TABLE 123e-2 WORLD HEALTH ORGANIZATION (WHO) HISTOLOGIC CLASSIFICATION OF THYMUS TUMORS

Type	Histologic Description
A	Medullary thymoma
AB	Mixed thymoma
B1	Predominantly cortical thymoma
B2	Cortical thymoma
B3	Well-differentiated thymic carcinoma
C	Thymic carcinoma

Type	Distribution, %	Prognosis (10-year disease-free survival), %
A	8	100
AB	26	90–100
B1	15	78–94
B2	28	83
B3	15	36
C	8	0–35

Source: From S Tomaszek et al: Ann Thorac Surg 87:1973, 2009.

and noninvasive, and about 35% are invasive. They may have a variable percentage of lymphocytes within the tumor, but genetic studies suggest that the lymphocytes are benign polyclonal cells. The epithelial component of the tumor may consist primarily of round or oval cells derived mainly from the cortex or spindle-shaped cells derived mainly from the medulla or combinations of the two types (World Health Organization classification; Table 123e-2). Cytologic features are not reliable predictors of biologic behavior. In part, this unreliability may be related to the moderate reproducibility of the system. About 90% of A, AB, and B1 tumors are localized. A very small number of patients have aggressive histology features characteristic of carcinomas. Thymic carcinomas are invasive and have a poor prognosis.

Genetic lesions are common in thymomas. The most common abnormalities affect chromosome 6p21.3 (the MHC locus) and 6p25.2-25.3 (usually loss of heterozygosity). Abnormalities affecting a number of other genes altered in other types of tumors are also seen, including *p53*, *RB*, *FHIT*, and *APC*. Thymic carcinomas may overexpress c-kit, HER2, or growth factor receptor genes (epidermal growth factor receptor and insulin-like growth factor receptor). Some data suggest that Epstein-Barr virus may be associated with thymomas. Some tumors overexpress the p21 *ras* gene product. However, molecular pathogenesis remains undefined. A thymoma susceptibility locus has been defined on *rat* chromosome 7, but the relationship between this gene locus, termed *Tsr1*, and human thymoma has not been examined.

INFLUENCE OF THYMECTOMY ON THE COURSE OF ACCOMPANYING DISEASES

Patients with myasthenia gravis have a high incidence of thymic abnormalities (~80%), but overt thymoma is present in only ~10–15% of patients with myasthenia gravis. It is thought that the thymus plays a role in breaking self-tolerance and generating T cells that recognize the acetylcholine receptor as a foreign antigen. Although patients with thymoma and myasthenia gravis are less likely to have a remission in the myasthenia as a consequence of thymectomy than are patients with thymic abnormalities other than thymoma, the course of myasthenia gravis is not significantly different in patients with or without thymoma. Thymectomy produces at least some symptomatic improvement in ~65% of patients with myasthenia gravis. In one large series, thymoma patients with myasthenia gravis had a better long-term survival from thymoma resection than did those without myasthenia gravis.

About 30–50% of patients with pure red cell aplasia have a thymoma. Thymectomy results in the resolution of pure red cell aplasia in ~30% of patients. About 10% of patients with hypogammaglobulinemia have a thymoma, but hypogammaglobulinemia rarely responds to thymectomy.

TREATMENT THYMOMA

Treatment is determined by the stage of disease. For patients with encapsulated tumors and stage I disease, complete resection is sufficient to cure 96% of patients. For patients with stage II disease, complete resection may be followed by 30–60 Gy of postoperative radiation therapy to the site of the primary tumor. However, the value of radiation therapy in this setting has not been established. The main predictors of long-term survival are Masaoka stage and completeness of resection. For patients with stage III and IV disease, the use of neoadjuvant chemotherapy followed by radical surgery, with or without additional radiation therapy, and additional consolidation chemotherapy has been associated with excellent survival. Chemotherapy regimens that are most effective generally include a platinum compound (either cisplatin or carboplatin) and an anthracycline. Addition of cyclophosphamide, vincristine, and prednisone seems to improve response rates. Response rates of 50–93% have been reported in series of patients each of which involved fewer than 40 patients. A single most effective regimen has not been defined. No randomized controlled phase III studies have been reported. If surgery after neoadjuvant chemotherapy fails to produce a complete resection of residual disease, radiation therapy (50–60 Gy) may help reduce recurrence rates.

This multimodality approach appears to be superior to the use of surgery followed by radiation therapy alone, which produces a 5-year survival of ≤50% in patients with advanced-stage disease.

Some thymic carcinomas express *c-kit*, and one patient whose *c-kit* locus was mutated responded dramatically to imatinib. Many thymomas express epidermal growth factor receptors, but the antibodies to the receptor and the kinase inhibitors that block its action have not been evaluated systematically. Octreotide plus prednisone produces responses in about one-third of patients.