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Chapter

Thymoma and Thymic Carcinoma

Annette Rebecca Bijsmans and Robin Cornelissen

Abstract

Malignancies of the thymus are a rare entity and are often without local symptoms. However, paraneoplastic syndromes can give symptoms varying from very mild to life-threatening. The diagnostic workup and management of these tumors warrant a multidisciplinary approach. Treatment choice is mainly decided upon by pathological World Health Organization (WHO) subtype and clinical staging. In contrast to historical belief, biopsy could be considered when indicated. For resectable tumors, surgical approach is advised, with adjuvant radiotherapy for Masaoka-Koga stage III tumors. Whether Masaoka-Koga stage II tumors should be treated with radiotherapy is controversial given different outcomes in multiple studies. In Masaoka-Koga stage III, combinations with induction chemotherapy are the standard. A surgical approach should be considered even in stage IVa disease. If distant metastases are present, the patient can be treated with systemic chemotherapy. Despite many phase II studies having been published, there is no randomized controlled phase III data regarding optimal treatment available. In addition to chemotherapy, sunitinib and octreotide have been described to be effective. Immunotherapy is seen as Pandora's box given the possibility of immune-related side effects in this immunological organ. All known data regarding immunotherapy will be discussed.

Keywords: thymoma, thymic carcinoma, autoimmune paraneoplastic syndromes, surgery, radiation, chemotherapy, immunotherapy, targeted therapy

1. Introduction

Malignancies of the thymus are rare accounting for <1% of all adult neoplasms. Thymoma and thymus carcinoma account for 20% of tumors in the anterior mediastinum and are therefore the most commonly found malignancy in that specific location.

There are several groups of thymic tumors to distinguish thymic epithelial tumors, germ cell tumors, lymphoid and hematological malignancies, and mesenchymal tumors. It is known that they derive from or differentiate toward thymic cellular components, but the etiology of thymic neoplasms is largely unknown [1].

This chapter is about the epithelial tumors thymoma and thymic carcinoma (which include the neuroendocrine tumors). These tumors are histologically characterized by thymic stroma and lymphocytes. Thymomas usually exhibit a slow growth pattern, but they do have malignant potential and show a propensity for local invasion and intrathoracic recurrence. Extrathoracic metastases of thymomas are quite rare [2]. Thymic carcinomas are more aggressive, with invasion in the surrounding mediastinal structures. Extrathoracic metastases occur in <7% of patients [3]. Although thymomas and thymic carcinomas arise mostly in the anterior

mediastinum, they can also be found in other mediastinal compartments, as well as in the neck, lung, pleura, and thyroid, due to ectopic thymic tissue [1, 4, 5].

Approximately 1000 new cases are diagnosed per year in Europe [6]. Patients are usually between 20 and 70 years of age, with a peak in 30–40 years for those with myasthenia gravis and 60–70 years for those without myasthenia gravis. Incidence is similar in men and women [3, 7]. There are no known risk factors [3, 7], although clusters of thymoma are described in patients with multiple endocrine neoplasia type 1 (MEN1) syndrome [8] and an association between the Epstein–Barr virus and myasthenia gravis in thymoma patients has been suggested [9].

2. WHO histological classification

Numerous classifications for thymic neoplasms, based on different histological and clinical criteria, have been proposed in the past. For universal agreement purposes, the International Committee of the World Health Organization (WHO) developed a classification system that distinguishes five histological subtypes of thymomas that differ in both morphological and clinical presentation and which correlate with invasion [1]. The WHO classification is increasingly more malignant from A to B3. Thymomas are composed of a mixture of neoplastic epithelial cells and normal T lymphocytes and exhibit a resemblance to the normal thymic architecture, which cannot be found in other organs. In contrast, thymic carcinoma (in the past considered as a thymoma type C) is similar to carcinomas found outside the thymus. Although most thymomas have an excellent prognosis, they can be locally invasive and are (although rarely) able to spread to lymph nodes or extrathoracic sites, so the term "benign" should be avoided.

Type A thymoma is composed of spindle cells and a few to no lymphocytes. About 24% of the type A thymomas are found in patients suffering from myasthenia gravis, and pure red cell aplasia may occur. Eighty percent of type A thymomas are Masaoka-Koga stage I on presentation (for explanation on the Masaoka-Koga staging system, see paragraph on staging). Stage IV is rare in this histological subtype [1, 3]. The prognosis of type A thymoma is excellent with 5- and 10-year survival rates close to 100% [10].

Type AB thymoma is composed of a mixture of lymphocyte-poor type A thymoma and more lymphocyte-rich type B. Approximately 14% of type AB thymomas are associated with the development of myasthenia gravis. Paraneoplastic pure red cell aplasia has also been also reported. Seventy-two percent is Masaoka-Koga stage I at presentation, 22% stage II, and 6% stage III. As in WHO type A disease, stage IV is rare [1]. Overall 5- and 10-year survival is reported 80–100% for stages I and II.

Type B1 thymoma is composed of thymic epithelial cells which are practically indistinguishable from the normal thymus cortex and medulla. A prominent population of immature lymphocytes is present. Like the other types, type B1 thymoma is associated with myasthenia gravis, but additionally hypogammaglobulinemia and pure red cell aplasia have been reported. Invasion in adjacent organs occurs in 12% of patients [11]. Complete surgical resection is possible in 94% of the cases with a recurrence rate of 10%. Ten-year survival rate is >90% [10].

Type B2 thymomas are usually at a more advanced stage. They are predominantly composed of large, polygonal tumor cells in the background of a large population of immature T lymphocytes. The most frequent manifestations (up to 80%) are symptoms arising from myasthenia gravis. Pure red cell aplasia, hypogammaglobulinemia, and other paraneoplastic autoimmune diseases have been described. Up to 53% are stage Masaoka-Koga I or III at presentation, and 8.2% is

stage IV. In 5–15% of cases, they are non-resectable, and recurrence rates are 9% after complete resection [10, 12]. Reported 10-year survival rates are between 50 and 100% [1].

Type B3 thymomas are almost always invasive and unresectable at presentation. Like the other types of thymomas, the most frequent association is myasthenia gravis. Pure red cell aplasia and hypogammaglobinemia are rare. The majority of patients are Masaoka-Koga stage II or III at presentation, and stage IV occurs in 20%. Ten-year survival rates range between 50 and 70% [10, 12, 13].

Thymic carcinomas are atypical, invasive epithelial tumors that show resemblance to carcinomas outside the thymus and show a lot of differentiation. Squamous cell carcinomas and undifferentiated carcinomas are the most common subtypes. They are composed of polygonal or round epithelial cells with mild atypia. Invasion of adjacent structures has been reported to occur in 83% of cases. In contrast to thymomas, paraneoplastic syndromes are very rare. Thymic carcinomas have the worst survival rate of the thymic malignancies with only 35% 5-year survival [1, 10, 14].

3. Clinical presentation

Patients with a thymus malignancy can present themselves with complaints due to local compression/invasion or due to a paraneoplastic autoimmune phenomenon, but ~40% of the thymic neoplasms are asymptomatic incidental findings.

Local symptoms are related to the site and size of tumor and compression or invasion on the surrounding tissue. Patients can present themselves with symptoms as chest pain, cough, dysphagia, or stridor. A superior vena cava syndrome can cause swelling of the face and arms and dyspnea. Dyspnea can also be the result of unilateral or bilateral phrenic nerve palsy and pleural or pericardial involvement. The latter can also elicit tachycardia [3]. Systemic symptoms such as fever or weight loss are possible.

3.1 Paraneoplastic autoimmune syndromes

About 40–50% of thymomas are associated with a variety of paraneoplastic autoimmune syndromes, and over 30 associations have been described [1, 15, 16] (**Table 1**). Up to 25% deaths in thymoma are due to the complications of autoimmune syndromes.

The most common paraneoplastic syndrome is myasthenia gravis, followed by pure red cell aplasia and hypogammaglobinemia (Good syndrome).

Ten to twenty percent of patients with myasthenia gravis have a thymoma, and 30–50% of patients with thymoma have myasthenia gravis. It is a neuromuscular disease that leads to varying degrees of muscle weakness. It is caused by autoantibodies that interfere with the acetylcholine receptors in the neuromuscular junction of the voluntary muscles, but the exact mechanism how has yet to be discovered. Systemic symptoms consist of fatigue and general muscle weakness leading to troubles with walking. Myasthenia gravis can antedate the diagnosis of thymoma, be diagnosed concurrently, or occur after thymectomy, with or without recurrence of thymoma [15–17].

Pure red cell aplasia is a profound non-regenerative anemia, characterized by a severe reduction in reticulocytes and absence of erythrocyte precursors in the bone marrow. Five to fifteen percent of patients with thymoma have pure red cell aplasia [16]. It is more common in older women. Remission following surgical excision of the thymoma is uncommon [18].

Neuromuscular diseases	**Myasthenia gravis** Neuromyotonia Rippling muscle disease Polymyositis/dermatomyositis Encephalitis Intestinal pseudo-obstruction
Hematologic autoimmune diseases	Anemia **Pure red cell anemia** Pernicious anemia Hemolytic anemia Aplastic anemia Other isolated cytopenia Immunodeficiencies **Hypogammaglobinemia/Good syndrome** T-cell deficiencies
Dermatologic diseases	Pemphigus Lichen planus Alopecia areata
Endocrine disorders	Addison's disease Cushing's disease Graves' disease
Renal and hepatic disease	Glomerulonephritis Autoimmune hepatitis
Systemic autoimmune diseases	SLE Sjogren's disease Systemic sclerosis **Thymoma-associated multiorgan autoimmunity (TAMA)**

Table 1.
Examples of autoimmune syndromes associated with thymoma.

Patients suffering from hypogammaglobulinemia (or Good syndrome) suffer from recurrent episodes of diarrhea, pulmonary infections, urinary tract infections, and several other bacterial and viral infections. Five percent of patients with Good syndrome have a thymoma, and 10% of patients with a thymoma have hypergammaglobulinemia. Thymectomy does not normalize immunoglobulin levels. Treatment consists of administration of intravenous immunoglobulin [16, 19].

Thymoma-associated multiorgan autoimmunity (TAMA) is a severe and often fatal graft-versus-host-like disease that requires special mention. Symptoms are T-cell mediated and cause skin disruptions, liver failure, and diarrhea [3]. Immunoglobulin and methylprednisolone have been described as treatment [20].

4. Diagnostics

4.1 Imaging

Thymic epithelial tumors arise in the anterior mediastinum and are most commonly located between the sternum, the great vessels, and the pericardium. All anterior mediastinal masses should be assessed with a chest computed tomography (CT) with IV contrast [21]. Chest CT can usually show if a thymic tumor is well circumscribed and if invasion in mediastinal fat, the surrounding vessels, or the adjacent lung is present. It can also show the presence of pericardial and/or pleural seeding [16]. Magnetic resonance imaging (MRI) can be used to assess involvement of surrounding tissues [22] and can also be useful to differentiate between

thymoma and thymic cysts that demonstrate increased CT attenuation due to hemorrhage or high mucinous content [16]. It can also be considered in patients that cannot tolerate radiocontrast administration.

Thymomas are usually encapsulated, homogenous, and round or oval structures with smooth contours. A cystic component is common. They can range from microscopic size to >30 cm in diameter. Type B thymomas and thymic carcinomas can show calcifications [22]. Thymic carcinomas tend to have irregular borders and necrotic areas and are usually much larger than thymomas. Pleural seeding is seen in both invasive thymoma and thymic carcinoma [23].

Positron-emission tomography (PET) can be useful in the case of thymic carcinoma. Thymic carcinomas have a higher fludeoxyglucose (FDG-18) PET uptake than thymomas. Using a standardized uptake value (SUV) cutoff point of 5.0, thymic carcinoma can be distinguished from thymomas with a sensitivity of 84.6% and a specificity of 92.3%. PET can also be useful for diagnosis of extra thoracic metastases in thymus carcinoma [24].

4.2 Biopsy

When a thymic tumor is considered likely and microscopical complete resection is considered possible, pathological evaluation should be done following surgery. Most thymomas can reliably be identified on the clinical presentation and imaging without the need for a biopsy. Histological classification may be difficult when there is a limited amount of tissue, and invasion in the surrounding tissue cannot be identified on biopsy alone. So even when the diagnosis is uncertain based on clinical presentation and imaging alone, complete surgical resection is advised for both diagnostic and treatment purposes [21].

Historically, it is thought that biopsy can cause pleural seeding. This is the main reason it is recommended to avoid a biopsy when resectable thymoma is suspected [21, 25]. However, there are no known exact data available to describe the proportion of this risk. There are only three case reports published for needle tract implantation of a thymoma reported in the chest wall after biopsy [26–28]. To abstain from a needle biopsy in order to avoid the risk of pleural seeding therefore seems unfounded [29].

In the case of potentially resectable or unresectable disease or when another diagnosis, such as lymphoma, is strongly suspected, tissue diagnosis is necessary. Biopsy should avoid a transpleural approach to prevent tumor seeding in the pleural space [21, 30]. Note that differentiation between lymphoma and thymoma can be difficult when a fine needle aspiration is done, so core needle biopsy or surgical biopsies are preferred [31].

5. Staging

There are several different staging systems for thymoma and thymic carcinoma, but the Masaoka-Koga staging system [32] and the American Joint Committee on Cancer (AJCC) the eighth edition of the TNM prognostic staging system [33] are the most commonly used.

Both staging systems are based on the extent of the primary tumor, invasion of adjacent structures and dissemination. In contrast to other thoracic cancers, both lymph node and distant metastases are considered stage IV disease. The Masaoka-Koga staging system (**Table 2**) is a surgical-pathological system that can only be definitely ascertained after surgery is performed. Historically this has been the most widely used staging system, so most data supporting treatment options is based on patients staged according to the Masaoka-Koga system.

Masaoka-Koga stage	Diagnostic criteria
Stage I	Macroscopically and microscopically completely encapsulated
Stage II	a. Microscopic transcapsular invasion b. Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organs (i.e., pericardium, great vessels, lung) a. Without invasion in the great vessels b. With invasion in great vessels
Stage IV	a. Pleural or pericardial dissemination b. Lymphogenous or hematogenous metastases

Table 2.
Masaoka-Koga staging system.

TNM staging AJCC eighth edition			
Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor encapsulated or extending into the mediastinal fat may involve the mediastinal pleura T1a Tumor with no mediastinal pleural involvement T1b tumor with direct invasion of mediastinal pleura		
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)		
T3	Tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins		
T4	Tumor with invasion into any of the following: aorta, arch vessels, intrapericardial pulmonary artery, myocardium, or trachea esophagus		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	Metastases in anterior (perithymic) lymph nodes		
N2	Metastases in deep intrathoracic or cervical lymph nodes		
Distant metastases (M)			
M0	No pleural, pericardial, or distant metastases		
M1	Pleural, pericardial, or distant metastases M1a separate pleural or pericardial nodules M1b pulmonary intraparenchymal nodule or distant organ metastases		
Prognostic stage groups			
	T	N	M
Stage I	T1a,b	N0	M0
Stage II	T2	N0	M0
Stage IIIa	T3	N0	M0
Stage IIIb	T4	N0	M0
Stage IVa	Any T	N1 N0–N1	M0 M1a
Stage IVb	Any T	N2 Any N	M0–M1a M1b

Table 3.
TNM staging AJCC eighth edition.

In 2018, the AJCC published the eighth edition of the TNM staging system (**Table 3**). They incorporated a proposal from the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG) for the staging of thymoma and thymic carcinoma based on the anatomical extend of the tumor combined with prognostic factor. Survival data of 10,808 patients was used [33]. Because of this larger dataset, the addition of nodal metastasis and a better correlation with prognosis, we would advise the AJCC TNM staging system.

6. Management

There are no phase III randomized, clinical trials on the treatment of thymoma and thymic carcinoma. Although they are two different entities, the general management per stage is almost the same. Surgery aimed at complete resection is the cornerstone of thymoma and thymic carcinoma management and should always be pursued.

All patients should be managed by a multidisciplinary team with experience in the management of thymoma and thymic carcinoma. The choice of treatment depends on resectability, stage, and whether or not myasthenia gravis is present. In all stages of thymoma and thymic carcinoma, resectability should be considered. When deemed possible in stages IIIb and IVa, surgery is part of a multimodality approach [25, 34–37].

An example of management according to stage could be as shown in **Table 4**. One should realize though that there is no advise based on phase III randomized controlled trails available and every case should be considered individually and there are different options, as discussed below.

6.1 Treatment thymoma

6.1.1 Resectable disease

Once complete resection of a thymoma is deemed possible, complete resection of the thymus, the tumor, and the invaded structures (including resection of the lung parenchyma or pericardium and vena cava reconstruction if necessary) is

Treatment thymoma and thymic carcinoma according to stage		
AJCC TMN stage	Thymoma	Thymic carcinoma
Stage I	Complete resection	Complete resection
Stage II	Complete resection Consider PORT in WHO type B2/3	Complete resection and PORT
Stage III	**Resectable or potentially resectable disease:** Multimodality approach Consider neoadjuvant chemotherapy in IIIA tumors. Neoadjuvant chemotherapy in IIIb tumors Complete resection or, when not feasible during surgery, maximum debulking PORT **Unresectable disease** Chemoradiation	**Resectable or potentially resectable disease:** Multimodality approach Consider neoadjuvant chemotherapy in IIIA tumors. Neoadjuvant chemotherapy in IIIb tumors Complete resection or, when not feasible during surgery, maximum debulking PORT **Unresectable disease** Chemoradiation
Stage IV	IVA same as stage III IVB chemotherapy or individual approach	IVA same as stage III IVB chemotherapy

Table 4.
Treatment thymoma and thymic carcinoma according to stage.

recommended [21, 25, 34, 36]. Preoperative evaluation for myasthenia gravis is advised. If this is diagnosed, treatment is essential, as myasthenia gravis can cause a postoperative myasthenic crisis or respiratory failure [38]. Thymoma Masaoka-Koga stages I and II have a 5-year survival rate of 100% after surgery [1].

In the case of an incomplete resection, postoperative radiotherapy (PORT), either on the primary tumor or on isolated metastasis, is recommended to reduce the risk of recurrence [35, 39]. In the past PORT was considered standard treatment for stage II completely resected tumors [7, 40]. Nowadays PORT in completely resected stages I and II WHO type A, AB, and B1 thymoma is not considered useful [10, 41–43]. Because of a high recurrence rate (even after R0 resection) PORT is advised for the higher stages and for WHO-type B2/3 thymoma and thymic carcinoma [21, 44], although the data are somewhat conflicting in this [7].

6.1.2 Potentially resectable disease

More extensive thymomas can be initially irresectable but potentially resectable after neoadjuvant treatment. A multimodality approach containing neoadjuvant chemotherapy with or without postoperative radiotherapy should be used, depending on WHO type and resection margins [21, 35, 45–47].

Potential advantages of neoadjuvant chemotherapy are tumor downstaging and increasing the likelihood of complete resection. However, because the available data on chemotherapy in thymoma is based on small, phase II studies, there is no optimal chemotherapeutic regime established [21]. Potential disadvantages could be complications due to chemotherapy and longer operating time [48]. There is even some recent data suggesting that there is no overall survival benefit to be expected from neoadjuvant chemotherapy before surgery [48–50]. In the cases of extensive pleural disease, several institutions have reported small series of extrapleural pneumonectomy for stage IVA disease with excellent outcomes and low morbidity [51].

There are no RCT's available to settle this matter. For now, it is recommended to use neoadjuvant chemotherapy to downstage unresectable thymic malignancies before surgery [21]. Obviously, reevaluation after neoadjuvant therapy to determine whether or not the tumor responded sufficiently is mandatory. There is evidence supporting maximum debulking, combined with PORT and/or adjuvant chemotherapy, to benefit survival from a thymoma which turns out to be unresectable during surgery. This is, however, based on retrospective data, so selection bias could cloud this positive outcome [3, 52].

6.1.3 Unresectable disease

In the case of unresectable disease or the patients is inoperable due to condition or comorbidity, the possibility of radiation therapy should be assessed. If radiation is feasible, concurrent chemoradiation is advised. If radiation is not possible due to a too large field, palliative chemotherapy is recommended. But even in that setting, long-term disease control and survival can be sometimes pursued, and even a combination of radiation on the primary tumor combined with resection of metastasis could be considered [21].

Chemotherapy is the primary modality in systemic management of unresectable thymoma. Thymomas are known to be sensitive to chemotherapy, possible due to a "lymphocytic effect" of cytotoxic agents. Due to the rarity of the disease and surgery with or without PORT being the cornerstone of treatment, there are no randomized controlled trails available to select a preferred regime. Platinum-based combinations are standard of care, the most popular regimes being cisplatin with anthracycline and/or etoposide. The response rate range of these regimens is

between 25 and 100% [53]. The preferred regime by the NCCN is cisplatin/doxorubicin/cyclophosphamide [21, 54].

Stereotactic radiotherapy (SBRT) may be appropriate for limited focal metastasis; conventional fractionation is appropriate for larger metastasis [21].

Response rates for second-line therapy range from 15 to 39% [55]. Pemetrexed and paclitaxel are considered the most efficacious in second-line treatment of thymic malignancies, although this is based on small phase II studies and expert opinion [21, 56, 57].

Checkpoint inhibitors. Programmed death ligand 1 (PD-L1) expression is high (82%) in thymoma, especially in WHO type B thymoma [58]. Even so, based on a phase II study on pembrolizumab (a humanized IgG4 antibody to PD-L1) in 33 thymic epithelial tumors (including 7 thymomas), immunotherapy is not recommended in thymoma. This is because of the high grade of immune-related events that was shown in seven thymoma patients during this study; 71% had grade 3 or higher immune-related adverse events (including myocarditis) [59]. Avelumab is a fully human IgG1 anti-PD-L1 antibody that showed less adverse events (38%) in a phase I trial (n = 7). However, it is currently under clinical development, and no phase II data is available [60].

The high rate of immune-related side effect was expected; the physiological role of the thymus is to induce tolerance to self-antigens and deletion of autoimmune T cells. In the normal thymus, PD-1/PL-D1 expression regulates this self-tolerant T-cell repertoire. It is thought that disruption of the PD-1/PDL-1 system could lead to significant alteration of the T-cell population and therefore cause autoimmune-related adverse events in the case of checkpoint inhibition [61].

Targeted therapies. Although there is high epidermal growth factor receptor (EGFR) expression in immunohistochemical staining of thymic epithelial tumors (71% for thymoma and 53% for thymic carcinoma), there is no correlation between the EGFR status and EGFR mutations. Experience with targeted therapies in thymoma is very limited and based on a small number of heterogenic phase II studies, but as for now this shows that there is no place for EGFR inhibitors in the treatment of thymoma and thymic carcinoma [7]. KIT-inhibition (inhibition of a transmembrane type III tyrosine kinase receptor) may show some promises in thymic carcinomas, but as thymomas do not show c-KIT expression [62], KIT-inhibition is not effective. There is some phase II experience in insulin-like growth factor (IGFR) inhibitors in thymoma patients that have shown some promising results [63]. Octreotide (a somatostatin analog) plus prednisolone may be useful in patients who have a positive octreotide scan [64].

6.1.4 Recurrent disease

The recurrence rate of thymoma after complete resection is 10–30%, and this can occur many years after initial treatment. Surgical resection of recurrent disease can be associated with long-term survival and should be considered for patients with recurrent thymoma. In pleural "drop" lesions, repeated resection is considered safe [50, 65].

6.2 Treatment thymic carcinoma

Similar to thymoma, surgery aimed at complete resection is the cornerstone of thymic carcinoma treatment, and the principles of first-line treatment in resectable disease are more or less the same. Five-year survival rate of 100% is reported for completely resected stage I disease going down to 17% in stage IVb disease [66]. Patients with a thymic carcinoma have a high risk of recurrent disease. Therefore,

some centers offer PORT (with or without chemotherapy) regardless of stage and resection margins [3, 21]. The available data is yet again limited, and there are indications that adjuvant therapy is not beneficial in R0-resected stage I thymic carcinoma [21, 42, 67].

Chemotherapy. Thymic carcinomas respond less to chemotherapy than thymomas. Carboplatin/paclitaxel has the highest response rate in patients with thymic carcinoma, but even so this is only 22–36% [21, 55]. Response rates for second-line chemotherapy in thymic carcinoma are even worse (4–12%) [55].

Checkpoint inhibitors. Second-line treatment with pembrolizumab showed promising results in a phase II trial containing 40 patients with thymic carcinoma. There was an ORR of 22.5%, and the median duration of response was 22 months. While less in thymomas, there was still a high rate of immune-related adverse events (15%), including two cases of severe myocarditis [59]. A recently published study on nivolumab in thymic carcinoma patients showed no objective response in 15 patients, although 5 patients showed stable disease for more than 24 weeks [68].

Targeted therapies. The same as in thymoma, experience with targeted therapies in thymoma is very limited and based on small phase II studies and individual case reports. Sunitinib may be beneficial for patients with a c-KIT mutation, although the mutation rate is rare <10% [10, 69]. IGFR inhibition and octreotide did not show any activity in thymic carcinoma, in contrast to thymomas [63, 64].

6.3 Follow-up

After primary resection, expert opinion on follow-up consists of a CT scan every 6 months for 2 years, then annually for 5 years for thymic carcinoma and annually for 10 years for thymomas [21], although an exceptional case of late recurrence has been reported [70].

7. Conclusion

Thymomas and thymic carcinomas are rare mediastinal tumors, and although the course of a thymoma can be indolent, they can indeed be locally invasive and metastasize. Thymic carcinomas more often are disseminated at presentation. Therefore, both are considered malignant. Forty to fifty percent of thymomas are related to autoimmune paraneoplastic syndromes, the most common being myasthenia gravis. Resection of the thymus can also act as treatment for the paraneoplastic syndrome. However, thymic treatment does not always resolve those paraneoplastic syndromes.

Because of the improved representation of the N-stage and correlation to prognosis, rather than surgical resectability, we recommend the AJCC eighth TMN classification.

There is no phase III data available on the management of thymic epithelial tumors. Surgery is considered the cornerstone of thymoma and thymic carcinoma management in resectable disease and even in recurrent disease. Neoadjuvant treatment and PORT should be considered according to stage.

In metastatic disease chemotherapy containing an anthracycline is advised. For recurrent metastatic disease sunitinib and octreotide, among other things, could be considered. A special note on checkpoint inhibitors should be made. Although they do show promising results in thymic carcinoma, the rate of immune-related adverse events is too high to consider this a valuable option for the treatment of thymoma right now.

The lack of phase III level evidence due to the rarity of the disease calls for collaboration in research to improve the quality and impact of thymic malignancy treatment. Such efforts are currently underway, and hopefully this will lead to better and more treatment options in the future.

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