Thymoma update 2011

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Thymomas belong to the group of tumours originating in the anterior mediastinum with a low incidence of 0.13 per 100,000 persons (SEER database). A thymoma is a slowly growing tumour, which has its prevalence most often in the fifth or sixth decade. In the early cases, the diagnosis is often made by coincidence due to other investigations. These patients can easily be operated upon with extremely good ten-year survival figures of up to 90% when tumour is encapsulated and is removed in total. In one third of the cases, patients present with complaints of myasthenia gravis, a well-known neurotransmitter disorder. Despite the favourable five-year and ten-year survival figures, one has to consider thymoma to have malignant potential. Growth through the capsule is often the primary cause of dissemination in the pleural space or in other mediastinal structures. Because of the low incidence, mostly retrospective studies of low scientific value have been published. Only a few studies report cohorts of more than 100 patients. In the following paragraphs the staging systems, treatment options and guidelines will be presented.

Staging

Two staging systems are currently in use. In 2009, the World Health Organization published a classification based on the histopathology of the tumour. In Table 1 different histological subtypes are described. A meta-analysis demonstrated that only three WHO categories of thymomas are associated with significant survival differences [1]. These are: A/AB/B1 versus B2 versus B3. The C-classification indicates that this is a thymic carcinoma, but it has the same survival figures. The histological subtyping is clearly correlated with the risk of invasiveness ranging from less than 40% to almost 90% for type B3. In addition to this system, the Masaoka staging system has been developed. In Table 2 the different stages are presented and focus on the magnitude of invasion of the tumour. In stage 1, the capsule is intact. In stage 2, there is intracapsular invasion up to the pleura. In stage 3, the surrounding tissues are involved in the tumour, like pericardium, lung or vessels. In stage 4A, dissemination in the pleural space has occurred, and stage 4B shows lymphatic or haematogenic metastases. Both the WHO and the Masaoka staging systems correlate with survival and chance of recurrence. The early stages show very good general survival of up to 90%. The advanced stages, like stage 4B, have consequences for treatment and those patients will eventually die from this disease. In the differential diagnosis, one should consider lymphomas, extragonadal teratomas, sarcoidosis, etc.

Table 1
The WHO classification system

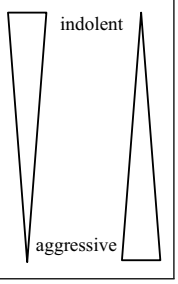
WHO Type	Old terminology [2]	Biological behaviour
A	Medullary thymoma	
AB	Mixed type	
B1	Predominantly cortical	
B2	Cortical	
B3	Well-differentiated thymic carcinoma	
C	Squamous cell carcinoma Undifferentiated carcinoma Sarcomatoid carcinoma Lymphoepithelioma-like carcinoma	

Table 2
The modified Masaoka staging system

Stage I	Completely encapsulated tumour
Stage II	Micro- or macroscopic invasion into adjacent mediastinal tissue
Stage III	Macroscopic invasion into surrounding structures, such as the pleura, lung, pericardium and great vessels
Stage IV-A	Distant pleural metastases
Stage IV-B	Distant metastases outside the thoracic cavity

Note: this staging system is based on surgical exploration and histological examination.

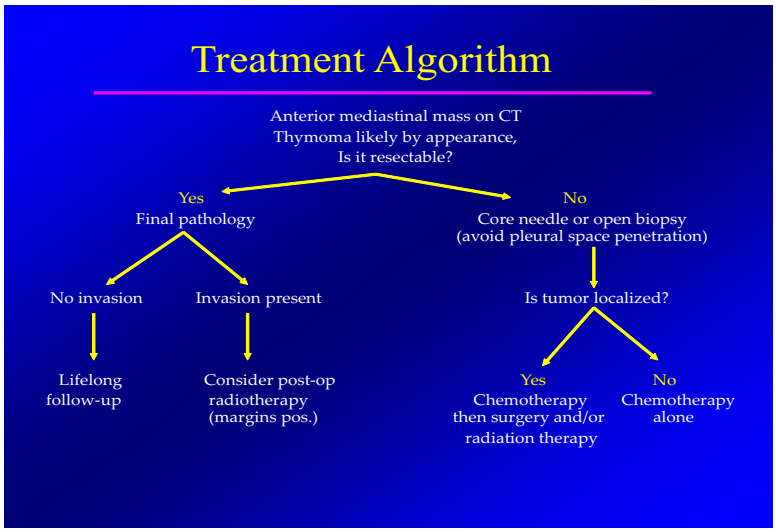


Fig. 1. Treatment algorithm for thymoma.

Treatment options

The primary approach for a suspected thymoma is radical surgical resection. If this can be achieved, the chances of recurrence are very small and patients can be scheduled for yearly follow-up. Based on the retrospective data for the more advanced stages, the meta-analysis by Korst and colleagues [1] indicates that after R1 resection in stage 2, or resection in stage 3, radiation therapy should be considered. The American SEER database did not show any positive effects of the addition of postoperative radiotherapy in five-year survival figures. Chemotherapy has attracted a lot of attention, but no randomised studies have been performed. In general, they are based on treatment with cisplatin, and two regimens, which were introduced in the 1980s, are still of use. These are cyclophosphamide, adriamycin and platinum, or platinum with etoposide. A number of other small studies have investigated the effect of single or combination treatments, but have not led to any significant improvements. With the use of molecular biology techniques, the expression of the epidermal growth factor receptor mutation has been investigated. In a small subgroup of the more advanced tumours, one of these mutations might indicate that treatment with a tyrosine kinase inhibitor or imatinib may be indicated. The more advanced cases are also treated in a multimodal fashion. For large primary tumours in the anterior mediastinum, neo-adjuvant radiotherapy and/or chemotherapy can be applied to allow better surgical resection. In the case of late recurrences in the pleura, treatment with thoracotomy and picking out the metastases might be considered. In some cases adjuvant radiotherapy is proposed. However, no randomised studies have been performed in this field and the side effects of the thoracotomy must be balanced against the possible survival benefit.

Guidelines

In 2010, the National Comprehensive Cancer Network published guidelines for the treatment of thymomas or thymic tumours. It is stated that a multidisciplinary team should decide on the optimal approach for the patient and care must be taken to administer radiotherapy in the case of an R1 resection. In the case of a more advanced type, like thymic carcinoma, or in an R2 resection, chemotherapy should be considered. In Fig. 1 a diagnostic flow chart is proposed and it is advisable that more advanced cases should be treated in a centre.

Conflict of interest statement

The authors have no potential conflict of interest to disclose.

References

1 Korst RJ, Kansler AL, Christos PF, Mandal S. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. *Ann Thorac Surg* 2009;**87**:1641–7.
2 Marino M, Müller-Hermelink HK. Thymoma and thymic carcinoma. Relation of thymoma epithelial cells to the cortical and medullary differentiation of thymus. *Virchows Arch A Pathol Anat Histopathol* 1985;**407**(2):119–49.