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NCCN Clinical Practice Guidelines in Oncology™

Thymic Malignancies

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Table of Contents

[NCCN Thymic Malignancies Panel Members](#)

[Summary of Guidelines Updates](#)

- [Initial Evaluation \(THYM-1\)](#)
- [Initial Management \(THYM-2\)](#)
- [Postoperative Disease \(THYM-3\)](#)
- [Unresectable Disease \(THYM-4\)](#)
- [Principles of Surgical Resection \(THYM-A\)](#)
- [Principles of Radiation Therapy \(THYM-B\)](#)
- [Principles of Chemotherapy \(THYM-C\)](#)

[Guidelines Index](#)

[Print the Thymic Malignancies Guideline](#)

**[For help using these documents,
please click here](#)**

[Staging](#)

[Discussion](#)

[References](#)

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.

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 the Guidelines updates

The 2.2009 version of the Thymic Malignancies Guidelines represents the addition of the Discussion section correspondent to the changes in the algorithm.

Summary of the changes in the 1.2009 version of the Thymic Malignancies Guidelines from the 2.2008 version include:

THYM-1

- Pulmonary function tests were added to the workup section.

THYM-3

- “Consider chemotherapy and/or RT” was replaced with “RT ± chemotherapy” for patients with an R2 resection.

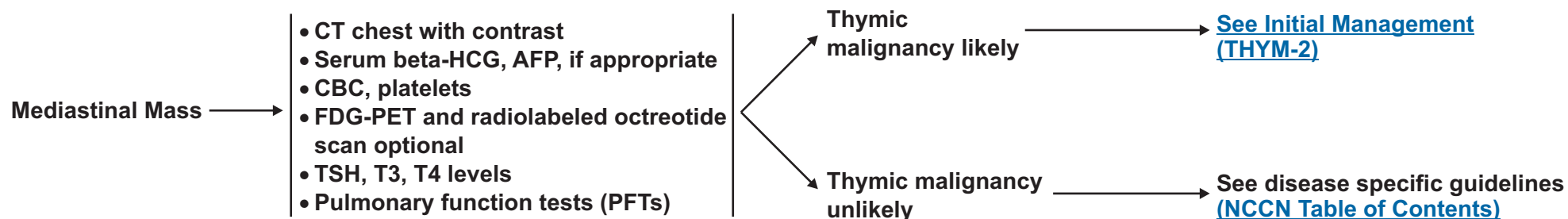
THYM-4

- “Resection of isolated oligometastases” was added as a treatment option for localized tumors.

THYM-A

- The first bullet was clarified to include medical management of myasthenia gravis for patients presenting with signs and symptoms.
- The last bullet regarding VATS and VATS-assisted techniques was removed.

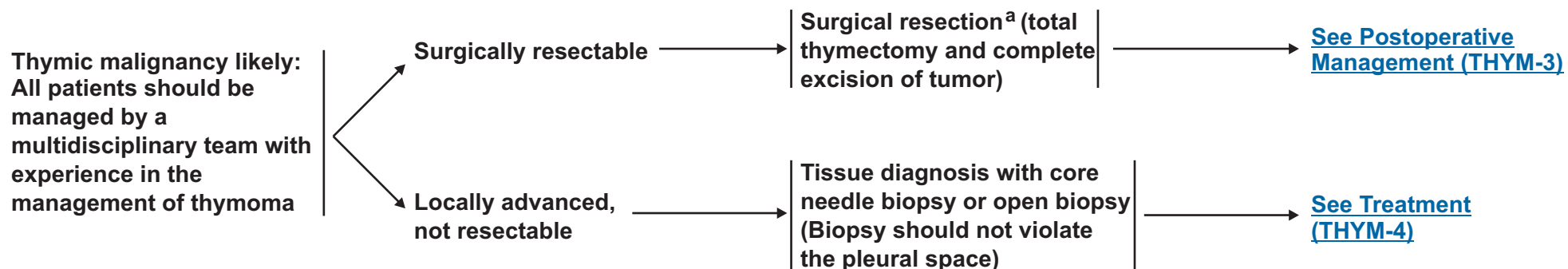
INITIAL EVALUATION



Note: All recommendations are category 2A unless otherwise indicated.

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INITIAL MANAGEMENT



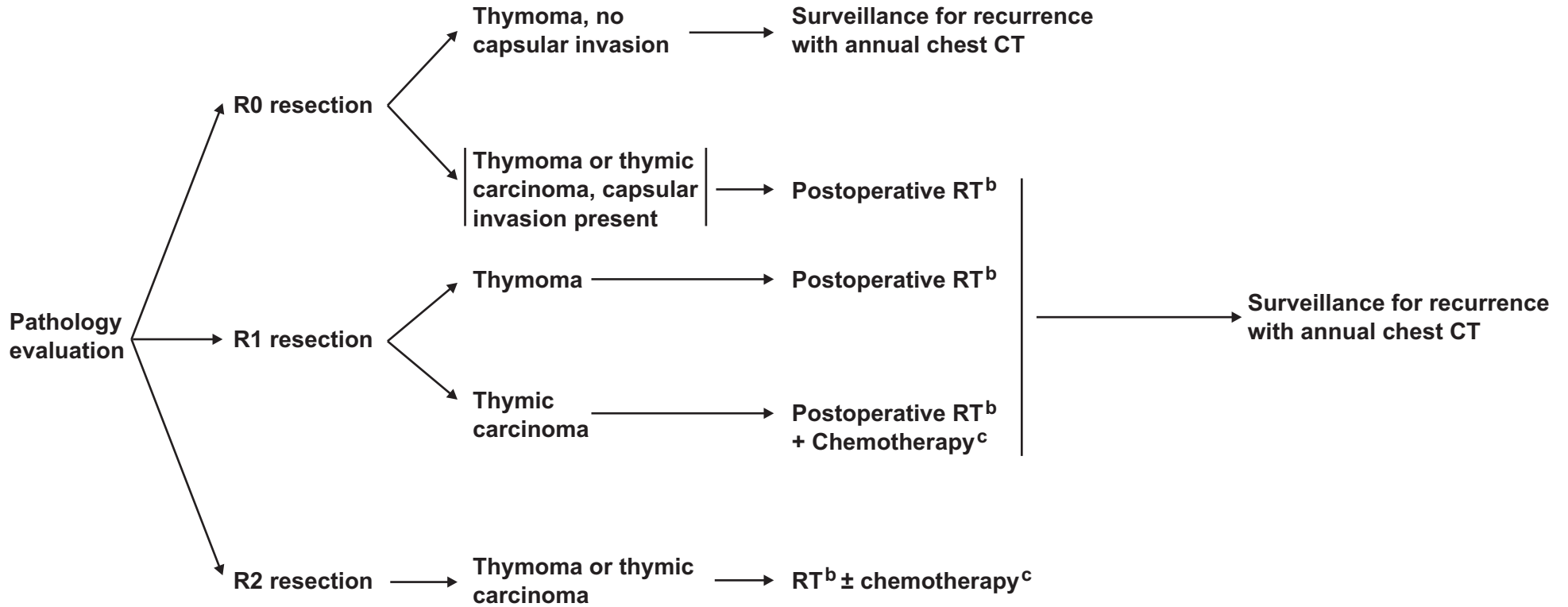
^a[See Principles of Surgical Resection for Thymic Malignancies \(THYM-A\).](#)

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RESECTABLE DISEASE

POSTOPERATIVE MANAGEMENT



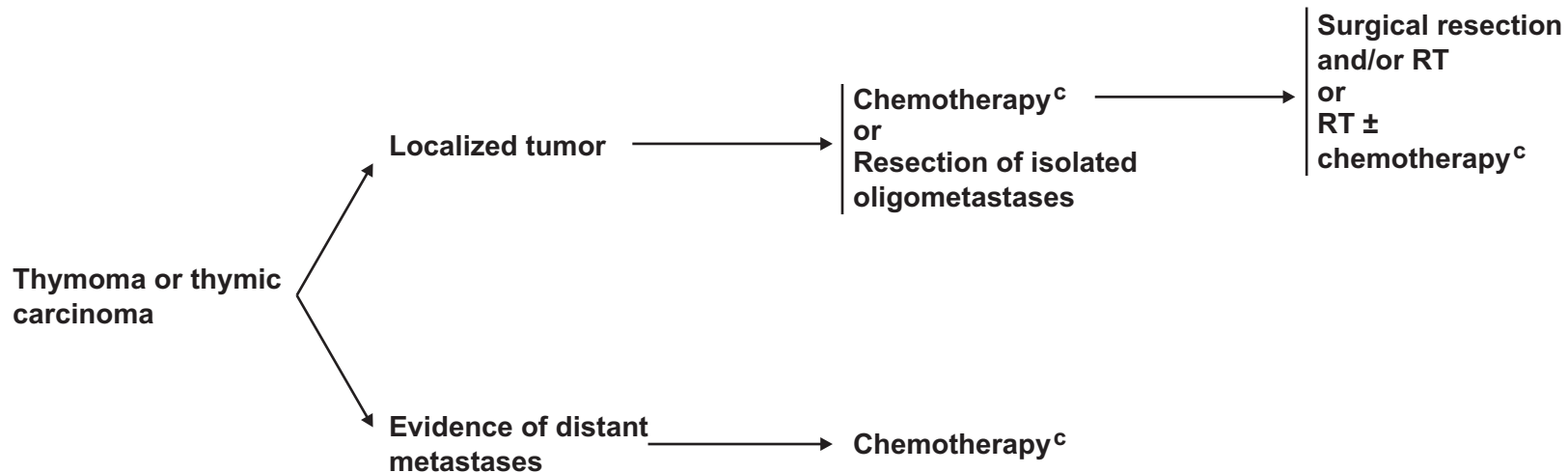
^bSee Principles of Radiation Therapy for Thymic Malignancies (THYM-B).

^cSee Principles of Chemotherapy for Thymic Malignancies (THYM-C).

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UNRESECTABLE DISEASE

TREATMENT



^cSee Principles of Chemotherapy for Thymic Malignancies (THYM-C).

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PRINCIPLES OF SURGICAL RESECTION FOR THYMIC MALIGNANCIES

- 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
- Procedure of choice is total thymectomy and complete resection of contiguous and noncontiguous disease
- Complete resection may require the resection of adjacent structures including pericardium, pleura, lung, and even major vascular structures.

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PRINCIPLES OF RADIATION THERAPY FOR THYMIC MALIGNANCIES

- Prior to surgery, all patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists and pulmonologists for evaluation resectability of the tumor and operability of the patients.
- Goal of radiation therapy is to reduce local recurrence.
- Radiation therapy needs to be given for patients with unresectable, incompletely resected and invasive thymoma or thymic carcinoma.
- Radiation therapy should be given by 3 dimensional radiotherapy or intensity modulated radiotherapy to reduce surrounding normal tissue damage, e.g. heart, lungs, esophagus and spinal cord.
- Prior radiation therapy, any cardiac, pulmonary and or neurological toxicities related to the paraneoplastic syndrome, surgery or the induction chemotherapy need to be documented as baseline
- Radiation oncologists need to communicate with the surgeons to investigate the operative findings and the pathologists regarding the detailed pathology report regarding extra-capsular extension and histology.

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PRINCIPLES OF CHEMOTHERAPY FOR THYMIC MALIGNANCIES

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

CAP¹	Cisplatin 50 mg/m ² IV d1 Doxorubicin 50 mg/m ² IV d1 Cyclophosphamide 500 mg/m ² IV d1 Administered every 3 weeks	PE⁴	Cisplatin 60 mg/m ² IV d1 Etoposide 120 mg/m ² /d IV d1-3 Administered every 3 weeks
CAP with Prednisone²	Cisplatin 30 mg/m ² d1-3 Doxorubicin, 20 mg/m ² /d IV continuous infusion on d 1 to 3 Cyclophosphamide 500 mg/m ² IV on d 1 Prednisone 100 mg/day d1-5 Administered every 3 weeks	VIP⁵	Etoposide 75 mg/m ² on d 1-4 Ifosfamide 1.2 g/m ² on d 1-4 Cisplatin 20 mg/m ² on d 1-4 Administered every 3 weeks
ADOC³	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 weeks	Carboplatin/Paclitaxel	Carboplatin AUC 6 Paclitaxel 200 mg/m ² administered every 3 weeks

SECOND-LINE CHEMOTHERAPY

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

¹Loehrer, 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,
²Shin DM, et al. A multidisciplinary approach to therapy for unresectable malignant thymoma. Ann Intern Med 1998; 129: 100–4.
³Fornasiero, A et al. Chemotherapy for invasive thymoma. A 13-year experience. Cancer 1991; 68:30
⁴Giaccone, G 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. Journal of Clinical Oncology 1996; 14:814
⁵Loehrer PJ Sr, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. Cancer 2001; 91: 2010–5.

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Staging

Modified Masaoka clinical staging of thymoma*

<u>Masaoka stage</u>	<u>Diagnostic criteria</u>
Stage I	Macroscopically and microscopically completely encapsulated
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 (i.e., pericardium, great vessels, lung). (A) Without invasion of great vessels. (B) With invasion of great vessels
Stage IV	(A) Pleural or pericardial dissemination. (C) Lymphogenous or hematogenous metastasis

*Wright CD. Management of thymomas. Crit Rev Oncol Hematol 2008;65(2):109-120. Epub 2007 Jun 14.

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Discussion

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.

Overview

Masses in the anterior mediastinum can be either neoplasms (such as, thymomas, lymphomas, thymic carcinomas) or non-neoplastic conditions (such as, goiter, thymic cysts).¹ Many mediastinal masses are benign, especially those occurring in asymptomatic patients; however, symptomatic patients often have malignant mediastinal lesions. Thymomas are the most common tumor in the anterior mediastinum. The NCCN guideline for Thymic Malignancies (see [THYM-1](#)) outlines the evaluation, treatment, and management of thymomas and thymic carcinomas (see “Thymic Masses”).

Thymic Masses

Masses in the anterior mediastinum can be either neoplasms (such as, thymomas, lymphomas, thymic carcinomas, thymic carcinoids, thymolipomas, germ cell tumors, parathyroid adenomas) or non-

neoplastic conditions (such as, intrathoracic goiter, thymic cysts, lymphangiomas, aortic aneurysms).^{1,2} Lymphomas typically manifest as generalized disease but can also be primary anterior mediastinal lesions (such as, 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](#)).^{2,3} Thymic carcinoids are rare tumors that are discussed in the [NCCN Neuroendocrine Tumors Guideline](#). Teratomas are discussed in the [NCCN Testicular Cancer Guideline](#).

Alpha-fetoprotein (AFP) and beta—human chorionic gonadotropin (beta-HCG) levels should be obtained to rule out germ cell tumors (see [THYM-1](#)). Thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) levels should also be measured to rule out mediastinal goiter. All patients with a mediastinal mass should also have other studies to determine the type of mass and to determine the extent of disease; these tests should include chest CT with contrast, FDG-PET, radiolabeled octreotide scan (optional), complete blood counts, platelets, and pulmonary function tests. On CT, thymoma can look like malignant mesothelioma; however, pleural effusion does not typically occur with thymoma.

Thymomas

Thymomas are the most common tumor in the anterior mediastinum.¹ 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 typically encapsulated. Total thymectomy and complete surgical excision are generally appropriate for most cases. Although thymomas can be locally invasive (pleura, lung), they rarely spread to regional lymph nodes or distant sites. The Masaoka staging system is useful for management and prognosis (see [ST-1](#)).⁴ Patients without invasive

thymomas have a 5-year survival rate of about 70% versus 50% for invasive tumors.^{5,6} For invasive or incompletely resected tumors, postoperative radiation therapy is recommended (see [THYM-3](#)); for unresectable or metastatic disease, chemotherapy with (or without) RT is recommended (see [THYM-C](#)).⁷⁻¹⁴ For patients who have complete resection, surveillance should include annual chest CT.

About 30% to 50% of patients with thymomas have myasthenia gravis; therefore, patients should be evaluated for myasthenia gravis. Before any surgical procedure, all patients suspected of having thymomas (even those without symptoms) should have their serum antiacetylcholine receptor antibody levels measured to determine whether they have myasthenia gravis to avoid respiratory failure during surgery; if they have myasthenia gravis, they should be medically controlled before undergoing surgical resection (see [THYM-A](#)).^{15,16} Less frequently, patients may have hypogammaglobulinemia and red cell aplasia.

Thymic Carcinomas

Thymic carcinomas are rare aggressive tumors that often metastasize to regional lymph nodes and distant sites; thus, they have a worse prognosis than thymomas (5-year survival rates, 20% to 30%).^{1,2,17} These tumors can be distinguished from thymomas because of their malignant features; however, thymic carcinomas should be differentiated from primary lung malignancies that metastasize to the thymus. Unlike thymomas, thymic carcinomas often cause pericardial and pleural effusions.

After resection of thymic carcinomas, postoperative management includes RT with (or without) chemotherapy, depending on the extent of resection (see [THYM-3](#)). For unresectable or metastatic thymic carcinomas, patients should receive chemotherapy with (or without) RT.¹⁸⁻²⁰

References

1. Strollo DC, Rosado de Christenson ML, Jett JR. Primary mediastinal tumors. Part 1: tumors of the anterior mediastinum. *Chest* 1997;112(2):511-522.
2. Strollo DC, Rosado-de-Christenson ML, Jett JR. Primary mediastinal tumors: part II. Tumors of the middle and posterior mediastinum. *Chest* 1997;112(5):1344-1357.
3. Barth TF, Leithäuser F, Joos S, et al. Mediastinal (thymic) large B-cell lymphoma: where do we stand? *Lancet Oncol* 2002;3(4):229-234.
4. Wright CD. Management of thymomas. *Crit Rev Oncol Hematol* 2008;65:109-120.
5. Lewis JE, Wick MR, Scheithauer BW, et al. Thymoma. A clinicopathologic review. *Cancer* 1987;60(11):2727-2743.
6. Park HS, Shin DM, Lee JS, et al. Thymoma. A retrospective study of 87 cases. *Cancer* 1994;73(10):2491-2498.
7. 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(6):1164-1168.
8. 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(3):814-820.
9. Shin DM, Walsh GL, Komaki R, et al. A multidisciplinary approach to therapy for unresectable malignant thymoma. *Ann Intern Med* 1998;129(2):100-104.
10. Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy for invasive thymoma. A 13-year experience. *Cancer* 1991;68(1):30-33.
11. 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(11):2010-2015.
12. 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: final report. *Lung Cancer* 2004;44(3):369-379.
13. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: a single-institution experience with a long follow-up. *J Thorac Oncol* 2006;1(4):308-313.
14. Yokoi K, Matsuguma H, Nakahara R, et al. Multidisciplinary treatment for advanced invasive thymoma with cisplatin, doxorubicin, and methylprednisolone. *J Thorac Oncol* 2007;2(1):73-78.
15. Autoantibodies to acetylcholine receptors in myasthenia gravis. *N Engl J Med* 1983;308(7):402-403.
16. Howard FM Jr, Lennon VA, Finley J, et al. Clinical correlations of antibodies that bind, block, or modulate human acetylcholine receptors in myasthenia gravis. *Ann N Y Acad Sci* 1987;505:526-538.
17. Suster S, Rosai J. Thymic carcinoma. A clinicopathologic study of 60 cases. *Cancer* 1991;67(4):1025-1032.
18. Weide LG, Ulbright TM, Loehrer PJ Sr, Williams SD. Thymic carcinoma. A distinct clinical entity responsive to chemotherapy. *Cancer* 1993;71(4):1219-1223.
19. Lucchi M, Mussi A, Ambrogi M, et al. Thymic carcinoma: a report of 13 cases. *Eur J Surg Oncol* 2001;27(7):636-640.
20. Yoh K, Goto K, Ishii G, et al. Weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide is an effective treatment for advanced thymic carcinoma. *Cancer* 2003;98(5):926-931.