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Thymic Malignancies*

Clinical Practice Guidelines in Oncology

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Overview

Masses in the anterior mediastinum include neoplasms (e.g., thymomas, lymphomas, thymic carcinomas, thymic carcinoids, thymolipomas, germ cell tumors, parathyroid adenomas) or nonneoplastic conditions (e.g., intrathoracic goiter, thymic cysts, lymphangiomas, aortic aneurysms).[1,2] Thymomas are the most common tumor in the anterior mediastinum.[1,3,4] Many mediastinal masses are benign, especially those occurring in asymptomatic patients; however, symptomatic patients often have malig-

NCCN Clinical Practice Guidelines in Oncology for Thymic Malignancies*

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, thymoma, thymic carcinoma, mediastinal tumor *(JNCCN* 2010;8:1302–1315)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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

***Note: For 2011 and ongoing, these NCCN Guidelines have been renamed to Thymomas and Thymic Carcinomas.**

Please Note

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Disclosures for the NCCN Guidelines Panel for Thymic Malignancies

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Thymic Malignancies panel members can be found on page 1315. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

nant mediastinal lesions. These guidelines outline the evaluation, treatment, and management of thymomas and thymic carcinomas (see Thymic Masses, opposite column).

The WHO histologic classification system can be used to distinguish among thymomas, thymic carcinomas, and thymic carcinoids.[3] Lymphomas typically manifest as generalized disease but can also be primary anterior mediastinal lesions (i.e., nodular sclerosing Hodgkin disease and non-Hodgkin's lymphomas [large B-cell lymphoma and lymphoblastic lymphoma]); patients typically have lymphadenopathy [see the NCCN Clinical Practice Guidelines in Oncology {NCCN Guidelines} for Non-Hodgkin's Lymphomas and Hodgkin Lymphoma].[2,5] Thymic carcinoids are rare tumors that are discussed in the NCCN Guidelines for Neuroendocrine Tumors. Teratomas are discussed in the NCCN Guidelines for Testicular Cancer. (To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.)

Thymic Masses

All patients with a mediastinal mass should undergo studies to determine the type of mass and extent of disease; these tests should include chest CT with contrast, fludeoxyglucose (FDG)–PET, radiolabeled octreotide scan (optional), complete blood cell counts, and platelets. Pulmonary function tests and MRI of the chest can also be done if clinically indicated. On CT, thymoma can look like malignant mesothelioma; however, pleural effusion does not typi-

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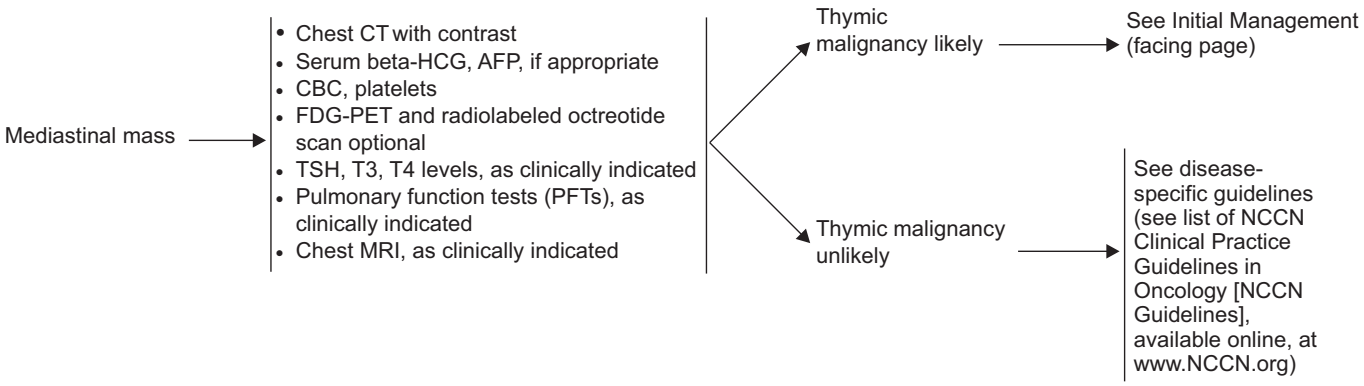
INITIAL EVALUATION



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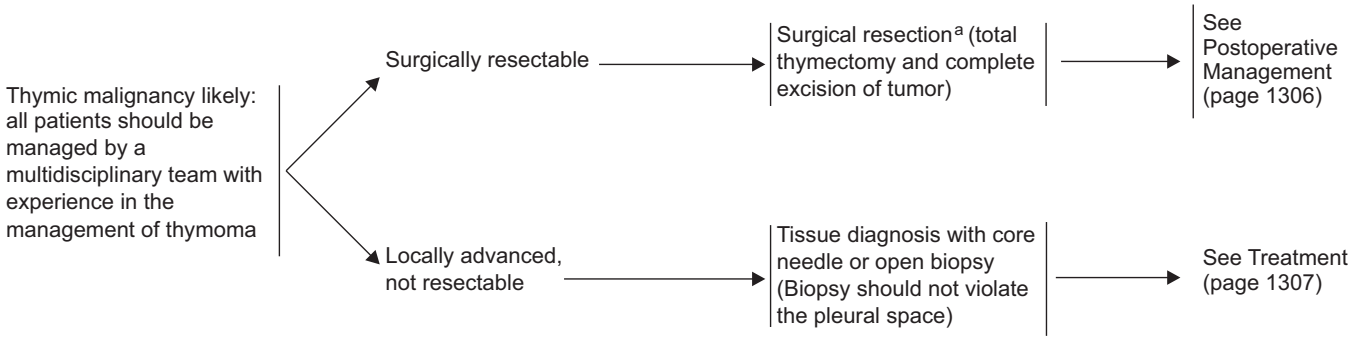
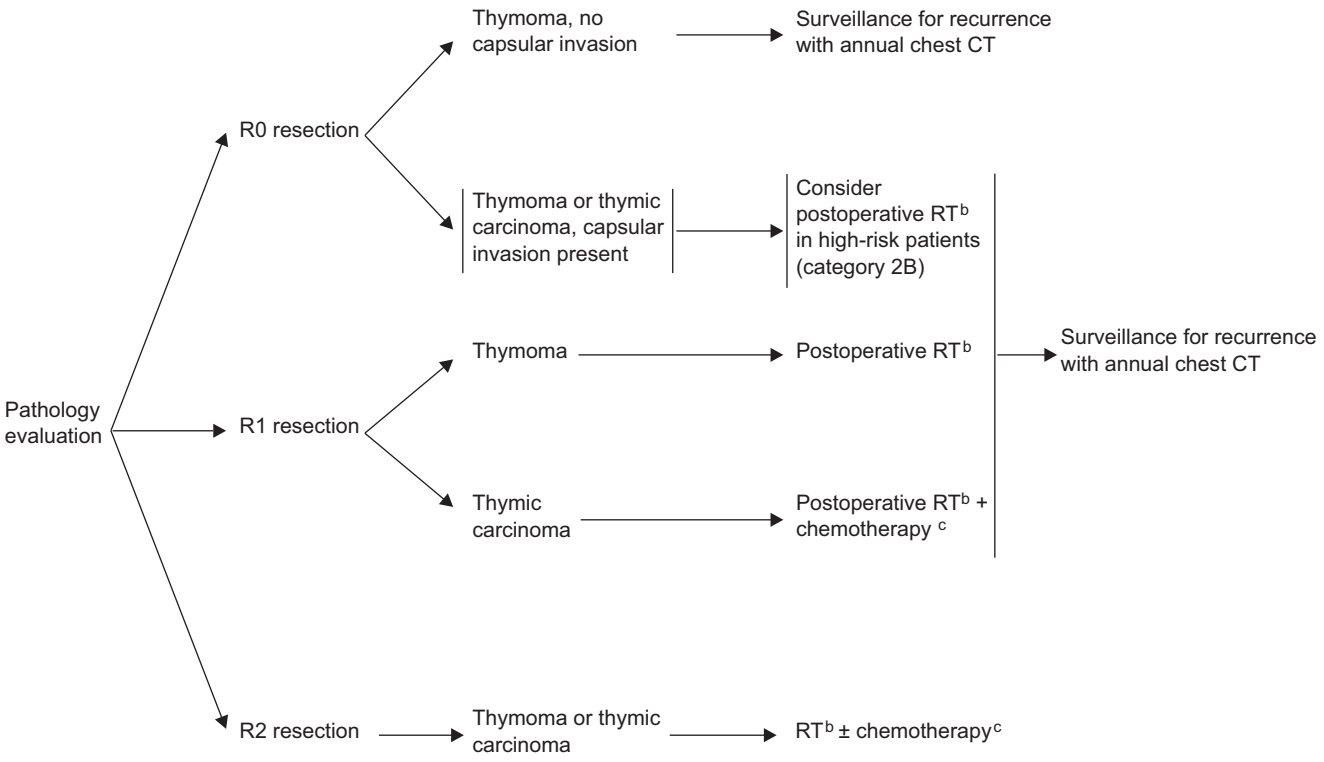
INITIAL MANAGEMENT



[a] See Principles of Surgical Resection for Thymic Malignancies (page 1308).

RESECTABLE DISEASE[a] POSTOPERATIVE MANAGEMENT



[a]See Principles of Surgical Resection for Thymic Malignancies (page 1308).
[b]See Principles of Radiation Therapy for Thymic Malignancies (pages 1309 and 1310).
[c]See Principles of Chemotherapy for Thymic Malignancies (page 1311).

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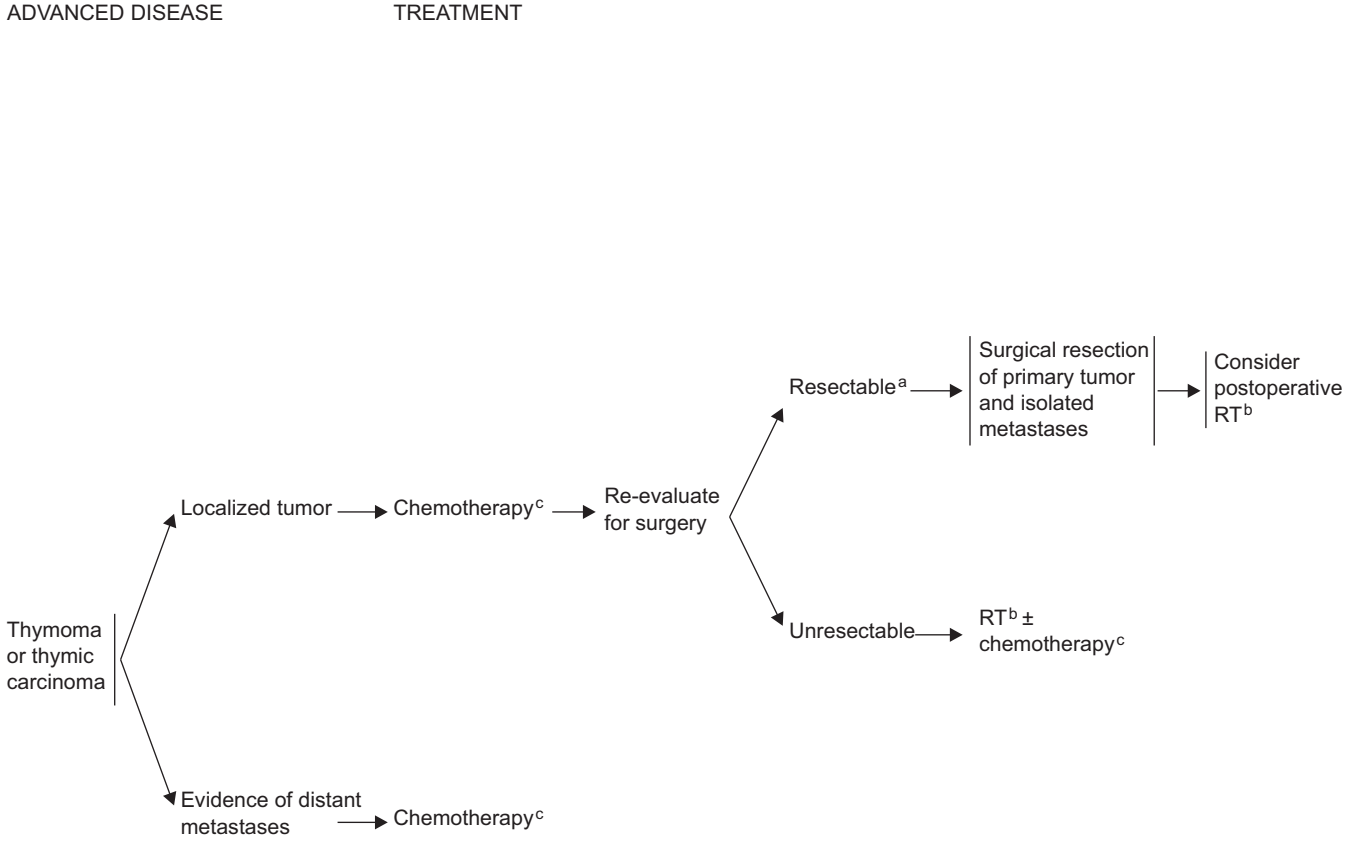

[a] See Principles of Surgical Resection for Thymic Malignancies (page 1308).
[b] See Principles of Radiation Therapy for Thymic Malignancies (pages 1309 and 1310).
[c] See Principles of Chemotherapy for Thymic Malignancies (page 1311).

PRINCIPLES OF SURGICAL RESECTION FOR THYMIC MALIGNANCIES

- Surgical biopsy should be avoided if a resectable thymoma is strongly suspected based on clinical and radiologic features (category 2B).
- Biopsy of a possible thymoma should avoid a transpleural approach (category 2B).
- Before 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 because of lack of long-term data.

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PRINCIPLES OF RADIATION THERAPY FOR THYMIC MALIGNANCIES (1 of 2)

General Principles

- Before surgery, all patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists for evaluation of resectability of the tumor and operability of the patients.
- RT should be given for patients with unresectable (after failure of induction chemotherapy) or incompletely resected invasive thymoma or thymic carcinoma.
- Prior to RT, any cardiac, pulmonary, and/or neurologic toxicities related to the paraneoplastic syndrome, surgery, or induction chemotherapy must be documented as baseline.
- Radiation oncologists must communicate with the surgeon to review the operative findings and help determine the target volume at risk, and also with the pathologist about the detailed pathology report regarding extracapsular extension and histology.
- Acronyms and abbreviations of RT are the same as listed in the Principles of Radiation Therapy for non-small cell lung cancer in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

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] when conventional fractionation (1.8-2.0 Gy per daily fraction) is applied.

See Radiation Volume and Radiation Techniques (page 1310)

[1] Mornex F, Resbeut M, Richaud P, et al. Radiotherapy and chemotherapy for invasive thymomas: a multicentric retrospective review of 90 cases. The FNCLCC trialists. Federation Nationale des Centres de Lutte Contre le Cancer. Int J Radiat Oncol Biol Phys 1995;32:651-659.

PRINCIPLES OF RADIATION THERAPY FOR THYMIC MALIGNANCIES (2 of 2)

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) 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, because thymomas do not commonly metastasize to regional lymph nodes.[2]
- 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 (arms raised above head). Simulations of target motion are encouraged whenever possible. CT scans can be performed at the end of natural inhale, exhale, and duringfree breathing, when more sophisticated techniques, such as 4-dimensional CT, gated CT, or active breathing control (ABC) are not available. Target motion should be managed using the Principles of Radiation Therapy in the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org. 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 2-dimensional era, can generate excessive dose to normal tissue.
- RT should be given by 3-dimensional 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 dose to the normal tissue as indicated. If IMRT is applied, the American Society for Radiation Oncology (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 Radiation Therapy in the NCCN Guidelines for Non-Small Cell Lung Cancer (available at www.NCCN.org), special attention should be paid to minimize the dose volumes to all the normal structures. Because these patients are younger and mostly long-term survivors, the dose to the total heart should be limited to ≤ 30 Gy.

See General Principles and Radiation Dose, page 1309

[2] Ruffini E, Mancuso M, Oliaro A, et al. Recurrence of thymoma: analysis of clinicopathologic features, treatment, and outcome. J Thorac Cardiovasc Surg 1997;113:55-63.

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PRINCIPLES OF CHEMOTHERAPY FOR THYMIC MALIGNANCIES

First-Line Combination Chemotherapy Regimens

CAP[1]
Cisplatin 50 mg/m^2 IV d1
Doxorubicin 50 mg/m^2 IV d1
Cyclophosphamide 500 mg/m^2 IV d1
Administered every 3 wk

CAP with Prednisone[2]
Cisplatin 30 mg/m^2 d1-3
Doxorubicin, 20 mg/m^2/d
IV continuous infusion on d1-3
Cyclophosphamide 500 mg/m^2 IV on d1
Prednisone 100 mg/day d1-5
Administered every 3 wk

ADOC[3]
Cisplatin 50 mg/m^2 IV d1
Doxorubicin 40 mg/m^2 IV d1
Vincristine 0.6 mg/m^2 IV d3
Cyclophosphamide 700 mg/m^2 IV d4
Administered every 4 wk

PE[4]
Cisplatin 60 mg/m^2 IV d1
Etoposide 120 mg/m^2/d IV d1-3
Administered every 3 wk

VIP[5]
Etoposide 75 mg/m^2 on d1-4
Ifosfamide 1.2 g/m^2 on d1-4
Cisplatin 20 mg/m^2 on d1-4
Administered every 3 wk

Carboplatin/Paclitaxel[6]
Carboplatin AUC 5
Paclitaxel 225 mg/m^2
Administered every 3 wk

Second-Line Chemotherapy

Etoposide
Ifosfamide
Pemetrexed
Octreotide +/- prednisone
5-Fluorouracil and leucovorin
Gemcitabine
Paclitaxel

[1] Loehrer PJ Sr, Kim K, Aisner SC, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an Intergroup trial. The European Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. J Clin Oncol 1994;12:1164.
[2] Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: a final report. Lung Cancer 2004;44:369-379.
[3] Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy for invasive thymoma. A 13-year experience. Cancer 1991;68:30-33.
[4] Giaccone G, Ardizzoni A, Kirkpatrick A, et al. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. J Clin Oncol 1996;14:814-820.
[5] Loehrer PJ Sr, Jiroutek M, Aisner S, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. Cancer 2001; 91: 2010–2015.
[6] Lemma GL, Loehrer PJ, Lee JW, et al. A phase II study of carboplatin plus paclitaxel in advanced thymoma or thymic carcinoma: E1C99 [abstract]. J Clin Oncol 2008;26(Suppl 1):Abstract 8018.

Text continued from p. 1303

cally occur with thymoma. Alpha-fetoprotein (AFP) and β–human chorionic gonadotropin (β-HCG) levels should be measured (if appropriate) to rule out germ cell tumors (see page 1304). Thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) levels should also be measured, as clinically indicated, to rule out mediastinal goiter.

Thymomas

Thymomas typically occur in adults older than 40 years, and 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 believe 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 diagnosis. Total thymectomy and complete surgical excision are generally appropriate for most patients.[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 managing patients and determining prognosis (available online, in these guidelines, at www.NCCN.org [ST1]).[9–11] Patients with stage I–III thymomas have a 5-year survival rate of approximately 70% compared with 50% for those with stage IV disease.[12,13]

For incompletely resected thymomas, postoperative radiation therapy (RT) is recommended (see page 1306). Note that extensive elective nodal radiation is not recommended, because thymomas do not typically metastasize to regional lymph nodes.[14] CT-based planning is highly recommended (see pages 1309 and 1310). RT should be given using 3-dimensional 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 American Society for Radiation Oncology (ASTRO) IMRT guidelines should be followed strictly (http://www.astro.org/Research/ResearchHighlights/documents/Imrt.pdf). In addition to following the normal tissue constraints recommendation (see Principles of Radiation Therapy in the NCCN Guidelines for Non–Small Cell Lung Cancer, available at www.NCCN.org), special attention should be paid to minimizing the dose volumes to all the normal structures (see NCCN Guidelines for Non–Small Cell Lung Cancer, available at www.NCCN.org).[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 to 70 Gy is given to patients with unresectable disease. For adjuvant treatment, a total dose of 45 to 50 Gy is used for clear or close margins; a total dose of 54 Gy is used for microscopically positive resection margins (see pages 1309 and 1310). However, a total dose of 60 Gy or more (1.8–2.0 Gy per daily fraction) is given for patients with gross residual disease after surgery.[17,18]

Postoperative RT can be considered in some higher-risk patients after an R0 resection, although this is a category 2B recommendation (see page 1306).[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 therefore postoperative radiation can be used to maximize local control. Growing evidence shows that patients with stage II thymoma may not benefit from postoperative radiation. For advanced disease, chemotherapy with (or without) RT is recommended (see page 1311).[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, this surveillance should continue for at least 10 years.

Because approximately 30% to 50% of patients with thymomas have myasthenia gravis, patients should be evaluated for this disease. 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. In patients who have myasthenia gravis, the disease should be medically controlled before surgi-

cal resection is performed (see page 1308).[33,34] 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.[35] Minimally invasive procedures are not routinely recommended because of 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%–30%).[1,2,36,37] These tumors can be distinguished from thymomas because of their malignant histologic features.[3] 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 (available online, in these guidelines, at www.NCCN.org [ST1]).[38]

After resection of thymic carcinomas, postoperative management includes RT with (or without) chemotherapy, depending on the completeness of resection (see page 1306). For unresectable or metastatic thymic carcinomas, patients should undergo chemotherapy with (or without) RT.[31,39–45]

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Individual Disclosures for the NCCN Thymic Malignancies Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Wallace Akerley, MD	Genentech, Inc.; and OSI Pharmaceuticals, Inc.	Genentech, Inc.	None	None	4/25/10
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Richard T. Cheney, MD	None	None	None	None	12/8/09
Lucian R. Chirieac, MD	None	None	None	None	2/23/10
Thomas A. D'Amico, MD	None	Covidien AG; and Scanlan	None	None	9/21/10
Todd L. Demmy, MD	None	Covidien AG	None	None	7/13/09
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Ramaswamy Govindan, MD	None	AstraZeneca Pharmaceuticals LP; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Eli Lilly and Company; Genentech, Inc.; and sanofi-aventis U.S.	None	None	6/4/10
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David H. Johnson, MD	Merck & Co., Inc.; and Theradex (Idera)	None	None	None	1/4/10
Anne Kessinger, MD	Pharmacyclics; and sanofi-aventis U.S.	None	None	None	12/16/09
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Dr. Hughes has disclosed that she has a patent, equity, or royality in Myriad Genetic Laboratories, Inc.; Affymetrix; and Qiagen NV. The remaining guidelines staff have disclosed that they have no conflicts of interest.

