



Protocol for the Examination of Specimens From Patients With Thymic Tumors

Version: Thymus 4.0.0.0

Protocol Posting Date: June 2017

Includes pTNM requirements from the 8th Edition, AJCC Staging Manual

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 (eg, 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 Hodgkin or non-Hodgkin Lymphoma protocols)
Sarcoma (consider the Soft Tissue protocol)

Authors

Sanja Dacic, MD, PhD*; Mary Beth Beasley, MD; Michael Berman, MD; Kelly J. Butnor, MD; Feng-Ming Kong, MD, PhD, MPH; Alberto Marchevsky, MD; Robert J. McKenna, MD; Nader T. Okby, MD; Victor L. Roggli, MD; Saul Suster, MD; Henry D. Tazelaar, MD; William D. Travis, MD

With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

* Denotes primary author. All other contributing authors are listed alphabetically.

Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is “not applicable” or “cannot be determined.”
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with “+” and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

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 must 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.

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2018*

* Beginning January 1, 2018, the 8th edition AJCC Staging Manual should be used for reporting pTNM.

CAP Thymic Tumor Protocol Summary of Changes

The following data elements were modified:

Pathologic Stage Classification (pTNM, AJCC 8th Edition)

Surgical Pathology Cancer Case Summary

Protocol posting date: June 2017

THYMUS:**Select a single response unless otherwise indicated.****Procedure**

- Thymectomy
 Partial thymectomy
 Other (specify): _____
 Not specified

Tumor Size

- Greatest dimension (centimeters): ____ cm
 + Additional dimensions (centimeters): ____ x ____ cm
 Cannot be determined (see Comment)

Histologic Type (Note A)Thymoma

- Type A thymoma
 Type AB thymoma
 Type B1 thymoma
 Type B2 thymoma
 Type B3 thymoma

Thymic Carcinoma

- Squamous cell carcinoma
 Basaloid carcinoma
 Mucoepidermoid carcinoma
 Lymphoepithelioma-like carcinoma
 Clear cell carcinoma
 Sarcomatoid carcinoma
 Adenocarcinoma
 NUT carcinoma
 Undifferentiated carcinoma

Thymic Neuroendocrine Tumors

- Typical carcinoid
 Atypical carcinoid
 Large cell neuroendocrine carcinoma
 Small cell carcinoma

Other histologic type not listed (specify): _____

Transcapsular Invasion (applies only to thymomas)

- Present
 Absent
 Cannot be determined

Tumor Extension (select all that apply)

- Tumor confined to thymus
 Tumor extends to the mediastinal fat

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

- Tumor involves pulmonary parenchyma
+ Specify lobe(s) of lung: _____
- Tumor involves mediastinal pleura
- Tumor invades pericardium
- Tumor invades diaphragm
- Tumor invades adjacent organs or structures[#] (specify): _____
- Other (specify): _____
- Cannot be assessed
- Not applicable

[#] Note: Adjacent structures or organs 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.

Margins (Note B)

- Cannot be assessed
- Uninvolved by tumor
Distance of tumor from closest margin (millimeters): ____ mm
- Involved by tumor
Specify margin(s): _____

Treatment Effect

- No known presurgical therapy
- Not identified
- Present (specify percentage of residual viable tumor): ____%
- Cannot be determined

Lymphovascular Invasion

- Not identified
- Present
- Cannot be determined

Regional Lymph Nodes

- No lymph nodes submitted or found

Lymph Node Examination (required only if lymph nodes are present in the specimen)

- Number of Lymph Nodes Involved: _____
- Number cannot be determined (explain): _____
- Specify Site(s)[#]: _____

[#] Note: Sites may include anterior (perithymic), deep intrathoracic, cervical, or other lymph nodes.

- Number of Lymph Nodes Examined: _____
- Number cannot be determined (explain): _____

Pathologic Stage Classification (pTNM, AJCC 8th Edition) (Note C)

Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.

TNM Descriptors (required only if applicable) (select all that apply)

- m (multiple primary tumors)
- r (recurrent)
- y (posttreatment)

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

Primary Tumor (pT)

- 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

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

Note: 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.

Regional Lymph Nodes (pN)

- 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

Distant Metastasis (pM) (required only if confirmed pathologically in this case)

- pM1: Pleural, pericardial, or distant metastasis
- pM1a: Separate pleural or pericardial nodule(s)
- pM1b: Pulmonary intraparenchymal nodule or distant organ metastasis
- Specify site(s), if known: _____

+ Modified Masaoka Stage (applies only to thymomas) (Note C)

- + Stage I: Grossly and microscopically encapsulated (includes microscopic invasion into, but not through, the capsule)
- + Stage IIa: Microscopic transcapsular invasion
- + Stage IIb: Macroscopic capsular invasion
- + Stage III: Macroscopic invasion of neighboring organs
- + Stage IVa: Pleural or pericardial dissemination
- + Stage IVb: Hematogenous or lymphatic dissemination
- + Cannot be determined

+ Additional Pathologic Findings (select all that apply)

- + Age-appropriate involution changes
- + Fibrosis
- + Follicular thymic hyperplasia
- + Epithelial thymic hyperplasia
- + True thymic hyperplasia
- + Cystic changes in tumor
- + Cystic changes in adjacent thymus
- + Other (specify): _____

+ Ancillary Studies (Note E)

- + Immunohistochemical staining (specify results): _____

+ Comment(s)

- + Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

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 The histologic types are listed in this protocol in the order they appear in the WHO classification.

Type A, AB, and B thymomas show thymic architectural features.¹ Thymic carcinomas are a heterogeneous group of malignant epithelial tumors with diverse morphology showing morphologies that resemble carcinomas encountered outside the thymus.¹ The nomenclature and criteria of thymic neuroendocrine tumors (typical and atypical carcinoids, large cell neuroendocrine carcinoma [LCNEC], and small cell carcinoma) are the same as in the 2004 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}

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 (eg, 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.^{3,4}

C. Pathologic Staging of Thymic Epithelial Neoplasms

The AJCC staging manual, 8th edition (released in October 2016), is the first staging system for thymic tumors and 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 institutions.⁵

The Masaoka-Koga system is the most frequently used staging system for thymic neoplasms.⁶⁻⁸ However, there are significant discrepancies in the interpretation of ambiguously defined criteria between different institutions. 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 (ie, transcapsular invasion) into the mediastinal fat, whereas widely invasive tumors directly extend into adjacent structures such as the lung or pericardium.⁵ 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. Areas of tumor adherence to other mediastinal structures could be the result of tumor invasion or only chronic inflammation with fibrosis. Focus on tumor encapsulation is mostly based on the speculation that this may distinguish benign thymomas. This approach is becoming obsolete because all thymomas are considered malignant.^{9,10} Data analysis of the IASLC/ITMIG database confirmed prior observation that the capsule and involvement of the mediastinal pleura have little clinical significance.¹⁰⁻¹²

E. 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} 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. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG, eds. *World Health Organization Classification of Tumours of the Lung, Pleura, Thymus and Heart*. 4th edition, Geneva, Switzerland: WHO Press; 2015.
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. Huang J, Detterbeck FC, Wang Z, Loehrer PJ Sr. Standard outcome measures for thymic malignancies. *J Thorac Oncol*. 2010;5(12):2017-2023.
4. 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.
5. 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.
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.
9. Detterbeck F. Stage classification and prediction of prognosis: difference between accountants and speculators. *J Thorac Oncol*. 2013;8:820-822.
10. 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.
11. Gupta R, Marchevsky AM, McKenna RJ, et al. Evidence-based pathology and the pathologic evaluation of thymomas: transcapsular invasion is not a significant prognostic feature. *Arch Pathol Lab Med*. 2008;132:926-930.
12. 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.