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SUPPLEMENT ARTICLE

Thymoma and thymic carcinoma in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations

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Abstract

Thymic tumors are epithelial tumors arising from the anterior mediastinum and constitute 0.2–1.5% of all adult malignancies but are exceptional in pediatric population. Thymic epithelial tumors (TETs) encompass a variety of histologic subtypes associated with different clinical outcomes. Due to its rarity in children, TETs' management requires a multidisciplinary approach. However, prognosis remains still poor, especially among patients with thymic carcinoma. This study presents the internationally recognized recommendations for the diagnosis and treatment of thymic tumors in children and adolescents, established by the European Cooperative Study Group for Pediatric

Abbreviations: AC, amrubicin and carboplatin; AFP, alpha-fetoprotein; B-HCG, beta-subunit of human chorionic gonadotrophin; CAP, cyclophosphamide, doxorubicin, cisplatin; CT, computed tomography; EXPeRT, European Cooperative Study Group for Pediatric Rare Tumors; FNA, fine-needle aspiration; GCT, germinal cell tumor; LDH, lactate dehydrogenase; MDT, multidisciplinary team; MIT, minimally invasive techniques; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PARTNER, Paediatric Rare Tumours Network - European Registry; PE, cisplatin, etoposide; PET, positron emission tomography; RT, radiotherapy; RYTHMIC, Reseau Tumeurs Thymiques et Cancer; TC, thymic carcinoma; TET, thymic epithelial tumor; WHO, World Health Organization.

Rare Tumors (EXPeRT) group within the EU-funded project Paediatric Rare Tumours Network - European Registry (PARTNER).

KEYWORDS
adolescents, children, EXPeRT, guidelines, PARTNER, thymic carcinoma, thymic epithelial tumors, thymoma

1 | INTRODUCTION

Thymic epithelial tumors (TETs) are very rare neoplasms arising from thymic epithelial cells and constituting 0.2–1.5% of all adult malignancies.[1] In pediatric age, these tumors are exceptional and may occur at a median age of 11.4 years. According to the World Health Organization (WHO),[2] TETs encompass a variety of histologic subtypes associated with different clinical outcomes. Thymomas may be divided into type A, type AB, type B1, type B2, and type B3. Type A and AB tumors, which have a tendency to invade surrounding organs, rarely give distant metastasis[3,4]; whereas thymic carcinomas (TCs), according to the WHO classification (Table 1), are frequently associated with distant metastases.

Staging of TETs is currently based on the Masaoka–Koga system (Table 2),[5] and/or on the TNM-based system for the 8th Edition of the American Joint Committee on Cancer/Union for International Canner Control (AJCC/UICC) staging classification of tumors (Table 3).[6]

In the adult population with TETs, the three major prognostic factors are completeness of resection, stage, and TETs subtype.[7] Of note, a correlation exists between histologic subtype and stage. Stage is lower in type A (90% in stages I–II) and AB than B1–B3 thymomas (38% of type B3 in stage III).[8] Prognosis remains poor especially among patients with TC.

In children, the 5-year survival for children with TETs depends on stage and histology. It may vary from 90% for patients with thymomas to 21 ± 10% for patients with TC.[9]

The aim of this manuscript is to establish internationally recognized recommendations for the diagnosis and treatment of children and adolescents with TETs according to the Consensus Conference Standard Operating Procedure methodology with definition of level of evidence (Levels I–V) and grades of recommendation (Grades A–E).[10]

2 | INITIAL ASSESSMENT

2.1 | Clinical presentation

Thymic tumors, as other more frequent anterior mediastinal masses, are characterized by local symptoms, such as shortness of breath, persistent cough, chest pain, difficulty with swallowing, appetite and

TABLE 1 World Health Organization (WHO) classification of thymic epithelial tumors

Type	Histology
A	Tumor composed of neoplastic thymic epithelial cells with spindle/oval shape. No atypia and a few or no nonneoplastic lymphocytes
AB	Type A thymoma with focuses of lymphocytes
B1	Plump epithelioid cells with areas resembling thymic medulla
B2	Scattered focuses of atypical epithelial cells with lymphocytes
B3	Epithelial cells having a round or polygonal shape and exhibiting no or mild atypia with minor component of lymphocytes
Thymic carcinoma	Tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features analogous to those seen in carcinomas in other organs

TABLE 2 Masaoka–Koga system

Stage	Description
I	Grossly and microscopically completely encapsulated tumor
IIa	Microscopically transcapsular invasion
IIb	Macroscopic invasion into thymic or surrounding fatty tissue or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into adjacent organs
IVa	Pleural or pericardial metastases
IVb	Hematogenous or lymphogenous metastases

TABLE 3 8th TNM classification

Category		Definition
T1		
	a	Encapsulated or unencapsulated, extension into mediastinal fat present or not
	b	Mediastinal pleura extension
T2		Pericardium involvement
T3		Involvement of lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels
T4		Aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus
N0		No nodal involvement
N1		Anterior (perithymic) nodes
N2		Deep intrathoracic or cervical nodes
M0		No metastatic pleural, pericardial, or distant sites
M1		
	a	Separate pleural or pericardial nodule(s)
	b	Pulmonary intraparenchymal nodule or distant organ metastasis

TNM	Stage grouping			
Stage	*T*	*N*	*M*	Masaoka–Koga
I	T1	N0	M0	I, IIa, IIb, III
II	T2	N0	M0	III
IIIa	T3	N0	M0	III
IIIb	T4	N0	M0	III
IVa	T any	N1	M0	IVa
	T any	N0,1	M1a	IVb
IVb	T any	N2	M0,1a	IVb
	T any	N any	M1b	

weight loss, superior vena cava syndrome, although it may be discovered incidentally following an imaging done for another purpose.

As a result of the role of thymus in the immune system, approximately one third of adult patients with thymoma may present with autoimmune disorders, mainly myasthenia gravis: it is common in type AB, B1, and B2 thymomas and almost always associated with anti-acetylcholine receptor antibodies.[11] Vice versa, only 20% patients with myasthenia gravis may have a thymoma. In pediatric age, thymoma is less frequently associated with myasthenia gravis.[12] About 15% of thymomas are associated with other paraneoplastic disease including gastrointestinal disorders (ulcerative colitis), collagen and autoimmune disorders (Sjogren's syndrome, sclerodermia, and polymyositis), hypogammaglobulinemia (Good syndrome, 5% of cases), dermatological disorders (alopecia), endocrine disorders (Cushing's syndrome), renal disease (nephrosis), and hematological syndromes (pure red cell aplasia in 5% of cases, agranulocytosis).[13] It has been recently presented that autoimmune disorders are associated with favorable features but are not independent good prognostic factors for patients with TETs.[14]

TETs are very rare neoplasms, and thus uniform recommendations are difficult to achieve both in adults including young population and children/adolescents. A lot of effort has been put in recommendations development. Such groups as International Thymic Malignancy Interest Group (ITMIG) or at the national level *Reseau Tumeurs Thymiques et Cancer* (RYTHMIC), or in children EXPeRT (European Cooperative Study Group for Pediatric Rare Tumors) project, ERN-PAEDCAN (European Reference Network for Pediatric Oncology) and many others, focus on unification diagnostic approach and treatment strategy.

2.2 | Imaging assessment

Imaging assessment of TETs plays a very important role: (1) to exclude other tumors, (2) to evaluate the extension, and (3) to determine if the tumor is resectable, and thus plan the treatment strategy of these patients. The primary tumor and its locoregional extension should be evaluated by chest and abdomen computed tomography (CT) and/or magnetic resonance imaging (MRI) with contrast enhancement. An evaluation of lymph nodes, mediastinum, cardiac and pericardial involvement must be done (Level IV; Grade A).

TET with well-delineated contours and homogeneous enhancement on CT are considered to be completely resectable.[15] Tumor invasion of a great vessel is significant predictor for poor prognosis. The presence of tumor invasion is therefore important to evaluate and to recognize on CT and MRI.[16] The presence of a lobulated or irregular con-

tour, or heterogenous enhancement, necrotic or cystic component, and lymphadenopathy is suggestive of TC.[17,18]

Thoracic MRI may help to rule out thymic hyperplasia from thymic malignancy (phase in/out is recommended) (Level IV; Grade B). A differential diagnosis with thymic hyperplasia should be made when the patient is treated with chemotherapy for another disease.

Further imaging includes abdominal CT or MRI to identify metastases to the liver and kidney (Level IV; Grade B) and brain MRI in TC (Level IV; Grade C).

In addition, pulmonary function tests could be done in case of lung or bronchial involvement (Level III; Grade C), tracheobronchoscopy may be necessary in case of suspected bronchi invasion (Level IV; Grade B), and echocardiography to identify vascular invasion and intra-cardiac involvement (atria and ventricles) (Level IV; Grade A).

Positron emission tomography (PET)-CT with 18F fluorodeoxyglucose (18-FDG) is recommended in case of highly suspected TC as well as in any invasive thymic malignancy or in case of recurrence (Level IV; Grade B). Some authors proposed to use PET to differentiate thymic hyperplasia from neoplasia and showed that semi-quantitative maximum standardized uptake value (SUVmax) may distinguish low-grade thymoma from TC[19,20] (Supporting Material S1).

2.3 | Biological investigations

Biological investigations at diagnosis must include alpha-fetoprotein (AFP), beta-subunit of human chorionic gonadotrophin (B-HCG) serum level, and lactate dehydrogenase (LDH) (Level IV; Grade A). These markers are key to exclude other more frequent malignancies developed in the thymic region such as germ cell tumors (GCT) and non-Hodgkin and Hodgkin lymphoma (Level IV; Grade A). Due to the frequent association with an autoimmune disease or with a paraneoplastic disease, it is strongly recommended to perform blood test such as red, white and platelet count, reticulocytes, protein electrophoresis, immunoglobulins dosage, thyroid function, anti-acetylcholine receptor antibodies, regardless of symptoms or not (Level IV; Grade A).

Other diagnoses should be taken into account: non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, benign or malignant GCT (AFP/B-HCG markers and LDH), nuclear protein in testis (NUT)-midline carcinoma (especially in squamous histology subtype), sarcomas, and benign thymic hyperplasia. Imaging alone is often unable to ensure the diagnosis of TETs as others more frequent lesions of the same region may have a similar aspect.

2.4 | Diagnosis

Histopathological evaluation is mandatory after biopsy or upfront resection to confirm the clinical suspicion and to allow the histological stratification of TET (Level IV; Grade A). A revision of the histological slides from a pathologist with proven experience in pediatric tumors and especially in TETs is highly recommended (Level IV; Grade A). TC is not a single entity and requires subtyping (e.g., into squamous cell, lymphoepithelioma-like [EBV-associated], neuroendocrine, and others).

In the majority of cases, a percutaneous tumor biopsy or an incisional biopsy should be performed to distinguish it from other malignant or benign conditions (Level IV; Grade A). In the experience reported by Rod et al.,[4] fine-needle aspiration (FNA) was unable to establish the diagnosis, and therefore surgical biopsy should be preferred to FNA to obtain sufficient material for histopathologic examination. Nevertheless, special attention is required when respiratory difficulties are present, attesting advanced mediastinal compression, especially at diagnosis when general anesthesia may be needed for biopsy (Level IV; Grade A).

Immunohistochemistry with anti-CD117/KIT and anti-CD5 antibodies helps to establish the thymic origin in ~80% of mediastinal carcinomas. It is strongly recommended to store a frozen tumor sample and blood sample on EDTA in a tumor bank for possible biological studies (Level IV; Grade A). Due to the rarity of TETs, the multidisciplinary team (MDT) discussion in reference centers and the central review of the histology are of great importance (Level IV; Grade A).

2.5 | Staging system

The WHO classification (Table 1), the Masaoka–Koga system (Table 2), and the 8th TNM classification (Table 3) are used in adults and are the basis for establishing treatment and predicting disease prognosis. The same systems should be used in pediatric patients (Level IV; Grade A).

Thymomas type A, AB, and B1 have relatively good prognoses (local invasiveness of these tumors is 11.1%, 41.6%, and 47.3%, respectively); B2 and B3 are more aggressive (69.1% and 84.6%) and have intermediate survival rates. TC has the worst outcome and should be considered an aggressive neoplasm. The 20-year survival rates in adults are 89%, 91%, 49%, and 0% for Masaoka–Koga stages I, II, III, and IV, respectively.[21]

3 | THERAPEUTIC RECOMMENDATIONS

MDT referral is mandatory at diagnosis and during therapy (Level IV; Grade A). Patients and families should be proposed the enrolment in a prospective trial if available, and data collection in national or international databases (Level IV; Grade A).

3.1 | Surgery

The best treatment option is complete resection with no adjuvant approach in early stages (Level IV; Grade A). Surgical planning is essential in TETs as vital structures of the mediastinum and thoracic cavity may be involved in aggressive types.

A complete resection including the whole thymus (R0), performed through classical median sternotomy, video-assisted techniques or robotic approach, is the mainstay of treatment in TET[22–24] and the abil-

ity to accomplish a complete resection appears to be the most important prognostic factor[25,26] (Level III; Grade A). Incomplete tumor resection is associated with a high-recurrence rate and poor prognosis and should be avoided (Level IV; Grade B).[25]

The standard approach is midline sternotomy that allows the best view to evaluate limits of the tumor (capsular invasion, infiltration of peri-thymic and mediastinal fat, pleura and involvement of surrounding structures) and to control all mediastinal structures (Level IV; Grade B). As quality of the resection is a major prognostic factor, complex procedures, including extra-corporal circulation, may be mandatory in advanced disease (Level IV; Grade B).[27] Therefore, patients with thymic tumors should be referred to expert thoracic surgeons (Level IV; Grade B). Collaboration with adult surgeons may be of great value in complex cases (Level IV; Grade B).

In the last decade, however, a minimally invasive approach (both thoracoscopic and robotic) to early-stage thymic tumors has gained relevance in the adult population. In adults, video-assisted thymectomy (VAT) and robotic-assisted thymectomy (RAT) has been shown to have similar results both in terms of rate of complications and of oncological outcome and they may be considered safe and reliable approach for the treatment of early-stage tumors.[28,29] Therefore, minimally invasive techniques (MIT) could be considered in pediatric age, but their use should be limited to (a) low-stage thymoma without invasion of surrounding structures at preoperative imaging, and (b) tertiary care centers with surgeons' experience in MIT, and (c) older children and adolescents (Level V; Grade B).

3.2 | Radiotherapy

The mainstay treatment for TETs remains surgical resection. Radiotherapy (RT) is also applied as a palliative or adjuvant therapy because of the radiosensitive nature of the tumors, but the efficacy of postoperative RT remains unclear (Level IV; Grade C).[1]

3.3 | Chemotherapy

In advanced stages polychemotherapy remains the cornerstone for both TC and thymomas. For thymomas, it seems that the best regimens are anthracycline based (CAP: cyclophosphamide, doxorubicin, and cisplatin; ADOC: doxorubicin, cisplatin, vincristine, and cyclophosphamide; AC: amrubicin and carboplatin).[30]

According to available evidences in adults, anthracycline-based polychemotherapy is the most active treatment for histology A to B3. Based on activity and toxicity, CAP is the preferred regimen, however other regimens such as AC, ADOC are also acceptable.[30]

Association of carboplatin and paclitaxel is the preferred regimen for TCs, as highlighted in phase II clinical trials conducted in patients with this histology showing the best response rate (about 30%).[30] The combination of platinum and etoposide can be considered an option in case of contraindications to anthracycline or taxanes or unfit patients. Due to the lack of prospective clinical randomized trials, there is no evidence-based optimal chemotherapy established for children to date (Level IV; Grade C). In European experience, chemotherapy was administrated to patients with inoperable or metastatic tumors, however results from adults suggest that chemotherapy should be administered for a maximum of six cycles with an intermediate reassessment with the same imaging technique. RECIST 1.1 criteria should be followed for assessment of response metastatic thymic tumors. Preoperative chemotherapy can decrease tumor volume and increase the possibility of resecting residual tumor with the same regimens.

Pediatric observations from the EXPeRT group on 16 children from France, Italy, Germany, and Poland proved that outcome in TC is still poor in this group of patients with 21% of 5-year overall survival (OS), despite multimodality treatment. Patients were mainly treated using standard cytostatic drugs including among the others doxorubicin, etoposide, or cisplatin.[9]

The role of immunotherapy is still debatable, in particular in thymomas for the immune-related adverse events and nowadays it does not represent an option.

Pembrolizumab, monoclonal antibody that targets PD-1, was assessed in a phase 2 study. Forty patients (out of 41) with advanced TC were enrolled. One patient achieved clinical remission (CR), eight partial responses (PR), and 21 stable diseases (SD), with 15% of patients presenting severe toxicity-autoimmune, including two with myocarditis.[31] In another study (PRIMER study: single-arm, multicenter, phase 2), IgG4 anti-PD-1 monoclonal antibody nivolumab was tested against unresectable or recurrent TC: they reported 15 patients with a median PFS of 3.8 months.[32] Fully human monoclonal antibody (IgG1) against vascular endothelial growth factor receptor 2 (VEGFR-2) is evaluated in "RELEVENT Phase II trial of ramucirumab, carboplatin, and paclitaxel in previously untreated TC/B3 thymoma with carcinoma." The study is recruiting with aim to check activity of ramucirumab in combination with carboplatin and paclitaxel in chemotherapy-naive patients and secondary to assess efficacy of above treatment.[33] Rajan et al.[34] checked efficacy of fully human IgG1 monoclonal antibody targeting the insulin-like growth factor 1 receptor, cixutumumab, in previously treated patients. In this multicenter, open-label, phase 2 trail, 37 patients with thymomas and 12 with TCs were enrolled. Among patients with TC, 42% had a SD and 58% a PD. No objective response was noted. Those with thymoma presented with SD in 76% and PD 11%. Tyrosine kinase inhibitor, sunitinib, seems to be active in patients with refractory disease after chemotherapy based on platinum in open-label phase 2 clinical trial with 41 patients with thymoma and TC. Among them 23 were with TC: 26% had PR, 65% SD, 9% PD.[35] Due to the absence of data on these drugs in children, they should not be delivered out of a protocol (Level V; Grade D).

For those with unresectable or metastatic disease, systemic therapy is the first treatment of choice. Still classical cytostatic drugs play a main role with the best results for anthracycline-based schemes. Spectacular effects were described in quite ancient study by Fornasiero et al.[36] using ADOC scheme in 37 adult patients with a response ratio 91.8%, including 43% of complete remission. The average response time to treatment was 12 months and the median OS reached 15 months. Similarly, Rea et al.[37] analyzed 16 patients treated with

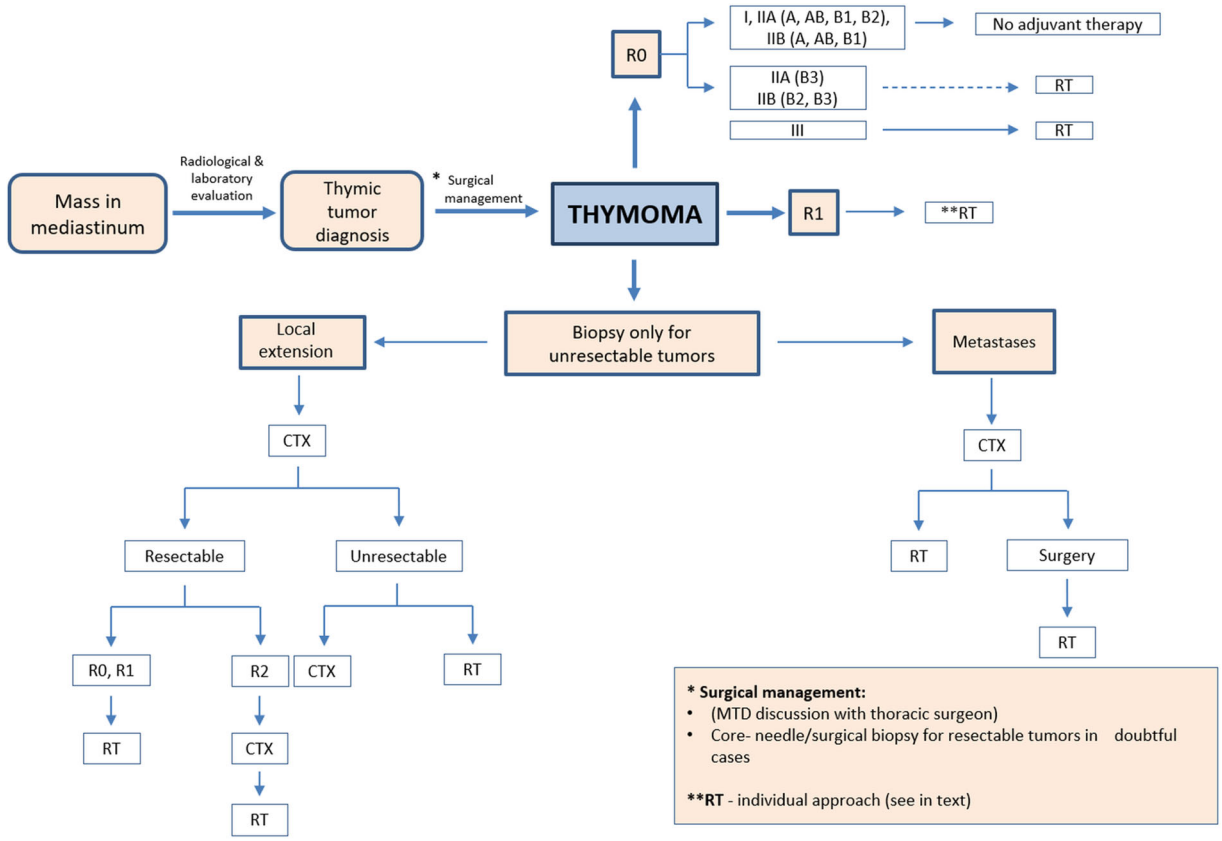

FIGURE 1 Overall strategy proposal by the Paediatric Rare Tumours Network - European Registry (PARTNER)/European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) groups for pediatric patients with thymoma according to Masaoka–Koga staging system

ADOC and had a 100% objective response rate (ORR), including 43% of CR. Due to the cardiotoxicity of anthracyclines, other combinations are sought but none of them occurred to be efficient in the same matter. Giaccone et al.[38] performed first prospective trial of phase 2 with cisplatin and etoposide. The results were 56% of ORR, with a 51.5-month median survival. Therefore, the most common chemotherapeutic regimens comprise of ADOC; cisplatin, etoposide (PE), cyclophosphamide, doxorubicin, cisplatin (CAP) with or without prednisone; and etoposide, ifosfamide, cisplatin (VIP). For patients with recurrent disease or primary dissemination molecular targeted treatment may be proposed.

4 | OVERALL STRATEGY PROPOSED BY THE EXPeRT MEMBERS (Figures 1 and 2, Supporting Material S2)

4.1 | Resectable tumors

4.1.1 | Surgery

The cornerstone of treatment of resectable thymomas and TC is the "en bloc" resection of the tumor. When the tumor is judged unresectable, a core-needle or surgical biopsy should be considered (Level IV; Grade A). Anterior mediastinal approach is preferred to thoracoscopic procedure to avoid pleural tumor spillage. FNA is not considered sufficient for diagnosis of TETs (Level IV; Grade C).

Tumor resection including the whole thymus and peri-thymic fat is recommended (Level IV; Grade B). In stages III/IV, complete excision of the tumor sometimes requires the resection of adjacent structures with the pericardium, phrenic nerve (not bilateral), pleura, lung, and major vascular structures (Level IV; Grade A). In case of lung invasion, atypical resections should be preferred. Based on new TNM staging, locoregional lymphadenectomy should be carried out during resection of all types of thymic tumors, including anterior mediastinal and cervical nodes. Systematic sampling of any doubtful lesion of the pleura, lung, or mediastinum is encouraged in stage III/IV tumors. In case of TC, systemic lymphadenectomy of the supraclavicular and paratracheal region is highly recommended[39,40] (Level V; Grade B).

4.1.2 | Radiotherapy

Indications, fields, and total dosages should consider patients' age, cardiac fields, and initial tumor extension. RT should be delivered within 3 months after operation for a total dose of 45–50 Gy if R0, 50–54 Gy after R1 resection (in the French RYTHMIC Group, 56 Gy + boost 10 Gy in surgical zone for R1 is advised), and 60 Gy in case of R2 resec-

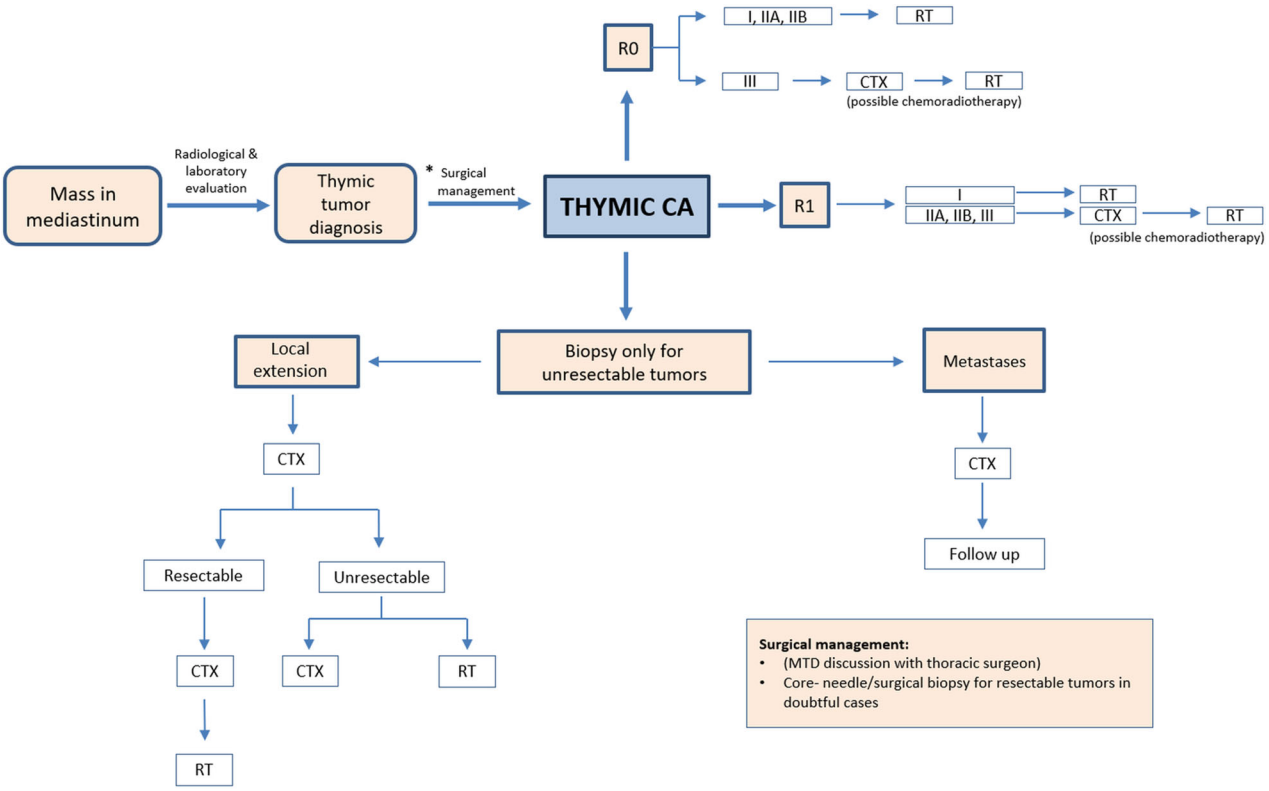

FIGURE 2 Overall strategy proposal by the Paediatric Rare Tumours Network - European Registry (PARTNER)/European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) groups for pediatric patients with thymic carcinoma according to Masaoka–Koga staging system

tion with a 10 Gy boost to areas of residual disease (Level IV; Grade C). A daily dose of conventional fractionation 1.8–2 Gy through 4–6 weeks is possible (Level IV; Grade C).

4.1.3 | Chemotherapy

Adjuvant chemotherapy is recommended only in TC II, III, IV stages independently whether R0 or R1. Chemotherapy regimen with platin compounds and etoposide is a possibility (PE) (Supporting Material S3) (Level III; Grade C). After adjuvant chemotherapy, adjuvant RT must be performed (Level IV; Grade A).

4.2 | Unresectable tumors

A percutaneous or incisional biopsy is recommended (Level IV; Grade A). Induction treatment is recommended in unresectable stages IIIA–IVA TETs, with the aim to reduce tumor volume and allow a delayed surgery. Optimal neoadjuvant chemotherapy regimen is not determined but most common regimens used are CAP, PE or carboplatin, paclitaxel (with more evidence in TC) (Level IV; Grade A). Targeted therapies are not a standard in neoadjuvant setting (Level III; Grade C). Almost 80% of tumors respond after two or four cycles of induction chemotherapy and surgery should be rediscussed, at each step when the tumor appears resectable after reduction (Level III; Grade B).

Despite lack of evidence, adjuvant chemotherapy may be recommended in case of TC regardless of type of resection (R0, R1, or R2) or in case of stages III–IVA Masaoka stage thymoma with R2 resection. Adjuvant RT must be administered in all cases (45–50 Gy if R0 resection, 50–54 Gy after R1 resection, and 60 Gy in R2 resection). Debulking surgery may be offered in thymoma, but is not recommended in the case of TC (Level IV; Grade B). After debulking surgery, postoperative chemo-RT may be considered.

For those TETs that remain stable and still unresectable after induction chemotherapy, definitive RT (total dosage of 60–66 Gy in 30–33 fractions) should be delivered. Other option is concurrent chemo-RT with PE (Level III; Grade B).

4.3 | Metastatic thymic tumors

Chemotherapy should be offered as single-modality treatment in metastatic TETs. The standard regimen remains unknown. Multiagent combination regimens and anthracycline-based regimens appear to have improved response rates compared with etoposide-based regimens, so CAP could be an optimal option (Level III; Grade B) in case of TC, carboplatin–paclitaxel as a potential alternative (Level III; Grade

B). No specific recommendations could be done on local therapies for metastatic sites (surgery and/or RT) (Level IV; Grade C). Local thymic primary site could follow the general rules for localized disease (Level IV; Grade A).

4.4 | Recurrent disease

The majority of publications suggest that the most common sites of recurrence are the lung, pleura, and diaphragm, even when incompletely resected patients are included. The initial management should be the same as in case a newly diagnosed tumor but considering previous therapies. Data exist only in adults. Complete excision and/or RT of local recurrence are recommended. In unresectable lesions, several courses of chemotherapy may be delivered as first approach. The re-administration of previously effective regimen should be considered (Level IV; Grade C in adult). Second lines of chemotherapy could contain carboplatin with paclitaxel +/− bevacizumab, platinum plus etoposide or capecitabine plus gemcitabine or oral etoposide (Level III; Grade C in adults). Targeted therapies known to be efficient in adult TETs as sunitinib, everolimus could be discussed (Level III; Grade C in adults). More recently anti-PD1 such as pembrolizumab have reported efficacy in previously treated TCs.[33]

5 | RECOMMENDATIONS FOR FOLLOW-UP

Due to the risk of relapse after successful finishing of treatment, patients need regular control assessment and should be adapted to tumor characteristics and overall therapies. Based on consensus established in adults and proposed by Girard et al.,[1] we recommend as follows (Level V, Grade C):

- Thoracic CT-scan 3 months after the surgery then,
- For stages I and II, R0 thymoma, Chest CT-scan every year for first 5 years and after that every 2 years
- Fort stages III/IV thymoma and TC and R1 or R2, we suggest thoracic CT every 3 months in the first year, then every 6 months in second year, then once a year.

6 | CONCLUSIONS

Clinical as well as radiological examinations are necessary in order to plan accurate surgical treatment. For advanced tumors, providing proper adjuvant/neoadjuvant chemotherapy is of importance. Efficacy of postoperative RT remains unclear. Molecular profiling is a promising direction for establishing targeted therapy. Centralization of data to improve knowledge about TETs seems necessary.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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