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

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Summary of changes in the 2.2012 version of the Thymomas and Thymic Carcinomas Guidelines from the 1.2012 version include:

**MS-1**
- The discussion section was updated to reflect the changes in the algorithm.

Summary of changes in the 1.2012 version of the Thymomas and Thymic Carcinomas Guidelines from the 2.2011 version include:

**THYM-1**
- Initial evaluation, PET-CT: “and radiolabeled octreotide” deleted.

**THYM-2**
- Footnote “a” modified: “Determination of resectability should be made by a board-certified thoracic surgeon.”

**THYM-3**
- Footnote “c” new to the page to provide definitions of resections.

**THYM-4**
- The following added to the first node, thymoma or thymic carcinoma: “All patients should be managed by a multidisciplinary team with experience in the management of thymoma and thymic carcinoma.”
- Localized tumor changed to Locally advanced.
- The category of “Isolated solitary metastasis” added with treatment recommendations.

**THYM-A**
- Bullet 1: The following sentence added, “Locally advanced ( unresectable) and resected stage > II cases should be discussed and evaluated by a multidisciplinary team.”
- Bullet 6: The following sentence added, “Bilateral phrenic nerve resection should be avoided due to severe respiratory morbidity.”
- Bullet 8: The following sentence added, “However, minimally invasive procedures may be considered in select patients if done in specialized centers by surgeons with experience in these techniques.” A reference also added.

**THYM-B 1 of 2**
- General principles, bullet 1 added: Recommendations regarding radiation therapy should be made by a board-certified radiation oncologist.

**THYM-B 2 of 2**
- Radiation volume, bullet 1 modified: The gross tumor volume (GTV) should include any grossly visible tumor. Surgical clips indicative of gross residual tumor should be included for postoperative cases adjuvant RT.

**THYM-C**
- First-line Combination Regimens: “Preferred for thymoma” added to the CAP regimen.”Preferred for thymic carcinoma” added to the carboplatin/paclitaxel regimen.
- Second-line Chemotherapy: Octreotide - “including LAR” added.
INITIAL EVALUATION

Mediastinal Mass

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

Thymic malignancy likely

Thymic malignancy unlikely

See Initial Management (THYM-2)

See disease specific guidelines (NCCN Table of Contents)

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Thymic malignancy likely

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

See Principles of Surgical Resection for Thymic Malignancies (THYM-A).
RESECTABLE DISEASE

Pathology evaluation

- **R0 resection**
  - Thymoma, no capsular invasion stage I
    - Surveillance for recurrence with annual chest CT
    → Recurrence, see THYM-4

- **R1 resection**
  - Thymoma or thymic carcinoma, capsular invasion present stages II-IV
    - Consider postoperative RT (category 2B)

- **R2 resection**
  - Thymoma
    - Postoperative RT
  - Thymic carcinoma
    - Postoperative RT and chemotherapy
  - Thymoma
    - RT ± chemotherapy
  - Thymic carcinoma
    - RT + chemotherapy

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- **See Principles of Surgical Resection for Thymic Malignancies (THYM-A)**
- **See Principles of Radiation Therapy for Thymic Malignancies (THYM-B)**
- **See Principles of Chemotherapy for Thymic Malignancies (THYM-C)**
Thymomas and Thymic Carcinomas

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.

- Locally advanced
  - Chemotherapy
  - Re-evaluate for surgery

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

- Evidence of distant metastases
  - Chemotherapy

Resectable
- Surgical resection of primary tumor and isolated metastases
- Consider postoperative RT

Unresectable
- RT ± chemotherapy

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\( ^a \) Determination of resectability should be made by a thoracic surgeon.
\( ^b \) See Principles of Surgical Resection for Thymic Malignancies (THYM-A).
\( ^d \) See Principles of Radiation Therapy for Thymic Malignancies (THYM-B).
\( ^e \) 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 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. 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 lack of long-term data. However, minimally invasive procedures may be considered in select patients if done in specialized centers by surgeons with experience in these techniques.¹

PRINCIPLES OF RADIATION THERAPY (1 of 2)

General principles

- Recommendations regarding radiation therapy should be made by a board-certified radiation oncologist.
- 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),\(^1,^2\) when conventional fractionation (1.8 to 2.0 Gy per daily fraction) is applied.

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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 adjuvant RT.
- 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. \(^3\)
- 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 \(\leq 30\) Gy.

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See General Principles and Radiation Dose THYM-B 1 of 2
PRINCIPLES OF CHEMOTHERAPY FOR THYMIC MALIGNANCIES

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

CAP¹ (preferred for thymoma)
- Cisplatin 50 mg/m² IV d1
- Doxorubicin 50 mg/m² IV d1
- Cyclophosphamide 500 mg/m² IV d1
Administered every 3 weeks

CAP with Prednisone²
- 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

ADOC³
- 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

PE⁴
- Cisplatin 60 mg/m² IV d1
- Etoposide 120 mg/m²/d IV d1-3
Administered every 3 weeks

VIP⁵
- 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/Paclitaxel⁶ (preferred for thymic carcinoma)
- Carboplatin AUC 5
- Paclitaxel 225 mg/m²
Administered every 3 weeks

SECOND-LINE CHEMOTHERAPY

Etoposide
Ifosfamide
Pemetrexed
Octreotide (including LAR) +/- prednisone
5-Fluorouracil and Leucovorin
Gemcitabine
Paclitaxel

¹ Loehrer, PJ et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an Intergroup trial. J Clin Oncol 1994; 12:1164,

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Staging

Table 1. Modified Masaoka clinical staging of thymoma1,2

<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>
<tr>
<td>Stage II</td>
<td>(A) Microscopic transcapsular invasion.</td>
</tr>
<tr>
<td></td>
<td>(B) Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium</td>
</tr>
<tr>
<td>Stage III</td>
<td>Macroscopic invasion into neighboring organs (i.e., pericardium, great vessels, lung).</td>
</tr>
<tr>
<td>Stage IV</td>
<td>(A) Pleural or pericardial dissemination.</td>
</tr>
<tr>
<td></td>
<td>(B) Lymphogenous or hematogenous metastasis</td>
</tr>
</tbody>
</table>

Table 2. World Health Organization Histologic Classification3

<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>

2Note the Masaoka staging system is also used to stage thymic carcinomas.

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Thymomas and Thymic Carcinomas

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.

Overview

Thymomas are the most common tumor in the anterior mediastinum, although they are rare tumors (0.15 cases per 100,000).\(^1\)-\(^3\) 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 about 78%.\(^4\) However, 5-year survival rates for thymic carcinomas are only about 40%.\(^5,6\) The NCCN Thymomas and Thymic Carcinomas Guideline outlines the evaluation, treatment, and management of these mediastinal tumors.

Mediastinal Masses

Masses in the anterior mediastinum can be neoplasms (i.e., thymomas, lymphomas, thymic carcinomas, thymic carcinoids, thymolipomas, germ cell tumors, lung metastases) or non-neoplastic conditions (i.e., intrathoracic goiter, thymic cysts, lymphangiomas, aortic aneurysms).\(^2,7\) 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 Thymomas and Thymic Carcinomas algorithm). It is important to differentiate between thymic malignancies and other conditions (e.g., lymphoma, goiter, germ cell tumors) before treatment, because management differs for these conditions.\(^8\)

Patients with thymomas often have an indolent presentation, whereas those with lymphoma or germ cell tumors have a rapid onset of symptoms.\(^8\) 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).\(^7,9\) Thymic carcinoids are rare tumors that are discussed in the NCCN Neuroendocrine Tumors Guideline. Lung carcinoids are discussed in the NCCN Small Cell Lung Cancer Guideline (see section on “Lung Neuroendocrine Tumors”). Extragonadal germ cell tumors are rare tumors that occur in teenagers and young adults (http://www.cancer.gov/cancertopics/types/extragonadal-germ-cell).

Recommended tests for assessing mediastinal masses include chest computed tomography (CT) with contrast and blood chemistry studies (see “Initial Evaluation” in the NCCN Thymomas and Thymic Carcinomas algorithm).\(^10\)-\(^12\) On CT, thymoma is usually a well-defined round or oval mass in the thymus.\(^10\) Recently, low-dose computed tomography (LDCT) was found to be useful for detecting lung cancer in
high-risk individuals (see the NCCN Lung Cancer Screening guidelines).13 Mediastinal masses (e.g., thymomas, thymic carcinomas) may be detected in individuals undergoing lung cancer screening.

In patients who cannot tolerate iodinated contrast, magnetic resonance imaging (MRI) of the chest may be useful.10 Combined PET-CT (positron-emission tomography–computed tomography) may be useful for determining whether distant metastases are present.14 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 Thymomas and Thymic Carcinomas algorithm). Thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) levels may be measured to rule out mediastinal goiter.

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.15 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 Thymomas and Thymic Carcinomas algorithm).4,5,8,16,17 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.18-20 Minimally invasive procedures are not typically recommended, because there are no long-term data regarding recurrence and survival.

However, minimally invasive procedures may be considered for select patients with thymic tumors.21-23 Although there are several staging systems, Masaoka staging is the most widely accepted system for management and determination of prognosis for both thymomas and thymic carcinomas (see Table 1).4,5,24-27 Patients with stage I-III thymomas have a 5-year survival rate of about 85% versus 65% for stage IV disease.4,28,29

The World Health Organization (WHO) histologic classification system can be used to distinguish between thymomas, thymic carcinomas, and thymic carcinoids (see Table 2).30,31 The WHO classification is also used to differentiate among different histologic types of thymoma (i.e., A, AB, B1, B2, and B3). Thymic carcinomas are type C in the WHO classification, although they are very different from thymomas and are not advanced thymomas (see section on “Thymic Carcinomas” in this Discussion).32 However, the histologic subtype is less important for management than the extent of resection (i.e., R0, R1, or R2) (see the NCCN Thymomas and Thymic Carcinomas algorithm algorithm).5,33-36 For stage III-IV thymomas, 5-year survival rates have been reported to be 90% in patients with total resection.5 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; they are rare in children or adolescents.6 Although some patients are asymptomatic, others present with chest pain, cough, or dyspnea. About 30% to 50% of patients with thymomas have myasthenia gravis; therefore, patients should be evaluated for myasthenia gravis (e.g., by history and/or measuring serum antiacetylcholine receptor antibody levels).28 Although thymomas can be locally invasive (pleura, lung), they uncommonly spread to regional lymph nodes or distant sites.4,28
Surgery (i.e., 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 (about 90% and 70%, respectively). Complete 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 (e.g., patients have characteristic mass on CT and have myasthenia gravis). 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.

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

Use of intensity-modulated RT (IMRT) may decrease the dose to the normal tissues. However, if IMRT is used, the NCT/ASTRO IMRT guidelines should be followed. Although the normal tissue constraints recommendation for lung cancer may be used (see the “Principles of RT” in the NCCN Non-Small Cell Lung Cancer algorithm), 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 60-70 Gy is recommended for patients with unresectable disease. For adjuvant treatment, a total dose of 45-50 Gy is recommended for clear or close margins; a total dose of 54 Gy is recommended for microscopically positive resection margins (see “Principles of Radiation Therapy” in the NCCN Thymomas and Thymic Carcinomas algorithm). However, a total dose of 60 Gy or more (1.8 to 2 Gy/fraction per day) is recommended for patients with gross residual disease after surgery.

Postoperative RT can be considered in patients with thymoma and thymic carcinoma who have capsular invasion after an R0 resection, although this is a category 2B recommendation (see “Postoperative Management” in the NCCN Thymomas and Thymic Carcinomas algorithm). 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.
Thymomas and Thymic Carcinomas

Evidence that patients with stage II thymoma may not benefit from postoperative radiation.16,43,44,53

For advanced disease, chemotherapy with (or without) RT is recommended (see “Principles of Chemotherapy” in the NCCN Thymomas and Thymic Carcinomas algorithm).44,57-67 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.16,68,69 However, non-anthracycline regimens (e.g., cisplatin/etoposide [with or without ifosfamide], carboplatin/paclitaxel) may be useful for patients who cannot tolerate the more aggressive regimens.69,70 For thymic carcinoma, the panel recommends carboplatin/paclitaxel. Induction therapy followed by surgery may be useful for thymic malignancies initially considered unresectable.63,71,72

Second-line systemic therapy includes etoposide, ifosfamide, pemetrexed, octreotide (with or without prednisone), 5-fluorouracil, gemcitabine, and paclitaxel.69,73-75 After resection, surveillance for recurrence should include annual chest CT.10 Given the risk of later recurrence for thymoma, surveillance should continue for at least 10 years. Patients with thymoma also have an increased risk for second malignancies, although there are no particular screening studies that are recommended.76

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% to 50%).2,5-7,35,36,77,78 These tumors can be distinguished from thymomas because of their malignant histologic features and their different immunohistochemical and genetic features.31,32 However, thymic carcinomas should be differentiated from primary lung malignancies that metastasize to the thymus and have a similar histologic appearance.79,80 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 Table 1).81,82 It is important to note that thymomas are very different from thymic carcinomas.32

Similar to thymomas, patients with complete resection have longer survival than those who are either incompletely resected or are unresectable.35 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 Thymomas and Thymic Carcinomas algorithm).35,36 For unresectable or metastatic thymic carcinomas, chemotherapy with (or without) RT is recommended (see also “Principles of Radiation Therapy” and Principles of Chemotherapy” in the NCCN Thymomas and Thymic Carcinomas algorithm).58 Unfortunately, thymic carcinomas respond poorly to chemotherapy; carboplatin/paclitaxel is recommended, because it has the highest response rate among thymic carcinomas in clinical trials.66,70,83-90 Targeted therapy (e.g., sunitinib, sorafenib) may be useful for patients with c-Kit mutations; however, these mutations are rare in thymic carcinomas (< 10%).91-94 Patients with thymomas do not have c-Kit mutations.79
References


64. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: a single-institution experience with a long


