Review Article

# Perspectives on surgical treatment for thymic epithelial tumors: a narrative review

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**Background and Objective:** Thymic epithelial tumors are relatively rare; thus, mostly retrospective studies and a few prospective randomized controlled trials have been conducted on the treatment and the biomarkers, with no standard therapy established. Indications for extended thymectomy, robot-assisted thoracic surgery, and multidisciplinary treatment are controversial. Here, we considered the prospects of surgical treatment and the possibility of immune checkpoint inhibitor (ICI) treatment for thymic epithelial tumors.

**Methods:** This is a narrative review; PubMed was searched using a set of keywords related to thymoma and its proposed treatments over the last 5 years.

**Key Content and Findings:** Thymic epithelial tumors are associated with autoimmune diseases. They are relatively rare, and their pathology remains unclear. Therefore, accumulating more case reports is important. Surgical resection is generally considered for both diagnosis and treatment. If the tumor has a strong tendency to invade surrounding areas, such as thymic carcinoma/thymoma, the diagnosis may be confirmed preoperatively by needle biopsy, and induction chemotherapy may be selected. Surgical resection is the most effective treatment, and complete resection is important. In cases where complete resection is difficult, multidisciplinary treatment is performed. Although there are various obstacles, using ICIs may prove effective for treatment both as preoperative and postoperative chemotherapy in the future, as shown for other cancers. Programmed cell death-ligand 1 (PD-L1) is an immunoinhibitory molecule that suppresses T cells activation, leading to tumor progression. Overexpression of PD-L1 in some cancers is associated with poor clinical outcomes. However, the role of PD-L1 expression as a prognostic factor remains controversial. Therefore, various biomarkers other than PD-L1 have been identified.

**Conclusions:** We reviewed the latest treatments for thymic epithelial tumors. If new therapeutic agents such as ICIs and molecular-targeted drugs are developed, this review suggests that surgery will become more important not only as therapy but also as part of multidisciplinary treatment that includes tissue collection.

**Keywords:** Extended thymectomy; immune checkpoint inhibitor (ICI); multidisciplinary treatment; surgery; thymoma

Submitted Nov 03, 2023. Accepted for publication Jan 20, 2024. Published online Feb 20, 2024.
doi: 10.21037/gs-23-453
**View this article at:** https://dx.doi.org/10.21037/gs-23-453

## Introduction

### *Background*

Thymic epithelial tumors are uncommon tumors that originate from the epithelial cells of the thymus, and the relatively rare diseases mainly occur in the anterior mediastinum and undergo malignant progression owing to recurrence and distant metastasis (1-3). These tumors

include thymoma, thymic carcinoma, and neuroendocrine tumors. Generally, surgery is performed for both diagnostic and therapeutic purposes. Complete surgical resection is considered the best prognostic factor for treatment, and multidisciplinary treatment is selected in cases in which complete resection is not possible (4).

Tumors have a mechanism to suppress human immune activation, and programmed cell death-ligand 1 (PD-L1) expression is one such suppressive mechanism. Moreover, there is increasing evidence relating PD-L1 and immune checkpoint inhibitor (ICI) in thymic epithelial tumors. PD-L1 expression and ICI therapeutic efficacy are not necessarily correlated, and the surrounding tumor immune microenvironment also influences therapeutic efficacy. In recent years, resistance to ICI treatment has been reported (5,6), and in addition, it is also necessary to search for new biomarkers for thymic epithelial tumors.

### *Rationale and knowledge gap*

The surgical treatment of thymic epithelial tumors generally involves complete resection. This disease is relatively rare, and most of the literature reporting on surgical methods and novel anticancer agents is retrospective, with only a few prospective randomized controlled trials. Although the major guidelines and thoracic societies suggest extended thymectomy as the preferred surgical procedure for thymoma, some papers suggest reduction surgery (7,8).

The surgical methods for early-stage thymic epithelial tumors include tumor resection, thymothymectomy, and extended thymothymectomy; the choice of surgical method is left to the discretion of each institution.

The effectiveness of the minimally invasive surgical approach against thymic epithelial tumors is also gradually being proven (9-11). Extended thymectomy, which was previously performed through midline sternotomy, can now be performed with minimal invasiveness using video-assisted thoracic surgery (VATS) and robot-assisted thoracic surgery (RATS) (11).

First, the indications for extended thymectomy remain controversial. This procedure is performed for thymomas accompanied by myasthenia gravis (MG) to reduce the risk of postoperative MG. However, some studies have suggested extended thymectomy regardless of the presence or absence of MG, because in addition to the presence of microthymoma in the ectopic thymus, thymoma resection alone or thymectomy is not helpful in the treatment of MG (12,13).

Second, the indications for RATS are debatable. RATS is a more precise and delicate surgical technique that uses three-dimensional (3D) spatial images and an arm with a wide range of motion that rotates 360°. Even in a narrow space within the mediastinum, a minimally invasive surgical approach can be performed by taking advantage of the wide range of motion.

Finally, multidisciplinary treatment needs improvement. Despite improvements in surgical techniques and the development of new anticancer drugs such as ICIs, the treatment of thymic epithelial tumors is not well established and has not changed to any great extent in recent years. Therefore, reviewing the current treatment methods and developing better ones is necessary. We investigated and reviewed the latest literature regarding thymic epithelial tumors and surgical treatment.

### *Objective*

In this review, we report the latest surgical treatments for thymic epithelial tumors. With the advent of new therapeutic agents such as the ICIs, the position of surgical treatment is changing, and the significance of surgery not only in treatment but also in tissue diagnosis may become important. We present this article in accordance with the Narrative Review reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-453/rc).

## Methods

We conducted a non-systematic review using PubMed as the primary source. We searched relevant literature on August 30, 2023. The search string was as follows: ("Thymoma") AND ("Surgery") AND (("Multidisciplinary Treatment" OR "ICI" OR "PD-L1" OR "RATS" OR "Extended Thymectomy")) NOT ("Review") AND (y_5 [Filter]). Consequently, 86 documents were retrieved. The exclusion criteria included: (I) literature that we could not obtain from nonmember journals, (II) articles unrelated to thymomas, such as those on thymectomy for non-thymomatous MG, (III) articles not written in English or Japanese, and (IV) editorial comment articles. Finally, 69 studies were reviewed (*Figure 1*). Furthermore, we added literature related to thymic epithelial tumors published within the past year and reviewed the latest findings. We present an overview of the search strategy summary in *Table 1*.

### *Thymic epithelial tumors*

Thymic epithelial tumors are associated with autoimmune diseases. In addition to MG, this disease may be complicated by various autoimmune diseases or may be accompanied by paraneoplastic symptoms (14-17). Thymic epithelial tumors are relatively rare, and their pathology remains unclear. Therefore, accumulating more case reports is important. The case reports confirmed in this survey are summarized in *Table 2* (14-31). As shown in *Table 2*, many institutions choose extended thymectomy for thymic epithelial tumors with MG, other autoimmune diseases, and paraneoplastic symptoms. There have been two reports of paraneoplastic symptoms' relapse following extended thymectomy. In Case 3, polymyalgia rheumatica symptoms relapsed due to thymoma recurrence (16), and in Case 18, exacerbation of MG symptoms was observed post-surgery with symptoms improving following eculizumab administration (31). Case 2 required treatment with oral prednisolone because the postoperative symptoms showed partial remission (15). In the two reported cases of thymic cancer, extended thymectomy was performed; however, in Case 10, MG symptoms did not improve post-surgery. Therefore, administration of pyridostigmine was necessary (23). Further, in Case 15, the Lambert-Eaton myasthenic syndrome did not improve, and anticholinesterase treatment was required (28). In cases with paraneoplastic symptoms, additional treatment is required after surgery, and multidisciplinary treatment may control paraneoplastic symptoms (15-18,21,23,25,31).

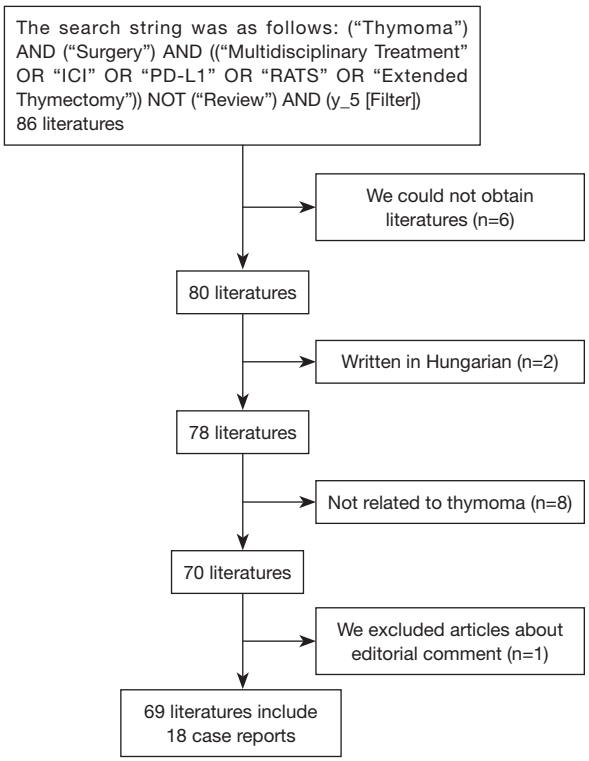


**Figure 1** Inclusion and exclusion criteria.

Most thymic epithelial tumors (87.6%) occur in the anterior and superior mediastinum (1). If the tumor has a strong tendency to invade surrounding areas, such as thymic cancer, the diagnosis may be confirmed preoperatively by needle biopsy, and induction chemotherapy may be chosen.

Surgical resection is the most effective treatment, and

**Table 1** Search strategy summary

| Items | Specification |
|---|---|
| Date of search | August 30, 2023 |
| Databases and other sources searched | PubMed |
| Search terms used | Thymoma, surgery, multidisciplinary treatment, ICI, PD-L1, RATS, extended thymectomy |
| Timeframe | Past 5 years |
| Inclusion and exclusion criteria | We targeted literature written in English or Japanese that were searchable on PubMed. Literature written in languages other than English or Japanese was excluded. In addition, review literature was excluded regardless of language |
| Selection process | Y.N. independently selected the literature. The selection process was checked by M.I. and J.Y. |
| Any additional considerations, if applicable | We excluded the literature that we could not obtain from non-member journals |

ICI, immune checkpoint inhibitor; RATS, robot-assisted thoracic surgery; PD-L1, programmed cell death-ligand 1.

**Table 2** List of case reports

| Case | Age (years) | Gender | CT size (cm) | Diagnosis | Surgical method | Content |
|---|---|---|---|---|---|---|
| 1 | 60 | Female | 12.5 | Type A thymoma | Total thymectomy | Thymoma associated with pancytopenia and Good's syndrome |
| 2 | 68 | Female | 5.4 | Type B1 thymoma | Extended thymectomy | Thymoma-induced pure red cell aplasia |
| 3 | 68 | Male | 8.5 | Type A thymoma | Extended thymectomy | Atypical type A thymoma variant manifesting polymyalgia rheumatica |
| 4 | 26 | Female | 6 | Type B3 thymoma | Extended thymectomy | Thymoma-related stiff-person syndrome |
| 5 | 60 | Female | 6 | Type AB thymoma | Extended thymectomy | Autoimmune alopecia areata due to thymoma |
| 6 | 71 | Male | – | Type A thymoma | Thoracoscopic tumor biopsy | Neoplastic cardiac tamponade |
| 7 | 49 | Male | 6 | Type B2 thymoma | Extended thymectomy | Combined thymoma and a multilocular thymic cyst discovered due to chest pain |
| 8 | 44 | Male | 11 | Type B2 thymoma | Extended thymectomy | Thymoma exhibiting spontaneous regression with developing MG |
| 9 | – | – | – | Recurrence thymoma | – | The addition of L-carnitine to the immunotherapy rechallenge regimen effectively relieved and prevented the reoccurrence of MG |
| 10 | 63 | Male | 2.3 | Type B3 thymoma | Extended thymectomy | Multiple thymoma were possible malignant transformation |
| | | | 1.4 | Squamous cell carcinoma | | Thymic carcinoma should be considered in the differential diagnosis |
| | | | 0.6 | Squamous cell carcinoma | | Extended thymectomy should be the treatment of choice for minimize the chance of recurrence |
| 11 | 66 | Male | 6 | Type A thymoma | CT-guided needle biopsy | If surgery is challenging, anticoagulants might be considered before chemotherapy to prevent thrombus formation |
| 12 | 72 | Male | 2 | Type AB thymoma | Extended thymectomy | Extremely rare case of thymoma with raised levels of CA 19-9 |
| 13 | 55 | Female | – | Type B3 thymoma | Extended thymectomy | Robotic surgery might expand the indications for minimally invasive thymectomy |
| 14 | 63 | Female | 5.6 | Type B2 thymoma | Thymectomy | AIH should be carefully considered in thymoma patients with liver dysfunction |
| 15 | 71 | Male | 2.7 | Thymic small cell carcinoma | Extended thymectomy | After surgery the patient's symptoms had not improved |
| | | | | | | Anticholinesterase treatment alleviated his symptoms |
| 16 | 71 | Male | 3.8 | MTWLS | Extended thymectomy | MTWLS is a very rare type of thymoma, which could be best treated by surgical resection |
| 17 | 78 | Female | – | Thymoma (WHO type B2 > B3) | Local resection | Isolated local resection of ectopic thymoma may be enough for controlling MG especially in elderly patients |
| 18 | 62 | Female | 4 | Type B2 thymoma | Extended thymectomy | Efficacy of eculizumab for postoperative exacerbation of thymoma-associated MG |

MG, myasthenia gravis; AIH, autoimmune hepatitis; MTWLS, micronodular thymoma with lymphoid stroma; WHO, World Health Organization.

complete resection is important. Although chemotherapy has not been established, multidisciplinary treatment is performed in cases in which complete resection is difficult, and developing effective therapeutic agents for thymic epithelial tumors is necessary (4).

For stage I thymomas, some facilities treat the tumor as an anterior mediastinal tumor and perform complete surgery by removing the tumor for both diagnosis and treatment. However, in patients with pathological stage I thymoma without MG, those who underwent thymothymectomy exhibited no difference in their postoperative complication rate (13.3% *vs.* 12.5%), 30-day mortality rate (2.6% *vs.* 6.3%), or postoperative hospital stay compared with those who underwent simple thymomectomy (7). Some reports revealed that the recurrence rate was significantly lower with thymothymectomy, and the postoperative morbidity rate did not increase (thymothymectomy group *vs.* simple thymomectomy group: 5-year overall survival rate, 89% *vs.* 55%, 5-year recurrence-free rate, 96% *vs.* 79%) (7). However, the extent of resection for stage I thymoma remains controversial, as it is unclear how much of the surrounding fat tissue should be removed to influence prognosis.

### *Extended thymectomy*

Patients with MG with thymoma have significantly more frequent and severe postoperative complications than patients with MG without thymoma (patients with thymoma with MG: patients with MG without thymoma, 18.4%: 3.9%) (32). For thymomas associated with MG, extended thymectomy is selected to reduce the risk of postoperative MG.

Factors that improve MG symptoms include age (33,34) and early surgical intervention (33,35). Older age (36,37) and advanced-stage thymoma (36-38) have been identified as poor prognostic factors for postoperative MG symptoms. Most older patients (80%) who undergo thymectomy within 1 year after MG onset have good long-term outcomes (33). Thymectomy may be an option for older patients if surgery is performed early following disease onset. Incomplete resection and young age have been identified as risk factors for tumor recurrence (37).

However, extensive pericardial adipose tissue resection may not be necessary for all patients with MG undergoing extended thymectomy (39). Previous studies have suggested that extended thymectomy for thymic epithelial tumors is not associated with MG (12,13). This is based on the development of robotic surgical technology, and extended thymectomy can now be performed in a less invasive manner. Extended thymectomy may be an option for early-stage thymic epithelial tumors without MG if it is a minimally invasive, low-risk operation. The effectiveness of extended thymectomy for early thymic epithelial tumors without MG is controversial, as it is unclear whether the benefits outweigh the invasiveness of surgery.

### *Minimally invasive surgery*

In addition to thoracoscopic surgery, the usefulness of robotic surgery has been reported in recent years (29,36-40). Robotic surgery uses 3D image construction and an arm with a 360° range of motion, making it effective for approaching narrow spaces within the mediastinum. Robot-assisted thoracoscopic thymectomy is advantageous because it reduces the total volume of postoperative drainage and shortens the hospital stay (41). Robotic resection is safe and feasible even for thymic epithelial tumors up to 10 cm in size (42-44). However, owing to the lack of tactile and force feedback, safety has not been established for tumors with vascular invasion that require advanced techniques such as combined vascular resection and artificial vascular replacement.

Various approaches to VATS and RATS are available. Unilateral or bilateral intrathoracic approaches are often used; however, reports of subxiphoid (45-48), transcervical (49), and inframammary approaches exist (50), which are less invasive. Uniportal VATS thymectomy may be effective if no tumor invasion into the adjacent vessels [for example, the superior vena cava (SVC) and brachiocephalic vein] is observed on computed tomography or if there is no history of radiation exposure to the mediastinum (51). The advantages and disadvantages of each surgical approach are summarized in *Table 3*.

However, the cohort follow-up period was too short in that study; therefore, the impact on oncological outcomes remains unclear. Multimodal treatment is commonly used for advanced thymic epithelial tumors. Surgical treatment has been reported to be effective, with complete resection being the most effective; and debulking surgery may also have a survival effect (52). VATS or RATS may be selected in cases of pericardial invasion or pleural dissemination; however, if SVC or aortic invasion is present, artificial blood vessel replacement or angioplasty is required, and open-heart surgery is indicated. However, open-heart surgery is associated with a high incidence of postoperative

**Table 3** Advantages and disadvantages of each surgical approach

| Approach | Advantages | Disadvantages |
|---|---|---|
| Subxiphoid | Easy identification of bilateral phrenic nerves | Deep perception and limited forceps movement |
| | Good view of the thymus in the cervical region | Not suitable for tumors with vascular invasion |
| Transcervical | Low cost | Not suitable for thymoma cases |
| | | Not suitable for cases where the neck cannot be extended |
| Inframammary | Low cost | Not suitable for tumors with vascular invasion |
| | Direct incision possible | |
| Median sternotomy | Directly palpable and provides a wide surgical field of view | Extension of hospitalization period |
| | Applicable even if you have a history of radiation therapy | Increased bleeding |
| | Combined resection of blood vessels is possible | Big scar |

complications and prolonged hospital stay (53).

Cases of thymic cancer or distant metastasis are considered poor prognostic factors (52); nevertheless, surgery is considered an effective treatment option. In clinical stage III advanced thymic cancer, extended thymectomy with vascular resection may significantly improve overall survival and prognosis compared with no surgical intervention (operation subgroup *vs.* non-operation subgroup: overall survival, 48 *vs.* 26 months; distant metastasis-free survival, 47 *vs.* 18 months) (54).

### *Multidisciplinary treatment*

Because a tumor size of >5 cm is a prognostic predictor in addition to the World Health Organization and tumor-node-metastasis (TNM) classifications, multidisciplinary treatment should be developed for patients with thymic epithelial tumors with large diameters (55). Multidisciplinary treatment for advanced thymic epithelial tumors is considered effective (2,4), and aggressive multidisciplinary treatment, including postoperative radiotherapy (PORT) and chemotherapy, is effective in patients with surgically resected thymoma with lymph node metastasis and may improve survival (2). In addition, extrapleural pneumonectomy (EPP) following induction chemotherapy in patients with thymoma and pleural dissemination is associated with a low recurrence rate, and young patients with good cardiopulmonary function and well-controlled MG may be good candidates (4).

Chemotherapy for thymic epithelial tumors comprises the use of platinum drugs, anthracyclines, and taxanes, and molecular target drugs and ICIs may be second-line drug options; however, a lack of randomized controlled trials is an issue for both (56).

Recently, ICI therapy has been used for thymic epithelial tumors, and although there are some reports indicating that ICI is effective, the incidence of immune-related adverse events is high (3).

To date, dozens of biomarkers associated with checkpoint inhibitors have been identified (57). PD-L1 is one of them.

PD-L1 is typically expressed in 23–92% of thymomas (57,58) and 36–80% of thymic carcinomas (57,59). PD-L1 expression levels are determined by the histological type of thymic epithelial tumor (58,60-62), Masaoka Koga classification (48,58,60), $^{18}$F-FDG accumulation (60,63), and presence or absence of MG (58). Thymic carcinoma has a "hot" immune structure exhibiting abundant PD-L1 expression and high tumor-infiltrating lymphocytes (TILs) density (59). PD-L1 expression following induction therapy in thymic carcinoma is significantly higher than that before induction therapy. PD-L1 expression may be upregulated during epithelial-mesenchymal transition (EMT), and anti-programmed cell death 1/PD-L1 immunity therapy may be a reliable treatment in combination with chemotherapy (64).

Widespread PD-L1 expression in thymic epithelial tumors is associated with poor prognosis (62). However, patients with PD-L1-positive thymomas do not have a significantly worse prognosis than those with PD-L1-negative tumors (60). The role of PD-L1 expression as a prognostic factor is uncertain. It will be important to study more cases in the future.

Immunotherapy shows significant tumor-selective

**Table 4** Biomarkers of thymic epithelial tumors

| Methods | Thymoma | Thymic carcinoma | Thymic epithelial tumor |
|---|---|---|---|
| Genetic mutation | ZNF721, PABPC1, GTF2I | EGFR, ZNF429, BAP1, ABI1, BCL9L, CHEK2 | – |
| Gene expression | – | – | CLDN4, FGF7, FGF10 |
| Immunohistochemistry | – | CD70, $CD8^+$, $CD20^+$, $CD204^+$, TIIC | SOX9, MAGE-A, NY-ESO-1, MAGE-C1, SAGE, GAGE7 |
| qRT-PCR analysis | – | – | XLOC_003810 |
| Serum concentration | – | – | HSP90α |

EGFR, epidermal growth factor receptor; qRT-PCR, quantitative real-time polymerase chain reaction; HSP90α, heat shock protein 90α.

therapeutic effects, but most patients show only a transient response, making it important to understand the mechanisms underlying resistance (5). In addition to PD-L1, various tumor microenvironments are involved.

Twenty-five percent of thymic cancers are positive for epidermal growth factor receptor (EGFR) mutations (65). Other parameters that can be used as biomarkers for thymic epithelial tumors are summarized in *Table 4* (57,64-74).

In the future, ICI treatment may prove effective for thymic epithelial tumors as preoperative and postoperative chemotherapy, as has been shown for other cancers; although various obstacles exist. First, thymic epithelial tumors are relatively rare and collecting cases is challenging. Prospective trials are also difficult to conduct. ICI use can cause adverse events related to autoimmune diseases, and individuals with a predisposition to autoimmune diseases are at particular risk. Thymic epithelial tumors are frequently associated with autoimmune diseases. Therefore, testing for autoimmune diseases before administering ICIs is necessary. The prognosis of thymic epithelial tumors improves if complete resection is possible; however, as surgery may become impossible due to the autoimmune disease, using ICIs as preoperative induction therapy is risky, and consideration should be given to the disadvantages that may arise. In some cases, ICI use is effective against thymic epithelial tumors, and we believe that ICI administration as a multidisciplinary treatment option is effective if appropriate cases are selected.

The prognosis for unresectable advanced thymic epithelial tumors may improve by performing selective postoperative treatment following debulking surgery, which also collects sufficient tissue for measuring PD-L1 and biomarkers. Developing ICIs and molecular-targeted drugs may expand the indications for weight-loss surgery.

Thymic cancer often advances before surgery, and ICI administration may be considered a preoperative induction therapy for cases in which complete resection is difficult.

### *Perioperative management of thymic epithelial tumor complicated by MG*

Thymomas with large tumor sizes, partial thymectomy, histopathology of Type A or Type AB, and older patients are considered to have a higher risk of postoperative MG recurrence (75). Furthermore, in patients with thymomatous MG undergoing thymectomy, being aged 42 years or older and Masaoka-Koga stage > I are associated with poor prognosis (36). In such cases where the risk of postoperative MG recurrence is expected to be high, we believe that postoperative management in an intensive care unit is necessary to enable prompt response in the event of MG recurrence. Measurement of anti-acetylcholine receptor (AChR) antibodies (nmol/L) is required to evaluate MG before and after surgery (75).

### *Strength of this review, and limitations*

In this review, to the best of our knowledge, 56.5% (39 of 69 cases) of the literature was retrospective, accounting for more than half of the manuscripts reviewed. Only 5.8% (4 out of 69 cases) of the literature was prospective, and there were six cases in which it was unclear whether the study was retrospective or prospective.

The strength of this review is that it summarizes the latest treatment options for thymic epithelial tumors. In particular, the possibility of multidisciplinary treatment, including ICI administration, has been mentioned. In addition, by compiling the case reports in a table, possible comorbidities that may occur with thymic epithelial tumors

have been listed, which will aid in more careful treatment management.

Retrospective single-center studies are uniform in surgical techniques, facility equipment, and measurement methods. Understanding the limitations of each manuscript that comprised this literature review and comprehensively evaluating the content will contribute to determining future treatment strategies.

The limitations of this review include the inability to retrieve all searched articles and the exclusion of articles in languages other than English and Japanese, which may introduce bias. In addition, because the search was conducted only through PubMed, there is a bias in the search method used.

This report has reviewed the literature and found it to be heterogeneous in how the results were defined and measured. In addition, the keyword search may have biased the selected literature, perhaps overrepresenting the positive results. A further consideration is that the review may not have evaluated the content correctly owing to differences in the outcome definitions and/or the measurement methods.

## Conclusions

We reviewed the latest treatments for thymic epithelial tumors. When a disease is associated with a thymic epithelial tumor, extended thymectomy may be considered regardless of the presence or absence of MG. Furthermore, if the technology of VATS and RATS improves and a less invasive approach becomes possible, the indications for extended thymectomy may expand. Finally, if new therapeutic agents, such as ICIs and molecular-targeted drugs are developed, we believe that surgery will become more important not only as therapy but also as part of multidisciplinary treatment that includes tissue collection.

## Acknowledgments

We thank Editage (www.editage.com) for the English language editing.
*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-453/rc

*Peer Review File:* Available at https://gs.amegroups.com/article/view/10.21037/gs-23-453/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-453/coif). J.Y. served as the principal investigator for Insmed Inc. and Janssen Pharmaceutical. The other authors have no conflicts of interest to declare.

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



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**Cite this article as:** Nabe Y, Inoue M, Yoshida J. Perspectives on surgical treatment for thymic epithelial tumors: a narrative review. Gland Surg 2024;13(2):225-235. doi: 10.21037/gs-23-453