

# Treatment of thymoma and thymic carcinoma

Giuseppe Giaccone

*Division of Medical Oncology, University Hospital Vrije Universiteit, Amsterdam, The Netherlands*

## Natural history

Thymomas and thymus carcinomas are tumours arising from the thymic gland, which in adult life is replaced by fat tissue [1]. Whereas thymic carcinomas have cytological characteristics of malignant tumours, thymomas are essentially benign tumours and their malignant behaviour is basically indicated by the extent of invasion through the capsule. This information can only be adequately obtained by operation. Another major difference between thymomas and thymic carcinomas is that unlike thymic carcinomas, thymomas are often associated with paraneoplastic syndromes, such as myasthenia gravis (30% of patients with thymoma, whereas approximately 10–15% of patients with myasthenia gravis will have a thymoma) and many others. Although both tumour types occur in the anterior mediastinum thymic carcinomas tend to be more infiltrating and rapidly aggressive than thymomas. The age of occurrence of these tumours is in the fourth–fifth decade, although virtually all ages have been involved, and there is no sex preference.

Thymomas tend to be localised and only infrequently distant metastases are encountered. The most frequent metastatic site is the pleura.

## Diagnosis

The diagnosis of these tumours is often difficult. Fine needle aspiration is mostly insufficient for a proper diagnosis and a core biopsy is indicated. In case of particularly difficult diagnosis, EM may help better identify the tumour type. Major differential diagnoses in this anatomical area are lymphomas and germ cell tumours. Immunohistochemistry and serum tumour markers are of help in this diagnosis. Furthermore, germ cell tumours and lymphomas arise usually in young patients. Neuroendocrine tumours (carcinoids) may also infrequently start in the thymus gland and have usually an indolent growth behaviour. The stag-

ing of these tumours requires CT scan of the chest and sometimes MRI can give better insight into the vascular invasion. Occurrence of distant metastases is not frequent in these tumours, however pleural seeding may be found at diagnosis of thymomas.

The diagnosis of a thymoma can be made based on the presence of a well described paraneoplastic syndrome, such as myasthenia gravis. Thymectomy is usually indicated in the management of this disease and often intrathymic thymomas can be recognised in this situation. The development in the last 20 years of better anaesthesiological procedures has largely facilitated the operation of patients with myasthenia gravis.

The pathological classification of thymomas is complex. There is general agreement that the epithelial cells represent the malignant cells in this tumour type, and that probably the infiltrating lymphocytes are benign. The most common classifications describe the relative preponderance on one cell type on the other [2]. However, different classifications have been developed, which take into consideration the possible pathogenesis of these tumours. Some of these newer classifications are nevertheless not readily reproducible.

The staging of thymomas is essentially surgical [3]. Even though in thymomas a capsule is often easy to identify on CT scan, only the postoperative staging has prognostic value. The most used staging classification is the one of Masaoka et al. [4]. Recently the French Group of Thymic Tumours has proposed another classification in which also the extent and radicality of the resection plays a role in the staging. There is however a high agreement between these two staging systems.

## Treatment

### Surgery

If a tumour is confined within the structures in the mediastinum and is felt to be operable, the operation

should be the treatment of choice. Even in case of doubtful radicality an attempt to debulking operation is justified in thymomas. There are in fact several series documenting the role of debulking surgery and possibly repeated operations in the management of thymomas [5]. This indication is less clear for thymic carcinomas, which are usually behaving more aggressively. The preferred surgical approach to the resection of thymomas is median sternotomy. Cervical approach should be discouraged, as it leads to frequent recurrences. Thoracotomy may be necessary, especially to handle recurrent tumours.

Thymomas are most often indolent tumours and relapses can occur 10–15 years after primary operation. Stage I and II according to the Masaoka classification have 10-year survivals of 90–100%, whereas the survival in stage III is around 50–60%. Even in stage IV survival at 5 years is over 10%.

#### *Adjuvant therapy*

The use of adjuvant radiotherapy has been used in many centres, but adjuvant radiation in radically resected well-encapsulated thymomas is probably not indicated, given the very low relapse rate. In contrast, patients with invasive thymomas are candidates for adjuvant radiation. Although no randomised trials exist, pooled data from several series employing or not adjuvant radiotherapy suggest that patients with radically resected invasive thymomas who do not receive adjuvant radiation have a chance of local recurrence of approximately 28%, vs. 5% for those who receive adjuvant radiation. Radiation doses of 40–50 Gy in 1.8–2 Gy per fraction have been used in several series.

Thymomas which cannot be radically resected may benefit from postoperative radiation treatment. Several series have been published, which indicate that thymomas are relatively radiosensitive tumours, and radiation given to unresected tumours may have some long-lasting effect on tumour control.

#### *Neoadjuvant therapy*

When the tumour is deemed to be clearly inoperable attempts to reduce its size before operation are indicated. Studies of neoadjuvant chemotherapy followed by surgery have been reported, showing high remission rates with a number of different regimens usually including cisplatin [6]. Responses in excess of 50% are commonly reported. The use of radiation has also been advocated in these cases, although the

port is usually so large that optimal doses cannot be given without major side effects. Postoperative radiation is indicated in cases that were not radically resected, but its use in radically resected thymomas is not established.

The efficacy of chemotherapy has been in doubt for a long time, but prospective evaluation of several agents and combinations has demonstrated that thymomas are relatively chemosensitive tumours. Cisplatin appears to be an important agent for this disease, as most active combinations contain this drug [7–9]. Cisplatin alone produced a response rate of only 10% in 21 assessable patients, but several combinations including cisplatin with either doxorubicin–cyclophosphamide with or without vincristine induced responses of 50–90%. In a study of cisplatin–etoposide 56% response rate was obtained in 16 patients, and the median duration of response was 3.4 years. A review of Tomiak and Evans [10] has addressed the role of chemotherapy in invasive thymoma.

#### References

- 1 Mullen B, Richardson JD. Primary anterior mediastinal tumors in children and adults. *Ann Thorac Surg* 1986; 42: 338–345.
- 2 Bernatz PE, Khonsari S, Harrison EG, et al. Thymoma: factors influencing prognosis. *Surg Clin North Am* 1973; 53: 885–893.
- 3 Thomas CR, Wright CD, Loehrer PJ. Thymoma: state of the art. *J Clin Oncol* 1999; 17: 2280–2289.
- 4 Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymoma with special reference to clinical stages. *Cancer* 1981; 48: 2485–2492.
- 5 Maggi G, Giaccone G, Donadio M. Thymomas: a review of 169 cases, with particular reference to results of surgical treatment. *Cancer* 1986; 58: 765–776.
- 6 Loehrer PJ, Chen M, Kim KM, et al. Cisplatin, doxorubicin and cyclophosphamide plus thoracic radiation therapy for limited stage, unresectable thymoma: an intergroup trial. *J Clin Oncol* 1997; 15: 3093–3099.
- 7 Giaccone G, Musella R, Bertetto O, et al. Cisplatin-containing chemotherapy in the treatment of invasive thymoma. *Cancer Treat Rep* 1995; 69: 695–697.
- 8 Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy for invasive thymoma: a 13 year experience. *Cancer* 1991; 68: 30–33.
- 9 Giaccone G, Ardizzoni A, Kirkpatrick A, et al. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma: a phase II study of the E.O.R.T.C. Lung Cancer Cooperative Group. *J Clin Oncol* 1996; 14: 814–820.
- 10 Tomiak EM, Evans WK. The role of chemotherapy in invasive thymoma: a review of the literature and considerations for future trials. *Crit Rev Oncol Hematol* 1993; 15: 113–124.