Review Article

Update on thymic epithelial tumors: a narrative review

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

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

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

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

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

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Introduction

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

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

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Table 1 The search strategy summary

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

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

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

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

Methods

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

Clinical and diagnostic

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

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

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

The most frequent thymoma's association is myasthenia

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

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

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

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

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

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

Pathology

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

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

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

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

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

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

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

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

EMA, epithelial membrane antigen.

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

Differential diagnosis and staging

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

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

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

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

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

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

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

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

Localized disease

Surgical approach of thymoma and thymic carcinoma

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

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

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

Thymoma

Resectable disease

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

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

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

TETs, thymic epithelial tumors.

Table 5 AJCC prognostic groups (1)

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

AJCC, American Joint Committee on Cancer.

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

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

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

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

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

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

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

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

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

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

Potentially resectable disease

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

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

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

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

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

Thymic carcinoma

Resectable disease

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

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

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

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

Potentially resectable disease

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

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

Table 9 Studies with a multidisciplinary approach of unresectable malignant thymomas

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

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

Table 10 Postoperative radiation in the adjuvant setting of thymic carcinomas

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

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

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

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

Recurrent disease

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

Table 11 Retrospective data on PORT for thymic neoplasms

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

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

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

NETTs

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

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

Unresectable/advanced disease

Thymoma and thymic carcinoma

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

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

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

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

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

First line

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

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

Subsequent therapy

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

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

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

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

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

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

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

Table 12 Chemotherapy regimens in unresectable/advanced TETs

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

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

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

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

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

Table 13 Systemic treatments in pretreated advanced thymic epithelial tumors

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

Table 13 (*continued*)

Table 13 (*continued*)

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

Table 13 (*continued*)

Table 13 (*continued*)

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

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

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

NETTs

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

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

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

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

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

New therapeutics options

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

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

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

Table 14 (*continued*)

Table 14 (*continued*)

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

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

main ongoing clinical trials in patients with advanced TETs.

Conclusions

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

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

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

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

Table 15 (*continued*)

Table 15 (*continued*)

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

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

rapamycin (mTOR) inhibitor, ICIs and their combinations.

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Footnote

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