# Thymoma and Thymic Carcinoma

## *Molecular Pathology and Targeted Therapy*

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**Abstract:** Thymomas and thymic carcinomas (TC) are rare epithelial tumors of the thymus. Although most thymomas have organotypic features (i.e., resemble the normal thymus), TC are morphologically undistinguishable from carcinomas in other organs. Apart from their different morphology, TC and thymomas differ also in functional terms (TC, in contrast to thymomas, have lost the capacity to promote the maturation of intratumorous lymphocytes), have different genetic features (discussed in this review), a different immunoprofile (most TC overexpress c-KIT, whereas thymomas are consistently negative), and different clinical features (TC, in contrast to thymomas, are not associated with paraneoplastic myasthenia gravis). Thus, although all the data suggest that the biology of thymomas and TC is different, in clinical practice, their therapeutic management up to now is identical. In the age of personalized medicine, the time may have come to think this over. We will briefly review the molecular genetics of malignant thymic tumors, summarize the current status of targeted therapies with an emphasis on the multitargeted kinase inhibitors sunitinib and sorafenib, and try to outline some future directions.

**Key Words:** Thymic carcinomas, Targeted therapies, Multitargeted kinase inhibitors.

(*J Thorac Oncol.* 2010;5: S286–S290)

## THYMOMA AND THYMIC CARCINOMA: DEFINITIONS AND CLINICOPATHOLOGIC FEATURES

Based on available current knowledge about the biology of these tumors, the World Health Organization (WHO) classification of thymic epithelial tumors[1] separates thymomas from thymic carcinomas.

Thymomas are defined as neoplasms arising from or exhibiting differentiation toward thymic epithelial cells, usually with a variable component of non-neoplastic lymphocytes.[1] From a morphologic point of view, there are two major types of thymoma: in type A, the neoplastic epithelial cells have a spindle- or oval-shaped nucleus with a uniform bland cytology. In type B, the tumor cells have a predominantly round or polygonal appearance. Type B thymomas are further subdivided depending on the degree of atypia and the size of the lymphocyte component into B1 (richest in lymphocytes), B2, and B3 (richest in epithelial cells). Thymomas combining type A with type B features are designated AB. Apart from their different morphology, type A, AB, and B thymomas also show differences with respect to molecular genetics (see below), expression of immunohistochemical markers, such as MHC class II or AIRE (autoimmune regulator),[2–4] a different capacity to promote maturation of intratumoral lymphocytes,[5,6] and different association with clinical autoimmune syndromes, such as myasthenia gravis (MG).[7–10] Together with gene expression data, these findings have led to the unifying hypothesis that the different histologic thymoma subtypes may reflect different maturational stages of a thymic epithelial progenitor cell.[11]

In most published series,[9,12–14] the predominant histologic subtypes are B2 and AB thymomas (each 20–35% of all cases), whereas type B1 and type A thymomas count among the rare types (5–10% in most studies). For clinical purposes, thymomas can be stratified into two different risk groups: type A, AB and B1 thymomas in most retrospective studies pursued an indolent course with 5- and 10-year overall survival rates between 80 and 100%.[9,13,15] By contrast, type B2 and B3 thymomas are potentially aggressive tumors with a potential for distant metastases (approximately 15% of cases),[7–9,13,16] usually to lung, liver, bone, and soft tissues. More frequently (up to 25% of cases in some series), these tumors show pleural dissemination. Lymph node metastases are exceedingly rare.[17]

Thymomas occur over a wide age range (Figure 1*A*) but most manifest in the age between 50 and 60 years. In our own series of about 1000 cases, thymomas before the age of 30 years usually belonged to the clinical high-risk group (Figure 1*B*).

Thymic carcinomas by definition[1] are malignant epithelial tumors with overt cytologic atypia, almost invariably invasiveness and lack the "organotypic" (thymus-like) features of thymomas. They are further subclassified into squamous cell, basaloid, lymphoepithelioma-like, neuroendocrine, and many other types. Squamous cell carcinoma is the

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/10/0510-0286

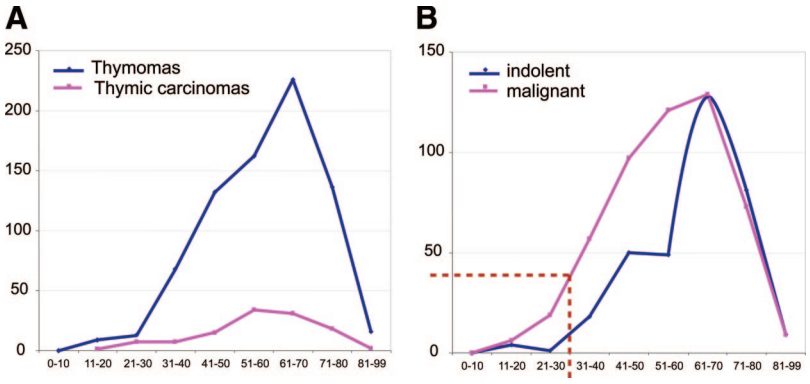


**FIGURE 1.** *A*, Age distribution of thymomas ($n$= 815) and thymic carcinomas ($n$ = 128) showing similar age peaks for the fifth to sixth decade. *B*, In patients younger than 30 years at primary diagnosis, most thymic epithelial tumors belonged to the malignant categories.

most frequent subtype with a higher incidence in Asia than in western countries.[9] The typical autoimmune phenomena seen in thymoma (MG, pure red cell aplasia) are not found in thymic carcinoma, although other paraneoplastic syndromes such as polymyositis can occur. In contrast to thymomas, thymic carcinomas may show metastasis to regional lymph nodes (mediastinal, cervical, and axillary), although in our experience this is still a rare event. They frequently express CD117 (c-KIT),[18,19] a helpful immunohistochemical feature, to differentiate thymic carcinomas from mediastinal metastases of carcinomas located elsewhere.[20]

## MOLECULAR GENETICS OF THYMOMAS AND THYMIC CARCINOMAS

### Molecular Genetics of Thymomas

The histologic thymoma subtypes listed in the WHO classification show distinct molecular genetic features. In summarizing a large body of data from CGH (comparative genomic hybridization)[21,22] and microsatellite/LOH (loss of heterozygosity) studies,[11,23,24] type A and AB thymomas show a low frequency (7–8%) of allelic imbalances, whereas type B2 and B3 thymomas show alterations in approximately 20% of cases.[11] However, if the percentage of cases with multiple affected chromosomes is considered, type AB thymomas (55% of cases) are intermediate between type A (10% of cases) and types B2 and B3 thymomas (75–100% of cases). Also, with respect to the affected chromosomal regions, type AB thymomas show overlap with both type A and type B thymomas but appear more akin to the B type. In microdissected samples, the "A component" in type AB thymomas was not genetically identical to genuine A thymomas.[11]

In more detail, the most frequent genetic alterations in all thymomas (and also in thymic squamous cell carcinomas) affect chromosome 6p21.3 (*MHC* locus) and 6q25.2–25.3.[11,21,23] The identification of a common genetic alteration on 6q25 across all histologic tumor subtypes suggests the presence of a yet undefined common tumor suppressor ("gate keeper") gene that may eventually play a role in the biology of the common thymic medullary/cortical progenitor cell. The responsible genes have not been identified so far. Additional alterations that usually affect the aggressive subtypes B2 and B3 are located on chromosome 5q21–22 (the *APC* locus), chromosome 7p15.3, and chromosome 8p11.21. Interestingly, a few type AB thymomas also showed LOH of the *APC* locus and the "high risk" alteration on chromosome 8p11.21, but this appeared not to be associated with a more aggressive phenotype in these tumors, suggesting that these high-risk mutations were counterbalanced by an unknown tumor suppressor. Although type B2 and B3 show similar genetic alterations, the combination of LOH of the *APC*, *RB*, and *TP53* locus has so far only been described in B3 thymomas. An alternative oncogenic route to the "canonical pathway" described above may be microsatellite instability that has been found in a small percentage of thymomas (but so far not in thymic carcinomas) (Figure 2).[24]

### Molecular Genetics of Thymic Carcinomas

Thymic squamous cell carcinomas frequently show gains of chromosomes 1q, 17q, and 18 and losses of chromosomes 3p, 6, 16q, and 17p.[21,22] Apart from the consistent "thymic stemness" alteration on chromosome 6q25, they share some similarities with type B3 thymomas, namely gain of 1q and loss of chromosome 6, but overall, they are genetically distinct from thymomas, justifying their listing as a separate entity in the WHO classification. Of note, the genetic alterations found in thymic squamous carcinomas of the thymus are very distinctive, and the overlap with histologically similar, "environmental" tumors of the lung, head, and neck is minimal.[22,25]

## THERAPEUTIC APPROACHES TO THYMOMA AND THYMIC CARCINOMA

### Chemotherapy-Based Multimodal Approaches

Although the treatment of malignant thymomas and thymic carcinomas in daily clinical practice is identical, the available data (see above) suggest that their biology is different and that in fact they may also require different therapeutic approaches. Advanced thymomas and TC that cannot be completely resected require neoadjuvant or adjuvant systemic treatment, often in combination with radiotherapy.[26] Cisplatin-based regimens, such as the PAC scheme (cisplatin, adriamycin, and cyclophosphamide) are most often used.[27,28] Relapses or progressive disease can be expected to occur in 10 to 30% of all patients. In 20 to 30% of these patients, objective remissions can be achieved by cisplatin-based reg-

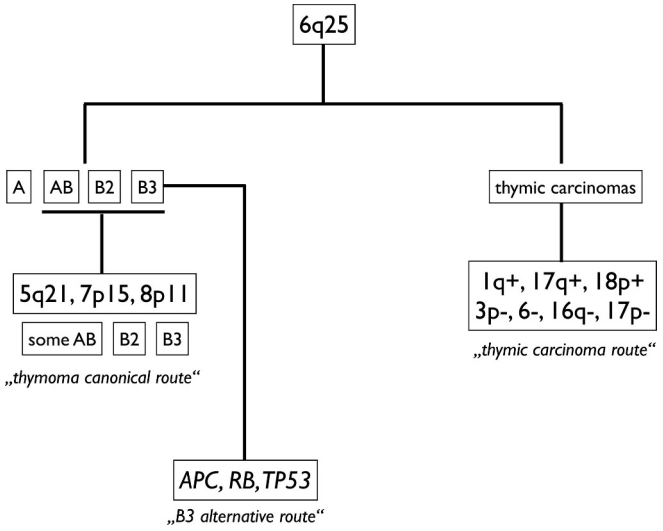


**FIGURE 2.** Molecular genetic routes in thymomas and thymic carcinomas. Genetic alterations of chr. 6q25 are found in all entities, suggesting the presence of a "gatekeeper" mutation in a common progenitor cell. Type AB, B2, and B3 thymomas show some genetic similarities with respect to common alterations. Part of B3 thymomas may develop along an alternative route, as indicated by the presence of mutations within the *APC*, *RB*, and *TP53* gene locus, which is in good agreement with their slightly more aggressive behavior compared with type B2. Thymic carcinomas not only show some genetic overlap with B3 thymomas, namely gain of chromosome 1q and losses of chromosome 16q, but also show additional recurrent alterations that are not found in B3 thymomas.

imens after relapse-free intervals. Approximately 50% of patients with an advanced malignant thymoma or thymic carcinoma will be candidates for a—so far undefined—second-line treatment.

## Interference with Receptor Tyrosine Kinases (So-Called Targeted Approaches)

Targeted molecular therapy is a new paradigm in cancer treatment, where drugs selectively interfere with molecules considered important in oncogenesis. While conventional chemotherapy aims to kill off all proliferating cells including tumors, molecularly targeted therapy aims to disrupt cancer-specific signaling pathways involved in tumor growth and proliferation.[29] Compared with the toxicity of chemotherapy, targeted molecular therapies seem relatively tolerable.[30] Tyrosine kinases regulate important cell functions including survival, differentiation, and proliferation.[29]

### Interference with Single Receptor Tyrosine Kinases

***c-KIT.*** A clinical response to imatinib in a thymic carcinoma with a V560 mutation of *c-KIT* was previously described.[31] However, KIT is never expressed by malignant thymomas and *KIT* mutations are rare (in the range of 10%),[22,32] even in thymic carcinomas overexpressing KIT by immunohistochemistry.[22,32–34] Another case report mentioned the unsuccessful last-resort use of imatinib in a pediatric patient.[35] These findings together with the disappointing results of two recent clinical phase II trials[36,37] suggest that imatinib will be a therapeutic option only for the small subset of thymic carcinoma patients with *KIT* mutations.

***EGFR.*** In theory, the epidermal growth factor receptor (EGFR) is an attractive target in thymomas. Most malignant thymomas and many thymic carcinomas show EGFR overexpression by immunohistochemistry,[18,38,39] and some exhibit *EGFR* gene amplifications.[39] Downstream mutations that could interfere with EGFR antagonists, such as *KRAS* or *BRAF*, are exceedingly rare.[22] Although single case observations suggest that EGFR targeting may be effective in some patients,[40–42] two clinical phase II studies using erlotinib[43] and gefitinib[44] in a total of 44 patients resulted in no complete remission and only two partial remissions. So far, there have been no studies to directly compare the effect of monoclonal antibodies (e.g., cetuximab) versus small molecule inhibitors. It is not known whether the *EGFR* gene amplification status influences the therapeutic response.

### Interference with Multiple Receptor Tyrosine Kinases

***Sorafenib.*** In addition to multiple receptor tyrosine kinases, such as PDGFR, c-KIT, and VEGFR, sorafenib also inhibits wild-type and V600E-mutated Raf.[45] One case report described a patient with chemotherapy-resistant metastatic thymic carcinoma, where administration of sorafenib led to substantial tumor reduction by 4 months and stable disease for another 5 months.[46] To this, we can add the descriptions of two patients with therapy-refractory type B3 thymomas who were treated with sorafenib in our institution.

*Case 1.* A 56-year-old woman presented with histologically proven liver and chest wall metastases as a second relapse of a type B3 thymoma 17 years after initial diagnosis (then a Masaoka stage IVa tumor) and 7 years after the first tumor relapse. The primary tumor had been treated by extended resection of the primary and pleural metastases, followed by radiation therapy. The tumor was a classic c-KIT-negative type B3 thymoma. Sequencing of EGFR, KRAS, and BRAF was unremarkable. The patient was administered two cycles of ACO (adriamycin, cyclophosphamide, and cisplatin), later chlorambucil/dexamethasone, without obtaining tumor control. Because of progressive disease with new liver metastasis, the patient was given sunitinib for 2 months but developed new lung metastases and progression of liver foci. The patient then received experimental treatment with sorafenib. A control PET scan after 8 weeks showed reduced glucose uptake in all lesions. The patient had severe diarrhea as side effect of her medication. Twenty-four weeks later, the lung metastasis was still unchanged on CT scan, but glucose uptake on PET was increased again and her liver metastases

showed progression on both CT and PET scan, and sorafenib was discontinued.

*Case 2.* A 44-year-old woman presented with a type B3 thymoma Masaoka stage III with infiltration of pleura and lung in 1995. The tumor was completely resected and adjuvant irradiation was applied. The patient suffered from paraneoplastic MG, which was treated with azathioprine. Twelve years later (2007), rising anti-acetylcholine receptor (AChR) antibodies heralded a multifocal intrathoracal tumor relapse, which was confirmed by histology and was treated by lung lobectomy, pericardial resection, and resection of parts of the diaphragm and of the right phrenic nerve. Despite ongoing corticosteroid treatment after surgery, anti-AChR autoantibody titers continued to rise and myasthenic symptoms deteriorated. Under the suspicion of imminent thymoma relapse, the patient received an experimental therapy with sorafenib 400 mg/d. An FDG-PET scan 5 months later showed two preaortal and prehepatic hypermetabolic foci. The patient developed massive hand-foot skin reactions but carried on with sorafenib for 4 months. During that time, her anti-AChR titers declined from 54 to 15 nmol/l. FDG-PET revealed slightly reduced uptake of the preaortal lesion, whereas uptake of the prehepatic focus was unchanged.

In summary, the available evidence is very preliminary but suggests that sorafenib could be biologically active in some malignant thymomas and thymic carcinomas and may merit further clinical study. It seems that different metastatic lesions in one patient may be heterogeneous and may show a mixed response to such targeted (and "conventional" chemotherapeutic) treatments.

***Sunitinib.*** Sunitinib is a multitarget tyrosine kinase inhibitor that was designed to block intracellular receptor binding sites of several tyrosine kinases including vascular endothelial growth factors 1–3 (VEGF1–3), FMS-like tyrosine kinase 3 (FLT3), stem cell growth factor (c-KIT), platelet-derived growth factors $\alpha$ and $\beta$ (PDGF$\alpha$-$\beta$), colony-stimulating factor 1 (CSF1), and the "RET" receptor for glial-derived neurotrophic factors.[47] Inhibition through sunitinib is believed to ultimately result in tumor regression through antiangiogenic effects and also through direct tumor cell apoptosis.

We have recently described initial clinical experience with sunitinib in four patients with advanced thymic carcinomas refractory to conventional therapies.[48] Administration of sunitinib was based on the observation that these tumors showed simultaneous activation of several receptor tyrosine kinases, including the EGFR, TYRO3, insulin receptor, and insulin-like growth factor-1 receptor (IGF1R). Administration of sunitinib yielded a partial remission (lasting 2–18+ months) according to RECIST[49] in three patients and stable disease with excellent metabolic response in 18F-FDG-PET in another one patient. Overall survival with sunitinib treatment ranged from 4 to 40+ months. Withdrawal of the drug in one patient prompted rapid tumor progression that could be controlled by readministration of sunitinib. The latter observation provides very strong circumstantial evidence that sunitinib was able to control the patient's tumor over more than 3 years and even at relapse of sunitinib-pretreated metastases. Similar favorable findings in two other patients with long-term stable remissions indicate that sunitinib may be able to block tumor escape mechanisms in at least some thymic carcinomas and may be a promising option for long-term treatment. At this moment, the exact mode of action of sunitinib in thymic carcinomas is not clear. There were no mutations of c-KIT (exons 9, 11, 13, and 17), KRAS, BRAF, or EGFR, so apparently the effectiveness of sunitinib does not depend on such abnormalities. Interestingly, Girard et al. recently described a novel H697Y c-KIT mutation in exon 14 (which had not been sequenced in our study) in a thymic carcinoma, which conferred sensitivity to sunitinib when transfected into a cell line. It will be important to determine the frequency of this mutation in a larger case series. However, c-KIT was not strongly activated in a sensitive phosphoblot assay in our sunitinib-responsive clinical cases and thus was an unlikely prime target. Based on published data,[50] it is conceivable that sunitinib's predominant mechanism of action was antiangiogenesis, even though its main known targets (e.g., the VEGFRs) were not prominently activated in the tumor samples studied in our series. Further clinical studies will be needed to analyze the underlying mechanisms more thoroughly to determine whether the respective targets are also present in malignant thymomas and to establish biomarkers to predict therapeutic response to sunitinib.

## CONCLUDING REMARKS

In summary, all available data to date indicate that thymoma and thymic carcinoma are distinct entities that may require different therapeutic approaches in the near future, despite the fact that this would mean just another obstacle in clinical research by further decreasing case numbers. Nevertheless, emerging gene expression and sequencing data point to the fact that there is probably considerable heterogeneity even among tumors of the same histotype. In the age of personalized medicine, international efforts are mandatory to overcome these new limitations and to finally advance the treatment of thymomas and thymic carcinomas.

## ACKNOWLEDGMENTS

*Supported by grant # 10-1740 from the Deutsche Krebshilfe and by Project grant 781025 of the Tumorzentrum Heidelberg/Mannheim. The authors wish to thank Dr. Giuseppe Giaccone for critically reading this manuscript.*

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