Review Article



# Current immunotherapy for thymic epithelial tumors: a narrative review

**Yoko Yamamoto[1,2,3], Kota Iwahori[3,4]^, Yasushi Shintani[2]**

[1]Department of General Thoracic Surgery, Sakai City Medical Center, Osaka, Japan; [2]Department of General Thoracic Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan; [3]Department of Clinical Research in Tumor Immunology, Graduate School of Medicine, Osaka University, Osaka, Japan; [4]Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University, Osaka, Japan

*Contributions:* (I) Conception and design: Y Yamamoto, K Iwahori; (II) Administrative support: Y Shintani; (III) Provision of study materials or patients: Y Yamamoto, K Iwahori; (IV) Collection and assembly of data: Y Yamamoto; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Kota Iwahori, MD, PhD. Department of Clinical Research in Tumor Immunology, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan; Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University, Osaka, Japan. Email: iwahori@climm.med.osaka-u.ac.jp.

**Background and Objective:** Thymic epithelial tumors (TETs) are the most common neoplasm of the prevascular mediastinal compartment and are characterized by their rarity and variable clinical presentation. The present study aimed to explore the current management of patients with TET with a special focus on immunotherapy for advanced disease.

**Methods:** Relevant studies published between 1981 and 2024 were searched in PubMed using search terms "Thymoma", "Thymic cancer", "Myasthenia gravis", "Radiation therapy", "Surgery", and "Immunotherapy".

**Key Content and Findings:** The International Thymic Malignancy Interest Group and the International Association for the Study of Lung Cancer established the tumor-node-metastasis (TNM) staging system for TET based on an overall survival (OS) analysis of a retrospective international database. While complete surgical resection is the mainstay for resectable TET, there are currently no clear guidelines on systemic treatments for advanced TET because of the complexity, rarity, and heterogeneity of this disease and the lack of *in vivo* and *in vitro* models. With the development of immunotherapy, the application of the anti-programmed cell death-1 (anti-PD-1) antibody is expanding and includes TET. Clinical trials on immune checkpoint inhibitors (ICIs) are ongoing, and the acceptable clinical efficacy of the anti-PD-1 antibody for TET has been reported. On the other hand, there have been reports of a heightened frequency of severe immune-related adverse events (irAEs) in TET.

**Conclusions:** ICIs have the potential for patients with TET. The benefit-toxicity ratio of ICI treatment needs to be carefully evaluated for those patients.

**Keywords:** Thymoma; thymic carcinoma; immunotherapy; tumor microenvironment

Received: 05 June 2024; Accepted: 29 August 2024; Published online: 11 October 2024.
doi: 10.21037/med-24-24
**View this article at:** https://dx.doi.org/10.21037/med-24-24

^ ORCID: 0000-0002-9891-6003.

## Introduction

The majority of prevascular mediastinal compartment tumors are thymic epithelial tumors (TETs) and include thymoma, thymic carcinoma, and neuroendocrine tumors, which originate in the thymus (1). These tumors are malignant tumors and have unique biological behaviors. Thymoma is histologically comprised of various percentages of epithelial and lymphocytic components. These lymphocytes are comprised mainly of immature T lymphocytes, namely, double-positive T (DPT) cells that resemble the normal cells of the thymus. However, these cells are nearly absent in type A thymomas (2). Thymomas often invade adjacent organs, disseminate within the thoracic cavity, and rarely metastasize lymphogenously or hematogenously. Thymic carcinoma is a more aggressive malignant TET with clear nuclear atypia and no immature T cells and is often diagnosed in the advanced stage because of a lack of evident symptoms during its initiation and early progression. Thymoma is associated with autoimmune complications, such as myasthenia gravis, pure red cell aplasia, hypogammaglobulinemia, and the absence of B cells. Myasthenia gravis is attributed to the incomplete induction of tolerance to self-antigens in T cells that mature within thymic tumors due to the function of thymoma epithelial cells (3). On the other hand, thymic carcinoma that has lost epithelial cell function is not only associated with myasthenia gravis, but also not with other autoimmune conditions.

The detailed etiology of TET remains unclear. Difficulties are associated with generating cell lines from the tumor cells of TET because of their rarity, histological diversity, and the presence of intra-tumoral lymphocytes to varying degrees, and animal experiments are also challenging. Therefore, basic research on TET is insufficient, and, as a consequence, a standard treatment has not yet been established.

A recent study reported that the 10-year overall, disease-specific, and recurrence-free survival rates of thymoma and thymic carcinoma were 88.1% and 54.3%, 96.5% and 62.1%, and 89.2% and 51.1%, respectively (4). Complete surgical resection reportedly represents the solitary opportunity for achieving a curative outcome in cases of TET (5,6). Nonetheless, achieving complete resection remains an elusive goal in instances of advanced TET, and notwithstanding successful resection, the rates of recurrence for type B3 and thymic carcinoma stand at 27.5% and 50.0%, respectively (7). Furthermore, surgical intervention may not be viable for certain patients afflicted by tumors infiltrating adjacent vital structures such as the heart and major vasculature, or those manifesting metastatic dissemination across multiple organs. TET of more aggressive histological subtypes frequently manifests at an advanced disease stage, precipitating poorer overall survival (OS) outcomes. Complementary therapeutic modalities including chemotherapy, radiation therapy, and molecular-targeted agents constitute viable adjuncts in the treatment armamentarium (8,9). The advent of immune checkpoint inhibitors (ICIs) heralds a paradigm shift in cancer immunotherapy. Notably, the anti-programmed cell death-1 (anti-PD-1) antibody confers discernible benefits upon a select subset of cancer patients. Ongoing clinical trials investigating the efficacy of ICI are underway, with reports delineating the favorable clinical outcomes associated with the anti-PD-1 antibody in TET cases (10-17). According to the recent National Comprehensive Cancer Network (NCCN) guidelines (18), pembrolizumab has been approved as a second-line treatment for thymic carcinoma because of its promising antitumor activity.

This review provides an overview of the current management of patients with TET with a special focus on immunotherapy for advanced disease. We discussed the future direction of development for immunotherapy of TET. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-24/rc).

## Methods

Relevant studies published between 1981 and 2024 were searched using the search terms “Thymoma”, “Thymic cancer”, “Myasthenia gravis”, “Radiation therapy”, “Surgery”, and “Immunotherapy”. Prospective and retrospective studies, meta-analyses, review articles, and case studies were included as references. Papers were chosen based on relevance because the current study is not a systematic review. The biggest limitation of this study is the lack of randomized clinical trials because of tumor rarity. We excluded studies that we considered with low reliability, such as no mention of the stage, clinical data, treatment details, and without full texts, or those not written in English. The search strategy is summarized in *Table 1*.

## Histopathological classification and staging

According to the histopathological classification delineated

**Table 1** The search strategy summary

| Items | Specification |
|---|---|
| Date of search | April 3, 2024 to May 4, 2024 |
| Databases and other sources searched | PubMed |
| Search terms used | "Thymoma", "Thymic cancer", "Myasthenia gravis", "Radiation therapy", "Surgery" and "Immunotherapy" |
| Timeframe | 1981–2024 |
| Inclusion and exclusion criteria | Prospective studies, retrospective studies, meta-analyses, and case studies were included |
| | Papers that we considered with low reliability and non-English papers were excluded |
| Selection process | Y.Y. conducted the literature search. All the authors subsequently discussed and agreed on the literature |

by the World Health Organization (WHO), TETs are categorized into thymoma (including types A, AB, B1, B2, and B3) or thymic carcinoma, predicated upon the morphology of epithelial tumor cells and the degree of intratumoral lymphocytic infiltration (2,19). Thymic carcinoma encompasses various subtypes, with squamous cell carcinoma standing out as the most prevalent among them. The WHO classification reflects the characteristics of each tumor, correlates with myasthenia gravis as a complication, the degree of tumor invasion, and prognosis, and has become a clinically valuable classification that is now widely used (20).

Masaoka *et al.* proposed a clinicopathological staging system (21) that is used worldwide and is accepted as the standard because it accurately reflects the oncological behavior of TET, particularly in thymoma (22). In recent years, the International Thymic Malignancy Interest Group and the International Association for the Study of Lung Cancer established a tumor-node-metastasis (TNM) staging system for TET based on OS analysis of a retrospective international database (23-26). It is important to note that the Masaoka staging system is based on surgical pathology and TNM staging may be desirable in the presence of lymph nodal and distant metastasis.

## Current management of TET

Before commencing any therapeutic intervention, it is imperative to ascertain the serum levels of anti-acetylcholine receptor antibodies in all individuals suspected of harboring thymoma, irrespective of symptomatic presentation, to discern the presence of myasthenia gravis and avert the onset of myasthenic crises (27,28). The management of patients with TET requires a multidisciplinary team involving oncologists, thoracic surgeons, radiologists, neurologists, and pathologists. Surgical intervention assumes a pivotal role in the therapeutic management of TET due to the curative potential associated with complete surgical excision. As delineated in the latest directives from the NCCN, the therapeutic pathway for resectable thymic neoplasms (Masaoka I–II) entails initial surgical intervention, with subsequent therapeutic modalities such as systemic therapy or radiotherapy being contingent upon factors such as the adequacy of resection, histological subtype, and tumor staging. Minimally invasive approaches, such as unilateral trans-thoracic, trans-subxiphoid, video-assisted thoracoscopic, and robotic-assisted thoracoscopic surgeries, are options for early-stage TET (29-32), but not advanced TET. Therefore, the surgical approach needs to be carefully selected based on the tumor size, location, and whether the combined resection of other organs is required (33-35).

The efficacy of postoperative radiotherapy (PORT) for TET is controversial. A recent meta-analysis revealed that PORT was beneficial for Masaoka II and III thymoma (36). However, Omasa *et al.* reported the effectiveness of PORT for thymic carcinoma, but not for Masaoka II and III thymoma (37). PORT was also found to be effective for patients with positive surgical margins (38). Contemporary guidelines advocate for radiotherapy dosage and fractionation protocols predicated upon the rationale for radiation utilization and the extent of surgical excision achieved in postoperative scenarios.

The completeness of resection is a crucial factor affecting the prognosis of patients, even for stage III and IV tumors. Adjacent organ invasion, including great vessels, pericardium, heart, lung, and chest wall, as well as pleural dissemination, make complete resection difficult to

 

achieve. When complete resection cannot be anticipated, the treatment requires a tumor biopsy and the confirmation of the histological type followed by chemotherapy or chemoradiotherapy as the initial treatment before surgery. Although a standard chemotherapy regimen has not yet been established, previous studies demonstrated that multidisciplinary treatment improved complete resection outcomes and increased survival rates (39,40). High-dose methylprednisolone is also reportedly effective against B1 thymoma, which is rich in immature T lymphocytes that differentiate and mature within the tumor due to the effects of tumorigenic thymic epithelial cells (41), suggesting its potential as a preoperative treatment (42,43). In addition, since steroid receptors are present in tumor thymic epithelial cells, steroids may directly affect the tumor cells themselves as a treatment for thymoma (44).

The most frequent site of recurrence for thymoma is the pleura (45). Re-resection was previously reported as an acceptable option for the recurrent pleural dissemination of thymoma (46-48). Although the standard management of recurrent TET has not yet been established, prolonged survival is expected for patients with surgical indications.

Chemoradiotherapy or chemotherapy alone is considered for unresectable TET. According to the guidelines established by the NCCN, the prevailing standard therapeutic protocol encompasses platinum-based chemotherapy regimens in conjunction with anthracycline (CAP or ADOC regimens) or etoposide for thymoma (49) and paclitaxel for thymic carcinoma (50,51). The second line of systemic therapy comprises etoposide, everolimus, 5-fluorouracil (5-FU) and leucovorin, gemcitabine, ifosfamide, octreotide, paclitaxel, and pemetrexed for thymoma, while pembrolizumab (10), sunitinib (52), and lenvatinib (53) are recommended for thymic carcinoma. Lenvatinib, functioning as a multi-targeted inhibitor targeting VEGFR, FGFR, RET, c-kit, and other kinases, demonstrates favorable therapeutic efficacy. The REMORA trial underscored the safety and efficacy of lenvatinib in patients afflicted with advanced and metastatic thymic carcinoma, with a notable response rate of 38% [90% confidence interval (CI): 25.6–52.0%; P<0.0001] (53).

## Immunotherapy for TET

The advent of ICI heralded a paradigm shift in the landscape of cancer immunotherapy. The efficacy of the anti-PD-1 antibody extends to a select cohort of cancer patients. Its indications are progressively broadening, now encompassing TET. Ongoing clinical trials investigating ICI are underway, with reports indicating the favorable clinical outcomes associated with the anti-PD-1 antibody in TET cases (10-17). Furthermore, Yang *et al.* showed a single case report that a patient with thymic carcinoma and multiple lung metastases responded well to anti-PD-1 therapy (54). According to the recent NCCN guidelines, pembrolizumab has been approved as a second-line treatment for thymic carcinoma because of its promising antitumor activity.

*Table 2* summarizes the outcomes of clinical trials on patients with advanced TET who were treated with immunotherapy. Between 2018 and 2023, eight clinical studies (one phase I trial and seven phase II trials) investigated the effects of immunotherapy in patients with TET. The administered drug was pembrolizumab in two, nivolumab in two, atezolizumab in one, avelumab in one, the combination of avelumab and axitinib in one, and a WT1 peptide vaccine in one. All patients had stage III or IV disease. The overall response rate (ORR) ranged between 0 and 38.5% for all patients, while median progression-free survival (PFS) was 3.8 to 11.7 months. Median OS was 14.1 to 26.6 months. Treatment-related severe immune-related adverse events (irAEs) occurred in 0 to 71.4% of patients.

In more detail, Rajan *et al.* conducted a phase 1 trial of the anti-programmed cell death-ligand 1 (anti-PD-L1) antibody avelumab, including seven patients with relapsed thymoma and one patient with thymic carcinoma treated with at least one prior standard therapy (14). The ORR of thymoma and thymic carcinoma were 28.5% and 0%, respectively. Grade ≥3 irAEs were reported in five out of eight patients (62.5%). This study initially provided the efficiency of immunotherapy for thymoma. Cho *et al.* reported a single-center, phase 2 study of anti-PD-1 antibody, pembrolizumab in 26 patients with thymic carcinoma and 7 patients with thymoma whose disease progressed after at least one line of platinum-based chemotherapy (11). Notably, this study included three patients who were previously diagnosed with myasthenia gravis without receiving immunosuppressive treatment at least 1 year before enrollment. This report showed the ORR of thymoma and thymic carcinoma were 28.6% and 19.2%, respectively. The median PFS was 6.1 months for both thymoma and thymic carcinoma, the median OS was not reached for thymoma, and 14.5 months for thymic carcinoma. Five patients with thymoma (71.4%) and three patients with thymic carcinoma (11.5%) discontinued pembrolizumab treatment because of grade 3 or 4 irAEs. Moreover, three patients who had a previous history of

**Table 2** Summary of clinical trials

| Author | Treatment | Disease | N | Median age (years) | Response rate (%) | Median PFS (95% CI) (months) | Median OS (95% CI) (months) | Severe irAEs (%) |
|---|---|---|---|---|---|---|---|---|
| Giaccone (10) | Pembrolizumab | TC | 40 | 57 | 22.5 | 4.2 (2.9–10.3) | 24.9 (15.5–not reached) | 14.6 |
| Cho (11) | Pembrolizumab | T | 7 | 57 | 28.6 | 6.1 (4.3–7.9) | Not reached | 71.4 |
| | | TC | 26 | 57 | 19.2 | 6.1 (5.1–7.1) | 14.5 | 11.5 |
| Oji (12) | WT1 peptide vaccine | T | 4 | 57 | 0 | Not reported | Not reported | 25.0 |
| | | TC | 11 | 53 | 0 | Not reported | Not reported | 0 |
| Katsuya (13) | Nivolumab | TC | 15 | 55 | 0 | 3.8 (1.9–7.0) | 14.1 (11.1–not estimated) | 13.3 |
| Rajan (14) | Avelumab | T | 7 | 53 | 28.5 | Not available | Not available | 62.5 |
| | | TC | 1 | | 0 | Not available | Not available | |
| Tabernero (15) | Atezolizumab | T | 13 | 61 | 38.5 | 11.7 (3.22–37.22) | Not estimated | 35.7 |
| Conforti (16) | Avelumab + axitinib | T | 3 | 62 | 34.4 | 7.5 (3.7–10.0) | 26.6 (17.0–30.3) | 12.5 |
| | | T or TC | 2 | | | | | |
| | | TC | 27 | | | | | |
| Girard (17) | Nivolumab | T | 10 | 58 | 14.3 | 6.2 (3.1–10.4) | 21.3 (11.6–not estimated) | 34.0 |
| | | TC | 43 | | | | | |

N, number; PFS, progression-free survival; CI, confidence interval; OS, overall survival; irAEs, immune-related adverse events; TC, thymic carcinoma; T, thymoma.

myasthenia gravis developed serious irAEs, including myasthenia, autoimmune hepatitis, and myocarditis, leading to discontinuation after the first cycle of pembrolizumab. Giaccone *et al.* reported a single-center, phase 2 study of pembrolizumab in 40 patients with recurrent thymic carcinoma who had progressed after at least one line of chemotherapy (10). The median follow-up was 20 months and the ORR was 22.5%. This report also demonstrated that PFS and OS were longer in patients with high PD-L1 expression than in those with low or no PD-L1 expression. Although patients without a history of autoimmune disease were enrolled, six patients (14.6%) developed serious irAEs including myocarditis, hepatitis, pancreatitis, bullous pemphigoid, and myasthenia gravis. In the PRIMER study, a Japanese multi-center phase 2 study of the anti-PD-1 antibody nivolumab in the same patient population, showed that 15 patients were enrolled, and no objective responses were observed, two out of 15 (13.3%) patients observed serious irAE [grade 3 aspartate aminotransferase (AST) increase and grade 2 adrenal insufficiency] (13). In this study, nivolumab did not demonstrate similar efficacy to pembrolizumab. On the other hand, the NIVOTHYM study from Europe, a phase 2 trial of nivolumab in 53 patients with advanced or relapsed type B3 thymoma and thymic carcinoma failed after at least one line of platinum-based chemotherapy, showed the ORR was 14.3% and grade ≥3 irAEs were observed in 18 cases (34.0%) including myocarditis, transaminitis, and neutropenia (17). Tabernero *et al.* reported that a phase 2 multicohort study of anti-PD-L1 antibody atezolizumab in multiple solid cancers progressed after one or more lines of systemic treatment (15). In this study, 13 thymoma patients were efficacy evaluable and the ORR was 38.5%. The point to note is that the thymoma cohort showed the highest rate of irAEs (35.7%) among the other solid cancers.

In the CAVEATT study, a multicenter phase 2 trial of a combined use of avelumab and the anti-angiogenic agent axitinib in 32 pre-treated patients (27 thymic carcinoma, three B3 thymoma, two mixed-type thymic carcinoma and thymoma B3) with at least one line of platinum-based chemotherapy received (16). The ORR was 34.4% and four out of 32 patients (12.5%) developed serious irAEs including interstitial pneumonitis and polymyositis. This study provided a positive outcome of the

 

combination of anti-angiogenic therapy and ICI. Oji *et al.* reported a phase 2 trial of the WT1 peptide vaccine in 11 patients with thymic carcinoma and four patients with thymoma (12). Fourteen patients received chemotherapy and the remaining one received radiation therapy alone due to complications with a hemostatic defect. Although the majority of patients demonstrated a WT1-specific immune response, no objective responses were observed. Although these immunotherapy clinical trials have shown efficacy in patients with advanced TET, additional biomarkers research to identify patients who can benefit from immunotherapy and develop serious irAEs is warranted.

To underpin the rationale for employing immunotherapy in the context of TET, a preclinical investigation conducted phenotypic and functional assessments of T cells derived from surgically excised TET specimens, focusing on the single-positive T cells therein. Utilizing flow cytometric data, a cluster analysis of T-cell phenotypes revealed that type B3 thymoma and thymic carcinoma pertained to the "hot" cluster, characterized by a notable prevalence of Tim-$3^+$ and $CD103^+$ expression within CD4 and CD8 single-positive T cells. Significant amplifications in cytokine secretion and cytotoxicity elicited by T cells upon exposure to the anti-PD-1 antibody were notably conspicuous in these histological subtypes. These observations underscore the potential utility of immunotherapeutic approaches for patients with type B3 thymoma and thymic carcinoma (55). On the other hand, Furuya *et al.* reported that the majority of PD-$1^+$ T cells in type AB/B1/B2 thymomas were intratumoral developing T cells and not tumor-infiltrating lymphocytes (56). Genetic differences have been reported between type B3 thymoma/thymic carcinoma and type AB/B1/B2 thymoma tumor cells in TET (57-59) and significant increases in the tumor mutation burden have been observed in type B3 thymoma and thymic carcinoma, particularly thymic carcinoma (58,60). These findings provide a rationale for the application of immunotherapy to type B3 thymoma and thymic carcinoma.

However, the high incidence of severe irAEs in TET remains a concern. Tabernero *et al.* demonstrated that the thymoma cohort exhibited the highest incidence of adverse events, with 35.7% of patients experiencing severe irAEs in their cohort study. Notably, two patients each presented with hepatitis and myasthenia gravis, the latter proving fatal in one patient (15). This observation could potentially be elucidated by the immune microenvironment, characterized by the presence of immature T cells, which may underlie autoimmune reactions and subsequent irAEs (61). Fenioux *et al.* reported that ICIs were more frequently associated with ICI myotoxicity in patients with TET than in those with other cancers, and myocarditis occurred earlier after the initiation of ICI in the former than in the latter and was more severe in terms of life-threatening arrhythmias and concurrent myositis (62). Furthermore, the presence of anti-acetylcholine-receptor antibodies was more prevalent in patients with than in those without ICI-related myocarditis. This study also suggested the potential of anti-acetylcholine-receptor antibodies as a predictive biomarker for severe myotoxicity (62). Therefore, due to the high incidence of severe irAEs in TET, particularly in thymoma, the indication of ICI remains a critical issue for patients with thymoma or those with a previous history of autoimmune syndrome. In addition to patients who will benefit from immunotherapy, it is important to identify those who are most likely to develop serious irAEs.

## Limitations

In this narrative review, we focused on immunotherapy for TET. Although there have been clinical trials of TET that showed favorable clinical outcomes associated with ICI, the high incidence of severe irAEs was also reported. There were limitations in the present study. Because of the rarity and heterogeneity of TET, the patient cohort size in each clinical trial was relatively modest. Specifically, a substantial cohort size is requisite for the assessment of irAEs in TET. We must deliberate on immunotherapy for TET based on forthcoming extensive clinical studies involving large cohorts.

## Conclusions

Complete surgical resection is the mainstay for resectable TET; however, there are no clear guidelines on systemic treatments for advanced TET. Regarding immunotherapy, ICIs have potential for patients with TET; however, a higher incidence of ICI-related myocarditis and myositis was reported in these patients. Therefore, the benefit-toxicity ratio of ICI treatment needs to be carefully evaluated. Future studies are needed to establish the efficacy and safety of immunotherapy.

## Acknowledgments

We would like to sincerely thank the editorial board of *Mediastinum* for inviting us to write this narrative review.
*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-24-24/rc

*Peer Review File:* Available at https://med.amegroups.com/article/view/10.21037/med-24-24/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-24-24/coif). The 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.



## References

1. Marx A, Chan JKC, Chalabreysse L, et al. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors? J Thorac Oncol 2022;17:200-13.
2. Marx A, Chan JK, Coindre JM, et al. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. J Thorac Oncol 2015;10:1383-95.
3. Inoue M, Okumura M, Miyoshi S, et al. Impaired expression of MHC class II molecules in response to interferon-gamma (IFN-gamma) on human thymoma neoplastic epithelial cells. Clin Exp Immunol 1999;117:1-7.
4. Okumura M, Yoshino I, Funaki S, et al. Long-term outcomes following surgical treatment for thymic epithelial tumor in Japan and an analysis of prognostic factors based on the Japanese Association for Research on the Thymus nationwide database. Surg Today 2023;53:1247-59.
5. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878-84; discussion 884-5.
6. Hishida T, Nomura S, Yano M, et al. Long-term outcome and prognostic factors of surgically treated thymic carcinoma: results of 306 cases from a Japanese Nationwide Database Study. Eur J Cardiothorac Surg 2016;49:835-41.
7. Wright CD, Wain JC, Wong DR, et al. Predictors of recurrence in thymic tumors: importance of invasion, World Health Organization histology, and size. J Thorac Cardiovasc Surg 2005;130:1413-21.
8. Bott MJ, Wang H, Travis W, et al. Management and outcomes of relapse after treatment for thymoma and thymic carcinoma. Ann Thorac Surg 2011;92:1984-91; discussion 1991-2.
9. Merveilleux du Vignaux C, Maury JM, Girard N. Novel Agents in the Treatment of Thymic Malignancies. Curr Treat Options Oncol 2017;18:52.
10. Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. Lancet Oncol 2018;19:347-55.
11. Cho J, Kim HS, Ku BM, et al. Pembrolizumab for Patients With Refractory or Relapsed Thymic Epithelial Tumor: An Open-Label Phase II Trial. J Clin Oncol 2019;37:2162-70.
12. Oji Y, Inoue M, Takeda Y, et al. WT1 peptide-based immunotherapy for advanced thymic epithelial malignancies. Int J Cancer 2018;142:2375-82.
13. Katsuya Y, Horinouchi H, Seto T, et al. Single-arm, multicentre, phase II trial of nivolumab for unresectable or recurrent thymic carcinoma: PRIMER study. Eur J Cancer 2019;113:78-86.
14. Rajan A, Heery CR, Thomas A, et al. Efficacy and tolerability of anti-programmed death-ligand 1 (PD-L1) antibody (Avelumab) treatment in advanced thymoma. J Immunother Cancer 2019;7:269.
15. Tabernero J, Andre F, Blay JY, et al. Phase II multicohort study of atezolizumab monotherapy in multiple advanced solid cancers. ESMO Open 2022;7:100419.
16. Conforti F, Zucali PA, Pala L, et al. Avelumab plus axitinib in unresectable or metastatic type B3 thymomas and thymic carcinomas (CAVEATT): a single-arm, multicentre, phase 2 trial. Lancet Oncol 2022;23:1287-96.
17. Girard N, Ponce Aix S, Cedres S, et al. Efficacy and safety of nivolumab for patients with pre-treated type B3 thymoma and thymic carcinoma: results from the EORTC-ETOP NIVOTHYM phase II trial. ESMO Open 2023;8:101576.

18. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Thymomas and Thymic Carcinomas, Version 1. 2024 (Accessed January 24, 2024). Available online: https://www.nccn.org/professionals/physician_gls/pdf/thymic.pdf
19. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-60.
20. Okumura M, Ohta M, Tateyama H, et al. The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. Cancer 2002;94:624-32.
21. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485-92.
22. Okumura M, Miyoshi S, Takeuchi Y, et al. Results of surgical treatment of thymomas with special reference to the involved organs. J Thorac Cardiovasc Surg 1999;117:605-13.
23. Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol 2014;9:S65-72.
24. Nicholson AG, Detterbeck FC, Marino M, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposals for the T Component for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol 2014;9:S73-80.
25. Kondo K, Van Schil P, Detterbeck FC, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposals for the N and M components for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol 2014;9:S81-7.
26. Bhora FY, Chen DJ, Detterbeck FC, et al. The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: A Proposed Lymph Node Map for Thymic Epithelial Tumors in the Forthcoming 8th Edition of the TNM Classification of Malignant Tumors. J Thorac Oncol 2014;9:S88-96.
27. Watanabe A, Watanabe T, Obama T, et al. Prognostic factors for myasthenic crisis after transsternal thymectomy in patients with myasthenia gravis. J Thorac Cardiovasc Surg 2004;127:868-76.
28. Fujiwara A, Inoue M, Kusumoto H, et al. Myasthenic crisis caused by preoperative chemotherapy with steroid for advanced thymoma. Ann Thorac Surg 2015;99:e11-3.
29. Ohta M, Hirabayasi H, Okumura M, et al. Thoracoscopic thymectomy using anterior chest wall lifting method. Ann Thorac Surg 2003;76:1310-1.
30. Kido T, Hazama K, Inoue Y, et al. Resection of anterior mediastinal masses through an infrasternal approach. Ann Thorac Surg 1999;67:263-5.
31. Shimomura M, Ishihara S, Okada S, et al. Robotic subxiphoid-optical thymectomy. Interact Cardiovasc Thorac Surg 2022;35:ivac104.
32. Suda T, Hachimaru A, Tochii D, et al. Video-assisted thoracoscopic thymectomy versus subxiphoid single-port thymectomy: initial results†. Eur J Cardiothorac Surg 2016;49 Suppl 1:i54-8.
33. Friedant AJ, Handorf EA, Su S, et al. Minimally Invasive versus Open Thymectomy for Thymic Malignancies: Systematic Review and Meta-Analysis. J Thorac Oncol 2016;11:30-8.
34. Kimura T, Inoue M, Kadota Y, et al. The oncological feasibility and limitations of video-assisted thoracoscopic thymectomy for early-stage thymomas. Eur J Cardiothorac Surg 2013;44:e214-8.
35. Shintani Y, Funaki S, Ose N, et al. Surgical approach for thymic epithelial tumor. J Thorac Dis 2019;11:E127-30.
36. Tateishi Y, Horita N, Namkoong H, et al. Postoperative Radiotherapy for Completely Resected Masaoka/Masaoka-Koga Stage II/III Thymoma Improves Overall Survival: An Updated Meta-Analysis of 4746 Patients. J Thorac Oncol 2021;16:677-85.
37. Omasa M, Date H, Sozu T, et al. Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: the Japanese Association for Research on the Thymus Database Study. Cancer 2015;121:1008-16.
38. Jackson MW, Palma DA, Camidge DR, et al. The Impact of Postoperative Radiotherapy for Thymoma and Thymic Carcinoma. J Thorac Oncol 2017;12:734-44.
39. Kanzaki R, Kanou T, Ose N, et al. Long-term outcomes of advanced thymoma in patients undergoing preoperative chemotherapy or chemoradiotherapy followed by surgery: a 20-year experience. Interact Cardiovasc Thorac Surg 2019;28:360-7.
40. Shintani Y, Inoue M, Kawamura T, et al. Multimodality treatment for advanced thymic carcinoma: outcomes of induction therapy followed by surgical resection in 16 cases at a single institution. Gen Thorac Cardiovasc Surg 2015;63:159-63.
41. Kodama K, Doi O, Higashiyama M, et al. Dramatic

 

response of postthymomectomy myasthenia gravis with multiple lung nodules to corticosteroids. Ann Thorac Surg 1997;64:555-7.
42. Kobayashi Y, Fujii Y, Yano M, et al. Preoperative steroid pulse therapy for invasive thymoma: clinical experience and mechanism of action. Cancer 2006;106:1901-7.
43. Inoue M, Fujii Y, Okumura M, et al. Neoplastic thymic epithelial cells of human thymoma support T cell development from CD4-CD8- cells to CD4+CD8+ cells in vitro. Clin Exp Immunol 1998;112:419-26.
44. Funakoshi Y, Shiono H, Inoue M, et al. Glucocorticoids induce G1 cell cycle arrest in human neoplastic thymic epithelial cells. J Cancer Res Clin Oncol 2005;131:314-22.
45. Mizuno T, Okumura M, Asamura H, et al. Surgical management of recurrent thymic epithelial tumors: a retrospective analysis based on the Japanese nationwide database. J Thorac Oncol 2015;10:199-205.
46. Okumura M, Shiono H, Inoue M, et al. Outcome of surgical treatment for recurrent thymic epithelial tumors with reference to world health organization histologic classification system. J Surg Oncol 2007;95:40-4.
47. Kimura K, Kanzaki R, Kimura T, et al. Long-Term Outcomes After Surgical Resection for Pleural Dissemination of Thymoma. Ann Surg Oncol 2019;26:2073-80.
48. Yamamoto Y, Kodama K, Maniwa T, et al. Successful treatment of advanced thymic carcinoma with lymph node and pleural metastases: A case report. Mol Clin Oncol 2016;5:550-2.
49. Loehrer PJ Sr, Kim K, Aisner SC, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. J Clin Oncol 1994;12:1164-8.
50. Hirai F, Yamanaka T, Taguchi K, et al. A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L. Ann Oncol 2015;26:363-8.
51. Lemma GL, Lee JW, Aisner SC, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. J Clin Oncol 2011;29:2060-5.
52. Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. Lancet Oncol 2015;16:177-86.
53. Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. Lancet Oncol 2020;21:843-50.
54. Yang Y, Ding L, Wang P. Dramatic response to anti-PD-1 therapy in a patient of squamous cell carcinoma of thymus with multiple lung metastases. J Thorac Dis 2016;8:E535-7.
55. Yamamoto Y, Iwahori K, Funaki S, et al. Immunotherapeutic potential of CD4 and CD8 single-positive T cells in thymic epithelial tumors. Sci Rep 2020;10:4064.
56. Furuya T, Ishihara S, Ogi H, et al. Characteristic differences in the abundance of tumor-infiltrating lymphocytes and intratumoral developing T cells in thymoma, with special reference to PD-1 expression. Cancer Immunol Immunother 2023;72:2585-96.
57. Radovich M, Pickering CR, Felau I, et al. The Integrated Genomic Landscape of Thymic Epithelial Tumors. Cancer Cell 2018;33:244-258.e10.
58. Petrini I, Meltzer PS, Kim IK, et al. A specific missense mutation in GTF2I occurs at high frequency in thymic epithelial tumors. Nat Genet 2014;46:844-9.
59. Lee HS, Jang HJ, Shah R, et al. Genomic Analysis of Thymic Epithelial Tumors Identifies Novel Subtypes Associated with Distinct Clinical Features. Clin Cancer Res 2017;23:4855-64.
60. Girard N, Basse C, Schrock A, et al. Comprehensive Genomic Profiling of 274 Thymic Epithelial Tumors Unveils Oncogenic Pathways and Predictive Biomarkers. Oncologist 2022;27:919-29.
61. Ohm B, Jungraithmayr W. Balancing the Risk of Adverse Events against the Efficacy of Immunotherapy in Advanced Thymic Epithelial Tumors. Cancers (Basel) 2022;15:289.
62. Fenioux C, Abbar B, Boussouar S, et al. Thymus alterations and susceptibility to immune checkpoint inhibitor myocarditis. Nat Med 2023;29:3100-10.

doi: 10.21037/med-24-24
**Cite this article as:** Yamamoto Y, Iwahori K, Shintani Y. Current immunotherapy for thymic epithelial tumors: a narrative review. Mediastinum 2024;8:47.