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Thymomas and Thymic Carcinomas

Clinical Practice Guidelines in Oncology

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Overview

Thymomas are the most common primary tumor in the anterior mediastinum, although they are rare (1.5 cases/million).[1–3] Thymic carcinomas are very rare. Thymomas and thymic carcinomas originate in the thymus. Although thymomas can spread locally, they are much less invasive than thymic carcinomas.[1] Patients with thymomas have 5-year survival rates of approximately 78%.[4] However, 5-year survival rates

Abstract

Masses in the anterior mediastinum can be neoplasms (eg, thymomas, thymic carcinomas, or lung metastases) or non-neoplastic conditions (eg, intrathoracic goiter). Thymomas are the most common primary tumor in the anterior mediastinum, although they are rare. 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. Patients with thymomas have 5-year survival rates of approximately 78%. However, 5-year survival rates for thymic carcinomas are only approximately 40%. These guidelines outline the evaluation, treatment, and management of these mediastinal tumors. (*JNCCN* 2013;11:562–576)

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.

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

Please Note

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Disclosures for the NCCN Thymomas and Thymic Carcinomas Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Thymomas and Thymic Carcinomas Panel members can be found on page 576. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

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

for thymic carcinomas are only approximately 40%.[5,6] These guidelines outline the evaluation, treatment, and management of these mediastinal tumors.

Mediastinal Masses

Masses in the anterior mediastinum can be neoplasms (eg, thymomas, lymphomas, thymic carcinomas, thymic carcinoids, thymolipomas, germ cell tumors, lung metastases) or nonneoplastic conditions (eg, 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 the extent of disease before treatment (see "Initial Evaluation," page 4). It is essential to differentiate between thymic malignancies and other conditions (eg, lung metastases, lymphoma, goiter, and germ cell tumors) before treatment, because management differs for these conditions.[9] Most masses in the mediastinum are metastases from a primary lung cancer (eg, non–small cell lung cancer). However, most primary cancers in the anterior mediastinum are thymomas.

Patients with thymomas often have an indolent presentation, whereas those with lymphoma or germ cell tumors have a rapid onset of symptoms.[9] Lymphomas typically manifest as generalized disease but can also be primary anterior mediastinal lesions (ie, nodular sclerosing Hodgkin disease, non-Hodgkin's

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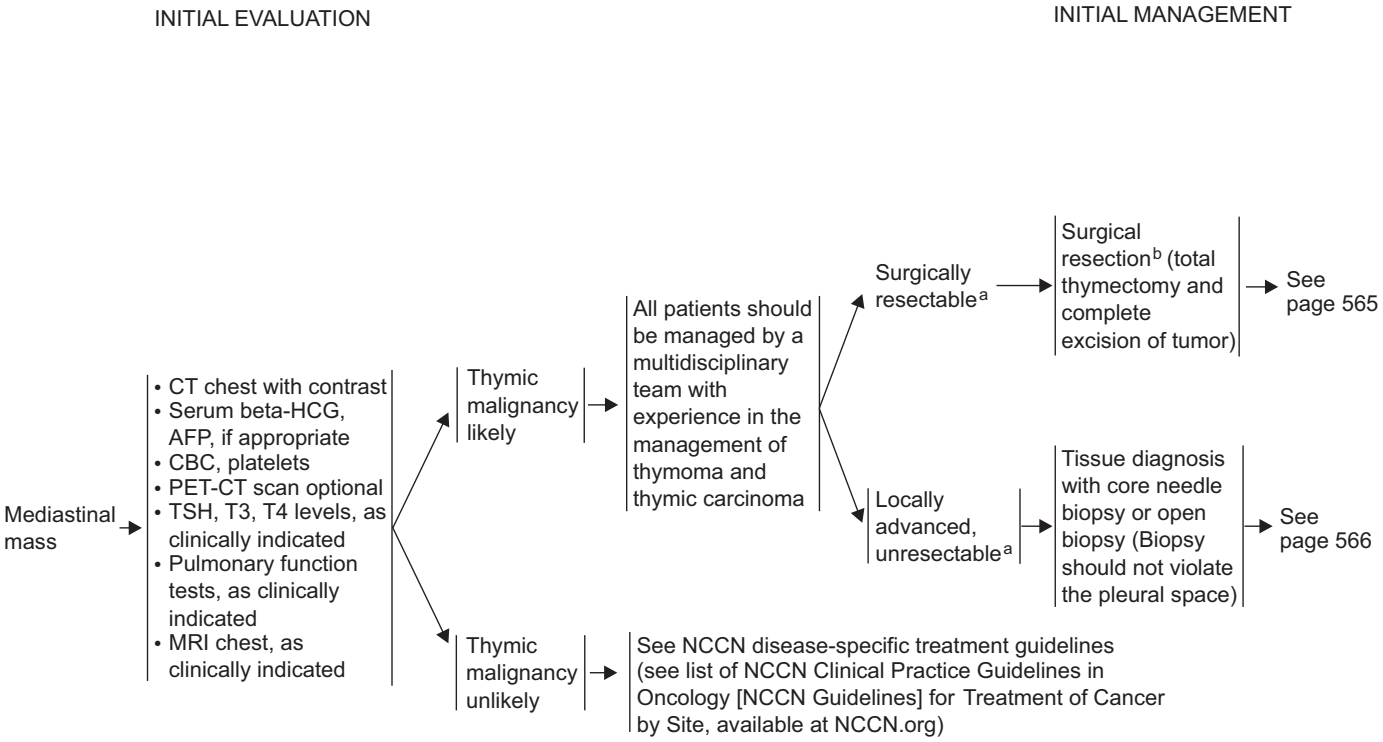

[a]Determination of resectability should be made by a board certified thoracic surgeon.
[b]See Principles of Surgical Resection (page 567)

THYM-1
THYM-2

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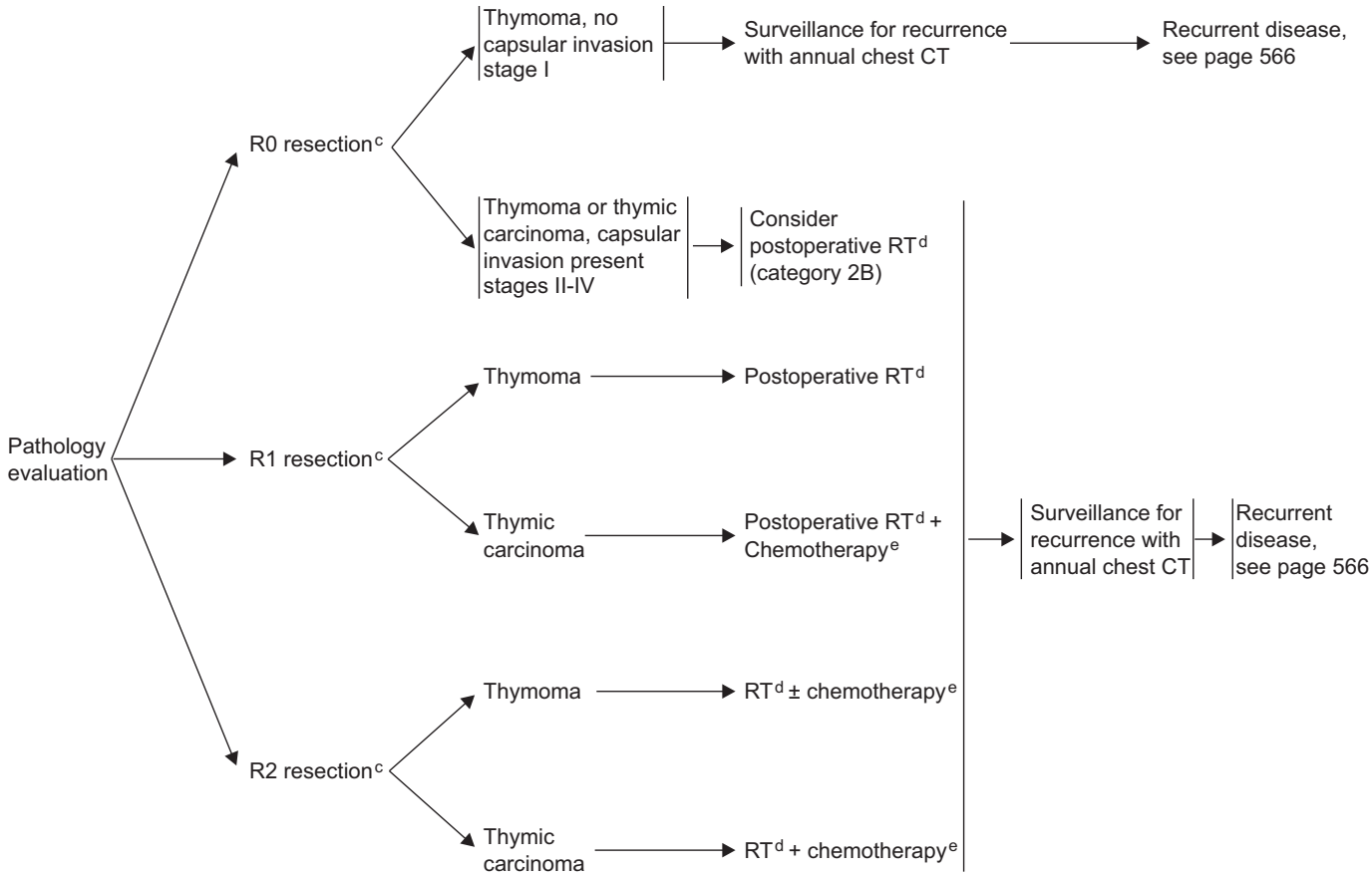
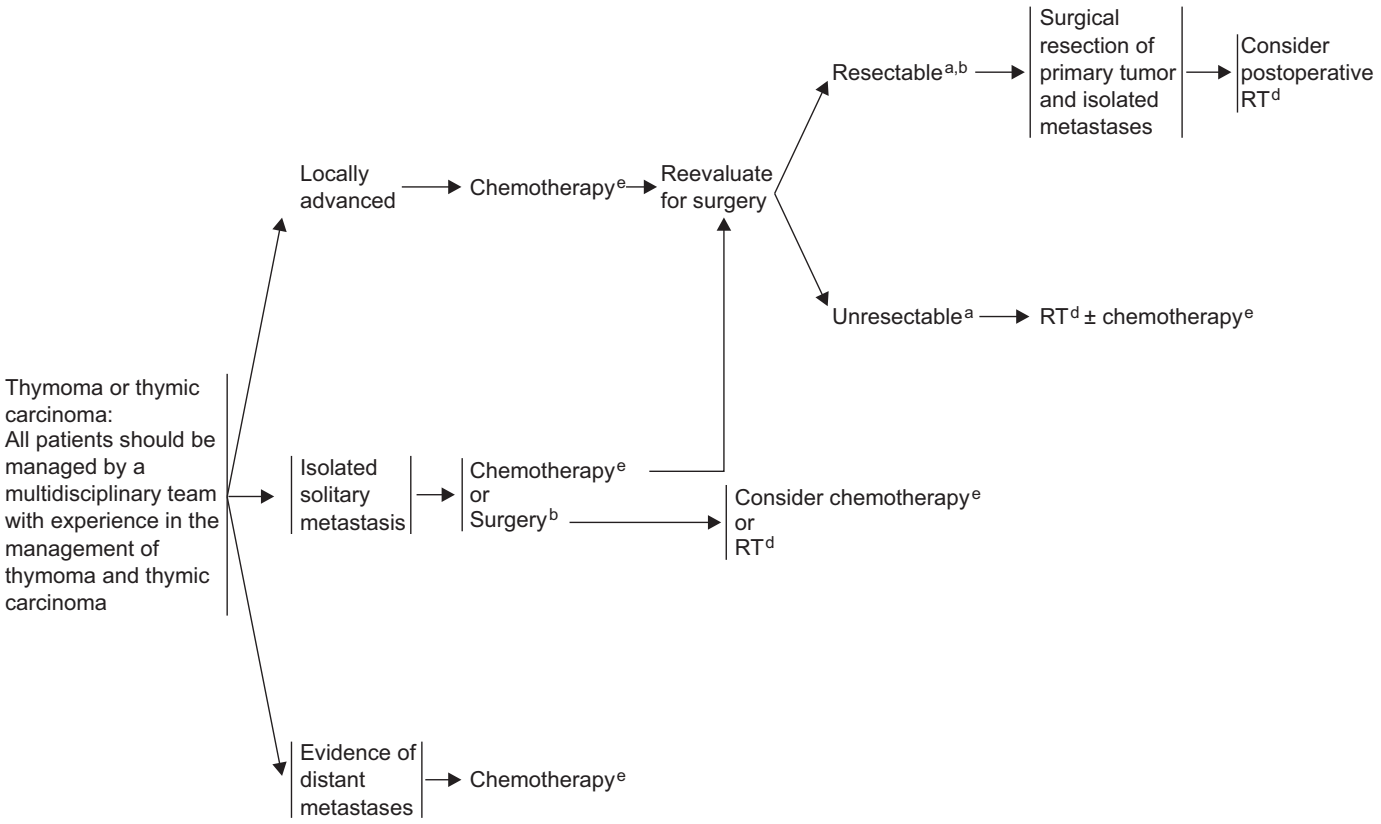
RESECTABLE DISEASE[b] POSTOPERATIVE MANAGEMENT



[b] See Principles of Surgical Resection (page 567).
[c] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[d] See Principles of Radiation Therapy (page 568).
[e] See Principles of Chemotherapy for Thymic Malignancies (page 569).

LOCALLY ADVANCED, ADVANCED, OR RECURRENT DISEASE

TREATMENT



[a]Determination of resectability should be made by a board certified thoracic surgeon.
[b]See Principles of Surgical Resection (page 567).
[d]See Principles of Radiation Therapy (page 568).
[e]See Principles of Chemotherapy for Thymic Malignancies (page 569).

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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 this should be medically controlled prior to undergoing surgical resection.
- Goal of surgery is complete excision of the lesion with total thymectomy and complete resection of contiguous and noncontiguous disease.
- Complete resection may require the resection of adjacent structures, including the pericardium, phrenic nerve, pleura, lung, and even major vascular structures. Bilateral phrenic nerve resection should be avoided due to severe respiratory morbidity.
- During thymectomy, the pleural surfaces should be examined for pleural metastases. In some cases, resection of pleural metastases to achieve complete gross resection may be appropriate.
- Minimally invasive procedures are not routinely recommended due to the lack of long-term data. However, minimally invasive procedures may be considered if all oncologic goals can be met as in standard procedures, and if performed in specialized centers by surgeons with experience in these techniques.[1]

[1] Pennathur A, Qureshi I, Schubert MJ, et al. Comparison of surgical techniques for early stage thymoma: feasibility of minimally invasive thymectomy and comparison with open resection. J Thorac Cardiovasc Surg 2011;141:694-701.

PRINCIPLES OF RADIATION THERAPY[1,2]

General Principles

- Recommendations regarding RT 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. 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 "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 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),[3,4] when conventional fractionation (1.8 to 2.0 Gy per daily fraction) is applied.

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 4D CT , gated CT, or active breathing control are not available. Target motion should be managed according to the Principles of Radiation Therapy for non-small cell lung cancer in the NCCN Guidelines for Non-Small Cell Lung Cancer (available at 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 ports weighting more anteriorly, or wedge pair technique may be considered. These techniques, although commonly used during the traditional 2D 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 3D 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 dose to the total heart should be limited to ≤30 Gy.

[1] Gomez D, Komaki R, Yu J, et al. Radiation therapy definitions and reporting guidelines for thymic malignancies. J Thorac Oncol 2011;6:S1743-1748.
[2] Gomez D, Komaki R. Technical advances of radiation therapy for thymic malignancies. J Thorac Oncol 2010;5:S336-343.
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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 to 3
Cyclophosphamide, 500 mg/m^2 IV on day 1
Prednisone, 100 mg/d 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

Etoposide[4]
Ifosfamide[7]
Pemetrexed[8,9]
Octreotide (including LAR) +/- prednisone[10]
5-FU and leucovorin[11,12]
Gemcitabine[13]
Paclitaxel[14,15]

[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 Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. J Clin Oncol 1994;12:1164–1168.
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[3] Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy for invasive thymoma. A 13-year experience. Cancer 1991;68:30–33.
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THYM-C

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lymphomas [diffuse large B-cell lymphoma and acute lymphoblastic lymphoma]); patients typically have lymphadenopathy (see the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Non-Hodgkin's Lymphomas and Hodgkin Lymphoma; to view the most recent version of these guidelines, visit NCCN.org).[8,10] Thymic carcinoids are rare tumors that are discussed in the NCCN Guidelines for Neuroendocrine Tumors (available at NCCN.org); they are associated with multiple endocrine neoplasia type 1 syndrome (MEN1).[11,12] Lung carcinoids are discussed in the NCCN Guidelines for Small Cell Lung Cancer (see "Lung Neuroendocrine Tumors"; available at NCCN.org). 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 CT with contrast and blood chemistry studies (see "Initial Evaluation," page 564).[13–15] On CT, a thymoma is usually a well-defined round or oval mass in the thymus.[13,16] Recently, low-dose CT (LDCT) was found to be useful for detecting lung cancer in high-risk individuals (see the NCCN Guidelines for Lung Cancer Screening; available at NCCN.org).[17] Mediastinal masses (eg, 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.[13] Combined PET/CT may be useful for determining whether distant metastases are present.[18] PET/CT provides better correlation with anatomic structures than PET alone. Alpha-fetoprotein (AFP) levels and beta-human chorionic gonadotropin (β-hCG) levels may be measured to rule out germ cell tumors (see "Initial Evaluation," page 564). 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.[19] 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," page 567).[4,5,9,20,21] 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.[22–24] Core-needle or open biopsy is recommended for locally advanced unresectable thymic masses.[7]

Minimally invasive procedures are not typically recommended, because long-term data are not available regarding recurrence and survival. However, minimally invasive procedures may be considered if standard oncologic goals can be met (as described previously) and if performed in specialized centers with surgeons with expertise in these techniques.[25–28] Although several staging systems exist, the Masaoka staging system is the most widely accepted system for management and determination of prognosis for both thymomas and thymic carcinomas (see Table 1 in the complete version of these guidelines, available at NCCN.org [ST-1]).[4,5,29–35] The International Thymic Malignancy Interest Group (ITMIG) suggests using the Masaoka-Koga stage classification.[29] The TNM staging system is less commonly used (see Table 2 in the complete version of these guidelines, available at NCCN.org [ST-1]).[36] Patients with stage I to III thymomas have a 5-year survival rate of approximately 85% versus 65% for stage IV disease.[4,37,38] In approximately 50% of patients, mortality is not related to thymoma.[30] In approximately 20% of patients, mortality is related to myasthenia gravis.

The WHO histologic classification system can be used to distinguish among thymomas, thymic carcinomas, and thymic carcinoids (see Table 3 in the complete version of these guidelines, available at NCCN.org [ST-2]).[36,39] The WHO classification is also used to differentiate among different histologic types of thymomas (ie, A, AB, B1, B2, B3); however, thymomas are difficult to classify.[40] Thymic carcinomas are type C in the WHO classification, although they are very different from thymomas and are not advanced thymomas (see "Thymic Carcinomas," page 572).[41] However, the histologic subtype is less important for management than the extent of resection (ie, R0, R1, R2) (see "Postoperative Manage-

ment," page 565).[5,42–45] For stage III to 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.[46]

Thymomas

Thymomas typically occur in adults 40 to 70 years of age; they are rare in children or adolescents.[9] 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).[37] Although thymomas can be locally invasive (eg, pleura, lung), they uncommonly spread to regional lymph nodes or distant sites.[4,37] 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).[9,47] 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).[9] A transpleural approach should be avoided during biopsy of a possible thymoma.[48,49] Small biopsy sampling (fine-needle or core-needle biopsy) does not always indicate whether invasion is present.[50] The ITMIG has established procedures for reporting the surgical and pathologic findings from resection specimens.[51]

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.[48,52–54]

Adjuvant therapy is not recommended for completely resected (R0) stage I thymomas.[20,55,56] For incompletely resected thymomas, postoperative radiation therapy (RT) is recommended (see "Postoperative Management," page 565).[20,57] Note that extensive elective nodal radiation is not recommended, because thymomas do not typically metastasize to regional lymph nodes.[4,58] CT-based treatment planning is highly recommended before RT (see "Principles of Radiation Therapy," page 568).[59] RT should be given using the 3D 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.[59,60] However, if IMRT is used, guidelines from the Advanced Technology Consortium (ATC)/NCI and American Society for Radiation Oncology/American College of Radiology (ASTRO/ACR) should be followed (http://rrp.cancer.gov/content/docs/imrt.doc).[61–64] 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; to view the most recent version of these guidelines, visit NCCN.org), more conservative limits are recommended to minimize the dose volumes to all of the normal structures.[65,66] Because these patients are younger and usually long-term survivors, the total dose to the heart should be limited to 30 Gy or less.

A definitive total dose of 60 to 70 Gy is recommended for patients with unresectable disease. For adjuvant treatment, a total dose of 45 to 50 Gy is recommended for clear or close margins; a total dose of 54 Gy is recommended for microscopically positive resection margins (see "Principles of Radiation Therapy," page 568).[59,60] However, a total dose of 60 Gy or more (1.8–2.0 Gy/fraction per day) is recommended for patients with gross residual disease after surgery.[67,68]

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," page 565).[56,59,69–71] 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 is recommended to maximize local control.[72,73] Increasing evidence suggests that patients with stage II thymoma may not benefit from postoperative radiation.[20,55,56,70] Postoperative

chemotherapy is also not beneficial.[74]

For advanced disease, chemotherapy with (or without) RT is recommended (see "Principles of Chemotherapy for Thymic Malignancies," page 569).[56,75–87] 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 preferred regimen for thymoma.[20,88,89] However, nonanthracycline regimens (eg, cisplatin/etoposide [with or without ifosfamide], carboplatin/paclitaxel) may be useful for patients who cannot tolerate the more aggressive regimens.[89,90] For thymic carcinoma, the panel recommends carboplatin/paclitaxel.[90,91] Induction therapy followed by surgery may be useful for thymic malignancies initially considered unresectable.[46,83,92,93]

Second-line systemic therapy includes etoposide, ifosfamide, pemetrexed, octreotide (long-acting release [LAR]; with or without prednisone), 5-FU, gemcitabine, and paclitaxel.[75,76,89,94–97] 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, surveillance for recurrence should include annual chest CT.[13] 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 no particular screening studies are recommended.[98]

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%).[2,5,6,8,44,45,99,100] These tumors can be distinguished from thymomas because of their malignant histologic features and their different immunohistochemical and genetic features.[7,36,41] However, thymic carcinomas should be differentiated from primary lung malignancies that metastasize to the thymus and have a similar histologic appearance.[101,102] Thymic carcinomas often cause pericardial and pleural effusions. The Masaoka staging system can also be used to stage thymic carcinomas (see Table 1 in the complete version of these guidelines, available at NCCN.org [ST-1]).[29,103,104] It is important to note that thymic carcinomas are very different from thymomas.[41]

Similar to thymomas, patients with completely resected thymic carcinomas have longer survival than those with either incompletely resected or are unresectable disease.[44,46] 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," page 565).[44,45,59] For unresectable or metastatic thymic carcinomas, chemotherapy with (or without) RT is recommended (see "Principles of Radiation Therapy" and "Principles of Chemotherapy for Thymic Malignancies," pages 568 and 569).[88]

Unfortunately, thymic carcinomas respond poorly to chemotherapy; carboplatin/paclitaxel is recommended, because it has the highest response rate among thymic carcinomas in clinical trials.[86,90,105–112] Data suggest that the ADOC (cisplatin, doxorubicin, vincristine, and cyclophosphamide) regimen is also effective, but it is more toxic than carboplatin/paclitaxel.[110] Data are lacking regarding second-line chemotherapy for thymic carcinomas.[75] Most of the second-line agents in the NCCN algorithm are appropriate for thymomas.[76] However, S-1 (an oral fluorouracil) appears to be active in patients with thymic carcinomas.[113,114] Targeted therapy (eg, sunitinib, sorafenib) may be useful for patients with *c-Kit* mutations; however, these mutations are rare in thymic carcinomas (<10%).[115–118] Patients with thymomas do not have *c-Kit* mutations.[101]

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Individual Disclosures for the NCCN Thymomas and Thymic Carcinomas Panel

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