

REVIEW

Clinical management of patients with thymic epithelial tumors: the recommendations endorsed by the Italian Association of Medical Oncology (AIOM)

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The Italian Association of Medical Oncology recommendations on thymic epithelial tumors, which have been drawn up for the first time in 2020 through an evidence-based approach, report indications on all the main aspects of clinical management of this group of rare diseases, from diagnosis and staging, to new available systemic treatments, such as targeted therapies and immunotherapies. A summary of key recommendations is presented here and complete recommendations are reported as [Supplementary Materials](https://doi.org/10.1016/j.esmoop.2021.100188), available at <https://doi.org/10.1016/j.esmoop.2021.100188>.

Key words: thymic epithelial tumors, recommendations, AIOM

INTRODUCTION

Italian recommendations for the diagnostic work-up and therapeutic management of patients with thymic epithelial tumors (TETs) have been drawn up for the first time in Italy in 2020 by a multidisciplinary panel including pathologists, thoracic surgeons, radiotherapists, medical oncologists, and neurologists from referral cancer centers, dedicated to the cure of patients with TETs.

A patient representative belonging to the association of patients with TETs was included in this panel.

A systematic review of literature was conducted before the drafting of the document, updated to June 2020.

In the absence of scientific evidence from randomized trials, the recommendations reported are supported by evidence derived firstly from prospective phase II studies and secondly from retrospective studies. In the absence of scientific evidence, recommendations follow international guideline indications and/or the expertise of panel members.

Each recommendation reported was first discussed by the reference group, and then collectively discussed by all panel members, and for each recommendation reported, the number of members who agreed, disagreed, or abstained is indicated.

The panel strongly suggests that patients with TETs should be evaluated at referral centers for the management of this disease.

The rarity and clinical complexity of this disease warrants a multidisciplinary management of all diagnostic—therapeutic options.

The recommendations have been finally endorsed by the Italian Association of Medical Oncology (AIOM).

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BACKGROUND

TETs are rare neoplasms which arise from thymic epithelial cells (ECs).

Their incidence is ~0.15 per 100 000 person-years, with a peak of incidence in the seventh decade of life.^{1,2}

They are slightly more common in males as compared with females (1.4 : 1), and in Afro-Americans and Asians.^{1,2}

Such ethnic differences in incidence rates could suggest a potential role for genetic factors in the pathogenesis of TETs.³

In the last few years, major findings in the biology of TETs support the hypothesis that the different histological subtypes are distinct biological entities, with peculiar molecular and genomic alterations, rather than a continuum spectrum of a unique disease.⁴⁻⁶

Whole-exome sequencing analysis allowed to identify several recurrent molecular aberrations, including *GTF2I* gene mutation, occurring in 39% of cases, mainly in type A (82%) and AB thymomas (TMs).

Interestingly, the *GTF2I* gene, which is rarely mutated in other malignancies, is involved in the development of some diseases including neurocognitive disorders and autoimmune diseases such as systemic lupus erythematosus.⁷⁻⁹

Patients with TMs, especially type B1 and B2, have a high risk of developing autoimmune disorders, mainly myasthenia gravis (MG) (i.e. ~30% of cases), but also less frequently systemic lupus erythematosus (2%-5%) or red cell aplasia (1%).¹⁰

Recently, new evidences shed light on the pathogenic mechanisms underlying the association between TETs and autoimmune diseases, which deserve further investigations for the potential therapeutic implications.⁴

Particularly, a molecular mimicry mechanism has been hypothesized for the development of MG in patients with TETs, which consists in an immune activation against antigens similar or in common between cancer and a self-tissue.⁴

Two disease staging systems are currently available, the TNM (tumor—node—metastasis) system (International Association for the Study of Lung Cancer/International Thymic Malignancy Interest Group), which is recommended as the recognized standard, accompanied by the Masaoka—Koga staging system, which is still useful since this has been the longstanding staging system widely used in most studies.^{11,12}

The rarity and clinical complexity of this disease warrants a multidisciplinary management of all diagnostic—therapeutic choices.

Although many clinical indications of the diagnostic and therapeutic patients' management are common for TMs and thymic carcinomas (TCs), others are not, and required a histotype-tailored approach, as discussed in detail below.

Treatment strategy of TETs first relies on assessment of radical resectability of the neoplastic lesion.

Upfront surgery represents the first step of treatment for the large majority of cases, eventually followed by further post-operative (adjuvant) treatments.

If the lesion is judged locally advanced and/or unresectable, preoperative induction therapy (chemotherapy) may be indicated after discussion in a multidisciplinary setting.

Post-operative radiotherapy is considered in TMs and TCs in case of aggressive histology and extracapsular involvement or in case of microscopical or macroscopical residual disease (R1 and R2).

The main treatment option for patients with advanced, metastatic diseases is represented by systemic palliative treatments.

Platinum-based chemotherapy remains currently the standard first-line treatment for patients with advanced or metastatic TETs.

Beyond chemotherapy, meaningful recent advances in the knowledge of molecular alterations involved in the pathogenesis of TETs led to identification of new potential molecular targets.¹³⁻¹⁸

Among the several classes of targeted therapies tested so far, antivascular agents (including sunitinib and lenvatinib) showed the greatest antitumor activity, mainly in patients with TC, and represent a currently available treatment option.¹⁹⁻²¹

Due to its relevant antitumoral activity, pembrolizumab has been recently added within the National Comprehensive Cancer Network guidelines for the treatment of patients with TCs refractory to chemotherapy.

Since patients with TM have a higher risk of developing autoimmune disorders, and the incidence of severe immune-related adverse events observed in few patients with TMs treated with programmed cell death protein 1 (PD-1) inhibitors is significantly higher than that observed in patients with TC or with other solid tumors, their use should be strictly limited to clinical studies.

Several clinical trials testing new drugs and interesting combinations are currently ongoing and discussed at the end of this paper.

RECOMMENDATIONS

Selected relevant indications related to the diagnostic and staging work-up, as well as to surgical, radiotherapeutic, and systemic treatment management of patients with TET, are reported in the main text of this paper. [Supplementary Materials](https://doi.org/10.1016/j.esmoop.2021.100188), available at <https://doi.org/10.1016/j.esmoop.2021.100188>, report the complete AIOM recommendations, including panelists' agreement on each recommendation reported.

Diagnostic work-up

1. Diagnostic suspicion is based on clinical presentation after recording a complete medical history and conducting a full clinical examination, combined with laboratory tests and imaging.
2. Chest and upper abdomen contrast-enhanced computed tomography is the imaging modality of choice for TM diagnosis and for assessment of surgical resectability.

3. Chest magnetic resonance imaging should be considered when contrast medium is contraindicated (e.g. iodized contrast agent allergy) or in particular cases to evaluate involvement of vascular and cardiac structures before surgery.
4. Positron emission tomography remains a potentially useful option to complete staging work-up of secondary lesions and in suspect recurrences in TETs with aggressive histology and advanced stage.
5. If a thymic lesion highly suspicious to be a TET is radically resectable, upfront surgery with no prior diagnostic typing is generally recommended to avoid breaching of the capsule.
6. If a suspected TET is unresectable or requires preoperative treatment or differential diagnosis, pretreatment diagnostic typing is recommended.
7. Percutaneous core-needle, incisional surgical biopsy through anterior mediastinoscopy (without resection of cartilage), anterior mediastinotomy (with resection of cartilage), mini-thoracotomy, or video-assisted thoracic surgery (VATS) are the preferred biopsy approaches. Deep and multiple biopsies of the mass should be carried out. Fine-needle aspiration is generally not recommended.

Histopathological classification of TETs

1. Histopathological diagnosis must be made by a pathologist with specific expertise and validated by a referral center.
2. Histopathological diagnosis must be based on World Health Organization (WHO) classification criteria (a new edition of WHO classification is expected in 2021).
3. Diagnosis of TM and typing may often be made on the basis of morphological findings (i.e. hematoxylin and eosin stain). 'Mandatory' and 'optional' criteria for diagnostics have been introduced. It is frequently advisable to use immunohistochemical markers such as p63, p40, or CK34 β E12 to evaluate EC density to support the differentiation between B1 and B2 TMs; the presence of aberrant CD20 positivity in EC is associated with A and AB TMs.
4. TC diagnosis can be made from the resection specimen and biopsy, with identification of aggressive histotypes.
5. TC must be distinguished from TM and from metastatic carcinomas from other sites as patients undergo a different clinical management.
6. Several immunohistochemical markers for ECs (CD5, CD117, Glut1) and for thymocytes (TdT, CD1a) are useful in distinguishing TCs from TMs and from thymic metastases.
7. Histopathological diagnosis must indicate: histotype, disease extension, angioinvasion, presence of satellite nodules, state of margins, state of lymph nodes, and staging according to TNM.

TREATMENT OF THE PRIMARY TUMOR

Surgery

1. Complete thymectomy comprising removal of the TET, residual thymus, and perithymic fat is the surgical procedure of choice.
2. In locally advanced TETs, en bloc removal of all affected structures must be carried out, including lung parenchyma, pericardium, large venous vessels, nerves, and any pleural deposits whenever feasible.
3. Minimally invasive surgery [through thoracoscopic (VATS) or robotic (robot-assisted thoracic surgery) approach] is an option for early-stage cancers if carried out by experienced thoracic surgeons.
4. Routine removal of anterior mediastinal lymph nodes and anterior cervical lymph nodes (N1 stations) is recommended in all early-stage TMs.
5. In locally advanced TMs (III/IVa), in TCs/neuroendocrine tumors of the thymus of any stage, in addition to removal of N1 lymph nodes, sampling of some N2 stations (at least the paratracheal station) is recommended.

Radiotherapy

1. There is not sufficient evidence to recommend adjuvant radiotherapy to all patients with TETs. The level of evidence supporting post-operative adjuvant radiotherapy in completely surgically resected TETs is limited, and clinical and radiological follow-up should be considered as an alternative approach case by case.
2. Radiotherapy may be considered within a multidisciplinary assessment for patients with tumors at high risk of relapse and in case of residual disease after surgery.
3. In early stage such as stage I (T1a) radically resected TM (R0), post-operative radiotherapy may be considered in case of extracapsular involvement in aggressive histology (B3) and/or massive extracapsular involvement despite histology.
4. In stage II-III radically resected TM (R0), post-operative radiotherapy is indicated.
5. In stage IVA pN1 M0 radically resected TM (R0), post-operative radiotherapy is indicated.
6. In early TC (pT1a), radiotherapy is indicated in selected cases.
7. In stage I pT1b, II-III radically resected TC (R0), post-operative radiotherapy is indicated.
8. In stage I-III TC not radically resected (R1-R2), radiotherapy is indicated.
9. In stage IVA pN1 M0 radically resected TC (R0), post-operative radiotherapy is indicated.
10. The usual dosage is 45-50 Gy (1.8-2 Gy/fraction) for R0 margins, followed by a boost according to margin status.

SYSTEMIC THERAPY

Thymoma

Resectable and locally advanced unresectable disease.

1. In patients with resectable disease, adjuvant or neoadjuvant chemotherapy is not indicated because there is no evidence demonstrating an advantage in survival.
2. In patients with locally advanced unresectable disease (i.e. Masaoka III and TNM IIIA/T3 and IIIB/T4), induction chemotherapy is indicated in a multimodal approach, including subsequent surgery and radiotherapy if the tumor becomes resectable, or definitive radiotherapy when unresectable.
3. The induction chemotherapy regimen proposed consists of a combination of doxorubicin, cisplatin, and cyclophosphamide (CAP regimen).
4. In the absence of evidence on the optimal duration of induction treatment, the recommendation is to continue chemotherapy to maximal response and/or tolerance, for a maximum of 4-6 cycles.

Metastatic disease

1. In patients with resectable metastatic disease confined to the pleura and/or pericardium (Masaoka stage IVA or TNM IVA/M1a), induction chemotherapy is recommended as part of a multimodal approach, integrated by subsequent surgery and/or radiotherapy.
2. However, in the absence of evidence demonstrating a benefit in survival by multimodal approach with neoadjuvant chemotherapy followed by local treatment, versus upfront surgery, the latter option can be discussed with the patient.
3. In patients with unresectable metastatic disease (Masaoka IVB and TNM IVB/M1b) or when local treatment is not appropriate, palliative systemic chemotherapy is indicated.¹⁻³
4. First-line chemotherapy regimen of choice is CAP regimen.
5. In indolent and paucisymptomatic disease, monotherapy (preferably with anthracyclines) may be considered.
6. Continuation of first-line treatment to maximal response and/or tolerance for a maximum of 6 cycles is recommended.
7. Patients progressing with first line and with performance status (PS) 0-2 according to ECOG scale, should be enrolled in clinical trials if open, or alternatively receive second-line chemotherapy.
8. In octreoscan-positive patients not eligible for chemotherapy, octreotide ± prednisone is a therapeutic option.
9. Some evidences support antitumor activity of everolimus in patients who received at least one line of chemotherapy with platinum salts, but it is currently not approved by regulatory agencies.

10. Anti-PD-1 or anti-programmed death-ligand 1 (PD-L1) immunotherapy should not be administered out of clinical trials.

Thymic carcinoma

Resectable and locally advanced unresectable disease.

1. In stage I and II resectable disease, (neo)adjuvant chemotherapy is not indicated.
2. In stage III cancer after R0 surgery, considering the higher risk recurrence, adjuvant chemotherapy may be discussed with the patient, but highlighting the absence of evidence from randomized clinical trials.
3. In non-radical R1 or R2 resections, post-operative chemotherapy must be considered.
4. In locally advanced unresectable disease, multimodal treatment including induction polychemotherapy is indicated. The chemotherapy regimen of choice is the association of carboplatinum and paclitaxel (CBDCA + TXL).
5. Continuation of induction treatment to maximal response and/or tolerance for a maximum of 4-6 cycles is recommended.

Metastatic disease

1. In stage IV disease, in fit patients, palliative polychemotherapy is indicated.
2. Frontline chemotherapy of choice is a combination of CBDCA + TXL.
3. Continuation of first-line treatment to maximal response and/or tolerance for a maximum of 6 cycles is recommended.
4. Patients in progression from first line with Eastern Cooperative Oncology Group PS 0-2 should be enrolled in clinical trials if available, or alternatively receive second-line treatment.
5. Sunitinib is the second-line treatment of choice.
6. Further lines of treatment in fit patients are represented by combination therapies with gemcitabine and capecitabine, anthracycline with or without cyclophosphamide, or monotherapy with pemetrexed, ifosfamide, etoposide, paclitaxel, or 5-fluorouracil.
7. In patients who received at least one line of chemotherapy with platin, pembrolizumab is a therapeutic option.
8. Some evidences support antitumor activity of everolimus and lenvatinib in patients who received at least one line of chemotherapy with platinum salts, but they are currently not approved by regulatory agencies.

FUTURE PERSPECTIVES: TRIALS ONGOING WITH NEW DRUGS OR COMBINATIONS

Recurrently mutated oncogenes in TETs, such as *HRAS* and *NRAS*, are not targetable at this time.²²

Hyper-activation of exportin-1 (XPO1) protein is one of the molecular mechanisms that cancers, including TETs, use to inactivate tumor suppressor proteins.

Selinexor, a selective inhibitor of XPO1, showed relevant activity in TET cell lines and mouse xenografts²³ and anti-tumor activity has been reported in four patients with TETs treated in a phase I trial.²⁴ Two phase II trials are currently testing the activity of selinexor in advanced and pretreated TETs (NCT03193437, NCT03466827).

Recurrent alterations of the cell cycle reported in TETs represent the rationale to test palbociclib, a cyclin-dependent kinase 4/6 inhibitors, in an ongoing phase II trial which enrolls advanced TETs after failure of at least one cytotoxic chemotherapy regimen (NCT03219554).

The combination of anti-PD-1/PD-L1 with anti-cytotoxic T-lymphocyte antigen 4 or anti-angiogenic drugs is under evaluation in several clinical trials.

The Nivolumab in Patients With Type B3 Thymoma and Thymic Carcinoma (NIVOTHYM) trial, sponsored by the European Organisation for Research and Treatment of Cancer, is evaluating nivolumab alone or in combination with ipilimumab in patients with advanced B3 TM and TC (NCT03134118).

The phase II Combined Avelumab and Axitinib in Thymic Tumors (CAVEATT) is testing the activity of the combination of the anti-PD-L1 avelumab with the anti-angiogenic drug axitinib, in patients with pretreated advanced TMs B3 or TCs. This therapeutic strategy has recently demonstrated impressive efficacy in patients with metastatic renal cancers.²⁴

The combination of pembrolizumab and sunitinib is under evaluation in a phase II trial enrolling patients with advanced and pretreated TCs (NCT03463460).

The enzyme indoleamine 2,3-dioxygenase (IDO), which converts tryptophan into kynurenine, may play an important role in cancer immune evasion and immunosuppression mechanisms.

A study with the combination of pembrolizumab plus the IDO inhibitor epacadostat, which was under evaluation in advanced TCs (NCT023640769), has recently closed to accrual, after a large randomized phase III trial in advanced melanoma failed to achieve the primary endpoint.²⁵

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DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES

- Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and associations with subsequent malignancies. *Int J Cancer*. 2003;105:546-551.
- Weis CA, Yao X, Deng Y, et al. The impact of thymoma histotype on prognosis in a worldwide database. *J Thorac Oncol*. 2015;10(2):367-372.
- Kangueane P. Major histocompatibility complex (MHC) and peptide binding. In: *Bioinformation Discovery: Data to Knowledge in Biology*. New York, NY: Springer; 2009. p. 111-130.
- Radovich M, Pickering CR, Felau I, et al. The integrated genomic landscape of thymic epithelial tumors. *Cancer Cell*. 2018;33:244-258.
- Badve S, Goswami C, Gokmen-Polar Y, et al. Molecular analysis of thymoma. *PLoS One*. 2012;7(8):e42669.
- Girard N, Shen R, Guo T, et al. Comprehensive genomic analysis reveals clinically relevant molecular distinctions between carcinomas and thymomas. *Clin Cancer Res*. 2009;15(22):6790-6799.
- Sun C, Molineros JE, Looger LL, et al. High-density genotyping of immune-related loci identifies new SLE risk variants in individuals with Asian ancestry. *Nat Genet*. 2016;48:323-330.
- Barak B, Feng G. Neurobiology of social behavior abnormalities in autism and Williams syndrome. *Nat Neurosci*. 2016;19:647-655.
- Roy AL. Pathophysiology of TFI-1: old guard wearing new hats. *Trends Mol Med*. 2017;23(6):501-511.
- Zekheridou A, McKeon A, Lennon VA. Frequency of synaptic autoantibody accompaniments and neurological manifestations of thymoma. *JAMA Neurol*. 2016;73(7):853-859.
- Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2014;9(9 suppl 2):S65-S72.
- Roden AC, Yi ES, Jenkins SM, et al. Modified Masaoka stage and size are independent prognostic predictors in thymoma and modified Masaoka stage is superior to histopathologic classifications. *J Thorac Oncol*. 2015;10(4):691-700.
- Petrini I, Zucali PA, Lee HS, et al. Expression and mutational status of c-kit in thymic epithelial tumors. *J Thorac Oncol*. 2010;5(9):1447-1453.
- Yoh K, Nishiwaki Y, Ishii G, et al. Mutational status of EGFR and KIT in thymoma and thymic carcinoma. *Lung Cancer*. 2008;62:316-320.
- Cimpean AM, Raica M, Encica S, et al. Immunohistochemical expression of vascular endothelial growth factor A (VEGF), and its receptors (VEGFR1, 2) in normal and pathologic conditions of the human thymus. *Ann Anat*. 2008;190:238-245.
- Alberobello AT, Wang Y, Beerens FJ, et al. PI3K as a potential therapeutic target in thymic epithelial tumors. *J Thorac Oncol*. 2016;11:1345-1356.
- Petrini I, Wang Y, Zucali PA, et al. Copy number aberrations of genes regulating normal thymus development in thymic epithelial tumors. *Clin Cancer Res*. 2013;19:1960-1971.
- Wang Y, Thomas A, Lau C, et al. Mutations of epigenetic regulatory genes are common in thymic carcinomas. *Sci Rep*. 2014;4:7336.
- Giaccone G, Rajan A, Berman A, et al. Phase II study of belinostat in patients with recurrent or refractory advanced thymic epithelial tumors. *J Clin Oncol*. 2011;29:2052-2059.
- Zucali PA, De Pas T, Palmieri G, et al. Phase II study of everolimus in patients with thymoma and thymic carcinoma previously treated with cisplatin-based chemotherapy. *J Clin Oncol*. 2018;36:342-349.
- Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. *Lancet Oncol*. 2018;19:347-355.
- Conforti F, Pala L, Giaccone G, De Pas T. Thymic epithelial tumors: from biology to treatment. *Cancer Treat Rev*. 2020;86:102014.
- Conforti F, Zhang X, Rao G, et al. Therapeutic effects of XPO1 inhibition in thymic epithelial tumors. *Cancer Res*. 2017;77(20):5614-5627.
- Choueri TK, Larkin J, Oya M, et al. Preliminary results for avelumab plus axitinib as first line therapy in patients with advanced clear-cell renal-cell carcinoma (Javelin Renal 100): an open label, dose finding and dose expansion, phase I b trial. *Lancet Oncol*. 2018;19:451-460.
- Long GV, Dummer R, Hamid O, et al. Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. *Lancet Oncol*. 2019;20(8):1083-1097.