TUMORS OF THE MEDIASTINUM (I) THYMOMA AND THYMIC CARCINOMA

EMAN MS MUHAMMAD

MEDISTINUM

- ***Mediastinum is the central space within the thoracic cavity bounded by:***
  - Sternum anteriorly
  - Lungs and parietal pleura laterally
  - Vertebral column posteriorly
  - Thoracic inlet superiorly
  - Diaphragm inferiorly
- *Mediastinum is divided into: superior and inferior compartments.*
- *The later is divided into anterior, middle and posterior compartments.*

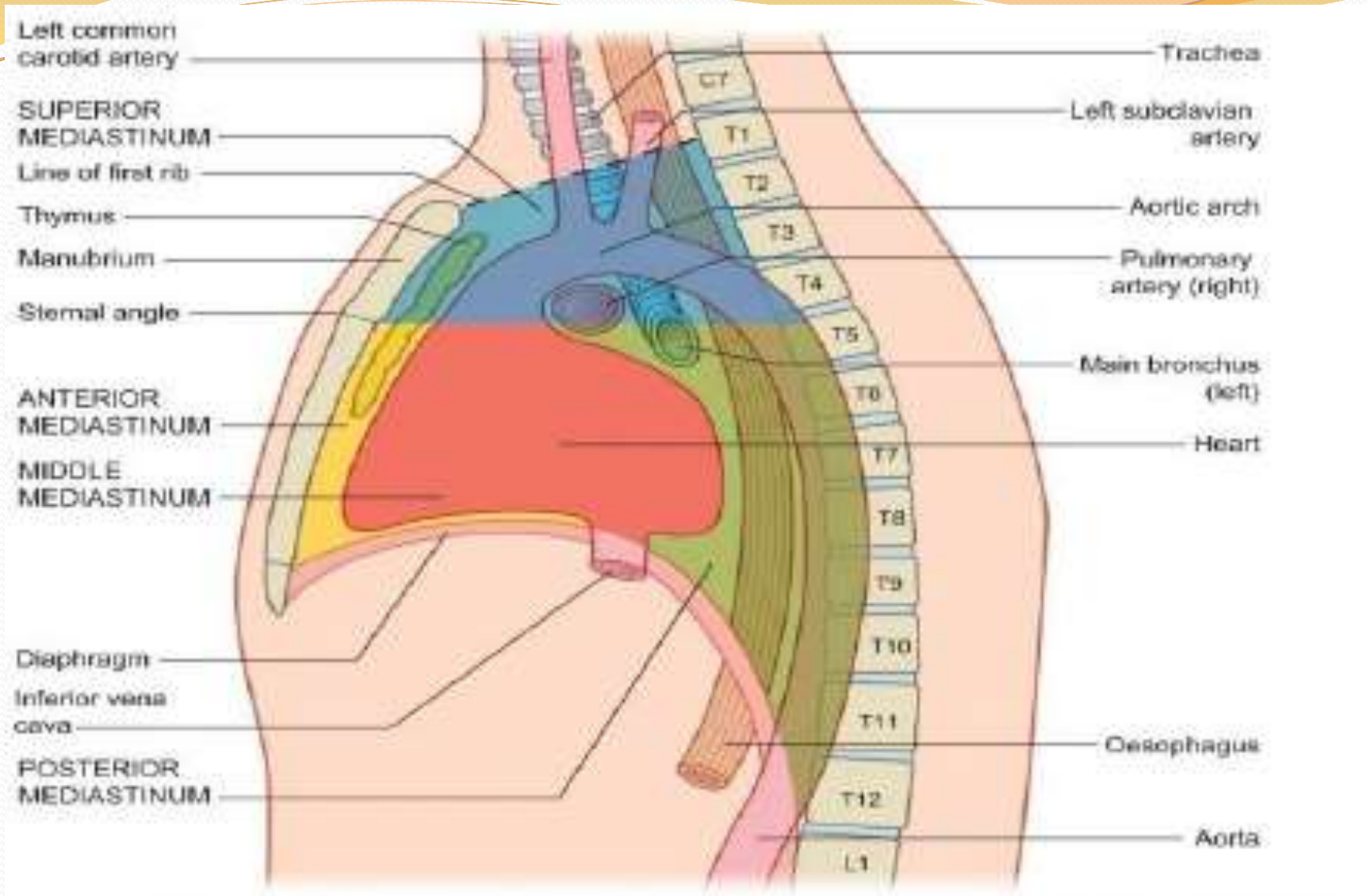
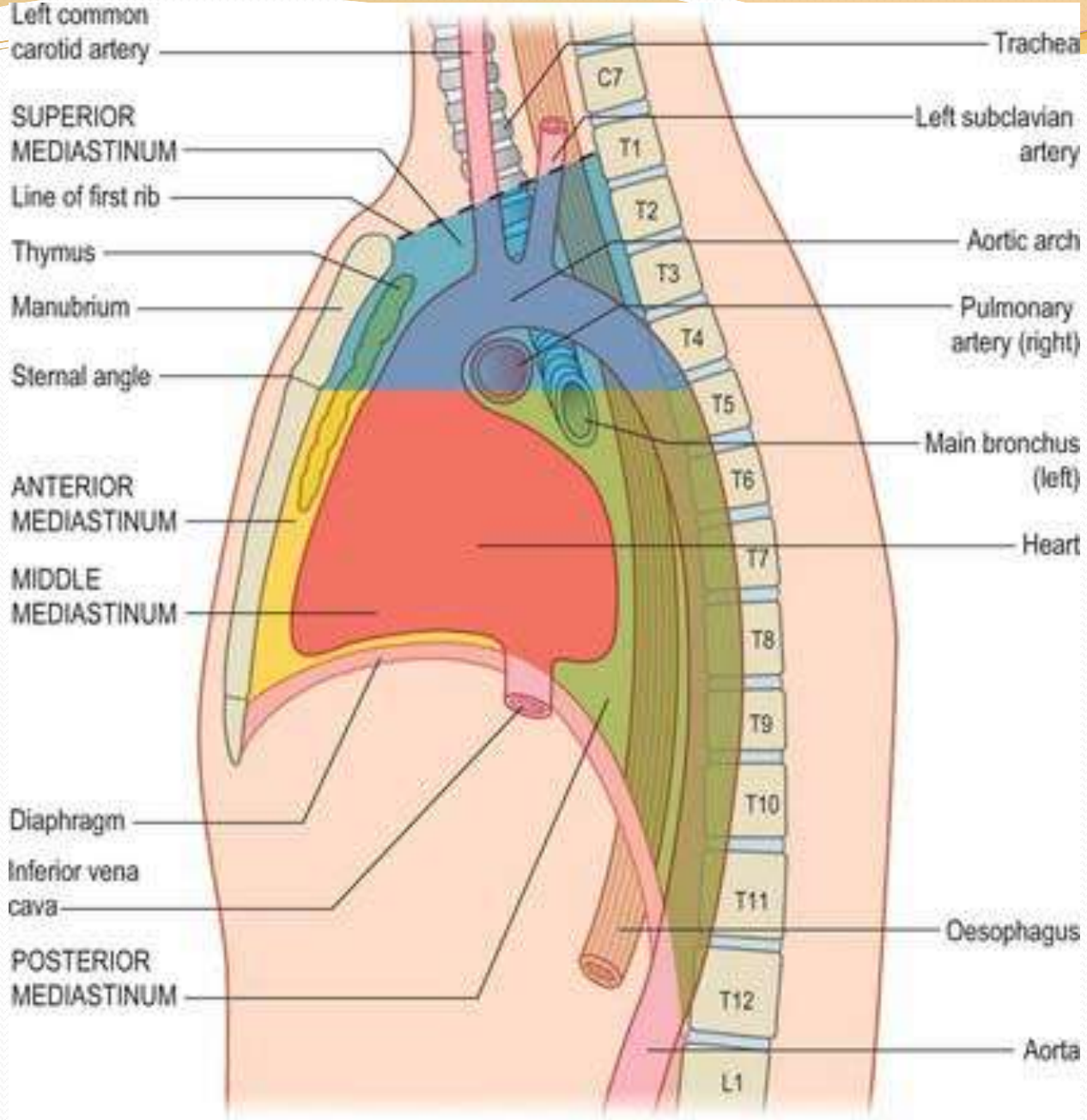


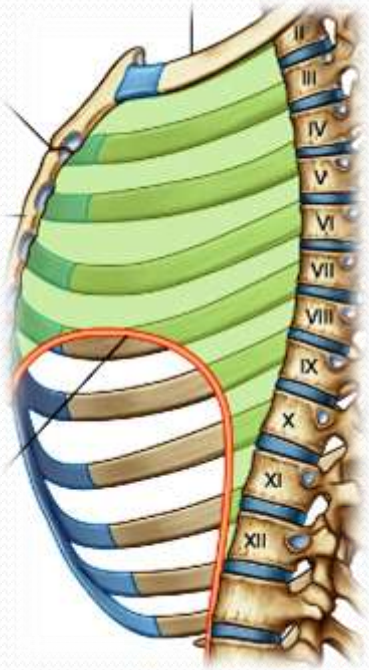
Fig. 56.1 The major divisions of the mediastinum (see text for further details). Note that not all mediastinal contents are depicted.


Left common carotid artery
SUPERIOR MEDIASTINUM
Line of first rib
Thymus
Manubrium
Sternal angle
ANTERIOR MEDIASTINUM
MIDDLE MEDIASTINUM
Diaphragm
Inferior vena cava
POSTERIOR MEDIASTINUM
Trachea
Left subclavian artery
Aortic arch
Pulmonary artery (right)
Main bronchus (left)
Heart
Oesophagus
Aorta
C7
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1

Location of most common mediastinal lesions

Superior:

- *Thymoma and thymic cysts*
- *Malignant lymphoma*
- *Thyroid lesions*
- *Parathyroid adenoma*



Posterior:

- *Neurogenic tumors:*
- **Schwannoma**
- **Neurofibroma**
- **Ganglioneuroma**
- **Ganglioneuroblastoma**
- **MPNST**
- **Neuroblastoma**
- **Paraganglioma**
- *Gastrogenic cysts*

***Anterior*:**

- *Thymoma and thymic cysts*
- *Germ cell tumours*
- *Thyroid lesions*
- *Parathyroid adenoma*
- *Malignant lymphoma*
- *Paraganglioma*
- *Hemangioma*
- *Lipoma*

Middle:

- *Pericardial cyst*
- *Bronchial cyst*
- *Malignant lymphoma*

Classification of Thymic Tumors

- *There is much controversy concerning the classification of thymic epithelial tumors.*
- **Historically,** **two** are the most influential.

I. ***The first is the descriptive scheme:***

- It was originally proposed by *Lattes et al., (1957) and adopted by Bernatz et al., (1961).*
- The histological classification of Bernatz et al. was widely used and it depends on the ***cytoarchitectural features***.

- *This classification was based on the relative proportion of tumor epithelial cells and lymphocytes and it classified thymomas into:*
  1. Predominantly spindle cell thymoma
  2. Predominantly lymphocytic thymoma
  3. Predominantly epithelial thymoma
  4. Predominantly mixed thymoma.
- *This classification was relatively easy for the pathologists to use.*

- *However, the histological subtypes so classified did not correlate with their clinical behaviors.*
- *Furthermore, it was found that, including non-neoplastic lymphocyte as a major component in the classification scheme was misleading.*
- *Therefore, this classification was abandoned.*

II. ***The second scheme based on topographic and morphofunctional characteristics:***

- *Marino and Muller-Hermelink and their co-authors, in the mid-1980s, developed classification for thymic epithelial neoplasms based on observations that cortical epithelial cells differ structurally from medullary epithelial cells.*

a. *Cortical epithelial cells are polygonal with distinct central nucleoli.*

b. *Medullary epithelial cells are elongated with diffuse chromatin and inconspicuous nucleoli.*

- *This classification was based on assumption that thymomas could be regarded as tumors arising from different compartments of normal thymus.*
- **They proposed that:**

a. *Thymomas composed of polygonal cells are derived from cortical epithelium.* and
b. *Thymomas composed of elongated cells are derive from medullary cells.*
c. *Thymomas containing both types of cells are classified as "**mixed**" epithelial.*

- **Müller-Hermelink scheme comprises the following 5 types:**
  1. Medullary thymoma
  2. Mixed thymoma
  3. Predominantly cortical (organoid) thymoma
  4. Cortical thymoma
  5. Well differentiated thymic carcinoma
- *Medullary and mixed thymomas were regarded as essentially benign nonaggressive tumors, whereas cortical, predominantly cortical, and WDTC were aggressive malignant tumors.*

- **They also supposed that:**

a. *Cortical thymomas have more aggressive course than medullary thymomas do, and*
b. *Cortical thymomas* are *more likely to be associated with myasthenia gravis.*

- However, *this classification system suffered from lack of direct histogenetic evidences to relate subtypes of thymoma*.
- Furthermore, *medullary and mixed thymomas are not absolutely benign tumors* as believed by Müller-Hermelink's group.
- The most confusing misconception in the Müller- Hermelink's classification is to *use the term "WDTC" for a subgroup of thymomas.*

- *It is simply not logical to call group of "thymomas" as "carcinomas" under the category of thymoma.*
- *This group of thymic tumors still maintain the lobular growth pattern of conventional thymoma and are accompanied by CD99+ thymocytes.*
- *Therefore, it is more appropriate to call them a type of "thymoma" rather than "thymic carcinoma".*
- *This view is further supported by their absence of CD5 expression and their frequent association with myasthenia gravis, two features usually seen in thymomas but not in thymic carcinomas.*

- The World Health Organization (WHO) committee for the histological classification of tumors of the thymus was organized by **Dr. Juan Rosai** including pathologists from eight countries in 1989.
- After more than a decade of debate among the committee members, a compromised histological classification system designated by letters and numbers was finally published in 1999.

- *The 2nd edition of the WHO Classification of Tumors of the Thymus, edited by Dr. Juan Rosai, and was published on 1999* ***addressed only thymic tumors*** *(not all mediastinal or thoracic tumors).*
- In this edition *the concept of type A, AB, B1–B3 nomenclature was introduced for thymomas.*
- In this edition also, the *WHO Committee for Histological Typing of Thymic Tumors, put new scheme incorporating the salient points of the two existing classifications but* ***takes into account two important factors:***

1. **First:** The thymus is unique in that *it can be viewed as two different organs;* **the active,** *functional gland of the fetus and infant,* and **the inactive,** *'postmature' structure of adult.*
2. **Second:** *Differentiation of the non-neoplastic lymphocytic component in tumors composed of functional thymic tissue should be considered.*

1. *Thymomas are divided into two major types depending on whether neoplastic epithelial cells and their nuclei have a spindle/oval shape (designated as type A), or have dendritic or plump ('epithelioid') appearance (designated as type B). Tumors combining these two morphologies are designated as type AB.*

- ***Type B thymomas are subdivided on the basis of** the proportional increase (in relation to the thymocytes "lymphocytes"), presence or absence of medullary differentiation, and atypia of the neoplastic epithelial cells, **into three subtypes, respectively designated as B1, B2, and B3.***

- ***For these, the general rules of tumor pathology was applied:***
- *The better differentiated tumors (lymphocyte-rich or predominantly cortical types) recapitulate the structure of the normal organ, in terms of both cortical and medullary regions.*
- *Progression in these tumors is manifested by an increase in the number of neoplastic epithelial cells, an increasing degree of atypia of these cells, and a corresponding decrease in the non-neoplastic lymphocytic component.*

- ***Thymic carcinomas*** was viewed as a subtype of thymoma ***(type C thymoma),*** an interpretation supported by the existence of hybrid and combined forms.
- For these cases, a term ***'combined thymoma'*** can be used, *followed by listing of various components and their relative amounts.*
- WHO scheme with the various tumor patterns assume *that 'A' stands for atrophic (the effete "bland-appearing" spindle thymic cell of adult life), 'B' for bioactive (the biologically active organ of the fetus and infant),* and *'C' for carcinoma.*

- *In addition to the* ***"classic thymomas"****, uncommon thymomas were described, including micronodular thymoma, microscopic thymoma, and metaplastic thymoma.*
- ***Thymic neuroendocrine tumors*** *identical to neuroendocrine tumors in the lung, including typical carcinoid tumor, atypical carcinoid tumor (defined as 2–10 mitoses per 10 high-power fields and/or necrosis), large cell neuroendocrine carcinoma, and small cell carcinoma were identified.*

- The WHO classification was revised in the ***3rd edition 2004,*** to include descriptions *of the clinical symptoms, macroscopic findings, IHC characteristics, genetic features, and prognostic data.*
- *The morphologic subtypes of thymomas remained unchanged.*
- *Type C thymoma in 1999 WHO classification was defined as thymic carcinoma.*
- *It was the first time that the WHO classification gathered all thoracic tumors in one book.*

- *The most recent **the 4th edition of the WHO classification 2015,** retained the designation of the tumors by letters and numbers.*
- *The thymic tumor classification, in the 4th edition of WHO Classification makes **minor changes** to the 2004 thymoma classification maintaining the type A, AB, B1, B2, and B3 types.*

- An effort was made by the **International Thymic Malignancy Interest Group (ITMIG)** to make refinements and to sharpen the diagnostic criteria.
- *This edition was strengthened by involving clinical experts from radiology, thoracic surgery and oncology and by the incorporation of CT images and cytology.*
- *The new genetic data provided support for the existing classification and potential for deeper insights into the molecular characteristics of these tumors.*

- Histomorphological features and IHC criteria were refined in an attempt for *diagnosis of thymomas with ambiguous histology, subtyping of thymomas and facilitating the distinction between thymomas and thymic carcinomas.*
- ***Mixed patterns are frequent and so*** *the 2015 WHO classification reported all thymoma subtypes in 10% increments (except type AB thymomas) if more than one subtype is identified in a resection specimen.*

- One new aspect is to *recognize histological criteria that are* ***"obligatory/indispensible"****, and others that are* ***"optional"****.*
- It is also recognized that ***all thymomas have malignant potential,*** because they can show an aggressive behavior, so *these tumors should not be regarded as benign.*
- Thymic carcinoma subtypes have been broadened and include the NUT carcinoma.

2004 WHO Classifications of Mediastinal tumors

I. **Epithelial tumors**

A. **Thymoma**

1. Type A (spindle cell; medullary)
2. Type AB (mixed)
3. Type B1 (lymphocyte-rich; lymphocytic predominantly cortical; organoid)
4. Type B2 (cortical)
5. Type B3 (epithelial; atypical; squamoid well-differentiated thymic carcinoma)

4. Micronodular thymoma
5. Metaplastic thymoma
6. Microscopic thymoma
7. Sclerosing thymoma
8. Lipofibroadenoma

B. **Thymic carcinoma (including neuroendocrine epithelial tumors of the thymus)**

1. Squamous cell carcinoma
2. Basaloid carcinoma
3. Mucoepidermoid carcinoma

4. Lymphoepithelioma-like carcinoma
5. Sarcomatoid carcinoma (carcinosarcoma)
6. Clear cell carcinoma
7. Adenocarcinoma
8. Papillary adenocarcinoma
9. Carcinoma with t(15;19) translocation
10. Well-differentiated neuroendocrine carcinomas (carcinoid tumors)
    a) Typical carcinoid
    b) Atypical carcinoid

11. Poorly differentiated neuroendocrine carcinomas
    a) Large cell neuroendocrine carcinoma
    b) Small cell carcinoma, neuroendocrine type
12. Undifferentiated carcinoma
13. Combined thymic epithelial tumors, including neuroendocrine carcinomas

II. Germ cell tumors (GCT) of the mediastinum

1. GCTs of one histological type (pure GCTs)
2. Seminoma
3. Embryonal carcinoma
4. Yolk sac tumor
5. Choriocarcinoma
6. Teratoma, mature
7. Teratoma, immature
8. GCTs of more than one histological type (mixed GCT)
   - Variant: Polyembryoma
9. GCTs with somatic-type malignancy
10. GCTs with associated hematologic malignancy

III. Mediastinal lymphomas and hematopoietic neoplasms

1. **B-cell lymphoma**
   a) Primary mediastinal large B-cell lymphoma
   b) Thymic extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)
2. **T-cell lymphoma**
   a) Precursor T-lymphoblastic lymphoma
   b) Precursor T-lymphoblastic leukemia
   c) Precursor T-cell acute lymphoblastic leukemia

d) (ALL)/Precursor T-cell lymphoblastic lymphoma (LBL)
e) Anaplastic large cell lymphoma and other rare mature
f) T- and NK-cell lymphomas of the mediastinum

3. **Hodgkin lymphoma of the mediastinum**
4. **“Grey zone “ between Hodgkin and Non-Hodgkin lymphoma**

5. **Histiocytic and dendritic cell tumors**
    a) Langerhans cell histiocytosis
    b) Langerhans cell sarcoma
    c) Histiocytic sarcoma
    d) Malignant histiocytosis
    e) Follicular dendritic cell tumor
    f) Follicular dendritic cell sarcoma
    g) Interdigitating dendritic cell tumor
    h) Interdigitating dendritic cell sarcoma
6. **Myeloid sarcoma and extramedullary acute myeloid leukemia**

IV. Mesenchymal tumors of the thymus and mediastinum

1. Thymolipoma
2. Lipoma of the mediastinum
3. Liposarcoma of the mediastinum
4. Solitary fibrous tumor
5. Synovial sarcoma
6. Vascular neoplasms
7. Rhabdomyosarcoma
8. Leiomyomatous tumors
9. Tumors of peripheral nerves

V. **Rare tumors of the mediastinum**

1) Ectopic tumors of the thymus
2) Ectopic thyroid tumors
3) Ectopic parathyroid tumors

VI. **Metastasis to thymus and anterior mediastinum**

2015 WHO Classification of Tumors of the Thymus

I. **Epithelial tumors**

A. **Thymoma**

1. Type A thymoma, including atypical variant
2. Type AB thymoma
3. Type B1 thymoma
4. Type B2 thymoma
5. Type B3 thymoma

6. Micronodular thymoma with lymphoid stroma
7. Metaplastic thymoma
8. ***Other rare thymomas***
    a) Microscopic thymoma
    b) Sclerosing thymoma
    c) Lipofibroadenoma

B. **Thymic carcinoma**

1. Squamous cell carcinoma
2. Basaloid carcinoma
3. Mucoepidermoid carcinoma
4. Lymphoepithelioma-like carcinoma
4. Clear cell carcinoma
5. Sarcomatoid carcinoma

6. ***Adenocarcinomas***
    a) *Papillary adenocarcinoma*
    b) *Thymic carcinoma with adenoid cystic carcinoma-like features*
    c) *Mucinous adenocarcinoma*
    d) *Adenocarcinoma, NOS*
7. NUT carcinoma
8. Undifferentiated carcinoma

9. ***Other rare thymic carcinomas***
   a) *Adenosquamous carcinoma*
   b) *Hepatoid carcinoma*
   c) *Thymic carcinoma, NOS*

C. **Thymic neuroendocrine tumors**

1. ***Carcinoid tumors***
   a) Typical carcinoid
   b) Atypical carcinoid
2. ***Large cell neuroendocrine carcinoma***
   - Combined large cell neuroendocrine carcinoma
3. ***Small cell carcinoma***
   - Combined small cell carcinoma

D. ***Combined thymic carcinomas***

E. **Germ cell tumors of the mediastinum**

1. Seminoma
2. Embryonal carcinoma
3. Yolk sac tumor
4. Choriocarcinoma
5. Teratoma
    a) Teratoma, mature
    b) Teratoma, immature

6. Mixed germ cell tumors
7. Germ cell tumors with somatic-type solid malignancy
8. Germ cell tumors with associated hematological malignancy

F. **Lymphomas of the mediastinum**

1. Primary mediastinal large B-cell lymphoma
2. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
3. Other mature B-cell lymphomas**
4. T lymphoblastic leukemia / lymphoma
5. Anaplastic large cell lymphoma (ALCL) and other rare mature T- and NK-cell lymphomas
    a) ALCL, ALK-positive (ALK+)
    b) ALCL, ALK-negative (ALK–)

6. Hodgkin lymphoma
7. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell and classical Hodgkin lymphoma

G. Histiocytic and dendritic cell neoplasms of the mediastinum

1. Langerhans cell lesions
2. Thymic Langerhans cell histocytosis
3. Langerhans cell sarcoma
4. Histiocytic sarcoma
5. Follicular dendritic cell sarcoma
6. Interdigitating dendritic cell sarcoma
7. *Fibroblastic reticular cell tumor*
8. *Indeterminate dendritic cell tumor*

H. **Myeloid sarcoma and extramedullary acute myeloid leukemia**

I. **Soft tissue tumors of the mediastinum**

1. Thymolipoma
2. Lipoma
3. Liposarcoma
    a) Well-differentiated
    b) Dedifferentiated
    c) Myxoid
    d) Pleomorphic

4. Solitary fibrous tumor
   - Malignant
5. Synovial sarcoma
   a) Synovial sarcoma, NOS
   b) Synovial sarcoma, spindle cell
   c) Synovial sarcoma, epithelioid cell
   d) Synovial sarcoma, biphasic
6. Vascular neoplasms
   a) Lymphangioma
   b) Hemangioma
   c) Angiosarcoma

J. **Neurogenic tumors**
   1. Tumors of peripheral nerves
   2. Ganglioneuroma
   3. Ganglioneuroblastoma
   4. Neuroblastoma

K. **Ectopic tumors of the thymus**
   1. Ectopic thyroid tumors
   2. Ectopic parathyroid tumors
   3. Other rare ectopic tumors

Thank you