THYMOMAS: A REVIEW

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Thymomas are neoplasms of thymic epithelial cells. They may be benign or malignant and may associate with local invasiveness and paraneoplastic diseases. Myasthenia gravis is often associated with thymomas, but this is not the rule. Several classifications have been proposed: some of them follow the histopathological findings (Rosai and Levine, Snover, Marino and Muller-Hermelink classification), other emphasizes the clinic-pathological stage (Masaoka, Verley and Hollmann stadiation). One third of thymomas is asymptomatic. Diagnosis is made often by plain X-ray and confirmed by Computed Tomography or fine needle biopsy. Surgery is effective in 100% of noninvasive cases and in 58% of invasive ones. Radio and chemotherapy are recommended only in advanced or inoperable stages.

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Introduction

Thymomas are "neoplasms of thymic epitelial cells, regardless of the presence or absence of a lymphoid component or the relative abundance of the latter" (Rosai and Levine)[1]. Thymic epithelial neoplasms are beningn and malignant tumors.

Epithelial tumors must be kept separated from the other thymic neoplasms originating from germ-cell, neurogenic, lymphoid and adipous tissues normally present in the thymus (Tab. I).

Epidemiology

Tumors of the thymus are rare. This might be the reason for disagreement and confusion over the diagnostic criteria, subclassification and clinicopathological correlations in former times[2].

Thymomas represent 60% of the entire thymic pathology; other neoplasms are more uncommon (Hodgkin 11%, cysts 10% approximately).

Thymoma is one of the most common neoplasms of the mediastinum (20% of all) and by far the most frequent of the anterosuperior compartment. There is no evidence from the published series of any preferences for a particular race, sex or geographic distribution; in the USA 86% of the reported patients are white and 13% are black. In the most published series males predominate slightly over females. Thymomas occur more frequently in increased age (mean age 45) and are exceptional in children (1-4% of all mediastinal tumors). The behaviour of these tumors in children is partially distinct with a much more rapid course and a poor prognosis[3].

Thymomas are sometime associated with paraneoplastic disease that characterize the clinical course without affecting the prognosis[4].

The most frequent associated syndrome is

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TABELLA I - *Thymic neoplasms.*

Epithelial	Others
— Thymoma	— Germ cell
Cortical	
Mixed	— Neurogenic
Medullary	
— Thymic Carcinoma	— Lymphoid
Squamous	
Lymphoepithelioma	— Adipous
Sarcomatoid	
Anaplastic	
Small cell	
Basalioid	
Mucoepidermoid	

Myasthenia Gravis (MG): a percentage from 10 to 50% of patients with thymoma presents a myasthenic syndrome and the 10-40% of myasthenic patients has a thymoma[5, 6].

Less frequently (5-17%) thymomas are associated with autoimmune diseases other than MG: red cell aplasia, reumatoid arthritis, Systemic Lupus Erythematous (SLE), Crohn disease, ulcerative colitis.

Gross pathology

Approximately 95% out of the thymomas occurs in the anterior-superior mediastinum[7], a scant number occupies the thoracic districts such as intrapulmonary or pleural spaces.

The size of thymomas approximately ranges from 2 cm to over 20 cm in diameter. Most of thymomas are encapsulated. The invasive pattern (capsule infiltration, pericapsular growth, involvement of intrathoracic structures, can be demonstrated only in 5-35% of cases. The involvement of intrathoracic structures includes pleura and lungs followed by pericardium, heart, great vessels; thymomas tend to relapse locally, their diffusion follows an unpredictable pattern: the death in this case is mostly caused by respiratory failure due to direct invasion or recurrent bronchopneumonia. Not uncommon is the transdiaphragmatic spread to the abdomen (stomach and liver).

Simultaneous metastases are mainly directed to thoracic structures (i. e. pleura, pericardium, lung, lymph nodes, chest wall, spine), extrathoracic metastases are quite uncommon and prelude to a worst prognosis[8].

Histology

The most serious problem about histological classification of thymic tumours was the difficulty to correlate the microscopical appearance to the most appropriate treatment and prognosis.

In the previous classifications, Rosai and Levine[1], modified by Snover[9] (Tab. 2) and Verley and Hollmann[4] (Tab. 3), thymomas were classified according to the type of epithelium (epithelioid, spindle and mixed), the degree of lymphocytic infiltration (absent, scant, moderate, predominant) and the invasive pattern. A cellular differentiation pattern with large, poligonal cells and well defined cell borders was called epithelioid cell type thymoma (55% of cases approximately).

In the spindle cell thymoma (17-20% of cases) the cells were elongated with spindle-shaped, mostly hyperchromatic nuclei and with a thin rim of eosinophilic cytoplasm.

A 20-25% of thymomas exhibited both the epithelioid cell type and the spindle-cell type in almost equal numbers, therefore they were classified as mixed type thymomas.

The spindle cell (type I), the lymphocytic-rich (type 2) and the differentiated epithelial cell (type 3) occurred with the frequency of about 30% each. The undifferentiated epithelial type (type 4) was much rare and occurred only in 7% of the patients. In patients with myasthenia gravis (MG) differentiated epithelial thymoma (type 3) was discovered in nearly 50% of the cases and spindle cell thymoma (type 1) in only 15%. The latter type (type 1) predominated in patients with other autoimmune disease (86% of cases). In patients without any autoimmune disorder differentiated epithelial thymoma (type 3) was less frequent (18%) than in patients with MG (47,6%), but the undifferentiated (type 4) was more frequent (12%).

New classification

The new classification set by Marino, Muller-Hermelink[10, 11] is based on the microscopic and histochemical feature of neoplastic epithelial cells. Such classification concerns only thymoma category I according Rosai Levine[1] unchanged the thymic carcinomas category. This classification is likely going to supplant the previous classification based on reactive lymphocytes, element not-neoplastic and not correctly suitable for classification.

Based on the light microscopic feature of normal thymic epithelial cells, human thymoma has been divided in different types namely cortical, medullary

TABLE II - *The Rosai, Levine (1) and Snover (9) classification.*

1) Benign encapsulated thymoma (circumscribed thymoma)
   A) large/epithelioid cells
   B) spindle/shaped cells with associated lymphocytic component
2) Malignant thymoma (Cat. I, Rosai)
   A) locally invasive
   B) with true lymphatic or (rare) hematogenous spread
3) Malignant thymoma with cytologic atypia (thymic carcinoma Cat. II, Rosai)
   A) squamous cell carcinoma
   B) lymphoepithelioma - like carcinoma
   C) sarcomatoid carcinoma
   D) undifferentiated (anaplastic) carcinoma
   E) mixed small-cell /anaplastic carcinoma
   F) basaloid carcinoma
   G) mucoepidermoid carcinoma

TABLE III - *The Verley and Hollmann (4) classification.*

Type 1, spindle and oval cell
type 2, lymphocyte-rich
type 3, differentiated epithelial-rich
type 4, undifferentiared epithelial-rich

and mixed ones according to the epithelial cell types[10,11].

In a retrospective study of 58 thymomas and 13 thymic carcinomas, these authors have found that malignant invasive character as well as the occurrence of MG had been related to the neoplastic proliferation of the cortical epithelial cells, whereas in the usual mixed type of thymoma and the medullary type no gross invasion or metastasis were noticed.

Histologically the cortical tumors show stellate with a ovalround nucleus, prominent nucleolus and a faintly eosinophilic cytoplasm. Medullary cells show a spindle shape with cytoplasmic processes strongly eosinophilic. Nucleuses are small and spindle-shaped with a little nucleolus.

In accordance to that structural difference, Nomori[12] has recently proposed an interesting evaluation of the malignant grade of thymoma based on the morphometric analysis of nuclear size. Invasive and MG-associated thymomas show a nucleus significantly larger than non-invasive thymomas and hyperplastic thymus[13].

The lymphocytic infiltration is higher in cortical types, but scant interdigitating reticulum cells (IDC) have been demonstrated. Fewer lymphocytes but more IDCs are present in the tumours of medullary type, although variable in those of mixed type.

Immunohistochemistry

This cortico-medullary difference among thymomas has been confirmed in some of them by the immunoperoxidase method on frozen sections with monoclonal antibodies. Cortical type tumours are HLA-DR positive in tumor cells and infiltrated predominantly with cortical thymocytes (OKT3-, OKT6, both Leu 3a/3b+ or OKT8+), whereas medullary-type are HLA-DR positive, primarily in IDCs, but not in tumour cells and are infiltrated more with medullary thymocytes (OKT6-, OKT3+, either Leu 3a/3b+ or OKT8+).

When tested with a series of monoclonal antibodies thymoma epithelial cells were all stained by the antibody Ki-M3 (as in the thymus), but reacted with anti-HLA-DR, anti HLA-A-B-C and with a new monoclonal antibody to weaker, variable intensity in comparison with the normal thymus. Cortical types were most reactive, medullary almost negative.

Thymomas, like normal thymus, showed different immunoreactivity patterns with antibodies to prekeratins of different specifities. Cortical thymomas and areas of mixed thymomas showed an epithelial cell staining with the antibody to non-squamous-type keratin (35 beta H11) whereas medullary thymomas showed staining with antibodies to squamous-type keratine (34 beta E12-IV/82) in addition.

Lymphoid cells with cortical (OKT6+, Leu1 weakly+, Leu2a+, Leu3a+) or mature medullary (OKT6-, Luel strongly+, Leu2a or Leu3a+) phenotype were found to colonize tumours with different epithelial types.

In addition, important differences have been observed in neoplastic cortical epithelial cells

concerning the HLA-DR and 21A6 immunoreactivity that may be intimately related to the neoplastic process and paraneoplastic phenomena.

The cellular composition and characteristics of lymphocytes and hystiocytes of thymomas and squamous carcinomas have been studied by Sato[14]. Almost all the lymphocytes in the mixed type and limphocytic type categories, either in the primary site or metastasis, were T-lymphocytes which showed the immature thymic lymphocyte-phenotype of the normal thymic cortex. On the other hand, the epithelial thymomas contain many mature T lymphocytes along with immature T cells, as in the normal thymic medulla.

The phenotypical and functional characteristics of the lymphoid component present in thymomas have been analyzed by Musiani[15]. In cortical thymomas a large proportion, clearly higher than that present in mixed thymomas of T6 positive lymphocytes was present. This T6 subset does not proliferate to mitogen, but contains almost all thymocytes able to spontaneously proliferate.

Higher proportions of T3 positive cells have been found in mixed type of thymomas than in cortical-type tumours. The occurrence of higher proliferative responses to the phytohemagglutinin, in the unfractioned population cells from mixed thymomas than in the cells of cortical thymomas has been attributed to the relative higher content to both T3 positive and T3-T6 negative thymocytes in the former. Unlike T6+ thymocytes, T3-T6 as well as T3+ cells were practically devoid of spontaneous proliferative capacity. The expansion of the intrathymic lymphoid component in the human thymomas should then be considered to be attributed to the "spontaneous" capacity of the T6+ cell pool. In this respect, cortical thymomas not only contain more T6+ cells than be mixed type but also exhibited a higher lymphocyte/epithelial cell ratio and more frequent mitotic figures.

Epithelial cells in thymomas have an intimate relationship with the coexisting lymphocytes and retain functional properties of the normal thymic epithelial counterpart. On the other hand, the specific function of thymic epithelial cells is no longer maintained in thymic squamous cell carcinoma, Kodama et al.[16] reported that normal thymic epithelial cells show zonal differentiation and neoplastic cells are considered to retain these characteristics to some extent; i. e., thymomas have the same phenotype of epithelial cells of the cortex, especially the outer cortex of the thymus, in some instances (Leu7-positive, keratin-positive) and of both cortex and medulla (mixure of Leu7 positive and negative cells) with organoid arrangement in other instances, and thymic squamous cell carcinoma have the same phenotype as epithelial cells in the thymic medulla (Leu7 negative, keratin positive).

Thymoma sample compared to age-matched normal thymuses and hyperplastic thymuses obtained from patients with MG show evident microenvironmetal differences. In all the thymoma samples, in fact, the neoplastic lobules appeared as grossly enlarged cortical-type area, formed by accumulation of T lymphocytes exibiting the cortical immature phenotype (TdT+, T6+), within a network of putatively neoplastic epithelial cells characterized by cortical phenotype as defined by reactivity with various monoclonal antibodies. These cortical epithelia show some abnormal feature such as lock of irregular distribution of HLA-DR and enhanced keratin expression. Small areas of "medullary" differentiation can be observed in 3/4 thymoma samples.

In thymic hyperplasia, on the other hand, the cortical areas appear somewhat compressed (but comparable to those observed in normal age-matched samples) by enlarged medullary areas. The expansion of medullary areas was due to the infiltration of "peripheral" lymphoid tissue intruding through the extraparenchimal zone and forming organized B and T areas[17].

Savino et al.[18] showed that thymoma epithelial cells (specifically identified by their keratin content) contain thymic hormones (thymulin and thymusin alpha 1), but they do not express HLA-DR and HLA-DC antigens as observed by immunofluorescence as well as by immunoblot analyses. It is well know that class II molecules play an essential role in intrathymic T cell differentiation. Conversely, MCH class I antigens (HLA-ABC) are normally expressed.

Schweigerer[19] observed that the opioid peptide beta-endorphin binds to the specific non-opioid binding sites that are present on the surface of thymoma cells. Beta-endorphin is then internalized and is subsequently found within intracellular, vescicular structures. These findings can suggest that beta-endorphin may modulate cellular functions, such as T-lymphocytes proliferation, at intracellular rather than cell surface sites.

Dardenne[20] has shown that thymomatous epithelial cells and skeletal muscle share a common epitope defined by a monoclonal antibody. Monoclonal antibodies have been raised against thymomatous epithelial cells by the use of fragments of a human thymoma as source of antigen. These monoclonal antibodies which do not react with cultured epithelial cells or sections from normal

thymus (except for some cells of Hassal's corpuscles) label a large number of cells in thymoma sections. In addition, they recognize cross-sections from skeletal muscle cells.

Immunoblotting studies reveal that the proteins recognized on thymoma and muscle are in the same molecular weight range, suggesting that these proteins, which share a common epitope, are identical. These findings indicate that the production of circulating anti-cross-striational antibodies observed in most patients with thymoma could derive from immunization against a protein abnormally expressed by neoplastic epithelial cells.

The immunophenotypic studies have shown that most lymphocytes in thymomas are identical to normal cortical thymocytes[21-23]. In some cases minor proportions of mature T-Lymphocytes can also be found in islands which show medullary differentiation. These areas are most frequently small, but normally organized[11].

It has already been demonstrated by conventional histology that thymomas contain lymphocytes with a "stimulated" or "activated" appearance, and some mitoses also have been seen[24].

Nevertheless the replicative potential of the lymphoid component in thymomas needs further study with more quantitative methods. Unfortunately autoradiographic analysis of the mitogen-responsive capacity of thymoma cells measured in vitro[15] may not give relevant information about their proliferative feature in vivo. Recent observation with Ki-67 antibody, a reagent test that binds to nuclear antigens expressed by cells in the prolipherative phases G1, G2, M and S[25] indicate that within the lymphoid lineage there is a close relationship between antibody reactivity and the cyclic of the cell (in G1, S or M phase).

Chilosi[17] has determined the replicative fraction of thymocytes using the immunohistochemical detection of Ki-67-antigen. He found a marked activity of thymocytes in all thymomatous samples. An internal control for each sample has been provided by the remnant of medullary areas where all cells were virtually devoid of Ki-67 staining.

Chilosi[17] suggests that the proliferating T-cell precursors in thymoma are part of a microenvironmental constituted by an abnormal cortical epithelium, which is frequently HLA-DR negative. Education in such a microenvironment in thymoma may lead to the export of functionally handicapped T-cell clones. This factor may represent the key factor in the frequent development of autoimmunity in thymomas[17].

Clinical-pathological staging

The invasiveness is one of the major prognostic factor in thymomas, for this reason to define an accurate staging classification for those tumours is very important.

One of the first attempt is based on Wilkins and Castelman's study (1979)[26] slightly modified by Masaoka (1981)[27] (Tab. 4).

Verley[4] presented in 1985 a new classification similar to that proposed by Masaoka, but based on gross invasion observed at surgery (Tab. 5).

Verley[4] in a series of 200 patients confirmed that the macroscopic invasive trend was the most accurate index in thymoma survival, on the contrary the

TABLE IV. - *The Wilkins and Castleman (26) stadiation modified by Masaoka (27).*

Stage	
I	macroscopically completely encapsulated microscopically no capsular invasion.
II	*macroscopic invasion into surrounding fatty tissue or mediastinal pleura or pericardium **microscopic invasion into capsule
III	macroscopic invasion into neighboring organs, i.e. pericardium, great vessels or lung
IVa	pleural or pericardial dissemination
IVb	lymphogenous or hematogenous metastasis

TABLE V - *The Verley (4) stadiation of thymomas.*

Stage	
I	Encapsulated tumour, non invasive, total excision
Ia	Without adhesion to the environment
Ib	With areas of adhesion
II	Localized invasiveness (ig. pericapsular growth into the mediastinal fat tissue or adjacent pleura or mediastinum)
IIa	tumour completely resectable
IIb	incomplete excision, with local remnants of tumour
III	Largely invading tumour
IIIa	invasive growth into the surrounding organs and/or intrathoracic tumour grafts
IIIb	lymphogenous metastasis

association with autoimmune disease had no effect on the prognosis of thymoma, even if Spath[28] seems to support an opposite idea.

The survival rate decreased progressively with the degree of invasion of the tumour. Nevertheless whereas the difference was significant between non invasive tumours of clinical stage Ia and largely invasive tumours of stage IIIa, there was no significant difference between stages Ia and Ib, Ib and IIa and IIb, and IIb and IIIa (moderate vs massive invasion). Most of the deaths are recorded with in the first year after the operation.

Patients with spindle cell thymoma (type 1) or lymphocytic rich thymoma (type 2) had a 80% 5-years and 75% 10 years survival rate. There was no difference between the two groups. The prognosis in case of patients with differentiated epithelial thymoma (type 3) was poorer, with a survival rate of 72% at 5 years and 50% at 10 years. In patients with undifferentiated epithelial thymoma (type 4) the survival rates was nil at 5 years. The difference was significant between spindle cell or lymphocyte-rich thymomas and undifferentiated epithelial tumours. The difference was very significant between undifferentiated epithelial thymoma and all other histologic types. Recurrence rate and death by tumour have demonstrated an analogous trend.

The new classification seems to be very accurate to identify the long term survival class of patients, those with medullary type thymomas. On the contrary, cortical type thymomas are always associated with the worst prognosis. Invasiveness and cortical type are two findings often associated[11].

Clinical findings

Thymomas have a great capacity to dissimulate their symptoms: at least one third of thymomas is asymptomatic[7] detected fortuitously on routine X-ray. Asthenia, local pain, dyspnoea, cough are the commonest early symptoms, followed by dysphagia, weight loss, recurrent pneumonia, superior vena cava syndrome (left-sided) when the size and the invasiveness of the tumour increases. Often onset symptoms are related to the associated syndromes (MG and/or other diseases mainly autoimmune).

The incidence of MG in thymic tumour ranges between 10 and 60% and, viceversa, 23% of myasthenic patients have a thymoma (4-6, 29-34) (Tab. 5 and 6).

The other associated diseases include haematologic, osteoarticular, connectival, endocrine, neurologic, renal disorders. All of them are sensibly uncommon compared to MG.

Diagnosis

On plain two-planes X-ray, thymomas appear as a space/occuping lesion growing into the anterior-superior mediastinum markedly retrosternal, round-shaped and sometime lobulated, protruding on right and/or on left hemithorax. Most of thymomas are detectable by plain X-ray, only few cases result negative.

On Computed Tomography (TC), the infiltration into the surrounding tissues can be demonstrated.

TABLE VI - *The incidence of thymoma in myastenic patients (5, 6, 29-31).*

Author	Year	N. of MG cases	N.of MG+thymomas
Papatestas	1971	185	74 (40.0%)
Kornfeld	1978	1557	163 (10.5%)
Paletto	1982	320	80 (25.0%)
Le Brigand	1982	248	73 (29.4%)
Monden	1984	235	65 (27.7%)

The incidence of myasthenia in thymomatous patients (4, 32-34).

Author	Year	N. of MG cases	N.of MG+thymomas
Bernantz	1973	181	80 (44.2%)
Levasseur	1984	194	108 (55.0%)
Verley	1985	200	105 (52.5%)
Maggi	1986	169	123 (73.0%)

Patané[35] studied six cases of pleural implants completely separated from invasive thymomas (examined by conventional X-ray and CT): they concluded that CT was more effective than chest X-ray and provided a densitometric evaluation of the pleural pathology being useful in differential diagnosis. Watanabe in 1986[36] performed a comparative study between CT characteristics of malignant and benign thymomas: differentiation on the basis of shape, contour, invasiveness and potential metastasis, makes most of the thymomas classifiable preoperativaly into malignant or benign. CT scan has became a fondamental tool in metastasis detection and gains space in routine post-treatment follow up. CT can also be helpful as a guide to the fine needle biopsy. Ultrastructural and immunohistochemical studies have become now imperative in order to accomplish a correct differential diagnosis and a significant prognostic evaluation of all mediastinal masses. Fine needle biopsy can provide with high precision and low side-effect specimens fit to this purpose as demonstrated by Finley[37] since 1985. Radioisotopes uptake (Tl 201, Ga 67, Se 75) in thymoma are incidentally reported[38].

Therapy

Surgery is able to resect completely 100% of non invasive thymomas and 58% of invasive cases. Less than 2% of non invasive thymomas relapse after early and radical resection[39].

Invasive thymoma patients who received radical surgery survived 80% at 5 years with respect to 59% and 45% of patients who had a subtotal resection or biopsy only, respectively. Because of the tendency to recur or to develop local metastases, especially when the integrity of the capsule is breached, thymoma should be approached through a median sternotomy and removed en-bloc with the adjiacent mediastinal fat; biopsy should be avoided. The presence of an associated autoimmune disease should compel to an extended resection, in fact thymic islands may lead to persistence of autoimmune symptoms even if the thymoma is radically resected. One third of myasthenic patients with associated thymoma can be cured by thymectomy[5,6].

Obviously clinical stage affected the extension of the resection: radical surgery becomes impossible for advanced stage (III or IV Masaoka) and implies the sacrificing of nervous and/or vascular structures, such as phrenic nerve, recurrent nerve, left innominate vein, superior cava vein. Other massive resections involving pericardium, diaphragm, pleura, part or entire lung, chest wall, in spite of their greatest morbidity and mortality permit a better and longer survival.

Wonden et al[40] have investigated the factors influencing the recurrence or persistence of thymoma after therapy, recurrence rate was higher (31% vs 11%) in non-myasthenic thymomatous patients. The more advanced the clinical stage, the higher the rate of recurrance-persistence especially in non myasthenic operated patients. These results suggest that non myasthenic thymoma is more malignant than myasthenic thymoma. Postoperative radiotherapy was effective in preventing the recurrence-persistence of resected thymoma. Many authors do not agree with this statement and the effectiveness of post-operative radiotherapy is still debated.

In spite of the clear radiosensitivity of thymic tumours, the lack of an uniform histologic classification, the empiric protocols and the small number of patients do not allow a correct definition of the radiotherapy role. Indeed non invasive thymomas do not need post-operative radiotherapy; routine CT scan may detect early recurrence very sensible to radiotherapy.

Invasive thymomas, especially if subtotally resected or unresectable, necessitate post-operative radiotherapy: recurrence rate decreases in most of the series. Long term local control can be reached by a dose of 40-50 Gy (2 Gy/day). To prevent local recurrence the irradiation fields can include also upper (supraclaviclar fossa) and lower mediastinum, but in order to avoid pleural relapse Uematsu and Kondo[41] recommend to extend the field to the hila or to and entire hemithorax providing a low-doses prophylactic irradiation.

Even chemotherapy has been proposed by many authors[42-44], the indications were similar to radiotherapy, in most of the cases chemo is followed by radiotherapy. The most active drugs look cisplatin and prednison even if the association cyclophosphamide, adriamycin and vincristina (CAV) has been successfully employed[44]. Nevertheless at the present moment no clinical trial can demonstrate the real effectiveness of non-surgical treatment.

RIASSUNTO

I TIMOMI: RASSEGNA

I tumori sono neoplasie ad origine dalle cellule epiteliali del timo. Possono essere benigni e maligni, presentare invasività locale e associarsi a sindromi paraneoplastiche. La Miastenia Grave è spesso associata ai timomi, ma questa non è la regola. Numerose classificazioni sono state proposte: alcune di esse sono state formulate sulla base dei caratteri istopatologici (Rosai e Levine, Snover, Marino e Muller-Hermelink) altre in base allo stadio clinico-patologico (Masaoka, Verley e Hollmann).

Un terzo dei timomi è asintomatico. La diagnosi viene spesso posta mediante la radiografia del torace e confermata per mezzo della tomografia computerizzata o dell'agobiopsia con ago sottile.

La chirurgia è curativa nel 100% dei casi non invasivi e nel 58% di quelli invasivi. La radio e la chemioterapia sono consigliate soltanto negli stadi avanzati o nei pazienti inoperabili.

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