Protocol for the Examination of Specimens from Patients with Thymic Tumors

Version: 5.0.0.0
Protocol Posting Date: December 2024
CAP Laboratory Accreditation Program Protocol Required Use Date: September 2025
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes specimens designated thymectomy and partial thymectomy
Tumor Type	**Description**
Thymoma	
Carcinoma	Includes neuroendocrine carcinoma
Carcinoid tumor	

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Carcinoma not involving the thymus
Mediastinal germ cell tumors
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)
Sarcoma (consider the Soft Tissue protocol)

Version Contributors
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Glossary:
Author: Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.
Expert Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements

Synoptic reporting with core and conditional data elements for designated specimen types* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with "+". Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under Accreditation Checklists.

A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.

**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location
- Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 5.0.0.0

- Cover page update
- Updates to content and explanatory notes, to incorporate pTNM updates to AJCC Version 9
- Removed Modified Masaoka Stage
- Update to Sites(s) Involved by Direct Tumor Invasion question
- Added Closest Margin to Invasive Tumor question
- LVI question update from “Lymphovascular Invasion” to “Lymphatic and / or Vascular Invasion”

Reporting Template
Protocol Posting Date: December 2024
Select a single response unless otherwise indicated.
CASE SUMMARY: (THYMUS)
Standard(s): AJCC 9

SPECIMEN

Procedure
___ Thymectomy
___ Partial thymectomy
___ Other (specify): _____
___ Not specified

TUMOR

Tumor Site
___ Thymus
___ Other (specify): _____

Histologic Type (Note A)
Thymoma
___ Type A thymoma (including atypical subtype)
___ Type AB thymoma
___ Type B1 thymoma
___ Type B2 thymoma
___ Type B3 thymoma
___ Micronodular thymoma with lymphoid stroma
___ Metaplastic thymoma
___ Thymoma with more than one histological pattern
+Histological Patterns Present (percentages must total 100%) (select all that apply)
___ A: _____ %
___ B1: _____ %
___ B2: _____ %
___ B3: _____ %
___ Other (specify): _____
Squamous Carcinomas
___ Squamous cell carcinoma, NOS
___ Basaloid carcinoma
___ Lymphoepithelial carcinoma
Adenocarcinomas
___ Adenocarcinoma, NOS
___ Low-grade papillary adenocarcinoma
___ Thymic carcinoma with adenoid cystic carcinoma-like features
___ Enteric-type adenocarcinoma
Adenosquamous Carcinomas
___ Adenosquamous carcinoma

NUT Carcinomas
___ NUT carcinoma
Salivary gland-like Carcinomas
___ Mucoepidermoid carcinoma
___ Clear cell carcinoma
___ Sarcomatoid carcinoma
Undifferentiated Carcinomas
___ Undifferentiated carcinoma
Thymic Carcinomas
___ Thymic carcinoma, NOS
Neuroendocrine Tumors
___ Carcinoid tumor, NOS / Neuroendocrine tumor, NOS
___ Typical carcinoid / Neuroendocrine tumor, grade 1
___ Atypical carcinoid / Neuroendocrine tumor, grade 2
Neuroendocrine Carcinomas
___ Small cell carcinoma
___ Large cell neuroendocrine carcinoma
Other
___ Other histologic type not listed (specify): _____
___ Cannot be determined (explain): _____

+Histologic Type Comment: _____

Tumor Size
___ Greatest dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _____

Lymphatic and / or Vascular Invasion
___ Not identified
___ Present
___ Cannot be determined: _____

Treatment Effect
___ No known presurgical therapy
___ Not identified
___ Present
Percentage of Residual Viable Tumor
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined: _____
___ Cannot be determined: _____

Site(s) Involved by Direct Tumor Invasion (select all that apply)
___ Tumor limited to the thymus
___ Mediastinal fat

___ Mediastinal pleura
___ Pericardium (either partial or full thickness)
___ Phrenic nerve
___ Lung (specify lobe(s) involved): _____
___ Brachiocephalic vein
___ Superior vena cava
___ Chest wall
___ Extrapericardial pulmonary artery
___ Extrapericardial pulmonary veins
___ Ascending aorta
___ Aortic arch
___ Descending aorta
___ Arch vessels
___ Intrapericardial pulmonary artery
___ Intrapericardial pulmonary veins
___ Myocardium
___ Trachea
___ Esophagus
___ Diaphragm
___ Other (specify): _____
___ Cannot be determined: _____
___ Not applicable: _____

+Tumor Comment: _____

MARGINS (Note B)

Margin Status
___ All margins negative for tumor
Closest Margin(s) to Invasive Tumor
___ Specify closest margin(s): _____
___ Cannot be determined (explain): _____
Distance from Tumor to Closest Margin
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ At least: _____ mm
___ Less than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Tumor present at margin
Margin(s) Involved by Tumor
___ Specify involved margin(s): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)
Number of Lymph Nodes with Tumor
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Nodal Site(s) with Tumor (select all that apply)
___ Anterior (perithymic): _____
___ Deep intrathoracic: _____
___ Cervical: _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Pleural nodule(s): _____
___ Pericardial nodule(s): _____
___ Intraparenchymal pulmonary nodule(s): _____
___ Other distant organs (specify): _____
___ Cannot be determined: _____

pTNM CLASSIFICATION (AJCC Version 9) (Note C)

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

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

Modified Classification (required only if applicable) (select all that apply)

___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category

___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor

pT1: Tumor limited to the thymus with or without encapsulation, or directly invades into the mediastinal fat only, or directly invades the mediastinal pleura but does not involve any other mediastinal structure

___ pT1a: Tumor less than or equal to 5 cm in greatest dimension limited to the thymus with or without encapsulation; or Tumor less than or equal to 5 cm in greatest dimension that directly invades into the mediastinal fat only; or Tumor less than or equal to 5 cm in greatest dimension that directly invades the mediastinal pleura but does not involve any other mediastinal structure
___ pT1b: Tumor greater than 5 cm in greatest dimension limited to the thymus with or without encapsulation; or Tumor greater than 5 cm in greatest dimension that directly invades into the mediastinal fat only; or Tumor greater than 5 cm in greatest dimension that directly invades the mediastinal pleura but does not involve any other mediastinal structure
___ pT1 (subcategory cannot be determined)
___ pT2: Tumor with direct invasion of the pericardium (either partial or full thickness), or the lung, or the phrenic nerve
___ pT3: Tumor with direct invasion into any of the following: brachiocephalic vein, superior vena cava, chest wall, or extrapericardial pulmonary arteries or veins
___ pT4: Tumor with direct invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery or veins, myocardium, trachea, esophagus

T Suffix (required only if applicable)

___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category

___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No tumor involvement of regional lymph node(s)
___ pN1: Tumor involvement of anterior (perithymic) lymph nodes
___ pN2: Tumor involvement of deep intrathoracic or cervical lymph nodes (e.g., paratracheal, subcarinal, aortopulmonary window, hilar, jugular and / or supraclavicular nodes)

N Suffix (required only if applicable) (select all that apply)
___ Not applicable
___ (sn) Sentinel node procedure
___ (f) FNA or core needle biopsy

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
pM1: Microscopic confirmation of distant metastasis
___ pM1a: Microscopic confirmation of separate pleural or pericardial nodule(s)
___ pM1b: Microscopic confirmation of pulmonary intraparenchymal nodule or other distant metastasis
___ pM1 (subcategory cannot be determined)

ADDITIONAL FINDINGS

+Additional Findings (select all that apply)
___ Age-appropriate involutional changes
___ Fibrosis
___ Follicular thymic hyperplasia
___ Epithelial thymic hyperplasia
___ True thymic hyperplasia
___ Cystic changes in tumor
___ Cystic changes in adjacent thymus
___ Other (specify): _____

SPECIAL STUDIES (Note D)

+Immunohistochemistry (specify stains and results): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Histologic Type
For consistency in reporting, the histologic classification published by the World Health Organization (WHO) for tumors of the thymus is recommended.[1]

Type A, AB, and B thymomas show thymic architectural features.[1] Sclerosing thymoma was removed from the fifth edition of the WHO classification because it is thought to represent sclerotic changes in various types of thymomas rather than a distinctive form of thymoma. The protocol now supports reporting of thymomas exhibiting more than one histological pattern. It is recommended that the diagnosis lists the predominant histological pattern observed, followed by minor components (e.g., "thymoma, with type B2 (80%) and type B3 (20%) components".[1] However, type AB thymoma should be reported as such and not divided into type A and type B components.

Thymic carcinomas are a heterogeneous group of malignant epithelial tumors with diverse morphology showing morphologies that resemble carcinomas encountered outside the thymus.[1] The classification of thymic carcinomas in the fifth edition of the WHO classification is basically similar to that in the fourth edition. Micronodular thymic carcinoma with lymphoid hyperplasia is provisionally added as a subtype of squamous cell carcinoma. Clear cell carcinoma, a hyalinizing subtype characterized by EWSR1 gene translocation is recognized, analogous to hyalinizing clear cell carcinoma of salivary gland. For primary thymic adenocarcinoma, the various subtypes are maintained, but with minor changes in terminology, from "papillary adenocarcinoma" to "low-grade papillary adenocarcinoma", and from "mucinous adenocarcinoma" to "enteric-type adenocarcinoma".[1]

The nomenclature and diagnostic criteria for thymic neuroendocrine tumors (typical and atypical carcinoids, large cell neuroendocrine carcinoma [LCNEC], and small cell carcinoma) are retained from previous editions of the WHO classification.[1,2] The descriptive terms "well-differentiated neuroendocrine carcinoma" (referring to carcinoids) and "poorly differentiated neuroendocrine carcinoma" (referring to LCNEC and small cell carcinoma) should not be used.[1,2]

References

1. WHO Classification of Tumours Editorial Board. *Thoracic tumours.* Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 5). https://publications.iarc.fr/595
2. Marx A, Chan JK, Coindre JM, Detterbeck F, et al. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. *J Thorac Oncol.* 2015;10(10):1383-1395.

B. Margins
Thymectomy involves dissection and mobilization of the thymus from the pericardium and mediastinal pleura. In most thymectomy specimens, the posterior surface constitutes a true margin. Unless it has been marked by the surgeon, the posterior surface of thymectomy specimens is difficult to locate. If the completeness of excision is in question, the orientation of the specimen should be confirmed by the surgeon before grossing, and all surgical margins inked. In addition to thymus, some specimens also include attached neighboring structures (e.g., pleura, pericardium, lung). The margins of any attached structures should be properly identified by the surgeon and inked to facilitate accurate histologic assessment of margin

status. In addition to tumor stage and histologic type, completeness of resection is an important prognostic parameter.[1,2] Current protocol requires to specify the closest margin to invasive tumor.

References

1. Huang J, Detterbeck FC, Wang Z, Loehrer PJ Sr. Standard outcome measures for thymic malignancies. *J Thorac Oncol.* 2010;5(12):2017-2023.
2. Detterbeck FC, Moran C, Huang J, et al. Which way is up?: policies and procedures for surgeons and pathologists regarding resection specimens of thymic malignancy. *J Thorac Oncol.* 2011;6(7 Suppl 3):S1730.

C. pTNM Classification

The 8th edition of the AJCC staging manual introduced a TNM classification and staging system for thymic tumors. It includes thymoma, thymic carcinoma, thymic neuroendocrine tumors, and combined thymic carcinoma. The AJCC staging is based on the proposal by the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG) that is founded on the analyses of an international database with 10,808 patients from 105 sites.[1,2,3]

The AJCC Version 9 includes sub classification of T1 category into T1a (<5 cm) and T1b (>5 cm), irrespective of mediastinal pleura invasion;T2 includes direct invasion of the pericardium, lung, or phrenic nerve; T3 denotes direct invasion of the brachiocephalic vein, superior vena cava, chest wall, or extrapericardial pulmonary arteries and veins; and T4 category remains the same as in the eighth edition classification, involving direct invasion of the aorta and arch vessels, intrapericardial pulmonary arteries and veins, myocardium, trachea, or esophagus.[4] No changes are proposed from the eighth edition for the N and M components.[5] The Masaoka-Koga system is the most frequently used staging system for thymic neoplasms.[6,7,8] However, there are significant discrepancies in the interpretation of ambiguously defined criteria between different institutions. Classification of a thymoma according to the Masaoka-Koga system should always be accompanied by (and does not replace) TNM classification.

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. Assessment of capsular invasion is sometimes difficult, because a capsule may be either partially or entirely lacking in some thymomas and in a substantial proportion of thymic carcinomas.

Adherence to pleura or pericardium is interpreted by the ITMIG as, “making removal of these [structures] necessary during resection, with microscopic confirmation of perithymic invasion, but without microscopic extension into or through the mediastinal pleura or into the fibrous layer of the pericardium".[8] Areas of tumor adherence to mediastinal or other structures could be the result of tumor invasion or only chronic inflammation with fibrosis.

There are currently not enough data to support a particular T category for thymomas extending directly into the diaphragm because they are exceedingly rare. Until this situation is revisited when more data are available, it is probably fair to assume that the outcome of such tumors resembles thymomas classified pT3.

References

1. Detterbeck FC, Asamura H, Crowley J, et al. The IASLC/ITMIG thymic malignancies staging project: development of a stage classification for thymic malignancies. *J Thorac Oncol.* 2013;8(12):1467-1473.
2. Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol.* 2014;9(9 Suppl 2):S65-S72.
3. Nicholson AG, Detterbeck FC, Marino M, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposals for the T component for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol.* 2014;9(9 Suppl 2):S73-S80.
4. Okumura M, Marino M, Cilento V, Goren E, Ruffini E, et al. The International Association for the Study of Lung Cancer Thymic Epithelial Tumor Staging Project: Proposal for the T Component for the Forthcoming (Ninth) Edition of the TNM Classification of Malignant Tumors. *J Thorac Oncol.* 2023 Dec;18(12):1638-1654.
5. Fang W, Girard N, Cilento V, et al. The International Association for the Study of Lung Cancer Thymic Epithelial Tumors Staging Project: Proposals for the N and the M Components for the Forthcoming (Ninth) Edition of the TNM Classification of Malignant Tumors. *J Thorac Oncol.* 2024 Jan;19(1):52-70.
6. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. *Cancer.* 1981;48:2485-2492.
7. Koga K, Matsuno Y, Noguchi M, et al. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. *Pathol Int.* 1994;44:359-367.
8. Detterbeck FC, Nicholson AG, Kondo K, Van Schil P, Moran C. The Masaoka-Koga stage classification for thymic malignancies and definition of terms. *J Thorac Oncol.* 2011;6(7 Suppl 3); S1710-S1716.

D. Ancillary Studies

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 helpful in distinguishing between thymomas and lymphoid lesions. In selected cases, the use of immunohistochemistry for CD1a and terminal deoxynucleotidyl transferase (TdT) may be helpful in defining the cortical thymocyte phenotype of thymoma, as distinguished from the typical peripheral T-cell phenotype of tumor-infiltrating lymphocytes associated with other tumors. CD5, CD117, and MUC1 are expressed in about 70% of all thymic carcinomas and in about 80% of thymic squamous cell carcinomas, and may potentially be helpful in separating thymic carcinoma from thymoma. It should be noted that about 3% of thymomas, particularly B3 type, may express CD5 and CD117.[1,2] Pax8 immunohistochemical staining in thymic epithelial tumors is commonly seen with polyclonal, but not monoclonal, Pax8 antibodies.[3] Immunostains for human chorionic gonadotropin (HCG), placental alkaline phosphatase (PLAP), carcinoembryonic antigen (CEA), α-fetoprotein, SALL4, OCT4, and CD30 are helpful in differentiating between thymic carcinomas and mediastinal germ cell tumors. The diagnosis of NUT carcinoma is confirmed by immunohistochemical, FISH, or molecular studies.[1]

References

1. WHO Classification of Tumours Editorial Board. *Thoracic tumours*. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 5). https://publications.iarc.fr/595
2. Marx A, Chan JK, Coindre JM, Detterbeck F, et al. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. *J Thorac Oncol.* 2015;10(10):1383-1395.
3. Weissferdt A, Moran CA. Pax8 expression in thymic epithelial neoplasms: an immunohistochemical analysis. *Am J Surg Pathol.* 2011 Sep;35(9):1305-1310.