of proinflammatory cytokines but also a higher incidence of cancer and all-cause mortality compared to their non-thymectomized counterparts (44).

There is also controversy regarding the impact of age and timing from symptom onset on the efficacy of thymectomy. A study with 31% CSR and 62% symptom improvement rates following thymectomy in 13 patients with mean (range) age at thymectomy of 10.8 (1.4–18.6) years and mean (range) time from disease onset of 9.2 (0.6–33.0) months found that time from onset to surgery was a mean 199 days longer in those who did not respond to thymectomy (23). In a study performed on 141 patients with JMG with median (range) age at onset of 6 [1–18] years who underwent open transsternal resection at median (range) age of 12 [3–18] years found improved CSR rates if surgery is performed when patients are at least 12 years old (37). However, the same study, demonstrated improved postsurgical outcomes when thymectomy was performed within 12 months of onset of generalized symptoms (37). Conversely, a study by Kim *et al.* including 50 patients with JMG who underwent thoracoscopic thymectomy at mean (standard deviation, SD) age of 10.5 (0.8) years and mean (SD) time to thymectomy of 19.6 (4.2) months with 51.0% of patients with thymectomy within one year of disease onset found no difference in outcome when evaluating age or timing of thymectomy relative to symptom onset (45). A systematic review including 17 articles published between 1997 and 2020 encompassing 588 JMG patients who underwent thymectomy concluded that improved surgical outcomes may be associated with both early intervention and post-pubertal intervention (22). Moreover, by performing surgery early, children avoid growth failure, delay in bone aging and detrimental metabolic effects experienced by JMG patients who require prolonged corticosteroids (24). Overall, there may be benefit to performing surgery early relative to symptom onset, particularly for patients who are post-pubertal or with severe disease requiring prolonged use of high-dose steroids.

Surgical approach

Once the decision has been made to perform surgery, patients should be optimized medically and myasthenic symptoms well-controlled which may necessitate intravenous immunoglobulin administration or plasma exchange therapy (4). Traditionally performed through median sternotomy, the decision to pursue surgery required a careful consideration of the known risks of open thoracic surgery. The development of minimally invasive surgical (MIS) approaches, including both thoracoscopic and robotic thymectomy, was driven by the desire for decreased postoperative morbidity. However, as incomplete clearance of thymic tissue is associated with reduced remission rates, complete thymic resection in both thymomatous and non-thymomatous JMG is critical. As such, experts have voiced concern that MIS approaches provide inadequate visualization, and therefore, incomplete extirpation of mediastinal fat and ectopic foci of thymic tissue (46-49). Despite this controversy, there is paucity of high-level evidence to support an optimal approach to thymectomy in children (50). We identified twenty retrospective studies (*Table 4*) and two systematic reviews (*Table 3*) which evaluate and/or compare surgical approaches to thymectomy for JMG.

Table 4 Retrospective studies evaluating approach to thymectomy for juvenile myasthenia gravis

Authors, year published	Surgical approach [n]	Mean [range/± SD] age at thymectomy	Mean [range/± SD] disease duration prior to thymectomy	Key findings
Kolski, Vajsar and Kim (51), 2000	Thoracoscopic, right [6]	10.5 years	NR	(I) 0 postoperative complications (II) Mean follow-up 22 months (III) 100% with improvement, 50% in remission at mean follow-up 22 months
Kolski, Kim and Vajsar (52), 2001	Thoracoscopic, right [6] *vs.* open, transsternal [6]	11.3 [1.7–14.7] *vs.* 8.1 [1.9–15.8] years	0.8 [0.1–3.4] *vs.* 0.7 [0.1–1.4] years	(I) Thoracoscopic had shorter length of stay and less postoperative complications compared to open (II) 100% improved, 33% thoracoscopic were in CSR, 66% open CSR
Essa *et al.* (53), 2003	Open, transsternal-transcervical [30]	13.2 [4–16] years	19.3 [2–144] months	(I) Before surgery all patients underwent plasmapheresis and steroids weaned off (II) 90% effective, CSR 43.4% at mean follow-up 53.5 (range, 9–180) months (III) 33.3% ectopic thymic tissue which was found to be a significant poor prognostic factor for response to thymectomy
Seguier-Lipszyc *et al.* (54), 2005	Thoracoscopic, left [2]	10.75 years	4.5 years	(I) Ultrasound utilized intraoperatively to visualize the thymus (II) 0 complications (III) 100% improvement, 0% CSR
Wagner *et al.* (55), 2006	Thoracoscopic [6] *vs.* open, transsternal/ transcervical [5/3]	9.8 [2–24] *vs.* 9.5 [7–15] years	0.8 [0.5–2] *vs.* 2.8 [0.5–8.0] years	(I) No difference in operative time (II) Thoracoscopic had significantly less blood loss and shorter length of stay than open (III) No difference in surgical effectiveness at mean follow-up of 43 (range, 4–111) months
Kanzaki *et al.* (56), 2008	Open [3]	13.3 [12–15] years	11.3 [5–20] months	(I) Extended thymectomy combined with postoperative high-dose steroid therapy (II) 100% improvement, 33% CSR
Yeh *et al.* (57), 2011	Thoracoscopic-assisted, subxiphoid [4]	NR	NR	(I) 100% improvement, 25% CSR
Ware, Ryan and Kornberg (58), 2012	Thoracoscopic [9] or open, transsternal [1]	11.3 [4–14] years	15.3 [3–38] months	(I) 70% effective (II) 30% refractory to thymectomy—2 underwent repeat surgery and 1 had residual thymus confirmed on path and subsequently improved
Parikh, Vaidya and Jain (59), 2011	Thoracoscopic, right [4]	9.25 [2.5–16.0] years	5 [3–8] months	(I) Operative time 55 min–2.5 hours (II) Chest drain removed within 24 hours (III) 75% effective (2 steroid free, 1 steroids at lower dose) at follow-up time of 6 to 46 months

Table 4 *(continued)*

Table 4 *(continued)*

Authors, year published	Surgical approach [n]	Mean [range/± SD] age at thymectomy	Mean [range/± SD] disease duration prior to thymectomy	Key findings
Cheng *et al.* (37), 2013	Open, transsternal [141]	12 [3–18] years	NR	(I) 6.4% perioperative complication rate (II) 7.1% with postoperative myasthenic crisis (III) 91.1% response rate (25.2% CSR, 20.7% in pharmacologic remission, 45.2% improved, 3.7% unchanged, 5.2% worsened) (IV) 43.2% cumulative remission rate at 10 years (V) Disease onset >6 years had higher CSR rates (VI) >12 years old at thymectomy had higher CSR rates (VII) Early thymectomy for generalized (within 12 months of onset) associated with better response to thymectomy (VIII) No corticosteroid use postoperatively associated with better response to thymectomy
Christison-Lagay *et al.* (60), 2013	Thoracoscopic, right [15]	11.3 [2.0–15.9] years	12.5 [3–40] months	(I) Mean operative time 145 min (decreased throughout study) (II) 0 postoperative complications (III) 47% in medical remission or CSR (IV) Postoperative symptom trend: 50% improved at 1 year, 86% at 2 years, 75% at 3 years
Castro *et al.* (3), 2013	Thoracoscopic [4] or open, transsternal [28]	NR	NR	(I) 75% improvement (II) Of 25% that didn't improve, half underwent repeat thymectomy as they had undergone primary thoracoscopic (III) Path: 21% thymic hyperplasia, 6% thymoma
Heng *et al.* (38), 2014	Open, transsternal [20]	Median 11 years 1 month	Median 9 months	(I) 10% required intensive care unit support postoperatively (5% required preoperatively) (II) 20% had surgical site infections which responded to antibiotics alone (all on steroids) (III) 95% improvement with 30% CSR postoperatively at median follow-up of 32 months
Özkan *et al.* (61), 2015	Thoracoscopic, right [40]	14.8 [±2.2] years	15.9 [±28.9] months	(I) Mean surgical time 48.9 (±31.3) min (II) 7.5% postoperative complications (1 reintubation, 1 chest re-drainage, 1 atelectasis requiring bronchoscopy) (III) Mean chest tube duration 20.5 (±12.1) hours (IV) Mean length of stay 1.8 (±1.0) days

Table 4 *(continued)*

Table 4 *(continued)*

Authors, year published	Surgical approach [n]	Mean [range/± SD] age at thymectomy	Mean [range/± SD] disease duration prior to thymectomy	Key findings
Kitagawa *et al.* (36), 2015	Mediastinoscopic-assisted, subxiphoid [14]	9.4 [4–15] years	[3 months–7 years]	(I) Mean operative time 182 (±44 min) (II) Mean blood loss 34 (±43) cc (III) Chest tube removed postoperative day 1 (IV) Median length of stay 4.5 days (range, 4–6 days) (V) 2 patients with temporary incomplete paralysis of right recurrent laryngeal nerve (hoarseness resolved at 1 month and 3 months) (VI) 93% improved, 43% CSR at median follow-up of 27 months (range, 6–72 months)
Goldstein *et al.* (35), 2015	Thoracoscopic, right [12] *vs.* open, transsternal [16]	14 [±5.8] *vs.* 13 [±3.8] years	NR	(I) Utilized modified QMG score (II) Open had more severe disease preoperatively (mean MGFA 2.63 *vs.* 1.92) and lower pyridostigmine dose (III) Thoracoscopic had fewer complications, shorter postoperatively length of stay (IV) No difference in postoperative QMG score, steroid or pyridostigmine use between open and thoracoscopic approach at median follow-up of 23 months (thoracoscopic) and 44 months (open) (V) No difference in steroid dose pre- and postoperatively
Ashfaq *et al.* (62), 2016	Thoracoscopic, right [12]	Median 11 [3–17] years	Median 418 [75–1,756] days	(I) 0 postoperative complications (II) 100% improvement rate by DeFilippi classification
Kim *et al.* (45), 2019	Thoracoscopic, left [50]	10.5 [3–17] years	19.6 [0–168] months	(I) 0 postoperative complications (II) 45.5% Osserman I with no conversion to ≥ II postoperatively (III) Mean follow-up duration 37.9±4.2 months (IV) 49.8% of patients showed improvement after surgery (V) Increasing cumulative probability of improved status on Kaplan-Meier analysis at 3.5 years follow-up (VI) Weight-adjusted total daily steroid intake (mg/kg/day) decreased significantly over 3.5 years of follow-up
Jastrzebska *et al.* (63), 2019	Thoracoscopic [23] or open, transsternal [16] or thymectomy, unspecified [34]	14.6 [6–22] years	1 [0–8] years	(I) Path: 2.2% thymoma, 2.2% thymic atrophy, 95.7% hyperplastic thymus (II) 90% improved, 11.9% in CSR, 11.9% in pharmacologic remission
Derderian *et al.* (64), 2020	Open [18] *vs.* thoracoscopic, left/right [15/1]	15.6 [±4.4] *vs.* 11.9 [±4.3] years	10.3 [±8.8] *vs.* 10.7 [±7.1] months	(I) Thoracoscopic had longer operative time, less blood loss, shorter length of stay, and shorter duration of intravenous narcotic use compared to open (II) No difference in clinical improvement or CSR (III) Surgical pathology not predictive of outcome

CSR, complete stable remission; MGFA, Myasthenia Gravis Foundation of America; NR, not reported; QMG, quantitative myasthenia gravis score; SD, standard deviation.

Open thymectomy

First performed by Alfred Blalock in the 1940s, today's proponents for open thymectomy believe transsternal open thymectomy is the most reproducible method to achieve maximal dissection (65). As such, as of 2016 greater than 80% of thymectomies for JMG were performed by an open approach (26). When performed in children, disease improvement rates as high as 90–100% have been reported alongside CSR rates of 25–66% (37,38,52,56).

Earliest reports of thymectomy are described in the 19th century when it was performed through a cervical incision in infants and young children due to a belief that thymic enlargement caused respiratory obstruction and sudden death (66). Transcervical thymectomy was first reported for JMG in 1912 by Ferdinand Sauerbach to be replaced with the transsternal approach with advances in thoracic surgery (66,67). However, attempts at reducing morbidity and simplifying recovery after thymectomy lead to the reintroduction of the transcervical approach in the 1960s in young adults (66). A transverse incision is made just above the suprasternal notch through the platysma. The sternohyoid and sternothyroid muscles are retracted laterally and the cervical aspect of the thymus identified enabling traction upward and dissection and deliverance of the mediastinal portion of the thymus up above the manubrium (66). However, many find the inferior and lateral thymus to be poorly visualized in this technique making it susceptible to residual thymus end procedure (68,69). In a study using a hybrid transcervical-transsternal approach, as many as 33.3% of patients had ectopic thymic tissue which was associated with poor response to thymectomy (53). Today, transcervical thymectomy accounts for as few as 1% of thymectomies for JMG (26).

Hybrid approaches incorporating a subxiphoid incision assisted by either mediastinoscopy or thoracoscopy have aimed to improve visualization while still avoiding median sternotomy (36,57). Although data boast impressive improvement rates of 93–100% and CSR rates of 25–43%, little is published on these approaches. Perhaps for good reason in the case of subxiphoid-mediastinoscopy, as 14% of patients experienced incomplete right recurrent laryngeal nerve paralysis which resolved between 1 and 3 months postoperatively (36).

Thoracoscopic thymectomy

As the thymus resembles the anterior mediastinal and cervical fat it lies within and is laterally bounded by the phrenic nerves, adequate visualization is imperative to a safe and complete resection. However, the postoperative morbidity and cosmetic appearance following open thoracic surgery are suboptimal; therefore, the thoracoscopic approach to thymectomy was developed with the goal of achieving equivalent visualization, thymic resection and disease control as is achieved with the transsternal approach while decreasing postoperative recovery time and improving cosmesis.

Patients are positioned in a semi-lateral position at a 30° to 45° angle. Often, tracheal intubation affords superior exposure over selective endobronchial intubation as sufficient working space and visualization of the mediastinum are provided by capnopneumothorax with insufflation pressures of 4–8 mmHg while selective intubation results in a collapse of the chest wall (59). A 30° thoracoscope and three 5–10 mm ports are utilized, including at the anterior axillary line, the inframammary midclavicular line and in the posterior axillary line at the 3rd or 4th intercostal space.

Some surgeons prefer a right sided thoracoscopic approach due to a larger working space afforded by the right thoracic cavity as well as the superior ability to visualize the superior vena cava and trace it to the left brachiocephalic vein (35). However, those in favor of the left sided approach feel the left portion of the thymus is easier to approach from this side as it is oftentimes larger and can extend under the left phrenic nerve and up to the aortopulmonary window, a frequent location of ectopic thymus (70,71). Due to unique benefits afforded by both the right and left approaches, some support a bilateral thoracoscopic approach (52). Irrespective, a thoracostomy drain is typically left end-procedure and removed within the first 24 hours postoperatively, and the consequence of two thoracostomy drains should be considered if debating between a unilateral and bilateral approach.

Small noncomparative studies evaluating outcomes following right and left thoracoscopic approaches demonstrate 50–100% disease improvement rates with minimal to no postoperative complications (45,51,54,59-62). As mentioned, critics have argued that thoracoscopic thymectomy results in incomplete clearance of thymic tissue and is associated with lower remission rates compared to open thymectomy (3,48,49,72-75). However, retrospective studies comparing thoracoscopic and open thymectomy for JMG have found thoracoscopic thymectomy to have less operative blood loss, shorter postoperative length

of stay, improved cosmesis and either a comparable or lower postoperative complication rate with no difference in postoperative disease control (22,26,35,52,55,64,76). However, and notably, one study has identified incomplete resection with thoracoscopy (3,26).

Thoracoscopy's non-inferiority of resection extent and post-operative disease control has not been prospectively evaluated in adults or children to date (46,47,68). Despite this, it is suspected that as familiarity with thoracoscopic thymectomy continues to increase, not only will the proportion of thymectomies performed thoracoscopically increase, but as patients evade the morbidity of thoracotomy, the risk benefit ratio of surgical management will shift and thymectomy will be offered to an increasing proportion of JMG patients.

Robotic-assisted thymectomy

The first robotic-assisted thymectomy was performed for MG in 2003 (77), and since multiple approaches have been developed including left- and right-sided, bilateral and subxiphoid (71,77-80). However, the adoption of robotic-assisted surgery in children has been slow compared to adult surgery (24,25). We identified one study meeting our inclusion criteria which utilized robotic-assisted thymectomy for JMG (4). Employing the same procedural principles and considerations regarding sidedness as the thoracoscopic approach, the robotic approach delivers several technical advantages compared to traditional thoracoscopy. The robot camera affords a three-dimensional and magnified view of the operative field as well as operator control improving visuospatial orientation. In addition, the robotic articulating instruments provide a more natural dexterity than thoracoscopic instruments. This improves dissection capabilities, particularly for difficult to reach tissue planes, while eliminating instability secondary to tremor.

When compared to non-operative management, patients who underwent robotic thymectomy for JMG had a higher 5-year cumulative CSR rate as well as reduced daily dose of cholinesterase inhibitors and corticosteroids; however, with a 19.1% postoperative complication rate. Although studies have not yet compared robotic-assisted thymectomy to other surgical approaches for JMG, studies completed in adults, including comparisons between robotic-assisted and thoracoscopic thymectomy, have demonstrated its safety alongside comparable clinical outcomes relative to sternotomy and superior outcomes compared to thoracoscopy (14,78,81). However, increased cost and infrastructure requirements in addition to time required for docking or conversion to open in the event of emergent bleeding are significant barriers to the use of robotic-assisted thymectomy in JMG (71).

Limitations

As mentioned, data evaluating surgical management of JMG is restricted to small retrospective analyses leaving them limited by both power and selection bias. When comparisons are able to be made between cohorts, they are reduced by heterogenous populations often differing in one or more important confounding variables such as preoperative disease severity, patient age, symptom duration, antibody status and follow-up duration—all factors which contribute to a patient's response to thymectomy. Multicenter retrospective studies are a first and necessary step to enable corrected comparisons to be made. Furthermore, randomized prospective evaluation comparing optimal surgical to optimal medical management is necessary in order to appropriately understand the role of thymectomy in the management of JMG.

Conclusions

This review evaluated the role of surgical management for patients with thymectomy including important considerations when determining candidacy, timing and surgical approach. Although data specific to JMG are limited, available evidence supports equal if not improved disease control following thymectomy relative to medical management. Furthermore, data do not suggest any degree of immunodeficiency following thymectomy regardless of patient age at surgery, and outcomes may be optimized when surgery is performed earlier in the disease course, particularly for patients who are post-pubertal with generalized or severe disease and those necessitating high-dose steroid administration. Open transsternal resection was the historic gold-standard; however, as surgeons become more comfortable with thoracoscopic and robotic-assisted thymectomy, we anticipate increasing proportion of patients with JMG will undergo thymectomy and in a minimally invasive manner. As such, higher-level data, through the use of multi-institutional databases and randomized prospective evaluation, which compares surgical to medical therapy is warranted to understand which child warrants thymectomy, at what point in their disease course and their

development, and which surgical approach will optimize their postoperative outcomes.

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Footnote

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Review Article

Insights into molecular aspects and targeted therapy of thymic carcinoma: a narrative review

Tadashi Sakane[1,2]^, Hiroshi Haneda[1], Katsuhiro Okuda[2]

[1]Department of Thoracic Surgery, Nagoya City University West Medical Center, Nagoya, Japan; [2]Department of Thoracic and Pediatric Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

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Correspondence to: Tadashi Sakane, MD, PhD. Department of Thoracic Surgery, Nagoya City University West Medical Center, 1-1-1 Hirate-cho, Kita-ku, Nagoya 462-8508, Japan; Department of Thoracic and Pediatric Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan. Email: t.sakane@med.nagoya-cu.ac.jp.

Background and Objective: Thymic carcinomas are rare tumors derived from thymic epithelial cells. Owing to their rarity, the search for molecular biology has been conducted in combination with thymoma as one histological subtype, and only a few studies have exclusively focused on thymic carcinoma. Currently, no therapy is more effective than complete surgical resection, and the development of novel therapies, including targeted therapies, is hampered. In this review, we summarize the knowledge regarding altered genes and pathways in thymic carcinoma with recent preclinical and clinical targeted therapies.

Methods: We conducted a narrative review of the relevant English literature available in PubMed and Google Scholar on genomic characteristics and targeted therapies for thymic carcinoma.

Key Content and Findings: Although the literature consists of a relatively small series, it suggests that the frequently involved genes or pathways associated with thymic carcinoma are tumor suppressor genes, including *TP53* and *CDKN2A/B*, and the receptor tyrosine kinase pathway. Targeted therapy demonstrated antitumor activity with encouraging results. However, potential predictive biomarkers have not been identified and the response to these therapies appears to be irrelevant to gene alterations.

Conclusions: Some studies have revealed the molecular characteristics of thymic carcinoma, although the results of these studies have shown a different pattern of gene alterations. The further accumulation of data would be helpful in revealing the genomic landscape and establishing molecular-targeted therapies.

Keywords: Thymic carcinoma; molecular profile; targeted therapies

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Introduction

Thymic carcinoma is an extremely rare thymic neoplasm, accounting for approximately 10% of thymic epithelial tumors (TETs) (1). In addition to their rarity, thymic carcinomas include various histological subtypes, with squamous cell carcinoma being the most common (2). Thymic carcinomas exhibit more aggressive behavior and a higher metastatic potential than thymomas (3). The median overall survival (OS) is 6.6 years, with 5- and 10-year OS rates of 60% and 40%, respectively. The prognosis for advanced disease, which accounts for approximately

^ ORCID: 0000-0002-8038-4803.

Table 1 Search strategy summary

Items	Specification
Date of search	15th July–10th August 2023
Databases and other sources searched	PubMed and Google Scholar
Search terms used	'thymic carcinoma', 'thymic epithelial tumor', 'gene' or 'genetic', 'mutation' or 'aberration' or 'alteration', 'molecular', 'targeted' or 'molecular targeting' and 'therapy'
Timeframe	Date unrestricted to August 2023
Inclusion and exclusion criteria	Inclusion criteria: (I) English language; (II) meta-analyses, systematic reviews, prospective studies, retrospective studies, case studies, and previous related reviews
	Exclusion criteria: studies with incomplete or irrelevant data
Selection process	One author compiled a list of eligible studies followed by review by all authors to determine suitability

70–75% of all cases, is miserable; the 5-year OS rates were 63% for stage III, 42% for stage IVa and 30% for IVb (4,5).

The factors associated with the development of TETs remain unknown; however, the understanding of the aberrant gene pathways involved in TETs has been gradually improving over the last decade, largely through the advent of next-generation sequencing (NGS) technologies. Previous studies have found that different histological subtypes of TETs exhibit different molecular profiles (6-10). In thymomas, a significant and recurrent missense mutation in the general transcription factor IIi (*GTF2I*) have been identified in type A and AB subtypes, which is reputed to drive their growth (6,8). In thymic carcinomas, owing to the rarity of these tumors and their histological heterogeneity, the results of studies show a different pattern of molecular aberrations with only a few significantly and recurrently mutated genes. Accordingly, data on their biology and clinical behavior are limited. In this review, we discuss the recent advances in the investigation of the molecular characteristics of thymic carcinoma and the development of potential targeted therapies. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-48/rc).

Methods

An extended review of the relevant literature in PubMed and Google Scholar was conducted, using different combinations of search terms, including 'thymic carcinoma', 'thymic epithelial tumor', 'gene' or 'genetic', 'mutation' or 'aberration' or 'alteration', 'molecular', 'targeted' or 'molecular targeting' and 'therapy'. The types of articles included in the search criteria were meta-analyses, systematic reviews, prospective studies, retrospective studies, case studies, and previous related reviews. Additional papers were identified by reviewing the reference lists of relevant publications. Publications with incomplete or irrelevant data, and those written in languages other than English were excluded. The search strategy is presented in *Table 1*.

Genetic alterations in thymic carcinoma

Tumor suppressor genes

In addition to the two early reports by Hirabayashi *et al.* and Tateyama *et al.* that showed a high frequency *TP53* point mutations in thymic carcinoma, Wang *et al.* and Moreira *et al.* reported that *TP53* mutations were exclusively observed in thymic carcinoma and were associated with aggressive behavior (7,11-13). Petrini *et al.* also identified recurrent mutations in *TP53* in thymic carcinoma (6). Several studies have found a high frequency of *TP53* in thymic carcinoma (7.7–25.7%), some of which showed that the presence of *TP53* mutations was associated with a poor prognosis (14-22). A recent study conducted by Girard *et al.*, which included the largest cohort, identified *TP53* mutations in 25.9% of 174 thymic carcinoma cases (9).

CDKN2A and *CDKN2B*, located on chromosome 9p21, encode p16 and p15, respectively, which act by inhibiting CDK4 and CDK6, and are negative regulators of cell cycle progression (23,24). In thymic carcinoma, Aesif *et al.* examined the expression of p16 by immunohistochemistry (IHC) and cytogenetic abnormalities of *CDKN2A* by

fluorescence in situ hybridization (FISH) (25). They reported that 53.8% (14/26) of the cases showed the expression of p16 and 19.0% (4/21) had homozygous deletion of *CDKN2A*, suggesting that the loss of p16 expression and homozygous deletion of *CDKN2A* could be predictors of a poor prognosis. Another study reported that copy number aberrations of *CDKN2A* and *CDKN2B* are associated with a worse prognosis in thymic carcinoma (26). Two recent NGS analyses with large cohorts showed similar results: the mutation frequencies of *CDKN2A* and *CDKN2B* were high: approximately 40% for *CDKN2A* and approximately 25% for *CDKN2B* (9,27).

CYLD and *BAP1* are both tumor suppressor genes, and mutations in these genes have been detected in 8.5–18.8% and 8.2–12.5% of thymic carcinomas, respectively (6,7,9,13,27,28). According to the results of a phase 2 study of pembrolizumab by Giaccone *et al.*, there were five patients with a *CYLD* mutation (12.2%) among 41 patients with thymic carcinoma, and these five patients exhibited high expression of programmed death-ligand 1 (PD-L1), three of whom had a complete response (CR) or partial response (PR) (29). He *et al.* characterized the genomic profiles of ten patients with thymic carcinoma who received pembrolizumab and identified that alterations in *CYLD* were promising predictors of a response to pembrolizumab (30). Meanwhile, they found that mutations in *BAP1*, which were also correlated with the expression of PD-L1, were promising predictors of pembrolizumab resistance (30). Angirekula *et al.* demonstrated that 11.4% of thymic carcinomas had lost the nuclear expression of BAP1, and that the loss of BAP1 expression may help distinguish thymomas from thymic carcinomas (31).

Receptor tyrosine kinases

The epidermal growth factor receptor (EGFR) is frequently mutated and/or overexpressed in different types of human cancers and is a target of multiple cancer therapies (32). Several studies investigated the EGFR expression levels in thymic carcinoma using IHC and reported that EGFR was overexpressed in 20.0–100.0% of cases (33-39). However, *EGFR* mutations are rare in thymic carcinomas (18,21,35-37,40-42).

KIT plays a major role in the development and maintenance of gastrointestinal stromal tumors (GISTs). Since Pan *et al.* found that thymic carcinoma frequently overexpressed KIT, whereas thymoma was found to be consistently negative for KIT by a systematic survey using a tissue array technique, alterations or expression of KIT in thymic carcinoma have been well-demonstrated in the literature (43). Immunohistochemical KIT positivity is found in 50.0–88.2%, although *KIT* mutations are relatively rare (19,33,37,44-46). The expression of KIT has been associated with activating mutations in exons 9, 11, 13, and 17 of *KIT*. *KIT* and *PDGFRA* are highly homologous and activate similar downstream signal transduction pathways (47). *PDGFRA* mutation, which is also considered to be a major driver gene of GISTs, is reported to occur in 0.0–5.6% of thymic carcinomas (19,42,44).

HER-2/neu is a proto-oncogene, and gene amplification and the overexpression of HER-2 have been demonstrated to be targets for several cancers (48). Pan *et al.* found that 47.1% (8/17) of thymic carcinoma overexpressed HER-2 by IHC, while no evidence of gene amplification was detected by FISH (49). According to a study conducted by Weissferdt *et al.*, the significant immunohistochemical expression of HER-2 was observed in 58.3% (14/24) of cases, while 4.2% (1/24) showed *HER-2/neu* gene amplification, and 75.0% (18/24) exhibited increased *HER-2/neu* gene copy numbers (39). Genetic alterations of *HER-2/neu* are rare (9,42).

Insulin-like growth factor 1 receptor (IGF-1R) is a transmembrane receptor involved in cancer development, metastasis, and therapeutic resistance (50). Zucali *et al.* analyzed the IGF-1R expression in eight cases of thymic carcinoma by IHC, and seven cases (87.5%) were positive for IGF-1R (51). They also found that the expression of IGF-1R was significantly more common in aggressive histological subtypes than in indolent ones. Meanwhile, *IGF-1R* mutations have been reported to be rare, with a frequency of less than 8.3% (9,14,21).

FGFR3 encodes a member of the FGFR family (52). Aberrant FGFR signaling has been reported in many cancers, including breast cancer and colorectal cancer, and contributes to oncogenesis, tumor progression, and resistance to anticancer therapies (53,54). Asselta *et al.* performed an NGS analysis targeting the hotspot regions of 50 oncogenes and tumor suppressor genes and found five *FGFR3* mutations in four (26.7%) out of 15 patients with thymic carcinoma (46). In this study, *FGFR3* was the most frequently mutated gene, and patients carrying *FGFR3* mutations showed significantly better survival. Enkner *et al.* reported, based on NGS with a gene panel, that 5.7% (2/35) of cases of thymic carcinoma harbored *FGFR3*

mutations; other NGS studies did not identify any *FGFR3* mutations (7,15-17,19).

Rat sarcoma virus (RAS)/mitogen-activated protein kinase (MAPK) cascade

EGFR-mediated activation of the canonical RAS/MAPK signaling cascade is responsible for cell proliferation and death. Gene mutations in this cascade are rare in thymic carcinoma. To date, only a few studies have identified low mutation rates of genes of the RAS family, including *HRAS*, *KRAS*, *NRAS*, as well as RAF genes, including *ARAF* and *BRAF* (9,18-20,42,46).

PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway

The frequency of gene alterations in this signaling pathway in thymic carcinoma is low. Alberobello *et al.* first reported mutations in the subunits of *PI3K* using thymic carcinoma cell lines (55). Several studies that used NGS have reported that mutations of *PI3K*, *Akt*, *mTOR*, and *TSC1/2* were detected in 0.0–5.0% of thymic carcinoma (6,8,9,14,17,27,46).

PTEN gene

PTEN is a tumor suppressor gene that plays a role in growth and survival and is a negative regulator of the PI3K/Akt signaling pathway (56). There have only been a few reports on PTEN expression or *PTEN* mutations. Masunaga *et al.* analyzed TET samples, including four cases of thymic carcinoma, for the expression of PTEN, *PTEN* exon mutations, and PTEN promoter methylation (57). They found that the PTEN protein was immunohistochemically expressed in all thymic carcinoma cases; however, they did not detect *PTEN* mutations. Enkner *et al.* reported that the expression of PTEN was found in 30 of 31 thymic carcinoma cases (96.8%), 14 (45.2%) of which showed high expression levels (15).

GTF2I gene

Previous reports have revealed that the *GTF2I* point mutation (L424H) was the most frequent mutation in thymomas, especially in indolent type A and AB thymomas (6,8). However, *GTF2I* mutations have not been identified in thymic carcinoma (6,8,58).

Tumor mutation burden (TMB) and microsatellite instability (MSI) in thymic carcinoma

Multiple biomarkers related to immune checkpoint inhibitors (ICIs), as well as the immunohistochemical detection of PD-L1 in tumor cells, have been identified. The TMB and MSI have been clinically used in several oncologic cases.

The TMB refers to the total number of somatic non-synonymous mutations in a particular region of the tumor genome. A TMB of ≥10 mutations per megabase was reported to predict a better response to ICIs in non-small cell lung cancer (NSCLC) (59). According to the comprehensive genomic analysis of TET in The Cancer Genome Atlas (TCGA) Project, the TMB of thymic carcinoma was high (21.29 mutations per megabase), while TETs had the lowest average TMB (0.48 mutations per megabase) among adult cancers (8). Hou *et al.* also found a similar trend, in that the TMB of thymic carcinoma was significantly higher than that of thymoma (58). In contrast, two studies from China reported that the average TMB value of patients with thymic carcinoma was 0.72 and 0.66 mutations per megabase (10,60). According to a recent study by Kurokawa *et al.*, who examined data from a cohort of TET cases in the United States using the Foundation Medicine Inc. research database, the prevalence of TMB-high cases was 7.0% (27). Conforti *et al.* conducted a phase 2 study of the combination of the anti-PD-L1 inhibitor avelumab with the anti-angiogenesis drug axitinib in patients with advanced thymic carcinoma (n=27), B3 thymoma (n=3), and mixed-type thymic carcinoma and B3 thymoma (n=2) (61). Although this population was not limited to patients with thymic carcinoma, there was a positive association between a higher TMB and the response rate.

Microsatellites are short tandem repeats scattered throughout the genome and are prone to a high mutation rate. MSI is defined as a hypermutable phenotype that occurs in genomic microsatellites in the presence of a deficient DNA mismatch repair machinery (62). Several clinical trials have revealed that patients with MSI-high colorectal cancer benefit from ICI treatment (63). The data on MSI in thymic carcinoma are limited. According to a study by Kurokawa *et al.*, MSI-high cases accounted for 2.3% of thymic carcinoma cases, and Girard *et al.* reported that no MSI-high cases were found in 174 thymic carcinoma cases (9,27).

Targeted therapy in thymic carcinoma

Despite significant research efforts, the development of new drugs for thymic carcinoma is slow. Lenvatinib was approved in 2021 on the basis of a phase 2 trial, the REMORA study (64). Lenvatinib is a multitargeted kinase inhibitor of VEGFR, FGFR, KIT, and other kinases (64). The REMORA study assessed the activity of lenvatinib as a second-line treatment in 42 patients with advanced or metastatic thymic carcinoma and showed that 38.1% of patients had PR and 57.1% had stable disease (SD) with a median progression-free survival (PFS) of 9.3 months, which could be considered as the most promising results for previously advanced or metastatic thymic carcinoma. Currently, predictive biomarkers for lenvatinib activity have not been identified. Tsukaguchi *et al.* reported a lenvatinib-refractory thymic mucinous adenocarcinoma, whose *PIK3CA* mutation could be associated with resistance to lenvatinib (65).

Activating mutations in *KIT* and *PDGFRA* in GISTs are related to the response to the KIT inhibitor imatinib (66). Despite the rare *KIT* mutations in thymic carcinoma, several studies found that *KIT*-mutated thymic carcinoma showed a significant clinical response to imatinib (67,68). Sunitinib and sorafenib are multitarget tyrosine kinase inhibitors (TKIs) of *KIT* and other kinases. Thomas *et al.* observed a PR to sunitinib in 26.1% (6/23) of patients with thymic carcinoma and a SD in 65.2% (15/23); disease control was achieved in 91.3% (21/23) (69). Recently, Proto *et al.* conducted a phase 2 trial of sunitinib in patients with thymic carcinoma and found that 3.6% of the patients had CR, 17.9% had PR and 67.9% had SD; the objective response rate (ORR) was 21.4% and the disease control rate was 89.3% (70). At present, the correlations between the response to sunitinib and *KIT* mutation status are uncertain. Pagano *et al.* retrospectively evaluated sorafenib activity in five patients with metastatic thymic carcinoma, and reported that two patients (40.0%) achieved PR and two (40.0%) achieved SD (44). They also reported that sorafenib activity seemed independent from the *KIT* and *PDGFRA* mutation status. Perrino *et al.* reported the results of the Resound Trial, which examined the efficacy of regorafenib in seven patients with thymic carcinoma (71). Regorafenib potentially inhibits angiogenic and stromal receptor tyrosine kinases, VEGFR1-3, tyrosine kinase with immunoglobulin-like and EGF-like domains 2, and PDGFRB, which have been approved by the Food and Drug Administration for the treatment of colorectal cancer and GIST. SD was observed in six patients (85.7%) and progressive disease (PD) was observed in one patient (14.3%); the response was not satisfactory (71). Anlotinib is a new oral multitarget TKI targeting VEGFR1-3, FGFR1-4, PDGF-A and -B, and KIT (72). Several retrospective studies have examined the efficacy and safety of anlotinib in patients with relapsed or refractory TET (73,74). Wang *et al.* reported an ORR of 41.1% and a median PFS of 6 months (74).

Zucali *et al.* conducted a phase 2 study of everolimus, a potent oral mTOR inhibitor, in 18 patients with thymic carcinoma (75). Disease control was achieved in 77.8% of the patients (CR, n=1; PR, n=2; SD, n=11); the median PFS was 5.6 months and the median OS was 14.7 months. Hellyer *et al.* performed NGS with a 130-gene targeted panel on samples from 12 TET patients, including three with thymic carcinoma; however, they failed to identify correlations between detectable tumor mutations and everolimus activity (76). Predictive biomarkers for everolimus remain unclear.

Aesif *et al.* reported that CDK4/6 inhibitors may be considered for targeted therapy (25). Recently, Jung *et al.* conducted a phase 2 trial of palbociclib, an oral inhibitor of CDK4/6, in patients with recurrent or refractory advanced TETs, including 23 cases of thymic carcinoma (77). The PFS at 6 months was 52.2% and the median PFS and OS were 9.2 and 25.6 months, respectively. Two patients (8.7%) achieved PR, 16 (69.8%) achieved SD, and 18 (78.3%) achieved disease control.

Rajan *et al.* investigated the efficacy of cixutumumab, a fully human IgG1 monoclonal antibody that targets IGF-1R, in patients with TETs (78). The thymic carcinoma cohort was closed after enrolling 12 patients due to lack of activity. Five (41.7%) of 12 patients had SD and seven (58.3%) patients had PD; there were no objective responses and the disease control rate was 41.7%, with a median time to progression of 1.7 months and a median survival of 8.4 months. The tumor expression of IGF-1R did not appear as a good biomarker predictive response to anti-IGF treatment, as well as the raise of serum IGF-1 level.

EGFR-TKIs, a standard treatment modality for *EGFR*-mutated NSCLC, have not been proven to be effective in thymic carcinoma, although only a few case reports have described the clinical activity of EGFR-TKIs (79,80). In 2005, Kurup *et al.* conducted a phase 2 study of gefitinib and failed to demonstrate any activity in seven cases of thymic carcinoma (81). In 2008, Bedano *et al.* performed a phase 2 study of erlotinib plus bevacizumab in seven cases

with thymic carcinoma, and reported that it was associated with a limited response (82).

Somatostatin (SST) is a naturally occurring peptide composed of 14 amino acids. Among the five SST receptors identified, the most common SST receptor expressed in human tumors is the SST2 subtype, which is visualized using radionuclide octreotide scintigraphy. The octapeptide SST analog has a high affinity for a selective SST subtype receptor (SST2). Palmieri *et al.* and Loehrer *et al.* have conducted phase 2 trials of octreotide alone or with prednisone in patients with refractory or unresectable, advanced TETs who were positive in an octreotide scan (83,84). In these studies, the ORRs of the entire TET cohort were 37.5% and 30.3%, respectively; however, thymic carcinoma treatment did not produce an objective response. Kirzinger *et al.* conducted another phase 2 trial of octreotide in combination with prednisone in 17 patients with primary or locally recurrent unresectable TETs, including two patients with thymic carcinoma (85). In this trial, one patient had SD and one had PD.

The wild-type Wilms tumor gene, *WT1* is expressed in various types of neoplasms and has been considered to be a tumor suppressor (86,87). In recent years, WT1 has been identified as a target antigen for tumor-specific immunotherapy. Oji *et al.* conducted a phase 2 study of cancer immunotherapy with the WT1 peptide vaccine in patients with advanced TET, including nine patients with thymic carcinoma, which overexpressed the WT1 protein in tumor cells (88). Unfortunately, no patients achieved a CR or PR; 75.0% of patients with thymic carcinoma had SD and the remaining 25.0% of patients had PD without serious adverse events. Autoimmune complications related to thymoma, pure red cell aplasia, and myasthenia gravis occurred in two of four patients with thymoma.

Conclusions

Thymic carcinomas have a distinct genomic landscape characterized by a high prevalence of specific genes and a high TMB. Despite the rarity and histological heterogeneity of these tumors, several studies have revealed significant molecular alterations. However, there have been few suitable alterations for targeted therapy and the identified alterations seem to have little correlation with activity. Most clinical trials for thymic carcinomas have been conducted in combination with thymoma, although thymic carcinomas exhibit different biological behavior from thymoma in genetic, clinical, and immunological aspects. Continued data sharing and international collaborations would be helpful in better understanding the genomic landscape, leading to molecular targeted therapies.

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Footnote

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Letter to the Editor

Full-circumferential tracheal replacement with cartilage-reinforced forearm free flaps in the real world

Alain Wurtz

Departement Hospitalo-Universitaire de Recherche et d'Enseignement (DHURE), CHU Lille, Lille, France

Correspondence to: Alain Wurtz, MD, PhD. Département Hospitalo-Universitaire de Recherche et d'Enseignement (DHURE), CHU Lille, 1 Place de Verdun, 59000 Lille, France. Email: afwurtz60@gmail.com.

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Following an invited Editorial (1), we have recently reanalyzed the harm-benefit of full-circumferential tracheal replacements (FCTRs) for tracheal adenoid cystic carcinoma (ACC) by means of the widely used tracheal substitutes: silicone-stented aortic allografts and cartilage-reinforced forearm free flaps. While no 90-day mortality (in-hospital mortality) was shown in our world-first case series of FCTR with silicone-stented aortic allografts for salivary gland-type carcinoma performed from April 2005 to September 2007, we were concerned by the results in term of in-hospital mortality (n=6) after FCTR with cartilage-reinforced forearm free flaps for ACC performed at the Marie-Lannelongue Hospital (Le Plessis Robinson, France) (2). In a reply, the team of this Institution reported on its overall experience of 30 patients. The authors claimed that they have used this technique "with only four postoperative deaths at the very beginning (before 2013) of our experience", "highlighting the presence of an important learning curve" (3).

With regard to this discrepancy (six versus four deceased patients in the postoperative period), we have pooled data from the five previously published articles by the Marie Lannelongue Hospital's team in the field since 2013 (4-8). The data analyzed are those of patients who underwent a FCTR for miscellaneous indications from August 2004 to December 2017 (4-7); and those of patients who subsequently underwent a similar procedure for ACC between 2017 and 2019 (8). Patient numbers and causes of in-hospital mortality as stated by the authors are reported in *Table 1*.

It appears to us that the results of this in-depth literature review contradict the author's assertion: the in-hospital mortality in all indications was actually seven patients and increased during the second period (five deceased patients after 2013). The main life-threatening surgical complication was tracheal flap ischemia that was shown in 10% of patients: one case during the learning curve period

Table 1 Articles reported patients undergoing FCTR with cartilage-reinforced forearm free flaps

Article, year	Reported patients	Causes of in-hospital mortality (n=7)
Fabre *et al.*, 2013 (4)	12 patients	Respiratory infection and excessive bronchial congestion (n=2). The flaps remained viable and functional
Fabre *et al.*, 2015 (5)	5 additional patients	None
Etienne *et al.*, 2018 (6)	No additional patients	None
Mercier *et al.*, 2018 (7)	2 additional patients	Additional death: myocardial infarction (n=1)
Estephan *et al.*, 2023 (8)	Reported patients with ACCs from 2007 to 2019 (n=15)[†]	Additional deaths: tracheal flap necrosis (n=2), anastomotic fistula (n=1), stroke (n=1)

Causes of in-hospital mortality (as stated by the authors in five articles). [†], ten patients from 2007 to 2017; and five patients between 2017 and 2019. FCTR, full-circumferential tracheal replacement; ACC, adenoid cystic carcinoma.

which needed an additional free-flap replacement as salvage surgery (4) (the "Discussion" section), and two fatal cases from flap necrosis during the second period (8). Finally, with regard to the major in-hospital mortality shown after FCTR for tracheal ACC (a radiosensitive tumor), and the lack of reliability of current tracheal substitutes, the procedure should not be proposed as we have been stating for a decade (1,2,9). Since the FCTR with cartilage-reinforced forearm free flaps "should be considered experimental" as stated by Eisenberg and Hofstetter (10), we think our complete literature analysis useful to maintain the integrity of the surgical research.

To develop of a reliable substitute currently remains a challenge of the utmost importance. In this setting, we launch an experimental project of tracheal substitute based on a pedicled thoracic flap reinforced by synthetic biocompatible tracheal rings.

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