Current histological classification and staging of primary thymic epithelial neoplasms

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AIMS

- Introduction to the histology of the normal thymus
- Differential diagnosis of anterior mediastinal masses
- Histologic classification of primary thymic epithelial neoplasms
- Staging of thymomas

SUMMARY

The thymus is a small organ located just behind the sternum in the front part of the chest known as the mediastinum, the space in the chest between the lungs that also contains the heart, part of the aorta, the esophagus, part of the trachea, and many lymph nodes. The thymus sits just in front of and above the heart.

The thymus is divided into 2 lobes. It has an irregular shape and a surface that is made up of many small lobules. The thymus has 3 main layers:

- The medulla is the innermost part of the thymus.
- The cortex is the layer surrounding the medulla.
- The capsule is the thin fibrous covering over the outside of the thymus.

The thymus reaches its maximum weight during puberty, then slowly decreases in size during adulthood as it is gradually replaced by fat tissue.

The thymus is an important part of the body’s immune system. During fetal development and childhood, the thymus is involved in the production and maturation of T lymphocytes, a type of white blood cell. T lymphocytes develop in the thymus and then travel to lymph nodes throughout the body, where they will exert their function.

The thymus has different types of cells, each of which can develop into different types of cancer:

- Epithelial cells give the thymus its structure and shape. Thymomas and thymic carcinomas, which are the main focus of this talk, develop from these cells.
- Lymphocytes make up most of the rest of the thymus. Whether in the thymus or in other parts of the body, these immune system cells can develop into cancers called Hodgkin and non-Hodgkin lymphoma.
- Kulchitsky cells, or neuroendocrine cells, are much less common cells that normally release certain hormones. These cells can give rise to cancers called carcinoid tumors.
Thymomas and thymic carcinomas are rare tumors that arise from thymic epithelial cells. Not all specialists agree about the best way to describe and classify these tumors. In the past, thymomas were divided into benign thymomas and malignant thymomas, based on whether they had grown beyond the thymus into other tissues or organs. Now, most specialists agree that all thymomas are potentially invasive, and the best way to predict how likely they are to come back after treatment is to describe whether they have grown into tissues beyond the thymus (and if so, how far). This is done by the surgeon who notes whether or not the tumor appears attached to nearby organs and by the pathologist who looks at samples from the margins of the tumor under the microscope. Both the systems used to classify thymomas and to describe the stage of the disease will be discussed.

**WHO classification system for thymomas**

Thymomas will be classified by the pathologist who investigates a tissue sample under the microscope; this is called the histologic typing.

The system used for this classification, which was developed in 1999 and updated in 2003 by the World Health Organization (WHO), assigns letters to the different types of thymomas.

- **Type A:** The cells in these tumors are spindle-shaped or oval epithelial cells that appear to be fairly normal looking. This is the rarest type of thymoma, but generally with the best prognosis.
- **Type AB:** This type, also known as a mixed thymoma, looks like type A except that there are also areas of lymphocytes mixed in the tumor.
- **Type B1:** This type looks a lot like the normal structure of the thymus. It has a lot of lymphocytes along with normal-appearing thymus cells.
- **Type B2:** This type also has a lot of lymphocytes, but the thymus epithelial cells are larger with abnormal nuclei.
- **Type B3:** This type has few lymphocytes and mostly consists of thymus epithelial cells that look close to normal.
- **Type C** has been replaced in the latest WHO edition by the term thymic carcinoma. This is the most malignant form and contains cells that have a very abnormal appearance. The cells may no longer even look like thymus cells. These tumors have often invade nearby tissues and/or metastasize at the time of presentation. This type of thymoma has the worst prognosis.

Type AB and type B2 are the most common types of thymoma, and type A is the least common. As you go from A to B3, the outcome for survival tends to get worse, with type A having the best outcome, and thymic carcinoma (type C) having the worst. Still, this is debatable and for most types of thymoma, the stage (extent of growth and spread) is a better predictor of a patient’s outcome.

In its attempt to unify previous classifications the current WHO classification has introduced some problems and inconsistencies. This has led to some recent efforts to simplify this WHO classification and make it more prognostically relevant.

**How is thymus cancer staged?**

Staging is the process of finding out if and how far a cancer has spread. The treatment and prognosis depends, to a large extent, on the cancer’s stage.

**Masaoka staging system**

There is no single staging system for thymomas that all specialists agree on, perhaps because these tumors are so uncommon. The system most often used to stage thymomas is the Masaoka system, although other systems exist.
Staging in the Masaoka system is based on:

- The extent of disease as seen on imaging tests such as CT or MRI scans
- Whether the surgeon finds the tumor hard to separate from nearby tissues (indicating the tumor is invasive)
- Whether the pathologist identifies tumor cells beyond the thymus when looking at the tumor sample under the microscope.

The Masaoka system has 4 main stages:

- **Stage I**: The thymoma is non-invasive. That is, it has not spread into the capsule of the thymus.
- **Stage II**, which is divided into IIA and IIB
  - Stage IIA: The thymoma is growing into the capsule.
  - Stage IIB: The tumor has grown through the capsule into the nearby fatty tissue, and may be stuck to the mediastinal pleura or the pericardium.
- **Stage III**: The thymoma is growing into nearby tissues or organs of the lower neck or upper chest area, including the pericardium, the lungs, or the main blood vessels going into or exiting from the heart (the superior vena cava and aorta).
- **Stage IV**, which is divided into IVA and IVB
  - Stage IVA: The thymoma has spread widely throughout the pleura and/or pericardium.
  - Stage IVB: The thymoma has spread to distant organs. The most common sites of spread are bone, the liver, and the lungs.

The Masaoka staging system divides thymomas into different groups that help give clinicians an idea about a patient’s prognosis. But for treatment purposes, clinicians often use a simpler system based on whether these cancers are likely to be resectable (where all visible tumor can be removed by surgery) or unresectable.

In general terms, almost all stage I and II thymomas, most stage III thymomas, and even some stage IV thymomas are potentially resectable, but there are exceptions. Resectability is based on whether the tumor appears to have grown into nearby tissues or spread to distant sites, as well as on whether or not a person is healthy enough to have surgery. Surgery is typically part of the treatment plan whenever possible. In some cases, other forms of treatment such as radiation therapy or chemotherapy may be recommended as well.

Because thymus cancers are not common, it is hard to find accurate survival rates based on the stage of the cancer. The prognosis after treatment of a thymoma will largely depend on its stage. But other features are important as well, such as its histologic classification and whether the surgeon is able to remove the entire tumor.

**Conclusions**

Progress has been made in the understanding of the biology and morphology of thymoma, but controversial issues still remain. Part of the solution may lie in simplifying the classification.

Although much emphasis in recent years has been placed on the histological classification of thymoma, the bulk of the evidence continues to point to clinical staging as the most important parameter for prognostication.
REFERENCES

1. The summary was based upon the overview on the layman’s summary from the American Cancer Society on http://www.cancer.org/acs/groups/cid/documents/webcontent/003143-pdf.pdf