Thymic tumours and their special features

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Number 11 in the Series "Thoracic oncology"
Edited by Rudolf Huber and Peter Dorfmüller

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Shareable abstract (@ERSpublications)
Thymic tumours are rare and heterogeneous tumours. Management is based on multidisciplinary discussion and networking. https://bit.ly/3kYAZ7u

Cite this article as: Basse C, Girard N. Thymic tumours and their special features. *Eur Respir Rev* 2021; 30: 200394 [DOI: 10.1183/16000617.0394-2020].

Received: 19 Jan 2021
Accepted: 2 March 2021

Abstract

Thymic tumours are rare thoracic malignancies, that may be aggressive and difficult to treat. The pillars of the management include pathological review, consideration of differential diagnoses, staging and multidisciplinary discussion. Assessment of resectability is key to drive the treatment sequencing. Association with autoimmune diseases, especially myasthenia gravis, is observed, which impacts the oncological management. Networks are being built at the national and international levels. This article provides an overview of the most recent findings in the diagnosis, staging, histology, and management strategies of thymic tumours.

Introduction

Thymic tumours are rare thoracic malignancies, that may be aggressive and difficult to treat [1]. Although they are the most common tumours in the anterior mediastinal compartment, thymic tumours represent a wide variety of entities, including thymomas, thymic carcinomas, and neuroendocrine thymic tumours (NETTs) [2]. The reported annual incidence ranges from 1.3 to 3.2 per million [1]. The mean age at diagnosis is 40–50 years old, but thymic tumours may actually be diagnosed in children as well as in elderly patients. The pathogenesis is virtually unknown, as no environmental or infectious factors have been demonstrated to be associated with these tumours. Association with autoimmune diseases, especially myasthenia gravis, is observed, what impacts the oncological management [3].

In the past decade, the scientific community has been increasingly interested in thymic malignancies, resulting in the creation of many dedicated working groups, including the International Thymic Malignancy Interest Group (ITMIG; www.itmig.org), or local organisations, such as the RYTHMIC (*Réseau tumeurs THYMiques et Cancer*; www.rythmic.org) network in France. These networks provide the opportunity of setting up databases with a long-term follow-up of patients This article provides an overview of the most recent findings in the diagnosis, staging, histology, and management strategies of thymic tumours.

The three pillars for the management of thymic tumours

Make sure of the diagnosis: imaging

The first step for the diagnosis of thymic tumours point is to make the differential diagnosis with other anterior mediastinal tumours, and non-malignant thymic lesions [4], using computed tomography (CT). The need for pre-treatment biopsy depends on whether the tumour is resectable upfront [1, 3, 5]. Thymic epithelial tumours (TETs) are the most frequent cause of anterior mediastinal mass, accounting for 35% of cases; other differential diagnoses include lymphomas (25% of cases), and germ-cell tumours, malignant or not (20% of cases) [6]; pathologically, thymic carcinoma has to be differentiated from lung squamous cell carcinoma, as well as from more rare entities, such as NUT-rearranged midline carcinomas [7].

Thymic lesion is then the most frequent diagnosis to consider when autoimmune disease is observed, especially myasthenia gravis [8]. In such situation, the second step is to differentiate thymic malignancy from hyperplasia or non-involuted thymus, what may be challenging. Thymic rebound hyperplasia has actually to be considered after stress, or most frequently corticosteroids or antihormonal treatment. Thymic lymphoid hyperplasia is observed in the setting of hyperthyroidism, conjunctive tissue or vascular disease, but also myasthenia gravis. CT features include low-attenuation, symmetric, and fatty pattern maintaining the bi-pyramidal shape of the thymus [9]. Chemical-shift MRI (as per Dixon's proposals) may detect fatty infiltration showing homogeneous signal decrease on opposed phase images relative to in-phase images, that is never seen in thymoma [9]. 18-fluorodesoxyglucose positron-emission tomography (PET)-scan is not recommended for thymic masses. Thymic hyperplasia may present with hypermetabolism [10]. A PET-scan may be optional in case of tumours with aggressive histology and advanced stage to further characterise subsequent lesions suspicious for recurrences.

Make sure of the diagnosis: histopathology

TETs are categorised histologically according to the World Health Organization (WHO) histological classification [2], recently updated in 2015 based on a consensus statement of ITMIG published in 2014 [11]. The classification distinguishes thymomas from thymic carcinomas; thymomas are further subdivided into different types (so-called A, AB, B1, B2, and B3) based upon the morphology of epithelial tumour cells (polygonal or spindle cells), the relative proportion of the non-tumoural lymphocytic component (decreasing from type B1 to B3), and resemblance to normal thymic architecture [2, 3]. Thymic carcinomas are similar to their extrathymic counterpart, and the most frequent subtype is squamous cell carcinoma; NETTs are very rare, with a management based on that proposed for other neuroendocrine tumours, and will not be further discussed in this article. While the interobserver reproducibility of the WHO classification has been questioned over time [12], the ITMIG consensus statement proposes major and minor morphological and immunohistochemical criteria to better individualise each TET entity; these criteria were defined based on a series of 58 prototypic and difficult-to-classify TETs [2]. Histologically, thymic carcinomas may be distinguished from primary lung carcinomas; a recommendation facing an intrathoracic carcinoma, especially with squamous cell subtype, is to perform immunohistochemistry for CD5 and CD117 which is exclusively observed in primary squamous cell thymic carcinoma [13]. Ultimately, an updated WHO classification publication is expected in 2021.

Pathologic central review of patients diagnosed with TET is recommended, as it ensures a better quality of diagnosis; from the RYTHMIC network experience of systematic review in 467 cases by a panel of 10 expert pathologists, histology was modified in nearly one third of patients [6].

Staging: from Masaoka–Koga to TNM

TETs were historically staged according to the Masaoka–Koga staging system (table 1) [14, 15], which is correlated with overall survival [16]. Masaoka–Koga staging is actually a surgical pathology system that is assessable only after surgical resection of the tumour. A unique feature of TETs is that the WHO classification is correlated with stage at diagnosis, what may explain its reported prognostic value [12]; indeed, the histopathological subtypes, from type A to type B3, are associated with more aggressive pattern [12].

The 8th Tumour Node Metastasis (TNM)-based staging system adopted by the American Joint Committee on Cancer/*Union Internationale Contre le Cancer* consortium, is now standard for thymic malignancies, based on overall survival analyses of a retrospective international database of more than 10 000 cases [17]. In this staging system, all Masaoka stage I, II, and some stage III TETs are merged together with stage I tumours, based on their similar prognosis; TNM stage II are defined by pericardium invasion; TNM stage III tumours are further subdivided into 2 groups (T3 and T4), aiming at providing more help in formalising resectability, a major driver of the treatment strategy in advanced TETs [1, 3]. Given the magnitude of data generated based on the Masaoka–Koga system, the two staging systems should be assessed for patients to help the decision making, especially for surgical and postoperative management.

There is then no clinical staging system for TETs, meaning no staging based only on imaging, which may not assess pericardial invasion, and the treatment strategy is then primarily based on whether the tumour may be resected upfront or not, as complete resection represents the most consistent and significant prognostic factor on disease-free and overall survival [15, 16]. Correlation between clinical and pathological stage is better in advanced stages, given the identification at imaging of vessel invasion, enlarged lymph nodes, pleural/pericardial lesions, or even systemic metastases [18].

TABLE 1 Staging of thymic tumours according to 8th Tumour Node Metastasis (TNM), and Masaoka–Koga staging systems

Stage		Descriptors
Tumour		
T1	T1a	Encapsulated or unencapsulated, with or without extension into the mediastinal fat
	T1b	Extension into the mediastinal pleura
T2		Direct invasion of the pericardium (partial or full-thickness)
T3		Direct invasion of the lung, the brachiocephalic vein, the superior vena cava, the chest wall, the phrenic nerve, and/or hilar (extrapericardial) pulmonary vessels
T4		Direct invasion of the aorta, arch vessels, the main pulmonary artery, the myocardium, the trachea, or the oesophagus
Node		
N0		N0 No nodal involvement
N1		N1 Anterior (perithymic) nodes (IASLC levels 1, 3a, 6 and/or supradiaphragmatic/inferior phrenics/pericardial)
N2		N2 Deep intrathoracic or cervical nodes (IASLC levels 2, 4, 5, 7, 10, and/or internal mammary nodes)
Metastasis		
M0		No metastatic pleural, pericardial, or distant sites
M1	M1a	Separate pleural or pericardial nodule(s)
	M1b	Pulmonary intraparenchymal nodule or distant organ metastasis

Stage grouping		Corresponding Masaoka–Koga stage
I	T1N0M0	I, IIA, IIB, III
II	T2N0M0	III
IIIa	T3N0M0	III
IIIb	T4N0M0	III
IVa	T any N0,1 M0,1a	IVA, IVB
IVb	T any N0-2 M0-1b	IVB

IASLC: International Association for the Study of Lung Cancer.

Multidisciplinary tumour board is mandatory

The management of patients with TETs requires continuous multidisciplinary expertise at any step of the disease [1]. The assessment of resectability is mostly based on the surgeon expertise, but may be complex, even if the 8th TNM staging allows a better definition of resectable anatomical structures (stage IIIA). Ultimately, stage IV disease does not mean that the tumour is not amenable to complete surgical resection, especially in the setting of pleural implants [19, 20]. Multidisciplinary tumour board is then highly valuable at any stage of the disease.

In France, RYTHMIC is a nationwide network dedicated to thymic tumours, which was recognised by the French National Cancer Institute, in 2012 [21–23]. The treatment of all patients with TET is discussed on a real-time basis at a national multidisciplinary tumour board, which is organised twice a month basis using a web-based system. Decision-making is based on consensual recommendations, that were originally established based on available evidence, and are updated and approved each year by all members of the network [1]. Similar thymoma-dedicated networks are now being implemented in France and in other European countries, such as Spain and Italy (the TYME collaborative group) [21, 24].

Across Europe, similar networking has been recognised. A European Reference Network (ERN) EURACAN (European Rare Cancer Network) domain is dedicated to rare thoracic tumours, and handles a network of 100+ healthcare providers; the objectives of EURACAN include the updating of current guidelines, educational programmes, dissemination and communication with patient advocacy groups, and the establishment of research projects. The Clinical Patient Management System (CPMS) is a EU-sponsored web-based platform that allows the discussion of patient cases with multidisciplinary experts from the ERNs.

ITMIG (International Thymic Malignancy Interest Group) was created in 2010 and was endorsed and supported by the most representative medical and surgical societies around the globe [25]. The mission of

ITMIG is to promote the advancement of clinical and basic science related to thymic malignancies. It provides infrastructure for international cooperation, maintains close collaboration with other related organisations, and facilitates the spread of knowledge about thymic neoplasms. An international virtual tumour board is organised on a monthly basis.

Resectable TETs: surgery and postoperative radiotherapy

In Masaoka–Koga stage I/II and some stage III tumours (classified as stage I, II, IIIA in the 8th TNM system), complete resection is usually achievable upfront, and surgery represents the first step of the treatment, possibly followed by postoperative radiotherapy [1, 3, 26, 27].

Surgery principles

Standard approach is median sternotomy, that allows the wide opening of the mediastinum and both pleural cavities, followed by assessment of macroscopic capsular invasion, infiltration of mediastinal fat, adherences, and involvement of surrounding tissues. Generally, complete thymectomy, including the tumour, the residual thymus, and perithymic fat, is preferred because local recurrences have been observed after partial thymectomy; thymomectomy alone is debatable [28]. If the tumour is invasive, *en bloc* removal of all affected structures, including lung parenchyma, usually through limited resection, great vessels, nerves, and pleural implants, should be performed. Areas of uncertain margins are marked with clips to allow precise delivery of postoperative radiotherapy [27]. Phrenic preservation does not affect overall survival but increases the risk of local recurrence [29], and may be balanced with the achievement of complete resection especially in patients with severe myasthenia gravis. Frozen sections to assess tumour involvement of resection margins are not recommended, as differentiating tumoural thymic epithelial cells from non-tumoural thymic epithelial cells is difficult on such specimens [2].

Minimally invasive surgery is becoming standard for stage I tumours in the hands of appropriately trained surgeons [30–32]. This includes transcervical, extended transcervical, video-assisted thoracoscopy, and robotic approaches (right or left, right and left, right and cervical, left and cervical, subxiphoid and right and left, cervical and subxiphoid). The choice for minimally invasive resection should not degrade or change the principles that are deemed appropriate for an open approach, especially the achievement of complete resection that ultimately may require conversion to open surgery.

Ultimately, communication between surgeons and pathologists is crucial for staging TETs [27]. The proper orientation of the specimen and the marking of involved structures, organs or areas of concern are done by operating surgeons, and may be done using a mediastinal board. Routine removal of anterior mediastinal nodes is recommended [33]. Systematic sampling of intrathoracic sites is encouraged (*i.e.* paratracheal, aortopulmonary window, subcarinal areas depending on tumour location) in stage III/IV tumours. The actual need and the importance of nodal resection remains highly debated [33].

In stage IVA thymoma, defined as intrapleural or intrapericardial dissemination of tumour cells without any distant metastasis, surgical options, in addition to thymectomy, are local pleura or pericardium resection, may include total pleurectomy, and pleuropneumonectomy [34, 35]. Although it seems to be a very aggressive approach, pleuropneumonectomy has been shown to be feasible with good outcomes in these patients. Intrathoracic chemohyperthermia (ITCH, or HITHOC: hyperthermic intra operative thoraco-abdominal chemotherapy) based on Cisplatin (from 50 to 100 $mg \cdot m^{-2}$) and possibly associated with other agents, associated with subtotal pleural decortication is feasible, but requires to be prospectively assessed [35].

Debulking has been defined as removing 90% or more of tumour burden [36, 37]. The indication of debulking still remains controversial but may be proposed in non resectable thymomas only, not carcinomas, with clearly inferior results as compared to standard, carcinologic surgery. Some authors advocate the place of debulking to improve efficacy of high doses radiotherapy by minimising fields and showed significantly better survival in stages III and even IVA.

Postoperative radiotherapy

Given the tendency of TETs towards local and regional recurrence, and their established radio-sensitivity, radiotherapy has historically been a component in the treatment strategy in the postoperative setting [1, 3, 5].

Current modalities of postoperative radiotherapy for thymic epithelial tumours include 1) the use of multi-field arrangement conformal radiotherapy and three-dimensional treatment planning [38]; 2) a clinical target volume including the whole thymic space, the tumour and its extensions, and the anterior, superior, and middle mediastinum; 3) a total dose of 45–50 Gy after complete resection, 50–54 Gy after

R1 resection, with a boost on areas of concern, as mentioned, surgical clips may be then useful to plan the gross tumour volume; and 4) the use of a standard-fractionation scheme consisting of daily doses from 1.8 to 2 Gy over a 4–6-week period. Proton-beam radiotherapy has also been used in the postoperative setting.

Unfortunately, the rarity of TETs, and the lack of prospective, randomised trials, make it difficult to draw high-level evidence-based recommendations regarding its actual efficacy in terms of reduction of the risk of recurrence and death. Evidence from retrospective series indicates: 1) the absence of survival benefit after radiotherapy in stage I thymoma, and a debatable survival benefit after R0 resection of stage II-III thymoma [39]; 2) a similar rate of recurrence whether or not patients received postoperative radiotherapy after complete resection of thymoma [40]; and 3) a recurrence-free and overall survival benefit after resection of thymic carcinoma [41, 42]. The recurrences actually occur mostly in the intrathoracic pleura, rather than in the mediastinal tumour bed [43].

In the ITMIG database report that included 1263 patients with completely resected (R0) stage II or III thymoma enrolled in a retrospective setting, postoperative radiotherapy (PORT) had been given to 55% of patients, and the 5- and 10-year overall survival rates for patients having undergone an operation plus PORT were 95% and 86%, respectively, compared with 90% and 79% for patients receiving an alone operation ($p=0.002$). This overall survival benefit remained significant when patients with stage II ($p=0.02$) and stage III thymoma ($p=0.0005$) were analysed separately [44]. However, there are major limitations in this analysis including its retrospective nature, the absence of a systematic review in the tumour staging, a potential heterogeneity among PORT indications from one centre to another, the imbalance in stage II *versus* stage III tumours in the surgery plus PORT *versus* the alone surgery groups (with higher stage being a strong decision factor which favours PORT), but mostly the overall survival analysis, when more than the half of deaths are not related to tumour progression [45]. Other large data base studies from the US or Asia have shown an impact of PORT on survival of stage II or III thymoma [46–49]. Especially, similar results were obtained from the analysis of the National Cancer Database in the US [47]. In the Japanese cohort of 1110 thymomas, PORT was not identified as a significant factor influencing overall survival [46]. Of note, those data are all based on the Masaoka–Koga staging system.

Current recommendations are the following: PORT is not indicated after complete resection of Masaoka–Koga stage I thymoma [1], and is routinely not recommended after complete resection of stage II thymoma; still, PORT may be considered in case of aggressive histology (type B2, B3) or transcapsular invasion (stage IIB). Postoperative radiotherapy is recommended after complete resection of stage III/IVA thymoma, and in thymic carcinomas, whatever is the stage; it is also delivered in case of microscopically (R1) or macroscopically incomplete (R2) resection.

Advanced TETs: systemic therapies

In Masaoka–Koga stage III/IVA tumours (classified as stage IIIA/IIIB/IVA in the 8th TNM proposed system), complete resection is usually no achievable upfront. A biopsy is performed, followed by primary/induction chemotherapy, in a curative-intent setting with subsequent surgery or radiotherapy [1, 3, 5, 50]. Cases not eligible for local treatment receive definitive chemotherapy.

Primary chemotherapy

Primary/induction chemotherapy is recommended in non-resectable advanced TETs [51–55]. Cisplatin-based combination regimens should be administered; combinations of cisplatin, adriamycin, and cyclophosphamide, and cisplatin and etoposide are recommended [1, 3, 5]. Primary chemoradiotherapy with platin and etoposide is an option, especially for thymic carcinomas or if the tumour is never expected to become eligible for surgical resection [56, 57].

Usually 2–4 cycles are administered before imaging is performed to reassess resectability of the tumour. Surgery should be offered to patients for whom complete resection is thought to be achievable, according to above discussed principles; extended resection may be required [58]. Postoperative radiotherapy is then usually delivered.

Definitive radiotherapy

When the patient is not deemed to be a surgical candidate, either because R0 resection is not thought to be achievable, definitive radiotherapy is recommended part of a sequential chemoradiotherapy strategy [55]. Combination with chemotherapy (including cisplatin, etoposide chemotherapy and a total dose of radiation of 60 Gy) may be considered [56].

Exclusive chemotherapy

Chemotherapy should be offered as the single modality treatment in advanced, non-resectable, non-irradiable or metastatic (stage IVB) TETs to improve tumour-related symptoms the aim is to improve tumour-related symptoms through obtention of tumour response, while no prolonged survival is uncertain. Cisplatin-based combination regimen should be administered [51, 57, 59–62]. No randomised studies have been conducted, and it is unclear which regimens are best; multi-agent combination regimens and anthracycline-based regimens appear to have improved response rates compared to others, especially the etoposide, ifosfamide and cisplatin combination [63, 64]; still response is hard to assess given the location of target lesions, and criteria have been recommended for pleural lesions include the use of short axis as the measurement plane, and the unidimensional measurement of two pleural tumour sites at three different levels [65]. Combinations of cisplatin, adriamycin, and cyclophosphamide is preferred. Combination of carboplatin and paclitaxel is an option for thymic carcinoma [60, 62].

Overall, ll consecutive patients for whom systemic treatment was discussed at the RYTHMIC Multidisciplinary Tumour Board from 2012 to 2015 and who received at least one cycle of treatment were analysed in a landmark study [64]. A total of 236 patients were included in this analysis. 91 patients received primary chemotherapy, leading to a response rate of 79%, and a median progression-free survival (PFS) of 23.2 months. Predictors of longer PFS were histology of thymoma and cyclophosphamide, adriamycin and platin regimen. Exclusive chemotherapy was delivered to 54 patients. Response rate was 35% and was higher with PAC regimen. Median PFS was 6.2 months, and was correlated to response rate.

Recurrent TETs

Recurrences of TETs are treated with an algorithm that is similar to that of newly diagnosed tumours. Complete resection of recurrent TET is a major predictor survival [66–68], and surgery is performed in case of resectable lesion, especially occurring in the pleura.

Systemic chemotherapy

In non-resectable recurrences, several consecutive lines of systemic treatment are delivered. PAC chemotherapy may be re-administered [64]. Preferred regimens for second-line treatment include carboplatin plus paclitaxel [60], and platin plus etoposide [57]. Options for subsequent lines include pemetrexed ($500\ mg \cdot m^{-2} \cdot 3\ weeks^{-1}$) [69], oral etoposide (100 mg daily). In the RYTHMIC cohort, chemotherapy for 1st, 2nd, 3rd and 4th recurrence was delivered to 114, 81, 51 and 27 patients, respectively [64]. Response rates ranged between 11 and 25%. Median PFS were 7.7, 6.2, 5.9, and 6.5 months, respectively.

Targeted agents

The carcinogenesis mechanisms of TETs are virtually unknown [70, 71]. Resistance to apoptosis is associated with copy number gains of the anti-apoptotic molecule BCL2. Deregulation of cell-cycle controlling molecules, including copy number loss of *CDKN2A/B*, hypermethylation of its promoter, is associated with a lack of expression of its related protein p16INK4. Activation of the PI3K-AKT-MTOR pathway and deleterious mutations of regulatory subunits of the PI3K gene, as well as activating mutation of the *KIT* gene in thymic carcinomas are identified [70–75].

In the clinic, the relevance of *KIT* mutations as a therapeutic target remains has to integrate that all of these are not be uniformly sensitive to available KIT inhibitors. KIT expression at immunohistochemistry is a hallmark, possibly a diagnostic marker, of thymic carcinomas and does not correlate with the occurrence of a *KIT* mutations. Single case reports of responses with the use KIT inhibitors, imatinib, sunitinib, or sorafenib, are published [1, 71].

Everolimus was assessed in a phase II trial enrolling 51 patients [76]. Stable disease was the most frequent response pattern, with disease control rate of 88%.

Anti-angiogenic agents

Multikinase inhibitors targeting KIT, such as imatinib and sunitinib, are also potent angiogenesis inhibitors. Sunitinib is considered an option for refractory TETs, based on the results of two phase II trials showing high disease control rates above 80% in thymoma and thymic carcinoma [77, 78]. In a retrospective cohort from RYTHMIC, sunitinib was delivered beyond fourth line treatment [79]. Lenvatinib is another antiangiogenic drug, that has been approved in Japan for the treatment of advanced, regractory thymic malignancies [80].

Hot topic: immunotherapy

Immune-related characteristics

One-third of patients diagnosed with thymoma present with autoimmune disorders, the most frequent being myasthenia gravis [1]. Other frequent disorders include pure red cell aplasia (5% of cases), and hypogammaglobulinaemia (5% of cases). Thymic carcinomas are not associated with such disorders. Carcinogenesis then disrupts the thymus physiological role of controlling central tolerance to self-antigens, with the positive and negative selection of immature T cells [81]. Medullary thymic tumour epithelial cells present with inabilities to express tissue-related antigens, related to a loss of expression of the transcription factor AIRE (autoimmune regulator), similar to what occurs in APECED (autoimmune polyendocrinopathy candidiasis ectodermal dystrophy).

PD-L1 expression is a hallmark of thymic epithelial cells, and such expression is not related to antitumour immune response nor as a predictive biomarker of efficacy for immune checkpoint inhibitors targeting PD-1 or PD-L1 [82, 83]. Tumour mutation burden is low both in thymomas and thymic carcinomas [74, 75].

PD-1/PD-L1 inhibitors in patients with advanced TETs were assessed in 4 trials.

A phase II trial with pembrolizumab enrolled 41 patients with thymic carcinomas [84], 15% of whom developed severe immune related adverse events, including polymyositis and myocarditis, pancreatitis, hepatitis, diabetes mellitus type 1, or bullous pemphigoid. Response rate was 23%. A similar trial was conducted in Korea [85], both in thymic carcinomas and thymomas. Results were similar. A phase II trial with nivolumab failed to achieve clinical significance. A phase I trial with avelumab [86, 87] was conducted mostly in thymomas; three patients showed response after a single dose of treatment. Treatment was discontinued in five patients for toxicities.

Overall, immunotherapy is effective in thymic carcinomas, with a concern for toxicities leading extensive baseline immune check-up to be recommended. Trials are ongoing, such as those assessing nivolumab (NIVOTHYM) or pembrolizumab (PECATI)-based regimens.

Conclusion

Thymic malignancies are rare cancers, with complex classifications and treatment strategies based on multidisciplinary expertise and consensus. Lack of clinical trials and access to new therapies is a concern. Many academic groups are launching initiatives and projects, making the field very active and a model of implementation for orphan cancers.

Provenance: Commissioned article, peer reviewed.

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Conflict of interest: C. Girard has nothing to disclose. N. Basse has nothing to disclose.

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