NCCN Guidelines Version 2.2016 Panel Members
Thymomas and Thymic Carcinomas

NCCN Guidelines Panel Disclosures

Version 2.2016, 03/16/16 © National Comprehensive Cancer Network, Inc. 2016, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.
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 Chemotherapy for Thymic Malignancies (THYM-C)
World Health Organization Histologic Classification (THYM-D)
Staging (ST-1)

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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. ©2016.
Updates in Version 2.2016 of the NCCN Guidelines for Thymomas and Thymic Carcinomas from Version 1.2016 include:

**MS-1**
- The discussion section was updated.

INITIAL EVALUATION

Mediastinal mass

- CT chest with contrast
- Serum beta-HCG, AFP, if appropriate
- CBC, platelets
- PET-CT scan optional
- Pulmonary function tests, as clinically indicated
- MRI chest, as clinically indicated

Thymic tumor likely\(^a\)

See Initial Management (THYM-2)

Thymic tumor unlikely

See disease-specific guidelines as appropriate (NCCN Table of Contents)

\(^a\)Well-defined anterior mediastinal mass in the thymic bed, tumor markers negative, absence of other adenopathy, and absence of continuity with the thyroid.
Thymic tumor likely\(^{a}\)

All patients should be managed by a multidisciplinary team with experience in the management of thymoma and thymic carcinoma

Surgically resectable\(^{b}\)

Surgical resection\(^{c}\) (total thymectomy and complete excision of tumor)

See Postoperative Management (THYM-3)

Locally advanced, unresectable\(^{b}\)

Tissue diagnosis with core needle biopsy or open biopsy (Avoid transpleural approach)

See Treatment (THYM-4)

---

\(^{a}\)Well-defined anterior mediastinal mass in the thymic bed, tumor markers negative, absence of other adenopathy, and absence of continuity with the thyroid.

\(^{b}\)Determination of resectability should be made by a board-certified thoracic surgeon, with primary focus on thoracic oncology.

\(^{c}\)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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**POSTOPERATIVE TREATMENT**

- **R0 resection**
  - Thymoma, no capsular invasion or thymic carcinoma, stage I
- **R1 resection**
  - Thymoma or thymic carcinoma, capsular invasion present stages II–IV
- **R2 resection**
  - Thymoma
  - Thymic carcinoma

**POSTOPERATIVE MANAGEMENT**

- Surveillance for recurrence with CT every 6 mo for 2 y, then annually for thymic carcinoma and annually for thymoma
- Recurrent disease, see THYM-4

**Pathology evaluation**

- **R0 resection**
  - Consider postoperative RT (category 2B)
- **R1 resection**
  - Postoperative RT ± chemotherapy
- **R2 resection**
  - Definitive RT ± chemotherapy
  - Definitive RT + chemotherapy

---

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

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

---

**See Principles of Surgical Resection (THYM-A).**

**R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.**

**See Principles of Radiation Therapy (THYM-B).**

**See Principles of Chemotherapy for Thymic Malignancies (THYM-C).**

**The duration for surveillance has not been established.**
Thymoma or thymic carcinoma: All patients should be managed by a multidisciplinary team with experience in the management of thymoma and thymic carcinoma.

Locally advanced → Chemotherapy

Solitary metastasis or ipsilateral pleural metastasis → Chemotherapy or Surgery

Evidence of extrathoracic metastases → Chemotherapy

Re-evaluate for surgery

Resectable → Surgical resection of primary tumor and isolated metastases → Consider Postoperative RT

Unresectable → RT ± chemotherapy

Consider chemotherapy for surgery

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

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

b Determination of resectability should be made by a board-certified thoracic surgeon, with primary focus on thoracic oncology.

c See Principles of Surgical Resection (THYM-A).

e See Principles of Radiation Therapy (THYM-B).

f See Principles of Chemotherapy for Thymic Malignancies (THYM-C).
Surgical resection should be performed on carefully evaluated patients by board-certified thoracic surgeons. Locally advanced (unresectable) and resectable stage ≥ 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.

Biopsy of a possible thymoma should avoid a transpleural approach.

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.

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 if all oncologic goals can be met as in standard procedures, and if performed in specialized centers by surgeons with experience in these techniques.1-5

PRINCIPLES OF RADIATION THERAPY (1 of 2)\(^1,2\)

**General Principles**
- Recommendations regarding RT should be made by a board-certified radiation oncologist.
- 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.
- Acronyms and abbreviations for RT are the same as listed in the Principles of RT for non-small cell lung cancer. See 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 Gy and above should be given to patients with gross residual disease (similar to patients with unresectable disease),\(^3,4\) when conventional fractionation (1.8–2.0 Gy per daily fraction) is applied.


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


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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### PRINCIPLES OF CHEMOTHERAPY FOR THYMIC MALIGNANCIES

#### FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosing</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP&lt;sup&gt;1&lt;/sup&gt; (preferred for thymoma)</td>
<td>Cisplatin 50 mg/m² IV day 1, Doxorubicin 50 mg/m² IV day 1, Cyclophosphamide 500 mg/m² IV day 1</td>
<td>Administered every 3 weeks</td>
</tr>
<tr>
<td>CAP with prednisone&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Cisplatin 30 mg/m² days 1–3, Doxorubicin, 20 mg/m²/d IV continuous infusion on days 1–3, Cyclophosphamide 500 mg/m² IV on day 1</td>
<td>Prednisone 100 mg/day days 1–5, Administered every 3 weeks</td>
</tr>
<tr>
<td>ADOC&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Cisplatin 50 mg/m² IV day 1, Doxorubicin 40 mg/m² IV day 1, Vincristine 0.6 mg/m² IV day 3, Cyclophosphamide 700 mg/m² IV day 4</td>
<td>Administered every 3 weeks</td>
</tr>
<tr>
<td>CAP with prednisone&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Cisplatin 30 mg/m² days 1–3, Doxorubicin, 20 mg/m²/d IV continuous infusion on days 1–3, Cyclophosphamide 500 mg/m² IV on day 1</td>
<td>Prednisone 100 mg/day days 1–5, Administered every 3 weeks</td>
</tr>
<tr>
<td>ADOC&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Cisplatin 50 mg/m² IV day 1, Doxorubicin 40 mg/m² IV day 1, Vincristine 0.6 mg/m² IV day 3, Cyclophosphamide 700 mg/m² IV day 4</td>
<td>Administered every 3 weeks</td>
</tr>
<tr>
<td>PE&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Cisplatin 60 mg/m² IV day 1, Etoposide 120 mg/m²/d IV days 1–3</td>
<td>Administered every 3 weeks</td>
</tr>
<tr>
<td>VIP&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Etoposide 75 mg/m² on days 1–4, Ifosfamide 1.2 g/m² on days 1–4, Cisplatin 20 mg/m² on days 1–4</td>
<td>Administered every 3 weeks</td>
</tr>
<tr>
<td>Carboplatin/Paclitaxel&lt;sup&gt;6&lt;/sup&gt; (preferred for thymic carcinoma)</td>
<td>Carboplatin AUC 6, Paclitaxel 225 mg/m²</td>
<td>Administered every 3 weeks</td>
</tr>
</tbody>
</table>

#### SECOND-LINE CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosing</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib (Thymic carcinomas only)&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemetrexed&lt;sup&gt;8&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus&lt;sup&gt;9&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel&lt;sup&gt;10-11&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide (including LAR) +/- prednisone&lt;sup&gt;12&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU and leucovorin&lt;sup&gt;14-15&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ifosfamide&lt;sup&gt;16&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### References on THYM-C 2 of 2

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

REFERENCES


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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### World Health Organization Histologic Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A tumor composed of a population of neoplastic thymic epithelial cells having spindle/oval shape, lacking nuclear atypia, and accompanied by few or no nonneoplastic lymphocytes.</td>
</tr>
<tr>
<td>AB</td>
<td>A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes.</td>
</tr>
<tr>
<td>B1</td>
<td>A tumor that resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla.</td>
</tr>
<tr>
<td>B2</td>
<td>A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes. Perivascular spaces are common and sometimes very prominent. A perivascular arrangement of tumor cells resulting in a palisading effect may be seen.</td>
</tr>
<tr>
<td>B3</td>
<td>A type of thymoma predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia. They are admixed with a mild component of lymphocytes, resulting in a sheetlike growth of the neoplastic epithelial cells.</td>
</tr>
<tr>
<td>C</td>
<td>A thymic tumor (thymic carcinoma) exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. Type C thymomas lack immature lymphocytes; whatever lymphocytes may be present are mature and usually admixed with plasma cells.</td>
</tr>
</tbody>
</table>

---

Staging

Table 1. Modified Masaoka clinical staging of thymoma

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

Table 2. TNM Classification

<table>
<thead>
<tr>
<th>T</th>
<th>Primary Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor completely encapsulated</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades pericapsular connective tissue</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades into neighboring structures, such as pericardium, mediastinal pleura, thoracic wall, great vessels and lung</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with pleural or pericardial dissemination</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Regional Lymph Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in anterior mediastinal lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in other intrathoracic lymph nodes excluding anterior mediastinal lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in scalene and/or supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Stage Grouping

<table>
<thead>
<tr>
<th>Stage Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>Stage II</td>
</tr>
<tr>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td>T1 N1 M0</td>
</tr>
<tr>
<td>T2 N1 M0</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
<tr>
<td>T4 Any N M0</td>
</tr>
<tr>
<td>Any T N2, 3 M0</td>
</tr>
<tr>
<td>Any T Any N M1</td>
</tr>
</tbody>
</table>

2Note that the Masaoka staging system is also used to stage thymic carcinomas.
3Travis WD, Brambilla E, Müller-Hermelink HK, Harris, CC. World Health Organization Classification of Tumours of the Lung Pleura, Thymus and Heart. IARC, Lyon, 2004.
Discussion

NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

*All recommendations are category 2A unless otherwise noted.*

Table of Contents

- Overview .................................................................................................................................................................................. MS-2
- Literature Search Criteria and Guidelines Update Methodology ................................................................................................ MS-2
- Mediastinal Masses ............................................................................................................................................................... MS-2
- Thymic Masses ........................................................................................................................................................................ MS-3
- Thymomas ................................................................................................................................................................................. MS-4
- Thymic Carcinomas ................................................................................................................................................................. MS-6
- References ................................................................................................................................................................................ MS-9
Overview

Thymic epithelial tumors originate in the thymus and include thymomas and thymic carcinomas.\(^1,2\) Thymomas are a common primary tumor in the anterior mediastinum, although they are rare (1.5 cases/million).\(^3,6\) Thymic carcinomas are very rare. Although thymomas can spread locally, they are much less invasive than thymic carcinomas.\(^4\) Patients with thymomas have 5-year survival rates of approximately 90%.\(^7,9\) However, 5-year survival rates for thymic carcinomas are only approximately 55%.\(^10,12\)

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 2010. This revised Discussion text now includes the updates from the 2015 NCCN Guidelines for Thymomas and Thymic Carcinomas and includes recent references; no changes were made to the algorithm for the 2016 update. 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.

Literature Search Criteria and Guidelines Update Methodology

Before 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 between September 1, 2014 and October 2, 2015 using the following search terms: Thymomas; Thymic Carcinomas. The PubMed database was chosen, because it is the most widely used resource for medical literature and indexes only 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 1; Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 25 citations and their potential relevance was examined. The data from key PubMed articles selected by the NCCN Panel for review during the NCCN Guidelines update meeting, as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the NCCN Panel, have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). If high-level evidence is lacking, recommendations 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 on the NCCN webpage.

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).\(^5,13-16\) Many mediastinal masses are benign, especially those occurring in asymptomatic patients; however, symptomatic patients often have malignant mediastinal lesions. All patients with a mediastinal mass should be evaluated to determine the type of mass and to determine the extent of disease before treatment (see Initial Evaluation in the NCCN Guidelines for Thymomas and Thymic Carcinomas). 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. Most masses in the mediastinum are metastases from a primary lung cancer (eg, non-small cell lung cancer). However, about 50% of primary cancers in the anterior mediastinum are thymomas.

Patients with thymomas often have an indolent presentation, whereas those with lymphoma or germ cell tumors have a rapid onset of symptoms. 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 Non-Hodgkin's Lymphomas and Hodgkin Lymphoma, available at NCCN.org). Thymic carcinoids are rare tumors that are discussed in the NCCN Guidelines for Neuroendocrine Tumors; they can be associated with multiple endocrine neoplasia type 1 (MEN1) syndrome (see the NCCN Guidelines for Neuroendocrine Tumors, available at NCCN.org).

Extragonadal germ cell tumors are rare tumors that may also occur in the mediastinum. Recommended tests for assessing mediastinal masses include chest CT with contrast and blood chemistry studies (see Initial Evaluation in the NCCN Guidelines for Thymomas and Thymic Carcinomas). On CT, a thymoma is usually a well-defined round or oval mass in the thymus without lymph node enlargement. Recently, low-dose CT was found to be useful for detecting lung cancer in patients at high risk (see the NCCN Guidelines for Lung Cancer Screening, available at NCCN.org). Medial masses (eg, lung metastases, thymomas, thymic carcinomas) may be detected in individuals undergoing lung cancer screening. However, data and guidelines about screening for lung cancer with low-dose CT do not apply to thymomas and thymic carcinomas; there are no data to suggest that screening improves survival for patients with thymomas and thymic carcinomas. In patients who cannot tolerate iodinated contrast, MRI of the chest may be useful. Combined PET-CT may be useful for determining whether extrathoracic metastases are present. PET-CT provides better correlation with anatomic structures than PET alone. 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 NCCN Guidelines for Thymomas and Thymic Carcinomas). 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.

Thymic Masses

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. 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 the gold standard of treatment and are recommended whenever possible for most resectable tumors (see Principles of Surgical Resection in the NCCN Guidelines for Thymomas and Thymic Carcinomas). 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. Core-needle or open biopsy is recommended for locally advanced, unresectable thymic masses.
Minimally invasive procedures are not routinely recommended, because only a few long-term studies are available regarding recurrence and survival. However, minimally invasive procedures may be considered if standard oncologic goals can be met (as previously described) and if performed in specialized centers with surgeons with expertise in these techniques. A recent systematic review of 1061 patients with thymomas reported that 5-year overall survival 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.

Although several staging systems exist, the Masaoka staging system is the most widely accepted system for management and determination of prognosis for both thymomas and thymic carcinomas (see Table 1 in the NCCN Guidelines for Thymomas and Thymic Carcinomas). The International Thymic Malignancy Interest Group (ITMIG) suggests using the Masaoka-Koga stage classification. A new proposal for a staging system for thymomas and thymic carcinomas is based on a combined effort by the ITMIG and International Association for the Study of Lung Cancer (IASLC). The TNM staging system is less commonly used (see Table 2 in the NCCN Guidelines for Thymomas and Thymic Carcinomas). The current TNM staging system will be revised when the new edition of the American Joint Committee on Cancer (AJCC 8th edition) becomes effective in January 2017. Patients with stage I to III thymomas have a 5-year survival rate of approximately 85% versus 65% for stage IV disease. In approximately 50% of patients, mortality is not related to thymoma. Mortality is related to myasthenia gravis in approximately 20% of patients.

The WHO histologic classification system can be used to distinguish between thymomas, thymic carcinomas, and thymic carcinoids (see Table 3 in the NCCN Guidelines for Thymomas and Thymic Carcinomas). 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. Thymic carcinomas are type C in the WHO classification, although they are very different from thymomas and are not advanced thymomas (see Thymic Carcinomas in this Discussion). The WHO histologic classification system was recently revised. However, the histologic subtype is less important for management than stage of disease and the extent of resection (ie, R0, R1, R2) (see Postoperative Management in the NCCN Guidelines for Thymomas and Thymic Carcinomas). For stage III to IV thymomas, 5-year survival rates have been reported to be 90% in patients with total resection. For thymic carcinomas, 5-year survival rates are lower, even in those with total resection.

Thymomas typically occur in adults 40 to 70 years of age; they are rare in children or adolescents. The etiology of thymomas is unknown; alcohol, tobacco smoking, and ionizing radiation do not appear to be risk factors for thymomas. The incidence of thymomas is higher in African Americans as well as Asians and Pacific Islanders, which suggests there may be a genetic component. Although some patients are asymptomatic, others present with chest pain, cough, or dyspnea. Approximately 30% to 50% of patients with thymomas have myasthenia gravis. Symptoms suggestive of myasthenia gravis include drooping eyelids, double vision, drooling, difficulty climbing stairs, hoarseness, and/or dyspnea. Before any surgical procedure, all patients suspected of having thymomas (even those without symptoms) should have their serum antiacetylcholine receptor antibody levels measured to determine
whether they have myasthenia gravis to avoid respiratory failure during surgery. If patients have myasthenia gravis, they should receive treatment by a neurologist with experience in myasthenia gravis before undergoing surgical resection.

Although thymomas can be locally invasive (eg, pleura, lung), they uncommonly spread to regional lymph nodes or extrathoracic sites. Surgery (ie, total thymectomy and complete excision of tumor) is recommended for all resectable thymomas for patients who can tolerate the surgery. For resected stage I and II thymomas, the 10-year survival rate is excellent (approximately 90% and 70%, respectively). Completeness of resection is the most important predictor of outcome. 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). A transpleural approach should be avoided during biopsy of a possible thymoma to prevent tumor seeding. Small biopsy sampling (fine-needle or core-needle biopsy) does not always indicate whether invasion is present. The ITMIG has established procedures for reporting the surgical and pathologic findings from resection specimens.

Adjuvant therapy is not recommended for completely resected (R0) stage I thymomas. For incompletely resected thymomas, postoperative radiation therapy (RT) is recommended (see Postoperative Management in the NCCN Guidelines for Thymomas and Thymic Carcinomas). Note that extensive elective nodal radiation is not recommended, because thymomas do not typically metastasize to regional lymph nodes. CT-based treatment planning is highly recommended before RT (see Principles of Radiation Therapy in the NCCN Guidelines for Thymomas and Thymic Carcinomas). RT should be given by the 3-D conformal technique to reduce damage to surrounding normal tissue (eg, heart, lungs, esophagus, spinal cord).

Use of intensity-modulated RT (IMRT) may decrease the dose to the normal tissues. However, if IMRT is used, guidelines from the ATC/NCI and ASTRO/ACR should be followed (http://rrp.cancer.gov/content/docs/imrt.doc). The ICRU-83 (International Commission on Radiation Units and Measurements Report 83) recommendations are also a useful resource. Although the normal tissue constraints recommendations for lung cancer may be used (see the Principles of Radiation Therapy in the NCCN Guidelines for Non-Small Cell Lung Cancer, available at NCCN.org), more conservative limits are recommended to minimize the dose volumes to all the normal structures. Because these patients are younger and usually long-term survivors, the mean dose to the heart should be as low as reasonably achievable.

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 NCCN Guidelines for Thymomas and Thymic Carcinomas). However, a total dose of 60 Gy or more (1.8–2 Gy/fraction per day) is recommended for patients with gross residual disease after surgery. In patients with thymomas who have capsular invasion after an R0 resection, postoperative RT can be considered although this is a category 2B recommendation (see Postoperative Management in the NCCN Guidelines for Thymomas and Thymic Carcinomas). Patients with stage III (with macroscopic invasion into neighboring organs) thymoma have higher risks of recurrent disease and, as such, postoperative radiation is recommended. Data suggest that patients with stage II thymoma
may not benefit from postoperative radiation. Postoperative chemotherapy is also not beneficial in this setting.

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 Treatment in the NCCN Guidelines for Thymomas and Thymic Carcinomas). For those with solitary metastasis or ipsilateral pleural metastases, options include induction chemotherapy or surgery. For patients with unresectable disease in both of these settings, RT with [or without] chemotherapy is recommended. For metastatic disease, chemotherapy is recommended (see Principles of Chemotherapy for Thymic Malignancies in the NCCN Guidelines for Thymomas and Thymic Carcinomas). Although 6 different combination regimens are provided in the NCCN algorithm, cisplatin/doxorubicin-based regimens seem to yield the best outcomes; the panel feels that cisplatin/doxorubicin/cyclophosphamide is the regimen of choice for thymoma. However, non-anthracycline regimens (eg, cisplatin/etoposide [with or without ifosfamide], carboplatin/paclitaxel) may be useful for patients who cannot tolerate the more aggressive regimens. Induction therapy followed by surgery may be useful for thymic malignancies initially considered unresectable.

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. 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.

Second-line systemic therapy includes sunitinib, pemetrexed, everolimus, paclitaxel, octreotide (long-acting release [LAR]) with or without prednisone, gemcitabine, 5-FU, etoposide, and ifosfamide. However, none of these agents has been assessed in randomized trials. Octreotide may be useful in patients with thymoma who have a positive octreotide scan or symptoms of carcinoid syndrome. Surgery is an option for patients with recurrent locally advanced disease, solitary metastases, or ipsilateral metastases.

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. Survival rates for thymic carcinomas vary depending on stage (stages 1–2: 91%; stages 3–4: 31%) and resectability (including completeness of resection). These tumors can be distinguished from thymomas because of their malignant histologic features and their different immunohistochemical and genetic features. 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. Thymic carcinomas often cause pericardial and pleural effusions. The Masaoka staging system can also be used to stage thymic carcinomas (see Table 1 in the NCCN Guidelines for Thymomas and Thymic Carcinomas).

It is important to note that thymic carcinomas are associated with a different clinical course from thymomas. Unlike thymomas, paraneoplastic syndromes, including myasthenia gravis, are very rare in
patients with thymic carcinoma. If myasthenia gravis is diagnosed, then the diagnosis of thymic carcinoma should be reassessed; the patient may actually have thymoma. 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 Caucasian individuals.

Similar to thymomas, patients with completely resected thymic carcinomas have longer survival than those who are either incompletely resected or are unresectable. Patients who have an R0 resection have a 5-year survival of about 60%. 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. After resection of thymic carcinomas, postoperative management includes RT with (or without) chemotherapy, depending on the completeness of resection (see Postoperative Management in the NCCN Guidelines for Thymomas and Thymic Carcinomas).

A recent study suggests that adjuvant therapy may not be necessary for early-stage thymic carcinomas. For unresectable or metastatic thymic carcinomas, chemotherapy with (or without) RT is recommended (see Principles of Chemotherapy for Thymic Malignancies and Principles of Radiation Therapy in the NCCN Guidelines for Thymomas and Thymic Carcinomas).

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 NCCN Guidelines for Thymomas and Thymic Carcinomas). However, a total dose of 60 Gy or more (1.8–2 Gy/fraction per day) is recommended for patients with gross residual disease after surgery. In patients with thymic carcinomas who have capsular invasion after an R0 resection, postoperative RT can be considered although this is a category 2B recommendation (see Postoperative Management in the NCCN Guidelines for Thymomas and Thymic Carcinomas).

Adjuvant therapy is not recommended for completely resected (R0) stage I thymic carcinomas. Unfortunately, thymic carcinomas respond poorly to chemotherapy; carboplatin/paclitaxel is recommended, because it has the highest response rate in patients with thymic carcinomas in clinical trials. Data suggest that the ADOC (cisplatin, doxorubicin, vincristine, and cyclophosphamide) regimen is also effective, but it is more toxic than carboplatin/paclitaxel. 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 Treatment in the NCCN Guidelines for Thymomas and Thymic Carcinomas).

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. 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. However, the duration, frequency, or type of imaging for surveillance for thymic carcinomas has not been established in published studies. Data are lacking regarding second-line chemotherapy for thymic carcinomas. Most of the second-line agents in the NCCN algorithm are appropriate for thymomas (see Principles of Chemotherapy for Thymic Malignancies in the NCCN Guidelines for Thymomas and Thymic Carcinomas). However, S-1 (an oral fluorouracil) appears to be active in patients with thymic carcinomas. Targeted therapy (eg,
sunitinib, sorafenib) may be useful for patients with c-Kit mutations; however, these mutations are rare in thymic carcinomas (<10%). Patients with thymomas do not have c-Kit mutations.147
References


