# NCCN Guidelines Version 1.2015 Panel Members

## Thymomas and Thymic Carcinomas

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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.
Updates in Version 1.2015 of the NCCN Guidelines for Thymomas and Thymic Carcinomas from Version 1.2014 include:

**THYM-1**
- Footnote “a” added: “Well-defined anterior mediastinal mass in the thymic bed, tumor markers negative, absence of other adenopathy, and absence of continuity with the thyroid.” (also applies to THYM-2)

**THYM-2**
- Footnote “b” modified: “Determination of resectability should be made by a board-certified thoracic surgeon, with primary focus on thoracic oncology.”
- Locally advanced, unresectable modified: “Biopsy should not violate the pleural space changed to Avoid transpleural approach.”

**THYM-3**
- Column heading changed from “Resectable Disease” to “Postoperative Management.”
- R1 resection, thymic carcinoma: Postoperative RT changed from “+ chemotherapy” to “± chemotherapy.”
- R2 resection: RT clarified as Definitive RT.

**THYM-4**
- “Isolated solitary metastasis” changed to “Solitary metastasis or ipsilateral pleural metastasis.”
- “Evidence of distant metastases” changed to “Evidence of extrathoracic metastases.”

**THYM-A**
- Bullet 7 modified: “During thymectomy, the pleural surfaces should be examined for pleural metastases. In some cases if feasible, resection of pleural metastases to achieve complete gross resection may be appropriate.”
- References 2–5 added.

**THYM-B 1 of 2**
- General Principles, bullet 2 was modified: “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.”

**THYM-B 2 of 2**
- Radiation Techniques, bullet 4 modified: “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 mean dose to the total heart should be limited to ≤30 Gy as low as reasonably achievable.”

**THYM-C 1 of 2**
- Sunitinib (Thymic carcinomas only) and everolimus added as treatment options in second-line chemotherapy with category 2A designations.
- References 7 and 9 added for sunitinib and everolimus. Reference 13 replaced.

**THYM-D**
- World Health Organization Histologic Classification moved from previous page ST-2.
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)

aWell-defined anterior mediastinal mass in the thymic bed, tumor markers negative, absence of other adenopathy, and absence of continuity with the thyroid.

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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 (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).
**POSTOPERATIVE TREATMENT**

**Pathology evaluation**

- **R0 resection**
  - Thymoma, no capsular invasion or thymic carcinoma, stage I
  
  **Consider postoperative RT** (category 2B)

- **Thymoma or thymic carcinoma, capsular invasion present stages II–IV**
  - Thymoma or thymic carcinoma
    
    **Postoperative RT**

- **R1 resection**
  - Thymoma or thymic carcinoma
    
    **Postoperative RT ± chemotherapy**

- **R2 resection**
  - Thymoma
    
    **Definitive RT ± chemotherapy**

  - Thymic carcinoma
    
    **Definitive RT + chemotherapy**

**POSTOPERATIVE MANAGEMENT**

- Surveillance for recurrence with CT every 6 mo for 2 y, then annually for thymic carcinoma and 10 y for thymoma

  → **Recurrent disease**, see THYM-4

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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
Re-evaluate for surgery

Solitary metastasis or ipsilateral pleural metastasis
Chemotherapy or Surgery

Evidence of extrathoracic metastases
Chemotherapy

Resectable
Surgical resection of primary tumor and isolated metastases

Unresectable
RT ± chemotherapy

Consider chemotherapy or RT

Consider Postoperative RT

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

See Principles of Surgical Resection (THYM-A).
See Principles of Radiation Therapy (THYM-B).
See Principles of Chemotherapy for Thymic Malignancies (THYM-C).
PRINCIPLES OF SURGICAL RESECTION

• 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


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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.

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

PRINCIPLES OF RADIATION THERAPY (2 of 2)

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 (eg, 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 mean dose to the total heart should be as low as reasonably achievable.

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

## PRINCIPLES OF CHEMOTHERAPY FOR THYMIC MALIGNANCIES

### FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

**CAP**\(^1\) (preferred for thymoma)
- Cisplatin 50 mg/m\(^2\) IV day 1
- Doxorubicin 50 mg/m\(^2\) IV day 1
- Cyclophosphamide 500 mg/m\(^2\) IV day 1
- Administered every 3 weeks

**CAP with Prednisone**\(^2\)
- Cisplatin 30 mg/m\(^2\) days 1–3
- Doxorubicin, 20 mg/m\(^2\)/d
- IV continuous infusion on days 1–3
- Cyclophosphamide 500 mg/m\(^2\) IV on day 1
- Prednisone 100 mg/day days 1–5
- Administered every 3 weeks

**ADOC**\(^3\)
- Cisplatin 50 mg/m\(^2\) IV day 1
- Doxorubicin 40 mg/m\(^2\) IV day 1
- Vincristine 0.6 mg/m\(^2\) IV day 3
- Cyclophosphamide 700 mg/m\(^2\) IV day 4
- Administered every 3 weeks

**PE**\(^4\)
- Cisplatin 60 mg/m\(^2\) IV day 1
- Etoposide 120 mg/m\(^2\)/d IV days 1–3
- Administered every 3 weeks

**VIP**\(^5\)
- Etoposide 75 mg/m\(^2\) on days 1–4
- Ifosfamide 1.2 g/m\(^2\) on days 1–4
- Cisplatin 20 mg/m\(^2\) on days 1–4
- Administered every 3 weeks

**Carboplatin/Paclitaxel**\(^6\) (preferred for thymic carcinoma)
- Carboplatin AUC 6
- Paclitaxel 225 mg/m\(^2\)
- Administered every 3 weeks

### SECOND-LINE CHEMOTHERAPY

**Sunitinib** (Thymic carcinomas only)\(^7\)

**Pemetrexed**\(^8\)

**Everolimus**\(^9\)

**Paclitaxel**\(^10-11\)

**Octreotide (including LAR) +/- prednisone**\(^12\)

**Gemcitabine**\(^13\)

**5-FU and leucovorin**\(^14-15\)

**Etoposide**\(^4\)

**Ifosfamide**\(^16\)

### References on THYM-C 2 of 2
PRINCIPLES OF CHEMOTHERAPY FOR THYMIC MALIGNANCIES

REFERENCES


### 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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Staging

Table 1. Modified Masaoka clinical staging of thymoma\textsuperscript{1,2}

<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>
</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 (ie, 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\textsuperscript{3}

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

<table>
<thead>
<tr>
<th>N</th>
<th>Regional Lymph Nodes</th>
</tr>
</thead>
<tbody>
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<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</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in scalene and/or supraclavicular lymph nodes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Distant Metastasis</th>
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</thead>
<tbody>
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<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>
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Stage Grouping

<table>
<thead>
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<th>Stage I</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
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<td>M0</td>
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<td>Any T</td>
<td>N2, 3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Reprinted from Crit Rev Oncol Hematol, 65, Wright CD, Management of thymomas, 109-120, Copyright (2008), with permission from Elsevier.

\textsuperscript{2}Note that the Masaoka staging system is also used to stage thymic carcinomas.

\textsuperscript{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.

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NCCN Guidelines Version 1.2015
Thymomas and Thymic Carcinomas

Discussion
This discussion is being updated to correspond with the newly updated algorithm. Last updated 08/13/13

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).\(^1\) 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. 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.\(^9,10\) 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.\(^11\)

Patients with thymomas often have an indolent presentation, whereas those with lymphoma or germ cell tumors have a rapid onset of symptoms.\(^10\) 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).\(^8,12\) Thymic carcinoids are rare tumors that are discussed in the NCCN Guidelines for Neuroendocrine Tumors; they are associated with multiple endocrine neoplasia type 1 (MEN1) syndrome.\(^13,14\) Lung carcinoids are discussed in the NCCN Guidelines for Small Cell Lung Cancer (see Lung Neuroendocrine Tumors). Extragonadal germ cell tumors are rare tumors that occur in teenagers and young adults.

Recommended tests for assessing mediastinal masses include chest CT with contrast and blood chemistry studies.\(^15-19\) 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.
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). 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.
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.

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.

Adjuvant therapy is not recommended for completely resected (R0) stage I thymomas or for stage I thymic carcinomas. 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. CT-based treatment planning is highly recommended before RT. 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. 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), 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 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. 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.

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. 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. 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.\textsuperscript{99,100} Induction therapy followed by surgery may be useful for thymic malignancies initially considered unresectable.\textsuperscript{53,92,101,102}

Second-line systemic therapy includes etoposide, ifosfamide, pemetrexed, octreotide (long-acting release [LAR]; with or without prednisone), 5-FU, gemcitabine, and paclitaxel.\textsuperscript{84,85,98,103-106} However, none of these agents have been assessed in randomized trials. Octreotide may be useful in patients with thymoma who have a positive octreotide 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.\textsuperscript{17} 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.\textsuperscript{107}

### 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%).\textsuperscript{2,5,6,8,51,52,108,109} These tumors can be distinguished from thymomas because of their malignant histologic features and their different immunohistochemical and genetic features.\textsuperscript{7,43,48} However, thymic carcinomas should be differentiated from primary lung malignancies that metastasize to the thymus and have a similar histologic appearance.\textsuperscript{110,111} Thymic carcinomas often cause pericardial and pleural effusions. The Masaoka staging system can also be used to stage thymic carcinomas.\textsuperscript{35,112,113} It is important to note that thymic carcinomas are very different from thymomas.\textsuperscript{48}

Similar to thymomas, patients with completely resected thymic carcinomas have longer survival than those who are either incompletely resected or are unresectable.\textsuperscript{51,53} 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.\textsuperscript{51,52,67} A recent study suggests that adjuvant therapy may not be necessary for early-stage thymic carcinomas.\textsuperscript{114} For unresectable or metastatic thymic carcinomas, chemotherapy with (or without) RT is recommended.\textsuperscript{97}

Unfortunately, thymic carcinomas respond poorly to chemotherapy; carboplatin/paclitaxel is recommended, because it has the highest response rate among thymic carcinomas in clinical trials.\textsuperscript{95,99,115-122} Data 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.\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


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