Best practices for the management of thymic epithelial tumors: A position paper by the Italian collaborative group for ThYmic MalignanciEs (TYME)

Tumour Review

Best practices for the management of thymic epithelial tumors: A position paper by the Italian collaborative group for ThYmic MalignanciEs (TYME)

Martina Imbimbo, Margaret Ottaviano, Milena Vitali, Alessandra Fabbri, Giovanni Leuzzi, Michele Fiore, Davide Franceschini, Giulia Pasello, Matteo Perrino, Marco Schiavon, Giancarlo Pruneri, Angelo Paolo Dei Tos, Claudia Sangalli, Marina Chiara Garassino, Rossana Berardi, Alessandra Alessi, Giuseppina Calareso, Iacopo Petrini, Marta Scorsetti, Vieri Scotti, Lorenzo Rosso, Federico Rea, Ugo Pastorino, Paolo Giovanni Casali, Sara Ramella, Umberto Ricardi, Laura Abate-Daga, Valter Torri, Annalisa Trama, Giovannella Palmieri, Mirella Marino, Paolo Andrea Zucali; TYME network collaborators

Introduction

Thymic epithelial tumors (TETs) are a heterogenous group of rare tumors, with a complex histopatological classification and staging system [1].

World annual incidence of TETs ranges from 1.3 to 3.2 per million. The monograph of the Italian Association of Cancer Registries (AIRTUM) on rare cancers reported an overall incidence of TETs of 3.6 per million person/year (around 230 new cases estimated/year) [http://www.registri-tumori.it/cms/it/Rapp2015]. Most of TETs are thymomas (incidence rate 2.8/1,000,000) whereas thymic carcinoma are extremely rare (incidence < 0.1/1,000,000). These data are likely to be underestimated as, referring to the period of diagnosis 2000–2010, are based on the old WHO classification, where some encapsulated tumors were not included in the definition of "malignant" and therefore not available in the AIRTUM database. Nevertheless, Italian data have shown to be coherent with those from European population-based cancer registries, which collect only malignant cancers as standard practice [2].

The relative survival (RS) rates of patients at 1-year and 5-year from diagnosis are 85% and 68%, respectively. However, differences exist between thymoma and thymic carcinoma with a 5 year RS of about 70% and 37%, respectively [3]. Around 1900 patients were estimated to be living with a diagnosis of TET in 2010 in Italy showing a non-negligible prevalence of these diseases (http://www.registri-tumori.it/cms/it/Rapp2015).

According to the World Health Organization (WHO) histopathological classification, TETs are divided into thymomas (Ts: A, A/B, B1, B2, B3 subtypes) and thymic carcinomas (TCs: C), with different biology and clinical behaviours [3].

The Masaoka Koga staging system has been the mostly widely used for routinely staging of TETs [4–6]. In 2011 a Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) was established by the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancies Interest Group (ITMIG) and proposed the first version of the TNM staging system and a node map based on overall survival analyses of an ITMIG retrospective international database of more than 10,000 cases from 105 institution worldwide [7–10]. This new classification has formally replaced Masaoka Koga staging system and although there are some similarities, the new TNM classification leads to a different distribution of some stages: I and II of Masaoka Koga are included in stage I of TNM system, pericardium invasion is classified as stage II of TNM, while stage III of TNM is further divided into 3a and 3b according to invasion of surrounding structures. All these changes lead to uncertainty in the therapeutic indications and further studies are required to validate the effective prognostic value of the new TNM staging system.

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines [11] on thymic cancers, provide recommendations on diagnosis, staging and risk assessment and management of resectable and advanced disease. However, being a rare disease, these guidelines are based on data from retrospective analyses, prospective non-randomized trials or experts' opinions. Therefore, the management of TETs is still very complex and it is crucial to create a network to coordinate the work among centres involved in the treatment of these diseases in order to offer the best diagnostic and therapeutic tools.

For this purpose, in 2014 a network for thymic malignancies named TYME (ThYmic MalignanciEs), was founded in Italy by 6 centres strongly committed in the treatment of these malignancies (Table 1). Among the activities of the network there are: the collection of clinical information for patients referred to the centres, histological revisions and referral for multidisciplinary team discussion (MTD) and for clinical trials.

To explore how these tumors are managed in the different centres of Italy compared to ESMO guidelines, a panel of multidisciplinary experts from TYME network and from other Italian centres strongly involved in TET diagnosis and treatment convened a first Italian Expert meeting

Table 1
List of centres of TYME network.

Centres of TYME network	City
Ospedali Riuniti di Ancona*	Ancona
ASST Bergamo Est Ospedale Bolognini	Seriate, Bergamo
Ospedale Maggiore	Bologna
Policlinico S. Orsola – Malpighi	Bologna
ASST Spedali Civili	Brescia
AOU Careggi	Firenze
Ospedale Policlinico San Martino	Genova
Ospedale dell'Angelo-ULSS 3 Serenissima	Mestre, Venezia
Fondazione IRCCS Istituto Nazionale dei Tumori*	Milano
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	Milano
Istituto Clinico Humanitas*	Rozzano, Milano
Istituto Europeo di Oncologia	Milano
Ospedale San Raffaele	Milano
IRCCS Istituto di Ricerche Farmacologiche Mario Negri	Milano
AOU Policlinico di Modena	Modena
Centro Riferimento Tumori Rari (CRTR) AOU "Federico II"*	Napoli
Istituto Nazionale Tumori-IRCCS "Fondazione G. Pascale"	Napoli
AORN Cardarelli	Napoli
AORN dei Colli - Ospedale Monaldi	Napoli
AOU Maggiore della Carità	Novara
Istituto Oncologico Veneto IRCCS*	Padova
AOU di Padova	Padova
Facoltà di Medicina - Università degli studi di Padova	Padova
AOU Pisana*	Pisa
Fondazione Policlinico Universitario A. Gemelli	Roma
IRCSS Istituto Nazionale Tumori Regina Elena	Roma
AO San Camillo-Forlanini	Roma
Università Campus Bio-Medico	Roma
AOU Senese	Siena
AOU Città della Salute e della Scienza	Torino
AOU San Luigi Gonzaga	Orbassano, Torino

* Founding centres of TYME network.

Fig. 1. Geographical distribution of centres of origin of physicians who attended the Italian experts meeting.

together with representatives of patient advocacy.

This paper summarizes the controversial issues highlighted during the discussion.

With the aim of harmonizing TET management we propose treatment recommendation based on Masaoka Koga and the new TNM staging system.

Materials and methods

Sixty-six representatives from 27 Italian centres involved in the management of TETs (Fig. 1) as well as the president of the association for patients affected by rare thoracic cancers Tu.To.R., 2 patients, and their relatives, attended the meeting that was hold on September 18th, 2017 in Milan, Italy.

The participating physicians included specialists in pathology, radiology, thoracic surgery, radiotherapy, medical oncology, nuclear medicine, palliative care, and neurology (Fig. 2). We included specialists involved in the treatment of at least 15 cases/year or centres included in the European Reference Network (ERN), selected through a survey conducted in the previous months.

All the participants attended a general session in which ESMO guidelines and issues in TETs diagnosis and treatment were presented and discussed. Then, using a tele voting system, the adherence to these guidelines was assessed. All the controversial issues were then discussed in three separated sessions (diagnosis; surgery; medical therapy and radiotherapy).

Results

Diagnosis

Imaging

All the participants agreed that i.v. contrast-enhanced computed tomography (CT) scan of the thorax represents the standard imaging procedure for TET diagnosis and evaluation of resectability (Fig. 3), while CT of the abdomen is recommended to rule out the presence of metastases. MRI is used in case of patients with i.v. contrast allergy and to discriminate between cancer and thymic hyperplasia.

Pre-treatment biopsy is considered necessary, except in case of highly suggesting imaging and resectable tumor [12,13]. Core needle biopsy or incisional surgical biopsy should be preferred to obtain tissue for histological diagnosis [14].

A relevant role of cytology in the diagnosis of TETs is considered not evident. A histological evaluation of an adequate biopsy or a surgical specimen should always be done.

FDG PET/CT is generally not recommended to assess a thymic mass but it can be used in selected cases. Preliminary studies indicate that

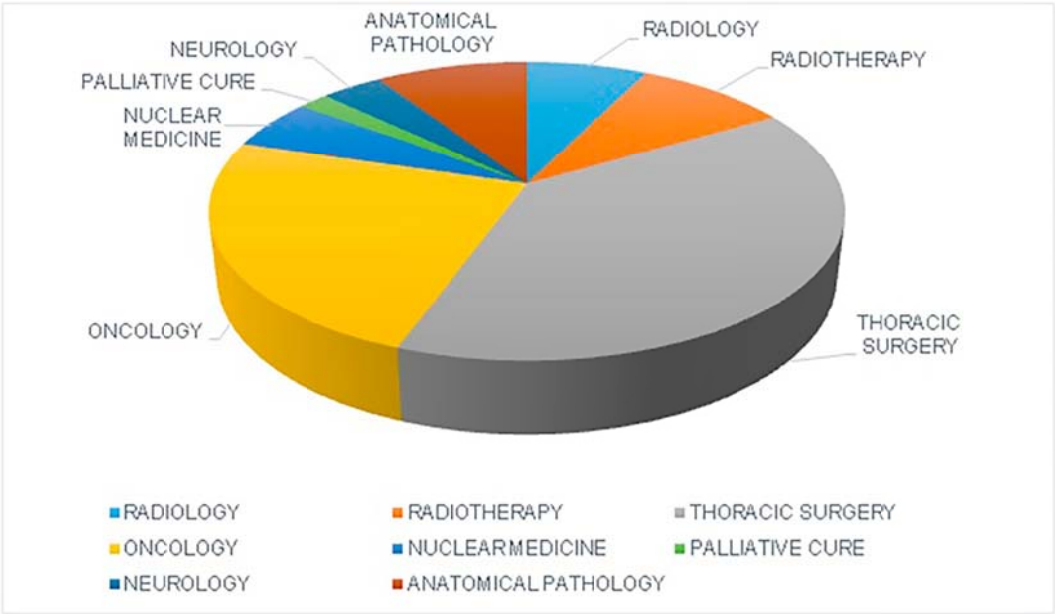

Fig. 2. Chart of distribution for area of specialty of physicians who voted in the Italian experts meeting.

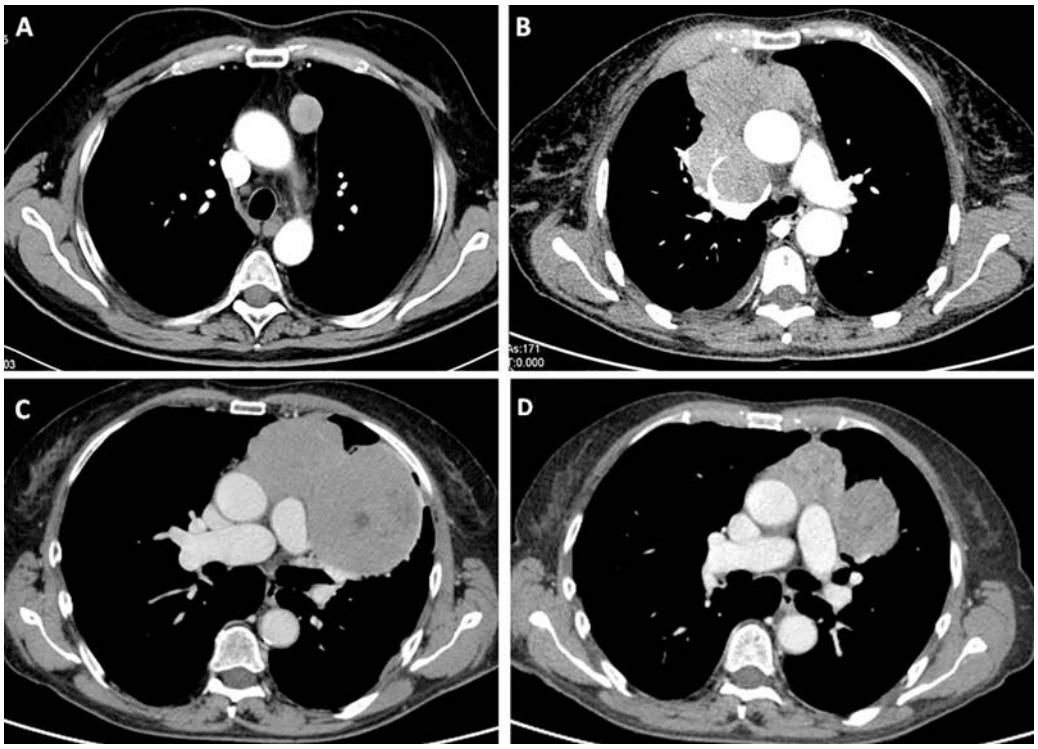

Fig. 3. A. A 65-year-old male presenting with a capsulated mediastinal nodule measuring 3 cm in the major axis. The patient underwent surgery. Pathological findings evidenced a B2 thymoma (Masaoka-Koga stage I). B. A 61-year-old female with B2 thymoma invading the aortic arch and superior vena cava (with a neoplastic thrombus inside). The patient was judged unresectable at the multidisciplinary board evaluation and started chemotherapy C. A 62-year-old female with B2 thymoma invading the pericardium, phrenic nerve, left anonym vein and the lung. D. CT-scan evaluation after induction therapy showing partial response to therapy. The patient underwent surgery. Pathological findings evidenced a B2 thymoma (Masaoka-Koga stage III).

FDG uptake, measured with SUV (Standard Uptake Value), may be higher in type B3 thymomas and thymic carcinomas; however, an increased SUV may also be assessed in thymic hyperplasia.

FDG PET/CT is considered optional in case of tumors with aggressive histology and advanced stage to complete the staging work-up or to characterize lesions detected by other imaging tools and considered suspicious for their recurrence. In case of recurrent or primary unresectable tumors treated with chemo and/or radiotherapy, FDG PET/CT is used for therapy monitoring.

Additional radiopharmaceuticals, such as ^{68}Gallium (^{68}Ga)-labeled somatostatin analogues, or somatostatin receptors scintigraphies could be used in patients not responding to therapy to evaluate additional therapeutic possibilities.

Pathology

All the participants agreed that the pathological diagnosis of TETs should be carried out or revised in a reference centre by expert pathologists. Knowledge of clinical and laboratory data and of associated autoimmune disorders will contribute to a correct diagnosis.

In case of surgical resection, it is suggested that surgeons provide the adequate information regarding the surgical procedure, specimen orientation, anatomical location, level of invasion and completeness of macroscopic resection. The pathologists should preserve the integrity and the correct orientation of surgical specimens as well as properly mark extra-thymic structures if included. After measuring of tissue specimen, adequate sampling of the tumor mass as well as of tumor nodules included in the peritumoral adipose tissue should be performed. Distinct tumor nodules should be separately sampled, diagnosed and staged [15].

As the role of cytology is rather limited, the majority of participants agreed that diagnosis of TETs should always achieved by the histological evaluation of an adequate biopsy or a surgical specimen. Frozen section examination is not regarded an adequate diagnostic procedure, although it may prove useful in assessing the adequacy of the material to be examined for a definitive diagnosis. In Italy, the histologic classification of thymic tumors follows the current WHO classification in association with the "refined criteria" and definitions proposed by a panel of experts in a pathology workshop promoted by ITMIG [3,16] (Fig. 4).

In the routine diagnostic workup, the histological pattern is usually diagnostic and specific for the surgically resected TETs. However, an accurate subtyping is performed by the use of few monoclonal antibodies such as cytokeratins, p63 or p40, and terminal deoxynucleotidyl transferase (Tdt). TC markers such as KIT (CD117), CD5, GLUT1 and MUC1, are recommended for differential diagnosis with other carcinomas. A panel considering these antibodies is recommended also in order to evaluate core or surgical biopsies for differential diagnosis with other non epithelial neoplasms. Furthermore, the adoption of a standardized pathological report [15] in order to provide in a reproducible way all the relevant diagnostic information is strongly recommended (Fig. 5).

In the group of TETs, the uncommon neuroendocrine thymic tumors are also included. In young patients presenting with a poorly differentiated squamous carcinoma, thymic NUT midline carcinoma should be considered, and therefore NUT protein and/or *NUT* gene and/or aberrations should be investigated [17]. After neoadjuvant therapy, the pathological evaluation of residual tumor follows similar procedures as for other organs/system [18,19].

Actionable mutations supportive of a targeted therapy are not available at the moment. However, suggestions for specific kit-based molecular studies have been proposed [20]. The Cancer Genome Atlas of Thymoma, just published, will certainly provide new field of investigation to establish a "precision medicine" for Thymoma and Thymic carcinoma [21].

Finally, the creation of a biobank including snap-frozen tumor tissue and matched blood samples is strongly recommended to contribute to specific molecular and/or multicentre studies.

Parathymic autoimmune diseases

The development of an autoimmune disease is an event quite common in patients with TETs compared with controls (32.7% vs 2.4%; $P < 0.001$) [22]. Myasthenia gravis (MG) is the most frequent diagnosed, as 15–20% of MG patients have a thymoma, while 24.5–40% of thymoma patients develop MG [23]. Other syndromes more often

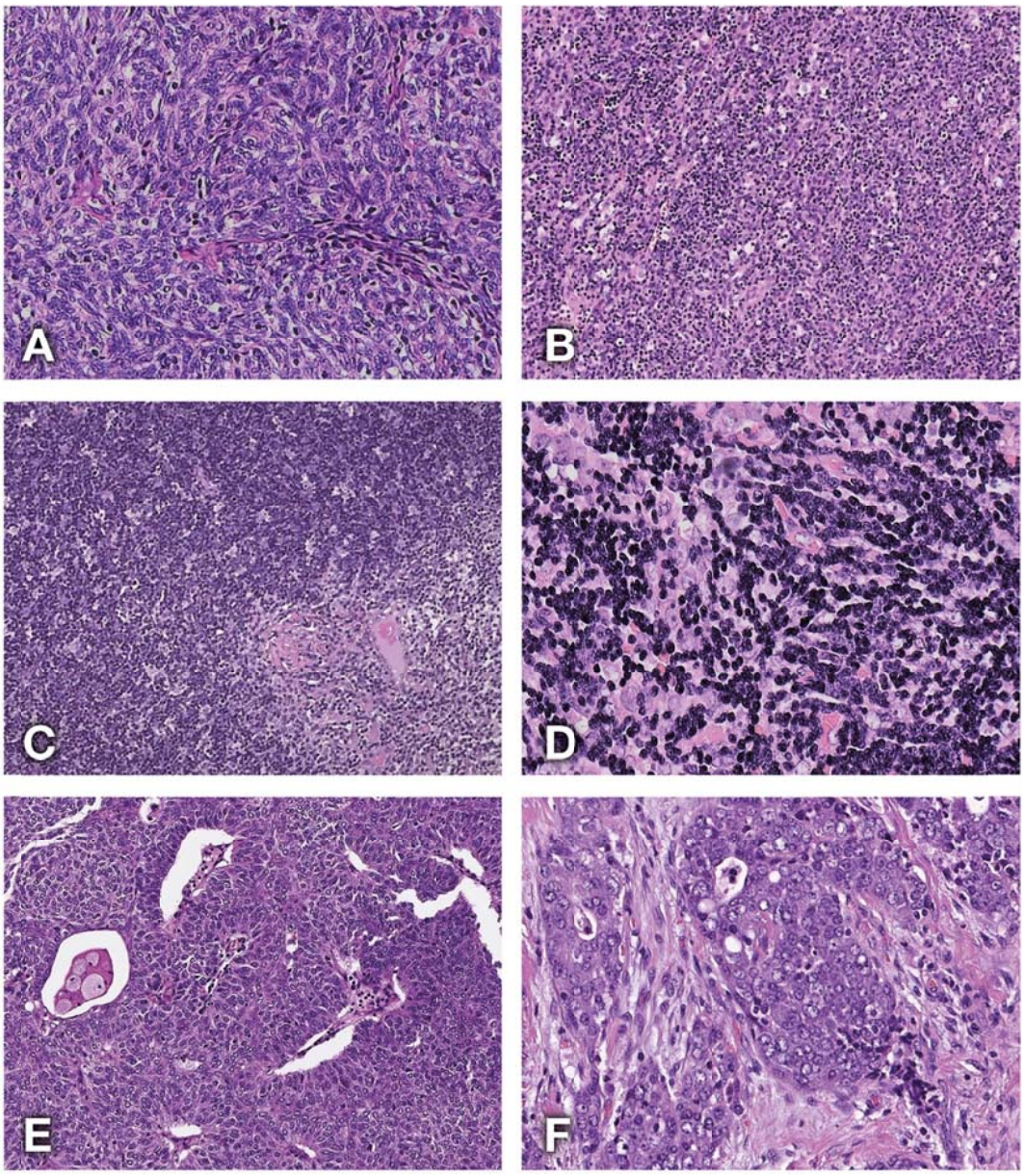

Fig. 4. TET according to WHO classification, H&E stain – an overview. (A) Type A thymoma according to the WHO classification: spindle-shaped epithelial cells (EC), very few mature lymphocytes (LY) interspersed, 200×. (B) Type AB thymoma: network of EC, with a variable LY content, mostly immature T cells; hystiocytes with clear cell cytoplasm are scattered, 100×. (C) Type B1 thymoma: the most organotypic histotype of thymoma: a loose network of EC is mostly hidden by a high amount of LY of the immature cortical type; a medullary island with a Hassall's body is seen on the right, 100×. (D) Type B2 thymoma: a dense network of EC stands out on the LY background of the cortical type, 400×. (E) Type B3 thymoma: sheets of EC with few LY interspersed, usually of immature type; the EC form palisades around vessels; perivascular spaces are seen, 100×. (F) Thymic carcinoma: in this case, nests of poorly differentiated EC in a fibrous stroma, 400×.

associated with TETs are Pure Red Cell Aplasia (5%) and Good's syndrome (5%) [24–26].

Therefore, in order to evaluate the presence of an autoimmune disease in patients with a newly diagnosed TET, all participants strongly recommended to collect clinical data regarding autoimmune related signs and symptoms (i.e. fatigable muscle weakness, neurological manifestations, recurrent infections and anemia) and to perform specific analyses (acetylcholine receptor antibody assay, blood count with reticulocytes count, dosage of immunoglobulins and immunophenotypic analysis on peripheral blood).

In case of diagnosis of an autoimmune disease, the patient should be addressed to the appropriate specialist (neurologist, immunologist and/or haematologist).

Management of TETs

The proposed management of TETs according to Masaoka Koga and TNM staging systems is discussed in the following sections and summarized in Tables 2 and 3.

Resectable disease

Surgery. In case of resectable thymic tumors (Masaoka-Koga stage I/II and selected stage III tumors or stage I, II, selected IIIA/T3 in the IASLC/ITMIG TNM staging system), all participants agreed that surgical intervention is the first step of treatment. Radical thymectomy is considered the gold standard procedure and consists in removing the tumor along with the residual thymus gland and perithymic fat. If these surgical principles are respected, surgery may be performed through open (sternotomy) or minimally invasive approach (transcervical,

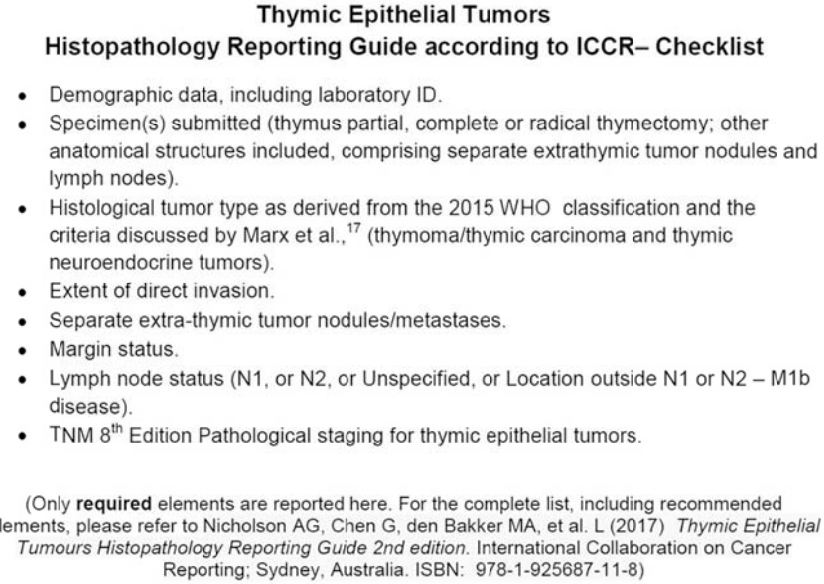

Fig. 5. Histopathology Reporting Guide according to ICCR – Checklist.

extended transcervical, video-assisted thoracoscopy [VATS] and robotic surgery [RATS]) according to surgeon's preference and expertise.

Minimally invasive surgery is recommended for a tumor dimension lower than 5 cm while in case of invasion of neighbour organs (pericardium, lung, mediastinal pleura or phrenic nerve), this procedure is not a contraindication in expert hands [27,28].

Thymomectomy (consisting in the removal of the tumor leaving residual thymic tissue and perithymic fat) should be carried out in selected cases only (clinical stage I, elderly, non-myasthenic patients, lateralized tumors distant from phrenic nerve or anonym veins).

Regarding lymphadenectomy, lymph-node sampling of the anterior region (N1) is highly recommended in localized disease (clinical stage I-II), regardless of tumor histology [18,29].

Dissection of lymph-nodes of deep region (N2) should be considered in advanced disease (stage III) and in thymic carcinomas [29].

The decision on whether performing primary surgery or induction therapy in patients with radiological signs of T3 invasion (lung, anonym vein, superior vena cava, phrenic nerve and extrapericardial pulmonary vessels) should be based on the multidisciplinary board evaluation, although induction therapy is highly suggested.

Adjuvant treatment. After a R1 resection, all participants agreed that adjuvant chemotherapy combined with radiotherapy should be recommended in case of thymic carcinoma while postoperative radiation therapy in case of thymomas. Indication to adjuvant treatments after R0 resection is still controversial because all data are biased by the absence of randomized controlled trials. However, on the basis of new evidences from literature, the use of adjuvant radiation treatment could be considered in selected clinical situations [30–35].

After a R0 resection, adjuvant treatments have no role in Masaoka/Koga stage I-IIa thymoma and thymic carcinoma. However, based on available evidences and on expert opinion, in Masaoka/Koga stage IIB, B2-B3 thymoma and thymic carcinoma, radiotherapy treatment is an option to consider. In pT1a tumors (TNM staging), most of participants consider radiotherapy as adjuvant therapy in case of a macroscopic infiltration into thymic capsule or surrounding fatty tissue and therefore if such features are not reported, it is recommended to discuss the type of treatment with the pathologist.

In Masaoka/Koga stage III (pT1b for mediastinal pleural-Stage I and also pT2 for pericardium invasion-Stage II of the TNM) radiotherapy treatment is recommended regardless of histology. On the basis of available evidences adjuvant chemotherapy is not recommended in thymomas while it could be proposed in stage III thymic carcinoma [36,37].

Finally, in Masaoka/Koga stage IVB (stage IVa or IVb of the TNM) thymoma and thymic carcinoma, radiotherapy treatment is suggested in case of lymph node metastasis (pN1/pN2).

In general participants agreed that indication to adjuvant treatments should take into account long term treatment strategies and expected toxicities, especially when given in combination or in recurrent disease.

The total adjuvant dose recommended is 45–50 Gy in case of R0 resection, whereas a dose of 54 Gy should be delivered in case of R1 resection. Dose up to 60–70 Gy should be given to patients with gross residual disease. Standard fractionation (1.8–2 Gy per daily fraction) is applied.

All participants agreed that adjuvant chemotherapy regimens should be chosen based on drugs combinations effective in the palliative setting taking into account cumulative toxicities. Four cycles of chemotherapy are recommended.

Adjuvant treatments should be administered within 8–12 weeks from surgery. If radiotherapy is indicated, it should be delivered after adjuvant chemotherapy.

A therapeutic algorithm for postoperative treatment is provided in Fig. 6.

Advanced disease

Locally advanced disease. In this setting of disease, most of participants agreed with ESMO guidelines. In case of locally advanced non-resectable TETs (Masaoka-Koga stage III/IVA tumors or TNM stage IIIA/T3, IIIB/T4, IVA) a biopsy for diagnosis is suggested. Primary/induction chemotherapy is recommended as part of a curative-intent strategy that comprises subsequent surgery or radiotherapy [11,38,39]. Patients not eligible for local treatment should receive only palliative chemotherapy.

Cisplatin-based combination regimens for at least two to four cycles are recommended before reassessing the resectability of the tumor through imaging re-staging. [40,41]. Combination polichemotherapy with CAP (Cisplatin 50 mg/mq, doxorubicin 50 mg/mq, ciclophosphamide 500 mg/mq every 21 days) is considered the regimen of

Table 2
Proposed management according to Masaoka-Koga staging system.

Masaoka-Koga	Thymoma	Thymic Carcinoma
Stage I	Upfront surgery No biopsy • If complete resection (R0): – no postoperative RT • If incomplete resection (R1): – postoperative RT (54 Gy)	Upfront surgery No biopsy • If complete resection (R0): – no postoperative RT • If incomplete resection (R1): – postoperative RT (54 Gy)
Stage IIA	Upfront surgery No biopsy • If complete resection (R0): – no postoperative RT • If incomplete resection (R1): – postoperative RT (54 Gy)	Upfront surgery No biopsy • If complete resection (R0): – no postoperative RT • If incomplete resection (R1): – postoperative RT (54 Gy) – consider postoperative chemotherapy
Stage IIB	Upfront surgery No biopsy • If complete resection (R0): – type A–B1: no postoperative RT – type B2–B3: consider postoperative RT (45–50 Gy) • If incomplete resection (R1): – postoperative RT (54 Gy)	Upfront surgery No biopsy • If complete resection (R0): – consider postoperative RT (45–50 Gy) • If incomplete resection (R1): – postoperative RT (54 Gy) – consider postoperative chemotherapy
Stage III Resectable disease	Upfront surgery No biopsy • If complete resection (R0): – postoperative RT (45–50 Gy) • If incomplete resection (R1): – type A–B2: postoperative RT (54 Gy) – type B3: postoperative RT (54 Gy) and consider postoperative chemotherapy	Upfront surgery No biopsy • If complete resection (R0): – postoperative RT (45–50 Gy) and consider postoperative chemotherapy • If incomplete resection (R1): – postoperative RT (54 Gy) and postoperative chemotherapy
Stage III Unresectable disease	Biopsy 1. Primary chemotherapy **If the tumor becomes resectable:** Surgery • If complete resection (R0): – postoperative RT (45–50 Gy) • If incomplete resection (R1): – postoperative RT (54 Gy) **If the tumor doesn't become resectable or R2:** – definitive RT (60–70 Gy) – consider concurrent chemo-RT (platinum-etoposide + RT 60–70 Gy) 2. Consider definitive concurrent chemo-RT (platinum-etoposide + RT 60–70 Gy)	Biopsy 1. Primary chemotherapy **If the tumor becomes resectable:** Surgery • If complete resection (R0): – postoperative RT (45–50 Gy) • If incomplete resection (R1): – postoperative RT (54 Gy) **If the tumor doesn't become resectable or R2:** – definitive RT (60–70 Gy) – consider concurrent chemo-RT (platinum-etoposide + RT 60–70 Gy) 2. Consider definitive concurrent chemo-RT (platinum-etoposide + RT 60–70 Gy)
Stage IVA	Biopsy Primary chemotherapy • If the tumor becomes resectable: – surgery – postoperative RT (45–50 Gy) only in N positive – RT boost on areas of concern (R1 resection) • If the tumor remains unresectable or R2: – definitive RT (60–70 Gy) – option: concurrent chemo-RT (60–70 Gy)	Biopsy Primary chemotherapy • If the tumor becomes resectable: – surgery – postoperative RT (45–50 Gy) only in N positive – RT boost on areas of concern (R1 resection) • If the tumor remains unresectable or R2: – definitive RT (60–70 Gy) – option: concurrent chemo-RT (60–70 Gy)
Stage IVB	Biopsy Definitive chemotherapy • If the tumor becomes resectable, consider: – surgery and postoperative RT – definitive RT	Biopsy Definitive chemotherapy • If the tumor becomes resectable, consider: – surgery and postoperative RT – definitive RT

RT = radiotherapy.

choice for thymoma, due to the high rate of tumor shrinkage, while carboplatin (AUC 5) paclitaxel (200 mg/mq) is preferred for thymic carcinoma [42–45]. Non-anthracycline regimens (e.g. cisplatin/etoposide, carboplatin/paclitaxel) may be considered for patients who cannot tolerate more aggressive treatments [45,46].

Patients with locally-advanced disease must be treated with the same surgical principles already explained in the resectable disease surgery session, except for lymphadenectomy that should include anterior as well as deep region sampling [18,29].

Patients with stage IIIB (according to TNM staging system) must undergo induction therapy. In case of tumor radiological response, surgery via median sternotomy should be performed only in highly-selected cases (invasion of pulmonary artery or great vessels, without invasion of trachea and esophagus).

Table 3
Proposed management according to TNM staging system.

TNM	Thymoma	Thymic Carcinoma
Stage I T1a N0 without extension into the mediastinal fat	Upfront surgery No biopsy ● If complete resection (R0): – no postoperative RT ● If incomplete resection (R1): – postoperative RT (54 Gy)	Upfront surgery No biopsy ● If complete resection (R0): – no postoperative RT ● If incomplete resection (R1): – postoperative RT (54 Gy)
Stage I T1a N0 with extension into the mediastinal fat	Upfront surgery No biopsy ● Type A–B1: – no postoperative RT ● Type B2–B3: – consider postoperative RT (45–50 Gy) ● If incomplete resection (R1): – postoperative RT (54 Gy)	Upfront surgery No biopsy ● If complete resection (R0): – consider postoperative RT (45–50 Gy) ● If incomplete resection (R1): – postoperative RT (54 Gy) – consider postoperative chemotherapy
Stage I T1b N0	Upfront surgery No biopsy ● If complete resection (R0): – postoperative RT (45–50 Gy) ● If incomplete resection (R1): – type A–B2: postoperative RT (54 Gy) – type B3: postoperative RT (54 Gy) and consider postoperative chemotherapy	Upfront surgery No biopsy ● If complete resection (R0): – postoperative RT (45–50 Gy) and consider postoperative chemotherapy ● If incomplete resection (R1): – postoperative RT (54 Gy) and postoperative chemotherapy
Stage II T2 N0	Upfront surgery No biopsy ● If complete resection (R0): – postoperative RT (45–50 Gy) ● If incomplete resection (R1): – type A–B2: postoperative RT (54 Gy) – type B3: postoperative RT (54 Gy) and consider postoperative chemotherapy	Upfront surgery No biopsy ● If complete resection (R0): – postoperative RT (45–50 Gy) and consider postoperative chemotherapy ● If incomplete resection (R1): – postoperative RT (54 Gy) and postoperative chemotherapy
Stage IIIA-IIIB T3 N0 T4 N0 Resectable disease	Upfront surgery No biopsy ● If complete resection (R0): – postoperative RT (45–50 Gy) ● If incomplete resection (R1): – type A–B2: postoperative RT (54 Gy) – type B3: postoperative RT (54 Gy) and consider postoperative chemotherapy	Upfront surgery No biopsy ● If complete resection (R0): – postoperative RT (45–50 Gy) and consider postoperative chemotherapy ● If incomplete resection (R1): – postoperative RT (54 Gy) and postoperative chemotherapy
Stage IIIA-IIIB T3 N0 T4 N0 Unresectable disease	Biopsy 1. Primary chemotherapy **If the tumor becomes resectable:** Surgery ● If complete resection (R0): – postoperative RT (45–50 Gy) ● If incomplete resection (R1): – postoperative RT (54 Gy) **If the tumor doesn't become resectable or R2:** – definitive RT (60–70 Gy) – consider concurrent chemo-RT (platinum-etoposide + RT 60–70 Gy) 2. Consider definitive concurrent chemo-RT (platinum-etoposide + RT 60–70 Gy)	Biopsy 1. Primary chemotherapy **If the tumor becomes resectable:** Surgery ● If complete resection (R0): – postoperative RT (45–50 Gy) ● If incomplete resection (R1): – postoperative RT (54 Gy) **If the tumor doesn't become resectable or R2:** – definitive RT (60–70 Gy) – consider concurrent chemo-RT (platinum-etoposide + RT 60–70 Gy) 2. Consider definitive concurrent chemo-RT (platinum-etoposide + RT 60–70 Gy)
Stage IVA Any T, N0-1; M0-1a	Biopsy Primary chemotherapy ● If the tumor becomes resect: – surgery – postoperative RT (45–50 Gy) only in N positive – RT boost on areas of concern (R1 resection)	Biopsy Primary chemotherapy ● If the tumor becomes resectable: – surgery – postoperative RT (45–50 Gy) only in N positive – RT boost on areas of concern (R1 resection)
	If the tumor remains unresectable or R2: – definitive RT (60–70 Gy) – option: concurrent chemo-RT (60–70 Gy)	If the tumor remains unresectable or R2: – definitive RT (60–70 Gy) – option: concurrent chemo-RT (60–70 Gy)
Stage IVB Any T, N0-2; M0-1b	Biopsy Definitive chemotherapy ● If the tumor becomes resectable, consider: – surgery and postoperative RT – definitive RT	Biopsy Definitive chemotherapy ● If the tumor becomes resectable, consider: – surgery and postoperative RT – definitive RT

RT = radiotherapy.

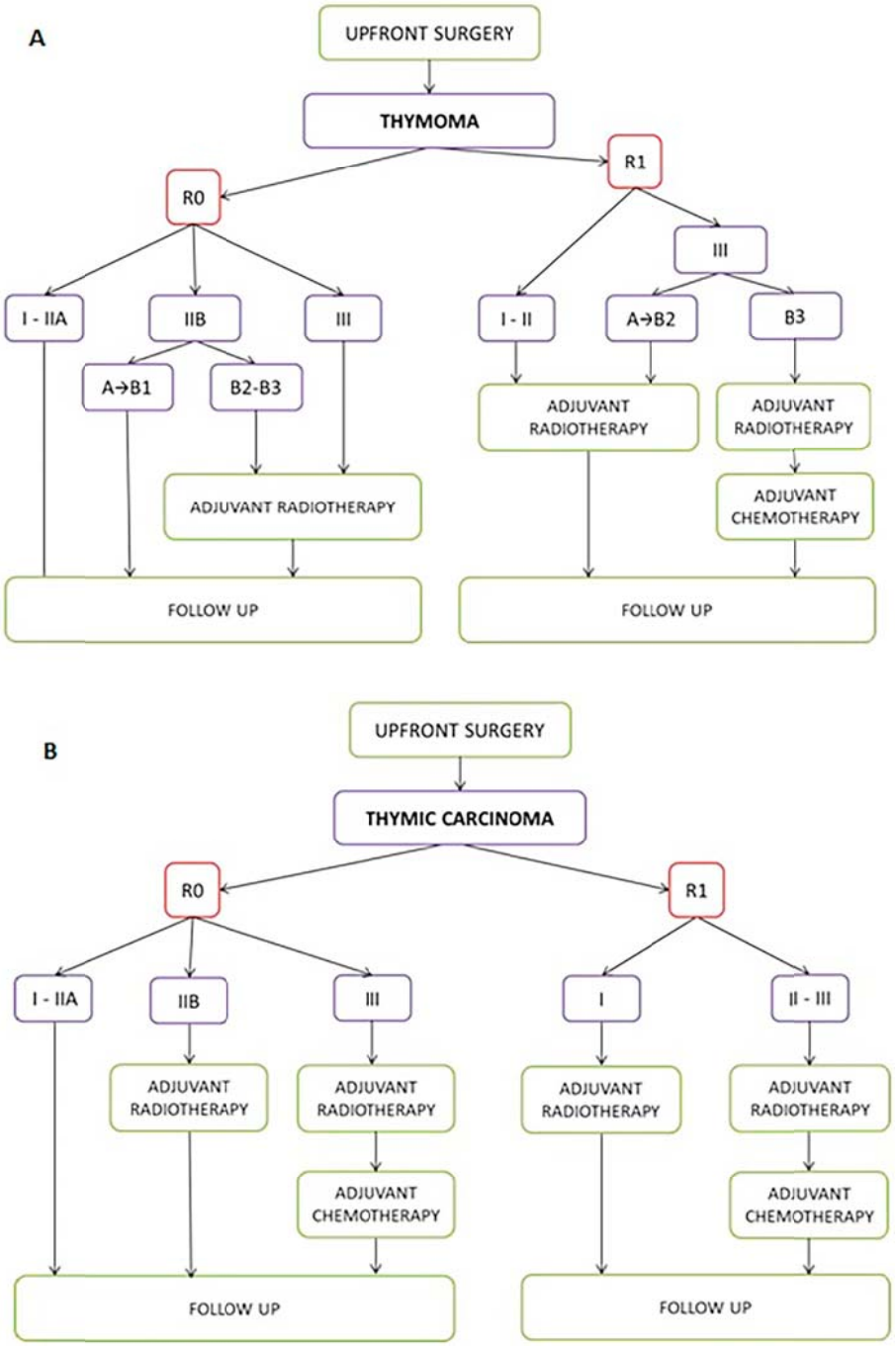

Fig. 6. Therapeutic algorithm for postoperative treatment of (A) thymoma and (B) thymic carcinoma.

In patients affected by stage IVA disease according to Masaoka and TNM stages (any T, N0 or N1, M0, M1 with pleural or pericardial nodule/s) and resectable tumors, surgery should be performed after induction chemotherapy only in patients with thymoma. Experts agreed that pleuro-pneumonectomy is not to be considered.

Adjuvant chemotherapy is indicated for tumors staged as IVa after primary surgery.

The option of primary chemoradiotherapy with platin and etoposide, especially in case of thymic carcinomas, is also supported [47,48]. In fit patients with unresectable disease, concomitant chemoradiotherapy can be also considered after induction chemotherapy.

Finally, a radical postoperative cisplatin/etoposide chemoradiotherapy should be considered after debulking/R2 resection.

Recurrent and metastatic disease. In case of recurrence of previously resected tumors (10–15% of all-stage resected tumors), surgical intervention aiming at R0 resection, is highly recommended [12,33]. In all the other cases, patients can receive systemic treatment, whose aim is symptoms palliation through activity, while survival benefit is still uncertain.

Several studies have shown objective response rates from 21 to 90% of patients and a 5-year survival of 30–55%, with studies conducted in thymic carcinomas showing lower response rates and worst survival [11,32].

According to available evidences, antracycline based poli-chemotherapy is the most active treatment for histologies A to B3. Based on activity and toxicity, CAP (cyclophosphamide, doxorubicine, cisplatin) is the preferred regimen [49].

Association of Carboplatin and Paclitaxel is the preferred regimen for thymic carcinomas, as highlighted in phase II clinical trials conducted in patients with this histology showing the best response rate (about 30%) [46,50].

The combination of platinum and etoposide can be considered a valid option in case of contraindications to antracycline or taxanes or unfit patients, as shown in several phase II clinical trials [49,50].

Chemotherapy should be administered for a maximum of 6 cycles with an intermediate reassessment with the same imaging technique. RECIST 1.1 criteria should be followed for assessment of response.

Patients with N2 disease or distant metastasis (Masaoka or TNM stage IVb) should be treated with chemotherapy as single modality treatment. In selected cases only, and in particular for thymoma histologies, surgical resection could be considered if the disease becomes resectable after systemic treatment. Such options should be carefully discussed within the MDT.

Debulking surgery is not an option to be proposed in this setting. Palliative radiotherapy for vascular compression or pain or other disease related symptoms should be considered.

Recurrences. After failure of platinum and/or anthracycline based chemotherapy, most of participants considered as second line treatment a combination or a single agent chemotherapy such as etoposide, ifosfamide, pemetrexed, octreotide −/+ prednisone, 5-fluorouracil, gemcitabine, and paclitaxel [11,53]. However, considering that prospective trials comparing the different agents are lacking and a decision making process has not been established yet, all participants agreed that it is important to enroll patients in clinical trials, if available.

The treatment with previously administered drugs, such as platinum [54], could be feasible in selected patients, according to prior response and time to progression, as well as cumulative toxicity, which should be well defined in case of anthracyclines or previous mediastinal radiotherapy [55]. A combination of carboplatinum plus paclitaxel [46,50], and platinum plus etoposide [51,52] may be considered. The combination of gemcitabine and capecitabine (intravenous gemcitabine 1000 mg/mq on days 1 and 8 every 3 weeks and oral capecitabine 650 mg/mq twice daily on days 1–14) is the regimen of choice since it showed the best results in a phase II clinical trial [56,57].

In patients with slow-growing lesions, not eligible to receive combination chemotherapy, several single agents may be administered.

In Octreoscan-positive thymoma unfit for cytotoxic drugs, octreotide alone or with prednisone may represent a valuable option, as shown in several phase II clinical trials [58,59,60]. Long-acting octreotide (30 mg intramuscular every 4 weeks) is an option based on a referral Italian study, in which stable disease, as best result, was achieved in aggressive histological types and advanced stage of disease [60]. Administration of etoposide alone at doses of 75 mg daily for 3 weeks, followed by 1 week off (4-week cycle) [61] or 50 mg daily [62], is a valuable option, since a disease control of about 100% has been assessed for thymoma, and an impressive benefit was observed also for thymic carcinoma, with an acceptable toxicity profile.

Targeted therapies. Thymic carcinomas present more somatic mutations in cancer-related genes than thymomas [63]. Therefore, it is not surprising that responses to targeted therapies are different in these two tumor types. Based on a phase II clinical trial, sunitinib is a reasonable second line treatment for thymic carcinomas [64]. Currently, sunitinib is not approved by European and Italian drug agencies for the treatment of TETs but according to the Italian law 648/96, it can be prescribed at the expense of the National Health Service or within the STYLE clinical trial both for thymomas and thymic carcinoma (NCT03449173).

Based on the activity of sunitinib and other antiangiogenic drugs in thymic carcinoma, a phase 2 trial of Ramucirumab in combination with carboplatin and paclitaxel in first line setting is ongoing [65].

The off-label use of imatinib in chemotherapy-pretreated patients should be considered only for extremely selected cases of thymic carcinomas with mutations in the KIT gene (about 10%) [66] for which anecdotal responses have been described [66–70].

The use of immune checkpoint inhibitors (pembrolizumab, nivolumab and avelumab) is still under investigations and their use should be limited to clinical trials. In a phase II trial, pembrolizumab has shown a promising activity in cases of pretreated thymic carcinomas [71].

Finally, everolimus is another off-label option for pretreated patients with TETs as shown in a phase II clinical trial where it seems to induce durable disease control in high percentage of patients with thymoma or thymic carcinoma [72].

Discussion

Management of TETs is complex due the rarity and the heterogeneity of this disease. Furthermore, the recent introduction of a new staging system, with its limitations, may create further difficulties.

Several guidelines for treatment of thymic tumors are available [11,12,38] and provide recommendations based mainly on non randomized trials and retrospective or limited series. Often the lack of evidence leads to formulation of indications based on expert opinions.

The expert meeting showed that in Italy there is good adherence to ESMO guidelines. Main topics of disagreement were related to postoperative treatments. The Panel did not agree with the indication for radiotherapy in stage IIA thymoma and thymic carcinomas since the evidence of survival benefit was considered not strong enough to justify a possible toxic treatment (often given to young patients). Instead, Italian experts strongly encouraged postoperative chemotherapy in stage III radically resected thymic carcinoma, even in the absence of certain data, due to the biology of the disease.

It has also emerged that different Italian centres manage similar clinical situations in different ways, often relying on their experience when evidences are limited. Thus, the aim of this meeting was also to provide guidelines for all Italian centres in order to uniform the treatment nationwide. It was also proposed management of TETs based on the eight edition of TNM staging system. In fact, even if the prognostic observations identified in institutional data sets are still to be confirmed at registry level data, the standard Masaoka-Koga staging system is scheduled to be replaced.

Even if this paper provides guidelines useful for clinicians, it is fundamental that patient treatment is discussed in expert centres by multidisciplinary teams where also the quality of diagnosis is ensured. TYME network is working to facilitate referral to such centres and is also organizing national web based MDT following the French model of network Rhytmic [73].

The experts who attended the meeting also highlighted the importance for patients to be involved in their diagnostic and therapeutic path. Information and awareness about the complexity of the disease should be given, as well as the right tools to access to the right specialists and centres. To this end, the Tu.To.R association for patients affected by rare thoracic cancers has been founded in 2017, with the endorsement and the scientific contribution of TYME network.

Finally, cooperation among National and International networks, such as ERN, is strongly encouraged in order to collect high quality data to prospectively validate the new staging system. Furthermore, collaboration is fundamental to promote prospective and randomized clinical trials focused on the unmet needs and clinical situations for which evidences are limited.

Conflict of interest

Marina Chiara Garassino declares consultancies from Astra Zeneca, Roche, Boehringer Ingelheim.

Paolo Zucali declares consultancies from Pfizer, BMS, Pierre Fabre, Janssen, Novartis, Ipsen, Astellas, Sanofi.

All remaining authors have no relationships to disclose.

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Appendix A

Tyme network collaborators

Marco Alloisio
Giovanni Apolone
Andrea Ardizzoni
Mauro Benvenuti
Alfredo Berruti
Cristiano Breda
Carlotta Buzzoni
Fiorella Calabrese
Augusto Caraceni
Giuseppe Cardillo
Caterina Casadio
Elio Cassi
Mauro Caterino
Fabiana Letizia Cecere
Arturo Chiti
Arturo Crippa
Carlo Curcio
Filippo De Braud
Tommaso De Pas
Luca Di Tommaso
Amelia Evoli
Francesco Facciolo
Giulia Galli
Ignazio Lopez
Giuseppe Lo Russo
Spinelli Luisella
Luca Luzzi
Cristina Mantovani
Alfonso Marchianò
Stefano Margaritora
Roberto Monaco
Uliano Morandi
Lorenzo Novellino
Maria Teresa Piras
Luca Porcu
Adriano Priola
Claudia Proto
Giovanni Battista Ratto
Ottavio Rena
Silvia Rinaldi
Elisa Roca
Gaetano Rocco
Enrico Ruffini
Diego Signorelli
Piergiorgio Solli
Lorenzo Spaggiari
Alessandro Stefani
Andrea Veltri
Valentina Vespro
Nicoletta Zilembo

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