



National Comprehensive  
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Thymomas and Thymic Carcinomas

Version 1.2023 — December 15, 2022

[NCCN.org](https://www.nccn.org)

[Continue](#)



**\*David S. Ettinger, MD/Chair †**  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

**\*Douglas E. Wood, MD/Vice Chair ¶**  
Fred Hutchinson Cancer Center

**\*Gregory J. Riely, MD, PhD/Lead † ‡**  
Memorial Sloan Kettering Cancer Center

**Dara L. Aisner, MD, PhD ≠**  
University of Colorado Cancer Center

**Wallace Akerley, MD †**  
Huntsman Cancer Institute  
at the University of Utah

**Jessica R. Bauman, MD ‡ †**  
Fox Chase Cancer Center

**Ankit Bharat, MD ¶**  
Robert H. Lurie Comprehensive Cancer  
Center of Northwestern University

**Debora S. Bruno, MD, MS †**  
Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer Center  
and Cleveland Clinic Taussig Cancer Institute

**Joe Y. Chang, MD, PhD §**  
The University of Texas  
MD Anderson Cancer Center

**Lucian R. Chirieac, MD ≠**  
Dana-Farber/Brigham and Women's  
Cancer Center

**Thomas A. D'Amico, MD ¶**  
Duke Cancer Institute

**Malcolm DeCamp, MD ¶**  
University of Wisconsin Carbone Cancer Center

**Thomas J. Dilling, MD, MS §**  
Moffitt Cancer Center

**Jonathan Dowell, MD †**  
UT Southwestern Simmons  
Comprehensive Cancer Center

**Gregory A. Durm, MD, MS †**  
Indiana University Melvin and Bren Simon  
Comprehensive Cancer Center

**Scott Gettinger, MD † ‡**  
Yale Cancer Center/Smilow Cancer Hospital

**Travis E. Grotz, MD ¶**  
Mayo Clinic Cancer Center

**Matthew A. Gubens, MD, MS †**  
UCSF Helen Diller Family  
Comprehensive Cancer Center

**Aparna Hegde, MD †**  
O'Neal Comprehensive Cancer Center at UAB

**Rudy P. Lackner, MD ¶**  
Fred & Pamela Buffett Cancer Center

**Michael Lanuti, MD ¶**  
Massachusetts General Hospital Cancer Center

**Jules Lin, MD ¶**  
University of Michigan Rogel Cancer Center

**Billy W. Loo, Jr., MD, PhD §**  
Stanford Cancer Institute

**Christine M. Lovly, MD, PhD †**  
Vanderbilt-Ingram Cancer Center

**Fabien Maldonado, MD £**  
Vanderbilt-Ingram Cancer Center

**Erminia Massarelli, MD, PhD, MS †**  
City of Hope National Medical Center

**Daniel Morgensztern, MD †**  
Siteman Cancer Center at Barnes-Jewish Hospital  
and Washington University School of Medicine

**Thomas Ng, MD ¶**  
The University of Tennessee  
Health Science Center

**Gregory A. Otterson, MD †**  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Sandip P. Patel, MD ‡ † ‡**  
UC San Diego Moores Cancer Center

**Tejas Patil, MD †**  
University of Colorado Cancer Center

**Patricio M. Polanco, MD ¶**  
UT Southwestern Simmons  
Comprehensive Cancer Center

**Jonathan Riess, MD ‡**  
UC Davis Comprehensive Cancer Center

**Steven E. Schild, MD §**  
Mayo Clinic Cancer Center

**Theresa A. Shapiro, MD, PhD ¥ ‡**  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

**Aditi P. Singh, MD †**  
Abramson Cancer Center at the  
University of Pennsylvania

**James Stevenson, MD †**  
Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer Center  
and Cleveland Clinic Taussig Cancer Institute

**Alda Tam, MD ϕ**  
The University of Texas  
MD Anderson Cancer Center

**Tawee Tanvetyanon, MD, MPH †**  
Moffitt Cancer Center

**Jane Yanagawa, MD ¶**  
UCLA Jonsson Comprehensive Cancer Center

**Stephen C. Yang, MD ¶**  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

**Edwin Yau, MD, PhD †**  
Roswell Park Comprehensive Cancer Center

**NCCN**

**Kristina Gregory, RN, MSN, OCN**  
**Miranda Hughes, PhD**

‡ Hematology/Hematology oncology	¶ Surgery/Surgical oncology
‡ Internal medicine	ϕ Diagnostic/Interventional radiology
† Medical oncology	£ Pulmonary medicine
≠ Pathology	* Discussion Section Writing Committee
¥ Patient advocacy	
§ Radiation oncology/Radiotherapy	

**Continue**



### [NCCN Thymomas and Thymic Carcinomas Panel Members](#) [Summary of Guidelines Updates](#)

#### [Initial Evaluation \(THYM-1\)](#)

#### [Initial Management \(THYM-2\)](#)

#### [Postoperative Treatment and Management \(THYM-3\)](#)

#### [Locally Advanced, Advanced, or Recurrent Disease \(THYM-4\)](#)

#### [Principles of Surgical Resection \(THYM-A\)](#)

#### [Principles of Radiation Therapy \(THYM-B\)](#)

#### [Principles of Systemic Therapy \(THYM-C\)](#)

#### [World Health Organization Histologic Classification \(THYM-D\)](#)

#### [Staging \(ST-1\)](#)

#### [Abbreviations \(ABBR-1\)](#)

**Clinical Trials:** NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Find an NCCN Member Institution:  
<https://www.nccn.org/home/member-institutions>.

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2022.



### Updates in Version 1.2023 of the NCCN Guidelines for Thymomas and Thymic Carcinomas from Version 2.2022 include:

#### **THYM-3**

- R0 resection; Consider Postoperative RT
  - ▶ Footnote g added: Decisions about adjuvant radiation therapy (RT) in this setting should be based on multidisciplinary evaluation.

#### **THYM-4**

- Solitary metastasis or ipsilateral pleural metastasis
  - ▶ Category added for medically inoperable/unresectable
    - ◇ Treatment options are consider local therapy or systemic therapy
    - ◇ Footnote I added: Local therapies can include image-guided thermal ablation or RT.

#### **THYM-A**

- References 7–10 added
  - Burt BM, Yao X, Shrager J, et al. Determinants of Complete resection of thymoma by minimally invasive and open thymectomy: Analysis of an International Registry. *J Thorac Oncol* 2017;12:129-136.
  - Jurado J, Javidfar J, Newmark A, et al. Minimally invasive thymectomy and open thymectomy: outcome analysis of 263 patients. *Ann Thorac Surg* 2012;94:974-981.
  - Hess N, Sarkaria I, Pennathur A, et al. Minimally invasive versus open thymectomy: A systematic review of surgical techniques, patient demographics, and perioperative outcomes. *Ann Cardiothorac Surg* 2016; 5:1-9.
  - Rowse P, Roden A, Corl F, et al. Minimally invasive thymectomy: The Mayo Clinic experience. *Ann Cardiothorac Surg* 2015;4:519-526.

#### **THYM-B 3 of 3**

- Reference 5 added: Rimner A, Yao X, Huang J, et al. Postoperative radiation therapy is associated with longer overall survival in completely resected stage II and III thymoma – an analysis of the International Thymic Malignancies Interest Group (ITMIG) retrospective database. *J Thorac Oncol* 2016;11:1785-1792.

#### **THYM-C 3 of 3**

- Reference 16 added: Kirzinger L, Boy S, Marienhagen J, et al. Octreotide LAR and prednisone as neoadjuvant treatment in patients with primary or locally recurrent unresectable thymic tumors: a phase II study. *PLoS One* 2016;11:e0168215.

#### **THYM-D 1 of 2**

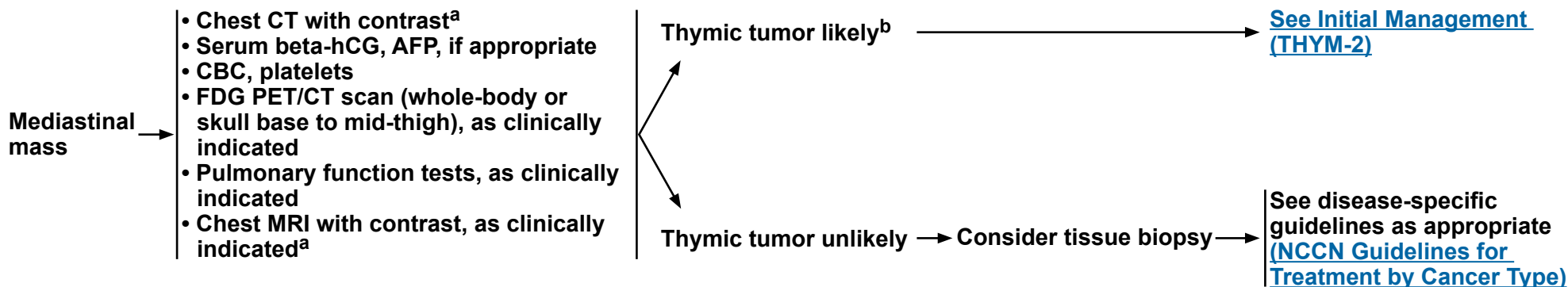
- Footnote a added: Thymoma composed of two or more types are termed “thymoma,” with listing of the components in 10% increments.

#### **ABBR-1**

- New section added: Abbreviations



### INITIAL EVALUATION



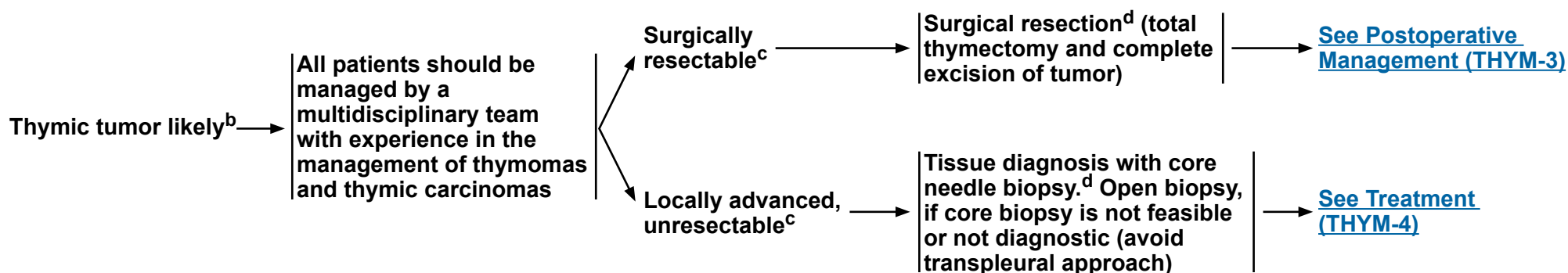
<sup>a</sup> When assessing a mediastinal mass, detection of thymic malignancy versus thymic cyst or thymic hyperplasia can be better discriminated with chest MRI compared to chest CT, potentially avoiding an unnecessary thymectomy.

<sup>b</sup> Well-defined anterior mediastinal mass in the thymic bed, tumor markers negative, absence of other adenopathy, and absence of continuity with the thyroid. Marom EM, et al. J Thorac Oncol 2011;6:S1717-S1723.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



### INITIAL MANAGEMENT



<sup>b</sup> Well-defined anterior mediastinal mass in the thymic bed, tumor markers negative, absence of other adenopathy, and absence of continuity with the thyroid. Marom EM, et al. J Thorac Oncol 2011;6:S1717-S1723.

<sup>c</sup> Determination of resectability should be made by a thoracic surgeon, with primary focus on thoracic oncology and in multidisciplinary consultation with medical oncology as needed. Resectability is defined as complete (R0) resection.

<sup>d</sup> [See Principles of Surgical Resection \(THYM-A\)](#).

**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

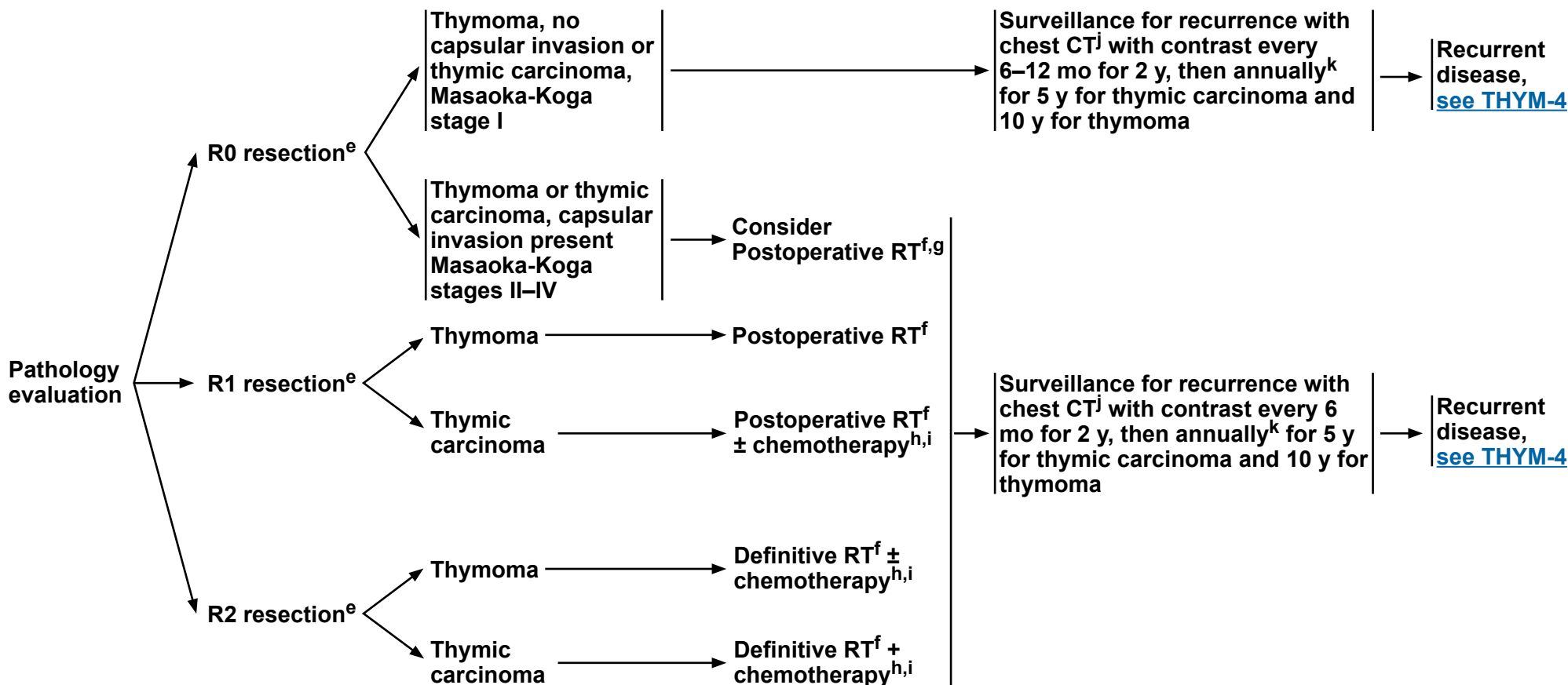


# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

### POSTOPERATIVE TREATMENT

### POSTOPERATIVE MANAGEMENT



<sup>e</sup> R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

<sup>f</sup> See [Principles of Radiation Therapy \(THYM-B\)](#).

<sup>g</sup> Decisions about adjuvant radiation therapy (RT) in this setting should be based on multidisciplinary evaluation.

<sup>h</sup> See [Principles of Systemic Therapy for Thymomas and Thymic Carcinomas \(THYM-C\)](#).

<sup>i</sup> There is a diversity of opinion on treatment approach. Ruffini E, et al. Eur J Cardiothorac Surg 2019;55:601-609.

<sup>j</sup> MRI is an appropriate alternative to CT in certain clinical situations.

<sup>k</sup> The duration for surveillance has not been established.

**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



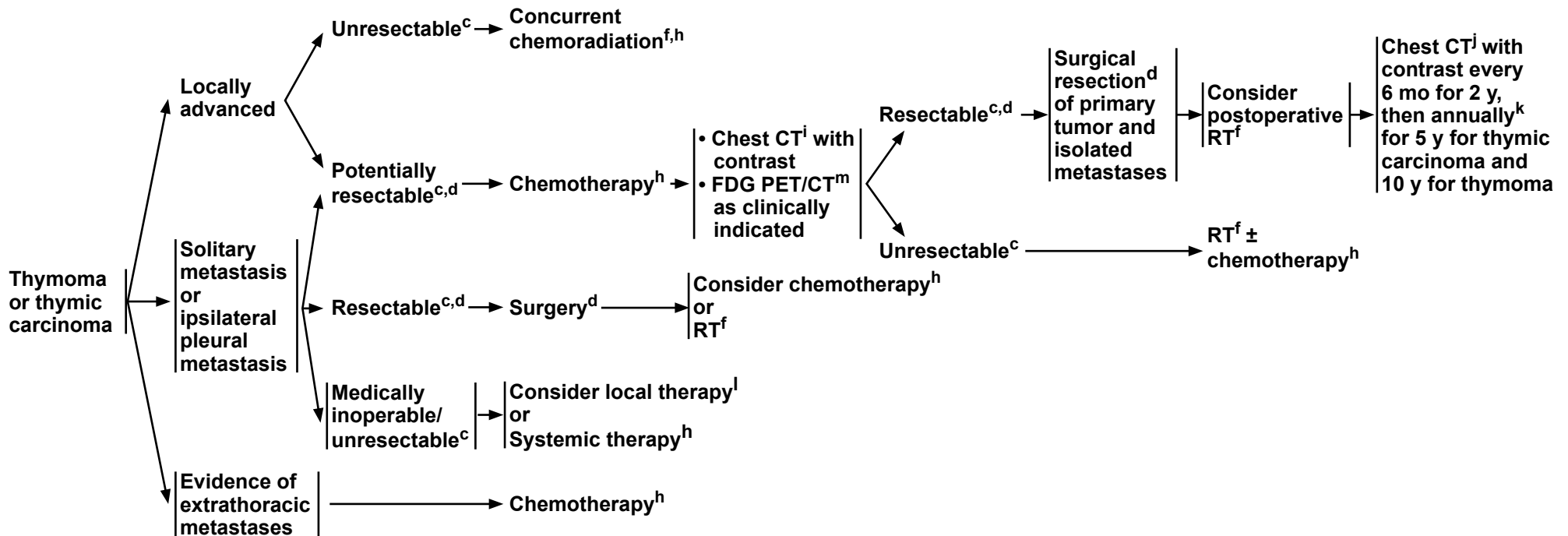
# NCCN Guidelines Version 1.2023 Thymomas and Thymic Carcinomas

**LOCALLY ADVANCED, ADVANCED, OR RECURRENT DISEASE**

**TREATMENT**

**SURVEILLANCE**

**ALL PATIENTS SHOULD BE MANAGED BY A MULTIDISCIPLINARY TEAM WITH EXPERIENCE IN THE MANAGEMENT OF THYMOMAS AND THYMIC CARCINOMAS**



<sup>c</sup> Determination of resectability should be made by a thoracic surgeon, with primary focus on thoracic oncology and in multidisciplinary consultation with medical oncology as needed. Resectability is defined as complete (R0) resection.

<sup>d</sup> See Principles of Surgical Resection (THYM-A).

<sup>f</sup> See Principles of Radiation Therapy (THYM-B).

<sup>h</sup> See Principles of Systemic Therapy for Thymomas and Thymic Carcinomas (THYM-C).

<sup>j</sup> MRI is an appropriate alternative to CT in certain clinical situations.

<sup>k</sup> The duration for surveillance has not been established.

<sup>l</sup> Local therapies can include image-guided thermal ablation or RT.

<sup>m</sup> FDG-PET includes whole-body or skull-base to mid-thigh.

**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



**PRINCIPLES OF SURGICAL RESECTION**

- **Surgical resection should be performed on carefully evaluated patients by thoracic surgeons with experience in managing thymomas and thymic carcinomas. Locally advanced (unresectable) and resectable stage  $\geq$  II cases should be discussed and evaluated by a multidisciplinary team.**
- **Surgical biopsy should be avoided if a resectable thymoma is strongly suspected based on clinical and radiologic features because of the substantial potential of tumor seeding when the tumor capsule is violated.**
- **Biopsy of a possible thymoma should avoid a transpleural approach because of the substantial risk of converting a stage I thymoma to a stage IV thymoma by spreading tumor within the pleural space.**
- **Prior to surgery, patients should be evaluated for signs and symptoms of myasthenia gravis and should be medically controlled prior to undergoing surgical resection.**
- **Goal of surgery is complete excision of the lesion with total thymectomy and complete resection of contiguous and noncontiguous disease.**
- **Complete resection may require the resection of adjacent structures, including the pericardium, phrenic nerve, pleura, lung, and even major vascular structures. Bilateral phrenic nerve resection should be avoided due to severe respiratory morbidity.**
- **Surgical clips should be placed at the time of resection to areas of close margins, residual disease, or tumor adhesion to unresected normal structures to help guide accurate RT when indicated.**
- **During thymectomy, the pleural surfaces should be examined for pleural metastases. If feasible, resection of pleural metastases to achieve complete gross resection is appropriate.**
- **Minimally invasive procedures are not routinely recommended due to the lack of long-term data. However, minimally invasive procedures may be considered for clinical stage I–II if all oncologic goals can be met as in standard procedures, and if performed in specialized centers by surgeons with experience in these techniques.<sup>1-10</sup>**

<sup>1</sup> Pennathur A, Qureshi I, Schubert MJ, et al. Comparison of surgical techniques for early stage thymoma: feasibility of minimally invasive thymectomy and comparison with open resection. *J Thorac Cardiovasc Surg* 2011;141:694-701.

<sup>2</sup> Ye B, Tantai JC, Ge XX, et al. Surgical techniques for early-stage thymoma: video-assisted thorascopic thymectomy versus transsternal thymectomy. *J Thorac Cardiovasc Surg* 2014;147:1599-1603.

<sup>3</sup> Sakamaki Y, Oda T, Kanazawa G, et al. Intermediate-term oncologic outcomes after video-assisted thorascopic thymectomy for early-stage thymoma. *J Thorac Cardiovasc Surg* 2014;148:1230-1237.

<sup>4</sup> Manoly I, Whistance RN, Sreekumar R, et al. Early and mid-term outcomes of trans-sternal and video-assisted thorascopic surgery for thymoma. *Eur J Cardiothorac Surg* 2014;45:e187-193.

<sup>5</sup> Liu TJ, Lin MW, Hsieh MS, et al. Video-assisted thorascopic surgical thymectomy to treat early thymoma: a comparison with the conventional transsternal approach. *Ann Surg Oncol* 2014;322-328.

<sup>6</sup> Friedant AJ, Handorf EA, Su S, Scott WJ. Minimally invasive versus open thymectomy for thymic malignancies: systematic review and meta-analysis. *J Thorac Oncol* 2016;11:30-38.

<sup>7</sup> Burt BM, Yao X, Shrager J, et al. Determinants of complete resection of thymoma by minimally invasive and open thymectomy: Analysis of an International Registry. *J Thorac Oncol* 2017;12:129-136.

<sup>8</sup> Jurado J, Javidfar J, Newmark A, et al. Minimally invasive thymectomy and open thymectomy: outcome analysis of 263 patients. *Ann Thorac Surg* 2012;94:974-981.

<sup>9</sup> Hess N, Sarkaria I, Pennathur A, et al. Minimally invasive versus open thymectomy: A systematic review of surgical techniques, patient demographics, and perioperative outcomes. *Ann Cardiothorac Surg* 2016; 5:1-9.

<sup>10</sup> Rowse P, Roden A, Corl F, et al. Minimally invasive thymectomy: The Mayo Clinic experience. *Ann Cardiothorac Surg* 2015;4:519-526.

**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

**PRINCIPLES OF RADIATION THERAPY<sup>1,2</sup>****General Principles**

- Recommendations regarding RT should be made by radiation oncologists with experience in managing thymomas and thymic carcinomas.
- Definitive RT should be given for patients with unresectable disease (if disease progresses on induction chemotherapy), incompletely resected invasive thymoma or thymic carcinoma, or as adjuvant therapy after chemotherapy and surgery for patients with locally advanced disease.
- Radiation oncologists need to communicate with the surgeon to review the operative findings and to help determine the target volume at risk. They also need to communicate with the pathologist regarding the detailed pathology on histology, disease extent such as extracapsular extension, and surgical margins.
- The review of preoperative imaging and co-registration of preoperative imaging into the planning system are helpful in defining treatment volumes.
- Acronyms and abbreviations for RT are the same as listed in the Principles of Radiation Therapy for the [NCCN Guidelines for Non-Small Cell Lung Cancer](#).

**Radiation Dose**

- The dose and fractionation schemes of RT depend on the indication of the radiation and the completeness of surgical resection in postoperative cases.
- A dose of 60 to 70 Gy should be given to patients with unresectable disease.
- For adjuvant treatment, the radiation dose consists of 45 to 50 Gy for clear/close margins and 54 Gy for microscopically positive resection margins. A total dose of 60–70 Gy should be given to patients with gross residual disease (similar to patients with unresectable disease),<sup>3,4,5</sup> when conventional fractionation (1.8–2.0 Gy per daily fraction) is applied.
- Depending on the treatment objectives in the palliative setting, typical palliative doses (eg, 8 Gy in a single fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions) up to definitive doses for more durable local control and highly conformal techniques for limited volume metastases may be appropriate, given the relatively long natural history of even metastatic thymoma.

**Radiation Volume**

- The gross tumor volume should include any grossly visible tumor. Surgical clips indicative of gross residual tumor should be included for postoperative adjuvant RT.
- The clinical target volume (CTV) for postoperative RT should encompass the entire thymus (for partial resection cases), surgical clips, and any potential sites with residual disease. The CTV should be reviewed with the thoracic surgeon.
- Extensive elective nodal irradiation (ENI) (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended, as thymomas do not commonly metastasize to regional lymph nodes.<sup>6</sup>
- The planning target volume (PTV) should consider the target motion and daily setup error. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of daily setup of each clinic.

[Radiation Techniques \(THYM-B 2 of 3\)](#)[References \(THYM-B 3 of 3\)](#)**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



### PRINCIPLES OF RADIATION THERAPY

#### Radiation Techniques

- Target motion should be managed using the Principles of Radiation Therapy in the [NCCN Guidelines for Non-Small Cell Lung Cancer](#). Intravenous contrast is beneficial in the unresectable setting.
- In addition to following the normal tissue constraints recommendation using the Principles of Radiation Therapy in the [NCCN Guidelines for Non-Small Cell Lung Cancer](#), more conservative limits are recommended to minimize the dose volumes to all the normal structures. Since these patients are younger and mostly long-term survivors, the mean total dose to the heart should be as low as reasonably achievable to potentially maximize survival.
- A minimum technological standard for RT is CT-planned 3-D conformal RT (3D-CRT). More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), image-guided RT (IGRT), motion management, and proton therapy. In particular, IMRT is preferred over 3D-CRT. Compared to IMRT, proton therapy has been shown to improve dosimetry, thus allowing for better sparing of normal organs (lungs, heart, and esophagus)<sup>7</sup> with favorable local control and toxicity, and is appropriate.<sup>8</sup>

[General Principles, Radiation Dose, and Radiation Volume \(THYM-B 1 of 3\)](#)

[References \(THYM-B 3 of 3\)](#)

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



### PRINCIPLES OF RADIATION THERAPY — REFERENCES

- <sup>1</sup> Gomez D, Komaki R, Yu J, et al. Radiation therapy definitions and reporting guidelines for thymic malignancies. *J Thorac Oncol* 2011;6:S1743-1748.
- <sup>2</sup> Gomez D, Komaki R. Technical advances of radiation therapy for thymic malignancies. *J Thorac Oncol* 2010;5:S336-343.
- <sup>3</sup> Mornex F, Resbeut M, Richaud P, et al. Radiotherapy and chemotherapy for invasive thymomas: a multicentric retrospective review of 90 cases. The FNCLCC trialists. Federation Nationale des Centres de Lutte Contre le Cancer. *Int J Radiat Oncol Biol Phys* 1995;32:651-659.
- <sup>4</sup> Myojin M, Choi NC, Wright CD, et al. Stage III thymoma: pattern of failure after surgery and postoperative radiotherapy and its implication for future study. *Int J Radiat Oncol Biol Phys* 2000;46:927-933.
- <sup>5</sup> Rimner A, Yao X, Huang J, et al. Postoperative radiation therapy is associated with longer overall survival in completely resected stage II and III thymoma – an analysis of the International Thymic Malignancies Interest Group (ITMIG) retrospective database. *J Thorac Oncol* 2016;11:1785-1792.
- <sup>6</sup> Ruffini E, Mancuso M, Oliaro A, et al. Recurrence of thymoma: analysis of clinicopathologic features, treatment, and outcome. *J Thorac Cardiovasc Surg* 1997;113:55-63.
- <sup>7</sup> Parikh RR, Rhome R, Hug E, et al. Adjuvant proton beam therapy in the management of thymoma: a dosimetric comparison and acute toxicities. *Clin Lung Cancer* 2016;17:362-366.
- <sup>8</sup> Vogel J, Berman AT, Pechet TT, et al. Prospective study of proton beam radiation therapy for adjuvant and definitive treatment of thymoma and thymic carcinoma: early response and toxicity assessment. *Radiother Oncol* 2016;118:504-509.

**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



### PRINCIPLES OF SYSTEMIC THERAPY

#### FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS<sup>a</sup>

##### THYMOMA

###### Preferred (Other Recommended for Thymic Carcinoma)

- CAP<sup>1</sup>  
Cisplatin 50 mg/m<sup>2</sup> IV day 1  
Doxorubicin 50 mg/m<sup>2</sup> IV day 1  
Cyclophosphamide 500 mg/m<sup>2</sup> IV day 1  
Administered every 3 weeks

###### Other Recommended for Thymic Carcinoma and Thymoma

- CAP with prednisone<sup>2</sup>  
Cyclophosphamide 500 mg/m<sup>2</sup> IV on day 1;  
Doxorubicin, 20 mg/m<sup>2</sup>/day IV continuous infusion on days 1–3;  
Cisplatin 30 mg/m<sup>2</sup> days 1–3;  
Prednisone 100 mg/day days 1–5;  
Administered every 3 weeks
- ADOC<sup>3</sup>  
Doxorubicin 40 mg/m<sup>2</sup> IV day 1;  
Cisplatin 50 mg/m<sup>2</sup> IV day 1;  
Vincristine 0.6 mg/m<sup>2</sup> IV day 3;  
Cyclophosphamide 700 mg/m<sup>2</sup> IV day 4  
Administered every 3 weeks
- PE<sup>4</sup>  
Cisplatin 60 mg/m<sup>2</sup> IV day 1; Etoposide 120 mg/m<sup>2</sup>/day IV days 1–3;  
Administered every 3 weeks
- Etoposide/ifosfamide/cisplatin<sup>5</sup>  
Etoposide 75 mg/m<sup>2</sup> on days 1–4; Ifosfamide 1.2 g/m<sup>2</sup> on days 1–4; Cisplatin 20 mg/m<sup>2</sup> on days 1–4  
Administered every 3 weeks

##### THYMIC CARCINOMA

###### Preferred (Other Recommended for Thymoma)

- Carboplatin/paclitaxel<sup>6,7</sup>  
Carboplatin AUC 6  
Paclitaxel 200 mg/m<sup>2</sup>  
Administered every 3 weeks

[Subsequent Therapy \(THYM-2 of 3\)](#)

[References \(THYM-C 3 of 3\)](#)

<sup>a</sup> If patients cannot tolerate first-line combination regimens, consider second-line systemic therapy options.

Note: All recommendations are category 2A unless otherwise indicated.  
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



### PRINCIPLES OF SYSTEMIC THERAPY

#### SECOND-LINE SYSTEMIC THERAPY (in alphabetical order)

##### THYMOMA

###### Other Recommended

- Etoposide<sup>4,8,9</sup>
- Everolimus<sup>10</sup>
- 5-FU and leucovorin<sup>11</sup>
- Gemcitabine ± capecitabine<sup>12,13</sup>
- Ifosfamide<sup>14</sup>
- Octreotide<sup>b</sup> (including LAR) +/- prednisone<sup>15,16</sup>
- Paclitaxel<sup>17</sup>
- Pemetrexed<sup>18</sup>

##### THYMIC CARCINOMA

###### Other Recommended

- Everolimus<sup>10</sup>
- 5-FU and leucovorin<sup>11</sup>
- Gemcitabine ± capecitabine<sup>12,13</sup>
- Lenvatinib<sup>c,19</sup>
- Paclitaxel<sup>17</sup>
- Pembrolizumab<sup>d,20,21</sup>
- Pemetrexed<sup>18</sup>
- Sunitinib<sup>22</sup>

###### Useful in Certain Circumstances

- Etoposide<sup>4,8,9</sup>
- Ifosfamide<sup>14</sup>

<sup>b</sup> Nuclear medicine scan to assess for octreotide-avid disease.

<sup>c</sup> There is a high risk for side effects and frequent dose reductions may be needed.

<sup>d</sup> Pembrolizumab is not recommended for patients with thymoma. In patients with thymic carcinoma, there is concern for a higher rate of immune-related adverse events than seen in most other malignancies treated with PD-1/PD-L1 inhibitor therapy. For example, grade 3–4 myocarditis has been reported in 5%–9% of patients receiving pembrolizumab.

#### [References THYM-C \(3 of 3\)](#)

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**PRINCIPLES OF SYSTEMIC THERAPY FOR THYMIC MALIGNANCIES — REFERENCES**

- 1 Loehrer PJ Sr, Kim K, Aisner SC, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. *J Clin Oncol* 1994;12:1164-1168.
- 2 Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. *Lung Cancer* 2004;44:369-379.
- 3 Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy for invasive thymoma. A 13-year experience. *Cancer* 1991;68:30-33.
- 4 Giaccone G, Ardizzoni A, Kirkpatrick A, et al. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol* 1996;14:814-820.
- 5 Loehrer PJ Sr, Jiroutek M, Aisner S, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. *Cancer* 2001;91:2010-2015.
- 6 Lemma GL, Lee JW, Aisner SC, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. *J Clin Oncol* 2011;29:2060-2065.
- 7 Hirai F, Yamanaka T, Taguchi K, et al. A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L. *Ann Oncol* 2015;26:363-368.
- 8 Bluthgen MV, Boutros C, Fayard F, et al. Activity and safety of oral etoposide in pretreated patients with metastatic or recurrent thymic epithelial tumors (TET): A single-institution experience. *Lung Cancer* 2016;99:111-116.
- 9 Johnson DH, Greco FA, Strupp J, et al. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. *J Clin Oncol* 1990;8:1613-1617.
- 10 Zucali PA, De Pas TM, Palmieri G, et al. Phase II study of everolimus in patients with thymoma and thymic carcinoma previously treated with cisplatin-based chemotherapy. *J Clin Oncol* 2018;36:342-349.
- 11 Thomas CR, Wright CD, Loehrer PJ. Thymoma: state of the art. *J Clin Oncol* 1999;17:2280-2289.
- 12 Palmieri G, Merola G, Federico P, et al. Preliminary results of phase II study of capecitabine and gemcitabine (CAP-GEM) in patients with metastatic pretreated thymic epithelial tumors (TETs). *Ann Oncol* 2010;21:1168-1172.
- 13 Palmieri G, Buonerba C, Ottaviano M, et al. Capecitabine plus gemcitabine in thymic epithelial tumors: final analysis of a phase II trial. *Future Oncol* 2014;10:2141-2147.
- 14 Highley MS, Underhill CR, Parnis FX, et al. Treatment of invasive thymoma with single-agent ifosfamide. *J Clin Oncol* 1999;17:2737-2744.
- 15 Loehrer PJ Sr, Wang W, Johnson DH, et al. Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: an Eastern Cooperative Oncology Group Phase II Trial. *J Clin Oncol* 2004;22:293-299.
- 16 Kirzinger L, Boy S, Marienhagen J, et al. Octreotide LAR and prednisone as neoadjuvant treatment in patients with primary or locally recurrent unresectable thymic tumors: a phase II study. *PLoS One* 2016;11:e0168215.
- 17 Umemura S, Segawa Y, Fujiwara K, et al. A case of recurrent metastatic thymoma showing a marked response to paclitaxel monotherapy. *Jpn J Clin Oncol* 2002;32:262-265.
- 18 Gbolahan OB, Porter RF, Salter JT, et al. A phase II study of pemetrexed in patients with recurrent thymoma and thymic carcinoma. *J Thorac Oncol* 2018;13:1940-1948.
- 19 Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. *Lancet Oncol* 2020;21:843-850.
- 20 Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. *Lancet Oncol* 2018;19:347-355.
- 21 Cho J, Kim HS, Ku BM, et al. Pembrolizumab for patients with refractory or relapsed thymic epithelial tumor: An open-label phase II trial. *J Clin Oncol* 2019;37:2162-2170.
- 22 Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. *Lancet Oncol* 2015;16:177-186.

**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**





# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

### WORLD HEALTH ORGANIZATION HISTOLOGIC CLASSIFICATION<sup>1</sup>

Thymoma subtype <sup>a</sup>	Obligatory criteria	Optional criteria
Type A	Occurrence of bland, spindle shaped epithelial cells (at least focally); paucity <sup>b</sup> or absence of immature (TdT+) 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 <sup>2</sup> ); nuclear crowding	Polygonal epithelial cells CD20+ epithelial cells
Type AB	Occurrence of bland, spindle shaped epithelial cells (at least focally); abundance <sup>b</sup> of immature (TdT+) T cells focally or throughout tumor	Polygonal epithelial cells CD20+ epithelial cells
Type B1	Thymus-like architecture and cytology: abundance of immature T cells, areas of medullary differentiation (medullary islands); paucity of polygonal or dendritic epithelia 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 immature T cells	Medullary islands; Hassall's corpuscles; perivascular spaces
Type B3	Sheets of polygonal slightly to moderately atypical epithelial cells; absent or rare intercellular bridges; paucity or absence of intermingled TdT+ T cells	Hassall's corpuscles; perivascular spaces
MNT <sup>c</sup>	Nodules of 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	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 <sup>d</sup>		

<sup>a</sup> Thymoma composed of two or more types are termed "thymoma," with listing of the components in 10% increments.

<sup>b</sup> Paucity versus abundance: any area of crowded immature T cells or moderate numbers of immature T cells in >10% of the investigated tumor are indicative of "abundance."

<sup>c</sup> MNT, micronodular thymoma with lymphoid stroma.

<sup>d</sup> Microscopic thymoma; sclerosing thymoma, lipofibroadenoma.

<sup>1</sup> Marx A, Detterback F, Marom EM, et al. Tumours of the thymus. In: WHO Classification of Tumours Editorial Board. Thoracic tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2021 [2021 9 12]. (WHO classification of tumours series, 5th ed.; vol. 5). Available from: <https://tumourclassification.iarc.who.int/chapters/35>.

**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**





### WORLD HEALTH ORGANIZATION HISTOLOGIC CLASSIFICATION<sup>1</sup>

#### **Thymic Carcinoma Subtypes**

- **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
- ▶ Adenocarcinoma, enteric-type

- **Adenosquamous carcinoma**

- **NUT carcinomas**

- **Salivary gland-like carcinomas**

- ▶ Mucoepidermoid carcinoma
- ▶ Clear cell carcinoma
- ▶ Sarcomatoid carcinoma
- ▶ Carcinosarcoma

- **Carcinoma, undifferentiated, NOS**

- **Thymic Carcinoma, NOS**

<sup>1</sup> Marx A, Detterback F, Marom EM, et al. Tumours of the thymus. In: WHO Classification of Tumours Editorial Board. Thoracic tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2021 [2021 9 12]. (WHO classification of tumours series, 5th ed.; vol. 5). Available from: <https://tumourclassification.iarc.who.int/chapters/35>.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



## Staging

**Table 1. Modified Masaoka clinical staging of thymoma<sup>1-3</sup>**

<b><u>Masaoka Stage</u></b>	<b><u>Diagnostic Criteria</u></b>
<b>Stage I</b>	<b>Macroscopically and microscopically completely encapsulated</b>
<b>Stage II</b>	<b>(A) Microscopic transcapsular invasion</b> <b>(B) Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium</b>
<b>Stage III</b>	<b>Macroscopic invasion into neighboring organs (ie, pericardium, great vessels, lung)</b> <b>(A) Without invasion of great vessels</b> <b>(B) With invasion of great vessels</b>
<b>Stage IV</b>	<b>(A) Pleural or pericardial dissemination</b> <b>(B) Lymphogenous or hematogenous metastasis</b>

<sup>1</sup> Reprinted from Wright CD. Management of thymomas. Crit Rev Oncol Hematol 2008;65:109-120, with permission from Elsevier.

<sup>2</sup> Note that the Masaoka staging system is also used to stage thymic carcinomas.

<sup>3</sup> Dettnerbeck FC, Nicholson AG, Kondo K, et al. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. J Thorac Oncol 2011;6:S1710-S1716.



## Staging

**Table 2. Definitions for TNM<sup>\*,\*\*</sup>****Primary Tumor (T)**

<b>TX</b>	Primary tumor cannot be assessed
<b>T0</b>	No evidence of primary tumor
<b>T1</b>	Tumor encapsulated or extending into the mediastinal fat; may involve the mediastinal pleura
T1a	Tumor with no mediastinal pleura involvement
T1b	Tumor with direct invasion of mediastinal pleura
<b>T2</b>	Tumor with direct invasion of the pericardium (either partial or full thickness)
<b>T3</b>	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
<b>T4</b>	Tumor with invasion into any of the following: aorta (ascending, arch, or descending) arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus

**Regional Lymph Nodes (N)**

<b>NX</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No regional lymph node metastasis
<b>N1</b>	Metastasis in anterior (perithymic) lymph nodes
<b>N2</b>	Metastasis in deep intrathoracic or cervical lymph nodes

**Distant Metastasis (M)**

<b>M0</b>	No pleural, pericardial, or distant metastasis
<b>M1</b>	Pleural, pericardial, or distant metastasis
M1a	Separate pleural or pericardial nodule(s)
M1b	Pulmonary intraparenchymal nodule or distant organ metastasis

\*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.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

**AJCC Prognostic Groups**

<b>Stage I</b>	T1a,b	N0	M0
<b>Stage II</b>	T2	N0	M0
<b>Stage IIIA</b>	T3	N0	M0
<b>Stage IIIB</b>	T4	N0	M0
<b>Stage IVA</b>	Any T	N1	M0
	Any T	N0-N1	M1a
<b>Stage IVB</b>	Any T	N2	M0-M1a
	Any T	Any N	M1b



### ABBREVIATIONS

<b>AFP</b>	<b>alpha-fetoprotein</b>
<b>beta-hCG</b>	<b>beta-human chorionic gonadotropin</b>
<b>CBC</b>	<b>complete blood count</b>
<b>NOS</b>	<b>not otherwise specified</b>
<b>NUT</b>	<b>nuclear protein in testis</b>
<b>RT</b>	<b>radiation therapy</b>



### NCCN Categories of Evidence and Consensus

<b>Category 1</b>	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
<b>Category 2A</b>	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
<b>Category 2B</b>	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
<b>Category 3</b>	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

### NCCN Categories of Preference

<b>Preferred intervention</b>	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
<b>Other recommended intervention</b>	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
<b>Useful in certain circumstances</b>	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



# NCCN Guidelines Version 1.2023 Thymomas and Thymic Carcinomas

## Discussion

This discussion corresponds to the NCCN Guidelines for Thymomas and Thymic Carcinomas. Last updated: May 3, 2022

## Table of Contents

Overview .....	MS-2
Literature Search Criteria and Guidelines Update Methodology.....	MS-2
Mediastinal Masses .....	MS-3
Thymic Masses .....	MS-4
Diagnosis .....	MS-4
Staging.....	MS-4
Treatment.....	MS-4
Thymomas .....	MS-5
Thymic Carcinomas.....	MS-8
Summary.....	MS-9
References.....	MS-11

Discussion  
update in  
progress



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

### Overview

Thymic epithelial tumors originate in the thymus and include thymomas and thymic carcinomas.<sup>1,2</sup> Thymomas are a common primary tumor in the anterior mediastinum, although they are rare (1.5 cases/million).<sup>3-6</sup> Thymic carcinomas are very rare. Although thymomas can spread locally, they are much less invasive than thymic carcinomas.<sup>4</sup> Patients with thymic carcinomas often present with metastases.<sup>7</sup> Patients with thymomas have 5-year survival rates of approximately 90%.<sup>8-10</sup> However, 5-year survival rates for thymic carcinomas are approximately 55%.<sup>11-13</sup>

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) focus on thymomas and thymic carcinomas and outline the evaluation, treatment, and management of these mediastinal tumors; these NCCN Guidelines® were first published in 2007 and have been subsequently updated every year. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2022, which are described in greater detail in this revised Discussion text; new references have been added. For example, panel members removed octreotide (including LAR [long-acting release]) with or without prednisone as a second-line therapy option for patients with thymic carcinoma. Additional supplementary material in the NCCN Guidelines for Thymomas and Thymic Carcinomas includes the *Principles of Surgical Resection*, *Principles of Radiation Therapy*, *Principles of Systemic Therapy for Thymic Malignancies*, and the *World Health Organization Histologic Classification*. These NCCN Guidelines for Thymomas and Thymic Carcinomas were developed and are updated by panel members who are also on the NCCN Guidelines for Non-Small Cell Lung Cancer Panel.

The NCCN Guidelines provide specific category designations for all treatment interventions in the guidelines, which are based on evidence from the biomedical literature and consensus among the panel members.

Category 1 recommendations indicate uniform NCCN consensus (at least 85% of the NCCN Member Institutions on the panel) that the intervention is appropriate based on high-level evidence, such as randomized phase 3 trials. Category 2A recommendations indicate uniform NCCN consensus that the intervention is appropriate based on lower level evidence, such as phase 2 trials. It is important to note that all recommendations are category 2A in the NCCN Guidelines unless otherwise indicated. Category 2B recommendations indicate NCCN consensus (50% to <85% of the NCCN Member Institutions on the panel) that the intervention is appropriate based on lower level evidence. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments.

All the systemic therapy regimens have been categorized by preference—based on the biomedical literature and experience of the panel members—using the following categories: 1) preferred interventions; 2) other recommended interventions; and 3) interventions that are useful in certain circumstances. These preference categories emphasize the preferred regimens in clinical practice and do not replace the NCCN categories of evidence and consensus, such as category 1 or category 2A. The preference categories and the categories of evidence/consensus are two separate systems.

### Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Thymomas and Thymic Carcinomas, an electronic search of the PubMed database was performed to obtain key literature in thymomas and thymic carcinomas published since the previous Guidelines update, using the following search terms: thymomas; thymic carcinomas. The PubMed





# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at [www.NCCN.org](http://www.NCCN.org).

### Mediastinal Masses

Masses in the anterior mediastinum can be neoplasms (eg, thymomas, lymphomas, thymic carcinomas, thymic carcinoids, thymolipomas, germ cell tumors, lung metastases) or non-neoplastic conditions (eg, intrathoracic goiter, thymic cysts, lymphangiomas, aortic aneurysms).<sup>5,14-17</sup> Many mediastinal masses are benign, especially those occurring in patients who are asymptomatic; however, patients who are symptomatic often have malignant mediastinal lesions. All patients with a mediastinal mass should be evaluated to determine the type of mass and the extent of disease before treatment (see *Initial Evaluation* in the algorithm). It is essential to differentiate between thymic malignancies and other conditions (eg, lung metastases, lymphoma, goiter, germ cell tumors) before treatment, because management differs for these conditions.<sup>2,18,19</sup> Most masses in the mediastinum are metastases from a primary lung

cancer (eg, non-small cell lung cancer). However, approximately 50% of primary cancers in the anterior mediastinum are thymomas.<sup>20</sup>

Patients with thymomas often have an indolent presentation, whereas those with lymphoma or germ cell tumors have a rapid onset of symptoms.<sup>19</sup> Lymphomas typically manifest as generalized disease but can also be primary anterior mediastinal lesions (ie, nodular sclerosing Hodgkin's disease, non-Hodgkin's lymphomas [diffuse large B-cell lymphoma and acute lymphoblastic lymphoma]); patients typically have lymphadenopathy (see the NCCN Guidelines for Hodgkin Lymphoma and the NCCN Guidelines for B-Cell Lymphomas, available at [www.NCCN.org](http://www.NCCN.org)).<sup>17,21</sup> Thymic carcinoids are rare neuroendocrine tumors that can be associated with multiple endocrine neoplasia type 1 (MEN1) syndrome (see the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, available at [www.NCCN.org](http://www.NCCN.org)).<sup>22,23</sup> Extragenital germ cell tumors are rare tumors that may also occur in the mediastinum.<sup>24,25</sup>

Low-dose CT is recommended for detecting lung cancer in individuals at high risk (see the NCCN Guidelines for Lung Cancer Screening, available at [www.NCCN.org](http://www.NCCN.org)).<sup>26</sup> There are no data to suggest that screening with low-dose CT improves survival for patients with thymomas and thymic carcinomas; therefore, low-dose CT screening is not recommended for detecting thymomas and thymic carcinomas.<sup>26</sup> However, mediastinal masses (eg, lung metastases, thymomas, thymic carcinomas) may be detected in individuals undergoing chest imaging.

Recommended tests for assessing mediastinal masses include chest CT with contrast and blood chemistry studies (see *Initial Evaluation* in the algorithm).<sup>15,27-35</sup> On CT, a thymoma is usually a well-defined round or oval mass in the thymus without lymph node enlargement.<sup>33,36,37</sup> When assessing a mediastinal mass, detection of thymic malignancy versus thymic cyst or thymic hyperplasia can be better discriminated with chest MRI compared to chest CT, potentially avoiding an unnecessary





# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

thymectomy.<sup>38</sup> In patients who cannot tolerate iodinated contrast, chest MRI is indicated.<sup>33</sup> Combined FDG PET/CT may be useful for determining whether extrathoracic metastases are present.<sup>39,40</sup> FDG PET/CT provides better correlation with anatomic structures than PET alone. FDG PET/CT scans are whole body or skull base to mid-thigh, as clinically indicated. Alpha-fetoprotein (AFP) levels and beta-human chorionic gonadotropin (beta-hCG) levels may be measured to rule out germ cell tumors (see *Initial Evaluation* in the algorithm). Thymic epithelial tumors are likely if the following are present: 1) a well-defined mediastinal mass in the thymic bed that is not continuous with the thyroid gland; 2) tumor markers for AFP or beta-hCG are negative; and 3) no other adenopathy is present.<sup>2</sup>

### Thymic Masses

#### Diagnosis

The World Health Organization (WHO) histologic classification system can be used to distinguish between thymomas, thymic carcinomas, and thymic carcinoids (see the algorithm).<sup>1,2</sup> The WHO classification is also used to differentiate among different histologic types of thymomas (ie, A, AB, B1, B2, B3); however, it is difficult to classify thymomas.<sup>41</sup> The WHO histologic classification system was revised in 2021.<sup>1,2</sup> Thymic carcinomas are categorized by larger subtype groups such as squamous carcinomas, adenocarcinomas, adenosquamous carcinoma, and carcinomas not otherwise specified (NOS).<sup>1,2</sup> However, the histologic subtype is less important for management than stage of disease and the extent of resection (ie, R0, R1, R2) (see *Postoperative Treatment and Management* in the algorithm).<sup>12,42-46</sup> For stage III–IV thymomas, 5-year survival rates have been reported to be 90% in patients with total resection.<sup>8,12</sup> For thymic carcinomas, 5-year survival rates are lower, even in those with total resection.<sup>11,47</sup>

#### Staging

Although several staging systems exist, the Masaoka-Koga staging system has been the most widely accepted system for management and determination of prognosis for both thymomas and thymic carcinomas (see Table 1 in the algorithm).<sup>10,12,48-54</sup> Another staging system for thymomas and thymic carcinomas is based on a combined effort by the International Thymic Malignancy Interest Group (ITMIG) and International Association for the Study of Lung Cancer (IASLC); this staging system was used as the basis for the AJCC TNM system for thymic malignancies (8<sup>th</sup> edition).<sup>55-62</sup> The AJCC staging system for thymic malignancies (8<sup>th</sup> edition) is also provided in the algorithm (see Table 2 in the algorithm).<sup>56</sup> Patients with stage I–III thymomas have a 5-year survival rate of approximately 85% versus 65% for those with stage IV disease.<sup>10,63,64</sup> In approximately 50% of patients, mortality is not related to thymoma.<sup>49</sup> Mortality is related to myasthenia gravis in approximately 20% of patients.

#### Treatment

The optimal plan of care for patients with thymic malignancies should be developed before treatment, after evaluation by radiation oncologists, thoracic surgeons, medical oncologists, and diagnostic imaging specialists.<sup>65,66</sup> It is critical to determine whether the mass can be surgically resected; a board-certified thoracic surgeon with a primary focus on thoracic oncology should make this decision. Total thymectomy and complete surgical excision of the tumor are recommended whenever possible for most resectable tumors (see *Principles of Surgical Resection* in the algorithm).<sup>10,12,19,67-69</sup> During thymectomy, the pleural surfaces should be examined for metastases. To achieve a complete gross resection, removal of pleural metastases may be appropriate in some patients.<sup>70-72</sup> Core needle biopsy is recommended for locally advanced, unresectable thymic masses. Open biopsy may be considered if core biopsy is not feasible nor diagnostic and transpleural approach should be



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

avoided. The cancer protocol for thymic tumors from the College of American Pathologists may be useful for assessing specimens.<sup>73</sup>

Minimally invasive procedures are not routinely recommended, because only a few long-term studies are available regarding recurrence and survival.<sup>74-76</sup> However, minimally invasive procedures may be considered if recommended oncologic goals can be met (as previously described) and if performed in specialized centers with surgeons with expertise in these techniques.<sup>76-80</sup> A systematic review of 1061 patients with thymomas reported that 5-year overall survival after video-assisted thoracoscopic surgery (VATS: 83%–100% vs. open: 79%–98%) and 10-year recurrence-free survival (VATS: 89%–100% vs. open: 80%–93%) were similar in patients undergoing VATS compared to open thymectomy, although outcomes may be skewed due to selection bias.<sup>74</sup> A retrospective review in 2835 patients assessed VATS thymectomy compared with sternotomy in patients with thymomas.<sup>81</sup> The 5-year overall survival rate was 97.9% in the VATS group. The overall survival rates were not significantly different when comparing the VATs group versus the sternotomy group ( $P = .74$ ). A meta-analysis also showed that VATS was safe and patients had similar overall survival when compared with those receiving open thymectomy.<sup>82</sup>

### Thymomas

Thymomas typically occur in adults aged 40 to 70 years; they are rare in children and adolescents.<sup>19,83</sup> The etiology of thymomas is unknown; alcohol, tobacco smoking, and ionizing radiation do not appear to be risk factors for thymomas.<sup>3</sup> The incidence of thymomas is higher in African Americans as well as Asians and Pacific Islanders, which suggests there may be a genetic component.<sup>3,84</sup> Although some patients are asymptomatic, others present with chest pain, cough, or dyspnea. Patients with thymomas often have autoimmune diseases. Approximately 30% to 50% of patients with thymomas have myasthenia gravis.<sup>85</sup> Symptoms

suggestive of myasthenia gravis include drooping eyelids, double vision, drooling, difficulty climbing stairs, hoarseness, and/or dyspnea. If patients have myasthenia gravis, they should receive treatment by a neurologist with experience in myasthenia gravis before undergoing surgical resection.<sup>86-89</sup>

Although thymomas can be locally invasive (eg, pleura, lung), they uncommonly spread to regional lymph nodes or extrathoracic sites.<sup>10,63,90,91</sup> Surgery (ie, total thymectomy and complete excision of tumor) is recommended for all resectable thymomas for patients who can tolerate the surgery.<sup>20,92,93</sup> For resected stage I and II thymomas, the 10-year survival rate is excellent (approximately 90% and 70%, respectively).<sup>19,94</sup> Completeness of resection is the most important predictor of outcome.<sup>8</sup> Surgical biopsy is not necessary if a resectable thymoma is strongly suspected based on clinical and radiologic features (eg, patients have myasthenia gravis and a characteristic mass on CT) because of the potential of tumor seeding when the tumor capsule is violated.<sup>19</sup> A transpleural approach should be avoided during biopsy of a possible thymoma for similar reasons.<sup>87,95</sup> Small biopsy sampling (fine-needle or core needle biopsy) does not always indicate whether invasion is present.<sup>96</sup> ITMIG and the College of American Pathologists have established procedures for reporting the surgical and pathologic findings from resection specimens.<sup>73,97</sup>

Adjuvant therapy is not recommended for completely resected (R0) stage I thymomas.<sup>68,98,99</sup> For incompletely resected thymomas, postoperative radiation therapy (RT) is recommended (see *Postoperative Treatment and Management* in the algorithm).<sup>65,68,100-102</sup> Note that extensive elective nodal radiation is not recommended, because thymomas do not typically metastasize to regional lymph nodes.<sup>10,103</sup>

Use of intensity-modulated RT (IMRT) may decrease the dose to the normal tissues.<sup>104,105</sup> If IMRT is used, guidelines from the NCI Advanced



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

Technology Center (ATC) and American Society for Radiation Oncology/American College of Radiology (ASTRO/ACR) should be followed.<sup>106-110</sup> The ICRU-83 (International Commission on Radiation Units and Measurements Report 83) recommendations are also a useful resource.<sup>109,111</sup> Although the normal tissue constraints recommendations for non-small cell lung cancer may be used (see the *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer, available at [www.NCCN.org](http://www.NCCN.org)), more conservative limits are recommended to minimize the dose volumes to all the normal structures.<sup>112-114</sup> Because these patients are younger and usually long-term survivors, the mean dose to the heart should be as low as reasonably achievable to potentially maximize survival.

A minimum technological standard for RT is CT-planned 3-D conformal radiation therapy (3D-CRT). More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/volumetric modulated arc therapy (VMAT), IGRT, motion management, and proton therapy. In particular, IMRT is preferred over 3D-CRT. Compared to IMRT, proton therapy has been shown to improve the dosimetry allowing better sparing of the normal tissues with favorable local control and toxicity, and is appropriate.<sup>115-117</sup>

A definitive dose of 60 to 70 Gy is recommended for patients with unresectable disease. For adjuvant treatment, a dose of 45 to 50 Gy is recommended for clear or close margins; a dose of 54 Gy is recommended for microscopically positive resection margins (see *Principles of Radiation Therapy* in the algorithm).<sup>104,105,118</sup> However, a total dose of 60 to 70 Gy (1.8–2 Gy/fraction per day) is recommended for patients with gross residual disease after surgery.<sup>119,120</sup> In patients with thymomas who have capsular invasion after an R0 resection, postoperative RT can be considered (see *Postoperative Treatment and*

*Management* in the algorithm).<sup>99,104,121-123</sup> Patients with stage III (with macroscopic invasion into neighboring organs) thymoma have higher risks of recurrent disease and, as such, postoperative radiation is recommended.<sup>124-127</sup> Data suggest that patients with stage II thymoma may not benefit from postoperative radiation.<sup>68,98,99,122,128</sup> Postoperative chemotherapy is also not beneficial in this setting.<sup>129,130</sup>

Induction therapy followed by surgery may be useful for potentially resectable thymic malignancies.<sup>47,131-136</sup> A recent cohort study reported that 5-year overall survival was similar for those receiving induction chemotherapy followed by surgery versus surgery alone (77.4% vs. 76.7%;  $P = .596$ ).<sup>131</sup> For locally advanced thymomas, induction chemotherapy is recommended followed by an evaluation for surgery; postoperative RT can be considered after surgical resection of the primary tumor and isolated metastases (see *Postoperative Treatment and Management* in the algorithm).<sup>136,137</sup> For those with solitary metastasis or ipsilateral pleural metastases, options include: 1) induction chemotherapy followed by surgery for resectable patients, or 2) surgery alone.<sup>131,132</sup> After induction chemotherapy, imaging is recommended (eg, chest CT, MRI, PET/CT) as clinically indicated to determine whether resection is feasible. For patients with unresectable disease in both of these settings, RT with [or without] chemotherapy is recommended. It is difficult to specify RT dosing regimens for metastatic disease given the broad range of metastatic scenarios that are possible. Stereotactic body radiation therapy (SBRT) may be appropriate for limited focal metastases, whereas conventional fractionation is appropriate for larger metastases. In the palliative setting, typical palliative doses may be used—8 Gy in a single fraction, 20 Gy in 5 fractions, or 30 Gy in 10 fractions—depending on the treatment objectives. However, RT dosing can extend up to definitive doses for more durable local control. Highly conformal techniques may be appropriate for limited volume metastases, given the relatively long natural history of even metastatic thymoma.<sup>65</sup> For metastatic disease, systemic





# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

therapy is recommended (see *Principles of Systemic Therapy for Thymic Malignancies* in the algorithm).<sup>7,99,136,138-150</sup>

Six first-line chemotherapy regimens are recommended in the NCCN Guidelines. The NCCN Panel has preference stratified the first-line regimens for patients with thymomas. The NCCN Panel voted that the preferred regimen for thymoma is cisplatin/doxorubicin/cyclophosphamide (CAP), because it seems to yield the best outcomes.<sup>68,151-153</sup> Response rates are approximately 44% with CAP for thymomas.<sup>7</sup> However, non-anthracycline regimens (eg, cisplatin/etoposide [with or without ifosfamide], carboplatin/paclitaxel) may be useful for patients who cannot tolerate the preferred regimen.<sup>153,154</sup> The NCCN Panel voted that the following are “other recommended” regimens for patients with thymomas: CAP with prednisone, doxorubicin/cisplatin/vincristine/cyclophosphamide (ADOC), cisplatin/etoposide (PE), etoposide/ifosfamide/cisplatin, and carboplatin/paclitaxel.<sup>136,142,143,145,146,154</sup> If patients cannot tolerate first-line combination regimens, consider second-line systemic therapy options.

After primary treatment for resectable thymomas, panel members agree that surveillance for recurrence should include chest CT every 6 months for 2 years, then annually for 10 years for thymoma.<sup>33</sup> MRI may be used for surveillance for certain clinical situations, including: 1) if patients cannot tolerate contrast; and 2) to decrease radiation if patients are young and will be screened for many years. Given the risk of later recurrence for thymoma, surveillance should continue for at least 10 years. However, the duration, frequency, and type of imaging for surveillance for patients with thymomas have not been established in published studies. Patients with thymoma also have an increased risk for second malignancies, although no particular screening studies are recommended.<sup>3,155,156</sup> Surgery is an option for patients with locally advanced recurrent disease, solitary metastases, or ipsilateral metastases.<sup>157</sup>

Second-line systemic therapy for thymomas includes pemetrexed, everolimus, paclitaxel, octreotide (LAR) with or without prednisone, gemcitabine with or without capecitabine, 5-fluorouracil (5-FU), etoposide, and ifosfamide.<sup>139,140,153,158-167</sup> However, none of these agents has been assessed in randomized phase 3 trials, because the rarity of this disease makes such trials challenging to complete. For thymomas, response rates for subsequent systemic therapy (ie, second-line and beyond) range from 15% to 39%.<sup>7</sup> Panel members feel that pemetrexed and paclitaxel are more efficacious as second-line therapy for thymomas than the other recommended agents (see the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with NCCN Evidence Blocks™ for Thymomas and Thymic Carcinomas, available at [www.NCCN.org](http://www.NCCN.org)).<sup>7</sup> A study of pemetrexed in patients with thymoma (n = 16) reported two complete responses and five partial responses.<sup>168</sup>

Capecitabine may be added to gemcitabine based on clinical trial data.<sup>159,166</sup> In 22 patients with thymomas receiving gemcitabine/capecitabine, there were three complete responses and five partial responses. Octreotide may be useful in patients with thymoma who have a positive octreotide scan or symptoms of carcinoid syndrome. Pembrolizumab is not recommended in patients with thymomas because of concerns about immune-related adverse events.<sup>169,170</sup> Of patients with thymoma receiving pembrolizumab, 71% (5/7) had grade 3 or higher immune-related adverse events including myocarditis.<sup>171</sup> Sunitinib is not recommended in patients with thymomas, because they do not have *c-Kit* mutations.<sup>172</sup> In a phase 2 study assessing everolimus, median overall survival was more than 25 months in patients with thymomas (n = 32), but there was a high risk of fatal pneumonitis.<sup>161</sup> The NCCN Panel has preference stratified the second-line regimens for patients with thymomas. The panel voted that the following are “other recommended” regimens including etoposide, everolimus, 5-FU, gemcitabine with or without



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

capecitabine, ifosfamide, octreotide (including LAR) with or without prednisone, paclitaxel, and pemetrexed.

### Thymic Carcinomas

Thymic carcinomas are rare aggressive tumors that often metastasize to regional lymph nodes and extrathoracic sites; thus, they have a worse prognosis than thymomas.<sup>5,9,12,13,17,45,46,173-175</sup> Survival rates for thymic carcinomas vary depending on stage (stages 1–2: 91%; stages 3–4: 31%) and resectability (including completeness of resection).<sup>11</sup> These tumors can be distinguished from thymomas because of their malignant histologic features and their different immunohistochemical and genetic features.<sup>1,2,16,176</sup> They are predominantly squamous cell carcinomas and undifferentiated carcinomas. However, thymic carcinomas should be differentiated from primary lung malignancies that metastasize to the thymus and have a similar histologic appearance.<sup>172,177</sup> Thymic carcinomas often cause pericardial and pleural effusions. The Masaoka-Koga staging system and the AJCC TNM staging system can also be used to stage thymic carcinomas (see Tables 1 and 2 in the algorithm).<sup>48,178,179</sup>

It is important to note that thymic carcinomas are associated with a different clinical course from thymomas.<sup>138,176,180</sup> Unlike thymomas, paraneoplastic syndromes, including myasthenia gravis, are very rare in patients with thymic carcinoma.<sup>118</sup> If myasthenia gravis is diagnosed, then the diagnosis of thymic carcinoma should be reassessed; the patient may actually have thymoma.<sup>11</sup> In contrast to thymomas (which mainly occur in adults), thymic carcinomas occur over a wide age range including adolescents when assessed in a single-institution Western population; they predominantly occur in white individuals.<sup>11</sup>

Similar to thymomas, patients with completely resected thymic carcinomas have longer survival than those whose tumors are either incompletely

resected or are unresectable.<sup>45,47,181</sup> Patients who have an R0 resection have a 5-year survival of approximately 60%.<sup>11</sup> Thus, management depends on the extent of resection. Patients with thymic carcinoma have higher risks of recurrent disease; therefore, postoperative radiation is recommended to maximize local control.<sup>11</sup> After resection of thymic carcinomas, postoperative management includes RT with (or without) chemotherapy, depending on the completeness of resection (see *Postoperative Treatment and Management* in the algorithm).<sup>11,45,46,104,128,182,183</sup> A study suggests that adjuvant therapy may not be necessary for early-stage thymic carcinomas.<sup>184</sup> For unresectable or metastatic thymic carcinomas, chemotherapy with (or without) RT is recommended (see *Principles of Systemic Therapy for Thymic Malignancies* and *Principles of Radiation Therapy* in the algorithm).<sup>152</sup>

A definitive dose of 60 to 70 Gy is recommended for patients with unresectable thymic carcinomas. For adjuvant treatment, a dose of 45 to 50 Gy is recommended for clear or close margins; a dose of 54 Gy is recommended for microscopically positive resection margins (see *Principles of Radiation Therapy* in the algorithm).<sup>104,105,118</sup> However, a total dose of 60 to 70 Gy (1.8–2 Gy/fraction per day) is recommended for patients with gross residual disease after surgery.<sup>119,120</sup> In patients with thymic carcinomas who have capsular invasion after an R0 resection, postoperative RT can be considered (see *Postoperative Treatment and Management* in the algorithm).<sup>99,104,121-123</sup> Adjuvant therapy is not recommended for completely resected (R0) stage I thymic carcinomas.<sup>68,98,99</sup>

Six first-line chemotherapy regimens are recommended in the NCCN Guidelines. Unfortunately, thymic carcinomas respond poorly to chemotherapy. The NCCN Panel has preference stratified the first-line regimens for patients with thymic carcinomas. The NCCN Panel voted that carboplatin/paclitaxel is preferred for first-line therapy, because it



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

has the highest response rate in patients with thymic carcinomas in clinical trials (overall response rate, 22%–36%).<sup>149,154,185-194</sup> Data suggest that the CAP and ADOC regimens are also effective for thymic carcinomas, but these regimens are more toxic than carboplatin/paclitaxel.<sup>7,192</sup> The NCCN Panel voted that the following are “other recommended” regimens for patients with thymic carcinomas: CAP with or without prednisone, ADOC, PE, and etoposide/ifosfamide/cisplatin.<sup>136,142,143,145,146</sup> Induction chemotherapy is recommended followed by an evaluation for surgery for locally advanced disease; postoperative RT can be considered after surgical resection of the primary tumor and isolated metastases (see *Postoperative Treatment and Management* in the algorithm).<sup>11</sup> Patients with unresectable disease can then receive RT with or without chemotherapy. For those with solitary metastasis or ipsilateral pleural metastases, options include induction chemotherapy or surgery. If patients cannot tolerate first-line combination regimens, consider second-line systemic therapy options. After primary treatment for resectable disease, panel members agree that surveillance for recurrence should include chest CT every 6 months for 2 years, then annually for 5 years for thymic carcinoma.<sup>33</sup> However, the duration, frequency, or type of imaging for surveillance for thymic carcinomas has not been established in published studies.

For thymic carcinomas, there are little data regarding second-line systemic therapy.<sup>139</sup> Second-line systemic therapy for thymic carcinomas includes sunitinib, pemetrexed, everolimus, paclitaxel, gemcitabine with or without capecitabine, 5-FU, etoposide, ifosfamide, lenvatinib, and pembrolizumab (see *Principles of Systemic Therapy for Thymic Malignancies* in the algorithm).<sup>7,139,140,158,168,195</sup> For thymic carcinomas, response rates for subsequent systemic therapy range from 4% to 21%.<sup>7</sup> Sunitinib is recommended for patients with thymic carcinoma regardless of *c-Kit* mutation status (these mutations occur in <10% of patients).<sup>84,140,162,196-202</sup> Patients with thymomas do not have *c-Kit*

mutations.<sup>172</sup> With lenvatinib, there is a high risk for side effects and frequent dose reductions may be needed.<sup>195</sup> For the 2022 update (Version 1), panel members removed octreotide (including LAR) with or without prednisone as a second-line therapy option for patients with thymic carcinoma. Octreotide and prednisone are not effective in thymic carcinoma as shown in multiple studies in which no responses were seen.<sup>165,203</sup>

Pembrolizumab is active (response rate, 22.5%; 95% CI, 10.8%–38.5%) as second-line therapy in patients with thymic carcinomas but is associated with a high rate of severe immune-related adverse events (15%).<sup>204,205</sup> For example, grade 3–4 myocarditis has been reported in 5% to 9% of patients with thymic carcinomas receiving pembrolizumab, which is a higher adverse rate than seen in patients with other malignancies who receive pembrolizumab.<sup>171,205</sup> The NCCN Panel recommends pembrolizumab as second-line systemic therapy for patients with thymic carcinomas based on the clinical data. Capecitabine may be added to gemcitabine based on clinical trial data.<sup>159,166</sup> There were three partial responses in eight patients with thymic carcinomas receiving gemcitabine/capecitabine. In a phase 2 study assessing everolimus, median overall survival was approximately 14 months in patients with thymic carcinomas (n = 19); one patient had a complete response.<sup>161</sup> However, there was a high risk of fatal pneumonitis.<sup>161</sup> The NCCN Panel has preference stratified the second-line regimens for patients with thymic carcinoma. The panel voted that the following agents are other recommended including everolimus, 5-FU, gemcitabine with or without capecitabine, lenvatinib, paclitaxel, pembrolizumab, pemetrexed, and sunitinib. Etoposide and ifosfamide are useful in certain circumstances.

### Summary

These NCCN Guidelines focus on thymomas and thymic carcinomas and outline the evaluation, treatment, and management of these mediastinal



## NCCN Guidelines Version 1.2023 Thymomas and Thymic Carcinomas

tumors. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2022, which are described in greater detail in this revised Discussion text; references have been added. For the 2022 update (Version 1), panel members removed octreotide (including LAR) with or without prednisone as a second-line therapy option for patients with thymic carcinoma. Octreotide and prednisone are not effective in patients with thymic carcinoma as shown in multiple studies in which no responses were seen.<sup>165,203</sup>

A large, light gray watermark is centered on the page. It consists of two concentric circles. Inside the circles, the text "Discussion update in progress" is written in a large, bold, sans-serif font, stacked in three lines.

Discussion  
update in  
progress





# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

### References

- Marx A, Chan JKC, Chalabreysse L, et al. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors? *J Thorac Oncol* 2022;17:200-213. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34695605>.
- Marx A, Detterback F, Marom EM. Tumors of the Thymus. WHO Classification of Tumours Editorial Board. *Thoracic Tumours*, 5th ed. Vol. 7: World Health Organization; 2021.
- Engels EA. Epidemiology of thymoma and associated malignancies. *J Thorac Oncol* 2010;5:S260-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20859116>.
- Proceedings of the First International Conference on Thymic Malignancies. August 20-21, 2009. Bethesda, Maryland, USA. *J Thorac Oncol* 2010;5:S259-370. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21275152>.
- Stollo DC, Rosado de Christenson ML, Jett JR. Primary mediastinal tumors. Part 1: tumors of the anterior mediastinum. *Chest* 1997;112:511-522. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9266892>.
- Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and associations with subsequent malignancies. *Int J Cancer* 2003;105:546-551. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12712448>.
- Merveilleux du Vignaux C, Dansin E, Mhanna L, et al. Systemic Therapy in Advanced Thymic Epithelial Tumors: Insights from the RYTHMIC Prospective Cohort. *J Thorac Oncol* 2018;13:1762-1770. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30138763>.
- Zhao Y, Shi J, Fan L, et al. Surgical treatment of thymoma: an 11-year experience with 761 patients. *Eur J Cardiothorac Surg* 2016;49:1144-1149. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26324679>.
- Huang J, Rizk NP, Travis WD, et al. Comparison of patterns of relapse in thymic carcinoma and thymoma. *J Thorac Cardiovasc Surg* 2009;138:26-31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19577051>.
- Masaoka A. Staging system of thymoma. *J Thorac Oncol* 2010;5:S304-312. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20859124>.
- Litvak AM, Woo K, Hayes S, et al. Clinical characteristics and outcomes for patients with thymic carcinoma: evaluation of Masaoka staging. *J Thorac Oncol* 2014;9:1810-1815. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25393794>.
- Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. *Ann Thorac Surg* 2003;76:878-884; discussion 884-885. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12963221>.
- Eng TY, Fuller CD, Jagirdar J, et al. Thymic carcinoma: state of the art review. *Int J Radiat Oncol Biol Phys* 2004;59:654-664. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15183468>.
- den Bakker MA, Marx A, Mukai K, Strobel P. Mesenchymal tumours of the mediastinum--part I. *Virchows Arch* 2015;467:487-500. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26358059>.
- Araki T, Nishino M, Gao W, et al. Anterior Mediastinal Masses in the Framingham Heart Study: Prevalence and CT Image Characteristics. *Eur J Radiol Open* 2015;2:26-31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25705709>.
- Marchevsky A, Marx A, Strobel P, et al. Policies and reporting guidelines for small biopsy specimens of mediastinal masses. *J Thorac Oncol* 2011;6:S1724-1729. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21847054>.





# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

17. Strollo DC, Rosado-de-Christenson ML, Jett JR. Primary mediastinal tumors: part II. Tumors of the middle and posterior mediastinum. Chest 1997;112:1344-1357. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9367479>.

18. Rashid OM, Cassano AD, Takabe K. Thymic neoplasm: a rare disease with a complex clinical presentation. J Thorac Dis 2013;5:173-183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23585946>.

19. Detterbeck FC, Parsons AM. Management of stage I and II thymoma. Thorac Surg Clin 2011;21:59-67, vi-vii. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21070987>.

20. Detterbeck FC, Zeeshan A. Thymoma: current diagnosis and treatment. Chin Med J (Engl) 2013;126:2186-2191. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23769581>.

21. Barth TFE, Leithäuser F, Joos S, et al. Mediastinal (thymic) large B-cell lymphoma: where do we stand? Lancet Oncol 2002;3:229-234. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12067685>.

22. Ferolla P, Falchetti A, Filosso P, et al. Thymic neuroendocrine carcinoma (carcinoid) in multiple endocrine neoplasia type 1 syndrome: the Italian series. J Clin Endocrinol Metab 2005;90:2603-2609. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15713725>.

23. Teh BT. Thymic carcinoids in multiple endocrine neoplasia type 1. J Intern Med 1998;243:501-504. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9681849>.

24. Moran CA, Suster S. Primary germ cell tumors of the mediastinum: I. Analysis of 322 cases with special emphasis on teratomatous lesions and a proposal for histopathologic classification and clinical staging. Cancer 1997;80:681-690. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9264351>.

25. McKenney JK, Heerema-McKenney A, Rouse RV. Extragonadal germ cell tumors: a review with emphasis on pathologic features, clinical prognostic variables, and differential diagnostic considerations. Adv Anat

Pathol 2007;14:69-92. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17471115>.

26. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21714641>.

27. Yokoi K, Kondo K, Fujimoto K, et al. JLCS medical practice guidelines for thymic tumors: summary of recommendations. Jpn J Clin Oncol 2017;47:1119-1122. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29036455>.

28. Carter BW, Benveniste MF, Madan R, et al. ITMIG Classification of Mediastinal Compartments and Multidisciplinary Approach to Mediastinal Masses. Radiographics 2017;37:413-436. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28129068>.

29. Priola AM, Priola SM. Imaging of thymus in myasthenia gravis: from thymic hyperplasia to thymic tumor. Clin Radiol 2014;69:e230-245. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24581970>.

30. Tomiyama N, Honda O, Tsubamoto M, et al. Anterior mediastinal tumors: diagnostic accuracy of CT and MRI. Eur J Radiol 2009;69:280-288. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18023547>.

31. Benveniste MF, Rosado-de-Christenson ML, Sabloff BS, et al. Role of imaging in the diagnosis, staging, and treatment of thymoma. Radiographics 2011;31:1847-1861; discussion 1861-1863. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22084174>.

32. Marom EM. Advances in thymoma imaging. J Thorac Imaging 2013;28:69-80; quiz 81-83. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23422781>.

33. Marom EM. Imaging thymoma. J Thorac Oncol 2010;5:S296-303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20859123>.



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

34. Rosado-de-Christenson ML, Strollo DC, Marom EM. Imaging of thymic epithelial neoplasms. *Hematol Oncol Clin North Am* 2008;22:409-431. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18514124>.
35. Sadohara J, Fujimoto K, Muller NL, et al. Thymic epithelial tumors: comparison of CT and MR imaging findings of low-risk thymomas, high-risk thymomas, and thymic carcinomas. *Eur J Radiol* 2006;60:70-79. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16766154>.
36. Quint LE, Reddy RM, Lin J, et al. Imaging in thoracic oncology: case studies from Multidisciplinary Thoracic Tumor Board: (part 2 of 2 part series). *Cancer Imaging* 2013;13:440-447. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24325879>.
37. Marom EM, Rosado-de-Christenson ML, Bruzzi JF, et al. Standard report terms for chest computed tomography reports of anterior mediastinal masses suspicious for thymoma. *J Thorac Oncol* 2011;6:S1717-1723. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21847053>.
38. Carter BW, Lichtenberger JP, 3rd, Benveniste MF. MR Imaging of Thymic Epithelial Neoplasms. *Top Magn Reson Imaging* 2018;27:65-71. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29613961>.
39. Treglia G, Sadeghi R, Giovanella L, et al. Is (18)F-FDG PET useful in predicting the WHO grade of malignancy in thymic epithelial tumors? A meta-analysis. *Lung Cancer* 2014;86:5-13. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25175317>.
40. Sung YM, Lee KS, Kim BT, et al. 18F-FDG PET/CT of thymic epithelial tumors: usefulness for distinguishing and staging tumor subgroups. *J Nucl Med* 2006;47:1628-1634. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17015898>.
41. Moran CA, Weissferdt A, Kalhor N, et al. Thymomas I: a clinicopathologic correlation of 250 cases with emphasis on the World Health Organization schema. *Am J Clin Pathol* 2012;137:444-450. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22338057>.
42. Ruffini E, Detterbeck F, Van Raemdonck D, et al. Tumours of the thymus: a cohort study of prognostic factors from the European Society of Thoracic Surgeons database. *Eur J Cardiothorac Surg* 2014;46:361-368. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24482389>.
43. Margaritora S, Cesario A, Cusumano G, et al. Thirty-five-year follow-up analysis of clinical and pathologic outcomes of thymoma surgery. *Ann Thorac Surg* 2010;89:245-252; discussion 252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20103246>.
44. Regnard JF, Magdeleinat P, Dromer C, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. *J Thorac Cardiovasc Surg* 1996;112:376-384. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8751506>.
45. Yano M, Sasaki H, Yokoyama T, et al. Thymic carcinoma: 30 cases at a single institution. *J Thorac Oncol* 2008;3:265-269. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18317069>.
46. Ogawa K, Toita T, Uno T, et al. Treatment and prognosis of thymic carcinoma: a retrospective analysis of 40 cases. *Cancer* 2002;94:3115-3119. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12115342>.
47. Okereke IC, Kesler KA, Freeman RK, et al. Thymic carcinoma: outcomes after surgical resection. *Ann Thorac Surg* 2012;93:1668-1672; discussion 1672-1673. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22421590>.
48. Detterbeck FC, Nicholson AG, Kondo K, et al. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. *J Thorac Oncol* 2011;6:S1710-1716. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21847052>.
49. Huang J, Detterbeck FC, Wang Z, Loehrer PJ, Sr. Standard outcome measures for thymic malignancies. *J Thorac Oncol* 2011;6:S1691-1697. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21847049>.



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

50. Moran CA, Walsh G, Suster S, Kaiser L. Thymomas II: a clinicopathologic correlation of 250 cases with a proposed staging system with emphasis on pathologic assessment. *Am J Clin Pathol* 2012;137:451-461. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22338058>.

51. Kondo K. Tumor-node metastasis staging system for thymic epithelial tumors. *J Thorac Oncol* 2010;5:S352-356. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20859132>.

52. Lee HS, Kim ST, Lee J, et al. A single institutional experience of thymic epithelial tumours over 11 years: clinical features and outcome and implications for future management. *Br J Cancer* 2007;97:22-28. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17592498>.

53. 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. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/7296496>.

54. Wright CD. Management of thymomas. *Crit Rev Oncol Hematol* 2008;65:109-120. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17570676>.

55. Benveniste MFK, Betancourt Cuellar SL, Carter BW, et al. Thymic Epithelial Neoplasms: Tumor-Node-Metastasis Staging. *Radiol Clin North Am* 2021;59:183-192. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33551080>.

56. Amin MB, Edge SB, Greene FL, et al. *AJCC Cancer Staging Manual*, 8th edition: Springer International Publishing; 2017:1-1032.

57. Carter BW, Benveniste MF, Madan R, et al. IASLC/ITMIG Staging System and Lymph Node Map for Thymic Epithelial Neoplasms. *Radiographics* 2017;37:758-776. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28493800>.

58. Meurgey A, Girard N, Merveilleux du Vignaux C, et al. Assessment of the ITMIG Statement on the WHO Histological Classification and of the

Eighth TNM Staging of Thymic Epithelial Tumors of a Series of 188 Thymic Epithelial Tumors. *J Thorac Oncol* 2017;12:1571-1581. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28694035>.

59. 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:S65-72. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25396314>.

60. Roden AC, Yi ES, Jenkins SM, et al. Reproducibility of 3 histologic classifications and 3 staging systems for thymic epithelial neoplasms and its effect on prognosis. *Am J Surg Pathol* 2015;39:427-441. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25634747>.

61. Fukui T, Fukumoto K, Okasaka T, et al. Clinical evaluation of a new tumour-node-metastasis staging system for thymic malignancies proposed by the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee and the International Thymic Malignancy Interest Group. *Eur J Cardiothorac Surg* 2016;49:574-579. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26547095>.

62. Bhora FY, Chen DJ, Detterbeck FC, et al. The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: A Proposed Lymph Node Map for Thymic Epithelial Tumors in the Forthcoming 8th Edition of the TNM Classification of Malignant Tumors. *J Thorac Oncol* 2014;9:S88-96. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25396317>.

63. Lewis JE, Wick MR, Scheithauer BW, et al. Thymoma. A clinicopathologic review. *Cancer* 1987;60:2727-2743. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/3677008>.

64. Park HS, Shin DM, Lee JS, et al. Thymoma. A retrospective study of 87 cases. *Cancer* 1994;73:2491-2498. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8174044>.

65. Basse C, Thureau S, Bota S, et al. Multidisciplinary Tumor Board Decision Making for Postoperative Radiotherapy in Thymic Epithelial Tumors: Insights from the RYTHMIC Prospective Cohort. *J Thorac Oncol*





# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

2017;12:1715-1722. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28774861>.

66. Ruffini E, Van Raemdonck D, Detterbeck F, et al. Management of thymic tumors: a survey of current practice among members of the European Society of Thoracic Surgeons. *J Thorac Oncol* 2011;6:614-623. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21266921>.

67. Fiorelli A, Natale G, Freda C, Santini M. Is thymectomy equivalent to complete thymectomy in non-myasthenic patients with early-stage thymoma? *Interact Cardiovasc Thorac Surg* 2019;28:399-403. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30188996>.

68. Kondo K. Optimal therapy for thymoma. *J Med Invest* 2008;55:17-28. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18319541>.

69. Detterbeck FC, Parsons AM. Thymic tumors. *Ann Thorac Surg* 2004;77:1860-1869. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15111216>.

70. Wright CD. Stage IVA thymoma: patterns of spread and surgical management. *Thorac Surg Clin* 2011;21:93-97, vii. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21070990>.

71. Wright CD. Extended resections for thymic malignancies. *J Thorac Oncol* 2010;5:S344-347. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20859130>.

72. Huang J, Rizk NP, Travis WD, et al. Feasibility of multimodality therapy including extended resections in stage IVA thymoma. *J Thorac Cardiovasc Surg* 2007;134:1477-1483; discussion 1483-1474. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18023668>.

73. Schneider F, Roden AC, Dacic S. Protocol for the examination of specimens from patients with thymic tumors: College of American Pathologists; 2021. Available at: [https://documents.cap.org/protocols/Thymus\\_4.1.0.0.REL\\_CAPCP.pdf](https://documents.cap.org/protocols/Thymus_4.1.0.0.REL_CAPCP.pdf).

74. Xie A, Tjahjono R, Phan K, Yan TD. Video-assisted thoracoscopic surgery versus open thymectomy for thymoma: a systematic review. *Ann Cardiothorac Surg* 2015;4:495-508. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26693145>.

75. Chao YK, Liu YH, Hsieh MJ, et al. Long-term outcomes after thoracoscopic resection of stage I and II thymoma: a propensity-matched study. *Ann Surg Oncol* 2015;22:1371-1376. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25256127>.

76. Liu TJ, Lin MW, Hsieh MS, et al. Video-assisted thoracoscopic surgical thymectomy to treat early thymoma: a comparison with the conventional transsternal approach. *Ann Surg Oncol* 2014;21:322-328. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23982255>.

77. Pennathur A, Qureshi I, Schuchert MJ, et al. Comparison of surgical techniques for early-stage thymoma: feasibility of minimally invasive thymectomy and comparison with open resection. *J Thorac Cardiovasc Surg* 2011;141:694-701. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21255798>.

78. Ye B, Tantai JC, Ge XX, et al. Surgical techniques for early-stage thymoma: video-assisted thoracoscopic thymectomy versus transsternal thymectomy. *J Thorac Cardiovasc Surg* 2014;147:1599-1603. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24290709>.

79. Sakamaki Y, Oda T, Kanazawa G, et al. Intermediate-term oncologic outcomes after video-assisted thoracoscopic thymectomy for early-stage thymoma. *J Thorac Cardiovasc Surg* 2014;148:1230-1237.e1231. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24560416>.

80. Manoly I, Whistance RN, Sreekumar R, et al. Early and mid-term outcomes of trans-sternal and video-assisted thoracoscopic surgery for thymoma. *Eur J Cardiothorac Surg* 2014;45:e187-193. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24616388>.

81. Agatsuma H, Yoshida K, Yoshino I, et al. Video-Assisted Thoracic Surgery Thymectomy Versus Sternotomy Thymectomy in Patients With



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

Thymoma. *Ann Thorac Surg* 2017;104:1047-1053. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28619540>.

82. Yang Y, Dong J, Huang Y. Thoracoscopic thymectomy versus open thymectomy for the treatment of thymoma: A meta-analysis. *Eur J Surg Oncol* 2016;42:1720-1728. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27139936>.

83. Yamada Y, Yoshino I, Nakajima J, et al. Surgical Outcomes of Patients With Stage III Thymoma in the Japanese Nationwide Database. *Ann Thorac Surg* 2015;100:961-967. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26163354>.

84. Kelly RJ, Petrini I, Rajan A, et al. Thymic malignancies: from clinical management to targeted therapies. *J Clin Oncol* 2011;29:4820-4827. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22105817>.

85. Bernard C, Frih H, Pasquet F, et al. Thymoma associated with autoimmune diseases: 85 cases and literature review. *Autoimmun Rev* 2016;15:82-92. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26408958>.

86. Gilhus NE, Owe JF, Hoff JM, et al. Myasthenia gravis: a review of available treatment approaches. *Autoimmune Dis* 2011;2011:847393. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22007295>.

87. Mehran R, Ghosh R, Maziak D, et al. Surgical treatment of thymoma. *Can J Surg* 2002;45:25-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11837917>.

88. Autoantibodies to acetylcholine receptors in myasthenia gravis. *N Engl J Med* 1983;308:402-403. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6823248>.

89. Howard FM, Lennon VA, Finley J, et al. Clinical correlations of antibodies that bind, block, or modulate human acetylcholine receptors in myasthenia gravis. *Ann N Y Acad Sci* 1987;505:526-538. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3479935>.

90. Benveniste MF, Korst RJ, Rajan A, et al. A practical guide from the International Thymic Malignancy Interest Group (ITMIG) regarding the radiographic assessment of treatment response of thymic epithelial tumors using modified RECIST criteria. *J Thorac Oncol* 2014;9:S119-124. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25396308>.

91. Hwang Y, Park IK, Park S, et al. Lymph Node Dissection in Thymic Malignancies: Implication of the ITMIG Lymph Node Map, TNM Stage Classification, and Recommendations. *J Thorac Oncol* 2016;11:108-114. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26762745>.

92. Bretti S, Berruti A, Loddo C, et al. Multimodal management of stages III-IVa malignant thymoma. *Lung Cancer* 2004;44:69-77. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15013585>.

93. Ried M, Potzger T, Sziklavari Z, et al. Extended surgical resections of advanced thymoma Masaoka stages III and IVa facilitate outcome. *Thorac Cardiovasc Surg* 2014;62:161-168. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23775415>.

94. Detterbeck F, Youssef S, Ruffini E, Okumura M. A review of prognostic factors in thymic malignancies. *J Thorac Oncol* 2011;6:S1698-1704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21847050>.

95. Murakawa T, Nakajima J, Kohno T, et al. Results from surgical treatment for thymoma. 43 years of experience. *Jpn J Thorac Cardiovasc Surg* 2000;48:89-95. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10769987>.

96. Wakely PE, Jr. Fine needle aspiration in the diagnosis of thymic epithelial neoplasms. *Hematol Oncol Clin North Am* 2008;22:433-442. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18514125>.

97. 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:S1730-1738. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21847055>.



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

98. Utsumi T, Shiono H, Kadota Y, et al. Postoperative radiation therapy after complete resection of thymoma has little impact on survival. *Cancer* 2009;115:5413-5420. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19685527>.

99. Korst RJ, Kansler AL, Christos PJ, Mandal S. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. *Ann Thorac Surg* 2009;87:1641-1647. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19379938>.

100. Tateishi Y, Horita N, Namkoong H, et al. Postoperative Radiotherapy for Completely Resected Masaoka/Masaoka-Koga Stage II/III Thymoma Improves Overall Survival: An Updated Meta-Analysis of 4746 Patients. *J Thorac Oncol* 2021;16:677-685. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33515812>.

101. Hamaji M, Shah RM, Ali SO, et al. A Meta-Analysis of Postoperative Radiotherapy for Thymic Carcinoma. *Ann Thorac Surg* 2017;103:1668-1675. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28366466>.

102. Forquer JA, Rong N, Fakiris AJ, et al. Postoperative radiotherapy after surgical resection of thymoma: differing roles in localized and regional disease. *Int J Radiat Oncol Biol Phys* 2010;76:440-445. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19427738>.

103. Ruffini E, Mancuso M, Oliaro A, et al. Recurrence of thymoma: analysis of clinicopathologic features, treatment, and outcome. *J Thorac Cardiovasc Surg* 1997;113:55-63. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9011702>.

104. Gomez D, Komaki R, Yu J, et al. Radiation therapy definitions and reporting guidelines for thymic malignancies. *J Thorac Oncol* 2011;6:S1743-1748. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21847057>.

105. Gomez D, Komaki R. Technical advances of radiation therapy for thymic malignancies. *J Thorac Oncol* 2010;5:S336-343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20859129>.

106. ATC Guidelines for the Use of IMRT (including Intra-Thoracic Treatments). May 31, 2006. Available at: <http://rrp.cancer.gov/content/docs/imrt.doc>.

107. Hartford AC, Palisca MG, Eichler TJ, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guidelines for Intensity-Modulated Radiation Therapy (IMRT). *Int J Radiat Oncol Biol Phys* 2009;73:9-14. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19100920>.

108. Moran JM, Dempsey M, Eisbruch A, et al. Safety considerations for IMRT: executive summary. *Med Phys* 2011;38:5067-5072. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21978051>.

109. Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). *Cancer Radiother* 2011;15:555-559. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21802333>.

110. Group IDW, Holmes T, Das R, et al. American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments. *Int J Radiat Oncol Biol Phys* 2009;74:1311-1318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19616738>.

111. ICRU Report 83: Prescribing, recording, and reporting intensity modulated photon beam therapy (IMRT). *Journal of the ICRU* 2010;10. Available at: <http://jicru.oxfordjournals.org/content/10/1.toc>.

112. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non Small Cell Lung Cancer (Version 3.2022). © 2022 National Comprehensive Cancer Network, Inc. . Available at: [www.NCCN.org](http://www.NCCN.org).

113. Kong FM, Pan C, Eisbruch A, Ten Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity. *Semin Radiat Oncol* 2007;17:108-120. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17395041>.





# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

114. Milano MT, Constine LS, Okunieff P. Normal tissue tolerance dose metrics for radiation therapy of major organs. *Semin Radiat Oncol* 2007;17:131-140. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17395043>.

115. Loap P, Scher N, Goudjil F, et al. Proton Beam Therapy for Thymic Carcinoma with Pericardial Involvement. *Int J Part Ther* 2021;7:65-70.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33604417>.

116. Parikh RR, Rhome R, Hug E, et al. Adjuvant Proton Beam Therapy in the Management of Thymoma: A Dosimetric Comparison and Acute Toxicities. *Clin Lung Cancer* 2016;17:362-366. Available at:

<https://pubmed.ncbi.nlm.nih.gov/27372386/>.

117. Vogel J, Berman AT, Lin L, et al. Prospective study of proton beam radiation therapy for adjuvant and definitive treatment of thymoma and thymic carcinoma: Early response and toxicity assessment. *Radiother Oncol* 2016;118:504-509. Available at:

<https://pubmed.ncbi.nlm.nih.gov/26895711/>.

118. Ruffini E, Venuta F. Management of thymic tumors: a European perspective. *J Thorac Dis* 2014;6 Suppl 2:S228-237. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24868441>.

119. Myojin M, Choi NC, Wright CD, et al. Stage III thymoma: pattern of failure after surgery and postoperative radiotherapy and its implication for future study. *Int J Radiat Oncol Biol Phys* 2000;46:927-933. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10705015>.

120. Mornex F, Resbeut M, Richaud P, et al. Radiotherapy and chemotherapy for invasive thymomas: a multicentric retrospective review of 90 cases. The FNCLCC trialists. *Federation Nationale des Centres de Lutte Contre le Cancer. Int J Radiat Oncol Biol Phys* 1995;32:651-659.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7790251>.

121. Singhal S, Shrager JB, Rosenthal DI, et al. Comparison of stages I-III thymoma treated by complete resection with or without adjuvant radiation. *Ann Thorac Surg* 2003;76:1635-1641; discussion 1641-1642. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/14602300>.

122. Rena O, Papalia E, Oliaro A, et al. Does adjuvant radiation therapy improve disease-free survival in completely resected Masaoka stage II thymoma? *Eur J Cardiothorac Surg* 2007;31:109-113. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17110124>.

123. Mangi AA, Wright CD, Allan JS, et al. Adjuvant radiation therapy for stage II thymoma. *Ann Thorac Surg* 2002;74:1033-1037. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12400741>.

124. Lim YJ, Kim HJ, Wu HG. Role of Postoperative Radiotherapy in Nonlocalized Thymoma: Propensity-Matched Analysis of Surveillance, Epidemiology, and End Results Database. *J Thorac Oncol* 2015;10:1357-1363. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26280586>.

125. Perri F, Pisconti S, Conson M, et al. Adjuvant treatment in patients at high risk of recurrence of thymoma: efficacy and safety of a three-dimensional conformal radiation therapy regimen. *Onco Targets Ther* 2015;8:1345-1349. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26089683>.

126. Sugie C, Shibamoto Y, Ikeya-Hashizume C, et al. Invasive thymoma: postoperative mediastinal irradiation, and low-dose entire hemithorax irradiation in patients with pleural dissemination. *J Thorac Oncol* 2008;3:75-81. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18166844>.

127. Ogawa K, Uno T, Toita T, et al. Postoperative radiotherapy for patients with completely resected thymoma: a multi-institutional, retrospective review of 103 patients. *Cancer* 2002;94:1405-1413.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11920495>.

128. Omasa M, Date H, Sozu T, et al. Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: the Japanese Association for Research on the Thymus Database Study. *Cancer* 2015;121:1008-1016. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25565590>.



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

129. Attaran S, McCormack D, Pilling J, Harrison-Phipps K. Which stages of thymoma benefit from adjuvant chemotherapy post-thymectomy? *Interact Cardiovasc Thorac Surg* 2012;15:273-275. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22552797>.

130. Cowen D, Richaud P, Mornex F, et al. Thymoma: results of a multicentric retrospective series of 149 non-metastatic irradiated patients and review of the literature. *FNCLCC trialists. Federation Nationale des Centres de Lutte Contre le Cancer. Radiother Oncol* 1995;34:9-16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7792406>.

131. Park S, Park IK, Kim YT, et al. Comparison of Neoadjuvant Chemotherapy Followed by Surgery to Upfront Surgery for Thymic Malignancy. *Ann Thorac Surg* 2019;107:355-362. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30316850>.

132. Ruffini E, Guerrera F, Brunelli A, et al. Report from the European Society of Thoracic Surgeons prospective thymic database 2017: a powerful resource for a collaborative global effort to manage thymic tumours. *Eur J Cardiothorac Surg* 2019;55:601-609. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30649256>.

133. Kanzaki R, Kanou T, Ose N, et al. Long-term outcomes of advanced thymoma in patients undergoing preoperative chemotherapy or chemoradiotherapy followed by surgery: a 20-year experience. *Interact Cardiovasc Thorac Surg* 2019;28:360-367. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30256943>.

134. Riely GJ, Huang J. Induction therapy for locally advanced thymoma. *J Thorac Oncol* 2010;5:S323-326. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20859127>.

135. Wright CD, Choi NC, Wain JC, et al. Induction chemoradiotherapy followed by resection for locally advanced Masaoka stage III and IVA thymic tumors. *Ann Thorac Surg* 2008;85:385-389. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18222230>.

136. Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by

surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. *Lung Cancer* 2004;44:369-379. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15140551>.

137. Hassan M, Seoud DE. Multimodality treatments in locally advanced stage thymomas. *Hematol Oncol Stem Cell Ther* 2009;2:340-344. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20118057>.

138. Kelly RJ. Systemic treatment of advanced thymic malignancies. *Am Soc Clin Oncol Educ Book* 2014:e367-373. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24857125>.

139. Girard N, Lal R, Wakelee H, et al. Chemotherapy definitions and policies for thymic malignancies. *J Thorac Oncol* 2011;6:S1749-1755. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21847058>.

140. Girard N. Chemotherapy and targeted agents for thymic malignancies. *Expert Rev Anticancer Ther* 2012;12:685-695. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22594902>.

141. Loehrer PJ, Sr., Chen M, Kim K, et al. Cisplatin, doxorubicin, and cyclophosphamide plus thoracic radiation therapy for limited-stage unresectable thymoma: an intergroup trial. *J Clin Oncol* 1997;15:3093-3099. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9294472>.

142. Loehrer PJ, Sr., Kim K, Aisner SC, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. *J Clin Oncol* 1994;12:1164-1168. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8201378>.

143. Giaccone G, Ardizzoni A, Kirkpatrick A, et al. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol*





# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

1996;14:814-820. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8622029>.

144. Shin DM, Walsh GL, Komaki R, et al. A multidisciplinary approach to therapy for unresectable malignant thymoma. *Ann Intern Med* 1998;129:100-104. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/9669967>.

<https://www.ncbi.nlm.nih.gov/pubmed/9669967>.

145. Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy for invasive thymoma. A 13-year experience. *Cancer* 1991;68:30-33. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/2049749>.

<https://www.ncbi.nlm.nih.gov/pubmed/2049749>.

146. Loehrer PJ, Sr., Jiroutek M, Aisner S, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. *Cancer* 2001;91:2010-2015. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11391579>.

<https://www.ncbi.nlm.nih.gov/pubmed/11391579>.

147. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: a single-institution experience with a long follow-up. *J Thorac Oncol* 2006;1:308-313. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17409875>.

<https://www.ncbi.nlm.nih.gov/pubmed/17409875>.

148. Yokoi K, Matsuguma H, Nakahara R, et al. Multidisciplinary treatment for advanced invasive thymoma with cisplatin, doxorubicin, and methylprednisolone. *J Thorac Oncol* 2007;2:73-78. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17410014>.

<https://www.ncbi.nlm.nih.gov/pubmed/17410014>.

149. Lemma GL, Loehrer PJ, Sr., Lee JW, et al. A phase II study of carboplatin plus paclitaxel in advanced thymoma or thymic carcinoma: E1C99 [abstract]. *J Clin Oncol* 2008;26(Suppl 15):Abstract 8018. Available at:

[https://ascopubs.org/doi/10.1200/jco.2008.26.15\\_suppl.8018](https://ascopubs.org/doi/10.1200/jco.2008.26.15_suppl.8018).

[https://ascopubs.org/doi/10.1200/jco.2008.26.15\\_suppl.8018](https://ascopubs.org/doi/10.1200/jco.2008.26.15_suppl.8018).

150. Venuta F, Rendina EA, Longo F, et al. Long-term outcome after multimodality treatment for stage III thymic tumors. *Ann Thorac Surg* 2003;76:1866-1872; discussion 1872. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/14667602>.

<https://www.ncbi.nlm.nih.gov/pubmed/14667602>.

151. Okuma Y, Saito M, Hosomi Y, et al. Key components of chemotherapy for thymic malignancies: a systematic review and pooled analysis for anthracycline-, carboplatin- or cisplatin-based chemotherapy. *J Cancer Res Clin Oncol* 2015;141:323-331. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25146529>.

<https://www.ncbi.nlm.nih.gov/pubmed/25146529>.

152. Rajan A, Giaccone G. Chemotherapy for thymic tumors: induction, consolidation, palliation. *Thorac Surg Clin* 2011;21:107-114, viii. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21070992>.

<https://www.ncbi.nlm.nih.gov/pubmed/21070992>.

153. Schmitt J, Loehrer PJ, Sr. The role of chemotherapy in advanced thymoma. *J Thorac Oncol* 2010;5:S357-360. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20859133>.

<https://www.ncbi.nlm.nih.gov/pubmed/20859133>.

154. Lemma GL, Lee JW, Aisner SC, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. *J Clin Oncol* 2011;29:2060-2065. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21502559>.

<https://www.ncbi.nlm.nih.gov/pubmed/21502559>.

155. Kumar V, Garg M, Goyal A, et al. Changing pattern of secondary cancers among patients with malignant thymoma in the USA. *Future Oncol* 2018;14:1943-1951. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/30081670>.

<https://www.ncbi.nlm.nih.gov/pubmed/30081670>.

156. Pan CC, Chen PC, Wang LS, et al. Thymoma is associated with an increased risk of second malignancy. *Cancer* 2001;92:2406-2411. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11745297>.

<https://www.ncbi.nlm.nih.gov/pubmed/11745297>.

157. Dai J, Song N, Yang Y, Jiang G. Is it valuable and safe to perform reoperation for recurrent thymoma? *Interact Cardiovasc Thorac Surg* 2015;21:526-531. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26105772>.

<https://www.ncbi.nlm.nih.gov/pubmed/26105772>.

158. Hellyer JA, Ouseph MM, Padda SK, Wakelee HA. Everolimus in the treatment of metastatic thymic epithelial tumors. *Lung Cancer* 2020;149:97-102. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33007678>.

<https://www.ncbi.nlm.nih.gov/pubmed/33007678>.



# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

159. Palmieri G, Buonerba C, Ottaviano M, et al. Capecitabine plus gemcitabine in thymic epithelial tumors: final analysis of a Phase II trial. *Future Oncol* 2014;10:2141-2147. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25471029>.

160. Bluthgen MV, Boutros C, Fayard F, et al. Activity and safety of oral etoposide in pretreated patients with metastatic or recurrent thymic epithelial tumors (TET): A single-institution experience. *Lung Cancer* 2016;99:111-116. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27565923>.

161. Zucali PA, De Pas T, Palmieri G, et al. Phase II Study of Everolimus in Patients With Thymoma and Thymic Carcinoma Previously Treated With Cisplatin-Based Chemotherapy. *J Clin Oncol* 2018;36:342-349. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29240542>.

162. Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. *Lancet Oncol* 2015;16:177-186. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25592632>.

163. Liang Y, Padda SK, Riess JW, et al. Pemetrexed in patients with thymic malignancies previously treated with chemotherapy. *Lung Cancer* 2015;87:34-38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25443273>.

164. Longo F, De Filippis L, Zivi A, et al. Efficacy and tolerability of long-acting octreotide in the treatment of thymic tumors: results of a pilot trial. *Am J Clin Oncol* 2012;35:105-109. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21325939>.

165. Loehrer PJ, Sr., Wang W, Johnson DH, et al. Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: an Eastern Cooperative Oncology Group Phase II Trial. *J Clin Oncol* 2004;22:293-299. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14722038>.

166. Palmieri G, Merola G, Federico P, et al. Preliminary results of phase II study of capecitabine and gemcitabine (CAP-GEM) in patients with

metastatic pretreated thymic epithelial tumors (TETs). *Ann Oncol* 2010;21:1168-1172. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19880439>.

167. Highley MS, Underhill CR, Parnis FX, et al. Treatment of invasive thymoma with single-agent ifosfamide. *J Clin Oncol* 1999;17:2737-2744. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10561348>.

168. Gbolahan OB, Porter RF, Salter JT, et al. A Phase II Study of Pemetrexed in Patients with Recurrent Thymoma and Thymic Carcinoma. *J Thorac Oncol* 2018;13:1940-1948. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30121390>.

169. Konstantina T, Konstantinos R, Anastasios K, et al. Fatal adverse events in two thymoma patients treated with anti-PD-1 immune check point inhibitor and literature review. *Lung Cancer* 2019;135:29-32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31446999>.

170. Argentiero A, Solimando AG, Ungaro V, et al. Case Report: Lymphocytosis Associated With Fatal Hepatitis in a Thymoma Patient Treated With Anti-PD1: New Insight Into the Immune-Related Storm. *Front Oncol* 2020;10:583781. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33381454>.

171. Cho J, Kim HS, Ku BM, et al. Pembrolizumab for Patients With Refractory or Relapsed Thymic Epithelial Tumor: An Open-Label Phase II Trial. *J Clin Oncol* 2019;37:2162-2170. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29906252>.

172. Strobel P, Hohenberger P, Marx A. Thymoma and thymic carcinoma: molecular pathology and targeted therapy. *J Thorac Oncol* 2010;5:S286-290. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20859121>.

173. Gharwan H, Kim C, Thomas A, et al. Thymic epithelial tumors and metastasis to the brain: a case series and systematic review. *Transl Lung Cancer Res* 2017;6:588-599. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29114474>.



## NCCN Guidelines Version 1.2023 Thymomas and Thymic Carcinomas

174. Wu JX, Chen HQ, Shao LD, et al. Long-term follow-up and prognostic factors for advanced thymic carcinoma. *Medicine (Baltimore)* 2014;93:e324. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25526488>.

175. Suster S, Rosai J. Thymic carcinoma. A clinicopathologic study of 60 cases. *Cancer* 1991;67:1025-1032. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1991250>.

176. Marx A, Rieker R, Toker A, et al. Thymic carcinoma: is it a separate entity? From molecular to clinical evidence. *Thorac Surg Clin* 2011;21:25-31 v-vi. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21070984>.

177. Moran CA, Suster S. Thymic carcinoma: current concepts and histologic features. *Hematol Oncol Clin North Am* 2008;22:393-407. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18514123>.

178. Hosaka Y, Tsuchida M, Toyabe S, et al. Masaoka stage and histologic grade predict prognosis in patients with thymic carcinoma. *Ann Thorac Surg* 2010;89:912-917. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20172153>.

179. Blumberg D, Burt ME, Bains MS, et al. Thymic carcinoma: current staging does not predict prognosis. *J Thorac Cardiovasc Surg* 1998;115:303-308; discussion 308-309. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9475524>.

180. Okuma Y, Hosomi Y, Watanabe K, et al. Clinicopathological analysis of thymic malignancies with a consistent retrospective database in a single institution: from Tokyo Metropolitan Cancer Center. *BMC Cancer* 2014;14:349. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24885581>.

181. Ruffini E, Detterbeck F, Van Raemdonck D, et al. Thymic carcinoma: a cohort study of patients from the European society of thoracic surgeons database. *J Thorac Oncol* 2014;9:541-548. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24736078>.

182. Ahmad U, Yao X, Detterbeck F, et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. *J Thorac Cardiovasc Surg* 2015;149:95-100, 101.e101-102. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25524678>.

183. Mao Y, Wu S. Treatment and survival analyses of completely resected thymic carcinoma patients. *Onco Targets Ther* 2015;8:2503-2507. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26392777>.

184. Sakai M, Onuki T, Inagaki M, et al. Early-stage thymic carcinoma: is adjuvant therapy required? *J Thorac Dis* 2013;5:161-164. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23585943>.

185. Hirai F, Yamanaka T, Taguchi K, et al. A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L. *Ann Oncol* 2015;26:363-368. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25403584>.

186. Furugen M, Sekine I, Tsuta K, et al. Combination chemotherapy with carboplatin and paclitaxel for advanced thymic cancer. *Jpn J Clin Oncol* 2011;41:1013-1016. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21742653>.

187. Maruyama R, Suemitsu R, Okamoto T, et al. Persistent and aggressive treatment for thymic carcinoma. Results of a single-institute experience with 25 patients. *Oncology* 2006;70:325-329. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17164588>.

188. Weide LG, Ulbright TM, Loehrer PJ, Sr., Williams SD. Thymic carcinoma. A distinct clinical entity responsive to chemotherapy. *Cancer* 1993;71:1219-1223. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8435796>.

189. Lucchi M, Mussi A, Ambrogi M, et al. Thymic carcinoma: a report of 13 cases. *Eur J Surg Oncol* 2001;27:636-640. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11669591>.





# NCCN Guidelines Version 1.2023

## Thymomas and Thymic Carcinomas

190. Yoh K, Goto K, Ishii G-i, et al. Weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide is an effective treatment for advanced thymic carcinoma. *Cancer* 2003;98:926-931. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12942558>.

191. Igawa S, Murakami H, Takahashi T, et al. Efficacy of chemotherapy with carboplatin and paclitaxel for unresectable thymic carcinoma. *Lung Cancer* 2010;67:194-197. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19409644>.

192. Koizumi T, Takabayashi Y, Yamagishi S, et al. Chemotherapy for advanced thymic carcinoma: clinical response to cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC chemotherapy). *Am J Clin Oncol* 2002;25:266-268. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12040285>.

193. Kanda S, Koizumi T, Komatsu Y, et al. Second-line chemotherapy of platinum compound plus CPT-11 following ADOC chemotherapy in advanced thymic carcinoma: analysis of seven cases. *Anticancer Res* 2007;27:3005-3008. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17695487>.

194. Komatsu Y, Koizumi T, Tanabe T, et al. Salvage chemotherapy with carboplatin and paclitaxel for cisplatin-resistant thymic carcinoma--three cases. *Anticancer Res* 2006;26:4851-4855. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17214351>.

195. Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. *Lancet Oncol* 2020;21:843-850. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32502444>.

196. Remon J, Girard N, Mazieres J, et al. Sunitinib in patients with advanced thymic malignancies: Cohort from the French RYTHMIC network. *Lung Cancer* 2016;97:99-104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27237035>.

197. Remon J, Girard N, Mazieres J, et al. Erratum to "Sunitinib in patients with advanced thymic malignancies: cohort from the French RYTHMIC

network" [*Lung Cancer*, 97 (July 2016), 99-104]. *Lung Cancer* 2016;101:146. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27720478>.

198. Palmieri G, Marino M, Buonerba C, et al. Imatinib mesylate in thymic epithelial malignancies. *Cancer Chemother Pharmacol* 2012;69:309-315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21710245>.

199. Strobel P, Bargou R, Wolff A, et al. Sunitinib in metastatic thymic carcinomas: laboratory findings and initial clinical experience. *Br J Cancer* 2010;103:196-200. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20571495>.

200. Bisagni G, Rossi G, Cavazza A, et al. Long lasting response to the multikinase inhibitor bay 43-9006 (Sorafenib) in a heavily pretreated metastatic thymic carcinoma. *J Thorac Oncol* 2009;4:773-775. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19461405>.

201. Strobel P, Hartmann M, Jakob A, et al. Thymic carcinoma with overexpression of mutated KIT and the response to imatinib. *N Engl J Med* 2004;350:2625-2626. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15201427>.

202. Girard N. Targeted therapies for thymic malignancies. *Thorac Surg Clin* 2011;21:115-123, viii. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21070993>.

203. Kirzinger L, Boy S, Marienhagen J, et al. Octreotide LAR and Prednisone as Neoadjuvant Treatment in Patients with Primary or Locally Recurrent Unresectable Thymic Tumors: A Phase II Study. *PLoS One* 2016;11:e0168215. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27992479>.

204. Giaccone G, Kim C. Durable Response in Patients With Thymic Carcinoma Treated With Pembrolizumab After Prolonged Follow-Up. *J Thorac Oncol* 2021;16:483-485. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33248322>.



205. Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. *Lancet Oncol* 2018;19:347-355. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29395863>.

A large, light gray circular graphic with a double-line border. Inside the circle, the text "Discussion update in progress" is written in a bold, sans-serif font, centered vertically and horizontally.

Discussion  
update in  
progress