Protocol for the Examination of Specimens from Patients with Thymic Tumors

Protocol applies to thymoma, carcinoma, including neuroendocrine carcinoma, and carcinoid tumor. This protocol does not apply to carcinoma not involving the thymus, mediastinal germ cell tumors, lymphoma, or sarcoma.

Based on:

AJCC/UICC TNM: 8th Edition
CAP Cancer Protocol version: Thymus 4.0.0.1
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Revision History:

None

Summary of Changes:

This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual and the current version of the CAP Cancer Protocol Thymus 4.0.0.1.

Procedures Covered in this Protocol:

- Thymectomy
- Partial Thymectomy

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The purpose of the Protocols is to support Laboratory Personnel engaged in the macroscopic examination of cancer resection specimens. The Protocols are based on specified relevant source documents, drafted by pathologists' assistant experts, and supported by information provided by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC). These Protocols are intended to serve patients by ensuring that the macroscopic examination of cancer resection specimens is compliant with CAP Cancer Protocols, the AJCC Cancer Staging Manual, and provide optimization of the pre-analytic steps necessary to promote appropriate molecular studies.

The AAPA cautions that the use of the Protocols in practice may require the use of additional considerations that are beyond the scope of the Protocols. The AAPA does not offer medical advice or diagnoses, or engage in the practice of medicine. The information provided in the Protocols is not intended or implied to be a substitute for the Laboratory Personnel's own training, professional medical opinion, diagnosis, or treatment advice. All content, including text, graphics, images and information contained in the Protocols are for the above stated purposes only. Laboratory Personnel are encouraged to confirm any information provided in these Protocols with other sources. The inclusion of a product name, organization, or service in an AAPA publication, including without limitation the Protocols, should not be construed as an endorsement of such product, organization, or service, nor is failure to include the name of a product, organization or service to be construed as disapproval.

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Molecular and Immunohistochemistry Considerations:

Ancillary studies, such as immunohistochemistry, are often employed in the diagnosis of thymic epithelial neoplasms. The types of ancillary studies utilized vary with the histologic appearance of the tumor.

Immunostaining for cytokeratins is useful in distinguishing thymomas from lymphoid lesions. CD1a and TdT may be useful in defining the cortical thymocyte phenotype of thymoma. CD5, CD117, and MUC1 are expressed in approximately 70% of all thymic carcinomas and in approximately 80% of thymic squamous cell carcinomas. These stains may also be helpful in separating thymic carcinoma from thymoma. Immunostains for HCG, PLAP, CEA, alpha-fetoprotein, SALL4, OCT4, and CD30 are useful in differentiating between thymic carcinomas and mediastinal germ cell tumors. NUT carcinoma is confirmed by immunohistochemical, FISH, or molecular studies.

Epstein-Barr virus (EBV) infection may play a role in a minority of thymic carcinomas. If requested, EBV DNA can be detected by In-Situ Hybridization (ISH) on formalin-fixed paraffin embedded (FFPE) tissue.

Tissue treated with decalcifying agents is not eligible for DNA analysis.

These tests can be performed on formalin-fixed, paraffin embedded tissue sections. The macroscopic description should provide the fixative used. 10% neutral buffered formalin is the preferred fixative. It is recommended that the duration of fixation be provided as well.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- Procedures Covered by this Protocol:

  - Total Thymectomy
  - Partial Thymectomy
  - Other (specify)

- Specimen Size and Extent of Resection:

  - Weigh and record measurements in three dimensions including adipose tissue. *

    *The adult thymus is atrophic with lobules of tan thymic parenchyma separated by fibrous septae and abundant adipose tissue.

  - Specify if tumor
    - is confined to the thymus
    - extends to the mediastinal fat
    - involves the lung and specify which lobe(s)
    - involves the mediastinal pleura
    - invades the pericardium
    - invades the diaphragm
    - invades adjacent organs or structures. *

    **Adjacent structures may include lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, extrapericardial pulmonary artery or veins, aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus, or other organs or structures.*

- Specimen Integrity and Adequacy:

  The completeness of resection is an important prognostic factor. Provide an assessment of the specimen integrity, paying close attention to the posterior surface of the specimen. Clearly state location of tumor to all defects and disruptions and consider differential application of ink to these areas to separate them from a true surgical margin. *

  *If the completeness of the excision is in question, the orientation of the specimen should be confirmed by the surgeon before macroscopic examination and before the application of ink to the surgical margins.

- **Include the following in the macroscopic description:**

  - Presence or absence of capsule
  - Capsular thickness
  - Continuity of capsule
  - Presence or absence of adherence and to which structure(s) *

    **Assessment of capsular invasion may be difficult, because a capsule may be either partially or entirely lacking in some thymomas and in a substantial proportion of thymic carcinomas. Areas of adherence to other mediastinal structures may be the result of*

capsular invasion by tumor or only chronic inflammation with fibrosis. This approach is becoming obsolete because all thymomas are considered malignant. Data analysis of the IASLC/ITMIG database confirmed prior observation that the capsule and involvement of the mediastinal pleura have little clinical significance.

The most clinically significant prognostic factors are tumor stage, histologic type and the completeness of resection. Consequently, while the sections submitted for microscopic evaluation should not ignore the interior of the tumor, care must be taken to submit sections for microscopic examination of the periphery of the tumor with inclusion of the capsule, attached tissues, and closest approach to the surgical margins.

TUMOR ("T" of TNM)

- Tumor Size:

  - Include three dimensions of each tumor in cm.

  Note: Though tumor size is not yet officially incorporated into T staging, critical dimensions of 11 cm and 15 cm have been reported by the World Health Organization (WHO). There are currently no changes in treatment as a result of tumor size.

- Tumor Staging and Relationship to Attached Organ/Structures:

  The AJCC Cancer Staging Manual, 8th edition is the first staging system for thymic tumors and includes thymoma, thymic carcinoma, thymic neuroendocrine tumors, and combined thymic carcinoma.

Definition of Primary Tumor (pT) *, **

pT Category	pT Description
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pT1	Tumor encapsulated or extending into the mediastinal fat; may involve the mediastinal pleura
pT1a	Tumor with no mediastinal pleura involvement
pT1b	Tumor with direct invasion of mediastinal pleura
pT2	Tumor with direct invasion of the pericardium (either partial or full thickness)
pT3	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
pT4	Tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus

**Involvement must be microscopically confirmed in pathological staging, if possible.*

*** T categories are defined by "levels" of invasion; they reflect the highest degree of invasion regardless of how many other (lower-level) structures are invaded.*
T1, level 1 structures: thymus, anterior mediastinal fat, mediastinal pleura;
T2, level 2 structures: pericardium;
T3, level 3 structures: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, hilar pulmonary vessels;
T4, level 4 structures: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus.

- Submit sections of all attached structures to rule out involvement.

Modified Masaoka Staging

The Masaoka -Koga system has been widely used as it is a prognostic indicator for thymic malignancy and a predictor of tumor recurrence.

Pathologic Staging of Thymomas (Modified Masaoka Stage, applies only to thymomas)

I	Macroscopically and microscopically encapsulated (includes microscopic invasion into, but not through the capsule)
IIa	Microscopic transcapsular invasion – focal invasion through capsule into mediastinal fat
IIb	Macroscopic capsular invasion into surrounding fatty tissue or mediastinal pleura
III	Macroscopic invasion of neighboring organs (i.e., pericardium, great vessels, or lung)
IVa	Pleural or pericardial dissemination
IVb	Lymphatic or hematogenous metastasis

The modified Masaoka staging scheme requires assessment of capsular invasion and invasion of adjacent structures.

- Encapsulated thymomas are completely surrounded by a fibrous capsule of variable thickness.
- Tumors that invade into but not through the capsule, should still be considered encapsulated.
- Minimally invasive tumors are those that focally invade through the capsule into the mediastinal fat.
- Widely invasive tumors directly extend into adjacent structures such as the lung or pericardium.

- Margins:
    - If margins are ***macroscopically negative***:
        - State distance and location of closest margin in mm.
        - Submit sections demonstrating the relationship of the tumor to the closest margin.
    - If margins are ***macroscopically positive***:
        - State location of margin involved.
        - Submit sections demonstrating the relationship of the tumor to the involved margin.
    - Margin submission, regardless of status:
        - *Posterior margin (opposing surfaces should be submitted if specimen is not oriented)
        - **Attached structures (if present)

    **In most thymectomy specimens, the posterior surface is a true surgical margin and should be painted with ink. Unless the specimen has been oriented by the surgeon, the posterior surface can be difficult to determine from the anterior surface. Consult the surgeon for clarification if needed. If the specimen is unoriented, and the surgeon cannot be reached for orientation, it is recommended to apply different colors of ink to each side (opposing surfaces) and submit the closest area on each side separately for accurate margin evaluation.*

    ***If there are attached structures such as pleura, pericardium or lung, the margin of each structure should be properly identified by the surgeon, applied with ink, and assessed to facilitate accurate histologic assessment.*

- Explanatory Notes

    Treatment effect:

    If a patient has had previous treatment, the percentage of macroscopic residual viable tumor should be estimated. Representative sections of the viable appearing areas should be submitted to ensure an accurate estimate of residual tumor. Macroscopic residual disease will influence definitive postoperative radiation and/or chemotherapy.

LYMPH NODES ("N" of TNM)

- Lymph Nodes:

Definition of Regional Lymph Node (pN) *

pN Category	pN Description
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in anterior (perithymic) lymph nodes
pN2	Metastasis in deep intrathoracic or cervical lymph nodes

**Involvement must be microscopically confirmed in pathological staging, if possible.*

Lymph Node Regions for Thymic Malignancies

	Region Boundaries	Node Groups
N1: Anterior Region	*Superior*: hyoid bone *Lateral (neck):* medial border of carotid sheaths *Lateral (chest):* mediastinal pleura *Anterior*: Sternum *Posterior (medially):* great vessels, pericardium *Posterior (laterally):* phrenic nerve *Inferior:* xiphoid, diaphragm	Low anterior cervical: pretracheal, paratracheal, peri-thyroid, precricoid/delphian Peri-thymic Prevascular Para-aortic, Ascending Aorta, Superior Phrenics Supradiaphragmatic / Inferior Phrenics / Pericardial
N2: Deep Region	*Superior:* level of lower border of cricoid cartilage *Anteriomedial (neck*): lateral border of sternohyoid, medial border of carotid sheath *Posteriolateral (neck):* anterior border of trapezius *Anterior (chest):* Right – anterior border of SVC; Left – aortic arch, aortopulmonary window *Posterior (chest):* esophagus *Lateral (chest):* pulmonary hilar *Inferior*: diaphragm	Lower Jugular Supraclavicular/venous angle: confluence of internal jugular and subclavian vein Internal Mammary nodes Upper Paratracheal Lower Paratracheal Subaortic / Aortopulmonary Window Subcarinal Hilar

A recent article states dissection of 10 or more lymph nodes from the anterior mediastinum and right paratracheal region is required to accurately predict prognosis in thymic carcinoma.

Lymph Node Examination:

Specify number and site of lymph nodes involved. *
Specify number of lymph nodes examined.

**Sites may include anterior (perithymic), deep intrathoracic, cervical, or other lymph nodes.*

Lymph Node Sampling:

- Count lymph nodes identified.
- Specify anatomic location of lymph nodes identified.
- Measure lymph nodes in three dimensions.
- Describe the cut surface of the identified lymph nodes.
- Submit all lymph nodes for microscopic examination.
    - Submit small lymph nodes in toto.
    - Serially section and entirely submit larger macroscopically negative lymph nodes.
    - Representative sections from macroscopically positive lymph nodes are adequate.
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- Take steps to ensure that an accurate lymph node count can be rendered.

METASTASIS ("M" of TNM)

- Metastasis:

Definition of Distant Metastasis (pM) (required only if confirmed pathologically)

pM Category	pM Description
M0	No pleural, pericardial, or distant metastasis
pM1	Pleural, pericardial, or distant metastasis
pM1a	Separate pleural or pericardial nodules(s)
pM1b	Pulmonary intraparenchymal nodule or distant organ metastasis

Specify the site of distant metastasis, if known.

The most common pattern of metastatic dissemination of thymic malignancies is the appearance of discrete subpleural nodules, either visceral or parietal, and pericardial nodules. Occasionally, intraparenchymal pulmonary nodules are also seen. Dissemination to other parts of the body may also occur.

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