National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Thymomas and Thymic Carcinomas

Version 3.2016

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NCCN Guidelines Version 3.2016 Panel Members
Thymomas and Thymic Carcinomas

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Discussion

* David S. Ettinger, MD/Chair †
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

* Douglas E. Wood, MD/Vice-Chair ¶
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

* Gregory J. Riely, MD, PhD/Lead †
Memorial Sloan Kettering Cancer Center

Wallace Akerley, MD †
Huntsman Cancer Institute at the University of Utah

Lyudmila A. Bazhenova, MD † ‡
UC San Diego Moores Cancer Center

Hossein Borghaei, DO, MS † ‡
Fox Chase Cancer Center

David Ross Camidge, MD, PhD †
University of Colorado Cancer Center

Richard T. Cheney, MD ≠
Roswell Park Cancer Institute

Lucian R. Chirieac, MD ≠
Dana-Farber/Brigham and Women's Cancer Center

Thomas A. D'Amico, MD ¶
Duke Cancer Institute

Todd L. Demmy, MD ¶
Roswell Park Cancer Institute

Thomas Dilling, MD, MS §
Moffitt Cancer Center

Ramaswamy Govindan, MD †
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Mark Hennon, MD ¶
Roswell Park Cancer Institute

Leora Horn, MD, MSc †
Vanderbilt-Ingram Cancer Center

Thierry M. Jahan, MD † ‡
UCSF Helen Diller Family Comprehensive Cancer Center

Ritsuko Komaki, MD §
The University of Texas MD Anderson Cancer Center

Rudy P. Lackner, MD ¶
Fred & Pamela Buffett Cancer Center

Michael Lanuti, MD ¶
Massachusetts General Hospital Cancer Center

Rogerio Lilenbaum, MD †
Yale Cancer Center/Smilow Cancer Hospital

Jules Lin, MD ¶
University of Michigan Comprehensive Cancer Center

Billy W. Loo, Jr., MD, PhD §
Stanford Cancer Institute

Renato Martins, MD, MPH †
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Gregory A. Otterson, MD †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Jyoti D. Patel, MD ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Katherine M. Pisters, MD †
The University of Texas MD Anderson Cancer Center

Karen Reckamp, MD, MS † ‡
City of Hope Comprehensive Cancer Center

Steven E. Schild, MD §
Mayo Clinic Cancer Center

Theresa A. Shapiro, MD, PhD ¥
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Neelesh Sharma, MD, PhD † ‡
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Scott J. Swanson, MD ¶
Dana-Farber/Brigham and Women's Cancer Center

James Stevenson, MD †
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Kurt Tauer, MD †
University of Tennessee Health Science Center

Stephen C. Yang, MD ¶
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

NCCN
Kristina Gregory, RN, MSN, OCN
Miranda Hughes, PhD

† Medical oncology
¶ Surgery/Surgical oncology
§ Radiation oncology/Radiotherapy
≠ Pathology
‡ Hematology/Hematology oncology
ф Diagnostic/Interventional radiology
¥ Patient advocate
*Writing committee member

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 3.2016 Updates Thymomas and Thymic Carcinomas

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Thymic Table of Contents
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Updates in Version 3.2016 of the NCCN Guidelines for Thymomas and Thymic Carcinomas from Version 2.2016 include:

THYM-1
- **Imaging clarfication: Chest MRI *with contrast*, as clinically indicated.**

THYM-3
- **Imaging clarfication: Surveillance for recurrence with *chest* CT *with contrast* every 6 mo for 2 y, then annually for 5 y for thymic carcinoma and 10 y for thymoma**

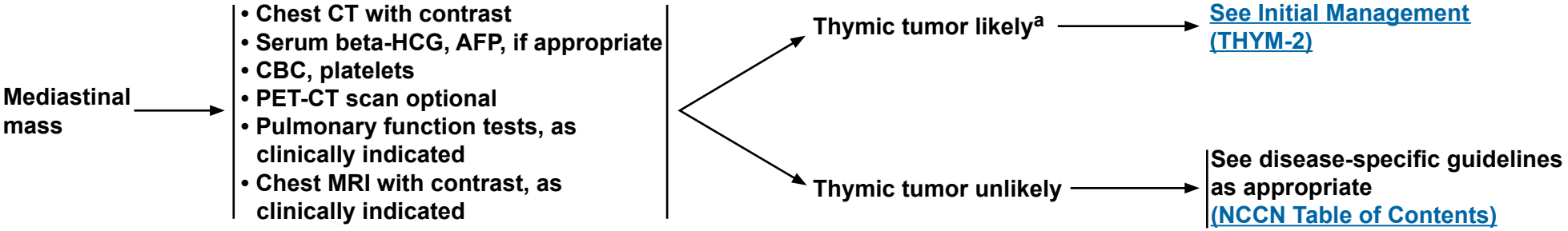
THYM-4
- **Imaging clarfication: Re-evaluate for surgery with *chest CT with contrast and PET-CT.***

Updates in Version 2.2016 of the NCCN Guidelines for Thymomas and Thymic Carcinomas from Version 1.2016 include:

MS-1
- **The discussion section was updated.**

No Updates in Version 1.2016 of the NCCN Guidelines for Thymomas and Thymic Carcinomas from Version 1.2015.

INITIAL EVALUATION



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

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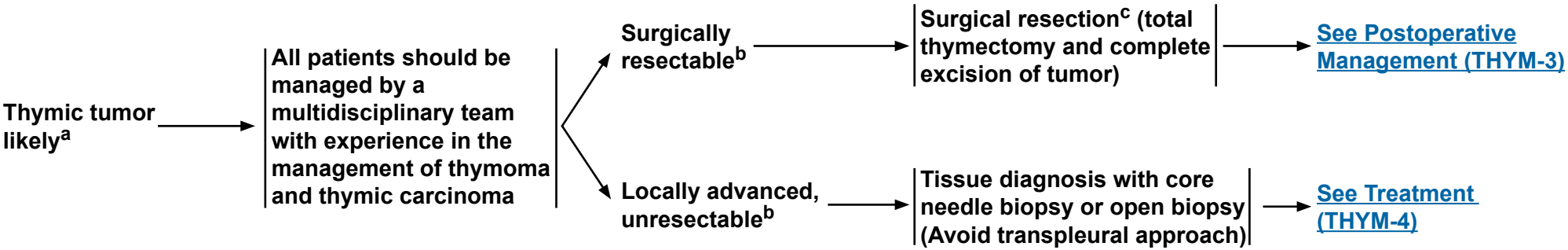
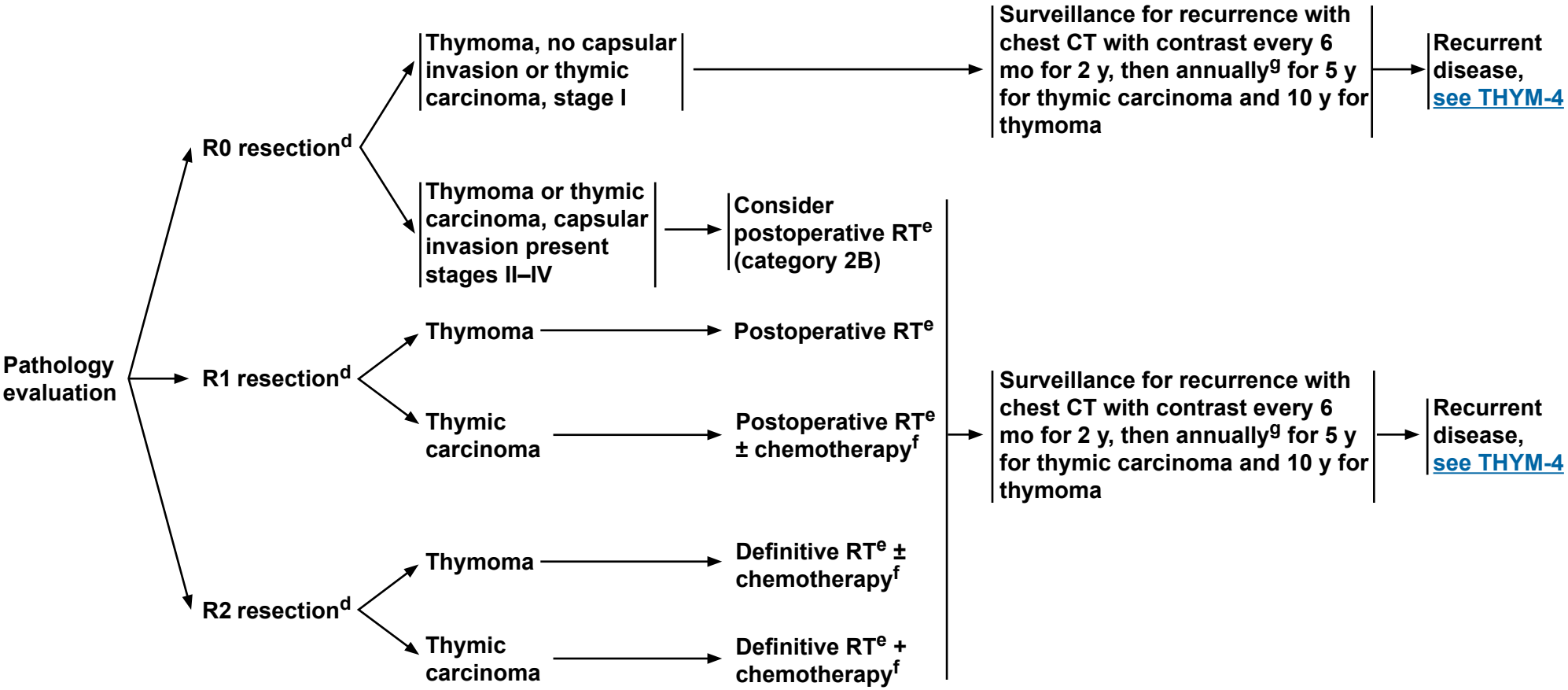
INITIAL MANAGEMENT



[a]Well-defined anterior mediastinal mass in the thymic bed, tumor markers negative, absence of other adenopathy, and absence of continuity with the thyroid.
[b]Determination of resectability should be made by a board-certified thoracic surgeon, with primary focus on thoracic oncology.
[c]See Principles of Surgical Resection (THYM-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

POSTOPERATIVE TREATMENT[c] | **POSTOPERATIVE MANAGEMENT**



[c] See Principles of Surgical Resection (THYM-A).
[d] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[e] See Principles of Radiation Therapy (THYM-B).
[f] See Principles of Chemotherapy for Thymic Malignancies (THYM-C).
[g] The duration for surveillance has not been established.

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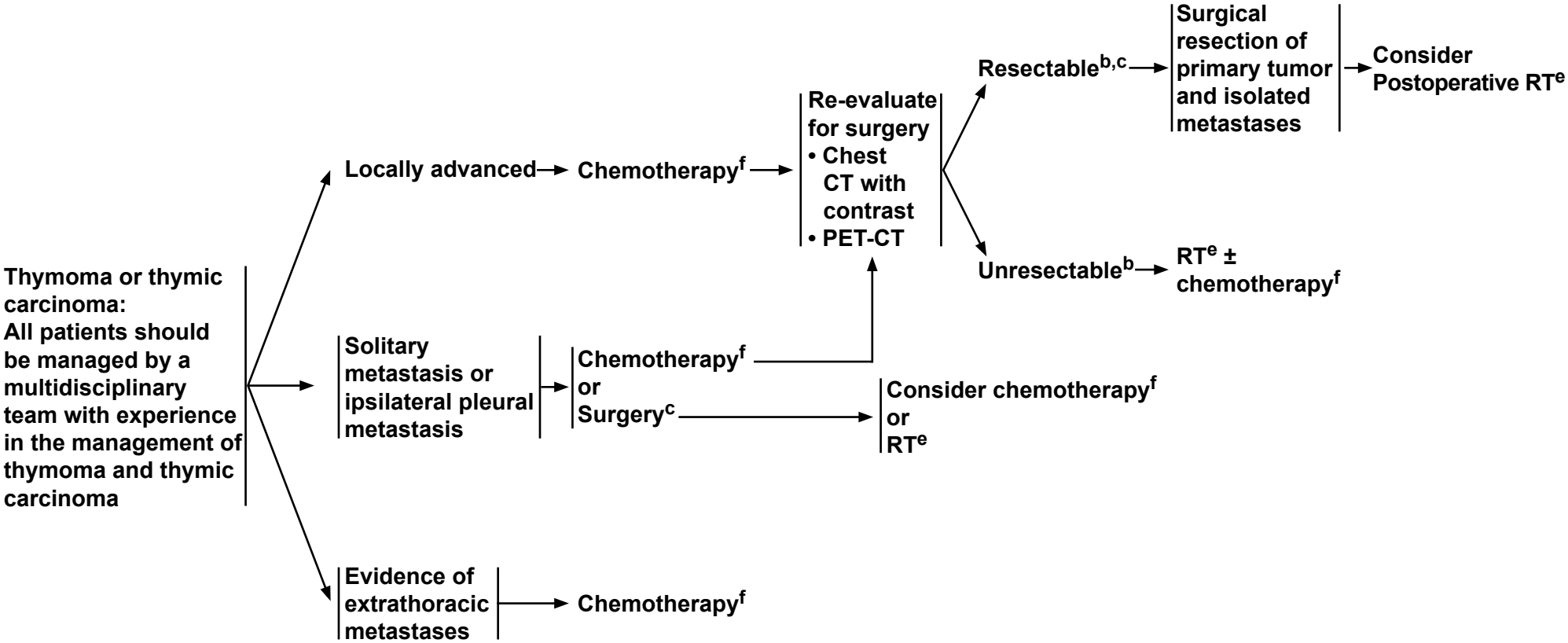
LOCALLY ADVANCED, ADVANCED, OR RECURRENT DISEASE

TREATMENT



[b]Determination of resectability should be made by a board-certified thoracic surgeon, with primary focus on thoracic oncology.
[c]See Principles of Surgical Resection (THYM-A).
[e]See Principles of Radiation Therapy (THYM-B).
[f]See Principles of Chemotherapy for Thymic Malignancies (THYM-C).

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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 should be medically controlled prior to undergoing surgical resection.**
- **Goal of surgery is complete excision of the lesion with total thymectomy and complete resection of contiguous and noncontiguous disease.**
- **Complete resection may require the resection of adjacent structures, including the pericardium, phrenic nerve, pleura, lung, and even major vascular structures. Bilateral phrenic nerve resection should be avoided due to severe respiratory morbidity.**
- **During thymectomy, the pleural surfaces should be examined for pleural metastases. If feasible, resection of pleural metastases to achieve complete gross resection is appropriate.**
- **Minimally invasive procedures are not routinely recommended due to the lack of long-term data. However, minimally invasive procedures may be considered if all oncologic goals can be met as in standard procedures, and if performed in specialized centers by surgeons with experience in these techniques.[1-5]**

[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.
[2]Ye B, Tantai JC, Ge XX, et al. Surgical techniques for early-stage thymoma: video-assisted thoracoscopic thymectomy versus transsternal thymectomy. J Thorac Cardiovasc Surg 2014;147:1599-1603.
[3]Sakamaki Y, Oda T, Kanazawa G, et al. Intermediate-term oncologic outcomes after video-assisted thoracoscopic thymectomy for early-stage thymoma. J Thorac Cardiovasc Surg 2014;148:1230-1237.
[4]Manoly I, Whistance RN, Sreekumar R, et al. Early and mid-term outcomes of trans-sternal and video-assisted thoracoscopic surgery for thymoma. Eur J Cardiothorac Surg 2014;45:e187-193.
[5]Liu TJ, Lin MW, Hsieh MS, et al. Video-assisted thoracoscopic surgical thymectomy to treat early thymoma: a comparison with the conventional transsternal approach. Ann Surg Oncol 2014;322-328.

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PRINCIPLES OF RADIATION THERAPY (1 of 2)[1,2]

General Principles

- **Recommendations regarding RT should be made by a board-certified radiation oncologist.**
- **Definitive RT should be given for patients with unresectable disease (if disease progresses on induction chemotherapy), incompletely resected invasive thymoma or thymic carcinoma, or as adjuvant therapy after chemotherapy and surgery for patients with locally advanced disease.**
- **Radiation oncologists need to communicate with the surgeon to review the operative findings and to help determine the target volume at risk. They also need to communicate with the pathologist regarding the detailed pathology on histology, disease extent such as extracapsular extension, and surgical margins.**
- **Acronyms and abbreviations for RT are the same as listed in the Principles of RT for non-small cell lung cancer. See NCCN Guidelines for Non-Small Cell Lung Cancer.**

Radiation Dose

- **The dose and fractionation schemes of RT depend on the indication of the radiation and the completeness of surgical resection in postoperative cases.**
- **A dose of 60 to 70 Gy should be given to patients with unresectable disease.**
- **For adjuvant treatment, the radiation dose consists of 45 to 50 Gy for clear/close margins and 54 Gy for microscopically positive resection margins. A total dose of 60 Gy and above should be given to patients with gross residual disease (similar to patients with unresectable disease),[3,4] when conventional fractionation (1.8–2.0 Gy per daily fraction) is applied.**

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

[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.
[3]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.
[4]Myojin M, Choi NC, Wright CD, et al. Stage III thymoma: pattern of failure after surgery and postoperative radiotherapy and its implication for future study. Int J Radiat Oncol Biol Phys. 2000;46(4):927-933.

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PRINCIPLES OF RADIATION THERAPY (2 of 2)

Radiation Volume

- **The gross tumor volume should include any grossly visible tumor. Surgical clips indicative of gross residual tumor should be included for postoperative adjuvant RT.**
- **The clinical target volume (CTV) for postoperative RT should encompass the entire thymus (for partial resection cases), surgical clips, and any potential sites with residual disease. The CTV should be reviewed with the thoracic surgeon.**
- **Extensive elective nodal irradiation (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended, as thymomas do not commonly metastasize to regional lymph nodes.[5]**
- **The planning target volume (PTV) should consider the target motion and daily setup error. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of daily setup of each clinic.**

Radiation Techniques

- **CT-based planning is highly recommended. CT scans should be taken in the treatment position with arms raised above the head (treatment position). Simulations of target motion are encouraged whenever possible. CT scans can be performed at the end of natural inhale, exhale, and under free breathing when more sophisticated techniques like 4-D CT, gated CT, or active breathing control are not available. Target motion should be managed using the Principles of RT for non-small cell lung cancer. See NCCN Guidelines for Non-Small Cell Lung Cancer. Intravenous contrast is beneficial in the unresectable setting.**
- **Radiation beam arrangements should be selected based on the shape of PTV aiming to confine the prescribed high dose to the target and minimize dose to adjacent critical structures. Anterior-posterior and posterior-anterior ports weighing more anteriorly, or wedge pair technique may be considered. These techniques, although commonly used during the traditional 2-D era, can generate an excessive dose to normal tissue. A dose-volume histogram of the lungs, heart, and cord need to be carefully reviewed for each plan.**
- **RT should be given by 3-D conformal technique to reduce surrounding normal tissue damage (eg, heart, lungs, esophagus, spinal cord). Intensity-modulated RT (IMRT) may further improve the dose distribution and decrease the dose to the normal tissue as indicated. If IMRT is applied, the ASTRO/ACR IMRT guidelines should be strictly followed.[6,7]**
- **In addition to following the normal tissue constraints recommendation using the Principles of RT for non-small cell lung cancer, more conservative limits are recommended to minimize the dose volumes to all the normal structures. Since these patients are younger and mostly long-term survivors, the mean dose to the total heart should be as low as reasonably achievable.**

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

[5]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.
[6]Moran JM, Dempsey M, Eisbruch A, et al. Safety considerations for IMRT: executive summary. Med Phys 2011;38:5067-5072.
[7]Hartford AC, Palisca MG, Eichler TJ, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guidelines for Intensity-Modulated Radiation Therapy (IMRT). Int J Radiat Oncol Biol Phys 2009;73:9-14.

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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 1–3
Cyclophosphamide 500 mg/m^2 IV on day 1
Prednisone 100 mg/day days 1–5
Administered every 3 weeks

ADOC[3]
Cisplatin 50 mg/m^2 IV day 1
Doxorubicin 40 mg/m^2 IV day 1
Vincristine 0.6 mg/m^2 IV day 3
Cyclophosphamide 700 mg/m^2 IV day 4
Administered every 3 weeks

PE[4]
Cisplatin 60 mg/m^2 IV day 1
Etoposide 120 mg/m^2/d IV days 1–3
Administered every 3 weeks

VIP[5]
Etoposide 75 mg/m^2 on days 1–4
Ifosfamide 1.2 g/m^2 on days 1–4
Cisplatin 20 mg/m^2 on days 1–4
Administered every 3 weeks

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

SECOND-LINE CHEMOTHERAPY

Sunitinib (Thymic carcinomas only)[7]
Pemetrexed[8]
Everolimus[9]
Paclitaxel[10-11]
Octreotide (including LAR) +/- prednisone[12]
Gemcitabine[13]
5-FU and leucovorin[14-15]
Etoposide[4]
Ifosfamide[16]

References on THYM-C 2 of 2

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PRINCIPLES OF CHEMOTHERAPY FOR THYMIC MALIGNANCIES
REFERENCES

[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.
[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: 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, Lee JW, Aisner SC, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. J Clin Oncol 2011;29:2060–2065.
[7]Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. Lancet Oncol 2015;16:177-186.
[8]Loehrer PJ, Yiannoutsos CT, Dropcho S, et al. A phase II trial of pemetrexed in patients with recurrent thymoma or thymic carcinoma [abstract]. J Clin Oncol 2006;24(Suppl 18):Abstract 7079.
[9]Zucali PA, De Pas TM, Palmieri G, et al. Phase II study of everolimus in patients with thymoma and thymic carcinoma previously treated with cisplatin-based chemotherapy [abstract]. J Clin Oncol 2014;32(suppl 5): Abstract 7527.
[10]Umemura S, Segawa Y, Fujiwara K, et al. A case of recurrent metastatic thymoma showing a marked response to paclitaxel monotherapy. Jpn J Clin Oncol 2002;32:262–265.
[11]Yamamoto N, Tsurutani J, Yoshimura N, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. Anticancer Res 2006;26:777–781.
[12]Loehrer PJ Sr, Wang W, Johnson DH, et al. Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: an Eastern Cooperative Oncology Group Phase II Trial. J Clin Oncol 2004;22:293–299.
[13]Palmieri G, Merola G, Federico P, et al. Preliminary results of phase II study of capecitabine and gemcitabine (CAP-GEM) in patients with metastatic pretreated thymic epithelial tumors (TETs). Ann Oncol 2010;21:1168-1172.
[14]Stewart DJ, Dahrouge S, Soltys KM, Evans WK. A phase II study of 5-fluorouracil plus high-dose folinic acid in the treatment of recurrent small cell lung cancer. Am J Clin Oncol 1995;18:130–132.
[15]André T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. Eur J Cancer 1999;35:1343–1347.
[16]Highley MS, Underhill CR, Parnis FX, et al. Treatment of invasive thymoma with single-agent ifosfamide. J Clin Oncol 1999;17:2737–2744.

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World Health Organization Histologic Classification[1]

Type	Description
A	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.
AB	A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes.
B1	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.
B2	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.
B3	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.
C	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.

[1]Kondo K, Yoshizawa K, Tsuyuguchi M, et al. WHO histologic classification is a prognostic indicator in thymoma. Ann Thorac Surg 2004;77:1183-1188.

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Staging

Table 1. Modified Masaoka clinical staging of thymoma[1,2]

Masaoka stage	Diagnostic criteria
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 (ie, pericardium, great vessels, lung)
	(A) Without invasion of great vessels
	(B) With invasion of great vessels
Stage IV	(A) Pleural or pericardial dissemination
	(B) Lymphogenous or hematogenous metastasis

Table 2. TNM Classification[3]

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor completely encapsulated
T2	Tumor invades pericapsular connective tissue
T3	Tumor invades into neighboring structures, such as pericardium, mediastinal pleura, thoracic wall, great vessels and lung
T4	Tumor with pleural or pericardial dissemination

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in anterior mediastinal lymph nodes
N2	Metastasis in other intrathoracic lymph nodes excluding anterior mediastinal lymph nodes
N3	Metastasis in scalene and/or supraclavicular lymph nodes

M	Distant Metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0, 1	M0
Stage IV	T4	Any N	M0
	Any T	N2, 3	M0
	Any T	Any N	M1

[1]Reprinted from Wright CD. Management of thymomas. Crit Rev Oncol Hematol 2008;65:109-120, with permission from Elsevier.
[2]Note that the Masaoka staging system is also used to stage thymic carcinomas.
[3]Travis WD, Brambilla E, Müller-Hermelink HK, Harris, CC. World Health Organization Classification of Tumours of the Lung Pleura, Thymus and Heart. IARC, Lyon, 2004.

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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.

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Overview

Thymic epithelial tumors originate in the thymus and include thymomas and thymic carcinomas.[1,2] Thymomas are a common primary tumor in the anterior mediastinum, although they are rare (1.5 cases/million).[3-6] Thymic carcinomas are very rare. Although thymomas can spread locally, they are much less invasive than thymic carcinomas.[4] Patients with thymomas have 5-year survival rates of approximately 90%.[7-9] However, 5-year survival rates for thymic carcinomas are only approximately 55%.[10-12]

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) focus on thymomas and thymic carcinomas and outline the evaluation, treatment, and management of these mediastinal tumors; these NCCN Guidelines® were first published in 2010. This revised Discussion text now includes the updates from the 2015 NCCN Guidelines for Thymomas and Thymic Carcinomas and includes recent references; no changes were made to the algorithm for the 2016 update. These NCCN Guidelines for Thymomas and Thymic Carcinomas were developed and are updated by panel members who are also on the NCCN Guidelines for Non-Small Cell Lung Cancer Panel.

Literature Search Criteria and Guidelines Update Methodology

Before the update of this version of the NCCN Guidelines for Thymomas and Thymic Carcinomas, an electronic search of the PubMed database was performed to obtain key literature in Thymomas and Thymic Carcinomas published between September 1, 2014 and October 2, 2015 using the following search terms: Thymomas; Thymic Carcinomas. The PubMed database was chosen, because it is the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 1; Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 25 citations and their potential relevance was examined. The data from key PubMed articles selected by the NCCN Panel for review during the NCCN Guidelines update meeting, as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the NCCN Panel, have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). If high-level evidence is lacking, recommendations are based on the panel's review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available on the NCCN webpage.

Mediastinal Masses

Masses in the anterior mediastinum can be neoplasms (eg, thymomas, lymphomas, thymic carcinomas, thymic carcinoids, thymolipomas, germ cell tumors, lung metastases) or non-neoplastic conditions (eg, intrathoracic goiter, thymic cysts, lymphangiomas, aortic aneurysms).[5,13-16] 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 Guidelines for Thymomas and Thymic Carcinomas). It is essential to differentiate between thymic malignancies and other conditions (eg,

lung metastases, lymphoma, goiter, germ cell tumors) before treatment, because management differs for these conditions.[1,17,18] Most masses in the mediastinum are metastases from a primary lung cancer (eg, non-small cell lung cancer). However, about 50% of primary cancers in the anterior mediastinum are thymomas.[19]

Patients with thymomas often have an indolent presentation, whereas those with lymphoma or germ cell tumors have a rapid onset of symptoms.[18] Lymphomas typically manifest as generalized disease but can also be primary anterior mediastinal lesions (ie, nodular sclerosing Hodgkin's disease, non-Hodgkin's lymphomas [diffuse large B-cell lymphoma and acute lymphoblastic lymphoma]); patients typically have lymphadenopathy (see the NCCN Guidelines for Non-Hodgkin's Lymphomas and Hodgkin Lymphoma, available at NCCN.org).[16,20] Thymic carcinoids are rare tumors that are discussed in the NCCN Guidelines for Neuroendocrine Tumors; they can be associated with multiple endocrine neoplasia type 1 (MEN1) syndrome (see the NCCN Guidelines for Neuroendocrine Tumors, available at NCCN.org).[21,22] Extragonadal germ cell tumors are rare tumors that may also occur in the mediastinum.[23,24]

Recommended tests for assessing mediastinal masses include chest CT with contrast and blood chemistry studies (see *Initial Evaluation* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[14,25-31] On CT, a thymoma is usually a well-defined round or oval mass in the thymus without lymph node enlargement.[29,32,33] Recently, low-dose CT was found to be useful for detecting lung cancer in patients at high risk (see the NCCN Guidelines for Lung Cancer Screening, available at NCCN.org).[34] Mediastinal masses (eg, lung metastases, thymomas, thymic carcinomas) may be detected in individuals undergoing lung cancer screening. However, data and guidelines about screening for lung cancer with low-dose CT do not apply to thymomas and thymic carcinomas; there are no data to suggest that screening improves survival for patients with thymomas and thymic carcinomas.[34] In patients who cannot tolerate iodinated contrast, MRI of the chest may be useful.[29] Combined PET-CT may be useful for determining whether extrathoracic metastases are present.[35,36] 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 Guidelines for Thymomas and Thymic Carcinomas). Thymic epithelial tumors are likely if the following are present: 1) a well-defined mediastinal mass in the thymic bed that is not continuous with the thyroid gland; 2) tumor markers for AFP or beta-hCG are negative; and 3) no other adenopathy is present.[1,2,37]

Thymic Masses

The optimal plan of care for patients with thymic malignancies should be developed before treatment, after evaluation by radiation oncologists, thoracic surgeons, medical oncologists, and diagnostic imaging specialists.[38] It is critical to determine whether the mass can be surgically resected; a board-certified thoracic surgeon with a primary focus on thoracic oncology 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 Guidelines for Thymomas and Thymic Carcinomas).[9,11,18,39,40] 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.[41-43] Core-needle or open biopsy is recommended for locally advanced, unresectable thymic masses.

Minimally invasive procedures are not routinely recommended, because only a few long-term studies are available regarding recurrence and survival.[44-46] However, minimally invasive procedures may be considered if standard oncologic goals can be met (as previously described) and if performed in specialized centers with surgeons with expertise in these techniques.[46-50] A recent systematic review of 1061 patients with thymomas reported that 5-year overall survival video-assisted thoracoscopic surgery (VATS: 83%–100% vs. open: 79%–98%) and 10-year recurrence-free survival (VATS: 89%–100% vs. open: 80%–93%) were similar in patients undergoing VATS compared to open thymectomy, although outcomes may be skewed due to selection bias.[44]

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 NCCN Guidelines for Thymomas and Thymic Carcinomas).[9,11,51-57] The International Thymic Malignancy Interest Group (ITMIG) suggests using the Masaoka-Koga stage classification.[51,58] A new proposal for a staging system for thymomas and thymic carcinomas is based on a combined effort by the ITMIG and International Association for the Study of Lung Cancer (IASLC).[37,59-62] The TNM staging system is less commonly used (see Table 2 in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[2,63] The current TNM staging system will be revised when the new edition of the American Joint Committee on Cancer (AJCC 8th edition) becomes effective in January 2017.[1] Patients with stage I to III thymomas have a 5-year survival rate of approximately 85% versus 65% for stage IV disease.[9,64,65] In approximately 50% of patients, mortality is not related to thymoma.[52] Mortality is related to myasthenia gravis in approximately 20% of patients.

The WHO histologic classification system can be used to distinguish between thymomas, thymic carcinomas, and thymic carcinoids (see Table 3 in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[63,66] The WHO classification is also used to differentiate among different histologic types of thymomas (ie, A, AB, B1, B2, B3); however, it is difficult to classify thymomas.[67] Thymic carcinomas are type C in the WHO classification, although they are very different from thymomas and are not advanced thymomas (see *Thymic Carcinomas* in this Discussion).[68] The WHO histologic classification system was recently revised.[1,2] However, the histologic subtype is less important for management than stage of disease and the extent of resection (ie, R0, R1, R2) (see *Postoperative Management* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[11,69-73] For stage III to IV thymomas, 5-year survival rates have been reported to be 90% in patients with total resection.[7,11] For thymic carcinomas, 5-year survival rates are lower, even in those with total resection.[10,74]

Thymomas

Thymomas typically occur in adults 40 to 70 years of age; they are rare in children or adolescents.[18,75] The etiology of thymomas is unknown; alcohol, tobacco smoking, and ionizing radiation do not appear to be risk factors for thymomas.[3] The incidence of thymomas is higher in African Americans as well as Asians and Pacific Islanders, which suggests there may be a genetic component.[3,76] Although some patients are asymptomatic, others present with chest pain, cough, or dyspnea. Approximately 30% to 50% of patients with thymomas have myasthenia gravis.[77] Symptoms suggestive of myasthenia gravis include drooping eyelids, double vision, drooling, difficulty climbing stairs, hoarseness, and/or dyspnea. 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.[64] If patients have myasthenia gravis, they should receive treatment by a neurologist with experience in myasthenia gravis before undergoing surgical resection.[78-81]

Although thymomas can be locally invasive (eg, pleura, lung), they uncommonly spread to regional lymph nodes or extrathoracic sites.[9,64,82,83] Surgery (ie, total thymectomy and complete excision of tumor) is recommended for all resectable thymomas for patients who can tolerate the surgery.[19,84] For resected stage I and II thymomas, the 10-year survival rate is excellent (approximately 90% and 70%, respectively).[18,85] Completeness of resection is the most important predictor of outcome.[7] 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).[18] A transpleural approach should be avoided during biopsy of a possible thymoma to prevent tumor seeding.[79,86] Small biopsy sampling (fine-needle or core-needle biopsy) does not always indicate whether invasion is present.[87] The ITMIG has established procedures for reporting the surgical and pathologic findings from resection specimens.[88]

Adjuvant therapy is not recommended for completely resected (R0) stage I thymomas.[39,89,90] For incompletely resected thymomas, postoperative radiation therapy (RT) is recommended (see *Postoperative Management* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[39,91] Note that extensive elective nodal radiation is not recommended, because thymomas do not typically metastasize to regional lymph nodes.[9,92] CT-based treatment planning is highly recommended before RT (see *Principles of Radiation Therapy* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[93] RT should be given by the 3-D conformal technique to reduce damage to surrounding normal tissue (eg, heart, lungs, esophagus, spinal cord).

Use of intensity-modulated RT (IMRT) may decrease the dose to the normal tissues.[93,94] However, if IMRT is used, guidelines from the ATC/NCI and ASTRO/ACR should be followed (http://rrp.cancer.gov/content/docs/imrt.doc).[95-98] The ICRU-83 (International Commission on Radiation Units and Measurements Report 83) recommendations are also a useful resource.[97,99] 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, available at NCCN.org), more conservative limits are recommended to minimize the dose volumes to all the normal structures.[100,101] Because these patients are younger and usually long-term survivors, the mean dose to the heart should be as low as reasonably achievable.

A definitive dose of 60 to 70 Gy is recommended for patients with unresectable disease. For adjuvant treatment, a dose of 45 to 50 Gy is recommended for clear or close margins; a dose of 54 Gy is recommended for microscopically positive resection margins (see *Principles of Radiation Therapy* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[93,94,102] However, a total dose of 60 Gy or more (1.8–2 Gy/fraction per day) is recommended for patients with gross residual disease after surgery.[103,104] In patients with thymomas who have capsular invasion after an R0 resection, postoperative RT can be considered although this is a category 2B recommendation (see *Postoperative Management* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[90,93,105-107] Patients with stage III (with macroscopic invasion into neighboring organs) thymoma have higher risks of recurrent disease and, as such, postoperative radiation is recommended.[108-111] Data suggest that patients with stage II thymoma

may not benefit from postoperative radiation.[39,89,90,106,112] Postoperative chemotherapy is also not beneficial in this setting.[113,114]

For locally advanced thymomas, induction chemotherapy is recommended followed by an evaluation for surgery; postoperative RT can be considered after surgical resection of the primary tumor and isolated metastases (see *Treatment* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[115,116] For those with solitary metastasis or ipsilateral pleural metastases, options include induction chemotherapy or surgery. For patients with unresectable disease in both of these settings, RT with [or without] chemotherapy is recommended. For metastatic disease, chemotherapy is recommended (see *Principles of Chemotherapy for Thymic Malignancies* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[90,115,117-129] 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.[39,130-132] However, non-anthracycline regimens (eg, cisplatin/etoposide [with or without ifosfamide], carboplatin/paclitaxel) may be useful for patients who cannot tolerate the more aggressive regimens.[132,133] Induction therapy followed by surgery may be useful for thymic malignancies initially considered unresectable.[74,115,134,135]

After primary treatment for resectable thymomas, panel members agree that surveillance for recurrence should include chest CT every 6 months for 2 years, then annually for 10 years for thymoma.[29] Given the risk of later recurrence for thymoma, surveillance should continue for at least 10 years. However, the duration, frequency, and type of imaging for surveillance for patients with thymomas have not been established in published studies. Patients with thymoma also have an increased risk for second malignancies, although no particular screening studies are recommended.[3,136]

Second-line systemic therapy includes sunitinib, pemetrexed, everolimus, paclitaxel, octreotide (long-acting release [LAR]) with or without prednisone, gemcitabine, 5-FU, etoposide, and ifosfamide.[118,119,132,137-143] However, none of these agents has been assessed in randomized trials. Octreotide may be useful in patients with thymoma who have a positive octreotide scan or symptoms of carcinoid syndrome. Surgery is an option for patients with recurrent locally advanced disease, solitary metastases, or ipsilateral metastases.[144]

Thymic Carcinomas

Thymic carcinomas are rare aggressive tumors that often metastasize to regional lymph nodes and extrathoracic sites; thus, they have a worse prognosis than thymomas.[5,8,11,12,16,72,73,145,146] Survival rates for thymic carcinomas vary depending on stage (stages 1–2: 91%; stages 3–4: 31%) and resectability (including completeness of resection).[10] These tumors can be distinguished from thymomas because of their malignant histologic features and their different immunohistochemical and genetic features.[15,63,68] They are predominantly squamous cell carcinomas and undifferentiated carcinomas. However, thymic carcinomas should be differentiated from primary lung malignancies that metastasize to the thymus and have a similar histologic appearance.[147,148] 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 NCCN Guidelines for Thymomas and Thymic Carcinomas).[51,149,150]

It is important to note that thymic carcinomas are associated with a different clinical course from thymomas.[68,117] Unlike thymomas, paraneoplastic syndromes, including myasthenia gravis, are very rare in

patients with thymic carcinoma.[102] If myasthenia gravis is diagnosed, then the diagnosis of thymic carcinoma should be reassessed; the patient may actually have thymoma.[10] In contrast to thymomas (which mainly occur in adults), thymic carcinomas occur over a wide age range including adolescents when assessed in a single-institution Western population; they predominantly occur in Caucasian individuals.[10]

Similar to thymomas, patients with completely resected thymic carcinomas have longer survival than those who are either incompletely resected or are unresectable.[72,74,151] Patients who have an R0 resection have a 5-year survival of about 60%.[10] Thus, management depends on the extent of resection. Patients with thymic carcinoma have higher risks of recurrent disease; therefore, postoperative radiation is recommended to maximize local control.[10] 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 Guidelines for Thymomas and Thymic Carcinomas).[10,72,73,93,112,152,153] A recent study suggests that adjuvant therapy may not be necessary for early-stage thymic carcinomas.[154] For unresectable or metastatic thymic carcinomas, chemotherapy with (or without) RT is recommended (see *Principles of Chemotherapy for Thymic Malignancies* and *Principles of Radiation Therapy* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[131]

A definitive dose of 60 to 70 Gy is recommended for patients with unresectable thymic carcinomas. For adjuvant treatment, a dose of 45 to 50 Gy is recommended for clear or close margins; a dose of 54 Gy is recommended for microscopically positive resection margins (see *Principles of Radiation Therapy* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[93,94,102] However, a total dose of 60 Gy or more (1.8–2 Gy/fraction per day) is recommended for patients with gross residual disease after surgery.[103,104] In patients with thymic carcinomas who have capsular invasion after an R0 resection, postoperative RT can be considered although this is a category 2B recommendation (see *Postoperative Management* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[90,93,105-107] Adjuvant therapy is not recommended for completely resected (R0) stage I thymic carcinomas.[39,89,90]

Unfortunately, thymic carcinomas respond poorly to chemotherapy; carboplatin/paclitaxel is recommended, because it has the highest response rate in patients with thymic carcinomas in clinical trials.[128,133,155-164] Data suggest that the ADOC (cisplatin, doxorubicin, vincristine, and cyclophosphamide) regimen is also effective, but it is more toxic than carboplatin/paclitaxel.[162] Induction chemotherapy is recommended followed by an evaluation for surgery for locally advanced disease; postoperative RT can be considered after surgical resection of the primary tumor and isolated metastases (see *Treatment* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[10] Patients with unresectable disease can then receive RT with [or without] chemotherapy. For those with solitary metastasis or ipsilateral pleural metastases, options include induction chemotherapy or surgery.

After primary treatment for resectable disease, panel members agree that surveillance for recurrence should include chest CT every 6 months for 2 years, then annually for 5 years for thymic carcinoma.[29] However, the duration, frequency, or type of imaging for surveillance for thymic carcinomas has not been established in published studies. Data are lacking regarding second-line chemotherapy for thymic carcinomas.[118] Most of the second-line agents in the NCCN algorithm are appropriate for thymomas (see *Principles of Chemotherapy for Thymic Malignancies* in the NCCN Guidelines for Thymomas and Thymic Carcinomas).[119] However, S-1 (an oral fluorouracil) appears to be active in patients with thymic carcinomas.[165,166] Targeted therapy (eg,

sunitinib, sorafenib) may be useful for patients with *c-Kit* mutations; however, these mutations are rare in thymic carcinomas (<10%).[76,119,137,167-170] Patients with thymomas do not have *c-Kit* mutations.[147]

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