Thymomas and Thymic Carcinomas

Version 1.2011

NCCN.org
## NCCN Guidelines™ Version 1.2011 Panel Members

### Thymomas and Thymic Carcinomas

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution/Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>David S. Ettinger, MD</em></td>
<td>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins</td>
</tr>
<tr>
<td>Wallace Akerley, MD</td>
<td>Huntsman Cancer Institute at the University of Utah</td>
</tr>
<tr>
<td>Hossein Borghaei, DO, MS</td>
<td>Fox Chase Cancer Center</td>
</tr>
<tr>
<td>Andrew Chang, MD</td>
<td>University of Michigan Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Richard T. Cheney, MD</td>
<td>Roswell Park Cancer Institute</td>
</tr>
<tr>
<td>Lucian R. Chirieac, MD</td>
<td>Dana-Farber/Brigham and Women's Cancer Center</td>
</tr>
<tr>
<td>Thomas A. D’Amico, MD</td>
<td>Duke Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Todd L. Demmy, MD</td>
<td>Roswell Park Cancer Institute</td>
</tr>
<tr>
<td>RamaswamyGovindan, MD</td>
<td>Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine</td>
</tr>
<tr>
<td>Frederic W. Grannis, Jr., MD</td>
<td>City of Hope Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Leora Horn, MD</td>
<td>Vanderbilt-Ingram Cancer Center</td>
</tr>
<tr>
<td>Thierry M. Jahan, MD</td>
<td>UCSF Helen Diller Family Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Anne Kessinger, MD</td>
<td>UNMC Eppley Cancer Center at The Nebraska Medical Center</td>
</tr>
<tr>
<td>Ritsuko Komaki, MD</td>
<td>The University of Texas MD Anderson Cancer Center</td>
</tr>
<tr>
<td>Feng-Ming (Spring) Kong, MD</td>
<td>University of Michigan Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Mark G. Kris, MD</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>Lee M. Krug, MD</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>Inga T. Lennies, MD</td>
<td>Massachusetts General Hospital Cancer Center</td>
</tr>
<tr>
<td>Billy W. Loo, Jr., MD</td>
<td>Stanford Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Renato Martins, MD</td>
<td>Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance</td>
</tr>
<tr>
<td>Janis O’Malley, MD</td>
<td>University of Alabama at Birmingham Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Raymond U. Osarogiagbon, MD</td>
<td>St. Jude Children’s Research Hospital/University of Tennessee Cancer Institute</td>
</tr>
<tr>
<td>Gregory A. Otterson, MD</td>
<td>Arthur G. James Cancer Hospital &amp; Richard J. Solove Research Institute at The Ohio State University</td>
</tr>
<tr>
<td>Jyoti D. Patel, MD</td>
<td>Robert H. Lurie Comprehensive Cancer Center of Northwestern University</td>
</tr>
<tr>
<td>Mary Pinder-Schenck, MD</td>
<td>H. Lee Moffitt Cancer Center &amp; Research Institute</td>
</tr>
<tr>
<td>Katherine M. Pisters, MD</td>
<td>The University of Texas MD Anderson Cancer Center</td>
</tr>
<tr>
<td>Karen Reckamp, MD</td>
<td>City of Hope Comprehensive Cancer Center</td>
</tr>
<tr>
<td><em>Gregory J. Riely, MD</em></td>
<td>Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>Eric Rohren, MD</td>
<td>The University of Texas MD Anderson Cancer Center</td>
</tr>
<tr>
<td>Scott J. Swanson, MD</td>
<td>Dana-Farber/Brigham and Women’s Cancer Center</td>
</tr>
<tr>
<td>Douglas E. Wood, MD</td>
<td>Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance</td>
</tr>
<tr>
<td>Stephen C. Yang, MD</td>
<td>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins</td>
</tr>
</tbody>
</table>

### NCCN Guidelines Panel Disclosures

- Medical Oncology
- * Writing Committee Member
- Surgery/Surgical oncology
- Pathology
- Radiotherapy
- Hematology/ Hematology oncology
- Hematology oncology
- Interventional Radiology

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NCCN Thymomas and Thymic Carcinomas Panel Members

Summary of Guidelines Updates
Initial Evaluation (THYM-1)
Initial Management (THYM-2)
Resectable Disease (THYM-3)
Advanced Disease (THYM-4)
Principles of Surgical Resection (THYM-A)
Principles of Radiation Therapy (THYM-B)
Principles of Chemotherapy (THYM-C)
Staging (ST-1)

Clinical Trials: The 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
Updates
Thymomas and Thymic Carcinomas

Summary of the changes in the 1.2010 version of the Thymomas and Thymic Carcinomas Guidelines from the 2.2010 version include:

Global Change
The title of the Guidelines changed from Thymic Malignancies to Thymomas and Thymic Carcinomas.

THYM-1
- FDG-PET changed to PET-CT.

THYM-2
- Footnote “a” added: “Determination of resectability should be made by a thoracic surgeon.”

THYM-3
- R0 resection, thymoma or thymic carcinoma, capsular invasion present: the category of “high risk patients” was removed from “Consider postoperative RT.”
- R2 resection: Recommendations listed separately for thymoma and thymic carcinoma. Combined chemotherapy/RT listed for thymic carcinoma and RT with optional chemotherapy listed as an option for thymoma.

THYM-A
- Bullet 2 and 3: The category 2B designation was changed to category 2A
- The following bullet was added: “Surgical resection should be performed on carefully evaluated patients by board-certified thoracic surgeons. Some cases should be discussed and evaluated by multidisciplinary conferences.”

ST-1
- The World Health Organization Histologic Classification system added for thymic tumors.
INITIAL EVALUATION

Mediastinal Mass

- CT chest with contrast
- Serum beta-HCG, AFP, if appropriate
- CBC, platelets
- PET-CT and radiolabeled octreotide scan optional
- TSH, T3, T4 levels, as clinically indicated
- Pulmonary function tests (PFTs), as clinically indicated
- MRI chest, as clinically indicated

<table>
<thead>
<tr>
<th>Thymic malignancy likely</th>
<th>See Initial Management (THYM-2)</th>
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</thead>
<tbody>
<tr>
<td>Thymic malignancy unlikely</td>
<td>See disease specific guidelines (NCCN Table of Contents)</td>
</tr>
</tbody>
</table>

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.
Thymic malignancy likely: All patients should be managed by a multidisciplinary team with experience in the management of thymoma.

- **Surgically resectable**
  - Surgical resection\(^b\) (total thymectomy and complete excision of tumor)
  - See Postoperative Management (THYM-3)

- **Locally advanced, unresectable\(^a\)**
  - Tissue diagnosis with core needle biopsy or open biopsy (Biopsy should not violate the pleural space)
  - See Treatment (THYM-4)

\(^a\) Determination of resectability should be made by a thoracic surgeon.

\(^b\) See Principles of Surgical Resection for Thymic Malignancies (THYM-A).

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**Thymomas and Thymic Carcinomas**

**RESECTABLE DISEASE**

- **R0 resection**
  - Thymoma, no capsular invasion → Surveillance for recurrence with annual chest CT

- **R1 resection**
  - Thymoma or thymic carcinoma, capsular invasion present → Consider postoperative RT\(^c\) (category 2B)
  - Thymoma → Postoperative RT\(^c\)
  - Thymic carcinoma → Postoperative RT\(^c\) + Chemotherapy\(^d\)

- **R2 resection**
  - Thymoma → RT\(^c\) ± chemotherapy\(^d\)
  - Thymic carcinoma → RT\(^c\) + chemotherapy\(^d\)

**POSTOPERATIVE MANAGEMENT**

- Surveillance for recurrence with annual chest CT

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\(b\) See Principles of Surgical Resection for Thymic Malignancies (THYM-A).

\(c\) See Principles of Radiation Therapy for Thymic Malignancies (THYM-B).

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

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ADVANCED DISEASE  

TREATMENT  

Localized tumor  →  Chemotherapy\(^c\)  →  Re-evaluate for surgery  

Thymoma or thymic carcinoma  

Evidence of distant metastases  →  Chemotherapy\(^c\)  

Resectable\(^a\)  →  Surgical resection of primary tumor and isolated metastases  

Consider postoperative RT\(^b\)  

Unresectable  →  RT\(^b\) ± chemotherapy\(^c\)  

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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 SURGICAL RESECTION

- Surgical resection should be performed on carefully evaluated patients by board-certified thoracic surgeons. Some cases should be discussed and evaluated by multidisciplinary conferences.
- 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 they 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 pericardium, phrenic nerve, pleura, lung, and even major vascular structures.
- 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 lack of long-term data.

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PRINCIPLES OF RADIATION THERAPY (1 of 2)

General principles

- RT should be given for patients with unresectable (after failure of 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, and also with the pathologist regarding the detailed pathology on histology, disease extent such as extracapsular extension, and surgical margins.
- Acronyms and abbreviations of RT are the same as listed in the Principles of RT for non-small cell lung cancer. See NCCN Non-Small Cell Lung Cancer Guidelines

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), when conventional fractionation (1.8 to 2.0 Gy per daily fraction) is applied.

See Radiation Volume and Radiation Techniques THYM-B 2 of 2

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Radiation Volume

- The gross tumor volume (GTV) should include any grossly visible tumor. Surgical clips indicative of gross residual tumor should be included for postoperative cases.
- The clinical tumor 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.  
- The planning target volume (PTV) should consider the target motion and daily set-up 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 set-up of each clinic.

Radiation Techniques

- CT-based planning is highly recommended. CT scans should be taken in the treatment position with arms raised above 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 4D CT, gated CT, or active breathing control (ABC) are not available. Target motion should be managed using the Principles of RT for non-small cell lung cancer. See NCCN Non-small Cell Lung Cancer Guidelines. 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 (AP/PA) ports weighting more anteriorly, or wedge pair technique may be considered. These techniques, although commonly used during the traditional 2D era, can generate excessive dose to normal tissue. Dose Volume Histogram (DVH) of lungs, heart and cord need to be carefully reviewed for each plan.
- RT should be given by 3D conformal technique to reduce surrounding normal tissue damage (e.g., heart, lungs, esophagus, and spinal cord). Intensity-modulated RT (IMRT) may further improve the dose distribution and decrease dose to the normal tissue as indicated. If IMRT is applied, the NCT/ASTRO IMRT guidelines (http://www.astro.org/Research/ResearchHighlights/documents/imrt.pdf) should be followed strictly.
- 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 ≤ 30 Gy.

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# Principles of Chemotherapy for Thymic Malignancies

## First-Line Combination Chemotherapy Regimens

| CAP | Cisplatin 50 mg/m² IV d1  
Doxorubicin 50 mg/m² IV d1  
Cyclophosphamide 500 mg/m² IV d1  
Administered every 3 weeks |
| CAP with Prednisone  | Cisplatin 30 mg/m² d1-3  
Doxorubicin, 20 mg/m²/d  
IV continuous infusion on d 1 to 3  
Cyclophosphamide 500 mg/m² IV on d 1  
Prednisone 100 mg/day d1-5  
Administered every 3 weeks |
| ADOC | Cisplatin 50 mg/m² IV d1  
Doxorubicin 40 mg/m² IV d1  
Vincristine 0.6 mg/m² IV d3  
Cyclophosphamide 700 mg/m² IV d4  
Administered every 4 weeks |
| PE | Cisplatin 60 mg/m² IV d1  
Etoposide 120 mg/m²/d IV d1-3  
Administered every 3 weeks |
| VIP | Etoposide 75 mg/m² on d 1-4  
Ifosfamide 1.2 g/m² on d 1-4  
Cisplatin 20 mg/m² on d 1-4  
Administered every 3 weeks |
| Carboplatin/Paclitaxel  | Carboplatin AUC 5  
Paclitaxel 225 mg/m²  
Administered every 3 weeks |

## Second-Line Chemotherapy

- Etoposide
- Ifosfamide
- Pemetrexed
- Octreotide +/- Prednisone
- 5-Fluorouracil and Leucovorin
- Gemcitabine
- Paclitaxel

## Notes


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Staging

Table 1. Modified Masaoka clinical staging of thymoma

<table>
<thead>
<tr>
<th>Masaoka stage</th>
<th>Diagnostic criteria</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Macroscopically and microscopically completely encapsulated</td>
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<tr>
<td>Stage II</td>
<td>(A) Microscopic transcapsular invasion.</td>
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<tr>
<td></td>
<td>(B) Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium</td>
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<tr>
<td>Stage III</td>
<td>Macroscopic invasion into neighboring organs (i.e., pericardium, great vessels, lung).</td>
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<tr>
<td>Stage IV</td>
<td>(A) Pleural or pericardial dissemination.</td>
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<td></td>
<td>(B) Lymphogenous or hematogenous metastasis</td>
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Table 2. World Health Organization Histologic Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<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>
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<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>
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<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>
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<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>
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<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>
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<tr>
<td>C</td>
<td>A thymic tumor 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>
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2Note the Masaoka staging system is also used to stage thymic carcinomas.


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Thymic Masses

Masses in the anterior mediastinum can be neoplasms (i.e., thymomas, lymphomas, thymic carcinomas, thymic carcinoids, thymolipomas, germ cell tumors, parathyroid adenomas) or non-neoplastic conditions (i.e., intrathoracic goiter, thymic cysts, lymphangiomas, aortic aneurysms). Lymphomas typically manifest as generalized disease but can also be primary anterior mediastinal lesions (i.e., nodular sclerosing Hodgkin’s disease, and non-Hodgkin’s lymphomas [large B-cell lymphoma and lymphoblastic lymphoma]); patients typically have lymphadenopathy (see the NCCN Non-Hodgkin’s Lymphomas Guidelines and the NCCN Hodgkin Disease/Lymphoma Guidelines). Thymic carcinoids are rare tumors that are discussed in the NCCN Neuroendocrine Tumors Guideline. Teratomas are discussed in the NCCN Testicular Cancer Guideline.

Overview

Masses in the anterior mediastinum can be neoplasms (e.g., thymomas, lymphomas, thymic carcinomas) or non-neoplastic conditions (e.g., goiter, thymic cysts). Many mediastinal masses are benign, especially those occurring in asymptomatic patients; however, symptomatic patients often have malignant mediastinal lesions. Thymomas are the most common tumor in the anterior mediastinum. The NCCN guideline for Thymic Malignancies outlines the evaluation, treatment, and management of thymomas and thymic carcinomas (see “Thymic Masses”).

Alpha-fetoprotein (AFP) and beta–human chorionic gonadotropin (beta-HCG) levels should be measured (if appropriate) to rule out germ cell tumors. Thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) levels should also be measured, as clinically indicated, to rule out mediastinal goiter. All patients with a mediastinal mass should also have other studies to determine the type of mass and to determine the extent of disease; these tests should include chest computed tomography (CT) with contrast, FDG–positron-emission tomography (PET), radiolabeled octreotide scan (optional), complete blood counts, and platelets. Pulmonary function tests and magnetic resonance imaging (MRI) of the chest can also be done if clinically indicated. On CT, thymoma can look like malignant mesothelioma; however, pleural effusion does not typically occur with thymoma.
Thymomas

Thymomas are the most common tumor in the anterior mediastinum\(^1\,\!^3\,\!^5\) and typically occur in adults older than 40 years; thymomas are rare in children or adolescents. Although some patients are asymptomatic, others present with chest pain, cough, or dyspnea. Thymomas are usually encapsulated. Some clinicians feel that surgical biopsy should be avoided if a resectable thymoma is strongly suspected based on clinical and radiologic features and that a transpleural approach should be avoided during biopsy of a possible thymoma (category 2B for both). However, others feel that development of pleural metastases is most likely not the result of biopsies because many patients who have never been biopsied have pleural disease at the time of diagnosis. Total thymectomy and complete surgical excision are generally appropriate for most cases.\(^6\,\!^8\) Before surgery, all patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists to determine the optimal plan of care.

Although thymomas can be locally invasive (pleura, lung), they rarely spread to regional lymph nodes or distant sites. The Masaoka staging system is useful for management and determination of prognosis (see ST-1).\(^9\,\!^{11}\) Patients with stage I-III thymomas have a 5-year survival rate of about 70% versus 50% for stage IV disease.\(^12\,\!^{13}\)

For incompletely resected thymomas, postoperative radiation therapy (RT) is recommended. Note that extensive elective nodal radiation is not recommended, because thymomas do not typically metastasize to regional lymph nodes.\(^14\) Computed tomography–based planning is highly recommended. RT should be given by 3D conformal technique to reduce surrounding normal tissue damage (e.g., heart, lungs, esophagus, spinal cord). Use of intensity-modulated RT (IMRT) may further improve the dose distribution and may decrease the dose to the normal tissue. However, if IMRT is applied, the NCT/ASTRO IMRT guidelines should be followed strictly [link]. In addition to following the normal tissue constraints recommendation (using the “Principles of RT for Non-Small Cell Lung Cancer”), special attention should be paid to minimize the dose volumes to all the normal structures (see NCCN Non-Small Cell Lung Cancer Guidelines).\(^15\,\!^{16}\)

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 60-70 Gy is given to patients with unresectable disease. For adjuvant treatment, a total dose of 45-50 Gy is used for clear or close margins; a total dose of 54 Gy is used for microscopically positive resection margins. However, a total dose of 60 Gy or more (1.8 to 2 Gy/fraction per day) is given for patients with gross residual disease after surgery.\(^17\,\!^{18}\)

Postoperative RT can be considered in some higher-risk patients after an RO resection, although this is a category 2B recommendation.\(^19\,\!^{22}\) 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 can be used to maximize local control. There is growing evidence that patients with stage II thymoma may not benefit from postoperative radiation. For advanced disease, chemotherapy with (or without) RT is recommended.\(^22\,\!^{32}\) Although 6 different combination regimens are provided, cisplatin/doxorubicin-based regimens seem to yield the best outcomes. For patients who have complete resection, surveillance should include annual chest CT. Given the risk of later recurrence for thymoma, such surveillance should continue for at least 10 years.
About 30% to 50% of patients with thymomas have myasthenia gravis; therefore, patients should be evaluated for myasthenia gravis. Before any surgical procedure, all patients suspected of having thymomas (even those without symptoms) should have their serum acetylcholine receptor antibody levels measured to determine whether they have myasthenia gravis to avoid respiratory failure during surgery. If they have myasthenia gravis, they should be medically controlled before undergoing surgical resection. Less frequently, patients may have hypogammaglobulinemia and red cell aplasia.

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 lack of long-term data.

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, 20% to 30%). These tumors can be distinguished from thymomas because of their malignant histologic features. However, thymic carcinomas should be differentiated from primary lung malignancies that metastasize to the thymus which can be similar histologically. Thymic carcinomas often cause pericardial and pleural effusions. The Masaoka staging system can also be used to stage thymic carcinomas, although this is controversial (see ST-1).

After resection of thymic carcinomas, postoperative management includes RT with (or without) chemotherapy, depending on the completeness of resection. For unresectable or metastatic thymic...
References


