Thymic tumours: An update

Valentina Polo1,2, Nicolas Girard3, Benjamin Besse1

1. Gustave Roussy, Department of Cancer Medicine, Villejuif, France
2. Oncologic Venetian Institute, Department of Second Medical Oncology, Padua, Italy
3. Hospices Civils de Lyon, Louis Pradel Hospital, Department of Respiratory Medicine, National Expert Centre for Thymic Malignancies, Reference Centre for Orphan Pulmonary Diseases, Lyon, France

Correspondence:
Benjamin Besse, Gustave Roussy, Department of Medicine, 114, rue Edouard-Vaillant, 94805 Villejuif, France.
benjamin.besse@gustaveroussy.fr

Available online:

Summary

Thymic malignancies are relatively uncommon tumours that display significant clinical, pathological, and molecular heterogeneity. Their management requires a multidisciplinary approach; because of their rarity, current indications are based on data from smaller, mostly institutional, series or retrospective analyses and controversies still exist. This article focuses on the principles of treatment of thymic malignancies. In the future, collaboration between many different institutions will open the opportunity to achieve a better understanding and management of the disease.

Autoimmune disease and thymomas

Because of the role of thymus in production of mature and functional T-cells and induction of self-tolerance, malignancies originated from thymus are linked to autoimmune disease [2]. In particular, the transcription factor autoimmune regulator gene (AIRE) regulates the presentation of ectopic tissue-specific autologous antigens by medullary epithelial cells to negatively select self-reactive thymocytes [3]. Thus, defective expression of AIRE in most thymomas leads to the development of self-reactive T-cell clones and consequently, to the development of auto-antibodies in the spleen, lymph nodes and bone marrow [4]. Approximately 40% of patients with thymoma develop an autoimmune disorder; the most frequent is myasthenia gravis that is
related to the presence of autoantibodies against post-synaptic acetylcholine receptors [2]. Considering that autoimmune disorders may significantly affect overall survival [5], these patients should receive adequate treatment for autoimmune disease in addition to oncological management; contrary to paraneoplastic disorders, the treatment of the thymic tumour does not improve systematically autoimmune disorders.

Staging

The most widely used staging system is that proposed by Masaoka et al. in 1981 [6] with the modification suggested subsequently by Koga et al. in 1994 [7]; recently, the International Thymic Malignancy Interest Group (ITMIG) has addressed the critical points of this classification by providing standard definitions (Table I) [8]. This system takes into account the integrity of the thymic capsule, the microscopic or macroscopic invasion into adjacent structures and the metastatic spread. Although lymph nodes metastases are much more commons in thymic carcinomas compared to thymomas, in this classification, evaluation of nodal involvement plays a minor role. Despite this observation could be a problem for thymic carcinomas, according to ITMIG, it is not recommended to use two different staging systems.

Histological classification

Several classifications have been developed over the years up to the current World Health Organization (WHO) classification of 2004 that distinguishes thymomas (type A, AB, B1, B2 and B3) and thymic carcinomas (Table II). This classification is based on the degree of atypia of epithelial cells (increasing degree from type A to thymic carcinoma), the proportion of non-tumoral lymphocytic component (decreasing from type B1 to type B3) and the resemblance to the normal thymic architecture [9].

Among thymic carcinomas, a variety of histopathologic subtypes have been described. In order to make uniform data and findings between different institutes, defined procedures regarding handling of resection specimen and reporting of findings by both surgeon and pathologist have been recently adopted by ITMIG. These recommendations are based on the importance of communication between surgeon and pathologist to achieve a correct diagnosis and staging. First thing, the pathologist, using the indications of the surgeon as described below must identify the anatomical aspects and areas of concern. Because of microscopic heterogeneity of these malignancies, at least one block for each centimeter of tumour should be submitted; random sections of the uninvolved contiguous tissues should be examined. Banking tissue for subsequent molecular research is critical to improve our understanding of the biology of these tumours; generally, it is feasible considering the large size of the tumours in most cases. The final pathological report must indicate whether the capsule surrounds the entire tumour or if there are missing areas, tumour invasion, also microscopic, beyond the capsule, and the relationship between the tumour and the pleura or the pericardium. Reporting the margin status and the distance of tumour to the closest margin whenever less or equal to 3 mm is also required; if this distance is less or equal to 1 mm, additional levels through this area should be examined. Finally if pre-operative chemotherapy has been administrated, more sections should be examined in order to have a valid representation of the histological features after treatment and pathologist should estimate grossly the percentage of remaining viable tumour [10].

Surgery

To date surgery remains the mainstay treatment in thymic malignancies and complete surgical resection (R0) is the most important prognostic factor for overall survival [11]. An open resection via sternotomy is the standard approach; open surgery allows examination of mediastinum and pleural cavities, evaluation of capsular invasion, involvement of perithymic and mediastinal fat and adjacent structures, and search for pleural or pericardial implants. By all these evaluations and final histological report, a correct staging can be performed. For early stages (I and IIA), complete thymectomy (including the tumour, the residual thymus and perithymic fat) is the encouraged approach. In locally advanced disease (stage III or IVA), a resection en bloc of all structures involved (lung parenchyma, great vessels, pleural implants and phrenic nerves) is recommended. In patients with myasthenia gravis, phrenic preservation should be considered [12,13].

Regarding lymphadenectomy, any suspicious nodes should be removed. In the case of encapsulated thymoma, removal of any adjacent anterior mediastinal nodes is encouraged; for stage III or IVA thymomas undergoing curative-intent resection, a removal

**Glossary**

| AIRE | Autoimmune regulator gene |
| ITMIG | International Thymic Malignancy Interest Group |
| WHO | World Health Organization |
| R0 resection | Complete surgical resection |
| R1 resection | Incomplete surgical resection with a positive margin |
| R2 resection | Incomplete surgical resection with gross residual disease |
| PAC | Cisplatin, doxorubicin and cyclophosphamide |
| VEGFR | Vascular endothelial growth factor receptor |
| VEGF | Vascular endothelial growth factor |
| RYTHMIC | Réseau tumeurs thymiques et cancer |

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of anterior mediastinal nodes is recommend as well as a sampl-
ing of all intrathoracic sites regardless of the tumour location. Because of the higher nodal invasion (27%), in thymic carci-
noma, a removal of anterior mediastinal, intra-thoracic, supra-
clavicular and lower cervical areas should be performed [10]. Since the last years, minimally invasive approaches have emerged for the management of thymic malignancies, that refer to any approach as long as no sternotomy or thoracotomy but still aiming a R0 resection. Minimally invasive surgery includes different access incisions methods of expo-
sure, visualisation and equipment (transcervical access, video assisted thoracoscopy, robotic approaches...). Its use remains a highly controversial field but no randomized trial has to date compared open surgery to minimally invasive surgery. As well as open surgery, complete exploration to assess the presence of tumour cells in surrounding tissues and resection of involved structures, is required. Conversion to open surgery is mandatory if by minimally invasive techniques, complete resection or not en bloc resection, are compromised, or in case of rupture of the capsule or disruption of the tissues exposing the tumour [14]. The role of hyperthermic intrapleural chemotherapy is under investigation for stage IVA tumours.

According to the above-mentioned ITMIG recommendations, at the time of dissection, the surgeon should orientate the

<table>
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<tr>
<th>STAGE</th>
<th>MASAOKA-KOGA Staging System</th>
<th>ITMIG definitions</th>
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<tr>
<td>I</td>
<td>Grossly and microscopically completely encapsulated tumour</td>
<td>This includes tumours with invasion into but not through the capsule, Tumours in which the capsule is missing but without invasion into surrounding tissues</td>
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<td>II</td>
<td>Microscopic transcapsular invasion</td>
<td>Microscopic transcapsular invasion (not grossly appreciated)</td>
</tr>
<tr>
<td>A</td>
<td>Macrosopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium</td>
<td>Gross visual tumour extension into normal thymus or perithymic fat surrounding the thymoma (microscopically confirmed), Adherence to pleura or pericardium making removal of these structures necessary during resection, with microscopic confirmation of perithymic invasion (but without microscopic extension into or through the mediastinal pleura or into the fibrous layer of the pericardium)</td>
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<tr>
<td>B</td>
<td>Macrosopic invasion into neighboring organ (i.e. pericardium, great vessel or lung)</td>
<td>Microscopic involvement of mediastinal pleura (either partial or penetrating the elastin layer), Microscopic involvement of the pericardium (either partial in the fibrous layer or penetrating through to the serosal layer), Microscopically confirmed direct penetration into the outer elastin layer of the visceral pleura or into the lung parenchyma, Invasion into the phrenic or vagus nerves (microscopically confirmed, adherence alone is not sufficient), Invasion into or penetration through major vascular structures (microscopically confirmed), Adherence (i.e. fibrous attachment) of lung or adjacent organs only if there is mediastinal pleural or pericardial invasion (microscopically confirmed)</td>
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<td>IV</td>
<td>Pleural or pericardial metastases</td>
<td>Microscopically confirmed nodules, separate from the primary tumor, involving the visceral or parietal pleural surfaces, or the pericardial or epicardial surfaces</td>
</tr>
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<td>A</td>
<td>Lymphogenous or hematogenous metastasis</td>
<td>Any nodal involvement (e.g. anterior mediastinal, intrathoracic, low/anterior cervical nodes, any other extrathoracic nodes), Distant metastases (i.e. extrathoracic and outside the cervical perithymic region) or pulmonary parenchymal nodules (not a pleural implant)</td>
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Source: Adapted from [7,8].
specimen, indicate the involved structures and where the margin was most concerning, and mark areas of concern on the specimen and areas of tissue disruption or distortion. Areas of concern should be marked with a clip also in the patient so they can be identified if post-operative radiotherapy is indicated. The use of frozen sections should be restricted considering the difficulty in interpreting frozen sections of thymomas [10].

Radiotherapy

Thymomas and thymic carcinomas are highly sensitive to radiotherapy; thus, its role as part of the multimodal treatment for these tumors is well established. Nevertheless, because of the low incidence of these malignancies, controversies still exist and definitive recommendations for the use of radiotherapy have not yet been developed. To date, prospective, large-scale and randomised trials evaluating the role of radiotherapy are not available and current indications are based on data from smaller, mostly institutional, series or retrospective analyses [15,16].

In the post-operative setting to discuss the benefit of radiotherapy patients should be stratified by tumor stage and characteristics of resection. While several studies agree in the lack of benefit from radiotherapy for stage I tumors underwent R0 resection [17,18], on the other hand, the role of radiotherapy for stages II and III remains debated. Indeed, from several studies countervailing findings emerged regarding the efficacy of post-operative radiotherapy in terms of overall survival and reduction of local and distant recurrences after R0 resection of stage II and III cancers. In such cases, histology may be useful to select patients who benefit from radiotherapy treatment: in a retrospective Japanese study of 324 patients who underwent thymic malignancy resection, authors observed that A, AB and B1 thymomas, according to WHO classification, did not to benefit from post-operative radiotherapy [19]. To date for stages III and IV, post-operative radiotherapy is encouraged. It is instead widely accepted that the benefit of radiotherapy after incomplete surgical resection with a positive margin (R1 resection) or with gross residual disease (R2 resection) regardless stage of disease.

Radiotherapy is administered within 3 months after surgery; the target volume includes the thymic space, the tumor and its extensions and the anterior, superior and middle mediastinum. Pre- and post-operative imaging and regions of risk marked by surgical clips should be considered to plan the treatment. Given the advances over the last years, 3D conformal therapy or intensity-modulated radiation therapy are recommended if available to reduce radiation to surrounding tissues.

The other most important scenario in which radiotherapy plays an important role is for unresectable thymic malignancies as part of definitive treatment in association with chemotherapy. Radiotherapy may be also useful for the management of recurrences.

Radiotherapy regimens for thymic malignancies traditionally use doses ranging from 45 to 60 Gy in 1.8 to 2.0 Gy fractions delivered over 3 to 6 weeks. Controversies still exist about the correlation between the dose used, and the specific setting and benefit expected; usually higher doses are delivered in the settings of definitive treatment and post-operative treatment following R2 resection.

The role of pre-operative radiotherapy with or without association with chemotherapy is not yet clearly established.

Chemotherapy and targeted therapy

Chemotherapy should be offered to patients with locally advanced thymic malignancies (stages III to IV) either as part of curative-intent treatment in combination with other local approaches (surgery and/or radiotherapy) or as palliative-intent treatment in inoperable recurrent or metastatic disease setting.

Table II

The World Health Organization (WHO) histopathological classification of thymic epithelial tumours

<table>
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<tr>
<th>Type</th>
<th>Pathological features</th>
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<tr>
<td>Thymomas</td>
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<tr>
<td>A</td>
<td>Oval or spindle cells; no atypia; few or no lymphocytes</td>
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<tr>
<td>AB</td>
<td>Mixture of a lymphocyte-poor type A thymoma component and a more lymphocyte-rich type B-like component</td>
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<td>B1</td>
<td>Cells with a histological appearance practically indistinguishable from the normal thymus; prominent population of immature lymphocytes</td>
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<tr>
<td>B2</td>
<td>Polygonal cells closely resembling the predominant epithelial cells of the normal thymic cortex; immature T-cells</td>
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<tr>
<td>B3</td>
<td>Round or polygonal cells with slight atypia; minor component of lymphocytes</td>
</tr>
<tr>
<td>Thymic carcinomas</td>
<td>Atypia; no organotypic features; diverse differentiations</td>
</tr>
</tbody>
</table>

Source: Adapted from [9].
In locally advanced tumours, patients usually received 3–4 cycles of therapy with a response rate of about 70–80% and if a complete resection is feasible patients underwent surgery and R0 resection is achieved in 50% of the cases. If R0 resection is unachievable or other conditions make the patient inoperable, a definitive treatment by radiotherapy should be considered. In the literature, only 10–21% of patients did not receive either surgery or radiation therapy after primary chemotherapy. In a palliative-intent setting, the goal is limited to a potential improvement of tumour-related symptoms and disease control.

In the post-operative setting of thymomas, there are no indications for chemotherapy following R0–R1 resection; on the contrary, chemotherapy may be delivered in combination with radiotherapy after a R2 resection. Considering the higher incidence in thymic carcinomas of local and distant recurrences after surgery, if no pre-operative treatment was administrated, post-operative chemotherapy combined with radiotherapy may be discussed [20]. Whatever setting chemotherapy is delivered in patients with thymic malignancy, cisplatin-based chemotherapy is the standard of care; over the years several combinations have been tested with different results in terms of response rate and overall survival. To date, the most employed is a three-drug combination therapy with cisplatin, doxorubicin and cyclophosphamide (PAC regimen).

Octreotide is an option for tumours with increase uptake at octreoscan scintigraphy [21]. Despite significant efforts, molecular pathways involved in thymic malignancies remain poorly understood; to date, according to the drugs available, the clinical relevant pathways identified are the KIT and the vascular endothelial growth factor receptor (VEGFR) pathway [22]. KIT is overexpressed in 2% of thymomas and in 79% of thymic carcinomas, but overexpression does not correlate with gene mutations, which are found in only 9% of thymic carcinomas. Some authors have described cases of response to imatinib in patients with an activating mutation in the KIT gene [23,24]; however, trials evaluating the KIT inhibitor imatinib did not show clinical benefit, probably due to the fact that patients were not selected for mutational status [25,26]. Vascular endothelial growth factor (VEGF) A, VEGFR-1 and -2 are overexpressed in thymic malignancies and microvessel density and VEGF expression level have been shown to correlate with clinical stage and tumour invasion [27]; however, limited data are available regarding efficacy of angiogenesis inhibitors. Some case reports have reported evidence of efficacy in terms of response rate and disease control, with multi-targeted tyrosine kinase inhibitors, such as sunitinib or sorafenib, especially in patients with thymic carcinoma, also in patients without KIT mutations; it is likely that this benefit come from their antiangiogenic activity.

Other targeted agents have been investigated in unselected patients by several phase II studies, such as erlotinib, gefitinib, bevacizumab and belinostat, but these drugs failed to demonstrate activity in advanced disease. According to Kossai et al., patients progressing after standard treatment could benefit from phase I trial agents; in particular mTOR inhibitors and antiangiogenic agents seem to yield a good clinical response [28].

**Nationwide network for thymic malignancies: the French paradigm, RYTHMIC**

The French National Cancer Institute has supported several rare cancer networks, including Réseau tumeurs THYMiques et Cancer (RYTHMIC), which is dedicated in thymic malignancies. One of the first objectives of RYTHMIC was to build a network of 12 regional expert centers and a bi-site national expert center. It is therefore mandatory to review each file of any patients newly diagnosed for a thymic malignancies at a regional multidisciplinary tumor board or during a bi-monthly national multidisciplinary board. Each new file is entered in a national database, updated on clinical and pathological characteristics. The decision-making process is based on national guidelines established by the network’s regional experts (that may be downloaded on www.rythmic.org). A central pathological review is performed for each cases submitted to a regional or national multidisciplinary staff. Fostering clinical, translational research and continuous medical education are part of RYTHMIC’s objectives. This first network dedicated to care and research should inspire, if successful, similar initiatives in other countries.

**Conclusion**

Finally, proper diagnosis and management of thymic malignancies arise from good multidisciplinary collaboration. Given the rarity of these tumours, according to ITMIG recommendations, common procedures and definitions should be adopted by all institutes in order to uniform findings; this could make possible inter-institutional collaborations and prospective studies that are required to achieve a better understanding of the disease and improvement in clinical management.

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