NCCN Thymomas and Thymic Carcinomas Panel Members

Summary of Guidelines Updates
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Initial Management (THYM-2)
Resectable Disease (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)
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

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Summary of changes in the 1.2014 version of the Guidelines for Thymomas and Thymic Carcinomas from the 2.2013 version include:

**THYM-1**
- The following was removed from the initial evaluation: “TSH, T3, T4 levels, as clinically indicated.”
- “Thymic malignancy likely” was changed to “Thymic tumor likely.”
- “Thymic malignancy unlikely” was changed to “Thymic tumor unlikely.”
- The qualifier “as appropriate” was added after “See disease-specific guidelines.”

**THYM-3**
- Thymic carcinoma was added to stage I category after R0 resection.
- Surveillance recommendations were modified: “Surveillance for recurrence with annual chest CT. CT every 6 mo for 2 y, then annually for 5 y for thymic carcinoma and 10 y for thymoma.”
- Footnote “f” was added: “The duration for surveillance has not been established.”

**THYM-B 1 of 2**
- General Principles, bullet 2 was modified: “RT should be given for patients with unresectable (after failure of if disease progresses on induction chemotherapy) or incompletely resected invasive thymoma or thymic carcinoma.”

**THYM-C 2 of 2**
- Previous reference 9 was removed.

**MS-1**
- The Discussion section has been updated to reflect the changes in the algorithm.
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

See Initial Management (THYM-2)

Thymic tumor unlikely

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

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INITIAL MANAGEMENT

Thymic tumor likely

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

Surgically resectable

Surgical resection (total thymectomy and complete excision of tumor)

See Postoperative Management (THYM-3)

Locally advanced, unresectable

Tissue diagnosis with core needle biopsy or open biopsy (Biopsy should not violate the pleural space)

See Treatment (THYM-4)

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a Determination of resectability should be made by a board-certified thoracic surgeon.

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

<table>
<thead>
<tr>
<th>Pathology evaluation</th>
<th>R0 resection</th>
<th>R1 resection</th>
<th>R2 resection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thymoma, no capsular invasion or thymic carcinoma, stage I</td>
<td>Thymoma or thymic carcinoma, capsular invasion present stages II-IV</td>
<td>Thymoma or thymic carcinoma, capsular invasion present stages II-IV</td>
</tr>
<tr>
<td></td>
<td>Consider postoperative RT (category 2B)</td>
<td>Postoperative RT</td>
<td>Postoperative RT</td>
</tr>
<tr>
<td></td>
<td>Surveillance for recurrence with CT every 6 mo for 2 y, then annually for 5 y for thymic carcinoma and 10 y for thymoma</td>
<td>Surveillance for recurrence with CT every 6 mo for 2 y, then annually for 5 y for thymic carcinoma and 10 y for thymoma</td>
<td>Surveillance for recurrence with CT every 6 mo for 2 y, then annually for 5 y for thymic carcinoma and 10 y for thymoma</td>
</tr>
</tbody>
</table>

**Thymoma**

- Consider postoperative RT (category 2B)
- Surveillance for recurrence with CT every 6 mo for 2 y, then annually for 5 y for thymic carcinoma and 10 y for thymoma

**Thymic Carcinoma**

- Postoperative RT + Chemotherapy
- Surveillance for recurrence with CT every 6 mo for 2 y, then annually for 5 y for thymic carcinoma and 10 y for thymoma

**Recurrent disease**

- See THYM-4

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**References:**

- 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 (THYM-C).
- The duration for surveillance has not been established.

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Version 1.2014, 08/12/13 © National Comprehensive Cancer Network, Inc. 2013, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.
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, ADVANCED, OR RECURRENT DISEASE**

- **Thymoma or thymic carcinoma:**
  - All patients should be managed by a multidisciplinary team with experience in the management of thymoma and thymic carcinoma.

**TREATMENT**

- **Locally advanced**
  - Chemotherapy → Re-evaluate for surgery → Surgical resection of primary tumor and isolated metastases → Consider Postoperative RT

- **Evidence of distant metastases** → Chemotherapy

- **Isolated solitary metastasis** → Chemotherapy or Surgery → Consider chemotherapy or RT

- **Unresectable**
  - RT ± chemotherapy

- **Resectable**
  - Consider chemotherapy or RT → Surgical resection of primary tumor and isolated metastases → Consider Postoperative RT

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- Determination of resectability should be made by a board-certified thoracic surgeon.
- See Principles of Surgical Resection (THYM-A).
- See Principles of Radiation Therapy (THYM-B).
- See Principles of Chemotherapy (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 tranpleural 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. In some cases, resection of pleural metastases to achieve complete gross resection may be 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

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

**General Principles**
- Recommendations regarding RT should be made by a board-certified radiation oncologist.
- RT should be given for patients with unresectable (if disease progresses on induction chemotherapy) or incompletely resected invasive thymoma or thymic carcinoma.
- 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 60-70 Gy should be given to patients with unresectable disease.
- For adjuvant treatment, the radiation dose consists of 45-50 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 to 2.0 Gy per daily fraction) is applied.

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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 (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended, as thymomas do not commonly metastasize to regional lymph nodes.\(^5\)
• 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

• CT-based planning is highly recommended. CT scans should be taken in the treatment position with arms raised above the head (treatment position). Simulations of target motion are encouraged whenever possible. CT scans can be performed at the end of natural inhale, exhale, and under free breathing when more sophisticated techniques like 4-D CT, gated CT, or active breathing control are not available. Target motion should be managed using the Principles of RT for non-small cell lung cancer. See NCCN Guidelines for Non-Small Cell Lung Cancer. Intravenous contrast is beneficial in the unresectable setting.
• Radiation beam arrangements should be selected based on the shape of PTV aiming to confine the prescribed high dose to the target and minimize dose to adjacent critical structures. Anterior-posterior and posterior-anterior ports weighing more anteriorly, or wedge pair technique may be considered. These techniques, although commonly used during the traditional 2-D era, can generate an excessive dose to normal tissue. A dose-volume histogram of the lungs, heart, and cord need to be carefully reviewed for each plan.
• RT should be given by 3-D conformal technique to reduce surrounding normal tissue damage (e.g., heart, lungs, esophagus, spinal cord). Intensity-modulated RT (IMRT) may further improve the dose distribution and decrease the dose to the normal tissue as indicated. If IMRT is applied, the ASTRO/ACR IMRT guidelines should be strictly followed.\(^6,7\)
• In addition to following the normal tissue constraints recommendation using the Principles of RT 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 dose to the total heart should be limited to \(\leq 30\) Gy.

See General Principles and Radiation Dose (THYM-B 1 of 2)

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### Principles of Chemotherapy for Thymic Malignancies

#### First-Line Combination Chemotherapy Regimens

**CAP** (preferred for thymoma)
- Cisplatin 50 mg/m² IV day 1
- Doxorubicin 50 mg/m² IV day 1
- Cyclophosphamide 500 mg/m² IV day 1
  - Administered every 3 weeks

**CAP with Prednisone**
- Cisplatin 30 mg/m² days 1-3
- Doxorubicin, 20 mg/m²/d
  - IV continuous infusion on days 1 to 3
- Cyclophosphamide 500 mg/m² IV on day 1
  - Prednisone 100 mg/day days 1-5
  - Administered every 3 weeks

**ADOC**
- 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
  - Administered every 3 weeks

**PE**
- Cisplatin 60 mg/m² IV day 1
- Etoposide 120 mg/m²/d IV days 1-3
  - Administered every 3 weeks

**VIP**
- 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
  - Administered every 3 weeks

**Carboplatin/Paclitaxel** (preferred for thymic carcinoma)
- Carboplatin AUC 6
- Paclitaxel 225 mg/m²
  - Administered every 3 weeks

#### Second-Line Chemotherapy

**Etoposide**
- Cisplatin 60 mg/m² IV day 1
- Etoposide 120 mg/m²/d IV days 1-3
  - Administered every 3 weeks

**Ifosfamide**
- 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
  - Administered every 3 weeks

**Pemetrexed**
- Octreotide (including LAR) +/- prednisone
- 5-FU and leucovorin
- Gemcitabine
- Paclitaxel

### References on THYM-C 2 of 2

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PRINCIPLES OF CHEMOTHERAPY FOR THYMIC MALIGNANCIES

REFERENCES


# Staging

## Table 1. Modified Masaoka clinical staging of thymoma\(^1,2\)

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

## Table 2. TNM Classification\(^3\)

<table>
<thead>
<tr>
<th>T</th>
<th>Primary Tumor</th>
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<tr>
<td>TX</td>
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<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>
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</table>

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

<table>
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<th>N Type</th>
<th>M Type</th>
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<tr>
<td>Stage I</td>
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<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
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<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
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<td>M0</td>
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<tr>
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<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

\(^1\) Reprinted from Crit Rev Oncol Hematol, 65, Wright CD, Management of thymomas, 109-120, Copyright (2008), with permission from Elsevier.  
\(^2\) Note that the Masaoka staging system is also used to stage thymic carcinomas.  
\(^3\) Travis WD, Brambilla E, Müller-Hermelink HK, Harris, CC. World Health Organization Classification of Tumours of the Lung Pleura, Thymus and Heart. IARC, Lyon, 2004.
Staging

Table 3. 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>


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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.

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Overview

Thymomas are a common primary tumor in the anterior mediastinum, although they are rare (1.5 cases/million).\(^1\)\(^-\)\(^3\) Thymic carcinomas are very rare. Thymomas and thymic carcinomas originate in the thymus. Although thymomas can spread locally, they are much less invasive than thymic carcinomas.\(^1\) Patients with thymomas have 5-year survival rates of approximately 78%.\(^4\) However, 5-year survival rates for thymic carcinomas are only approximately 40%.\(^5\)\(^,\)\(^6\) The NCCN Guidelines for Thymomas and Thymic Carcinomas outline the evaluation, treatment, and management of these mediastinal tumors; the Updates describe the most recent revisions. These NCCN Guidelines were first published in 2010.

Mediastinal Masses

Masses in the anterior mediastinum can be neoplasms (ie, thymomas, lymphomas, thymic carcinomas, thymic carcinoids, thymolipomas, germ cell tumors, lung metastases) or non-neoplastic conditions (ie, intrathoracic goiter, thymic cysts, lymphangiomas, aortic aneurysms).\(^2\)\(^,\)\(^7\)\(^,\)\(^8\) 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, intrathoracic goiter, thymic cysts, lymphangiomas, aortic aneurysms).\(^2\)\(^,\)\(^7\)\(^,\)\(^8\) 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).\(^15\)\(^-\)\(^19\) On CT, a thymoma is usually a well-defined round or oval mass in the thymus.\(^17\)\(^,\)\(^20\) Recently, low-dose CT was found to be useful for detecting lung cancer in high-risk individuals (see the NCCN Guidelines for Lung Cancer Screening).\(^21\) Mediastinal masses (eg, lung metastases, thymomas, thymic carcinomas) may be detected in individuals undergoing lung cancer screening.

In patients who cannot tolerate iodinated contrast, MRI of the chest may be useful.\(^17\) Combined PET-CT may be useful for determining whether distant metastases are present.\(^22\) 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 Masses

All patients with thymic malignancies should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists to determine the optimal plan of care before treatment. It is critical to determine whether the mass can be surgically resected; a board-certified thoracic surgeon 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 typically recommended, because long-term data are not 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.

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). The International Thymic Malignancy Interest Group (ITMIG) suggests using the Masaoka-Koga stage classification. The TNM staging system is less commonly used (see Table 2). 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. In approximately 20% of patients, mortality is related to myasthenia gravis.

The WHO histologic classification system can be used to distinguish between thymomas, thymic carcinomas, and thymic carcinoids (see Table 3). 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). However, the histologic subtype is less important for management than 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

Thymomas typically occur in adults 40 to 70 years of age; they are rare in children or adolescents. Although some patients are asymptomatic, others present with chest pain, cough, or dyspnea. Approximately 30% to 50% of patients with thymomas have myasthenia gravis; therefore, patients should be evaluated for myasthenia gravis (eg, by history and/or measuring serum antiacetylcholine receptor antibody levels). Although thymomas can be locally invasive (eg, pleura, lung), they uncommonly spread to regional lymph nodes or distant 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).\textsuperscript{10,55}
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).\textsuperscript{10} A transpleural approach should be avoided during biopsy of a possible thymoma.\textsuperscript{56,57} Small biopsy sampling (fine-needle or core-needle biopsy) does not always indicate whether invasion is present.\textsuperscript{58} The ITMIG has established procedures for reporting the surgical and pathologic findings from resection specimens.\textsuperscript{59}

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. 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.\textsuperscript{56,60-62}

Adjuvant therapy is not recommended for completely resected (R0) stage I thymomas or for stage I thymic carcinomas.\textsuperscript{24,63,64} For incompletely resected thymomas, postoperative radiation therapy (RT) is recommended (see \textit{Postoperative Management} in the NCCN Guidelines for Thymomas and Thymic Carcinomas).\textsuperscript{24,65} Note that extensive elective nodal radiation is not recommended, because thymomas do not typically metastasize to regional lymph nodes.\textsuperscript{4,66} CT-based treatment planning is highly recommended before RT (see \textit{Principles of Radiation Therapy} in the NCCN Guidelines for Thymomas and Thymic Carcinomas).\textsuperscript{67} 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.\textsuperscript{67,68} However, if IMRT is used, guidelines from the ATC/NCI and ASTRO/ACR should be followed (http://rrp.cancer.gov/content/docs/imrt.doc).\textsuperscript{69-72} The ICRU-83 (International Commission on Radiation Units and Measurements Report 83) recommendations are also a useful resource.\textsuperscript{71,73} Although the normal tissue constraints recommendations for lung cancer may be used (see the \textit{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.\textsuperscript{74,75} Because these patients are younger and usually long-term survivors, the total dose to the heart should be limited to 30 Gy or less.

A definitive total dose of 60 to 70 Gy is recommended for patients with unresectable disease. For adjuvant treatment, a total dose of 45 to 50 Gy is recommended for clear or close margins; a total dose of 54 Gy is recommended for microscopically positive resection margins (see \textit{Principles of Radiation Therapy} in the NCCN Guidelines for Thymomas and Thymic Carcinomas).\textsuperscript{67,68} 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.\textsuperscript{76,77} Postoperative RT can be considered in patients with thymomas and thymic carcinomas who have capsular invasion after an R0 resection, although this is a category 2B recommendation (see \textit{Postoperative Management} in the NCCN Guidelines for Thymomas and Thymic Carcinomas).\textsuperscript{64,67,78-80} Patients with stage III (with macroscopic invasion into neighboring organs) thymoma or those with thymic carcinoma have higher risks of recurrent disease and, as such, postoperative radiation is recommended to
maximize local control. Increasing evidence suggests that patients with stage II thymoma may not benefit from postoperative radiation. Postoperative chemotherapy is also not beneficial.

For advanced disease, chemotherapy with (or without) RT 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. For thymic carcinoma, the panel recommends 
carboplatin/paclitaxel. Induction therapy followed by surgery may be 
useful for thymic malignancies initially considered unresectable.

Second-line systemic therapy includes etoposide, ifosfamide, 
pemetrexed, octreotide (long-acting release [LAR]; with or without 
prednisone), 5-FU, gemcitabine, and paclitaxel. However, none of these agents have been assessed in randomized trials. 
Octreotide may be useful in patients with thymoma who have a positive 
ocreotide scan or symptoms of carcinoid syndrome. After resection, 
panel members agree that surveillance for recurrence should include 
chest CT every 6 months for 2 years, then annually for 10 years for 
thymoma and 5 years for thymic carcinoma. Given the risk of later 
recurrence for thymoma, surveillance should continue for at least 10 
years. However, the duration for surveillance for thymomas and thymic 
carcinomas has not been established in published studies. Patients with 
thymoma also have an increased risk for second malignancies, 
although no particular screening studies are recommended.

Thymic Carcinomas

Thymic carcinomas are rare aggressive tumors that often metastasize 
to regional lymph nodes and distant sites; thus, they have a worse 
prognosis than thymomas (5-year survival rates, 30%– 
50%). These tumors can be distinguished from thymomas 
because of their malignant histologic features and their different 
immunohistochemical and genetic features. 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). It is important to note that 
thymic carcinomas are very different from thymomas.

Similar to thymomas, patients with completely resected thymic 
carcinomas have longer survival than those who are either incompletely 
resected or are unresectable. Thus, management depends on the 
extent of resection. 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 Radiation Therapy and Principles of Chemotherapy for 
Thymic Malignancies in the NCCN Guidelines for Thymomas and Thymic 
Carcinomas).

Unfortunately, thymic carcinomas respond poorly to chemotherapy; 
carboplatin/paclitaxel is recommended, because it has the highest 
response rate among thymic carcinomas in clinical trials.
suggest that the ADOC (cisplatin, doxorubicin, vincristine, and cyclophosphamide) regimen is also effective, but it is more toxic than carboplatin/paclitaxel.\textsuperscript{120} Data are lacking regarding second-line chemotherapy for thymic carcinomas.\textsuperscript{84} 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).\textsuperscript{85} However, S-1 (an oral fluorouracil) appears to be active in patients with thymic carcinomas.\textsuperscript{123,124} Targeted therapy (eg, sunitinib, sorafenib) may be useful for patients with c-Kit mutations; however, these mutations are rare in thymic carcinomas (<10%).\textsuperscript{85,125-129} Patients with thymomas do not have c-Kit mutations.\textsuperscript{110}
References


