THYMIC EPITHELIAL TUMORS

Initial Diagnosis

- **Imaging: Anterior mediastinal mass:**
  - IV Enhanced CT scan of the thorax, mediastinum, and pleura.
  - MRI would differentiate tumors from hyperplasia or cystic lesions.
  - FDG-PET is optional for aggressive histology and advanced stages.
  - Testicular ultrasonography (US).
- **Immunohistochemistry IHC:**
  - Anti-CD 117 (KIT)
  - Anti-CD5 expression
  - Lymphoma pathologic diagnostic criteria.
- **Tumor markers:**
  - Human chorionic gonadotropin (β-HCG) and
  - Alpha-fetoprotein (AFP)
- **Pathology:**
  - Thymic Epithelial Tumors sub-divided according to the World Health Organization (WHO) histopathological classification system into: **A, AB, B1, B2, B3, MNTb, Metaplastic, rare others**
  - Classification is based on:
    - Morphology of epithelial tumor cells
    - The proportion of non-tumoral lymphocytic component
    - The resemblance to the normal thymic architecture
  - Pre-treatment biopsy is not required if imaging diagnosis is highly suspected, and upfront surgical resection is achievable.
  - Squamous cell carcinoma is the most frequent subtype of thymic carcinomas
  - Thymoma is the most likely diagnosis if facing a well-defined anterior mediastinal mass associated with autoimmune disorders, including myasthenia gravis, red cell aplasia, Systemic Lupus Erythematosis (SLE), multiple endocrine neoplasia.

- **The differential diagnosis for anterior mediastinal masses:**
  - Thymus
  - Thyroid and parathyroid
  - Thoracic Lymphoma
  - Teratoma and other germ cell tumors
  - Thoracic aortic aneurysm

WHO Pathological Classification

Thymoma subtype	Obligatory criteria	Optional criteria
Type A	• The occurrence of bland, spindle-shaped epithelial cells (at least focally) • Paucity or absence of immature T cells throughout the tumor.	• Polygonal epithelial cells CD20 + epithelial cells.

Atypical type A variant	• Criteria of type A thymoma;
	• In addition:
	  ○ Comedo-type tumor necrosis;
	  ○ Increased mitotic count > 4/2mm^2;
	  ○ Nuclear crowding
		• Polygonal epithelial cells CD20 + epithelial cells.

Type AB	• The occurrence of bland, spindle-shaped epithelial cells (at least focally); • The abundance of immature (TdT+) T cells focally or throughout the tumor.	• Polygonal epithelial cells CD20 + epithelial cells.
Type B1	• Thymus like architecture and cytology: • The abundance of immature T cells, • Areas of medullary differentiation (medullary islands); • Paucity of polygonal or dendritic epithelial cells without clustering (i.e., <3 contiguous epithelial cells)	• Hassall's corpuscles; • Perivascular spaces.
Type B2	• Increased numbers of single or clustered polygonal or dendritic epithelial cells intermingled with abundant T cells.	• Mudellary islands; • Hassalls corpuscles; • Perivascular spaces.
Type B3	• Sheets of polygonal slightly to moderately atypical epithelial cells; • Absent or rare intercellular bridge; • Paucity or absence of intermingling TdT+ cells	• Hassall's corpuscles; • Perivascular spaces.
MNTb	• Nodules of the bland spindle or oval epithelial cells surrounded by an epithelial cell-free lymphoid stroma.	• Lymphoid follicles; • Monoclonal B cells and/or plasma cells (rare).
Metaplastic thymoma	• A biphasic tumor composed of solid areas of epithelial cells in a background of bland-looking spindle cells; • Absence of immature T cells	• Pleomorphism of epithelial cells; • Actin, Keratin, or EMA-positive spindle cells.
Rare others		

Diagnostic Approaches

Proposed TNM staging (8th Edition) and Corresponding MASAOKA-KOGA staging:

T – Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor completely encapsulated or extending into the mediastinal fat, may involve the mediastinal pleura.
T1im	Minimally invasive adenocarcinoma (≤3 cm in greatest dimension) with predominantly lepidic pattern ≤ 5mm invasion.
T1a	Tumor with no mediastinal pleura involvement.
T1b	Tumor with direct invasion of mediastinal pleura.
T2	Tumor with direct invasion of the pericardium (either partial or full-thickness)
T3	Tumor with direct invasion into any of the following: Lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins.
T4	Tumor with invasion into any of the following: Aorta (ascending, arch or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, and esophagus.

N – Regional Lymph Nodes	
NX	Regional LN cannot be assessed.
N0	No regional LN metastasis.
N1	Metastasis in anterior (perithymic) LNs.
N2	Metastasis in deep intrathoracic or cervical LNs.

M – Distant Metastasis	
Mx	Distant metastasis cannot be assessed.
M0	No pleural, pericardial, or distant metastasis.
M1	Pleural, pericardial or distant metastasis.
M1a	Separate pleural or pericardial nodule(s).
M1b	distant organ metastasis beyond the pleura or pericardium.

Cancer Stage Grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T Any T	N1 N0 – N1	M0 M1a
Stage IVB	Any T Any T	N2 Any N	M0 – M1a M1b

Combined MASAOKA-KOGA (1994) and International Thymic Malignancy Interest Group ITMIG (2011) Detterberk J Thoracic Oncol 2011;6: S1710-6

Stage	Staging Criteria
Stage I	Macroscopically and microscopically completely encapsulated.
Stage II	Microscopic transcapsular invasion (<3 mm). Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not breaking through mediastinal pleura or pericardium.
Stage III	Macroscopic invasion into neighboring organs (i.e., pericardium, great vessels, lung) Also, microscopic invasion of these structures. Invasion of the phrenic or vagus nerves.
Stage IV	Pleural or pericardial dissemination, microscopically confirmed separate nodules in these linings. Lymphogenous or hematogenous metastasis

Management

A- Resectable disease:

- **Surgery:**
  - Surgery would be the first choice if R0 resection deemed to be achievable upfront.
  - Surgery is followed by postoperative radiation therapy and, less frequently, chemotherapy.
- **Adjuvant RT**
  - 3-dimension (3D) conformal or intensity-modulated radiation therapy (IMRT) is preferred taking into consideration:
    - The dosage,
    - The field to be irradiated and
    - The level of resection.
- **Mediastinal RT** if needed, may increase the risk of cardiac toxicity.

- **Adjuvant chemotherapy** is not recommended after R0-R1 resection.
- Chemotherapy may be considered for stages II/III/IV thymic carcinoma if not delivered as induction treatment.

B- Advanced disease

- If R0 resection is not likely to be achievable upfront based on imaging studies.

If eligible for local therapy
The patients should receive induction chemotherapy as part of a curative-intent sequential strategy that integrates subsequent surgery or RT.
If not eligible for local therapy
The patients should receive palliative chemotherapy alone.

Selected chemotherapy regimens for advanced thymic epithelial tumors based on phase II Trials

CAP	
Cisplatin (Platinum)	50 mg/m^2 D1
Adriamycin	50 mg/m^2 D1
Cyclophosphamide	500 mg/m^2 D1
It is administered every three weeks.	

PE	
Cisplatin (Platinum)	60 mg/m^2 D1
Etoposide	120 mg/m^2 D1-3
It is administered every three weeks.	

ADOC	
Cisplatin	50 mg/m^2 D1
Adriamycin	40 mg/m^2 D1
VCR (Oncovine)	0.6 mg/m^2 D3
Cyclophosphamide	700 mg/m^2 D4
It is administered every three weeks.	

VIP	
Etoposide (Vepside)	75 mg/m^2 D1-4

Ifosfamide	1.2 gm/m^2 D1-4
Cisplatin (Platinum)	20 mg/m^2 D1-4
It is administered every three weeks.	

Carboplatin/Paclitaxel	
Carboplatin	AUC 5- 6
Paclitaxel	200- 225 mg/m^2
It is administered every three weeks.	

CAP-GEM	
Capecitabine	650 mg/m^2 bid D1-14
Gemcitabine	1000m/m^2 D1, D8
It is administered every three weeks.	

Intent of Therapy

I. Induction

- CAP or PE are recommended for induction therapies.
- Usually, 2-4 cycles are administered prior to imaging assessment for resectability.

II. Definitive RT

- Indicated when:
  - R0 resection is unlikely or
  - Patients have poor PS or co-morbidities
- Combination with PE regimen of chemotherapy may be considered

III. Definitive chemotherapy

- Offered to control tumor-related symptoms in patients having:
  - unresectable,
  - non-irradiable, or
  - metastatic stage IVB thymic epithelial tumors

Recurrent Disease

- Recurrences occur in 10-15 % of all-stage resected tumors.
- R0 resection is still recommended for resectable recurrences since it is a major predictor for favorable outcomes.

Preferred second-line regimens include:

- Carboplatin-paclitaxel
- CAP-GEM
- PE

Further options include

- Pemetrexed
- Oral etoposide

Patients with octreoscan positive thymoma and non-eligible for chemotherapy may benefit from Octreotide, including LAR +/- prednisolone.

Refractory Tumors

- Check kit sequencing (exons 9-17) to assess for suitability of Imatinib.
- Sunitinib may be considered as a treatment option for thymic carcinoma, independent of kit mutation status.
- The mechanistic target of rapamycin (m-TOR) inhibitor, everolimus may be an option.

Follow Up

- Baseline CT Thorax should be conducted every 3-4 months after surgery.
- In patients achieving R0 resection for stage I/II, CT thorax is recommended annually.
- Those who underwent R1-2 resection or have stage III/IV, CT thorax is recommended:
  - Every six months for two years
  - Then annually.
- FU Should be continued for 10-15 years.
- Patients with Myasthenia gravis should be educated about the risks of myasthenic crisis