Locally advanced thymic epithelial tumors: a foreword to the special series

This special series contributes to improved management and better understanding of locally advanced thymic epithelial tumors (TETs), although definitions of locally advanced TETs vary. Locally advanced TETs have several radiological characteristics, such as tumors >8 cm in the greatest axial diameter and tumors with obvious great vessel and/or adjacent organ invasion or encirclement (1). Current guidelines recommended multidisciplinary management including induction therapy and adjuvant therapy (2,3).

Herein, the authors (*Figure 1*) in this series provided a comprehensive review of each topic.

Dr. So Takata focuses on its genetic profile to aid targeted therapy development. Analyses reveal *TP53*, *CDKN2A*, and other genes as frequently mutated, with *TP53* and *CDKN2A* linked to poor prognosis. *CYLD* mutations may predict immunotherapy response, while *KIT* mutations suggest targeted therapy potential. Thymic carcinoma's distinct genomic landscape, characterized by higher tumor mutation burden (TMB) and 16q loss, emphasizes the need for tailored treatments. Sharing molecular data could advance understanding and treatment options for this rare cancer.

Dr. Yoshihisa Shimada and his colleagues examined induction therapy followed by surgery for stage III or IV cases, revealing primarily retrospective studies and limited prospective trials. While randomized phase III studies are lacking, anthracycline-based chemotherapies are common. Reported rates of complete resection and 5-year overall survival (OS) suggest promise, supporting multimodal treatment for selected patients. Further research is needed to fully assess induction therapy's benefits.

Dr. Yoshito Yamada and his colleagues emphasized the re-evaluation process and surgical indications post-induction therapy for TETs. Induction therapy, comprising chemotherapy and/or radiation, aims to downstage advanced or unresectable tumors.

Figure 1 First authors of the included manuscripts. Dr. Yosuke Yamada, Dr. Hitomi Ajimizu, Dr. Yoshihisa Shimada, and Dr. Masaru Takenaka (top row left to right). Dr. So Takata, Dr. Sho Koyasu, Dr. Noriko Kishi, and Dr. Yoshito Yamada (bottom row left to right).

Re-evaluation is vital for gauging treatment response and deciding on surgical intervention. It explores concepts, methodologies, challenges, and future perspectives of re-evaluation, along with criteria for surgical decision-making in such patients.

Dr. Hitomi Ajimizu and Dr. Yuichi Sakamori focused on induction therapy, typically chemotherapy, aimed to downstage tumors for successful resection. Anthracycline-based regimens are common for thymomas, while alternatives like cisplatin and etoposide are considered for thymic carcinomas. Emerging immunotherapy and targeted therapies offer additional options. While induction radiotherapy alone is uncommon due to concerns of tissue damage, combining it with surgery shows promise. Concurrent chemoradiation is often preferred, particularly for thymic carcinoma patients. However, optimal treatment strategies for locally advanced TETs remain uncertain, necessitating further research and well-designed studies.

Dr. Yosuke Yamada and Dr. Hironori Haga offered pathological insights into tumors invading neighboring structures, crucial for understanding locally advanced TETs. Tumor subtype, whether thymoma or thymic carcinoma, also influences treatment decisions, with distinct biological features identified through studies like The Cancer Genome Atlas project. New features, particularly in epithelial-rich thymomas and thymic squamous cell carcinoma, are highlighted. Sharing these insights aids clinicians in daily practice and prepares them for the forthcoming 9th edition of the TNM classification.

Dr. Noriko Kishi and Dr. Yukinori Matsuo analyzed literature on postoperative radiotherapy (PORT) for TETs, considering Masaoka-Koga staging, histological subtypes, and resection status. While PORT's efficacy varies across stages, further research is needed to determine its optimal use, particularly for stage IIB–III TETs. Advanced radiotherapy techniques and emerging therapies offer promising avenues for improving outcomes, although their efficacy requires further investigation.

Dr. Sho Koyasu's review underscored the significance of precise diagnostic approaches for TETs, encompassing thymomas, thymic carcinomas, and thymic neuroendocrine tumors. Imaging plays a crucial role, particularly in differentiating solid and cystic lesions via contrast-enhanced computed tomography (CT). Thymomas exhibit distinct imaging characteristics, emphasizing the importance of histological classification. Case studies underscore diagnostic complexities and underscore the value of imaging modalities such as CT, magnetic resonance imaging (MRI), and fluorodeoxyglucose-positron emission tomography (FDG-PET). The review extends to rare mediastinal lesions, emphasizing the necessity of comprehensive evaluation for accurate identification and management.

Dr. Masaru Takenaka explored perioperative management and postoperative outcomes in patients with locally advanced TETs, frequently diagnosed at advanced stages. Surgical intervention following chemotherapy or chemoradiotherapy poses specific challenges, emphasizing the importance of perioperative care. Analysis of 18 references from 2000 to 2022 (n=646) reveals induction therapy aims for complete tumor resection, with systemic chemotherapy and chemoradiation commonly used. Surgical intervention may involve resection of surrounding organs and vascular structures, with varying rates of postoperative complications but low mortality. Careful patient evaluation and treatment response assessment are crucial for optimal surgical decision-making.

As described above, all the articles in this series should be read in detail and understood carefully. All the above contributions are seminal work that provides excellent learning opportunities for readers to overcome challenges of locally advanced TETs.

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Review Article

Genomic insights into molecular profiling of thymic carcinoma: a narrative review

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Background and Objective: Thymic carcinoma is an exceptionally rare cancer, with an annual incidence of just 0.15–0.29 per 100,000 people. Owing to its rarity, only few proven treatments have been developed. Understanding its genetic profile is crucial for the development of targeted therapies. However, limited studies have exclusively examined thymic carcinoma mutations, with most investigation combining thymomas and thymic carcinomas. This paper reviews findings from genetic studies focusing on thymic carcinoma alone and compares them to those of thymoma.

Methods: We conducted a PubMed search for relevant English studies on thymic carcinoma genomics. Then, key papers utilizing target sequencing or whole-exome sequencing were analyzed.

Key Content and Findings: The most frequently mutated genes were *TP53*, *CDKN2A*, *CDKN2B*, *CYLD*, *KIT*, *TET2*, *SETD2*, *BAP1*, and *ASXL1*. *TP53* and *CDKN2A* are correlated with poor prognosis. *CYLD*, which regulates signaling related with proliferation and interacts with AIRE expression and T cell development, might predict the immunotherapy response. *KIT* mutations might enable targeted therapy. *TET2*, *SETD2*, *BAP1*, and *ASXL1* regulate epigenetics, suggesting disruption of these mechanisms. Higher tumor mutational burden (TMB) and 16q loss distinguish thymic carcinoma from thymoma. Although some copy number aberrations are shared, thymic carcinoma exhibits a mutational profile distinct from that of thymoma.

Conclusions: Thymic carcinoma demonstrates a unique genomic landscape, suggesting a molecular pathogenesis distinct from that of thymoma. Our findings revealed prognostic biomarkers such as *TP53*/*CDKN2A* and potential therapeutic targets such as *KIT*. Because thymic carcinoma is extremely rare, sharing molecular profiling data could provide valuable insights into the molecular mechanisms driving the development of these tumors.

Keywords: Thymic carcinoma; genomics; mutation; copy number aberration

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Introduction

Background

Thymic carcinoma is a rare form of thymic epithelial tumor originating in the thymus. The overall incidence of thymic carcinoma in Japan is 0.15–0.29 per 100,000 person-years (1,2). Owing to its rarity, evidence-based treatments are limited. Notably, approximately around half of the patients with thymic carcinoma patients are unsuitable candidates for surgery (2,3), emphasizing the importance of exploring their genomic profile is crucial for an internal medicine approach.

Regarding treatment, multi-target tyrosine kinase inhibitors (TKIs) and immune checkpoint blockade (ICB) have been one of the treatment options. Sunitinib and lenvatinib showed response rates of 26% and 38% respectively in thymic carcinomas. ICB showed durable responses in 20–25% of patients with thymic carcinoma

Table 1 The search strategy summary

Items	Specification
Date of search	2023/6/1 to 2023/7/1
Databases and other sources searched	PubMed and Web of Science
Search terms used	Thymus and thymic
Timeframe	1982–2023
Inclusion criteria	Original article and review article regarding the genomic features of thymic carcinoma published in English
Selection process	S.T. did the search and selected the manuscript

(4-6). Also, several trials of combination of TKI and chemotherapy or ICB are ongoing (4,7). The reports for genomic findings of thymic carcinoma aimed at elucidating novel therapeutic targets and biomarkers predictive of response are limited.

Rationale and knowledge gap

Although thymic carcinoma is typically classified as a thymic epithelial tumor, Radovich *et al.* proposed it as a distinct entity of thymic epithelial tumors (8). Numerous studies have examined genomic alterations in thymic tumors, including both thymomas and thymic carcinomas. However, only a few studies have specifically focused on thymic carcinoma, owing to its uncommon nature. Therefore, our search was focused on the genomic profiles of thymic carcinoma. Furthermore, genomic findings varied depending on whether targeted or whole-exome sequencing was used.

Objective

Our objective was to provide comprehensive summary of the genomic discoveries related to thymic carcinoma. I present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-5/rc).

Methods

We systematically searched for relevant studies published on PubMed from 1982 to 2023, utilizing various combinations of the terms “thymic” and “thymus”. Articles related to genomics were selected by reviewing abstracts. Additional papers were identified by checking cited references and examining reference lists. Publications published in languages other than English were excluded. Data extraction was performed based on their relevance to the topic. Additional details of this method are presented in *Table 1*.

Results

Recurrent mutations

The most frequently mutated genes depend on the panel list of target genes, and these recurrent mutations are detailed in *Table 2*.

The results of whole-exome sequencing vary across different reports. Subsequently, recurrently reported mutations were focused. The most frequently reported genes were *TP53*, *CDKN2A*, *CDKN2B*, *CYLD*, *KIT*, *TET2*, *SETD2*, *BAP1*, *ASXL1* and *FGFR3* (*Table 2*). The pathological finding of immunohistochemical staining for TP53 was strongly correlated with *TP53* mutations in patients with thymic carcinoma, similar to observations in other cancer types (30), and *TP53* mutations were associated with poor prognosis (16). Cyclin dependent factor such as *CDKN2A* and *CDKN2B* were also frequently reported genes. Particularly, loss of $p16^{INK4A}$ (encoded by *CDKN2A*) expression due to a homozygous *CDKN2A* deletion was confirmed to be correlated with a worse prognosis, including earlier recurrence and shorter overall survival (31). Both *TP53* and *CDKN2A* are recurrently mutated and have been confirmed to be associated with poor prognosis. CYLD is a deubiquitinating enzyme, that regulates cell signaling pathways (32). COSMIC, the Catalogue of Somatic Mutations in Cancer, explain that *CYLD* gene role as tumor suppressor gene according to its multiple role such as regulator of multiple pathway involving EGFR pathway. CYLD is related with angiogenesis (33), which is one of central pathways of thymic carcinoma (7). In addition, its

Table 2 Genomic profiling of thymic carcinoma patients

Report No.	Method	Number*	Histological subtype [number of patients]	Genetic variations in each subtype	Number of target genes	Mutation [number of patients]	Country	Sample	Authors	Year
1	WES	10, 0	Sq [9], Undif [1]	Accessible	–	*TET2* [3], *ARID1B* [2], *CYLD* [2], *SETD2* [2]	Japan	FF	Saito *et al.* (9)	2017
2	WES	9, 1	Sq [4], Undif [4], LCNEC [1], unknown [1]	Accessible	–	*TP53* [1], *NRAS* [1]	USA	FF	Radovich *et al.* (8)	2018
3	WES	19 (TC)	–	No	–	*KMT2C* [2], *CYLD* [2], *NCOA1* [2], *NOTCH1* [2], *NSD1* [2], *WHSC1L1* [2]	China	FF	Fang *et al.* (10)	2021
4	WES	9 (TC)	–	No	–	*MYO16* [3]	China	FFPE	Yang *et al.* (11)	2023
5	WES & TS	16 (TC)	Sq [5], Undif [6], NEC [1], unknown [4]	No	197	*TP53* [4], *CYLD* [3], *BAP1* [2], *PBRM* [2], *CDKN2A* [2]	USA	FF and FFPE	Petrini *et al.* (12)	2014
6	WES & TS	11 (TC)	–	No	–	*CYLD* [3], *TP53* [2]	USA	No information	Ardeshir-Larijani *et al.* (13)	2023
7	TS	42, 5	–	No	197	*TP53* [12], *BAP1* [6], *CYLD* [4], *KIT* [4], *DNMT3A* [4], *SETD2* [4], *TET3* [6.4%]	USA	FFPE	Wang *et al.* (14)	2014
8	TS	12, 0	Sq [12]	No	409	*NF1* [2]	Japan	FF	Shitara *et al.* (15)	2014
9	TS	15 (TC)	Sq [14], Undif [1]	No	275	*TP53* [4], *KDM6A* [3], *SMAD4* [2], *CYLD* [2], *SETD2* [2], *KMT2C* [2], *KMT2D* [2]	USA	FF and FFPE	Moreira *et al.* (16)	2015
10	TS	15 (TC)		No	22	*PIK3CA* [2]	China	FFPE	Song *et al.* (17)	2016
11	TS	52[§]	Sq [47], Ad [2], SCC [1], poorly differentiated carcinoma [7], NOS [7]	No	50	*TP53* [4], *KRAS* [2]	Japan	FF and FFPE	Asao *et al.* (18)	2016
12	TS	34, 1	Sq [34], LEL [1]	No	50	*TP53* [9], *CDKN2A* [4], *FGFR3* [2], *KIT* [2]	Austria	FFPE	Enkner *et al.* (19)	2017
13	TS	5 (TC)	–	No	315	*KMT2C* [5], *ARID1A* [5], *MAP3K1* [5]	China	No information	Chen *et al.* (20)	2020
14	TS	15, 0	Sq [6], LEL [3], Ad [2], basaloid [4]	Accessible	50	*FGFR3* [5], CDKN2A [3], *SMARCB1* [2]	Italy	FFPE	Asselta *et al.* (21)	2021
15	TS	48, 6	Sq [44], Ad [4], carcinoid [5], LCNEC [1]	Accessible	50	*TP53* [12], *KIT* [4], *PDGFRA* [3], *PIK3CA* [3], *EGFR* [2], *KRAS* [2], *FBXW* [2], *VHL* [2]	Japan	FFPE	Sakane *et al.* (22)	2021
16	TS	15, 4	Sq [10], LEL [1], Ad [1], unknown [3], carcinoid [2], SCC [1], undefined [1]	Accessible	450	TC: *CDKN2A* [9], *CYLD* [6], *CDKN2B* [5], *TP53* [4] TNET: *MEN1* [2]	China	FFPE	Wang *et al.* (23)	2021
17	TS	28, 6	Sq [23], basaloid [1], Ad [1], Muco [1], NUT [1], LCNEC [6], NOS [1]	No	15	*TP53* [8], *KIT* [2], *ERBB2* [2]	Poland	FFPE	Szpechcinski *et al.* (24)	2022

Table 2 *(continued)*

Table 2 *(continued)*

Report No.	Method	Number*	Histological subtype [number of patients]	Genetic variations in each subtype	Number of target genes	Mutation [number of patients]	Country	Sample	Authors	Year
18	TS	174	Sq [69], Undif [54], NEC [30], LEL [5], basaloid [5], Ad [7], sarcomatoid [4]	Accessible	315	*CDKN2A* [65], *CDKN2B* [45], *TP53* [44], *CYLD* [19], *KIT* [15], *BAP1* [13]	USA	FFPE	Girard *et al.* (25)	2022
19	TS	8, 0	Sq [5], Ad [3]	No	315	*KMT2C* [5], *NFKBIA* [3], *TET2* [3], *TP53* [2], *RPTOR* [2], *ASXL1* [2], *BRCA2* [2]	China	FFPE	Tan *et al.* (26)	2023
20	TS	414 (FMI), 52 (CCAT)	–	No	324	FMI: *CDKN2A* [165], *TP53* [125], *CDKN2B* [102], *BAP1* [34], *TET2* [33], *KIT* [33], *SETD2* [32], *NFKBIA* [32], *ASXL1* [29], *KMT2D* [25] C-CAT: *CDKN2A* [20], *TP53* [19], *CDKN2B* [16], *KMT2D* [12], *MTAP* [12], *NFKBIA* [11]	USA and Japan	FFPE	Kurokawa *et al.* (27)	2023
21	Other†	7, 0	Sq [7]	No	12	*KIT* [2], *KRAS* [1]	USA	FF	Girard *et al.* (28)	2009
22	Other‡	48, 6	Sq [44], Ad [4], carcinoid [5], LCNEC [1]	Accessible	6	*KRAS* [6], *HRAS* [3], *TP53* [5]	Japan	FFPE	Sakane *et al.* (29)	2019

Listed with a frequency more than 5% in each cohort. *, the number of patients with thymic carcinoma and thymic neuroendocrine tumor were described respectively; †, array-based comparative genomic hybridization; ‡, single-base extension multiplex assay; §, total patients number was 64, of which 52 patients were analyzed for genetic testing. WES, whole exome sequencing; TS, target sequencing; FMI, Foundation Medicine Inc.; CCAT, Center for Cancer Genomics and Advanced Therapeutics; Sq, squamous; Undif, undifferentiated carcinoma; LCNEC, large cell neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; Ad, adenocarcinoma; SCC, small cell carcinoma; Muco, mucoepidermoid carcinoma; NOS, not otherwise specified; LEL, lympho-epithelial carcinoma; NUT, NUT carcinoma; C-CAT, Center for Cancer Genomics and Advanced Therapeutics; FF, fresh frozen; FFPE, formalin-fixed paraffin-embedded; TC, thymic carcinoma; TNET, thymic neuroendocrine tumor.

position locates in chromosome 16q, of which copy number loss is characteristic to thymic carcinoma (8). Additionally, it is related with differentiation and maturation of medullary thymic epithelial cells and the regulation of AIRE expression, essential for T cell development (34). The reported frequency of truncating mutations in *CYLD* in patients with thymic carcinoma through whole exome sequencing suggesting that loss of function of *CYLD* can influence tumorigenesis. Moreover, *CYLD* mutations can serve as candidate biomarkers for the response to ICB. In a small phase 2 study using pembrolizumab in thymic carcinoma patients, the responder group had a higher ratio of *CYLD* mutations than the non-responder group (35). This result may be related to the upregulation of PD-L1 expression via interferon gamma, resulting in the down-regulation of *CYLD in vitro* (36). In contrast, target sequencing did not reveal many *CYLD* mutations, as shown in *Table 2*. This is because CYLD is not included in the many of the panel lists of mutations. Further, *KIT* mutations are one of the druggable mutations. Buti *et al.* reported a patient with thymic carcinoma harboring *KIT* mutation showed an impressive response to imatinib treatment (37). Although two related small phase 2 studies using imatinib reported no response in patients with unselected thymic epithelial tumors (and possibly wild-type cKIT) (38), targeted therapy can be one of the treatment options for patients with thymic carcinoma who have *KIT* mutations. *TET2* mutation is mainly reported by Saito *et al.* (9). They identified three mutations in ten Japanese patients with thymic carcinoma. *TET2* affects DNA demethylation by converting 5methylcytosine to 5-hydroxymethylcytosine, resulting in abnormal genomic hypermethylation and

reduced repression of hypermethylated genes in acute myeloid leukemia (39). The author further analyzed the methylation status using the bead array method and emphasized the difference in the methylation status of *TET2* mutation-positive and *TET2* mutation-negative patients. Another group identified recurrent mutations in histone modification-related genes, such as *SETD2*, *BAP1*, and *ASXL1*. The authors suggested that a possible disruption of epigenetic regulation in thymic carcinoma, which is a characteristic of genome that differs from that of thymoma. Additionally, several epigenomic alteration of thymic carcinoma has been found, for example, abnormal methylation of *KSR1*, *ELF3*, *IL1RN*, and *RAG1* (40). *FGFR3 mutations* were found (26.6%) in four patients with thymic carcinoma in the report of Asselta *et al.* Also, the patients with *FGFR3* mutations conferred a statistically significant survival advantage in addition to the lower proliferation fraction using Ki-67 estimation. Dysregulation of the FGFR signaling pathway through genetic alterations in FGFR2/3 is implicated in driving carcinogenesis across various solid tumor types (21).

Because most of thymic carcinoma is squamous cell carcinoma, these recurrent genomic finding could be regarded as the characteristics of squamous cell carcinoma of thymus. Its rarity of other subtypes led disability of finding recurrent mutations in another subtypes. Thereafter focusing on unique mutation even if found in a few patients, two basaloid and one lymphoepithelioma-like carcinoma harbored *FGFR3* mutations, and a patient with adenocarcinoma intriguingly uniquely had *APC* out of frame deletion (21).

Mutations in thymic carcinoma compared to thymoma

The largest cohort study on target sequencing of thymic epithelial tumors suggested that *CDKN2A*, *CDKN2B* and *TP53* were more frequently altered in patients with thymic carcinoma than in those with thymoma (27). Additionally, *SETD2* mutations were common in both groups, which is consistent with another cohort study findings (14). Notably, *CYLD* mutation was specific to thymic carcinoma (12,14). Although this finding is intriguing, validation is required because the gene panel lists used in many other studies do not include the *CYLD* gene. Therefore, further analysis of large-scale cohorts is necessary. Regarding *KIT* mutations, a few thymic carcinoma patients had that, and one patient harbor pathogenic *KIT* p.(Leu576Pro) variant. Although a few thymoma patients had *KIT* mutations, they were considered variants of unknown significance, different from those observed in patients with thymic carcinoma (24). *TET2* mutations, emphasized by Saito *et al.* (9), were also unique to patients with thymic carcinoma in a study by Tan *et al.* (thymic carcinoma 3/8; thymoma 0/39) (26). *BAP1* mutations were slightly more common in patients with thymic carcinoma; however, they were also observed in some thymoma patients (12,14). *ASXL1* mutations were recurrent but not frequently enough to be evaluated.

Tumor mutational burden (TMB) and microsatellite instability (MSI) status

TMB is higher in thymic carcinomas than in thymic tumors, as indicated in several reports (8,25,27). However, thymic carcinomas exhibit elevated TMB compared to thymomas (8), accounting for 6–7% of cases (15,20). In addition, although few reports on MSI status are limited, the two largest studies utilizing target-sequencing indicate that high MSI cases are rare, ranging from 0–2.3% (25,27). Because of its rarity, it remains unclear whether the incidence of immune-related adverse events (irAEs) from ICB treatment is higher among thymic carcinoma patients compared to those with other solid tumors. Meanwhile, irAEs by using ICB for thymoma patients has reported clearly more frequently than individuals with other solid tumors (21). ICB can be a treatment option for patients with thymic carcinoma, although careful judgment is essential as a problem specific to immune organ (41).

Shared and divergent of copy number variations of thymic carcinoma and thymoma

The Cancer Genome Atlas (TCGA) project revealed that chromosome 16q loss is more common in thymic carcinoma than in thymoma (8). They estimated arm and focal-level copy number aberrations in 117 thymic epithelial tumor samples (107 thymomas and 10 thymic carcinomas). Also, chromosome 1q amplification and chromosome 6p and 6q loss were common in both thymic carcinomas and thymomas. This observation, consistent with prior report (42), has led to the hypothesis that thymomas (especially type B3 thymomas) and thymic carcinomas may represent sequential pathologies. However, the validity of this hypothesis remains unclear. The TCGA study revealed thymic carcinoma as distinct group with respect to molecular pathogenesis, based on multiomics analysis involving whole-exome sequencing. The assertion

is further supported by the detection of only two cases of combined thymic carcinoma and B3 thymomas among a substantial cohort of more than 600 thymomas, inclusive of type B2 and B3 thymomas (43). However, this concept does not entirely exclude the possibility of malignant transformation from thymoma to thymic carcinoma. Thymic carcinoma typically develops de novo, the copy number aberrations observed in thymic squamous tumors differ from those in squamous cells of other organs such as lung cancer (28), Despite these characteristics, given that thymoma and thymic carcinoma share chromosome 1q amplification and chromosome 6 loss, the possibility of thymoma rarely transforming in thymic carcinoma persists. Unlike the mixed types, there are reports of two cases that were diagnosed as thymoma at the time of initial diagnosis and were diagnosed as thymic carcinoma after a period of time (15 and 40 years later) (44,45). The transformation is challenging to study because of its rarity, however, it can be revealed by genomic profiling of heterochronic samples from the same patient who showed transformation from thymoma to thymic carcinoma.

Mutational signature

Saito *et al.* (9) reported mutational signatures in all analyzed patients with thymic carcinoma. The majority group, consisted of 8 out of 10 instances, exhibited primarily COSMIC signature 1 (clock-like, http://cancer.sanger.ac.uk/cosmic/signatures), associated with the spontaneous deamination of 5-methylcytosine. However, two cases stood out in the minority group, displaying COSMIC signatures 5 (clock-like) and 6 (DNA mismatch repair deficit). Additionally, a patient with TCGA referral demonstrated an unusually high TMB, showcasing a mutational pattern similar to COSMIC signature 6. This patient presented a pathogenic nonsense mutation of *MLH1*, accompanied by a lack of its expression.

Conclusions

Thymic carcinomas have unique genomic profiles compared to thymomas, however, they share certain copy number aberrations. These mutations may present novel targets for therapeutic approaches.

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Review Article

Postoperative radiotherapy for thymic epithelial tumors: a narrative review

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Background and Objective: Thymic epithelial tumors (TETs), including thymomas and thymic carcinomas, are rare mediastinal tumors. Surgical resection is the treatment strategy for resectable TETs, and postoperative radiotherapy (PORT) is administered to improve local control in patients with a high risk of recurrence. The rarity of TETs has led to a lack of randomized controlled trials, and the current indications for PORT rely largely on retrospective studies. This review analyzes the literature on TETs, highlighting PORT, to guide current research and future investigations.

Methods: Studies that focused on TETs, addressed topics on PORT, and had English abstracts accessible online were eligible for inclusion in our review. We excluded case reports or review articles, articles written in languages other than English, articles published >30 years ago, and articles concerning thymic neuroendocrine tumors.

Key Content and Findings: Masaoka or Masaoka-Koga staging, World Health Organization (WHO) histological subtype, and resection status indicate PORT in resected TETs. Current literature suggests that PORT does not improve overall survival in stage I–IIA TETs, with inconsistent results for stage IIB–III TETs. Patients with a higher risk, such as carcinomas or WHO type B, might benefit from PORT if they do not develop distant metastasis. Determining which patients will benefit most from PORT requires further investigation. For recurrent TETs, the significance of applying PORT is unclear because available data are limited. Given the long-term survival of TETs, late toxicities, including radiation pneumonitis, radiation-induced cardiotoxicities, and secondary malignancies, must be addressed. Proton beam radiotherapy might reduce toxicities by sparing organs at risk compared to conventional photon beam radiotherapy. The use of high-precision radiation therapy, along with emerging immunotherapy, targeted therapy, and minimally invasive surgery, could improve TET outcomes.

Conclusions: This review consolidates the literature on PORT for TETs, factoring in the Masaoka-Koga staging, WHO histological subtypes, and resection status. Varying results regarding PORT efficacy have led to an undefined strategy for stage IIB–III TETs. Although advanced radiotherapy techniques promise to reduce radiation-induced toxicities, further research is needed to investigate the efficacy of PORT and combination therapy.

Keywords: Postoperative radiotherapy; thymic carcinoma; thymic cancer; thymic epithelial tumors (TET)

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Introduction

Background

Thymic epithelial tumors (TETs) are rare primary tumors originating from the anterior mediastinum and include thymomas and thymic carcinomas. The incidence of thymomas is 1.5 cases per million people, and that of thymic carcinoma is 0.3 cases per million people (1,2). Thymomas have a good prognosis with a 5-year overall survival (OS) rate of 90%, whereas that of thymic carcinomas is 55%, and a higher stage is associated with worse OS (3-6).

The Masaoka-Koga staging system has been commonly used for management determination and prognosis estimation of TETs (7,8). It focuses on the local invasive extent of the primary tumor (stages I–III), and pleural, pericardial, lymphogenous, or hematogenous metastases are all included in stage IV, as TETs spread locally and rarely develop lymphatic dissemination. Surgical resection is the main treatment strategy for stages I–III and IV TETs.

Pathological findings are closely associated with the prognosis of TET and are heterogeneous. According to the fifth edition of the World Health Organization (WHO) classification of the thymus and mediastinum, TETs are categorized as type A thymoma, type AB thymoma, thymoma type B1-B2-B3, several other minor thymoma subtypes, and carcinomas, including squamous cell carcinoma and adenocarcinoma (9); 10-year OS for each subtype were 100, 100, 85, 85, 65, and 40% for type A, AB, B1, B2, and B3 thymomas, and thymic carcinomas, respectively (10,11). Geographic differences exist in the frequency of WHO histological subtypes, which impact recurrence (12).

When patients with TETs undergo surgical resection, postoperative radiotherapy (PORT) is often administered to improve local control, depending on the pathological findings of the stage and the residual tumor (13).

Rationale and knowledge gap

Owing to the rarity of TETs, no randomized controlled trials (RCTs) have been conducted to confirm the efficacy of PORT in TETs, and the current evidence levels are not high and are mainly based on retrospective studies. According to the National Comprehensive Cancer Network guidelines, completely resected Masaoka-Koga stage I thymomas do not require adjuvant therapy, whereas PORT is administered for TETs with microscopic (R1) or macroscopic (R2) residual tumors (13). For completely resected stage II–IV TETs, the guidelines recommend discussion by a multidisciplinary tumor board (MTB) to determine the patient's treatment strategy because the efficacy of PORT in this area remains controversial.

The Réseau Tumeurs Thymiques et Cancer (RYTHMIC), a nationwide network for TETs in France, has prospectively gathered data to determine whether decisions on PORT made at the MTBs align with RYTHMIC guidelines and whether they are ultimately implemented in patient care (14). Among 241 patients with stage I–III disease, the MTB's decision regarding PORT was not made in accordance with the ESMO/RYTHMIC guidelines in 20 patients. When the MTB recommended PORT in cases where the guidelines would have advised against it, a clear explanation for the inconsistency with the guidelines was not found; however, the cases were stage II thymomas with WHO type B2 or stage IIA thymomas with WHO type AB thymomas. Thus, the efficacy of PORT in TETs for these subjects could be considered a gray zone in the guidelines, where different MTBs would make different decisions.

Objective

This narrative review aimed to evaluate and summarize the current literature regarding PORT for TETs in terms of indications for PORT, radiotherapy techniques, and toxicities. This review sheds light on this understudied area by providing information on the current ongoing trials and recommendations for future research. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-38/rc).

Methods

A summary of the search strategies is provided in *Table 1*. N.K. developed and executed the PubMed search on August 5th, 2023. The reproducible search strategies for creating a narrative review are presented in *Table 2*. The studies included in the review met the following eligibility criteria: (I) articles focusing on TETs; (II) articles that included topics on PORT; and (III) articles with English abstracts available online. The exclusion criteria were as follows: (I) case reports or review articles; (II) articles written in languages other than English; and (III) articles on thymic neuroendocrine tumors.

Table 1 Search strategy summary

Items	Specification
Date of search (specified to date, month and year)	August 5th, 2023
Databases and other sources searched	PubMed
Search terms used	radiotherapy, adjuvant, postoperative, thymic, thymoma
Timeframe	Since August 1st, 1992, until August 5th, 2023
Inclusion and exclusion criteria	Inclusion criteria
	(I) Articles on thymic epithelial tumors excluding thymic neuroendocrine tumor
	(II) Articles on postoperative radiotherapy
	Exclusion criteria
	(I) Articles written in non-English language
	(II) Case reports, review articles, or guidelines
	(III) Articles published >30 years ago
	(IV) Pre-clinical studies
Selection process	N.K. conducted the selection independently and Y.M. reviewed the process

Table 2 Search strategy to create a narrative review (date of search: August 5th, 2023)

Search	Query	Items
#1	Has abstract	24,918,516
	"hasabstract" (All Fields)	
#2	Adjuvant radiotherapy OR Postoperative radiotherapy	425,765
	("radiotherapy, adjuvant"(MeSH Terms) OR ("radiotherapy"(All Fields) AND "adjuvant"(All Fields)) OR "adjuvant radiotherapy"(All Fields) OR ("adjuvant"(All Fields) AND "radiotherapy"(All Fields))) OR (("postoperative period"(MeSH Terms) OR ("postoperative"(All Fields) AND "period"(All Fields)) OR "postoperative period"(All Fields) OR "postop"(All Fields) OR "postoperative"(All Fields) OR "postoperatively"(All Fields) OR "postoperatives"(All Fields)) AND ("radiotherapy"(MeSH Terms) OR "radiotherapy"(All Fields) OR "radiotherapies"(All Fields) OR "radiotherapy"(MeSH Subheading) OR "radiotherapy s"(All Fields)))	
#3	Thymic (ti) OR Thymoma (ti)	16,097
	"Thymic"(Title) OR "Thymoma"(Title)	
#4	#1 AND #2 AND #3	488

Indications for PORT

One hundred eighty-four articles were identified in the search (*Figure 1*). As no RCTs have assessed the efficacy of PORT, established rationales are based on retrospective studies of large databases. Although multi- or single-institutional retrospective studies have smaller sample sizes than large database studies, they can offer more detailed results. We review both types of studies and highlight their strengths.

Resected TET

Three pathological indications for PORT in resectable TETs have been discussed in the literature: pathological staging, WHO classification of histological subtypes, and resectional status (margin status).

Masaoka or Masaoka-Koga staging

The Masaoka or Masaoka-Koga staging system has been widely used in pathological staging to determine

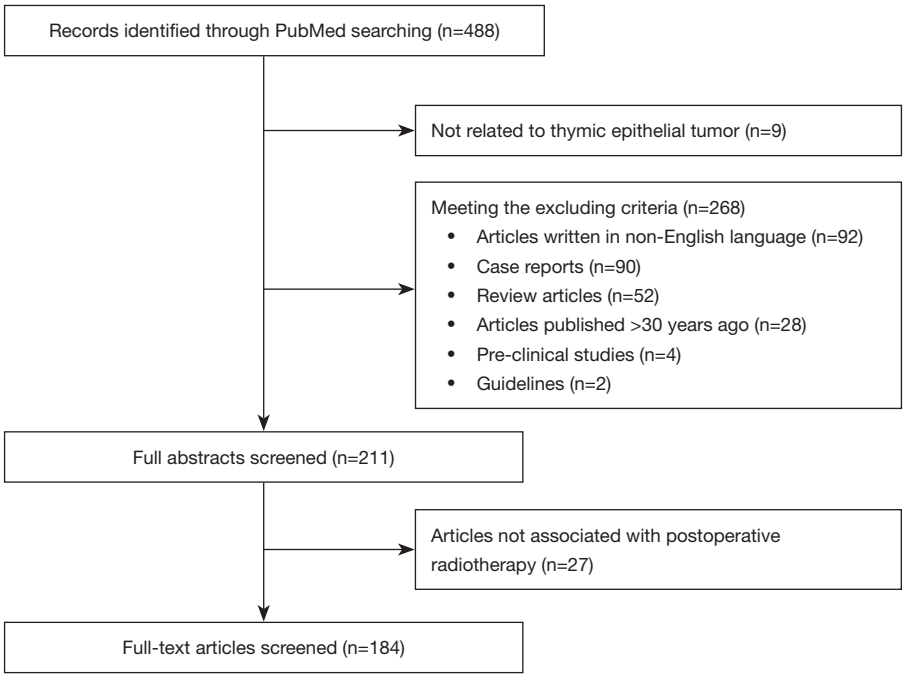

Figure 1 Flow chart for literature search and selection.

the indications for PORT in TETs. In contrast, the International Thymic Malignancy Interest Group (ITMIG), European Society of Thoracic Surgeons, Japanese Association of Research in Thymus, and Chinese Alliance for Research on Thymomas developed an international database, which resulted in the development of the TNM stage classification. It provides information on lymphatic involvement and tumor dissemination in addition to tumor invasion extent, and is comparable or superior in grouping TETs for predicting prognosis and guiding clinical management (15-17). However, previous reports on PORT were largely based on Masaoka or Masaoka-Koga staging, and a paradigm shift is occurring from the traditional Masaoka-Koga system to a TNM system. In this section, we outline the benefits of PORT according to the Masaoka or Masaoka-Koga stages. In *Table 3*, we present previous database studies that assessed the efficacy of PORT on OS, which have yielded conflicting results.

One of the largest retrospective database analyses using the National Cancer Data Base (NCDB) investigated 4,056 patients who underwent surgery for stage I–IV TETs (30). PORT positively correlated with improved OS in patients diagnosed with either thymoma or thymic carcinoma. For patients with stage IIB or III thymoma, PORT significantly increased OS. Among the subsets with margin-negative stage IIB thymoma, PORT was still associated with better OS. In patients with thymic carcinoma, PORT was significantly correlated with increased OS across the entire cohort. When classified into stages I–IIA, IIB, and III, no significant differences were noted, although a slight increase in OS was observed in patients with stage III disease. In another study using the ITMIG database, Rimner *et al.* reported an OS benefit with PORT in patients with completely resected stage II and III thymoma (29).

In contrast, a Surveillance, Epidemiology, and End Results (SEER) database study, which focused on 1,334 patients with thymoma between 1973 and 2005, did not show an OS benefit of PORT in patients with stage IIB disease (18). Lim *et al.* used a more recent patient cohort from the same database and reported that PORT in stages III–IV was associated with improved OS; however, no corresponding efficacy was observed in stage IIB (25). The Japanese Association for Research on the Thymus Database Study, which included 1,265 patients with TETs, showed that PORT improved recurrence-free survival (RFS) for stage II–III thymic carcinoma, but did not improve OS and RFS for stage II–III thymoma (23).

Five meta-analyses reported PORT for TETs: two TETs, two thymomas, and one thymic carcinoma. Two meta-analyses on PORT for TETs concluded that

Table 3 Previous database studies assessing the efficacy of postoperative radiotherapy on overall survival

Authors	N	Primary	Stage	Database	Masaoka or Masaoka-Koga staging					5-year OS in PORT *vs.* no PORT in stage II–IV
					I	IIA	IIB	III	IV	
Fernandes *et al.* (18)	1,334	Car	I–IV	SEER	NS (I–IIA)		NS	S (III–IV)		Median, 134 *vs.* 115 months (IIB)
Patel *et al.* (19)	1,464	Thy	I–IV	SEER	NS		S (II–III)		NA	64% *vs.* 53% (II–III)
Weksler *et al.* (20)	476	Thy	III	SEER	–	–	–	NS	–	Median, 127 *vs.*105 months
Mariano *et al.* (21)	171	Thy	I–IV	BCCAR	NA		NS (II)	NA	NA	NA
Ruffini *et al.* (22)	2,265	Car	I–IV	ESTS			S			69% *vs.* 61%
Omasa *et al.* (23)	1,265	TET	II–III	JART	–		NS (II)	NS	–	97% *vs*. 96% (II, Thy) 93% *vs*. 90% (III, Thy) 91% *vs*. 87% (II, Car) 65% *vs*. 64% (III, Car)
Hishida *et al.* (24)	306	Car	I–IV	JART			NS (I–IV)			78% *vs.* 74%
Lim *et al.* (25)	529	Thy	IIB–IV	SEER	–	–	NS	S	S	NA
Fu *et al.* (26)	329	Car	I–IV	ChART		NS (R0, I–II)		S (R0)	S (R0)	NA
							S (R1–2, I–IV)			
Wang *et al.* (27)	1,850	Thy	I–IV	ChART			NS (I–IV)			NA
Liu *et al.* (28)	1,546	TET	I–III	ChART	NS		NS (II)	NS	–	90% *vs.* 96%
Rimner *et al.* (29)	1,263	Thy	II–III	ITMIG	–		S (R0)	S (R0)	–	97% *vs*. 93% (II) 92% *vs*. 76% (III)
Jackson *et al.* (30)	4,056	TET	I–IV	NCDB	NS (I–IIA)		S (Thy), NS (Car)	S (Thy), NS (Car)	NA	NA
Lim *et al.* (31)	312	Car	I–IV	SEER		NS (I–II)		S	NS	NA
Mou *et al.* (32)	2,234	Thy	I–IV	SEER	NS (I–IIA)		NS	S (III–IV)		75.4% *vs.* 62.9% (III–IV)
Bian *et al.* (33)	1,272	Thy	I–IV	SEER	NS		S (IIA–III)		S	NA
Gu *et al.* (34)	1,087	TET	I–II*	ChART		NS (I–II)		–	–	NA
Kim *et al.* (35)	632	Car	IIB–III	NCDB	–	–	S NS (R0)	S	–	NA
Mou *et al.* (36)	2,236	Thy	I–IV	SEER	NS (I–IIA)		NS	S (III–IV)		NA
Wu *et al.* (37)	216	Car	I–IV	SEER			NS (I–IV)			NA
Muslim *et al.* (38)	1,120	Thy	IIB–IV	SEER	–	–	NS†	S†	NS†	NA
Lococo *et al.* (39)	203	Car	I–IV	ESTS			S			74% *vs.* 55%
Zhang *et al.* (40)	2,558	TET	I–IV	SEER	NS (I–IIA)		S	S (Thy), NS (Car)		82% *vs*. 75% (IIB, Thy) 66% *vs*. 46% (III–IV, Thy) 72% *vs*. 61% (IIB, Car) 38% *vs*. 23% (III–IV, Car)
Lin *et al.* (41)	700	Thy	IIB–III	SEER	–	–	NS	S	–	NA

*, UICC stage I (equal to Masaoka stages I and II); †, disease-specific survival, not OS. OS, overall survival; PORT, postoperative radiotherapy; Car, thymic carcinoma; SEER, Surveillance, Epidemiology, and End Results; NS, not significant; S, significant; Thy, thymoma; BCCAR, British Columbia Cancer Agency Registry; NA, not available; ESTS, European Society of Thoracic Surgeons; TET, thymic epithelial tumor; JART, Japanese Association for Research on the Thymus; ChART, Chinese Alliance for Research of Thymoma database; ITMIG, International Thymic Malignancies Interest Group ; NCDB, National Cancer Database.

Table 4 Summary table of advantages and disadvantages of large-database studies

Database	Pros	Cons
All	Large series of patients	Retrospective studies contain bias; no detailed records of failure patterns, chemotherapy, and radiotherapy
SEER	Propensity score-matched studies were performed; cause of death and second malignancy were available; can be focused on specific histological type	Surgical margin status, comorbidities, patient performance status, and Masaoka-Koga staging were unavailable; WHO histology classification was unavailable for the majority; no central review of histological classification was performed; the ethnic characteristics were diverse
ChART	Propensity score-matched studies were performed; TNM staging was utilized	Missing patient information caused the majority to excluded from the analysis; Masaoka-Koga staging was unavailable
JART	The number of patients with missing data (including OS) was very small; Masaoka staging was utilized	No central review of histological classification was performed
ESTS	Clinico-pathological variables affecting long-term survival were investigated; Masaoka staging was utilized; neuroendocrine thymic tumors were excluded from the analysis	Only surgical cases in high-volume centers were included; no central review of histological classification was performed; nodal status and the site of distant metastases were unavailable
NCDB	Margin status was incorporated into the analysis	Masaoka-Koga staging was unavailable; no central review of histological classification was performed
BCCAR	Variability in clinical behavior and practice variations were focused; Masaoka-Koga staging was utilized; pathology review and reclassification were performed	10% of the data were unavailable for analysis; the number of patients with stage I was limited
ITMIG	Completely resected stage II and III thymoma were the focus; Masaoka or Masaoka-Koga staging was utilized	Stages IIA, IIB, and II were all categorized as stage II.

SEER, Surveillance, Epidemiology, and End Results database; WHO, World Health Organization; ChART, Chinese Alliance for Research of Thymoma database; JART, Japanese Association for Research on the Thymus Database; OS, overall survival; ESTS, European Society of Thoracic Surgeons database; NCDB, National Cancer Database; BCCAR, British Columbia Cancer Agency Registry; ITMIG, International Thymic Malignancies Interest Group Retrospective Database.

current evidence did not support any benefit of PORT on recurrence in patients with complete resection of stage II or III TETs (42,43). Two meta-analyses, one with 3,823 patients from fourteen studies and the other with 4,746 patients from five studies, showed that increased OS was observed in the subgroup analysis of completely resected stage II or III thymoma (44,45). Hamaji *et al.* also showed that PORT improves the long-term survival outcomes of patients with thymic carcinoma, although stage-specific or resectional status-specific recommendations were not available in the meta-analysis (46).

These discrepancies among large database studies or meta-analyses can be attributed to the rarity of TETs and the inherent bias in studies, such as patient eligibility, lack of or missing covariates derived from the database, adjuvant radiotherapy, including concurrent use of chemotherapy, or the covariates utilized for propensity score matching analysis. Furthermore, information from Masaoka or Masaoka-Koga staging is not specifically recorded in the NCDB or the SEER database and is inferred and subjectively classified based on recorded information as far as possible. This could be a limitation of large database analysis (*Table 4*).

The incompleteness of the traditional Masaoka-Koga staging is also a limitation, as it provides no information on the number of involved organs or tumor size, both of which appear to be promising factors for prognostic stratification (17,47). Therefore, an optimal staging system to identify patients with poor prognosis who are at high risk for recurrence is necessary. Such patients could be ideal candidates for PORT or less-invasive surgery combined with PORT. For example, in patients with phrenic nerve involvement (Masaoka-Koga stage III or higher), *en bloc* resection can lead to diaphragmatic impairment and pulmonary function deterioration. Phrenic nerve-sparing surgery combined with PORT is feasible with an acceptable

local control rate of 92.9% (48). The ninth edition of the TNM stage classification, which is based on a large international database, is expected to contribute significantly to this field.

WHO histological subtypes

The patterns of metastasis and recurrence significantly differ across the WHO classification histological subtypes; the time to metastasis is shortest in thymic carcinoma, followed by high-risk thymoma (WHO types B2 and B3), and longest in low-risk thymoma (A, AB, and B1) (9,12,49,50). According to an analysis of the ITMIG retrospective database, PORT was associated with a trend toward better OS in all subgroups of stage II and III thymoma, and the greatest and most statistically significant survival advantage with PORT was observed in the subgroup of patients with stage III WHO types B1, B2, or B3 thymoma (29). In contrast, Muslim *et al.* reported that SEER database analysis did not reveal a significant disease-specific survival advantage of PORT in any of the WHO histological subtypes among patients with stage IIB–IV thymoma (38). This could be mainly due to differences in the stages of the eligible patient cohorts. For thymic carcinoma, we did not find any reports examining the differences between squamous cell carcinoma and adenocarcinoma.

Resectional status

Complete resection was associated with improved OS in patients with TETs. Resectional status is a well-known factor for indicating PORT in TETs because PORT is associated with improved OS in patients with incomplete resections or positive margins (28,30,35).

When total resection is not possible, subtotal resection, or debulking surgery, may yield a higher survival rate than that for inoperable thymoma but not for thymic carcinoma (5). Zhai *et al.* conducted a retrospective study on debulking surgery plus PORT versus radiotherapy in 47 patients with unresectable stage III thymic carcinoma (51). The results revealed 5-year OS rates of 54.4% and 0%, respectively. Thus, there may be merit in the so-called "debulking procedures" followed by PORT, but only in highly selected cases. Mastromarino *et al.* investigated 79 patients with types B2 and B3 thymomas, including R1 or R2 residual tumors (52). Regardless of whether residual tumors existed in the primary tumor or pleural space, PORT significantly improved progression-free survival in patients with R1 residual tumors, whereas postoperative chemotherapy or chemoradiotherapy improved cancer-specific survival in patients with R2 residual tumors.

In summary, the current literature suggests that PORT does not improve OS in stage I–IIA TETs, with inconsistent results for stage IIB–III TETs. The currently available data suggest that stage II–III TETs are a heterogeneous population; at least stages IIA and IIB need to be considered separately as indications for PORT, not considered together as stage II. PORT for stage III TETs can contribute to improved OS in patients with higher-risk grades, such as carcinoma or WHO type B2–B3, and may benefit from PORT in terms of improved OS when they do not develop distant metastasis. Identifying patients less likely to develop early distant metastases and can genuinely benefit from PORT remains a gray zone that requires further exploration.

Recurrent TET

After definitive radiotherapy or PORT, the 5-year cumulative incidence of all intrathoracic failures was 24% (53). The most common site of failure was the out-of-field pleural space, followed by the 5-year incidence of in-field failure of 7%. Although radiotherapy is critical in the multimodal treatment of intrathoracic recurrent TETs (54,55), several aspects warrant careful consideration.

First, the prognostic significance of PORT in patients with recurrent TETs remains unclear. Several studies with a limited sample size have indicated that adjuvant therapies, including PORT, do not effectively reduce recurrence or improve survival outcomes (56,57). Second, when considering PORT for recurrent TETs, examining the overlap between the field irradiated during initial PORT and the target volume at the time of recurrence is imperative. Furthermore, it is essential to ensure that the cumulative dose to the organs at risk is within the established dose constraints, as described in "Radiotherapy techniques". Recently, phase II trials have demonstrated that targeted therapies, including everolimus, lenvatinib, and sunitinib, may induce durable disease control in patients with recurrent TETs as second-line treatment (58-60). However, there is no evidence supporting the concurrent use of systemic therapies and radiotherapy. Therefore, when administering PORT for recurrent TETs, pausing targeted therapy before and after PORT based on its half-life should be considered.

Radiotherapy techniques

Photon beam radiotherapy

Photon beam radiotherapy is commonly used in PORT. In this section, we outline the standard procedures and techniques for photon beam radiotherapy based on previous literature and guidelines (13,61,62). Three-dimensional conformal radiotherapy (3D-CRT) is conventionally used as a common delivery technique. Recently, intensity-modulated radiotherapy (IMRT), which enables the delivery of conformal radiation doses to irregularly shaped target volumes with high-precision fitted dose distribution, could be expected to decrease the dose delivered to organs at risk, sparing over 3D-CRT and has been applied to PORT (63).

Before initiating PORT, physicians should ensure the absence of infection or wound dehiscence. While there is no definitive maximum period from surgery to PORT, it has been reported that a delay of more than 3 months post-surgery often leads physicians to decide to skip PORT (14). Given that the respiratory motion of the upper mediastinum is typically minimal, respiratory-gated radiotherapy or breath-hold radiotherapy techniques to reduce motion are not mandatory.

Postoperative changes should be considered when delineating target volumes. As expert agreement for delineating postoperative cases is low compared with that of definitive cases, a contouring atlas for TETs with expert consensus is urgently needed (64). The utilization of four-dimensional-CT and positron emission tomography-CT fusion should be implemented for contour delineation, if available (64). It is also recommended to fuse preoperative CT with treatment-planning CT and deform preoperative CT to fit the treatment-planning CT. Gross tumor volume was defined as incomplete resection. In cases of complete resection, the clinical target volume (CTV) should encompass the tumor bed, surgical clips, and potential sites of residual disease. In cases of incomplete resection, the entire thymus should be included in the CTV. In instances where the margins are close or positive, surgical clips are useful for identifying the site of boost irradiation. The rates of lymphogenous metastasis in thymoma and thymic carcinoma are 1.8 and 27%, respectively (65). There was no significant difference in 5-year OS between local radiation therapy (targeting the tumor bed and anterior mediastinal areas only) and elective nodal irradiation (targeting the entire mediastinal and supraclavicular regions) in patients with TETs (65,66). Therefore, elective nodal irradiation is not recommended for TETs. The prescribed doses range from 45–50 Gy for negative or close margins, 54 Gy for microscopically positive resection margins, and 60–70 Gy for gross residual disease, administered in 1.8–2.0 Gy fractions.

As the dose constraints of organs at risk, normal tissue dose-volume constraints for conventionally fractionated radiotherapy for lung cancer could be applied to PORT in TETs; spinal cord max dose ≤50 Gy; lung V_{20Gy} ≤35–40% (V_{xGy}: percentage of the volume receiving at least X Gy), mean dose ≤20 Gy; heart V_{50Gy} ≤25%, mean dose ≤20 Gy; esophagus mean dose ≤34 Gy, V_{60Gy} ≤17% (67).

Proton beam therapy

A dosimetric comparison study has shown that both proton beam radiotherapy and carbon-ion radiotherapy excel in sparing organs at risk, such as the heart, lungs, left ventricle, esophagus, and spinal cord, and in improving target volume coverage when compared to photon IMRT (63,68-72). This is anticipated to reduce toxicity, potentially decreasing major cardiac events and the occurrence of secondary malignant neoplasms. Previous studies on proton beam radiotherapy for TETs are presented in *Table 5*. No toxicities more severe than grade 3 were observed following proton beam radiotherapy, and the OS and locoregional control rates were comparable with those achieved with photon beam radiotherapy. It should be noted that the sample sizes in these studies were small and included both PORT and definitive RT. Future clinical trials with larger cohorts and direct comparisons between proton and photon beam radiotherapies are essential.

Toxicity

Common acute toxicities associated with PORT for TETs include fatigue, dermatitis, esophagitis, pneumonitis, and myelosuppression. Given the location of the anterior mediastinum, the severity of esophagitis is typically milder than in other intrathoracic tumors such as esophageal or lung cancers. Consequently, this study focused on detailing the more significant late toxicities that require special consideration, including pneumonitis, cardiotoxicities, and secondary malignancies.

Radiation pneumonitis

Previous studies have reported that the irradiated dose to the normal lung is one of the common risk factors for

Table 5 Literature on proton beam radiotherapy in TETs for PORT

Authors	Year	N [N of PORT]	Primary	Prescribed dose, median (range)	Efficacy	Toxicity ≥ grade 3
Vogel *et al.* (73)	2016	27 [17]	TET	61.2 CGE (50.4–70.0 CGE)	3-year OS: 94% 3-year regional control: 96%	No
Parikh *et al.* (71)	2016	4 [4]	Thymoma	57.0 CGE (50.4–66.6 CGE)	No death and no recurrences occurred	No
Zhu *et al.* (70)	2018	6 [5]	Thymoma	60 GyE (54–70 GyE)	3 patients experienced recurrences (0 local recurrence)	No
Mercado *et al.* (74)	2019	30 [26]	TET	54 GyE (45–70 GyE)	5 patients experienced recurrence (1 local recurrence) 4 died (3 died of TETs)	No

TET, thymic epithelial tumor; PORT, postoperative radiotherapy; CGE, cobalt-gray equivalent; OS, overall survival; GyE, gray equivalent.

developing radiation pneumonitis in patients with lung cancer: lung V_{20Gy}, mean lung dose, and absolute lung volume spared from a 5 Gy dose (75,76). In PORT for TETs, the irradiated dose to the normal lung is usually lower than that in definitive radiotherapy for lung cancer because the tumor bed is located in the mediastinum. The incidence of grade 2 or higher radiation pneumonitis in PORT for TETs is reported to be <10%, which is lower than that in definitive radiotherapy for lung cancer. Therefore, only a few studies have reported the risk factors for radiation pneumonitis in TETs. Moiseenko *et al.* quantified the influence of irradiated lung volume and dose on the lung response and showed that the mean lung dose was strongly correlated with lung complications, including pneumonitis and fibrosis (77). Tomita *et al.* reported that pulmonary artery V_{35Gy} was significantly associated with radiation pneumonitis in patients with TET (78). In summary, efforts should be made to reduce the irradiation dose to the normal lung as much as possible during PORT for TETs, even though the risk of radiation pneumonitis is very low.

Radiation-induced cardiotoxicities

The onset of radiation-induced cardiotoxicities occurs years or decades after PORT, and the typical symptoms are acute pericarditis, pericardial effusion, coronary artery disease, stenosis and regurgitation of valves, arrhythmia, and heart failure. Radiation-induced cardiotoxicities are a concern in long-term survivors of thoracic irradiation, such as patients with breast cancer or lymphoma. It is well known that after PORT in patients with breast cancer, the rates of major coronary events increase linearly with the mean dose to the heart by 7.4% per gray (79). Meanwhile, a SEER database analysis showed that radiotherapy does not increase the risk of cardiac mortality (12-year cumulative incidence or death, 10.2% radiation *vs.* 7.5% no radiation) in patients with thymoma (18). Given the prolonged survival of patients undergoing TETs, cardiotoxicity remains a critical concern following mediastinal irradiation via PORT. There is a pressing need for prospective studies that screen for cardiac event risks and consistently monitor radiation-induced cardiotoxicity.

Second malignancies

Thymomas are associated with an increased risk of secondary malignancies. Patients face a higher risk of death from this second type of cancer than from recurrence (80). The lifetime attributable risk of secondary fatal cancer in patients receiving PORT (50 Gy in 25 fractions) for thymoma has been reported to be approximately 1–3% (81). Mou *et al.* reported that patients with thymoma who underwent surgery with PORT had a higher rate of secondary cancers than those who underwent surgery without PORT, based on the SEER database (32). In contrast, two studies concluded that radiotherapy did not increase the risk of secondary malignancy in patients with thymoma (18,82).

The incidence of secondary malignancies and deaths from secondary malignancies are lower in thymic carcinoma than in thymoma (83).

The association between TETs and secondary malignancies cannot be attributed solely to radiotherapy. Further investigations with long-term follow-ups and large

sample sizes are needed because of the rare incidence of TETs and secondary malignancies.

Future indications

Radiotherapy has undergone significant advancements in recent decades. Research supporting the use of IMRT or particle therapy is ongoing, and accumulated data are expected to be published in the near future, contributing to the establishment of new evidence. Adopting these innovative radiotherapy techniques for TETs is expected to enhance patient outcomes (84). For definitive treatment or PORT, we have highlighted the radiotherapy techniques projected to be utilized for TETs in the coming years.

RADIORHYTHMIC, a phase III randomized study of PORT in stage IIB/III thymomas after complete surgical resection, was conducted by the RYTHMIC and is currently ongoing (85). Three hundred and fourteen patients will be randomized to either the PORT group (50–54 Gy to the mediastinum using IMRT or proton beam therapy) or the surveillance group. The results will be expected in 2028. Hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) for malignant pleural mesothelioma has been developed as part of a multimodality treatment for patients receiving pleurectomy/decortication to spare the affected side of the lung (86). As recurrent TETs often develop pleural dissemination, IMPRINT can be applied to control pleural dissemination (53,87). SABR-COMET, a randomized phase II study aimed at determining the effect of stereotactic body radiotherapy (SBRT) in patients with a controlled primary tumor and 1–5 oligometastatic lesions, demonstrated that SBRT was associated with improved OS (88). Yano *et al.* reported 24 patients with recurrent thymoma, revealing that patients with a limited number of recurrent lesions had a better prognosis regardless of treatment (89). Based on these findings, SBRT may be an effective treatment option for patients with oligometastatic TETs. Adaptive radiotherapy, which aims to decrease the dose to normal tissues and allow for dose escalation to the target volume by changing the radiation treatment plan delivered to a patient during the course of radiotherapy to account for either temporal changes in anatomy (e.g., tumor size, internal motion, variations in respiratory patterns, weight loss) or changes in tumor biology/function (e.g., hypoxia) (90), is promising for application in TETs (91,92). Intraoperative radiotherapy has been used for intractable cancers such as pancreatic cancer and osteosarcoma (93,94). Cui *et al.* applied intraoperative radiotherapy (8–10 Gy) to TETs and reported its safety and efficacy in 14 patients with invasive thymomas as a less time-consuming and less invasive radiotherapy technique for improving locoregional control (95). The mean time for installation and operation of the radiation equipment 57.6 minutes (range, 48–72 minutes). During a median follow-up period of 41 months, no recurrence, death, or severe toxicity were observed.

As part of the multimodal treatment, surgical approaches, systemic therapy, and radiotherapy techniques are drastically evolving. Salfity *et al.* reported on minimally invasive surgery in managing resectable thymomas based on the NCDB and showed that PORT was less frequent in thoracoscopic thymectomies than in traditional open sternotomy (96). As the efficacy of PORT in different surgical approaches remains unknown, future investigations may reveal the different indications and irradiation fields for PORT depending on the surgical approach. Several studies have reported abscopal and bystander effects after radiotherapy in thymic carcinoma (97,98). A combination of immunotherapy and radiotherapy is expected to enhance these effects and improve patient outcomes. The abscopal effect was proposed in 1953, and it is hypothesized that the immune system plays a role in mediating this phenomenon, leading to therapeutic effects on lesions located outside the irradiated field (99,100). Currently, a clinical investigation on the abscopal effect of radiotherapy in combination with recombinant human granulocyte-macrophage colony-stimulating factor for advanced TETs is ongoing in China (ClinicalTrials.gov; NCT05407649).

Advancements in radiotherapy techniques combined with other novel surgical or systematic approaches can further improve the outcomes. Therefore, an optimal treatment strategy combined with PORT should be identified using prospective data.

Conclusions

This narrative review presents a synthesis of the existing literature on the efficacy and toxicities of PORT in relation to OS. Considering the Masaoka-Koga staging, WHO histological subtypes, and resection status, indications for PORT have been determined for stage IIB–III TETs, although inconsistent results have been observed. Identifying patients who benefit from PORT for locoregional control can refine treatment strategies for TETs. Given that TETs typically result in long-term survival, late toxicities, such as radiation pneumonitis,

radiation-induced cardiac toxicities, and secondary malignancies, are significant. However, a decrease in these toxicities has been anticipated with the introduction of advanced radiotherapy techniques. Further studies are required to evaluate the value of PORT based on patient characteristics and combination therapy.

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Review Article

Imaging of thymic epithelial tumors—a clinical practice review

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Abstract: This review article comprehensively examines the diagnostic approach to thymic epithelial tumors (TETs) and other mediastinal masses, focusing on imaging modalities and differential diagnosis. Beginning with a discussion on traditional and contemporary classification systems for mediastinal tumors, including the Japanese Association for Research on the Thymus (JART) and International Thymic Interest Group (ITMIG) classifications, it highlights the shift towards computed tomography (CT)-based categorizations. Emphasis is placed on the importance of distinguishing between solid and cystic lesions in the anterior mediastinum, with detailed insights into imaging characteristics and histological features of various TET subtypes such as thymomas, thymic carcinomas, and thymic neuroendocrine tumors (NETs). The review also elucidates common differential diagnoses, including lymphomas and germ cell tumors, providing guidance on key imaging findings and considerations for accurate diagnosis. Furthermore, it underscores the significance of patient background and blood tests in differential diagnosis, discussing age-related prevalence patterns and tumor marker assessment. After addressing the diagnostic challenges posed by thymic cysts offering insights into their radiological features, management considerations, and potential complications, this review extends to other rare mediastinal lesions highlighting the need for a comprehensive evaluation for accurate identification and management of these tumors. Finally, as illustrative examples, we present six cases highlighting various aspects of anterior mediastinal tumors, including TET. These cases provide valuable insights into the diagnostic challenges, imaging characteristics, and management considerations encountered in clinical practice. The cases presented herein do not all illustrate typical images, courses, and diagnoses. However, they each contain significant implications. Thus, we present them with the belief that they will aid in understanding the intricate nuances of image diagnosis in actual clinical practice.

Keywords: Computed tomography (CT); magnetic resonance imaging (MRI); thymoma; thymic carcinoma; thymic epithelial tumor (TET)

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Introduction

Thymic epithelial tumors (TETs) represent a major subset of mediastinal tumors, located in the central compartment of the thoracic cavity known as the mediastinum. The mediastinum encompasses important structures such as the heart, major arteries and veins, esophagus, trachea, lymphatics and thymus, giving rise to a diverse series of potential neoplastic entities collectively termed mediastinal tumors. The complexity of mediastinal tumors demands a meticulous approach to differential diagnosis.

Traditionally, the classification of mediastinal tumors relied on classical mediastinal divisions derived from lateral chest radiographs or Felson's mediastinal classifications (1). However, the year 2009 marked a pivotal development with

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the introduction of the Japanese Association for Research on the Thymus (JART) classification, which utilized computed tomography (CT) cross-sectional images to categorize mediastinum (2). Subsequently, the International Thymic Interest Group (ITMIG) further streamlined the JART classification into the ITMIG classification, simplifying the approach to mediastinal tumor localization (3-5).

The primary distinction between the JART and ITMIG classifications lies in the definition of the superior mediastinum. Specifically, JART maintains the traditional concept of the superior mediastinum, whereas ITMIG opts for a more streamlined approach, categorizing the entire mediastinum into only three segments: the anterior, middle, and posterior mediastinum. The ITMIG classification opts for a three-compartment model for defining mediastinal compartments due to its simplicity and anatomical accuracy, despite potential limitations in adequately separating entities occurring in different locations. The four-compartment model, while offering similarity to existing models and potential effectiveness in distinguishing disease entities, suffers from complexity and non-anatomic boundaries. Concerns were raised about the artificial division between superior and inferior compartments, which may allow the spread of infectious, inflammatory processes, and tumors without restriction by fascial planes, and the lack of adherence by posterior neurogenic tumors to this division. Thus, experts' preference for the three-compartment model, citing reasons such as optimal distinction of diseases, familiarity, anatomical accuracy, and ease of use, led to its selection as the basis for the proposed CT-based classification scheme by ITMIG (3).

As conventionally recognized, the upper mediastinum harbors thyroid lesions, the middle mediastinum encompasses cystic lesions such as bronchogenic cysts, and the posterior mediastinum is associated with a higher incidence of neurogenic tumors.

This review focuses on TET, the majority of which manifest in the anterior mediastinum. However, tumors that occur in this region are not limited to TET, but range from malignant lymphoma to germ cell tumors. The differential diagnosis of TET, especially in the pre-diagnostic phase of imaging, can be aided by a combination of imaging and blood tests including tumor markers.

The aim of this review is to present comprehensive information on the imaging diagnosis of TET, the most frequent solid tumors arising in the anterior mediastinum, as well as other rare tumors of the anterior mediastinum among others.

Diagnostic approach of TETs

Tumors arising in the thymus are of various histological types, but three types of TET are the most frequent: thymomas, thymic carcinomas, and thymic neuroendocrine tumors (NETs) (6). Regardless of these subtypes, the initial step in the diagnostic process involves distinguishing between solid and cystic lesions. This is crucial as anterior mediastinal masses, including TET, often require differentiation from conditions such as pericardial cysts and thymic cysts, which are common cystic lesions in the anterior mediastinum. Contrast-enhanced CT proves invaluable in this context, with a post-contrast enhancement of generally 20 Hounsfield units (HU) or more indicative of a solid lesion. Conversely, 10–15 HU change in attenuation can be due to various non-specific factors, such as incorrect placement of the region of interest, patient motion, or beam hardening from adjacent enhancing structures (7). There may be high rate of unnecessary thymectomy due to misinterpretation of thymic cysts, thymic hyperplasia, and lymphoma as thymoma on chest CT. A recent study showed that differentiating features between thymoma, lymphoma, thymic hyperplasia, and thymic cysts on chest CT which may help triage more patients away from thymectomy toward less invasive and non-invasive means of diagnosis and thereby lower the non-therapeutic thymectomy rate (8). In instances where CT-based differentiation is challenging, T2-weighted images (T2WI), showing marked high signal intensity and high apparent diffusion coefficient (ADC) values, can suggest cystic lesions, whereas the absence of these features increases the likelihood of a solid lesion (9,10).

The subsequent step involves considering and ruling out other solid tumors occurring in the anterior mediastinum. The common differential diagnoses include lymphomas and germ cell tumors. When lymphomas arise in the mediastinum, three prevalent subtypes—Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, and T-lymphoblastic lymphoma—are frequently encountered. Shared characteristics among these lymphomas include a propensity to progress without directly invading or encasing existing blood vessels, while calcification is infrequent (11,12). However, distinctions arise in terms of necrosis; Hodgkin lymphoma exhibits a lower frequency of necrosis, while the other subtypes often present with pronounced necrosis, resulting in heterogeneous internal structures. Additionally, these two lymphomas may lead to complications such as pleural effusion or pericardial effusion (11). In addition, as mentioned earlier, the

common finding in lymphoma is a penetrating image of blood vessels. Lymphomas exhibit less desmoplastic change compared to solid tumors. In cases of lung or thymic epithelia tumors, during the infiltration process, there may be strong compression of blood vessels or direct infiltration leading to occlusion or severe stenosis. However, such imaging changes are less common in lymphomas, serving as a distinguishing feature from solid tumors. Additionally, in lymphomas (especially Hodgkin lymphoma), which develops multicentrically it is not uncommon for vessels to be surrounded. Nevertheless, even in such instances, relatively minimal stenosis is observed, sometimes resembling blood vessels penetrating the tumor interior, which can be considered a characteristic imaging feature of lymphomas. However, since the venous pressure is lower than that of arteries, stenosis or obstruction of superior vena cava (SVC) or innominate vein is rather common especially non-Hodgkin lymphoma (21%) (13). When a patient presents with SVC syndrome, we should be careful not to assume that lymphoma is ruled out only because of the presence of vascular compression. Ultrasound is a non-invasive and cost-effective imaging modality that can potentially be used to diagnose thymic lesions. Although ultrasound has some limitations in evaluating the entire thymus or thymic lesions especially when they are large, the thymus is reported to be visible in ultrasound examination in all age groups from the suprasternal view in children. Thymus or thymic tumors often extend upward to the cervical area or located in the neck (more common in younger patients), thus ultrasound may be a great help to distinguish cystic and solid lesions (14-16), or there might be a chance of early detection of incidental thymic lesions when observed during thyroid sonography.

Germ cell tumors are categorized into seminomas and non-seminomas. Seminomas typically present with relatively homogeneous internal structures and rare calcifications. In contrast, non-seminomatous germ cell tumors often manifest with internal heterogeneity, frequently accompanied by necrosis or hemorrhage, and may show calcifications (17). Notably, choriocarcinomas within non-seminomatous germ cell tumors can produce human chorionic gonadotropin (hCG), leading to gynecomastia in young males (18). Teratomas, characterized by the presence of diverse tissues, may exhibit features such as mixed fat and calcifications (19). It is well known that some cases of teratoma of the anterior mediastinum are detected by chest pain due to cyst wall disruption (20). It has also been reported that the inclusion of pancreatic tissue is associated with the risk of wall disruption (21).

Patient background and blood tests serve as valuable considerations in the differential diagnosis of these anterior mediastinal tumors. TET, including thymomas, often afflict individuals in the fifth and sixth decades of life (patient age range, 6–83 years; median: 58 years overall, but 48 years in the black population), and are exceedingly rare in children (6), while malignant lymphomas and germ cell tumors frequently occur in younger individuals (below 40 years) (22). Blood tests measuring tumor markers such as anti-acetylcholine receptor antibodies, complete blood count, gamma globulin, alpha-fetoprotein (AFP), beta-hCG (β-HCG), lactate dehydrogenase (LDH), and soluble interleukin-2 receptor (sIL-2R) aid in the differentiation (23). Thymomas, for instance, may exhibit positive anti-acetylcholine receptor antibodies, making it desirable to include their measurement as a screening tool for concurrent myasthenia gravis (24). Thymomas are also associated with conditions like pure red cell aplasia and hypogammaglobulinemia (Good syndrome), emphasizing the importance of checking complete blood count and globulin (25). In germ cell tumors, elevated levels of AFP, β-HCG, and LDH are common, while malignant lymphomas often present with elevated LDH and sIL-2R. Additionally, it is crucial not to overlook the possibility of primary lung cancer (or lesions associated with lung cancer), a frequent occurrence in mediastinal masses. Therefore, before categorizing a mediastinal mass as a thymic tumor, it is prudent to consider possibilities such as carcinoembryonic antigen (CEA), cytokeratin fragment (CYFRA), and pro-gastrin-releasing peptide (ProGRP) measurements.

With these considerations in mind, the subsequent sections will elaborate on general aspects and imaging diagnostics of TET, including thymomas, thymic carcinomas, and thymic NETs. In addition to these TET, it is also pertinent to mention thymic cysts (cystic lesions) at the end of this section.

Thymoma

Thymoma, the most common anterior mediastinal tumor, predominantly manifests in middle-aged individuals (range, 55–65 years) and is infrequent in children. Gender predilection is not observed. Often asymptomatic, it is frequently incidentally discovered through imaging studies. Thymoma is associated with various autoimmune disorders, with severe myasthenia gravis occurring in 17–54% of cases as mentioned above (6). The prevalences of myasthenia gravis are also reported to vary by ethnicity, with some

reports ranging from 5.7–82.4% (26).

Tumors are histologically classified into types A, AB, B1, B2, and B3 based on the morphology of tumor epithelial cells and the extent of lymphocyte infiltration. This classification correlates with prognosis, where types A to B3 show an increasing frequency of extracapsular invasion and poorer outcomes. Types A, AB, and B1 are considered low-risk, while B2 and B3 are high-risk. The Masaoka staging system, demonstrating a strong correlation between prognosis and clinical stage, is widely used (27). In contrast to thymic carcinoma, thymoma is often misunderstood as a benign tumor. However, its International Classification of Diseases for Oncology (ICD-O) coding ending in 3 classifies it as a potentially malignant lesion. We should recognize every thymoma has potential for metastasis to diverse sites, including the liver, muscles, ovaries, bones, central nervous system, and kidneys (28-31).

Imaging findings of thymoma include distinctive features depending on the histological type. Low-risk thymomas appear as well-circumscribed, smoothly contoured, circular masses with visible capsules and internal septa. They exhibit homogeneous enhancement, with minimal invasion into surrounding structures (32,33). Conversely, high-risk (B2/B3) thymomas often demonstrate irregular shapes with heterogeneous contrast enhancement. Margins are often lobulated, and may include cystic degeneration, necrosis, and hemorrhage, contributing to a tendency for uneven contrast enhancement. Excluding hemorrhagic or cystic components, ADC, which is commonly calculated using magnetic resonance imaging (MRI) with at least two diffusion-weighted imaging (DWI) with different b values, tends to be lower in high-risk thymomas than in low-risk counterparts (34). Although fluorodeoxyglucose-positron emission tomography-CT (FDG PET-CT) is not routinely used for TET, the maximum standardized uptake values (SUVmax) of high- and low-risk thymomas were significantly lower than those of thymic carcinomas (35). It also reported that B3 thymomas and thymic carcinomas tend to exhibit higher FDG uptake compared to low-risk thymomas (36).

Although distant metastasis and lymph node involvement are infrequent, thymomas often lead to pleural dissemination. Differential diagnosis may be challenging, particularly with thymic hyperplasia. In cases where CT findings seems inconclusive, MRI with chemical shift imaging becomes valuable, especially if fat components are present, suggesting the possibility of hyperplasia (37).

Thymic carcinoma

Thymic carcinoma, constituting 14–22% of TET, demonstrates a lower incidence compared to thymomas. Patients with thymic carcinoma often manifest symptoms related to mediastinal mass lesions, with high frequencies of invasion into surrounding organs, lymph node metastases, and distant metastases, resulting in a poor prognosis. Paraneoplastic syndromes that are commonly present in patients with thymoma are very rare (38). Imaging findings typically show irregular margins, presenting as irregular or lobulated forms, with cystic degeneration, hemorrhage, and necrosis observed inside the tumor. The distinction from thymic carcinoma and high-risk thymomas on imaging can be challenging, but thymic carcinoma tends to exhibit internal heterogeneity and higher rates of infiltration into the surrounding structures, along with increased frequency of distant metastases (32). Specific patterns on imaging, such as low T2 signal intensity in cases of squamous cell carcinoma (39) and evident calcifications in mucinous carcinoma (40), may support the diagnosis of carcinoma. In terms of the association between the volume-dependent parameters in FDG PET/CT and clinical prognosis, the metabolic tumor volume and total lesion glycolysis may be predictive of the postoperative recurrence of thymic carcinoma (41).

Carcinoid/NET of the thymus

NET arising from the thymus, characterized by the dominance or near-total presence of neuroendocrine cells in TET, account for 2–5% of TET. Most occur in adult patients. All thymic neuroendocrine neoplasms (NENs), which includes both NET and neuroendocrine carcinomas, share a propensity for recurrence, lymph node or distant metastasis, and tumor-associated death, with increasing risk from low-grade to high-grade tumors (42). Their radiological appearance is basically indistinguishable from that of thymic carcinomas (43). These tumors, classified into atypical carcinoids and typical carcinoids, often exhibit large, irregularly margined masses without distinct capsules on imaging. The internal signal and contrast effects on T2WI tend to be heterogeneous. The assessment of ADC values can be challenging due to necrosis and cystic degeneration. Atypical carcinoids, which are defined as having higher mitoses than typical carcinoids and/or having foci of necrosis, in particular, frequently display local

invasion and difficulty in differentiation on imaging, but the presence of abundant hemorrhagic components with a mesh-like septum internally may be indicative of this condition. Feeder vessels may also be identified on contrast-enhanced CT (44).

In the diagnostic imaging of NENs, the utility of nuclear medicine examinations utilizing somatostatin receptor (SSTR) expression, such as SSTR-single photon emission CT (SSTR-SPECT) and SSTR-PET, has recently been recognized. SSTRs, primarily SSTR2, have been identified in a subset of NETs and carcinomas. For instance, DOTATATE and DOTATOC are clinically available somatostatin analogues that bind to SSTR2. These agents can be linked to radionuclides like 68-gallium (^{68}Ga) for PET imaging. Reports have indicated that ^{68}Ga-DOTATATE PET scans correlated with SSTR2 expression in TET in most patients and appeared to be useful to identify patients with TET who may be amenable to treatment with somatostatin analogues (45). There are also reports of using SSTR-PET for the assessment of treatment response in TET (46). However, it is important to note that accumulation does not necessarily indicate NENs and may also be observed in squamous cell carcinomas and thymomas (45).

Thymic cysts (cystic lesions)

Thymic cysts occur within or arise from the thymus gland mainly in anterior mediastinum of rarely in other mediastinal compartment. They can be congenital or acquired, and may be associated with thymic tumors, inflammatory processes, or immunodeficiency. They are usually asymptomatic, but may cause cough, dyspnea, or chest pain if large or complicated. Thymic cysts can be diagnosed by their radiological features, such as unilocular or multilocular cystic masses with well-defined walls, lobulated shape, and variable attenuation depending on the presence of hemorrhage or infection. Thymic cysts are different from TET (thymomas, thymic carcinomas, and thymic NETs as above), which are solid neoplasms that may show heterogeneous enhancement, necrosis, invasion, or calcification. However, thymic cysts are often misinterpreted as solid lesions such as thymic epithelial neoplasms only by CT, or sometimes even by MRI because thymic cysts often showed features suggestive of intralesional microbleeding, inflammation, and fibrosis (47). Recent study describes that most thymic cysts changed in volume [31 of 34 cysts (91%)], CT attenuation [15 of 35 cysts (43%)], and T1-weighted MRI signal [12 of 18 cysts (67%)] over more than 5 years of follow-up, although none developed mural irregularity, nodularity, or septations (48). The treatment for thymic cysts depends on the size, location, and association with other diseases. Pure thymic cysts are considered benign and may not require any intervention if they are small and asymptomatic. However, some authors recommend surgical resection to confirm the diagnosis and prevent complications. Video-assisted thoracic surgery (VATS) is a reliable and minimally invasive approach for the surgical resection of thymic cysts.

Cases

Case 1

A female in her forties was incidentally identified with abnormalities during a health check-up, with no elevated tumor markers (AFP, CYFRA, CEA, NSE, SCC, SLX, GRP, and anti-AChR antibody: within normal limit). Chest X-ray revealed a protruding mediastinal mass on the left side with the hilum overlay sign (*Figure 1A*). A plain CT showed calcifications (*Figure 1B*, arrow). A contrast-enhanced CT showed intratumoral septal enhancement (*Figure 1C*, arrow). A low signal septum was seen in the same location on T2-weighted MRI (*Figure 1D*, arrow). FDG-PET/CT revealed intense FDG uptake (*Figure 1E*). Overall, the image findings were suggestive of a high-risk thymoma. The patient underwent anterior mediastinal tumor (thymus) resection, which revealed a partially calcified and hemorrhagic mass. Histologically, it was diagnosed as a B3-type thymoma (60% B3, 40% B2) with invasion into the mediastinal pleura. There was no lymph node metastasis and the staging was pT1b pN0 [Union for International Cancer Control (UICC) 8], Masaoka-Koga: IIb.

Case 2

A male patient in his fifties, without any noteworthy medical history, was diagnosed with numerous liver neoplasms during a regular health check-up abdominal ultrasound. A CT scan with contrast revealed ill-defined low-density lesions in the liver and a nodule in the anterior mediastinum (*Figure 2*). The liver biopsy revealed a diffuse proliferation of small to medium-sized T lymphocytes, implying T-lymphoblastic lymphoma/leukemia with terminal deoxynucleotidyl transferase (TdT) positivity. However, due to the presence of a mediastinal nodule and

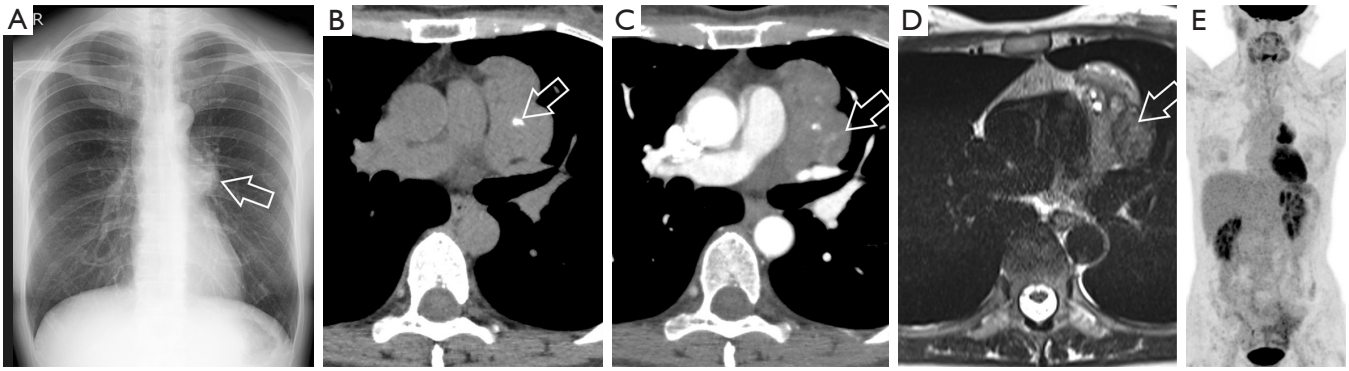

Figure 1 Case 1: a female in her forties was incidentally identified with abnormalities during a health check-up, with no elevated tumor markers. (A) Chest X-ray; (B) plain CT (axial); (C) contrast-enhanced CT (axial); (D) T2WI (axial); (E) FDG-PET (MIP). Chest X-ray revealed a protruding mediastinal mass on the left side with the hilum overlay sign (A, arrow). A plain CT showed calcifications (B, arrow). A contrast-enhanced CT showed intratumoral septal enhancement (C, arrow). A low signal septum was seen in the same location on T2-weighted MRI (D, arrow). FDG-PET/CT revealed intense FDG uptake. CT, computed tomography; T2WI, T2-weighted images; FDG, fluorodeoxyglucose; PET, positron emission tomography; MIP, maximum intensity projection; MRI, magnetic resonance imaging.

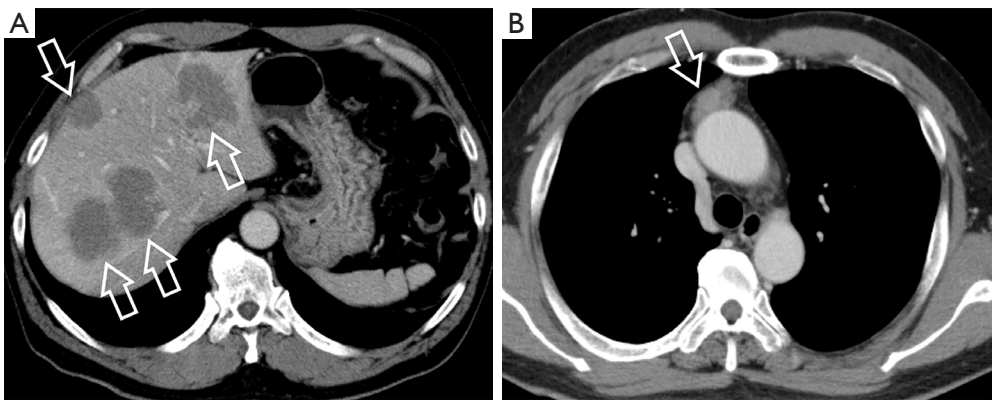

Figure 2 Case 2: a male patient in his fifties, without any noteworthy medical history, was diagnosed with numerous liver neoplasms during a regular health check-up abdominal ultrasound. (A) Contrast-enhanced CT (axial), the liver level; (B) contrast-enhanced CT (axial), the mediastinal level. A CT scan with contrast revealed multiple ill-defined low-density lesions in the liver (A, arrows) and a nodule in the anterior mediastinum (B, arrow). CT, computed tomography.

its slow enlargement, the diagnosis of thymoma was added to the list of differential diagnoses. Additional examination revealed less than 5% of the tumor to be CK5-positive epithelial cells, resulting in a diagnosis of type B1 thymoma that had metastasized to the liver. Chemotherapy was then initiated according to a thymoma protocol. Type B1 thymomas are characterized by a dominance of lymphocytes and may be challenging to differentiate from lymphomas based on histology alone. Importantly, thymomas can metastasize even at low grades [this case was also presented in the reference (31)].

Case 3

A male in his fifties, previously healthy with no significant medical history, presented with an abnormality on chest X-ray during a regular health check-up. Tumor markers such as CYFRA, CEA, NSE, SCC, SLX, GRP, sIL-2R, anti-AChR antibody, were within the normal range. Imaging revealed a well-defined 25 mm nodule in the anterior mediastinum. On plain CT, the lesion appeared hyperdense (*Figure 3A*), and on contrast-enhanced CT, there was enhancement only at the periphery of the lesion (*Figure 3B*).

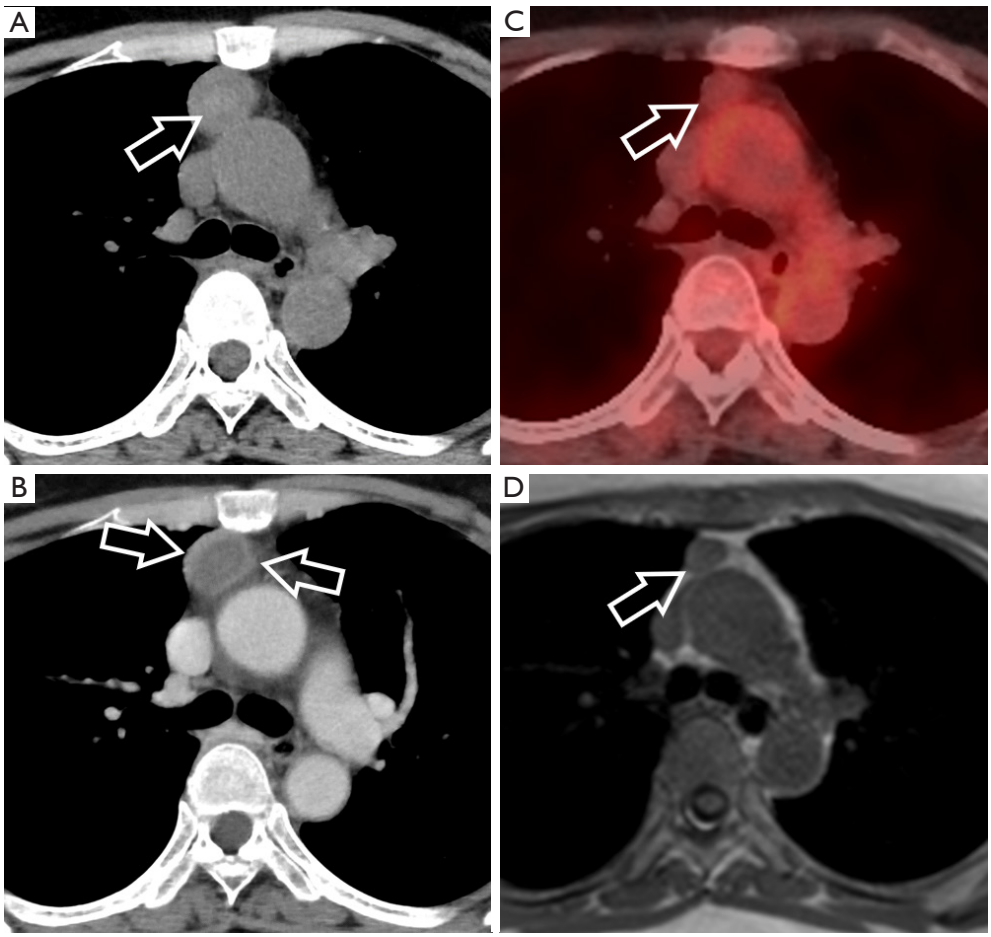

Figure 3 Case 3: a male in his fifties, previously healthy with no significant medical history, presented with an abnormality during a regular health check-up. (A) Plain CT (axial); (B) contrast-enhanced CT (axial); (C) FDG-PET/CT (axial), one and a half month after (A) and (B); (D) T2WI (axial), one and a half month after (A) and (B). The lesion appeared heterogeneously hyperdense in the center before the contrast agent was administered (A, arrow). On contrast-enhanced CT, there was enhancement only at the periphery of the lesion (B, arrows). Imaging performed one and a half months later with MRI and FDG-PET/CT showed a significant spontaneous size reduction from 25 to 15 mm (C,D, arrows). T1-weighted images showed slightly increased signal intensity without fat content. FDG uptake was minimal, but not as low as in cysts. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; T2WI, T2-weighted images; MRI, magnetic resonance imaging.

Imaging performed one and a half months later with MRI and FDG-PET/CT showed a significant spontaneous size reduction from 25 to 15 mm (*Figure 3C,3D*). T1-weighted images (T1WI) showed slightly increased signal intensity without fat content. FDG uptake was minimal, but not as low as in cysts. Together with internal hemorrhaging, these imaging findings led to a suspicion of a shrinking solid nodule, predominantly indicative of a thymoma. A thoracoscopic anterior mediastinal tumor resection was subsequently performed, confirming a thymoma B1 with massive hemorrhage and necrosis. The histopathological results matched the clinical presentation of spontaneous regression, and the lesion was categorized as pT1. This case highlights the significance of not eliminating thymomas from the list of differential diagnoses solely based on initial appearances that may resemble cystic lesions. Even if a lesion appears cystic at first, it is essential to evaluate its internal characteristics through imaging to consider the potential occurrence of a regressing solid nodule, especially concerning thymomas.

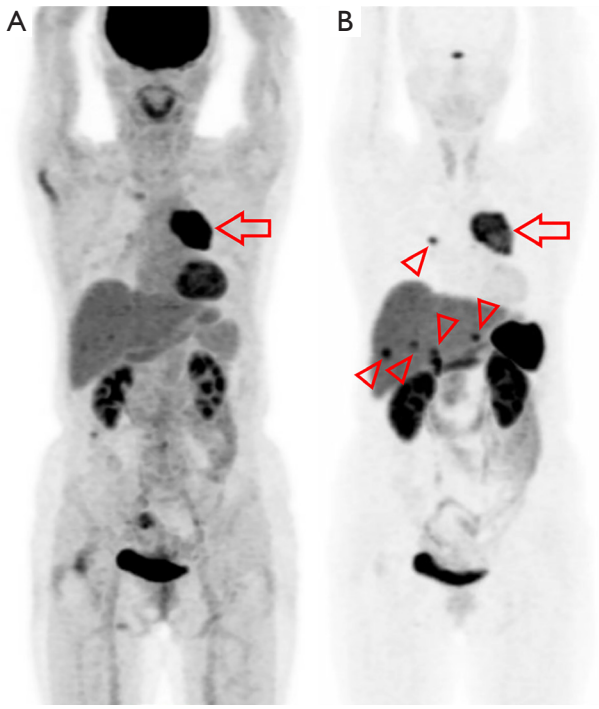

Figure 4 Case 4: a female in her seventies was evaluated by two nuclear medicine examinations. (A) FDG-PET (maximum intensity projection image); (B) ^{68}Ga DOTATOC-PET (maximum intensity projection image). FDG-PET demonstrated intense uptake at the anterior mediastinal mass (A, arrow), albeit without definitive uptake elsewhere. ^{68}Ga-DOTATOC PET revealed intense uptake not only in the anterior mediastinal mass (B, arrow), but also in the right lung hilum and liver, which strongly suggests multiple metastases (B, arrowheads). FDG, fluorodeoxyglucose; PET, positron emission tomography; ^{68}Ga, 68-gallium.

Case 4

A female in her seventies presented with a 6-month history of chest pain radiating from the left neck to the chest. Following evaluation by her primary care physician, a chest X-ray revealed a mass prompting referral to our institution. Given the suspicion of anterior mediastinal tumor, further investigations were pursued. FDG-PET/CT demonstrated intense uptake within the suspected tumor (*Figure 4A*), albeit without definitive uptake elsewhere. Subsequent ^{68}Ga-DOTATOC PET/CT revealed intense uptake in the anterior mediastinal mass, along with multiple clear accumulations in the right hilar region and liver (*Figure 4B*). MRI of the liver confirmed metastases (data not shown). Although lung involvement was suspected, histological confirmation was not performed. Ultrasound-guided biopsy of the anterior mediastinal tumor revealed histopathological features suggestive of squamous epithelial differentiation. Despite initial suspicion of the possibility of primary lung squamous cell carcinoma as well as thymic carcinoma, positivity for CD117, indicative of thymic origin, led to the diagnosis of thymic carcinoma. Neuroendocrine differentiation was absent in hematoxylin and eosin (HE), which was also supported by negative Chromogranin A staining. Given the diagnosis of stage IV thymic carcinoma with multiple hepatic metastases, chemotherapy with ADOC regimen was initiated. However, subsequent emergence of new lesions prompted a shift to best supportive care. In this case, it is evident that the presence of DOTATOC accumulation does not necessarily suggest the possibility of NENs. Particularly in thymic squamous cell carcinoma of thymic origin, where approximately 70% express SSTR2, as reported (45). However, when DOTATOC avidity is observed, lesions can be identified with higher contrast than those revealed by FDG PET, as experienced here.

In addition to the tumors originated from thymus described so far, there are many other neoplastic lesions that require to differentiate from thymoma, which, although less frequent, will be presented in the last section based on case examples.

Case 5

A male in his thirties with no significant medical history was found to have a mediastinal nodule incidentally during a routine health check-up. A contrast-enhanced CT scan showed a well-defined and relatively homogeneous lesion with clear margins (*Figure 5*). Despite his relatively young age, the nodule's location and characteristics caused suspicion of a thymoma. Consequently, the patient underwent a robot-assisted thymectomy.

The histological analysis revealed a significant enlargement of lymphoid follicles with prominent mantle zones and atrophic germinal centers. Hyalinization was observed in vessels within the follicles. Subsequent immunostaining, comprising CD3, CD20, CD21, Ig kappa [in situ hybridization (ISH)], Ig lambda (ISH), and IRTA1, did not provide any indication of lymphoma or other malignancies. Thus, the conclusive diagnosis was Castleman disease, hyaline vascular type (unicentric Castleman disease). There has been no evidence of recurrence during the 3-year postoperative follow-up. Upon retrospective assessment,

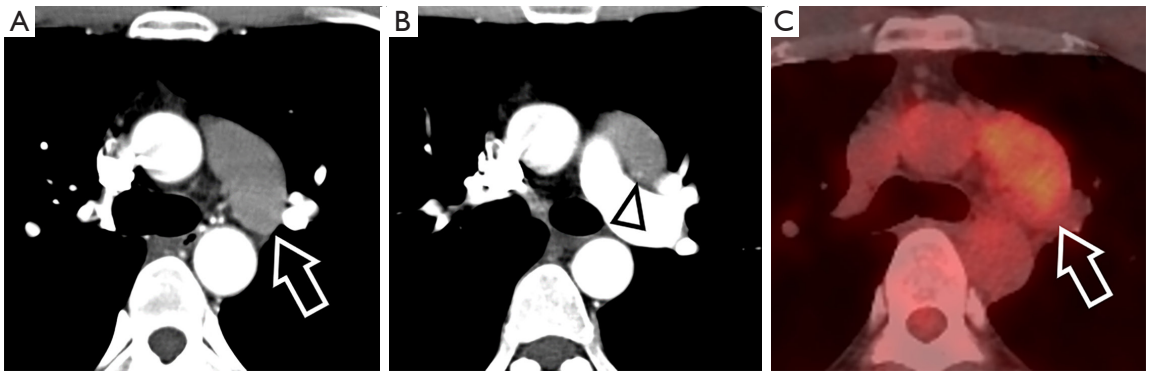

Figure 5 Case 5: a male in his thirties with no significant medical history was found to have a mediastinal nodule incidentally during a routine health check-up. (A,B) Contrast-enhanced CT in the early phase (axial); (C) FDG-PET/CT (axial). Contrast-enhanced imaging showed anterior mediastinal mass lesion (A, arrow) with a relatively prominent feeding vessel at the margins of the mass (B, arrowhead) which was relatively prominent for the size of the lesion. FDG uptake was not intense, but not as low as in cysts (C, arrow). CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

imaging showed a relatively prominent feeding vessel at the margins of the mass, which was relatively prominent for the size of the lesion and may have been a characteristic finding of Castleman disease. Moreover, the patient's young age was atypical for a thymoma.

Castleman disease, a benign lymphoproliferative disorder, deserves consideration. Castleman disease is thought to be a disease that includes several different etiological conditions. It is classified as unicentric or multicentric, and almost all cases of unicentric Castleman disease are of the hyaline vascular type. Hyaline vascular Castleman disease has distinct pathological features and is considered to be a benign clonal neoplasm derived from lymph node stromal cells, possibly follicular dendritic cells (49). As mediastinal pathology, it often presents as a solitary mass (unicentric) or sometimes multiple lesions (multicentric) in the mediastinum, and its distinction from other mediastinal tumors can be challenging. The disease exhibits characteristic features on imaging, such as early enhancement and dilated feeding vessels in the arterial-dominant phase. Approximately 10% of cases may display branching calcifications within the lesion (50). Preoperative diagnosis may still remain difficult as shown in our case, where Castleman disease was initially suspected as thymoma.

Case 6

A female patient in her fifties complained of hoarseness of one month's duration. Subsequent investigations confirmed left vocal cord paralysis and an upper mediastinal lesion. Three years ago, a CT scan did not reveal any abnormalities in the upper area of the chest, yet in the current check-up, a 30 mm mass was detected. The contrast-enhanced CT scan showed a lesion with slight enhancement (from 45 HU on the plain scan to 75 HU on the contrast-enhanced scan, *Figure 6A*). In MRI both T1WI and T2WI showed low signal intensity, and FDG uptake was moderate but relatively weak considering the lesion's size (*Figure 6B-6E*). Due to the suspicion of thymoma or a low-grade lymphoma, a biopsy was performed on the mediastinal lesion. Histologically, the specimen exhibited proliferating spindle-shaped cells with eosinophilic cytoplasm. Positive immunostaining was observed for alpha smooth muscle actin (SMA) and beta-catenin (nuclear, focal), while desmin, S-100, CK AE1/AE3, CD34, STAT6, and ALK were all negative. Based on these results and immunostaining, a histological diagnosis of desmoid-type fibromatosis was established. Retrospectively, opposed-phase T1-weighted imaging demonstrated linear low signal intensity within the lesion, suggesting the presence of fat tissue, and the imaging characteristics might raise the possibility of desmoid-type fibromatosis, although it initially mimicked a thymoma.

Desmoid fibromatosis is a fibroblastic neoplasm that exhibits a locally aggressive, non-metastasizing nature with infiltrative growth and a tendency for local recurrence. It is commonly known as aggressive fibromatosis or desmoid tumor. It predominantly develops in the chest wall, although some cases have been reported in the pleura, lung parenchyma and mediastinum. Clinical manifestations may include pain, dyspnea, and kyphoscoliosis. Additionally,

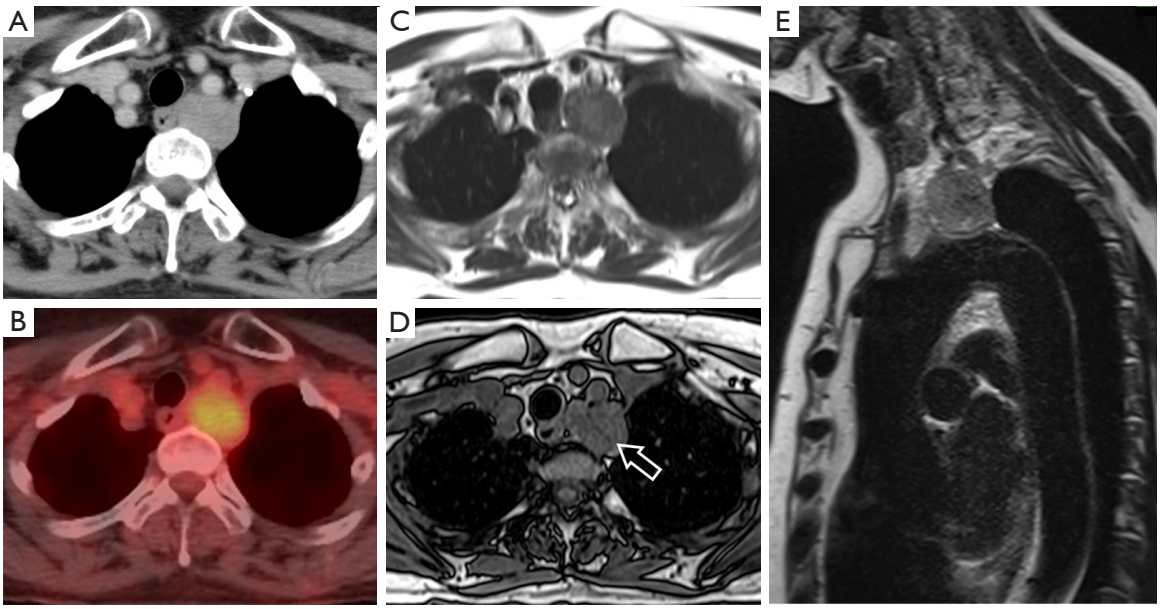

Figure 6 Case 6: a female patient in her fifties complained of hoarseness of 1 month's duration. (A) Contrast-enhanced CT (axial); (B) FDG-PET/CT (axial); (C) T1WI in phase (axial); (D) T1WI opposed phase (axial); (E) T2WI (sagittal). The contrast-enhanced CT scan showed a lesion with slight enhancement (from 45 HU on the plain scan to 75 HU on the contrast-enhanced scan, A). In MRI both T1WI and T2WI showed low signal intensity (C-E), and FDG uptake was moderate but relatively weak considering the lesion's size (B). Note that the opposed-phase T1-weighted imaging demonstrates linear low signal intensity within the lesion (D, arrow), suggesting the presence of fat tissue. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; T1WI, T1-weighted images; T2WI, T2-weighted images; HU, Hounsfield unit; MRI, magnetic resonance imaging.

it may also be detected incidentally or post-trauma/surgery (51-53). On CT, these tumors are usually well-circumscribed but may show ill-defined margins in more aggressive cases. They appear relatively homogenous or focally hyperattenuating on non-contrast scans, with enhancement following contrast administration. MRI is highly sensitive to local extension caused by its high cellularity. Signal characteristics include low intensity on T1WI and T2WI, and post-contrast T1 images may show variable enhancement patterns. The majority of incidences occur during adulthood and equally affect both genders. Genetic factors, such as somatic mutations in CTNNB1, contribute to the etiology, thereby activating the WNT/β-catenin pathway. Macroscopically, the lesion manifests as a poorly circumscribed solid mass exhibiting a whorled or trabecular cut surface. Histologically, long sweeping fascicles of fibroblasts infiltrate the surrounding tissue, expressing SMA, muscle specific actin (MSA), and nuclear β-catenin. Diagnosis through cytology from fine needle aspiration (FNA) may prove challenging. CTNNB1 mutation studies assist in diagnosing cases where morphological characteristics are ambiguous. The prognosis is uncertain, with recurrence rates up to 33%, and margin status inconsistently associated with recurrence risk. Asymptomatic patients may consider a watchful waiting approach (51-53).

Conclusions

Understanding the diagnosis of TETs involves recognizing the classification within the mediastinum, interpreting common imaging findings, and considering differential diagnoses. Here the initial importance of distinguishing between solid and cystic lesions in imaging evaluation has been emphasized. However, differentiation between TETs and other conditions may not always be straightforward based solely on imaging. This review also provides insights into scenarios that may occur in diagnosing TETs and highlights clinically relevant features that enhance imaging diagnosis, illustrated through six case presentations.

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Footnote

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Peer Review File: Available at https://med.amegroups.com/article/view/10.21037/med-23-66/prf

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-23-66/coif). The series "Locally Advanced Thymic Epithelial Tumors" was commissioned by the editorial office without any funding or sponsorship. The author has no other conflicts of interest to declare.

Ethical Statement: The author is 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 ethical committee of Kyoto University Hospital (No. R2996-1) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for the publication of this article and accompanying images.

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Review Article

Surgical outcomes of patients with locally advanced thymic epithelial tumor undergoing induction therapy followed by surgery: a narrative review

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Background and Objective: Thymic epithelial tumors (TETs), including thymomas and thymic cancers, are relatively rare malignancies originating from the thymus. Although complete surgical resection is the cornerstone of treatment for these tumors, the optimal management strategy for locally advanced cases remains uncertain. Neoadjuvant therapies, with their potential to improve the likelihood of complete resection, are promising, particularly in marginally operable cases. However, the current evidence supporting this approach is lacking. This review of the existing literature on the efficacy of induction therapy followed by surgical resection for stage III or IV locally advanced TETs aimed to provide an up-to-date perspective and highlighting directions for future clinical research.

Methods: PubMed was searched using the keywords "surgery," "survival", "thymoma", "thymic cancer", and "induction therapy". Relevant articles including case series, retrospective studies, prospective studies, and review articles were reviewed and selected for this comprehensive narrative review.

Key Content and Findings: This review included primarily revealed retrospective studies and a limited number of prospective phase II trials on induction therapy followed by surgery for stage III or IV locally advanced TETs. No randomized phase III studies were identified, indicating that a comprehensive evaluation of the benefits of induction therapy on overall survival (OS) has not yet been conducted. Induction therapies for both invasive thymoma and thymic cancer included chemotherapy, radiotherapy, and chemoradiotherapy, with anthracycline-based combination chemotherapies being the primary option. For exclusively invasive thymomas, the median rate of complete surgical resection and the 5-year OS rate were reported as 76% and 85%, respectively. Literature focusing on induction therapy for TETs, which includes both thymoma and thymic cancers, indicates that the rates of complete resection and 5-year OS are 76% and 70%, respectively.

Conclusions: Our narrative review of retrospective and prospective studies highlighted promising long-term OS rates in patients with advanced TETs who underwent induction therapy followed by surgical resection. These findings support this multimodal treatment strategy in selected patients with stage III and IV TETs.

Keywords: Thymoma; thymic cancer; survival; induction therapy; surgery

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Introduction

Thymic epithelial tumors (TETs), including thymomas and thymic carcinomas, are relatively rare, with an annual incidence of approximately 3.2 cases per million (1). Although complete surgical resection remains the gold standard treatment for TETs, achieving this is generally easier in the early stages. Based on the Masaoka (-Koga) staging system, invasion into neighboring structures or the presence of diffuse pleural or pericardial disseminations can hinder radical resection in stage III or IV locally advanced TETs. Patients with locally advanced TETs have poorer outcomes than those with early stages, highlighting the clinical need for multimodal approaches (2-5). For patients with marginally resectable TETs, the neoadjuvant approach can decrease the tumor burden to allow for successful resection. In advanced cases deemed inoperable during preoperative evaluations, the preference leans toward induction therapy, as it may increase the resection rate and decreases the incidence of systemic relapse. However, published data of the managing of locally advanced TETs is lacking, indicating that no standardized management guidelines exist. Given the paucity of robust evidence and the small sample sizes in published studies, we aimed to conduct a narrative review to thoroughly characterize the long-term survival outcomes of patients who underwent induction therapy followed by surgical resection for locally advanced TETs. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-57/rc).

Methods

The search strategy is summarized in *Table 1*. Briefly, we searched PubMed without date restrictions up to January 31, 2024. We only considered manuscripts written in English. The search strategy included the terms “surgery”, “survival”, “thymoma”, “thymic cancer”, and “induction therapy”. This strategy allowed for a selection of representative studies emphasizing tumor characteristics, types of induction therapy, adjuvant therapy, surgical outcomes, recurrences, and overall survival (OS) for stage III to IV TETs. As there is no definitive definition for locally advanced TETs, most studies addressing this topic include stage III (macroscopic invasion into neighboring organ) and IVa (pleural and pericardial metastases) TETs, however, treatment strategies involving preoperatively determined induction therapy, followed by surgical resection, have been employed even for stage IVb diseases (lymphogenous or hematogenous metastasis). This prompted us to collect reports on stage III and IV diseases, with the inclusion of invasive thymomas and thymic carcinoma and the exclusion of thymic neuroendocrine tumors. The article types included retrospective studies, prospective studies, and review articles. Articles without full texts or those with incomplete or irrelevant data were excluded.

Literature review method

We identified 37 studies that met our inclusion criteria. *Table 2* enumerates the studies related to thymoma, *Table 3* details studies concerning thymic cancer, and *Table 4* compiles studies addressing both thymoma and thymic cancers. We also referred to a meta-analysis on induction therapy for locally advanced TETs written by Hamaji *et al.* and a systematic review on overall treatment for TETs published by Falkson *et al.* (2,4). To date, no randomized trials have addressed the management of locally advanced TETs.

Patient and disease characteristics

The mean age at TET diagnosis is typically 50–60 years; however, these tumors can be diagnosed in both children and older individuals. A consistent sex bias for thymomas is generally not seen, although a mild female predominance is observed for type A, AB, and B1 subtypes, whereas carcinomas tend to show male predominance (5,43-46). In the 11 retrospective and two prospective studies addressing locally advanced thymoma, patient numbers varied between 7 and 370, as detailed in *Table 2*. For thymic cancer, the seven retrospective studies included patient counts ranging from 7 to 31, as shown in *Table 3*. A total of 14 retrospective and 3 prospective studies encompassing both invasive thymoma and thymic cancer reported patient numbers ranging from 6 to 301, as detailed in *Table 4*. Among the 37 studies, all but two reported an average patient age within the 40s and 50s. Specifically, the age range was 43.5–58 years for thymoma (*Table 2*), 47.3–60.8 years for thymic cancer (*Table 3*), and 41.8–65.2 years for studies including both thymoma and thymic cancer (*Table 4*). In the studies focusing on patients with thymoma, four studies targeted stage III disease, four studies examined stage IV disease, and the remaining studies included both stage III and IV diseases (*Table 2*). For thymic cancers, all studies encompassed stage III and IV diseases (*Table 3*). Specifically,

Table 1 The search strategy summary

Items	Specification
Date of search	January 30, 2024
Databases and other sources searched	PubMed
Search terms used	"Surgery", "survival", "thymoma", "thymic cancer", and "induction therapy"
Timeframe	Date unrestricted to January 30, 2024
Inclusion and exclusion criteria	Inclusion: English language, case series, retrospective study, prospective study, review article
	Exclusion: case report, no surgical cases
Selection process	Y.S. selected literature, and chose those for inclusion
Any additional considerations, if applicable	References of selected studies were reviewed for inclusion

Table 2 Summary of studies on induction therapy followed by surgery for locally advanced thymomas

Studies	Study period	No. of patients	Sex (female), n	Mean age (years)	Rate of InT (%)	Study type	Stage, n
Leuzzi *et al.* (2016 Italy) (6)	1990–2010	370	195	54	24.9	Retrospective	III
Yamada *et al.* (2015 Japan) (7)	1991–2010	310	140	58	13.5	Retrospective	III
Mineo *et al.* (2010 Italy) (8)	1989–2008	33	13	55.5	100	Retrospective	III
Kunitoh *et al.* (2010 Japan) (9)	1997–2005	23	6	56	100	Prospective (phase II)	III
Rena *et al.* (2012 Italy) (10)	1998–2008	18	8	54.5	100	Retrospective	IVa
Yang *et al.* (2011 Korea) (11)	1994–2009	7	3	49	57	Retrospective	IVa
Nakamura *et al.* (2019 Japan) (12)	2003–2017	19	8	49	100	Retrospective	IV
Huang *et al.* (2007 USA) (13)	1996–2006	18	10	43.5	100	Retrospective	IV
Jalil *et al.* (2023 Jordan) (14)	2015–2021	15	5	46.3	52	Retrospective	III, 3
							IV, 12
Yokoi *et al.* (2007 Japan) (15)	1998–2003	17	8	50.6	82	Retrospective	III, 4
							IVa, 9
							IVb, 4
Lucchi *et al.* (2006 Italy) (16)	1989–2004	30	17	53.7	100	Retrospective	III, 20
							IVa, 10
Kim *et al.* (2004 USA) (17)	1990–2000	22	13	47	100	Prospective (phase II)	III, 11
							IVa, 10
							IVb, 1
Bretti *et al.* (2004 Italy) (18)	1989–2000	63	26	51	52	Retrospective	III, 43
							IVa, 20

InT, induction therapy; Stage, Clinical Masaoka (-Koga) stage.

Table 3 Summary of studies on induction therapy followed by surgery for locally advanced thymic cancers

Studies	Study period	No. of patients	Sex (female), n	Mean age (years)	Rate of InT or PrT (%)	Study type	Stage, n
Shintani *et al.* (2015 Japan) (19)	1998–2014	16	5	52	100	Retrospective	III, 11
							IVb, 5
Kawasaki *et al.* (2014 Japan) (20)	2001–2010	7	1	47.3	100	Retrospective	III, 5
							IV, 2
Filosso *et al.* (2014 Italy) (21)	2000–2011	31 (40*)	15*	54.5*	35	Retrospective	III, 24
							IVa, 7
Okereke *et al.* (2012 USA) (22)	1990–2011	9 (16*)	7*	52*	56	Retrospective	III, 8
							IVa, 1
Yano *et al.* (2008 Japan) (23)	1983–2006	28 (30*)	14*	59*	18	Retrospective	III, 13
							IVa, 7
							IVb, 8
Suzuki *et al.* (2005 Japan) (24)	1997–2003	11	7	49	36	Retrospective	III, 4
							IVa, 1
							IVb, 6
Takeda *et al.* (2004 Japan) (25)	1983–2003	13 (15*)	5*	60.8*	31	Retrospective	III, 5
							IVa, 4
							IVb, 4

*, including stage I or II patients. InT, induction therapy; PrT, preceding treatment; Stage, Clinical Masaoka (-Koga) stage.

three studies concentrated on stage III disease, one study was exclusive to stage IV disease, and the remaining studies investigated both stage III and IV diseases (*Table 4*). Stage IV diseases could not be classified based on disease status, such as local invasion or dissemination, due to a lack of information in some studies. However, many studies involved cases of stage IV diseases that were initially considered unresectable. Despite these initial assessments, the primary therapeutic goal remained to achieve complete surgical resection, aiming for long-term survival.

Two prospective phase II studies specifically targeted locally advanced thymoma (*Table 2*). Kunitoh *et al.* demonstrated that a weekly dose-dense chemotherapy regimen with cisplatin, vincristine, doxorubicin, and etoposide, followed by surgical resection, was safely administered to 21 patients with stage III thymomas (9). This approach resulted in an 82% complete surgical resection rate (9). Conversely, Kim *et al.* found that induction chemotherapy using cyclophosphamide, doxorubicin, cisplatin, and prednisone, followed by surgical resection, achieved response rates of 80% and complete resection rates of 76% among 22 patients with stage III or IV thymomas (17). Shintani *et al.* reported the outcomes of a multimodal treatment approach for stage III and IV thymic carcinomas (19). Their study included 13 squamous cell carcinomas, two neuroendocrine carcinomas, and one undifferentiated carcinoma, and all patients underwent neoadjuvant chemotherapy. This study found that incomplete surgical resection and pathological vessel invasion were significant unfavorable factors for OS (19). In contrast, Kawasaki *et al.* administered weekly chemotherapy using a combination of cisplatin, vincristine, doxorubicin, and etoposide (CODE), followed by surgery, in seven cases of thymic cancers (20). These included six squamous cell carcinomas and one adenosquamous cell carcinoma. Notably, 4 of the 7 patients achieved an extended OS, surpassing 100 months after surgical resection (20).

The median percentages for each histologic subtype, based on the World Health Organization classification, were as follows: type A, 5% (range, 2–15%); type AB, 11%

Table 4 Summary of studies on induction therapy followed by surgery for locally advanced thymomas or thymic cancers

Studies	Study period	No. of patients	Sex (female), n	Mean age (years)	Rate of InT (%)	Study type	Diagnosis	Stage, n
Kirzinger *et al.* (2016 Germany) (26)	2005–2010	17	13	65.2	100	Prospective (phase II)	IT, 15	III, 17
							TC, 2	
Cardillo *et al.* (2016 Italy) (27)	1990–2010	108	47	51.5	100	Retrospective	IT, 88	III, 108
							TC, 20	
Marulli *et al.* (2011 Italy) (28)	1980–2009	249	112	50	37.8	Retrospective	IT, 221	III, 249
							TC, 28	
Kaba *et al.* (2018 Tarkey) (29)	2002–2015	39	17	41.8	64	Retrospective	IT, 30	IVa, 39
							TC, 9	
Guan *et al.* (2023 China) (30)	2008–2019	31	16	51.7	100	Retrospective	IT, 16	III, 20
							TC, 15	IVb, 11
Park *et al.* (2019 Korea) (31)	2000–2013	102	43	50	100	Retrospective	IT, 51	III, 38
							TC, 51	IV, 64
Ma *et al.* (2019 Taiwan region) (32)	2005–2013	45	24	59	100	Retrospective	IT, 15	III, 15
							TC, 30	IVa, 13
								IVb, 17
Suh *et al.* (2019 Korea) (33)	2000–2013	18	7	48.3	100	Retrospective	IT, 10	III, 13
							TC, 8	IVa, 3
								IVb, 2
Wei *et al.* (2016 China) (34)	1994–2012	68	25	44.8	100	Retrospective	IT, 32	III, 55
							TC, 36	IV, 13
Filosso *et al.* (2015 Italy) (35)	1990–2012	301 (797*)	388*	58*	15*	Retrospective	IT, 745*	III, 223
							TC, 52*	IV, 78
Ried *et al.* (2015 Germany) (36)	2010–2014	6	1	46	83	Retrospective	IT, 4	III, 4
							TC, 2	IVa, 2
Korst *et al.* (2014 USA) (37)	2007–2012	15 (21[#])	4	51	100	Prospective (phase II)	IT, 14	III, 12
							TC, 7	IVa, 1
								IVb, 2
Park *et al.* (2013 Korea) (38)	2007–2011	27	11	54	100	Prospective (phase II)	IT, 9	III, 8
							TC, 18	IVa, 17
								IVb, 2
Rea *et al.* (2011 Italy) (39)	1980–2008	75	43	53	51	Retrospective	IT, 68	III, 51
							TC, 7	IVa, 18
								IVb, 6
Wright *et al.* (2008 USA) (40)	1997–2006	10	7	51.4	100	Retrospective	IT, 9	III, 7
							TC, 1	IVa, 3
Lucchi *et al.* (2005 Italy) (41)	1976–2003	56	21	53.3	64.2	Retrospective	IT, 42	III, 40
							TC, 14	IVa, 16
Jacot *et al.* (2005 France) (42)	1995–2001	8	4	53.8	100	Retrospective	IT, 5	III, 3
							TC, 3	IV, 5

*, including stage I or II patients; [#], including stages I to IV patients. InT, induction therapy; Stage, Clinical Masaoka (-Koga) stage; IT, invasive thymoma; TC, thymic cancer.

(2–18%); type B1, 15% (1–30%); type B2, 28% (2–88%); type B3, 22% (5–50%); type B1+2, 9% (6–11%); type B1+3, 9% (6–11%); type B2+3, 11%; and type C, 25% (12–67%). The predominant histologic subtype was type B, and approximately 15% of cases exhibited a type A element. Studies have indicated that approximately 30% of patients with thymoma have myasthenia gravis (MG), and approximately 20% of patients with MG are diagnosed with thymoma (5). In this review, 13 retrospective studies referred to the presence of MG preoperatively, with a median prevalence of 22% (range, 0–46%).

Induction therapy

One of the standard treatment approaches for locally advanced TETs preoperative induction therapy followed by radical resection. Induction therapy is thought to diminish tumor size and surgical complexity, facilitating more comprehensive surgical resections, reducing local recurrence rates, and improving long-term survival in a subset of patients with locally advanced TETs. However, the efficacy of induction therapies, such as chemotherapy, radiotherapy (RT), and chemo-radiotherapy (CRT) remains uncertain. Falkson *et al.* found no significant difference in OS among patient with thymoma who received neoadjuvant therapy compared to those who did not (hazard ratio =1.53, 95% confidence interval: 0.77–3.33, P=0.29) (2). Very few studies have been conducted on induction therapy for thymic carcinomas and none have demonstrated significant differences in survival between patients who received neoadjuvant therapy and those who did not. Questions persist regarding the combination of modalities that is most effective and whether postoperative therapy is necessary for patients who have undergone induction treatment.

Table 5 presents the types, detailed regimens, and response rates of induction therapy followed by surgical resection for patients with invasive thymoma. Of the 13 studies analyzed, 9 (69%) used chemotherapy as an induction option; 2 (15%) employed either chemotherapy, RT, or CRT, 1 (8%) opted for chemotherapy or CRT, and 1 (8%) used chemotherapy or RT. The 13 studies featured a total of 9 types of chemotherapeutic regimens: CAP (cyclophosphamide + doxorubicin + cisplatin), CAMP (cisplatin + doxorubicin + methylprednisolone), ADOC (cyclophosphamide + doxorubicin + cisplatin + vincristine), PE (cisplatin + etoposide), CP (cisplatin + docetaxel), CAV, cyclophosphamide + doxorubicin + vincristine, VIP (cisplatin + vincristine + ifosfamide), CODE (doxorubicin + cisplatin + vincristine + etoposide), and CAP + prednisolone. Generally, chemotherapeutic regimens that include adriamycin and/or platinum-based multi-agent combinations are recommended unless patients are ineligible for anthracycline. In terms of therapeutic response, induction chemotherapy had a complete response (CR) of 0–14%, a partial response (PR) of 4–86%, and an overall response rate of 4–93%. Falkson *et al.* reported that anemia (39%) and leukopenia (30%) were the predominant chemotherapeutic side effects in patients with stage III or IV thymomas who received induction chemotherapy prior to surgery (2).

For the studies focusing on thymic cancer, the types, regimens, and response rates of induction therapy are shown in *Table 6*. Of the four studies, all used chemotherapy as induction treatment. The observed response rates only in two studies were CR of 0% and PR of 71% and 75%, respectively. Regimens used for thymic cancer included CP, TP (paclitaxel + carboplatin), CODE, PE, and ADOC. Furthermore, adverse events exceeding grade 3 included neutropenia (10–61%), leukopenia (7–57%), diarrhea (11%), alopecia (4%), and anemia (8%).

Among the 16 studies involving both thymoma and thymic cancer, chemotherapy was the induction treatment in 11 studies (69%), while CRT was utilized in three studies (19%), shown in *Table 7*. One study (6%) allowed a choice between chemotherapy, RT, or CRT, and another study provided an option between chemotherapy or CRT. Regimens used in the studies included CAP, CP, TP, ADOC, CAP, PE, octreotide + prednisolone, and CEE (cisplatin + epirubicin + etoposide). Guan *et al.* compared concurrent and sequential CRT for the induction treatment of stage III or IV TETs (30). Their findings indicated no statistically significant differences in the response rate, radical surgical resection rate, or survival between the two treatments; however, sequential CRT was associated with a lower likelihood of adverse events. Across the studies, the observed adverse events from induction chemotherapy included neutropenia (27–71%) and vomiting (5–72%), with variations based on the specific regimens. In a phase II study conducted by Korst *et al.*, induction CRT (PE and concurrent 45 Gy radiation) was administered to patients with stage III or IV TETs and 21 of 22 patients successfully completed the induction regimen (37).

Surgery and complication

Complete surgical resection is a critical determinant of

Table 5 Summary of studies on the effect of induction therapy and surgical outcomes in locally advanced thymomas

Studies	Type of InT	Regimens	Response (%)	Combined resection	Complete resection (%)	OS (%)	The incidence of recurrence (%)
Abdel Jalil *et al.* (2023 Jordan) (14)	CT	CAP	CR, 0; PR, 4	NI	78	115 M (mean)	22
Nakamura *et al.* (2019 Japan) (12)	CT	CAMP	CR, 0; PR, 79	NI	100	76.7 (5Y) 76.7 (10Y)	78 (7 of 9 RPD group)
Leuzzi *et al.* (2016 Italy) (6)	CT/RT/CRT	ADOC/CAP/ others	NI	NI	65	Tri, 86.3 (5Y) 84.9 (10Y)	17.5 (total)
Yamada *et al.* (2015 Japan) (7)	CT/RT/CRT	NI	CR, 2; PR, 37	Lu, PC, CW, V, Ph	80	80.2 (10Y)	27.5
Rena *et al.* (2012 Italy) (10)	CT	ADOC/PE	CR, 6; PR, 61	Lu, PC, Dia, V, Ph	67	85 (5Y) 53 (10Y)	56
Yang *et al.* (2011 Korea) (11)	CT	CP/CAV/VIP	NI	EPP	75	26 M (median)	25
Kunitoh *et al.* (2010 Japan) (9)	CT	CODE	NI	NI	82	91 (5Y)	61.9 (PT, PC, PL)
Mineo *et al.* (2010 Italy) (8)	CT	PE	Good, 37	Lu, PC, Dia, V	51	NI	NI
Yokoi *et al.* (2007 Japan) (15)	CT	CAMP	CR, 7; PR, 86	NI	22	80.7 (5Y) 80.7 (10Y)	100
Huang *et al.* (2007 USA) (13)	CT/CRT	CP/CAP/VIP/PE	CR, 0; PR, 67	Lu, PC, V, CW, Dia	67	78 (5Y) 65 (10Y)	NI
Lucchi *et al.* (2006 Italy) (16)	CT	CAP	CR, 7; PR, 67	NI	77	82.4 (10Y)	NI
Kim *et al.* (2004 USA) (17)	CT	CAP + prednisolone	CR, 14; PR, 64	NI	76	95 (5Y) 79 (7Y)	NI
Bretti *et al.* (2004 Italy) (18)	CT/RT	ADOC/PE	CR, 8; PR, 64	NI	67	Stage III, 142.1 M (median) Stage IVa, 45.9 M (median)	NI

InT, induction therapy; CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy; CAP, cyclophosphamide + doxorubicin + cisplatin; CAMP, cisplatin + doxorubicin + methylprednisolone; ADOC, cyclophosphamide + doxorubicin + cisplatin + vincristine; NI, no information; PE, cisplatin + etoposide; CP, cisplatin + docetaxel; CAV, cyclophosphamide + doxorubicin + vincristine; VIP, cisplatin + vincristine + ifosfamide; CODE, doxorubicin + cisplatin + vincristine + etoposide; CR, complete response; PR, partial response; Lu, lung; PC, pericardia; CW, chest wall; V, vessels; Ph, phrenic nerve; Dia, diaphragm; EPP, extrapleural pneumonectomy; OS, overall survival; M, months; Y, years; Tri, Tri-modality therapies; RPD, resection of pleural dissemination; PT, primary tumor; PL, pleura.

survival for patients with TETs, regardless of the disease stage or histological type. Even for those presenting with locally advanced, initially deemed unresectable TETs, achieving complete surgical resection is the foremost therapeutic objective to secure long-term survival. Surgical outcomes, such as the extent of resection and the rate of complete surgical resection for studies specifically addressing thymoma, are detailed in *Table 5*. Among the five studies, after excluding those lacking detailed information on concomitantly resected organs, the lungs, blood vessels

Table 6 Summary of studies on the effect of induction therapy and surgical outcomes in locally advanced thymic cancers

Studies	Type of InT	Regimens	Response (%)	Combined resection	Complete resection (%)	OS (%)	The incidence of recurrence (%)
Shintani *et al.* (2015 Japan) (19)	CT	CP/TP/CODE/PE/ADOC	NI	Lu, V, Ph	69	71 (5Y)	NI
Kawasaki *et al.* (2014 Japan) (20)	CT	CODE	CR, 0; PR, 71	Lu, PC, V	86	83 M (median)	42.8 (PL, LV, B)
Filosso *et al.* (2014 Italy) (21)	CT	NI	NI	NI	82	NI	NI
Suzuki *et al.* (2005 Japan) (24)	CT	ADOC/PE	CR, 0; PR, 75	V	75	NI	NI

InT, induction therapy; CT, chemotherapy; CP, cisplatin + docetaxel; TP, paclitaxel + carboplatin; CODE, doxorubicin + cisplatin + vincristine + etoposide; PE, cisplatin + etoposide; ADOC, cyclophosphamide + doxorubicin + cisplatin + vincristine; NI, no information; CR, complete response; PR, partial response; Lu, lung; V, vessels; Ph, phrenic nerve; PC, pericardia; OS, overall survival; Y, years; M, months; PL, pleura; LV, liver; B, bone.

(specifically the innominate vein, superior vena cava, and aorta), and pericardium were the organs most frequently resected alongside the thymus, with each being involved in four studies. Other structures commonly resected included the diaphragm in three studies, phrenic nerve in two studies, and chest wall in two studies. The median rate of complete surgical resection was 76% (range, 22–100%). The phrenic nerve is an organ commonly invaded by locally advanced TETs. However, Aprile has reported techniques for sparing the phrenic nerve in the context of locally advanced TETs. These techniques can be applied even in cases undergoing induction therapy, particularly for patients with severe comorbidities or poor performance status (47).

Table 6 details the surgical outcomes, such as the extent of resection and the rate of complete surgical resection, for studies focused on thymic cancer. Among the three studies, after excluding one study that lacked detailed information on concomitantly resected organs, blood vessels were the most frequently resected organ, involved in all the remaining studies. The median rate of complete surgical resection was 79% (range, 69–86%).

Table 7 provides an overview of surgical outcomes, including the extent of resection and the rate of complete surgical resection, across studies that encompass both thymoma and thymic cancer. Among the eight studies, excluding those without detailed information on concomitantly resected organs, the lungs and blood vessels emerged as the most frequently resected organs, each being involved in all the analyzed studies. The pericardium was another structure commonly resected, being involved in seven of the studies. The median rate of complete surgical resection was 76% (range, 52–82%). Korst *et al.* detailed the extent of resection, indicating that the lungs, vessels, pericardium, and phrenic nerve were resected in addition to the thymus (37).

Postoperative complications were noted in 20 studies. Only three studies reported postoperative 30-day mortality rates (1.0–9.5%). The median rate of postoperative complications was 26% (range, 19–42%). These adverse events included pneumonitis, bleeding, cardiac failure, atrial fibrillation, sternal dehiscence, pulmonary embolism, pleural effusion, pulmonary infarction, and cardiac arrest. Mineo *et al.* highlighted that, within the same timeframe, postoperative morbidity rates following resection after neoadjuvant therapy were significantly elevated compared with surgery performed on thymomas without preceding neoadjuvant chemotherapy (8).

Adjuvant therapy

In their systematic review, Falkson *et al.* highlighted the relative benefits of postoperative radiation therapy (PORT) in patients with thymomas (2). PORT demonstrated favorable results for OS and disease-free survival compared with the absence of PORT. Furthermore, patients with thymic carcinomas exhibited prolonged survival after PORT compared with those who did not receive it. Although these findings do not conclusively establish the superiority of PORT for locally advanced TETs due to the low certainty of the data, the overall results are promising. In contrast, few studies have compared the outcomes of adjuvant chemotherapy and the absence of such therapy, and their review by Falkson *et al.* found no statistically significant differences in the OS between these two groups (2). However, for patients with thymic carcinomas, there was a slight trend toward improved OS with adjuvant chemotherapy, albeit with very low certainty.

Among the 12 studies focusing on thymoma, seven provided data on adjuvant therapy, with a median 71%

Table 7 Summary of studies on the effect of induction therapy and surgical outcomes in locally advanced thymomas or thymic cancers

Studies	Type of InT	Regimens	Response (%)	Combined resection	Complete resection (%)	OS (%)	The incidence of recurrence (%)
Guan *et al.* (2023 China) (30)	CRT	CAP/CP/TP + RT (36–40 Gy)	CR, 19; PR, 52	PC, Lu, V, Ph	74	58.1 (5Y) 50.9 (10Y)	NI
Park *et al.* (2019 Korea) (31)	CT	ADOC/CAP/CP/ others	CR, 3; PR, 58	Lu, Dia, V, Ph	64	77.4 (5Y)	NI
Ma *et al.* (2019 Taiwan region) (32)	CT	NI	NI	NI	NI	IT 83.3 (5Y) TC 76.2 (10Y)	NI
Suh *et al.* (2019 Korea) (33)	CT/CRT	ADOC/CAP + RT	CR, 0; PR, 72	Lu, PC, Dia, V, Ph	72	69.1 (5Y)	NI
Kaba *et al.* (2018 Tarkey) (29)	CT	NI	NI	NI	NI	93 (5Y) 56 (10Y)	NI
Wei *et al.* (2016 China) (34)	CT/RT/CRT	CAP/PE/others +RT	NI	NI	76	49.7 (5Y) 19.9 (10Y)	44.9 (5Y)
Kirzinger *et al.* (2016 Germany) (26)	CT	Octreotide + prednisolone	ORR, 88	NI	52	NI	NI
Cardillo *et al.* (2016 Italy) (27)	CT	ADOC/CEE/CAP	NI	Lu, PC, CW, V, Ph	81	71 M (median)	35.2
Ried *et al.* (2015 Germany) (36)	CT	Octreotide + prednisolone/CAP	NI	V, PC, Lu, CW	67	14 M (median)	33
Korst *et al.* (2014 USA) (37)	CRT	PE + RT (45 Gy)	CR, 0; PR, 48	PC, Lu, Ph, V, others	77	71 (5Y)	10.5
Park *et al.* (2013 Korea) (38)	CT	CP	CR, 0; PR, 63	NI	79	79.4 (4Y)	NI
Marulli *et al.* (2011 Italy) (28)	CT	ADOC/CAP/CEE	CR, 6; PR, 63	Lu, PC, V, Ph	82	50 (10Y)	21.2 (R0)
Rea *et al.* (2011 Italy) (39)	CT	ADOC	Response (>50%) 66	NI	NI	52 (10Y)	NI
Wright *et al.* (2008 USA) (40)	CRT	PE + RT (33–49 Gy)	CR, 0; PR, 40	Lu, PC, V, Ph	80	69 (5Y)	30
Lucchi *et al.* (2005 Italy) (41)	CT	CEE	MOR, 67	NI	77.8	83 M (median, in both InT and non-InT)	NI
Jacot *et al.* (2005 France) (42)	CT	CAP	CR, 0; PR, 75	NI	38	34 M (median)	NI

InT, induction therapy; CRT, chemoradiotherapy; CT, chemotherapy; RT, radiotherapy; CAP, cyclophosphamide + doxorubicin + cisplatin; CP, cisplatin + docetaxel; TP, paclitaxel + carboplatin; ADOC, cyclophosphamide + doxorubicin + cisplatin + vincristine; NI, no information; PE, cisplatin + etoposide; CEE, cisplatin + epirubicin + etoposide; CR, complete response; PR, partial response; ORR, overall response rate; MOR, major objective response; PC, pericardia; Lu, lung; V, vessels; Ph, phrenic nerve; Dia, diaphragm; CW, chest wall; OS, overall survival; Y, years; IT, invasive thymoma; TC, thymic cancer; M, months.

of patients (range, 22–100%) receiving it. The adjuvant therapies utilized were diverse: two studies offered chemotherapy, RT, or CRT; two used chemotherapy or RT; one opted for CRT or chemotherapy; one exclusively used RT; and one study lacked detailed information. Yokoi *et al.* found that out of 14 patients who received induction chemotherapy (cisplatin, doxorubicin, and prednisolone), nine proceeded to surgical resection. Of these, only two achieved R0 resection, while the others had incomplete resections (15). PORT was administered to eight patients, including seven with incomplete resections. Notably, two of these patients with incomplete resections achieved long-term survival, lasting 72 and 180 months post-surgery (15).

Out of 17 studies addressing both thymoma and thymic cancer, nine offered data on adjuvant therapy, with a median of 66% of patients (range, 25–89%) undergoing treatment. The types of adjuvant therapy varied: two studies included chemotherapy, RT, or CRT; two employed chemotherapy or RT; two chose CRT or chemotherapy; and three studies did not specify the details. Filosso *et al.* noted that 62% of surgically treated patients received adjuvant therapy, which was linked to improved survival in multivariate analysis (35). However, the majority of the studies did not confirm adjuvant therapy's prognostic value for locally advanced TETs, leaving its overall impact still under discussion.

OS and recurrence

The 5-year, 10-year, and median OS rates, calculated from the initiation of induction therapy or at the time of surgery, were analyzed across various studies. For thymoma, OS outcomes were reported in 12 out of 13 studies, as summarized in *Table 5*. The median 5-year OS was 85% (range, 78–95%), and the 10-year OS was 76.7% (range, 53–84.9%). In the case of thymic cancer, OS results were provided by only two studies, detailed in *Table 6*. Shintani *et al.* reported a 5-year OS of 71% following induction chemotherapy and surgery for thymic cancers, while Kawasaki *et al.* observed a median OS of 83 months (19,20). Among 16 studies addressing both thymomas and thymic cancers to evaluate OS, the median 5-year OS was 70% (range, 49.7–93%), and the 10-year OS was 51% (range, 19.9–76.2%).

Throughout the postoperative follow-up period in various studies, the median recurrence rate was observed to be 30%, with a range from 17.5% to 100%. It is important to note that follow-up durations varied among these studies. In a phase II study by Kunitoh *et al.*, focusing on CODE therapy followed by surgery for stage III thymoma, a relapse rate of 61.9% was reported (9). The initial signs of recurrence in these patients were typically regrowth of the primary tumor or pleural or pericardial dissemination. Kawasaki *et al.* reported relapse sites in 3 out of 7 patients experiencing recurrence, identifying the pleura as the most common relapse site, followed by the liver and bones (20). Marulli *et al.* observed that among 203 patients who achieved R0 resection, 43 (21.2%) experienced recurrence, with a median time to relapse of 46 months (28). Intrathoracic relapse was seen in 13.3% of cases, while extrathoracic relapse occurred in 6.4%. Both intra- and extrathoracic relapses were noted in 1.5% of cases. Significantly, the recurrence rate was markedly higher in patients with histologic types B2-3 thymoma and thymic carcinoma compared to types A, AB, and B1 thymomas (28).

Strengths and limitations

The strengths of this narrative review lie in its approach of separately collating reports from retrospective and prospective studies. The prospective studies provided consistent sample sizes, induction treatment modalities, and regimens, enabling a detailed evaluation of therapeutic outcomes. These assessments shed light on the advantages and disadvantages of multimodal therapies for locally advanced TETs. However, enrolling patients proved challenging, resulting in smaller sizes than the retrospective studies. In contrast, the retrospective studies were much more abundant than the prospective ones, although they displayed higher variability in patient characteristics and induction treatments, such as RT, CRT, or chemotherapy. Nevertheless, upon consolidation of the data from both study types, factors such as curative resection rates, adverse events, postoperative complications, and prognosis were found to be comparable. This suggests that the strategy of induction treatment followed by surgical resection for locally advanced TETs with curative intent can be justified to a certain degree. This review emphasized the histological classification of thymoma and thymic cancer during data collection, given the relatively distinct biological nature of these two neoplasms. We analyzed studies that included both histological types and those that focused on one specific histology. Our findings suggested that multimodal strategies are feasible for both type of TETs from both prognostic and safety perspectives.

This narrative review faces multiple limitations. The

inherent rarity of TETs leads to small sample sizes in the reviewed studies, which, along with the extensive time span these studies cover, contributes to the heterogeneity of their populations. Additionally, the positive outcomes observed post-surgery in patients with stage III–IV advanced diseases may be influenced by selection bias. Secondly, the absence of prospective randomized studies leaves the benefit of adding surgical resection for curative intent, as opposed to multimodal treatment without surgery, an open question. Conducting phase III studies is notably challenging given the infrequency of this condition. Finally, the inability to distinguish between stage IV tumors that are locally invaded and those with pleural nodules, due to the limited information available even after reviewing a large corpus of literature, remains a significant constraint. It is our hope that future reviews will differentiate these two statuses, thereby shedding light on the clinical significance of induction treatment for locally advanced TETs.

Conclusions

This narrative review underscored the potential for encouraging curative surgical rates and long-term OS in patients with locally advanced TETs who received induction therapy followed by surgical resection. These results, drawn from both retrospective and prospective studies, support the consideration of an induction regimen before surgical resection in selected patients with stage III and IV TETs. Henceforth, joint efforts are essential for obtaining more extensive data from prospective studies on this topic.

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Review Article

Re-evaluation and operative indications after induction therapy for thymic epithelial tumors

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Abstract: Thymic epithelial tumors (TETs), encompassing thymoma and thymic carcinoma, represent a rare and heterogeneous group of thoracic malignancies with varying prognoses and treatment strategies. Surgical resection is the cornerstone of therapy for localized stages, but the management of locally advanced or unresectable TETs often involves induction therapy, including chemotherapy and/or radiation therapy, as a neoadjuvant approach aimed at downstaging the tumor to facilitate subsequent resection. This review synthesizes current knowledge on the re-evaluation process and operative indications following induction therapy for TETs, highlighting the pivotal role of accurate assessment in guiding surgical decisions and optimizing patient outcomes. Induction therapy's efficacy is contingent upon precise re-evaluation methods to accurately gauge treatment response and assess resectability post-therapy. This review discusses the various modalities employed in re-evaluation, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography-CT (PET-CT), and the significance of tumor markers, underlining their strengths and limitations. The adoption of modified RECIST criteria for TETs by the International Thymic Malignancy Interest Group (ITMIG) underscores the necessity for standardized assessment guidelines to ensure consistency and reliability across studies and clinical practices. Furthermore, we explore the implications of induction therapy on surgical decision-making, emphasizing the criteria for determining the suitability of patients for surgical intervention post-therapy. The review addresses the challenges and future perspectives associated with the re-evaluation process, including the potential for advanced imaging techniques and the integration of molecular and genetic markers to enhance the precision of treatment response assessment. In conclusion, the re-evaluation of TETs post-induction therapy is a complex but critical component of the multidisciplinary management approach for these patients. Standardizing re-evaluation methodologies and incorporating novel diagnostic tools could significantly improve the prognostication and treatment stratification, ultimately enhancing the therapeutic outcomes for patients with advanced TETs.

Keywords: Thymic epithelial tumors (TETs); re-evaluation; re-staging; induction therapy

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Introduction

Thymic epithelial tumors (TETs), including thymoma and thymic carcinoma, are rare, with an incidence rate of approximately 1.3–3.2 cases per million (1). Surgical resection is the primary treatment approach for stage I–III TETs; however, complete resection can be challenging in cases of locally advanced TETs. In such cases, preoperative induction therapies have been explored to achieve complete resection. Various chemotherapeutic regimens have been utilized, including adriamycin and/or platinum-based multiagent combinations (2). If remarkable tumor shrinkage occurs, extensive surgery should be offered, and postoperative radiotherapy might be considered. Conversely, in patients with unresectable tumor after systemic induction treatment, concomitant chemoradiotherapy may be considered (3,4). The latest National Comprehensive Cancer Network guidelines recommend induction chemotherapy for patients with potentially resectable locally advanced TETs (5). A significant clinical challenge lies in assessing potential resectability at two critical time points: before induction therapy (or any treatment) and after induction therapy but before surgery. Re-evaluation is important because it is related with the decision for an invasive surgery after burdensome systemic therapy. This review specifically focuses on the re-evaluation process and operative indications following induction therapy for TETs.

While recognizing the distinct oncological and clinical behaviors of thymoma and thymic carcinoma, the limited evidence in this field necessitates a discussion of these issues under the broader category of TETs, including both thymoma and thymic carcinoma. Where possible, we have endeavored to discuss them separately, acknowledging the nuances between the two.

This review focuses on the re-evaluation process and operative indications following induction therapy for TETs.

Re-evaluation methods

Computed tomography (CT) scan

In the re-evaluation of TETs after induction therapy as well as in the primary evaluation (6), CT is the reference standard for radiological evaluation (7). CT is primarily used to evaluate therapeutic effects of induction therapy. Measuring the tumor response to induction therapy is important for both clinical decision-making and in the setting of multi-institutional studies (8). Among various methods, the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 is most commonly used, and the International Thymic Malignancy Interest Group (ITMIG) has suggested using a practical guide for standard outcome measures of TETs (8,9). The RECIST criteria for TETs will be described below.

CT is also performed to assess resectability. Locally advanced TETs extend into the mediastinum and thoracic cavity and can encompass nearby structures (10). Although CT results cannot reveal a tumor cell-free border, it can still provide hints that might support performing complete resection. Particularly in contrast-enhanced CT scans, there is a potential to somewhat delineate the boundaries between the tumor and surrounding structures due to the contrast. According to a prospective study for thymoma conducted by Shen *et al.*, lobulated or irregular tumor shape, unsmooth contour, heterogeneous nature, heterogeneous enhancement pattern, and invasion of adjacent structures were found to be related to incomplete resection in univariable analysis (11). Subsequent multivariable logistic regression showed that only absence of arterial system invasion was a significant factor supportive of complete resection. Similarly, in a study by Hayes *et al.*, the factors related with incomplete resection of thymoma included a lobulated tumor contour, ≥50% abutment of the circumference of an adjacent vessel, thoracic lymphadenopathy, adjacent lung changes, and pleural nodularity (12). Tumor size was larger in the incompletely resected group than in the completely resected group. The multivariable analysis performed by Hayes *et al.* revealed that ≥50% abutment of the circumference of an adjacent vessel and pleural nodularity were independent predictors of incomplete resection. In the case of thymic carcinoma, Hayes *et al.* also found that incomplete resection was associated with tumors contacting >25% of an adjacent mediastinal structure and a tumor size of >7.5 cm (13). Furthermore, other radiographic characteristics associated with advanced stages of TETs consist of tumor sizes of ≥7 cm, a lobulated tumor contour, mediastinal fat infiltration, and an elevated hemidiaphragm (14,15). In recent years, evidence has emerged suggesting that the size of TETs plays a role in patient prognosis with several papers published assessing the impact of tumor size on survival (16). Additionally, the International Association for the Study of Lung Cancer Thymic Epithelial Tumor Staging Project recently proposed the ninth edition of the Tumor-Node-Metastasis (TNM) Classification of Malignant Tumors. This new classification includes the division of the T1 category into T1a (≤5 cm) and T1b (>5 cm) (17). However, there has been a debate regarding

the size threshold for predicting incomplete resection status or advanced stage because some larger thymomas can be noninvasive and fully resected upfront in asymptomatic patients (18). Furthermore, the necessity for phrenic nerve resection is challenging to predict solely based on imaging in the absence of an elevated hemidiaphragm, presenting an ongoing challenge for surgeons (19).

Magnetic resonance imaging (MRI)

MRI can be used in addition to CT for better evaluation of the tumor composition and in patients with suspicious tumor infiltration of adjacent structures (6,20). Particularly, cystic or necrotic parts combined with inhomogeneous contrast-enhancement strongly suggest invasiveness (21,22). However, MRI is incapable of precisely detecting low-level invasiveness. To overcome this problem, MRI with cine sequences may show sliding motions between the tumor and cardiovascular structures and might provide more reliable tumor invasion detection (23).

Positron emission tomography-CT (PET-CT)

Encouraging results showing the prognostic ability of PET-CT after induction therapy have been published, although the reports were from studies with a small number of patients (24). In a study with fourteen patients, Fukumoto *et al.* have documented a noteworthy decline in the standardized uptake value $(SUV)_{max}$ in six patients exhibiting an Ef2 response. Conversely, in 5 out of 8 patients with an Ef0–Ef1 response, there was a decrease in SUV_{max}, although it did not reach statistical significance (25). Korst *et al.* also suggested the effectiveness of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET-CT for tumor response assessment after induction therapy (26). Similarly, Matsumoto *et al.* reported the effectiveness of ^{18}F-FDG PET-CT for assessing the therapeutic efficacy in five patients with increased pathological responses associated with larger decreases in SUV_{max} (27).

Tumor markers

Although there are no specific tumor markers for thymoma, some are practically available for thymic carcinoma. A recent multi-institutional retrospective study on advanced thymic carcinoma has revealed significant insights into these markers. According to the NEJ 023 study (28), serum neuron-specific enolase (NSE) was identified as a potential prognostic tumor marker for advanced thymic carcinoma across various histological subtypes. Additionally, squamous cell carcinoma (SCC) antigen levels have shown promise as prognostic indicators in patients with thymic SCC. In fact, a case report involving a patient with thymic small cell carcinoma who underwent multimodal therapy revealed that NSE levels partly reflected tumor progression and treatment responsiveness (29). Another study highlighted the diagnostic potential of the cytokeratin 19 fragment (CYFRA 21-1) in thymic SCC (30). However, this marker was not found to be associated with overall survival or progression-free survival in a separate study (28). This discrepancy underscores the need for further investigation into the prognostic value of CYFRA 21-1. Therefore, for cases of advanced thymic carcinomas, it can be reasonably inferred that during the re-evaluation phase, measuring tumor markers has the potential to offer valuable insights for evaluating the therapeutic efficacy of initial treatment and making well-informed decisions regarding subsequent interventions.

Pathological examination

In the context of the re-evaluation, the role played by pathological examination may not be extensive. In fact, re-biopsy for TETs is infrequently performed. This procedure is typically considered when induction treatment proves ineffective in achieving the desired outcomes, and tumor regrowth is observed. A possible purpose of re-biopsy is to modify the treatment for the next therapeutic session (31,32).

On the other hand, pathological findings after the primary treatment provide valuable treatment-related information and insights into prognosis. Johnson *et al.* introduced a concept of tumor response grade (TRG), proposed by Mandard *et al.*, into TETs (33,34). Pathological tumor response after induction therapy is graded from 1 to 5 based on necrosis and viable tumor cells (33-35). Johnson *et al.* reported that TRG for TETs appeared reproducible and correlated with the radiologic response of tumor size. Moreover, Wang *et al.* identified TRG as one of the independent prognostic factors, alongside ypTNM, ypMasaoka, and complete resection, through multivariable analysis in a cohort of 81 patients with TETs undergoing induction therapy (35). Of note, clinical downstaging (c > yc) of TNM or Masaoka classifications did not change the pooled hazard ratio for survival in their study. This implies an interesting notion that pathological evaluation with TRG might be more accurate in predicting prognosis than

other radiological evaluations in the re-assessment phase.

Therefore, while re-biopsy might be considered important in cases requiring careful evaluation for surgery after neoadjuvant treatment in TETs, its effectiveness in guiding surgical decisions remains unproven. Similarly to TETs, although biopsy-guided pathological response assessment in cancers such as breast cancer and melanoma has shown promise, it has not been widely adopted in clinical practice due to a lack of conclusive evidence. This underscores the universal challenge in establishing the clinical utility of biopsy-based prognostic evaluations across different types of cancers.

Assessment of treatment response

The timing for the assessment

Surgical resection is typically considered 4 to 8 weeks after induction therapy, assuming patients are deemed to have sufficiently recovered (36,37). If delayed further, the efficacy of the induction therapy may diminish. Therefore, although there are no specific guidelines on the timing for reassessing the initial treatment's effectiveness, some literature suggests a window of 2 to 4 weeks after completing preoperative therapy (36).

Evaluation based on RECIST criteria

To evaluate the change in tumor burden after treatment, the ITMIG suggests using the modified RECIST criteria to perform a standardized assessment of the treatment response of TETs (8). Currently, the most commonly used method is RECIST version 1.1, which is basically a unidimensional tumor measurement. ITMIG recommends RECIST version 1.1 for response assessment, but with certain caveats and modifications (38). First, pretreatment and post-treatment imaging should be interpreted by the same individual. Second, because TETs tend to spread along the pleura, the RECIST version 1.1 criteria may not be ideal. Therefore, ITMIG recommends adhering to the criteria previously established for pleural measurements in mesothelioma, measuring the short axis of the tumor.

According to a meta-analysis, four studies have reported analyses correlating the completeness of resection with responses to induction therapy measured by RECIST criteria. (26,39-42). Collectively, these studies included a total of 105 patients. One study employed induction chemoradiotherapy with a radiation dose of 45 Gy, whereas the remaining studies focused solely on induction chemotherapy. All studies utilized cisplatin-based regimens. The pooled odds ratio assessed in the meta-analysis favored a response to induction therapy predicting complete resection, with a value of 1.4 (95% confidence interval: 0.49 to 4.0; P=0.53). Although the result did not reach statistical significance, the assessment by the RECIST criteria remains an essential tool to evaluate the therapeutic efficacy of induction therapy for TETs.

Re-staging

Theoretically, benefits of induction therapy lie in the downstaging of advanced TETs. However, according to Wang *et al.*'s retrospective study, clinical Masaoka downstaging was only observed in 24.7% of patients, while 46.9% experienced clinical TNM downstaging (35). They also noted that clinical outcomes were similar between patients who underwent clinical downstaging post induction therapy and those who did not. Whether it was the clinical downstaging of Masaoka, TNM, T, N, or M classifications, these factors didn't stand as independent prognostic variables. The authors suggested that assessing clinical re-staging was challenging due to other biases. Therefore, a possibility of underestimating clinical downstaging might be considered.

Evaluation beyond oncological aspects

Induction therapy, such as chemotherapy and radiation, may lead to a decline in the patient's overall health, potentially affecting their physical fitness for surgery. The treatment can also result in the impairment of specific organ functions, such as the heart, liver, kidneys, and lungs, which can impact the patient's ability to undergo surgical procedures. Thus, some patients may become ineligible for the intended surgical procedures after undergoing induction therapy, which raises the challenge of determining alternative treatment options. Therefore, assessing a patient's surgical tolerance after induction therapy is crucial to ensure that they can withstand the rigors of surgery (43).

When there is infiltration into the cardiovascular system, a more meticulous evaluation is required to assess the need for cardiopulmonary bypass and to determine the feasibility of surgical intervention (44). Close collaboration with cardiothoracic surgeons, anesthesiologists, and the cardiopulmonary bypass team is indispensable in such cases. In situations where patients have concomitant neurological

disorders like severe myasthenia gravis, it is necessary to coordinate with the neurology department for an evaluation of the specific condition. Even if no crisis is evident at the time of evaluation, it is imperative to anticipate the possibility of post-operative crises and engage in discussions involving anesthesiologists, neurologists, and intensive care unit physicians (45).

Surgical indication after induction therapy

Complete resection

The primary goal of induction therapy in TETs, as reiterated, is to achieve complete resection by reducing the tumor, inducing pathological changes in the tumor, downstaging, and other alterations, following the primary treatment. This is because achieving a complete resection after induction therapy may represent a significant prognostic factor or indicate a tendency for improved overall survival (39,41,46-48).

The final decision is typically entrusted to the surgeon's judgment regarding the invasiveness of TETs and the possibility of complete resection (19). However, determining the feasibility of complete resection is not a straightforward task. Hence, objective assessments using imaging studies, as mentioned earlier, become crucial. An analysis of the Japanese Association for Research on the Thymus database revealed that in patients with TETs infiltrating major vessels, the rate of complete resection was lower than that in patients with TET infiltration into the pericardium or lungs (49). In fact, resection of small wedge-shaped portions of the lung adjacent to the pericardium essentially does not increase morbidity associated with thymectomy and almost always achieves negative margins in these areas. Contrarily, vascular resections are far more complex and are associated with higher morbidity; therefore, surgeons outside high-volume centers may hesitate to perform such resections (19).

Considering the surgical approach is crucial. To achieve optimal exposure, the standard sternotomy is generally employed, with the addition of more extensive approaches such as the hemiclamshell, clamshell, or even the transmanubrial osteomuscular-sparing approach (50,51). Furthermore, video-assisted procedures can complement open thoracotomy to ensure an adequate surgical view (51). Recent reports have highlighted the successful application of minimally invasive approaches exclusively for the surgery of advanced TETs. Taken together, the choice of surgical approach should be individually tailored based on the tumor's location, degree of infiltration, response to initial treatment, patient-specific factors, and the surgeon's expertise (52,53).

Debulking surgery

Even if achieving complete resection is not feasible, debulking surgery or volume reduction surgery yields certain therapeutic effects. A meta-analysis demonstrated improved overall survival in patients undergoing debulking surgery for unresectable thymoma with radical intent compared to those undergoing surgical biopsy (54). Similarly, in cases of thymic cancer, maximal debulking surgery might be beneficial and warrant evaluation for advanced diseases where complete resection is challenging, as indicated by a nationwide database in Japan (55). Other researchers have suggested that combining debulking surgery with radiation could be a treatment option for unresectable TETs (56,57). Recently, Mastromarino *et al.* presented an intriguing study on unradical surgery for locally-advanced thymoma (58). In their research, patients who underwent incomplete resection followed by adjuvant treatments exhibited similar cancer-specific survival and overall survival rates to those who underwent complete resection in stage III–IVa thymomas. Certainly, the utility of debulking surgery requires further validation through prospective studies or similar research. Nevertheless, in scenarios where complete surgical removal of the tumor is not possible following initial treatments, debulking surgery could be considered as a viable treatment strategy.

Cessation of surgery after induction therapy

In certain cases, due to the morbidity associated with induction therapy and the potential for treatment-related complications or disease progression, secondary resection is not performed. The rate of surgery cessation after induction therapy varies widely, ranging from 4.8% to 38.1% (41,59-61). In these instances, induction therapy might unnecessarily delay or hinder curative resection, potentially allowing disease progression (60). Hence, when there exists a high level of confidence in the potential for achieving complete resection, opting for upfront surgical resection can be considered. Additionally, patients with a compromised performance status or comorbidities that might worsen due to chemotherapy or similar treatments might also be candidates for a surgical approach. As noted in a previous section, debulking surgery yields certain therapeutic effects.

In any case, the indication for induction therapy remains a significant issue to consider. Understanding such high-risk features that may hinder complete resection should help healthcare providers appropriately select patients for induction therapy. Candidate selection for induction therapy should be performed by a multidisciplinary oncology committee that includes oncologists, diagnostic radiologists, surgeons, therapeutic radiologists, and pathologists with experience in managing advanced thymic malignancies (62).

Future perspective in re-evaluation of induction therapy for TETs

Advancements in imaging techniques for accurate re-evaluation

In recent years, the field of radiology has witnessed remarkable advancements in imaging techniques, and their application in the re-evaluation of TETs has been particularly promising. High-resolution CT and PET-CT have become indispensable tools for precise disease evaluation after induction therapy. The integration of artificial intelligence and machine-learning algorithms into image interpretation has further improved the accuracy of identifying resectability of TETs (63-65). The development of more specific radiotracers and functional imaging modalities has offered enhanced sensitivity for detecting small residual lesions and assessing their metabolic activity. These advancements provide a foundation for more informed clinical decision-making, which enables selecting tailored therapeutic strategies based on the extent and characteristics of any remaining disease.

Incorporation of molecular and genetic markers for personalized treatment strategies

Recent advancements in precision medicine can now be applied to TETs (66). The programmed cell death ligand-1 (PD-L1) expression and the tumor mutational burden, biomarkers for response to immunotherapy, are studied well in this field (67). Although promising response rates and survival outcomes have been observed, the application of immunotherapy in TETs is complicated by the occurrence of severe autoimmune-related adverse events, highlighting the need for careful patient selection and management. Further research is essential to identify reliable predictive markers and to optimize the balance between efficacy and toxicity. Moreover, recent research has led to the identification of specific molecular alterations associated with TETs, such as GFT2I, HRAS, NRAS, TP53, c-KIT, EGFR and IGFR (68-70).

Then, the integration of molecular and genetic markers into re-evaluation is a promising approach. The identification of specific genetic alterations and biomarkers associated with TETs can guide tailored therapeutic approaches with the emergence of next-generation sequencing technologies, we can now delve into a tumor's genomic landscape, identifying mutations and alterations that might influence the treatment response. For instance, research into activating mutations in the *KIT* oncogene, found in approximately 5% of thymic carcinomas, has been pursued as a potential therapeutic target. Tyrosine kinase inhibitors such as imatinib and sunitinib, which target these mutations, have shown promising results in certain patients, according to studies (71,72).

Incorporation of these markers into re-evaluation enables assessment of treatment effectiveness and development of personalized treatment strategies. This molecular insight not only aids in the identification of targetable alterations but also offers valuable prognostic information that will help clinicians optimize the management of TETs.

Prospects of targeted therapies in the neoadjuvant setting

Targeted therapies have revolutionized cancer treatment, and their potential application in the neoadjuvant setting for TETs is an exciting new area (66). By understanding the genetic and molecular profiles of a patient's tumor through re-evaluation, clinicians can tailor neoadjuvant therapies to target specific pathways or mutations. Targeted agents, such as tyrosine kinase inhibitors and immune checkpoint inhibitors, hold promise in improving treatment responses and minimizing surgical complications. Early-phase clinical trials investigating the neoadjuvant use of these agents are underway with the aim of assessing their effect on disease downstaging, treatment tolerability, and long-term outcomes. As we gain a deeper understanding of the biological underpinnings of TETs, the integration of targeted therapies in the neoadjuvant context potentially can reshape the landscape of treatment strategies for these rare malignancies.

Discussion

One of the key limitations of this review article is the relatively limited number of published studies and clinical

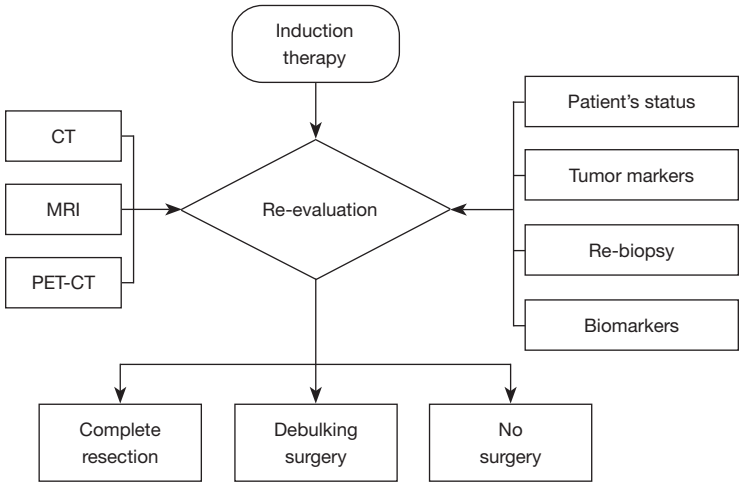

Figure 1 A flow chart of re-evaluation after induction therapy for thymic epithelial tumors. CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

trials in the field of TETs induction therapy and re-evaluation. The scarcity of high-quality, comprehensive data has made it challenging to draw robust conclusions. Our perspective, to a certain extent, was derived from the existing body of knowledge on TETs. Additionally, the heterogeneity in TETs' subtypes, treatment approaches, and evaluation systems across different institutions and regions has hindered our ability to perform a meta-analysis or provide a uniform, evidence-based guideline for re-evaluation protocols. Nevertheless, this review primarily explores current practices through the lens of available literature. We believe that by accumulating and discussing current clinical experiences and practices, this review can pave the way for future recommendations on how to proceed in the face of such evidence gaps.

Furthermore, another significant issue was our consolidation of discussions on thymoma and thymic carcinoma under the single umbrella of TETs, despite their distinct oncological and clinical profiles. This amalgamation was driven by the extreme scarcity of re-evaluation literature specific to each type, compelling us to address them as a collective entity. However, it is important to acknowledge that there are many commonalities between these two histological types, allowing for a degree of discussion from a comprehensive perspective. Where possible, we endeavored to discuss them separately, acknowledging the nuances between the two.

On the other hand, a notable strength of this review is its pioneering approach to the topic of TETs induction therapy and re-evaluation. To the best of our knowledge, no previous review has comprehensively addressed the specific challenges and opportunities related to re-evaluation in the context of TETs management. We consolidated existing knowledge and provided insights into this crucial aspect of TETs' treatment demonstrates. While the limitations mentioned earlier exist, our review incorporates the available evidence and provides a synthesis of the current state of knowledge. By doing so, we aim to guide clinicians in their decision-making processes and inspire additional research efforts that may eventually enhance our understanding of the re-evaluation and its implications for patient care.

Conclusions

We have conducted a review of induction therapy and re-evaluation for TETs. *Figure 1* shows a flow chart of re-evaluation after induction therapy for TETs. In practical terms, the decision-making process for surgery following induction therapy relies heavily on the empirical judgment of practicing surgeons. Consequently, our conclusion underscores the need for further data accumulation on this subject. If any guidance can be derived from existing retrospective case series, the next logical step should involve conducting randomized prospective trials across multiple institutions. Another critical aspect to address is the attempt to reduce the instances of failure to progress to surgery despite undergoing induction therapy. To this end, it is imperative to prioritize careful patient selection for initial treatment. The candidate selection for the treatment should

be performed by a multidisciplinary oncology committee that includes oncologists, surgeons, and radiation oncologists with experience in managing advanced TETs.

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Footnote

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Review Article

Narrative review of indication and management of induction therapy for thymic epithelial tumors

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Background and Objective: Thymic epithelial tumors (TETs) are rare and originate from the thymus. Thymomas and thymic carcinomas are the most common types of TETs. Of the two, thymomas tend to have a better prognosis and are typically localized, while thymic carcinomas have a worse prognosis and are more likely to spread. The Masaoka-Koga staging system is commonly used to determine the stage of TETs. Complete resection is the preferred treatment option, but treating locally advanced TETs can be challenging due to the invasion of surrounding structures. In such cases, induction therapy is administered to downstage the tumors and enable complete resection. We conducted this narrative review to evaluate the current progress in induction treatment for locally advanced TETs.

Methods: The literature search was performed using PubMed and Web of Science in June 2023. Prospective and retrospective published trials, systemic and narrative reviews, and meta-analyses were included.

Key Content and Findings: Induction chemotherapy is often used as a preoperative treatment for advanced TETs. Platinum and anthracycline-based chemotherapy regimens are commonly used for treating thymoma (response rate, 37–100%), and complete resection is highly common. Treatment with cisplatin and etoposide, carboplatin and paclitaxel, docetaxel and cisplatin have also demonstrated effectiveness, particularly in patients with thymic carcinoma or thymoma who cannot tolerate anthracycline regimens. The emergence of immunotherapy and targeted therapies may provide additional options for the treatment of TETs. Induction radiotherapy, as the sole treatment for TETs, is not widely practiced due to concerns about potential damage to surrounding tissues. However, combining modern radiation techniques with surgery has shown promising results in selected patients. Induction chemoradiotherapy, which combines chemotherapy and radiation, is an emerging approach for treating TETs. Despite the lack of randomized trials comparing chemotherapy with chemoradiotherapy, concurrent chemoradiation with radiation doses of 40–50 Gy is often considered the optimal induction therapy for thymic carcinoma patients or in more advanced special situations, such as great vessel invasion.

Conclusions: Overall, the optimal treatment for locally advanced TETs remains controversial. Induction therapy, including chemotherapy, radiotherapy, or chemoradiotherapy, is administered to downstage tumors and improve resectability. The choice of treatment depends on individual factors such as tumor stage, histology, and overall patient condition. However, further research and well-designed studies are needed to determine the most effective treatment strategies for locally advanced TETs.

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Keywords: Thymic epithelial tumors (TETs); locally advanced; induction therapy; chemotherapy; chemoradiotherapy

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Introduction

Background

Thymic epithelial tumors (TETs) are rare tumors originating from the epithelial cells of the thymus and include thymomas, and thymic carcinomas (TCs). The annual incidence of TETs ranges from 1.3 to 3.2 persons per million per year, with similar rates in both sexes, and the average age at diagnosis is 50–60 years. Thymoma is the most common primary tumor of the anterior mediastinum, yet it is rare, with an incidence of 0.2 to 0.5 cases per million people per year. On the other hand, TC is extremely rare (1). Thymomas exhibit slow behavior and present as localized disease, but they have the potential for intrathoracic and extrathoracic metastasis. In contrast, patients with TC have a worse disease course and histology than patients with thymoma and a higher rate of nodal and systemic metastasis (2).

The World Health Organization (WHO) histological classification system is used to distinguish between thymomas, TCs, and thymic carcinoids and to distinguish between different histological types of thymomas (i.e., A, AB, B1, B2, and B3). Revised in 2021, this classification system categorizes TCs into the following larger subtype groups: squamous, adenocarcinomas, adenosquamous, and carcinomas not otherwise specified. Histology plays an important role in disease biology because poor differentiation is correlated with shorter disease-free survival and overall survival (OS) (3).

The Masaoka-Koga staging system has been widely accepted for the management and determination of the prognosis of thymomas and TCs (4). Patients with stages I, II, and III thymomas have 5-year survival rates of 100%, 98%, and 85%, respectively. On the other hand, patients diagnosed with stage IVa or IVb thymoma exhibit 5-year survival rates of 55% and 77%, respectively (4). The chances of survival for patients with TC vary based on the stage of diagnosis: the higher the Masaoka stage is, the lower the OS rate. Patients with stage IVb disease have a 5-year OS of only 17%, whereas those with stage I disease have a 5-year OS of 100%, demonstrating a statistically significant difference (P<0.001) (5). To achieve a positive prognosis, thorough removal of tumors is crucial, especially in patients with advanced stage III or IV tumors (6,7). Unfortunately, a considerable proportion of these tumors fall under the Masaoka-Koga III–IVa category, which indicates that R0 resection is difficult owing to extensive spread of the disease in the surrounding area. In stage III tumors, mediastinal and intrathoracic structures, including the pericardium, heart, major blood vessels, and lungs, are invaded. In stage IVa tumors, there are pleural and/or pericardial implants as well. Therefore, for treating TETs, complete resection is essential to ensure a positive outcome (8).

It is strongly recommended in the European Society for Medical Oncology (ESMO) guidelines that complete resection be conducted and that all patients be discussed with a multidisciplinary cancer board comprising medical oncologists, radiation oncologists, and thoracic surgeons (1,9). The decision to pursue additional treatments is based on factors such as histology, stage, and degree of radicality achieved during surgery (R1 *vs.* R0) (1).

Objectives

In cases where complete removal of a tumor is not possible because of advanced-stage involvement in areas such as the lung, vessels, or heart, induction therapy may be administered to downstage the tumor and achieve clear surgical margins. This therapy can include chemotherapy, radiotherapy, or chemoradiotherapy. The best treatment for locally advanced TETs is still under debate, but recent advancements in various therapies, such as immunotherapy and targeted drugs, have shown promise. Therefore, we conducted this narrative review to evaluate the current progress in induction treatment for locally advanced TETs. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-30/rc).

Table 1 Search strategy summary

Items	Specification
Date of search	5/1/2023–6/6/2023
Databases and other sources searched	PubMed, Web of Science
Search terms used	"thymic epithelial tumors", "thymoma", "thymic carcinoma", "locally advanced", "neoadjuvant", "preoperative", "chemotherapy", "radiotherapy", "chemoradiotherapy", "immunotherapy", and "target therapy"
Timeframe	Up to 2023
Inclusion and exclusion criteria	Inclusion: retrospective studies, case studies, clinical trial
	Exclusion: case report, no mention of stage of disease, no mention of clinical data, no mention of TETs treatment details
Selection process	One author compiled a list of eligible studies followed by review by the other author to determine suitability

TETs, thymic epithelial tumors.

Methods

The literature search was performed using PubMed and Web of Science in June 2023. The keywords used for the research were "thymic epithelial tumors", "thymoma", "thymic carcinoma", "locally advanced", "neoadjuvant", "preoperative", "chemotherapy", "radiotherapy", "chemoradiotherapy", "immunotherapy", and "target therapy". Prospective and retrospective published trials, systemic and narrative reviews, and meta-analyses were included. No limits regarding the years of publication were applied, and only papers written in English were accepted (*Table 1*). Sixty-two articles were selected according to the inclusion criteria and exclusion criteria from 1,091 PubMed references identified by keywords and 431 Web of Science references identified by keywords; case reports were excluded by keywords.

Results

Induction chemotherapy

Recent studies have yielded promising results regarding surgical resection after induction therapy for advanced TETs. According to a meta-analysis by Hamaji *et al.* of 12 trials involving 266 patients, the pooled rate of response to induction therapy was 59%, with a pooled rate of complete resection of 73% and pooled 5- and 10-year OS rates of 87% and 76%, respectively (10). Park *et al.* (11) investigated the efficacy of neoadjuvant chemotherapy in 1,486 patients with surgically resected thymic tumors and reported that 110 patients (7.4%) underwent surgery after neoadjuvant chemotherapy, whereas 1,376 patients (92.6%) underwent upfront surgery. Propensity score matching was used to minimize differences in preoperative and intraoperative variables, and the two groups were compared for postoperative outcomes and survival.

The matched cohort analysis did not reveal significant differences in postoperative mortality (P value not calculated), postoperative complications (P=0.405), or length of hospital stay (P=0.821) between the neoadjuvant chemotherapy and upfront surgery groups. However, compared with those in the upfront surgery group, the patients in the neoadjuvant chemotherapy group exhibited significantly greater transfusion rates (P=0.003) and longer operation times (P<0.001). The pathological complete resection rate (P=0.382) and tumor size (P=0.286) were similar between the two groups. The 5-year OS rates were 77.4% and 76.7% (P=0.596) and the 3-year recurrence-free survival rates were 62.9% and 71.5% (P=0.070) in the neoadjuvant chemotherapy and upfront surgery groups, respectively (11).

The optimal neoadjuvant therapy regimen for minimizing operative morbidity and mortality and maximizing resectability and survival has not been established. *Table 2* provides a comprehensive overview of the induction chemotherapy regimens, complete resection rates, and response rates for patients with locally advanced TETs (8,12-31). Platinum- and anthracycline-based chemotherapy are the most commonly used regimens in clinical practice, with response rates ranging from 37% to 100%. In patients for whom radical surgery (R0 resection) is feasible, a surgical approach is pursued, and complete resection is achieved in approximately 50–80% of patients. However,

Table 2 Induction chemotherapy for locally advanced thymoma and TC

Author, year	Reference	Study design	Regimen	Stage	Tumor type (No. of locally advanced pts)	Response rate (%)	No. of R0/ No. of surgery
Rea, 2011	(8)	Retrospective analysis	ADOC	III–IV	T [32]/TC [6]	68 (T)/50 (TC)	28/38 (74%)
Shin, 1998	(12)	Prospective cohort study	PAC + predonisone	III–IVa	T [12]	91	9/11 (82%)
Kim, 2004	(13)	Prospective single arm phase II trial	PAC + predonisone	III–IV	T [22]	77	16/21 (76%)
Rea, 1993	(14)	Prospective interventional study	ADOC	III–IVa	T [16]	100	11/16 (69%)
Yokoi, 2007	(15)	Prospective interventional study	CAMP	III–IV	T [14]	92	2/9 (22%)
Hassan, 2009	(16)	Prospective cohort study	PE	III–IVA	T [9]	77	5/8 (63%)
Mineo, 2010	(17)	Retrospective analysis	PE	III	T [33]	37	17/33 (52%)
Furugen, 2011	(18)	Retrospective analysis	CP	IVa–IVb	TC [16]	37	1/16
Hirai, 2015	(19)	Prospective single arm phase II trial	CP	III–IVB	TC [39]	39	NA
Lemma, 2011	(20)	Prospective single arm phase II trial	CP	III–IVb	T [21]/TC [23]	42 (T)/21 (TC)	NA
Park, 2013	(21)	Prospective single arm phase II trial	TP	III–IV	T [9]/TC [18]	55 (T)/66 (TC)	15/19 (79%)
Macchiarini, 1991	(22)	Prospective interventional study	PAE	IA-IIIA	T [7]	100	4/7 (57%)
Lucchi, 2006	(23)	Prospective interventional study	PAE	III–IVA	T [30]	73	23/30 (77%)
Venuta, 2003	(24)	Prospective interventional study	PAE	III	T [9]/TC [6]	66 (T + TC)	13/15 (87%)
Kunitoh, 2010	(25)	Prospective single arm phase II trial	CODE	III	T [23]	62	9/13 (69%)
Berruti, 1993	(26)	Prospective interventional study	ADOC	III–IVa	T [6]	83	–/5
Berruti, 1999	(27)	Prospective interventional study	ADOC	III–IVa	T [16]	81	–/9
Bretti, 2004	(28)	Prospective interventional study	ADOC or PE	III–IVa	T + TC [25]	72 (T + TC)	11/14 (79%)
Cardillo, 2010	(29)	Retrospective analysis	PAC + predonisone	III–IVa	T [21]/TC [10]	61 (T)/50 (TC) Reduction >50%	NA
Ishikawa, 2009	(30)	Retrospective analysis	CAMP	IVa–IVb	T [11]	85	5/10 (50%)
Nakamura, 2019	(31)	Retrospective analysis	CAMP	IV	T [19]	78	NA

TC, thymic carcinoma; pts, patients; ADOC, cisplatin + adriamycin + cyclophosphamide + vincristine; T, thymoma; PAC, cisplatin + doxorubicin + cyclophosphamide; CAMP, cisplatin + doxorubicin + methylprednisolone; PE, cisplatin + etoposide; CP, carboplatin + paclitaxel; NA, not available; TP, docetaxel + cisplatin; PAE, cisplatin + etoposide + epirubicin; CODE, cisplatin + adriamycin + vincristine + etoposide.

only limited data are provided by prospective randomized trials comparing chemotherapy with chemoradiotherapy in this specific setting and previous reports do not include sufficient information. In cases where there is substantial tumor shrinkage or transition from an unresectable tumor to a potentially resectable tumor occurs, extensive surgery should be offered, and postoperative radiotherapy should be considered. The most commonly prescribed platinum and anthracycline-based regimens in clinical practice are cisplatin + doxorubicin + cyclophosphamide (PAC), cisplatin + adriamycin + cyclophosphamide + vincristine (ADOC), and cisplatin + doxorubicin + methylprednisolone (CAMP). In a study by Shin *et al.*, 12 patients with unresectable stage III–IVA thymoma received three courses of PAC + prednisolone; three patients achieved a complete response, while eight achieved a partial response. Of the 11 patients

who underwent subsequent surgical intervention, nine achieved R0 resection (12). Similarly, in a study by Kim *et al.*, 22 patients with stage III–IVb invasive thymoma received three courses of PAC + prednisolone; 17 exhibited major responses (complete responses, n=3; partial responses, n=14), and 21 were surgically treated (16 achieved R0 resection) (13). In a study by Rea *et al.*, 16 patients with stage III–IVA invasive thymomas were treated with the ADOC regimen; 100% (seven complete and nine partial) of the patients achieved a response, followed by surgery, and 11 patients (68%) achieved complete resection (14). CAMP is also frequently used in clinical trials. In a study by Yokoi *et al.*, the CAMP regimen was administered to 14 patients with invasive III–IVb stage thymoma in a neoadjuvant setting; 13 (92.9%) patients achieved a good response to this regimen, and nine underwent surgical treatment, with 2 (22.2%) achieving R0 resection (15).

Among these phase II trials or retrospective studies with a small number of patients, a pattern in the use of anthracyclines emerges when comparing platinum-based and anthracycline-based combination therapy with platinum-based and non-anthracycline-based combination therapy. In combination therapy with cisplatin and etoposide, the overall response rate (ORR) in both thymoma and TC patients were 51–62% (16,17). Carboplatin and paclitaxel have also shown promising results, with an ORR of 22–36% in patients with both thymoma and TC (18-20). Park *et al.* explored the impact of induction chemotherapy using docetaxel and cisplatin (TP) (21). In nine patients with thymomas (one with stage III disease and eight with stage IVA), five (55.6%) achieved a partial response, and four achieved a complete response. Moreover, seven patients were eligible for surgery, and all patients ultimately achieved R0 resection. For patients with thymoma who cannot tolerate anthracycline combination regimens, nonanthracycline regimens such as cisplatin + etoposide (EP), carboplatin + paclitaxel, or docetaxel and cisplatin (TP) can be used.

Unlike in patients with thymoma, in patients with TC, the ORR did not significantly differ between anthracycline and nonanthracycline regimens, and the key therapy was a platinum-containing regimen. Carboplatin + paclitaxel is the preferred choice for treating locally advanced TC. Anthracycline regimens, including CAP and ADOC, are also effective, but these regimens have greater toxicity.

Overall, neoadjuvant chemotherapy has proven to be effective in prospective and retrospective studies, with most regimens being well tolerated and resulting in a reasonable response rate in patients with locally advanced tumors. Thus, all available options must be discussed with patients and their medical team to make an informed decision regarding the ideal treatment plan.

Induction radiotherapy

Radiation therapy as a preoperative treatment for locally advanced thymic tumors has attracted considerable interest and research. However, most institutions currently favor chemotherapy as the preferred induction treatment. Radiation therapy poses a considerable challenge because of the potential damage it can inflict on adjacent tissues, particularly in patients where mediastinum radiation is involved. When administering radiation to this area, it is crucial to safeguard vital organs such as the heart, lungs, and esophagus. In addition, postoperative radiation therapy is generally considered for locally advanced thymic tumors. In cases where preoperative radiation therapy is considered, the risk of additional postoperative radiation therapy should also be considered.

In several studies, scholars have investigated the use of radiation therapy alone as an induction treatment for thymic tumors. In a multi-institutional study using the European Society of Thoracic Surgeons database, only 1% of patients (12 out of 2,030) received radiation monotherapy as induction therapy (32). Similarly, a review of the International Thymic Malignancy Interest Group database showed that only 6% of TC patients (48 out of 1,042) received induction radiation as the sole treatment (2).

Ribet *et al.* described a series of 113 patients, 19 of whom received preoperative radiation (33). Within this cohort, ten patients achieved complete resection, for a 5-year OS rate of 44%. Akaogi *et al.* reported 12 patients with thymic tumors that invaded the great vessels who underwent preoperative radiation. The cohort showed a 75% rate of complete resection, and ten patients also received adjuvant radiation, resulting in 5- and 10-year OS rates of 72% and 48%, respectively (34). The findings from various radiation experiences are summarized in *Table 3*.

In summary, radiation therapy as a preoperative induction treatment for locally advanced thymic tumors is not widely practiced. Most institutions prefer chemotherapy as the primary induction therapy. Based on the literature, radiotherapy may be effective to some extent. However, these previous studies involved a small number of patients; thus, there is little evidence that this treatment is more effective than preoperative chemotherapy

Table 3 Induction radiotherapy for locally advanced thymoma and TC

Author, year	Reference	Study design	Stage	Tumor type [No. of pts]	RT dose	Response rate (%)	No. of R0/No. of surgery
Yagi, 1996	(7)	Retrospective analysis	III–IV	T [11]	20–66 Gy	NA	NA
Bretti, 2004	(28)	Prospective interventional study	III–IVA	T + TC [8]	24–30 Gy	37	1/3 (33%)
Akaogi, 1996	(34)	Retrospective analysis	III–IV	T [12]	12–21 Gy	91	9/12 (75%)

TC, thymic carcinoma; pts, patients; RT, radiation therapy; T, thymoma; R0, complete resection; NA, not available.

Table 4 Induction chemoradiotherapy for locally advanced thymoma and TC

Author, year	Reference	Study design	Regimen	Stage	Tumor type [No. of pts]	RT dose	Response rate (%)	No. of R0/ No. of surgery
Korst, 2014	(35)	Prospective single-arm phase II trial	PE	I–IV	T [13]/TC [7]/ metaplastic [1]	40–45 Gy	47 (T + TC)	17/21 (77%)
Chu, 2020	(36)	Retrospective analysis	PAC or CP (with Radiotherapy)	III–IV	T [5]/TC [3]/ other [4]	60–70 Gy	NA	NA/1
Wright, 2008	(37)	Retrospective analysis	PE	III–VA	T [9]/TC [1]	33–45 Gy	40 (T + TC)	8/10 (80%)

TC, thymic carcinoma; pts, patients; RT, radiation therapy; R0, complete resection; PE, cisplatin + etoposide; T, thymoma; PAC, cisplatin + doxorubicin + cyclophosphamide; CP, carboplatin + paclitaxel; NA, not available.

or chemoradiotherapy. It should be used only in limited circumstances, such as severe organ dysfunction, where chemotherapy cannot be administered. In cases where radiation therapy is considered, the risk of additional postoperative radiation therapy should also be considered. Further research and well-designed studies are necessary to address these challenges and determine the optimal radiation therapy for the management of locally advanced thymic tumors.

Induction chemoradiotherapy

Preoperative chemoradiotherapy has emerged as a treatment strategy for TETs to increase the chances of complete tumor removal and improve response rates compared with chemotherapy alone. However, prospective randomized trials that directly compare chemotherapy with chemoradiotherapy in TET patients are rare, leading to inconclusive data (*Table 4*) (35-37). Concurrent chemoradiotherapy with 40–50 Gy radiation is often considered the optimal induction therapy for patients with TC (38). Several studies have reported encouraging results in investigating neoadjuvant chemoradiotherapy for locally advanced TETs. Korst *et al.* reported a phase 2 trial involving patients with thymoma or TC who underwent induction therapy with a combination of two cycles of cisplatin and etoposide combined with 45 Gy of thoracic radiotherapy. After induction therapy, computed tomography (CT) and positron emission tomography (PET) were performed, followed by attempted resection. The primary goal was to assess the pathologic response to induction therapy, while secondary endpoints included toxicity, surgical complications, radiographic response, and the rate of complete resection. Of the 22 patients enrolled, 21 completed induction therapy, and nine experienced severe toxicity. A partial radiographic response was observed in ten patients, while stable disease was detected in 11 patients. Approximately 77% of the patients underwent complete resection, 36% experienced surgical complications, and two died after the procedure. Although no patient achieved a pathological complete response, 24% of the specimens had <10% viable tumors (35). Chu *et al.* reported 114 TET patients who received chemotherapy or chemoradiotherapy as initial treatment and pre- and post-treatment scans at a tertiary academic cancer center between 2007 and July 2018. Of the 114 patients, 12 patients were in the chemotherapy group (ten with thymoma, one with TC, and one with an unclassifiable thymic tumor), and 12 were in the radiation therapy group (5 with thymoma, three with TC, and four with unclassifiable thymic tumors). All patients in both groups were in stage III–IV. After a median imaging follow-up of 15 months, chemoradiation

led to a greater radiological response than chemotherapy alone (volume: –47.0 cm^3 more, P<0.001; diameter: –0.8 cm more, P=0.03). Eight patients who received chemotherapy also experienced significant tumor shrinkage with additional radiation or chemoradiation. The median survival time was significantly longer for patients who ultimately underwent surgery than for patients who did not (46 *vs.* 14 months) (36).

Wright *et al.* reported the therapeutic effect of concurrent induction chemoradiotherapy in ten patients with initially unresectable locally advanced thymic tumors (including 9 with thymomas and 1 with TC). The therapeutic protocol consisted of two cycles of EP chemotherapy with concurrent radiotherapy (33–49 Gy) before surgery. Adjuvant EP chemotherapy was administered for patients with incomplete resection and a high risk of recurrence. After completion of induction chemoradiotherapy, 4 (40%) patients achieved a partial response, while the remaining 6 (60%) patients presented no changes. All ten patients were directed toward surgery, and R0 resection was achieved in 8 (80%) patients. The examination of resected specimens revealed substantial (>90%) tumor necrosis in four (40%) patients. No postoperative deaths were observed, and the estimated 5-year survival was 69% (37).

Based on these reports, chemoradiotherapy as induction treatment for unresectable locally advanced TETs may be as effective as preoperative chemotherapy. However, there are only a few reports on the vagueness of the definition of "unresectable" and the regimen to be used. The indication for additional radiation should be carefully considered in terms of the stage and histology of the target tumor, as additional radiation may increase toxicity.

Yamada *et al.* analyzed the extracted data of a total of 310 stage III thymoma patients from the Japanese National Database. Among the thymoma tumors in these cases, 194 (62.6%) involved the lungs, 151 (48.7%) involved the pericardium, 1,236 (40.6%) involved the great vessels, and 247 (79.7%) were completely resected. The complete resection rate was significantly lower in patients with invasion of the great vessels than in the other patients (73.8% *vs.* 83.7%, respectively; P=0.011) (39). Hassan *et al.* explored the function of induction chemotherapy in nine patients with locally advanced thymoma who underwent three cycles of EP before surgery (16). In three patients (37.5%) with confirmed invasion of the great vessels, including the ascending aorta, main pulmonary artery, superior vena cava, and heart, via anterior mediastinotomy and radiology, there was incomplete resection after induction chemotherapy; extended full-thickness tumor invasion of the vessels remained during surgery, causing incomplete resection. Therefore, in TET patients with great vessel invasion, chemotherapy alone may be insufficient, while chemoradiotherapy may enhance antitumor activity and the possibility of total resection.

In summary, the use of chemoradiotherapy as a preoperative induction treatment for TETs may improve the likelihood of complete tumor removal and enhance response rates. However, further research, including prospective randomized trials, is necessary to determine the optimal treatment approach for different histological subtypes and to assess the long-term outcomes of induction chemoradiotherapy in TET patients.

Induction immunotherapy

Immunotherapy, specifically programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) immune therapy, has emerged as a revolutionary approach for the treatment of TETs. PD-L1 expression is commonly used as a predictor of PD-1/PD-L1 immune therapy efficacy, and high PD-L1 expression is associated with aggressive histological type, advanced disease stage, and worse prognosis (40-45). Padda *et al.* examined PD-L1 expression in tissue microarrays (TMAs) of TETs. TMAs were generated from 69 TETs and 17 thymic controls, and the PD-L1 scores of the epithelial cells were evaluated. A high PDL1 score was more frequent in patients with TETs than in controls (68.1% *vs.* 17.6%; P=0.0036). Histology and PD-L1 expression were significantly correlated, with higher intensity staining according to the WHO classification B2/B3/C TETs. According to an adjusted analysis (for age and sex), patients with PD-L1-high TETs had a markedly worse OS than patients with PD-L1-low TETs [hazard ratio: 5.40, 95% confidence interval (CI): 1.13–25.89; P=0.035] and had a trend toward worse event-free survival (hazard ratio: 2.94, 95% CI: 0.94–9.24; P=0.064) (46). Tumor-infiltrating lymphocytes, which are crucial for immune system activation, are abundantly present in patients with TETs (47). These factors support the potential efficacy of PD-1/PD-L1 therapy for TETs.

Several trials have explored the efficacy and safety of immunotherapy for advanced or recurrent thymomas. For example, a phase II study by Cho *et al.* evaluated the role of pembrolizumab in 26 patients with TC and seven patients with refractory thymoma and reported partial responses in two thymoma patients and 5 TC patients (48). In addition to efficacy, toxicity is also an important consideration for

Table 5 Immunotherapy for advanced thymoma and TC

Author, year	Reference	Study design	Regimen	Stage	Tumor type [No. of pts]	Response rate (%)	No. of R0/ No. of surgery
Cho, 2019	(48)	Prospective single-arm phase II trial	Pembrolizumab	IV	T [7]/TC [26]	28 (T)/19 (TC)	NA
Giaccone, 2018	(50)	Prospective single-arm phase II trial	Pembrolizumab	III–IVb	TC [40]	22	NA
Rajan, 2019	(51)	Prospective single-arm phase I trial	Avelumab	IV	T [7]/TC [1]	57 (T)/0 (TC)	NA

TC, thymic carcinoma; pts, patients; RT, radiation therapy; R0, complete resection; T, thymoma; NA, not available.

treatment. Five of seven (71.4%) patients with thymoma and four of 26 (15.4%) patients with TC reported grade 3 immune-related adverse events (irAEs), including myocarditis, hepatitis, myasthenia gravis, colitis, thyroiditis, and glomerulonephritis. Moreover, in another study, the administration of anti-PD-1 therapy resulted in a storm of irAEs (including myasthenia gravis, myositis, myocarditis, and death) after the administration of the first treatment cycle (49). Patients with TC and type B3 thymoma, characterized by mature T lymphocyte infiltration, have lower risks of irAEs during immune checkpoint inhibitor therapy. These entities should be preferred when considering the use of these agents. Pembrolizumab has been included as a possible therapeutic option for refractory TC in the National Comprehensive Cancer Network (NCCN) guidelines. However, caution is warranted when using immune checkpoint inhibitors in thymomas due to the increased risk of irAEs. Clinical trials are warranted to determine the exact role of induction immunotherapy in patients with TETs. A notable ongoing Korean phase II study (NCT03858582) is evaluating the efficacy and safety of neoadjuvant therapy with pembrolizumab plus chemotherapy (docetaxel and cisplatin) for three cycles every 3 weeks. Patients who undergo R0 resection are receiving pembrolizumab, while those who undergo R1 or R2 resection are receiving radiation therapy and pembrolizumab.

Immunotherapy studies for TETs are presented in *Table 5*. Clinical trials should be conducted to assess the exact effect of induction immunotherapy in patients with TETs. Currently, studies on the efficacy and safety of immunotherapy as a preoperative option are limited. Toxicity must be avoided during preoperative treatment, as it could hinder or delay surgery. Prospective clinical trials, including safety studies, are necessary to provide more comprehensive data on the potential benefits and risks of induction immunotherapy in patients with TETs.

Induction-targeted therapy

The advances in the research of the molecular biology of TETs have increased the number of targeted therapies in clinical trials (52). However, in the neoadjuvant setting for TETs, the use of targeted treatment is supported by limited evidence. One ongoing clinical trial is investigating the effects of combining cetuximab with traditional platinum and anthracycline-based chemotherapy as neoadjuvant therapy for locally advanced thymoma (Clinical Trials. gov NCT01025089). This phase II study was designed to evaluate the combination of cetuximab and the PAC regimen as neoadjuvant chemotherapy for locally advanced thymoma. Initially, patients receive cetuximab weekly for up to 4 weeks to evaluate the tumor response to cetuximab alone. Subsequently, the continue to receive weekly cetuximab along with concurrent PAC for four cycles before surgery. The primary endpoint of the trial is the frequency of complete pathological response, with secondary endpoints including toxicity, treatment response, and R0 resection.

The activation of the PI3K/AKT pathway in TETs (53) led to the investigation of the mammalian target of rapamycin (mTOR) inhibitor everolimus in a phase II trial, which demonstrated a median progression-free survival (PFS) of 10.1 months and OS of 25.7 months in advanced, treatment-refractory thymoma and TC (54). Although epidermal growth factor receptors are often overexpressed in TETs, activating mutations are rarely observed (55). A phase II study using gefitinib showed poor response rates in patients with chemorefractory TETs (56). *KIT* overexpression has been reported in TCs; however, under 10% of tumors harbor a *KIT* mutation, and no response has been reported with the use of imatinib to date (57). Thymic tumors exhibit insulin-like growth factor receptor overexpression (58). A phase II study of cixutumumab enrolled 49 patients (37 with thymomas and 12 with TCs) with recurrent or refractory disease, five with thymoma and

Table 6 Targeted therapy for advanced thymoma and TC

Author, year	Reference	Study design	Regimen	Stage	Tumor type [No. of pts]	Response rate (%)	No. of R0/ No. of surgery
Zucali, 2018	(54)	Prospective single-arm phase II trial	Everolimus	III–IVb	T [32]/TC [18]	9 (T)/16 (TC)	NA
Giaccone, 2009	(57)	Prospective single-arm phase II trial	Imatinib	IV*	T [2]/TC [5]	0	NA
Rajan, 2014	(59)	Prospective single-arm phase II trial	Cixutumumab	Recurrent or chemotherapy refractory	T [37]/TC [12]	14 (T)/0 (TC)	NA
Thomas, 2015	(61)	Prospective single-arm phase II trial	Sunitinib	Chemotherapy refractory	T [16]/TC [24]	6 (T)/26 (TC)	NA
Remon, 2016	(62)	Retrospective analysis	Sunitinib	III–IV	T [7]/TC [20]	28 (T)/20 (TC)	NA
Sato, 2020	(63)	Prospective single-arm phase II trial	Lenvatinib	III–IV	TC [42]	38	NA

*, not stated whether the stage classification is based on Masaoka Classification. TC, thymic carcinoma; pts, patients; RT, radiation therapy; R0, complete resection; T, thymoma; NA, not available.

a partial tumor response, 28 with stable disease, and four with progressive disease. Among the 12 TC patients who received treatment, none responded, five had stable disease, and seven had progressive disease (59).

Vascular endothelial growth factor (VEGF) and VEGF receptors have been identified as possible targets in high-risk thymomas and TCs (60), suggesting the potential use of antiangiogenic agents such as sunitinib. An open-label phase II study of sunitinib in patients with chemorefractory TETs demonstrated a partial response in 6 patients and stable disease in 15 patients among 23 TC patients. Among the 16 thymoma patients, 1 had a partial response, while 12 had stable disease (61). A retrospective review of 28 patients (20 with TCs and eight with thymomas) of sunitinib in the off-label cohort study showed a response rate of 22% and a disease control rate (DCR) of 63%, with a median PFS of 3.7 months and a median OS of 14.5 months (62). A phase II trial of lenvatinib, an oral multitargeted kinase inhibitor for VEGFR, FGFR, and c-Kit, enrolled 42 patients with advanced TC who had progressed after at least one platinum-based chemotherapy (63). The ORR was 38%, the DCR was 95%, and the median PFS was 9.3 months. Of the 42 patients, 30 (71%) had squamous cell carcinoma, and 14 out of these 30 (47%) had a partial response. Two ongoing clinical trials of lenvatinib were identified.

An open-label, single-arm phase II study will evaluate the efficacy and safety of the combination treatment of pembrolizumab and lenvatinib in pretreated type B3 thymoma or TC patients who have progressed after at least one course of platinum-based chemotherapy for advanced disease without any previous immunotherapy (previous bevacizumab allowed but not sunitinib) and who are not suitable for curative-intent radical surgery and/or radiotherapy regardless of PD-L1 status (Clinical Trials.gov NCT04710628). Another phase II, investigator-initiated, nonrandomized, open-label, single-arm, multicenter study will evaluate the efficacy and safety of carboplatin, paclitaxel, lenvatinib, and pembrolizumab in combination for previously untreated advanced or recurrent TCs that are judged to be incapable of radical resection (Clinical Trials.gov NCT05832827).

A list of the major molecularly targeted agents reported for TETs is shown in *Table 6*. Targeted therapy may be an option for heavily pretreated patients in clinical practice, and some agents have shown promising effects with tolerable side effects. However, no previous study has shown more pronounced responses compared to chemotherapy or chemoradiotherapy. However, further studies are needed to investigate the benefits of incorporating targeted therapy into preoperative chemotherapy for TETs.

Discussion

The management of locally advanced TETs remains challenging. Complete resection is crucial for improving the

prognosis of these tumors, but achieving R0 resection can be difficult due to the invasion of surrounding structures and distant metastasis. In such cases, induction therapy plays an important role in downstaging the tumor and making it amenable to surgical resection. Currently, chemotherapy is the most widely used induction therapy for locally advanced thymomas, with platinum and anthracycline-based regimens being the standard approach; for TCs, chemotherapy with either platinum and anthracycline-based regimens or carboplatin and paclitaxel is favored. Furthermore, the emergence of immunotherapy and targeted therapies may provide additional options for the treatment of TETs.

Due to concerns about potential damage to surrounding tissues, radiation therapy as the sole induction treatment for locally advanced TETs is less common. However, combining modern radiation techniques with surgery has shown promising outcomes in some cases.

Preoperative chemoradiotherapy may be an emerging approach that is intended to improve the chances of complete tumor removal compared with chemotherapy in more advanced special situations, such as severe vessel invasion.

Neoadjuvant chemotherapy or chemoradiotherapy has shown promising results in terms of response rates and complete resection rates, although there are no prospective randomized trials comparing chemotherapy with chemoradiotherapy.

There is still insufficient evidence for the use of preoperative immunotherapy and preoperative targeted therapy. Close attention should be given to the emergence of irAEs during immunotherapy.

Since TETs are rare tumors, in most studies, there is clear selection bias with a shrinking denominator. Moreover, the level of evidence is limited in most publications. A multidisciplinary approach involving thoracic surgeons, medical oncologists, radiation oncologists, radiologists, immunologists, neurologists and pathologists is crucial for the comprehensive management of patients with TETs. Treatment decisions should be individualized based on factors such as histology, stage, and the feasibility of radical surgery. Close collaboration among medical teams and informed discussions with patients are essential for determining the most appropriate treatment plan.

Conclusions

In conclusion, the use of induction treatment for locally advanced TETs is evolving, highlighted by ongoing advancements in chemical regimens, radiotherapy technologies, immunotherapy, and targeted therapies. However, further research and well-designed studies are needed to address the remaining challenges and optimize the management of these rare tumors, ultimately improving patient outcomes.

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