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National Comprehensive
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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Thymomas and Thymic Carcinomas

Version 1.2025 — October 30, 2024

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Thymomas and Thymic Carcinomas

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Thymomas and Thymic Carcinomas

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See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

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Updates in Version 1.2025 of the NCCN Guidelines for Thymomas and Thymic Carcinomas from Version 1.2024 include:

THYM-2

- Footnote d modified: Determination of resectability should be made by a thoracic surgeon, with primary focus on thoracic oncology and in multidisciplinary consultation ~~with medical oncology~~ as needed. Resectability is defined as complete (R0) resection. (also applies to THYM-4)

THYM-A 1 of 2

- Bullet 5 modified: If an R0 resection ~~appears unlikely~~ is considered uncertain, patient should be considered for neoadjuvant systemic therapy. Debulking tumors is discouraged.

THYM-C 1 of 3 (First-line Combination Chemotherapy Regimens)

- The following regimen added as a Preferred option for Thymic Carcinoma
 - Carboplatin/paclitaxel/ramucirumab

Ramucirumab 10 mg/kg IV day 1

Paclitaxel 200 mg/m² IV day 1

Carboplatin AUC 5 IV day 1

Administered every 3 weeks, maximum of six cycles

Ramucirumab monotherapy every 3 weeks as maintenance therapy, until progressive disease or unacceptable toxicity

- Footnote c added: There is no published experience using this as a preoperative therapy. Patients with untreated brain metastases or major standard contraindications to antiangiogenics were excluded from the study.

THYM-C 2 of 3 (Second-line Systemic Therapy)

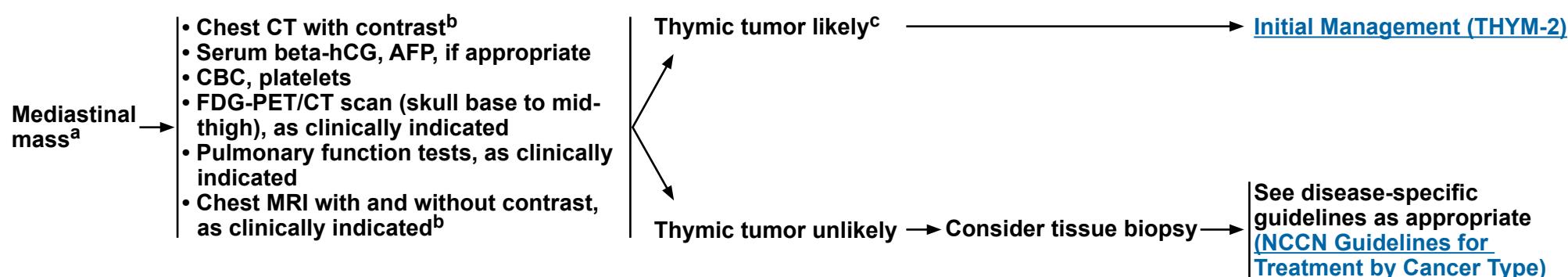
- Regimens noted in alphabetical order
- Preference stratification applied to the regimens for Thymoma
 - Moved from Other Recommended to Preferred
 - Everolimus, Gemcitabine ± capecitabine, Octreotide (including LAR) (if octreotide scan or dotatate PET/CT positive) ± prednisone, Pemetrexed
 - Moved from Other Recommended to Useful in Certain Circumstances
 - Etoposide, Ifosfamide
- The following regimen added as an Other Recommended option for Thymic Carcinoma
 - Avelumab + axitinib

THYM-C 3 of 3

- References added
 - Proto C, Ganzinelli M, Manglaviti S, et al. Efficacy and safety of ramucirumab plus carboplatin and paclitaxel in untreated metastatic thymic carcinoma: RELEVENT phase II trial (NCT03921671). Ann Oncol 2024;35:817-826.
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INITIAL EVALUATION



^a Patients with thymoma should be evaluated clinically for signs of myasthenia gravis and other paraneoplastic syndromes with appropriate workup and treatment.

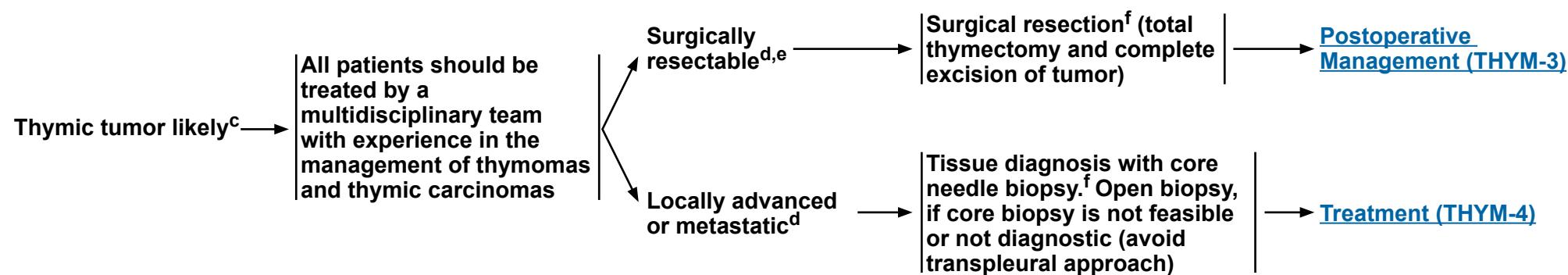
^b When assessing a mediastinal mass, detection of thymic malignancy versus thymic cyst or thymic hyperplasia can be better discriminated with chest MRI compared to chest CT, potentially avoiding an unnecessary thymectomy.

^c Well-defined anterior mediastinal mass in the thymic bed, tumor markers negative, absence of other adenopathy, and absence of continuity with the thyroid. Marom EM, et al. J Thorac Oncol 2011;6:S1717-S1723.

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



INITIAL MANAGEMENT



^c Well-defined anterior mediastinal mass in the thymic bed, tumor markers negative, absence of other adenopathy, and absence of continuity with the thyroid. Marom EM, et al. J Thorac Oncol 2011;6:S1717-S1723.

^d Determination of resectability should be made by a thoracic surgeon, with primary focus on thoracic oncology and in multidisciplinary consultation as needed. Resectability is defined as complete (R0) resection.

^e If R0 resection is considered uncertain, preoperative systemic therapy should be considered. See [Principles of Systemic Therapy \(THYM-C\)](#).

^f [Principles of Surgical Resection \(THYM-A\)](#).

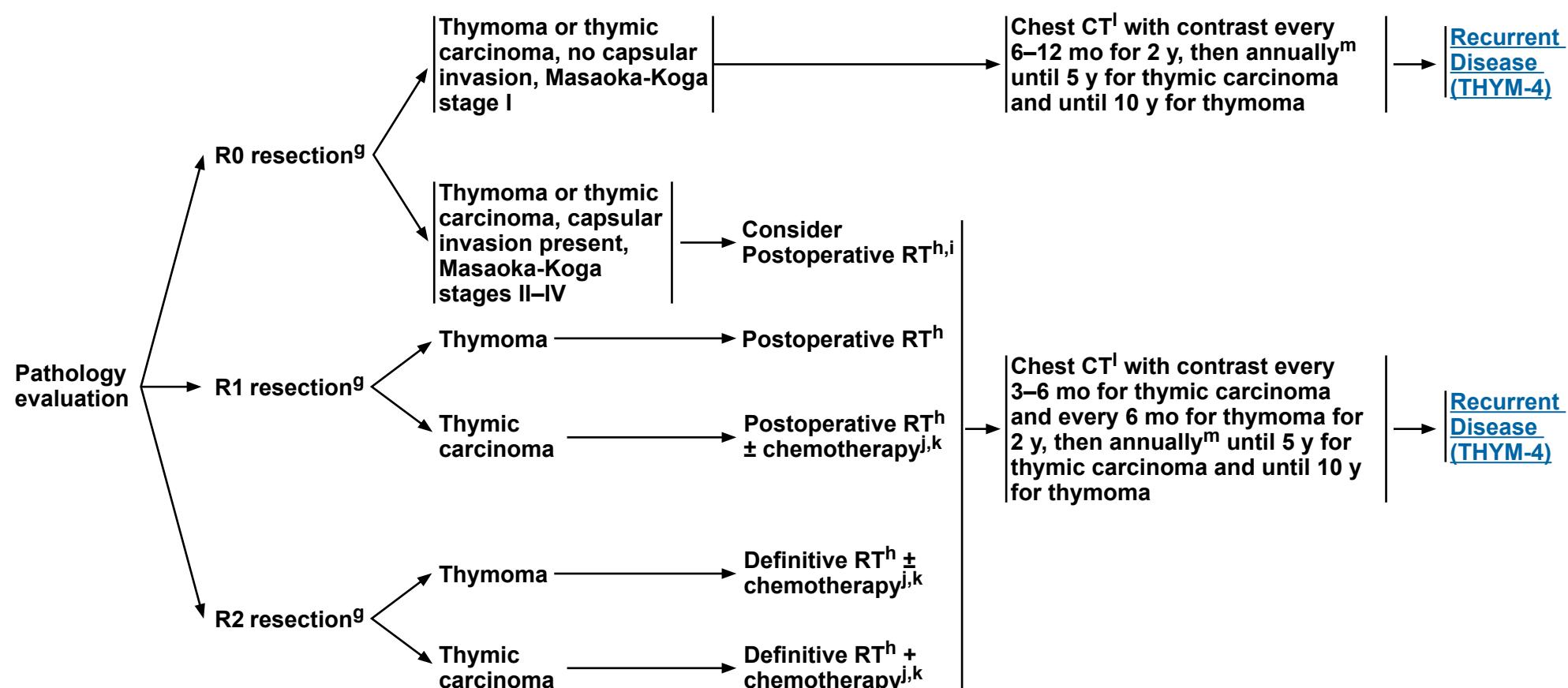
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Thymomas and Thymic Carcinomas

POSTOPERATIVE EVALUATION



^a Patients with thymoma should be evaluated clinically for signs of myasthenia gravis and other paraneoplastic syndromes with appropriate workup and treatment.

^g R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

^h [Principles of Radiation Therapy \(THYM-B\)](#).

ⁱ Decisions about adjuvant radiation therapy (RT) in this setting should be based on multidisciplinary evaluation.

^j [Principles of Systemic Therapy \(THYM-C\)](#).

^k There is a diversity of opinion on treatment approach. Ruffini E, et al. Eur J Cardiothorac Surg 2019;55:601-609.

^l MRI is an appropriate alternative to CT in certain clinical situations.

^m The duration for surveillance has not been established.

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



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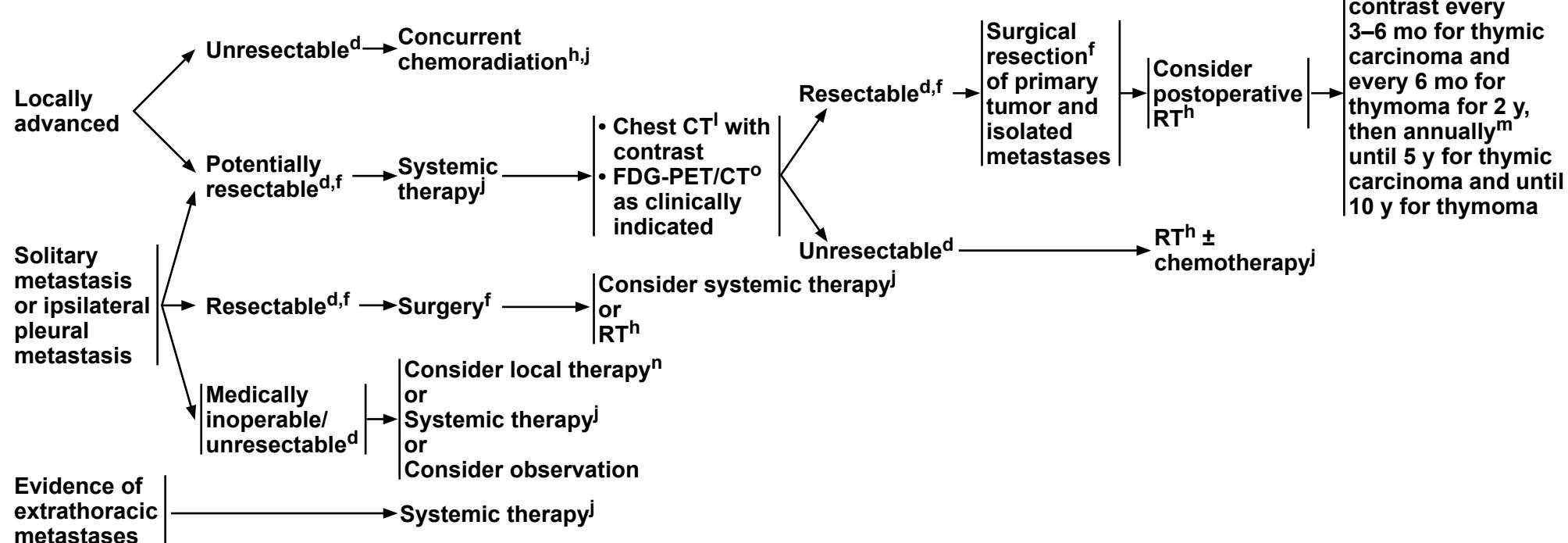
Thymomas and Thymic Carcinomas

RECURRENT, ADVANCED,
OR METASTATIC DISEASE

TREATMENT

SURVEILLANCE^a

ALL PATIENTS SHOULD BE TREATED BY A MULTIDISCIPLINARY TEAM WITH EXPERIENCE IN THE MANAGEMENT OF THYMOGRAS AND THYMIC CARCINOMAS



^a Patients with thymoma should be evaluated clinically for signs of myasthenia gravis and other paraneoplastic syndromes with appropriate workup and treatment.

^d Determination of resectability should be made by a thoracic surgeon, with primary focus on thoracic oncology and in multidisciplinary consultation as needed.

Resectability is defined as complete (R0) resection.

^f [Principles of Surgical Resection \(THYM-A\)](#).

^h [Principles of Radiation Therapy \(THYM-B\)](#).

^j [Principles of Systemic Therapy \(THYM-C\)](#).

^l MRI is an appropriate alternative to CT in certain clinical situations.

^m The duration for surveillance has not been established.

ⁿ Local therapies can include image-guided thermal ablation or RT.

^o FDG-PET/CT includes skull-base to mid-thigh.

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



PRINCIPLES OF SURGICAL RESECTION

- Surgical resection should be performed on carefully evaluated patients by thoracic surgeons with experience in managing thymomas and thymic carcinomas. Locally advanced (unresectable) and resectable stage \geq 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 because of the substantial potential of tumor seeding when the tumor capsule is violated.
- Biopsy of a possible thymoma should avoid a transpleural approach because of the substantial risk of converting a stage I thymoma to a stage IV thymoma by spreading tumor within the pleural space.
- Prior to surgery, patients should be evaluated for signs and symptoms of myasthenia gravis and should be medically controlled prior to undergoing surgical resection.
- If an R0 resection is considered uncertain, patients should be considered for neoadjuvant systemic therapy. Debulking tumors is discouraged.
- 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.
- Surgical clips should be placed at the time of resection to areas of close margins, residual disease, or tumor adhesion to unresected normal structures to help guide accurate RT when indicated.
- 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 for clinical stage I-II if all oncologic goals can be met as in standard procedures, and if performed in specialized centers by surgeons with experience in these techniques.¹⁻¹⁴

[References on THYM-A 2 OF 2](#)

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



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

THYM-A
2 OF 2



PRINCIPLES OF RADIATION THERAPY^{1,2}

General Principles

- Recommendations regarding RT should be made by radiation oncologists with experience in managing thymomas and thymic carcinomas.
- Definitive RT should be given for patients with unresectable disease (if disease progresses on induction systemic therapy), for patients with incompletely resected invasive thymoma or thymic carcinoma, or as adjuvant therapy after systemic therapy 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.
- The review of preoperative imaging and co-registration of preoperative imaging into the planning system are helpful in defining treatment volumes.

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 60–70 Gy should be given to patients with gross residual disease (similar to patients with unresectable disease),^{3,4,5} when conventional fractionation (1.8–2.0 Gy per daily fraction) is applied.
- Depending on the treatment objectives in the palliative setting, typical palliative doses (eg, 8 Gy in a single fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions) up to definitive doses for more durable local control and highly conformal techniques for limited volume metastases may be appropriate, given the relatively long natural history of even metastatic thymoma.

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 (ENI) (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended, as thymomas do not commonly metastasize to regional lymph nodes.⁶
- 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 THYM-B 2 of 3](#)

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

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Thymomas and Thymic Carcinomas

PRINCIPLES OF RADIATION THERAPY

Radiation Techniques

- Target motion should be managed using the Principles of Radiation Therapy in the [NCCN Guidelines for Non-Small Cell Lung Cancer](#). Intravenous contrast is beneficial in the unresectable setting.
- In addition to following the normal tissue constraints recommendation using the Principles of Radiation Therapy in the [NCCN Guidelines for Non-Small Cell Lung Cancer](#), 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 total dose to the heart should be as low as reasonably achievable to potentially maximize survival.
- A minimum technological standard for RT is CT-planned 3D conformal RT (3D-CRT). More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), image-guided RT (IGRT), motion management, and proton therapy. In particular, IMRT is preferred over 3D-CRT. Compared to IMRT, proton therapy has been shown to improve dosimetry, thus allowing for better sparing of normal organs (lungs, heart, and esophagus)⁷ with favorable local control and toxicity, and is appropriate.⁸

[General Principles, Radiation Dose, and Radiation Volume THYM-B 1 of 3](#)

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PRINCIPLES OF RADIATION THERAPY — REFERENCES

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

THYM-B
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Thymomas and Thymic Carcinomas

PRINCIPLES OF SYSTEMIC THERAPY

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS^a

THYMOMA

Preferred (Other Recommended for Thymic Carcinoma)

- CAP¹
Cisplatin 50 mg/m² IV day 1
Doxorubicin 50 mg/m² IV day 1
Cyclophosphamide 500 mg/m² IV day 1
Administered every 3 weeks

THYMIC CARCINOMA

Preferred (Other Recommended for Thymoma)

- Carboplatin/paclitaxel^{4,5,b}
Carboplatin AUC 6 IV day 1
Paclitaxel 200 mg/m² IV day 1
Administered every 3 weeks

Preferred (Thymic Carcinoma only)

- Carboplatin/paclitaxel/ramucirumab^{6,c}
Ramucirumab 10 mg/kg IV day 1
Paclitaxel 200 mg/m² IV day 1
Carboplatin AUC 5 IV day 1
Administered every 3 weeks, maximum of six cycles
Ramucirumab monotherapy every 3 weeks as maintenance therapy, until progressive disease or unacceptable toxicity

Other Recommended for Thymic Carcinoma and Thymoma

- CAP with prednisone²
Cyclophosphamide 500 mg/m² IV day 1;
Doxorubicin, 20 mg/m²/day IV continuous infusion days 1–3;
Cisplatin 30 mg/m²/day IV days 1–3;
Prednisone 100 mg/day PO days 1–5;
Administered every 3 weeks

- ADOC³
Doxorubicin 40 mg/m² IV day 1;
Cisplatin 50 mg/m² IV day 1;
Vincristine 0.6 mg/m² IV day 3;
Cyclophosphamide 700 mg/m² IV day 4
Administered every 3 weeks

- PE^{7,b}
Cisplatin 60 mg/m² IV day 1;
Etoposide 120 mg/m²/day IV days 1–3;
Administered every 3 weeks

- Etoposide/ifosfamide/cisplatin⁸
Etoposide 75 mg/m²/day IV days 1–4;
Ifosfamide 1.2 g/m²/day IV days 1–4;
Cisplatin 20 mg/m²/day IV days 1–4
Administered every 3 weeks

Subsequent Therapy THYM-2 of 3

References THYM-C 3 of 3

^a If patients cannot tolerate first-line combination regimens, consider second-line systemic therapy options.

^b Regimens can be used with RT, as definitive concurrent chemoradiation.

^c There is no published experience using this as a preoperative therapy. Patients with untreated brain metastases or major standard contraindications to antiangiogenics were excluded from the study.

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

THYM-C
1 OF 3



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Thymomas and Thymic Carcinomas

PRINCIPLES OF SYSTEMIC THERAPY

SECOND-LINE SYSTEMIC THERAPY (regimens noted in alphabetical order)

THYMOMA

Preferred

- Everolimus⁹
- Gemcitabine ± capecitabine^{10,11}
- Octreotide^d (including LAR) (if octreotide scan or dotatate PET/CT positive) ± prednisone^{12,13}
- Pemetrexed¹⁴

Other Recommended

- 5-FU and leucovorin¹⁵
- Paclitaxel¹⁶

Useful in Certain Circumstances

- Etoposide^{7,17}
- Ifosfamide¹⁸

THYMIC CARCINOMA

Preferred

- Gemcitabine ± capecitabine^{10,11}
- Lenvatinib,¹⁹
- Pembrolizumab^{f,20,21}
- Sunitinib²²

Other Recommended

- Avelumab + axitinib²³
- Everolimus⁹
- 5-FU and leucovorin¹⁵
- Paclitaxel¹⁶
- Pemetrexed¹⁴

Useful in Certain Circumstances

- Etoposide^{7,17}
- Ifosfamide¹⁸

[References THYM-C 3 of 3](#)

^d Nuclear medicine scan (octreotide scan or dotatate PET/CT [dotatate PET/CT preferred if available]) to assess for octreotide-avid disease.

^e There is a high risk for side effects and frequent dose reductions may be needed.

^f Pembrolizumab is not recommended for patients with thymoma. In patients with thymic carcinoma, there is concern for a higher rate of immune-related adverse events than seen in most other malignancies treated with PD-1/PD-L1 inhibitor therapy. For example, grade 3–4 myocarditis has been reported in 5%–9% of patients receiving pembrolizumab.

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



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Thymomas and Thymic Carcinomas

PRINCIPLES OF SYSTEMIC THERAPY — REFERENCES

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

THYM-C
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Thymomas and Thymic Carcinomas

WORLD HEALTH ORGANIZATION HISTOLOGIC CLASSIFICATION¹

Thymoma subtype ^a	Obligatory criteria	Optional criteria
Type A	Occurrence of bland, spindle shaped epithelial cells (at least focally); paucity ^b or absence of immature (TdT+) T cells throughout the tumor	Polygonal epithelial cells CD20+ epithelial cells
Atypical type A variant	Criteria of type A thymoma; in addition: comedo-type tumor necrosis; increased mitotic count (>4/2mm ²); nuclear crowding	Polygonal epithelial cells CD20+ epithelial cells
Type AB	Occurrence of bland, spindle shaped epithelial cells (at least focally); abundance ^b of immature (TdT+) T cells focally or throughout tumor	Polygonal epithelial cells CD20+ epithelial cells
Type B1	Thymus-like architecture and cytology: abundance of immature T cells, areas of medullary differentiation (medullary islands); paucity of polygonal or dendritic epithelia cells without clustering (i.e.<3 contiguous epithelial cells)	Hassall's corpuscles; perivascular spaces
Type B2	Increased numbers of single or clustered polygonal or dendritic epithelial cells intermingled with abundant immature T cells	Medullary islands; Hassall's corpuscles; perivascular spaces
Type B3	Sheets of polygonal slightly to moderately atypical epithelial cells; absent or rare intercellular bridges; paucity or absence of intermingled TdT+ T cells	Hassall's corpuscles; perivascular spaces
MNT ^c	Nodules of bland spindle or oval epithelial cells surrounded by an epithelial cell-free lymphoid stroma	Lymphoid follicles; monoclonal B cells and/or plasma cells (rare)
Metaplastic thymoma	Biphasic tumor composed of solid areas of epithelial cells in a background of bland-looking spindle cells; absence of immature T cells	Pleomorphism of epithelial cells; actin, keratin, or EMA-positive spindle cells
Rare others ^d		

^a For thymoma composed of two or more subtypes, components should be listed.

^b Paucity versus abundance: any area of crowded immature T cells or moderate numbers of immature T cells in >10% of the investigated tumor are indicative of "abundance."

^c MNT, micronodular thymoma with lymphoid stroma.

^d Lipofibroadenoma.

¹ Marx A, Detterbeck F, Marom EM, et al. Tumours of the thymus. In: WHO Classification of Tumours Editorial Board. Thoracic tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2021 [2021 9 12]. (WHO classification of tumours series, 5th ed; vol 5). Available from: <https://tumourclassification.iarc.who.int/chapters/35>.

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

THYM-D
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Thymomas and Thymic Carcinomas

WORLD HEALTH ORGANIZATION HISTOLOGIC CLASSIFICATION¹

Thymic Carcinoma Subtypes

- **Squamous carcinomas**

- ▶ Squamous cell carcinoma, NOS
- ▶ Basaloid carcinoma
- ▶ Lymphoepithelial carcinoma

- **Adenocarcinomas**

- ▶ Adenocarcinoma, NOS
- ▶ Low grade papillary adenocarcinoma
- ▶ Thymic carcinoma with adenoid cystic carcinoma-like features
- ▶ Adenocarcinoma, enteric-type

- **Adenosquamous carcinoma**

- **NUT carcinomas**

- **Salivary gland-like carcinomas**

- ▶ Mucoepidermoid carcinoma
- ▶ Clear cell carcinoma
- ▶ Sarcomatoid carcinoma
- ▶ Carcinosarcoma

- **Carcinoma, undifferentiated, NOS**

- **Thymic Carcinoma, NOS**

- **Neuroendocrine tumors ([NCCN Guidelines for Neuroendocrine and Adrenal Tumors](#))**

- ▶ Carcinoid tumor, NOS/neuroendocrine tumor, NOS
- ▶ Typical carcinoid/neuroendocrine tumor, grade 1
- ▶ Atypical carcinoid/neuroendocrine tumor, grade 2

- **Neuroendocrine carcinomas**

- ▶ Small cell carcinoma
- ▶ Combined small cell carcinoma
- ▶ Large cell neuroendocrine carcinoma

¹ Marx A, Detterbeck F, Marom EM, et al. Tumours of the thymus. In: WHO Classification of Tumours Editorial Board. Thoracic tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2021 [2021 9 12]. (WHO classification of tumours series, 5th ed; vol 5). Available from: <https://tumourclassification.iarc.who.int/chapters/35>.

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



Staging

Table 1. Modified Masaoka clinical staging of thymoma¹⁻³

<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 (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

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 Dettarbeck FC, Nicholson AG, Kondo K, et al. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. J Thorac Oncol 2011;6:S1710-S1716.



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Thymomas and Thymic Carcinomas

Staging

Table 2. Definitions for TNM*,**

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor encapsulated or extending into the mediastinal fat; may involve the mediastinal pleura
T1a	Tumor with no mediastinal pleura involvement
T1b	Tumor with direct invasion of mediastinal pleura
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)
T3	Tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins
T4	Tumor with invasion into any of the following: aorta (ascending, arch, or descending) arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus

AJCC Prognostic Groups

Stage I	T1a,b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
	Any T	N0-N1	M1a
Stage IVB	Any T	N2	M0-M1a
	Any T	Any N	M1b

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in anterior (perithymic) lymph nodes
N2	Metastasis in deep intrathoracic or cervical lymph nodes

Distant Metastasis (M)

M0	No pleural, pericardial, or distant metastasis
M1	Pleural, pericardial, or distant metastasis
M1a	Separate pleural or pericardial nodule(s)
M1b	Pulmonary intraparenchymal nodule or distant organ metastasis

*Involvement must be microscopically confirmed in pathological staging, if possible.

**T categories are defined by “levels” of invasion; they reflect the highest degree of invasion regardless of how many other (lower-level) structures are invaded. T1, level 1 structures: thymus, anterior mediastinal fat, mediastinal pleura; T2, level 2 structures: pericardium; T3, level 3 structures: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, hilar pulmonary vessels; T4, level 4 structures: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.



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Thymomas and Thymic Carcinomas

ABBREVIATIONS

3D-CRT	three-dimensional conformal radiation therapy	IGRT	image-guided radiation therapy
4D-CT	four-dimensional computed tomography	IMRT	intensity-modulated radiation therapy
AFP	alpha-fetoprotein	MNT	micronodular thymoma with lymphoid stroma
beta-hCG	beta-human chorionic gonadotropin	NOS	not otherwise specified
CBC	complete blood count	NUT	nuclear protein in testis
CTV	clinical target volume	PD-1	programmed cell death protein 1
EMA	epithelial membrane antigen	PD-L1	programmed death ligand 1
ENI	elective nodal irradiation	PTV	planning target volume
FDG	fluorodeoxyglucose	VMAT	volumetric modulated arc therapy



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Thymomas and Thymic Carcinomas

NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence (≥ 1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus ($\geq 50\%$, but $< 85\%$ support of the Panel) 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 indicated.

NCCN Categories of Preference

Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



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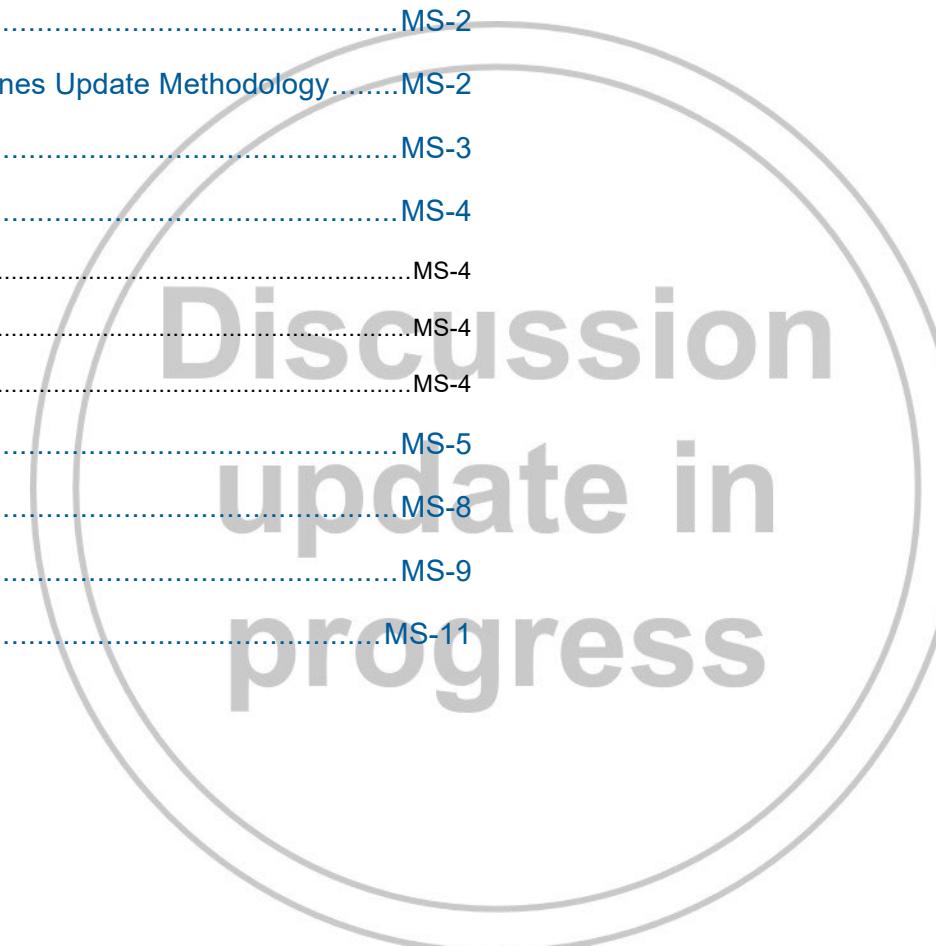
Thymomas and Thymic Carcinomas

Discussion

This discussion corresponds to the NCCN Guidelines for Thymomas and Thymic Carcinomas. Last updated: May 3, 2022

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Thymomas and Thymic Carcinomas

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 thymic carcinomas often present with metastases.⁷ Patients with thymomas have 5-year survival rates of approximately 90%.⁸⁻¹⁰ However, 5-year survival rates for thymic carcinomas are approximately 55%.¹¹⁻¹³

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 2007 and have been subsequently updated every year. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2022, which are described in greater detail in this revised Discussion text; new references have been added. For example, panel members removed octreotide (including LAR [long-acting release]) with or without prednisone as a second-line therapy option for patients with thymic carcinoma. Additional supplementary material in the NCCN Guidelines for Thymomas and Thymic Carcinomas includes the *Principles of Surgical Resection*, *Principles of Radiation Therapy*, *Principles of Systemic Therapy for Thymic Malignancies*, and the *World Health Organization Histologic Classification*. 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.

The NCCN Guidelines provide specific category designations for all treatment interventions in the guidelines, which are based on evidence from the biomedical literature and consensus among the panel members.

Category 1 recommendations indicate uniform NCCN consensus (at least 85% of the NCCN Member Institutions on the panel) that the intervention is appropriate based on high-level evidence, such as randomized phase 3 trials. Category 2A recommendations indicate uniform NCCN consensus that the intervention is appropriate based on lower level evidence, such as phase 2 trials. It is important to note that all recommendations are category 2A in the NCCN Guidelines unless otherwise indicated. Category 2B recommendations indicate NCCN consensus (50% to <85% of the NCCN Member Institutions on the panel) that the intervention is appropriate based on lower level evidence. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments.

All the systemic therapy regimens have been categorized by preference—based on the biomedical literature and experience of the panel members—using the following categories: 1) preferred interventions; 2) other recommended interventions; and 3) interventions that are useful in certain circumstances. These preference categories emphasize the preferred regimens in clinical practice and do not replace the NCCN categories of evidence and consensus, such as category 1 or category 2A. The preference categories and the categories of evidence/consensus are two separate systems.

Literature Search Criteria and Guidelines Update Methodology

Prior to 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 since the previous Guidelines update, using the following search terms: thymomas; thymic carcinomas. The PubMed



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database was chosen as it remains the most widely used resource for medical literature and indexes 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 II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking 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 at www.NCCN.org.

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).^{5,14–17} Many mediastinal masses are benign, especially those occurring in patients who are asymptomatic; however, patients who are symptomatic 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* in the algorithm). 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.^{2,18,19} Most masses in the mediastinum are metastases from a primary lung

cancer (eg, non-small cell lung cancer). However, approximately 50% of primary cancers in the anterior mediastinum are thymomas.²⁰

Patients with thymomas often have an indolent presentation, whereas those with lymphoma or germ cell tumors have a rapid onset of symptoms.¹⁹ 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 Hodgkin Lymphoma and the NCCN Guidelines for B-Cell Lymphomas, available at www.NCCN.org).^{17,21} Thymic carcinoids are rare neuroendocrine tumors that can be associated with multiple endocrine neoplasia type 1 (MEN1) syndrome (see the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org).^{22,23} Extragonadal germ cell tumors are rare tumors that may also occur in the mediastinum.^{24,25}

Low-dose CT is recommended for detecting lung cancer in individuals at high risk (see the NCCN Guidelines for Lung Cancer Screening, available at www.NCCN.org).²⁶ There are no data to suggest that screening with low-dose CT improves survival for patients with thymomas and thymic carcinomas; therefore, low-dose CT screening is not recommended for detecting thymomas and thymic carcinomas.²⁶ However, mediastinal masses (eg, lung metastases, thymomas, thymic carcinomas) may be detected in individuals undergoing chest imaging.

Recommended tests for assessing mediastinal masses include chest CT with contrast and blood chemistry studies (see *Initial Evaluation* in the algorithm).^{15,27–35} On CT, a thymoma is usually a well-defined round or oval mass in the thymus without lymph node enlargement.^{33,36,37} When assessing a mediastinal mass, detection of thymic malignancy versus thymic cyst or thymic hyperplasia can be better discriminated with chest MRI compared to chest CT, potentially avoiding an unnecessary



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thymectomy.³⁸ In patients who cannot tolerate iodinated contrast, chest MRI is indicated.³³ Combined FDG PET/CT may be useful for determining whether extrathoracic metastases are present.^{39,40} FDG PET/CT provides better correlation with anatomic structures than PET alone. FDG PET/CT scans are whole body or skull base to mid-thigh, as clinically indicated. 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 algorithm). 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.²

Thymic Masses

Diagnosis

The World Health Organization (WHO) histologic classification system can be used to distinguish between thymomas, thymic carcinomas, and thymic carcinoids (see the algorithm).^{1,2} 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.⁴¹ The WHO histologic classification system was revised in 2021.^{1,2} Thymic carcinomas are categorized by larger subtype groups such as squamous carcinomas, adenocarcinomas, adenosquamous carcinoma, and carcinomas not otherwise specified (NOS).^{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 Treatment and Management* in the algorithm).^{12,42-46} For stage III–IV thymomas, 5-year survival rates have been reported to be 90% in patients with total resection.^{8,12} For thymic carcinomas, 5-year survival rates are lower, even in those with total resection.^{11,47}

Staging

Although several staging systems exist, the Masaoka-Koga staging system has been the most widely accepted system for management and determination of prognosis for both thymomas and thymic carcinomas (see Table 1 in the algorithm).^{10,12,48-54} Another staging system for thymomas and thymic carcinomas is based on a combined effort by the International Thymic Malignancy Interest Group (ITMIG) and International Association for the Study of Lung Cancer (IASLC); this staging system was used as the basis for the AJCC TNM system for thymic malignancies (8th edition).⁵⁵⁻⁶² The AJCC staging system for thymic malignancies (8th edition) is also provided in the algorithm (see Table 2 in the algorithm).⁵⁶ Patients with stage I–III thymomas have a 5-year survival rate of approximately 85% versus 65% for those with stage IV disease.^{10,63,64} In approximately 50% of patients, mortality is not related to thymoma.⁴⁹ Mortality is related to myasthenia gravis in approximately 20% of patients.

Treatment

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.^{65,66} 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 recommended whenever possible for most resectable tumors (see *Principles of Surgical Resection* in the algorithm).^{10,12,19,67-69} 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.⁷⁰⁻⁷² Core needle biopsy is recommended for locally advanced, unresectable thymic masses. Open biopsy may be considered if core biopsy is not feasible nor diagnostic and transpleural approach should be



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Thymomas and Thymic Carcinomas

avoided. The cancer protocol for thymic tumors from the College of American Pathologists may be useful for assessing specimens.⁷³

Minimally invasive procedures are not routinely recommended, because only a few long-term studies are available regarding recurrence and survival.⁷⁴⁻⁷⁶ However, minimally invasive procedures may be considered if recommended oncologic goals can be met (as previously described) and if performed in specialized centers with surgeons with expertise in these techniques.⁷⁶⁻⁸⁰ A systematic review of 1061 patients with thymomas reported that 5-year overall survival after 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.⁷⁴ A retrospective review in 2835 patients assessed VATS thymectomy compared with sternotomy in patients with thymomas.⁸¹ The 5-year overall survival rate was 97.9% in the VATS group. The overall survival rates were not significantly different when comparing the VATS group versus the sternotomy group ($P = .74$). A meta-analysis also showed that VATS was safe and patients had similar overall survival when compared with those receiving open thymectomy.⁸²

Thymomas

Thymomas typically occur in adults aged 40 to 70 years; they are rare in children and adolescents.^{19,83} 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.^{3,84} Although some patients are asymptomatic, others present with chest pain, cough, or dyspnea. Patients with thymomas often have autoimmune diseases. Approximately 30% to 50% of patients with thymomas have myasthenia gravis.⁸⁵ 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.⁸⁶⁻⁸⁹

Although thymomas can be locally invasive (eg, pleura, lung), they uncommonly spread to regional lymph nodes or extrathoracic sites.^{10,63,90,91} Surgery (ie, total thymectomy and complete excision of tumor) is recommended for all resectable thymomas for patients who can tolerate the surgery.^{20,92,93} For resected stage I and II thymomas, the 10-year survival rate is excellent (approximately 90% and 70%, respectively).^{19,94} Completeness of resection is the most important predictor of outcome.⁸ 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) because of the potential of tumor seeding when the tumor capsule is violated.¹⁹ A transpleural approach should be avoided during biopsy of a possible thymoma for similar reasons.^{87,95} Small biopsy sampling (fine-needle or core needle biopsy) does not always indicate whether invasion is present.⁹⁶ ITMIG and the College of American Pathologists have established procedures for reporting the surgical and pathologic findings from resection specimens.^{73,97}

Adjuvant therapy is not recommended for completely resected (R0) stage I thymomas.^{68,98,99} For incompletely resected thymomas, postoperative radiation therapy (RT) is recommended (see *Postoperative Treatment and Management* in the algorithm).^{65,68,100-102} Note that extensive elective nodal radiation is not recommended, because thymomas do not typically metastasize to regional lymph nodes.^{10,103}

Use of intensity-modulated RT (IMRT) may decrease the dose to the normal tissues.^{104,105} If IMRT is used, guidelines from the NCI Advanced



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Technology Center (ATC) and American Society for Radiation Oncology/American College of Radiology (ASTRO/ACR) should be followed.¹⁰⁶⁻¹¹⁰ The ICRU-83 (International Commission on Radiation Units and Measurements Report 83) recommendations are also a useful resource.^{109,111} Although the normal tissue constraints recommendations for non-small cell lung cancer may be used (see the *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org), more conservative limits are recommended to minimize the dose volumes to all the normal structures.¹¹²⁻¹¹⁴ Because these patients are younger and usually long-term survivors, the mean dose to the heart should be as low as reasonably achievable to potentially maximize survival.

A minimum technological standard for RT is CT-planned 3-D conformal radiation therapy (3D-CRT). More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/volumetric modulated arc therapy (VMAT), IGRT, motion management, and proton therapy. In particular, IMRT is preferred over 3D-CRT. Compared to IMRT, proton therapy has been shown to improve the dosimetry allowing better sparing of the normal tissues with favorable local control and toxicity, and is appropriate.¹¹⁵⁻¹¹⁷

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 algorithm).^{104,105,118} However, a total dose of 60 to 70 Gy (1.8–2 Gy/fraction per day) is recommended for patients with gross residual disease after surgery.^{119,120} In patients with thymomas who have capsular invasion after an R0 resection, postoperative RT can be considered (see *Postoperative Treatment and*

Management in the algorithm).^{99,104,121-123} Patients with stage III (with macroscopic invasion into neighboring organs) thymoma have higher risks of recurrent disease and, as such, postoperative radiation is recommended.¹²⁴⁻¹²⁷ Data suggest that patients with stage II thymoma may not benefit from postoperative radiation.^{68,98,99,122,128} Postoperative chemotherapy is also not beneficial in this setting.^{129,130}

Induction therapy followed by surgery may be useful for potentially resectable thymic malignancies.^{47,131-136} A recent cohort study reported that 5-year overall survival was similar for those receiving induction chemotherapy followed by surgery versus surgery alone (77.4% vs. 76.7%; $P = .596$).¹³¹ 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 *Postoperative Treatment and Management in the algorithm*).^{136,137} For those with solitary metastasis or ipsilateral pleural metastases, options include: 1) induction chemotherapy followed by surgery for resectable patients, or 2) surgery alone.^{131,132} After induction chemotherapy, imaging is recommended (eg, chest CT, MRI, PET/CT) as clinically indicated to determine whether resection is feasible. For patients with unresectable disease in both of these settings, RT with [or without] chemotherapy is recommended. It is difficult to specify RT dosing regimens for metastatic disease given the broad range of metastatic scenarios that are possible. Stereotactic body radiation therapy (SBRT) may be appropriate for limited focal metastases, whereas conventional fractionation is appropriate for larger metastases. In the palliative setting, typical palliative doses may be used—8 Gy in a single fraction, 20 Gy in 5 fractions, or 30 Gy in 10 fractions—depending on the treatment objectives. However, RT dosing can extend up to definitive doses for more durable local control. Highly conformal techniques may be appropriate for limited volume metastases, given the relatively long natural history of even metastatic thymoma.⁶⁵ For metastatic disease, systemic



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therapy is recommended (see *Principles of Systemic Therapy for Thymic Malignancies* in the algorithm).^{7,99,136,138-150}

Six first-line chemotherapy regimens are recommended in the NCCN Guidelines. The NCCN Panel has preference stratified the first-line regimens for patients with thymomas. The NCCN Panel voted that the preferred regimen for thymoma is cisplatin/doxorubicin/cyclophosphamide (CAP), because it seems to yield the best outcomes.^{68,151-153} Response rates are approximately 44% with CAP for thymomas.⁷ However, non-anthracycline regimens (eg, cisplatin/etoposide [with or without ifosfamide], carboplatin/paclitaxel) may be useful for patients who cannot tolerate the preferred regimen.^{153,154} The NCCN Panel voted that the following are “other recommended” regimens for patients with thymomas: CAP with prednisone, doxorubicin/cisplatin/vincristine/cyclophosphamide (ADOC), cisplatin/etoposide (PE), etoposide/ifosfamide/cisplatin, and carboplatin/paclitaxel.^{136,142,143,145,146,154} If patients cannot tolerate first-line combination regimens, consider second-line systemic therapy options.

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.³³ MRI may be used for surveillance for certain clinical situations, including: 1) if patients cannot tolerate contrast; and 2) to decrease radiation if patients are young and will be screened for many years. 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.^{3,155,156} Surgery is an option for patients with locally advanced recurrent disease, solitary metastases, or ipsilateral metastases.¹⁵⁷

Second-line systemic therapy for thymomas includes pemetrexed, everolimus, paclitaxel, octreotide (LAR) with or without prednisone, gemcitabine with or without capecitabine, 5-fluorouracil (5-FU), etoposide, and ifosfamide.^{139,140,153,158-167} However, none of these agents has been assessed in randomized phase 3 trials, because the rarity of this disease makes such trials challenging to complete. For thymomas, response rates for subsequent systemic therapy (ie, second-line and beyond) range from 15% to 39%.⁷ Panel members feel that pemetrexed and paclitaxel are more efficacious as second-line therapy for thymomas than the other recommended agents (see the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with NCCN Evidence Blocks™ for Thymomas and Thymic Carcinomas, available at www.NCCN.org).⁷ A study of pemetrexed in patients with thymoma (n = 16) reported two complete responses and five partial responses.¹⁶⁸

Capecitabine may be added to gemcitabine based on clinical trial data.^{159,166} In 22 patients with thymomas receiving gemcitabine/capecitabine, there were three complete responses and five partial responses. Octreotide may be useful in patients with thymoma who have a positive octreotide scan or symptoms of carcinoid syndrome. Pembrolizumab is not recommended in patients with thymomas because of concerns about immune-related adverse events.^{169,170} Of patients with thymoma receiving pembrolizumab, 71% (5/7) had grade 3 or higher immune-related adverse events including myocarditis.¹⁷¹ Sunitinib is not recommended in patients with thymomas, because they do not have c-Kit mutations.¹⁷² In a phase 2 study assessing everolimus, median overall survival was more than 25 months in patients with thymomas (n = 32), but there was a high risk of fatal pneumonitis.¹⁶¹ The NCCN Panel has preference stratified the second-line regimens for patients with thymomas. The panel voted that the following are “other recommended” regimens including etoposide, everolimus, 5-FU, gemcitabine with or without



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capecitabine, ifosfamide, octreotide (including LAR) with or without prednisone, paclitaxel, and pemetrexed.

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.^{5,9,12,13,17,45,46,173-175} Survival rates for thymic carcinomas vary depending on stage (stages 1–2: 91%; stages 3–4: 31%) and resectability (including completeness of resection).¹¹ These tumors can be distinguished from thymomas because of their malignant histologic features and their different immunohistochemical and genetic features.^{1,2,16,176} 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.^{172,177} Thymic carcinomas often cause pericardial and pleural effusions. The Masaoka-Koga staging system and the AJCC TNM staging system can also be used to stage thymic carcinomas (see Tables 1 and 2 in the algorithm).^{48,178,179}

It is important to note that thymic carcinomas are associated with a different clinical course from thymomas.^{138,176,180} Unlike thymomas, paraneoplastic syndromes, including myasthenia gravis, are very rare in patients with thymic carcinoma.¹¹⁸ If myasthenia gravis is diagnosed, then the diagnosis of thymic carcinoma should be reassessed; the patient may actually have thymoma.¹¹ 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 white individuals.¹¹

Similar to thymomas, patients with completely resected thymic carcinomas have longer survival than those whose tumors are either incompletely

resected or are unresectable.^{45,47,181} Patients who have an R0 resection have a 5-year survival of approximately 60%.¹¹ 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.¹¹ After resection of thymic carcinomas, postoperative management includes RT with (or without) chemotherapy, depending on the completeness of resection (see *Postoperative Treatment and Management* in the algorithm).^{11,45,46,104,128,182,183} A study suggests that adjuvant therapy may not be necessary for early-stage thymic carcinomas.¹⁸⁴ For unresectable or metastatic thymic carcinomas, chemotherapy with (or without) RT is recommended (see *Principles of Systemic Therapy for Thymic Malignancies* and *Principles of Radiation Therapy* in the algorithm).¹⁵²

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 algorithm).^{104,105,118} However, a total dose of 60 to 70 Gy (1.8–2 Gy/fraction per day) is recommended for patients with gross residual disease after surgery.^{119,120} In patients with thymic carcinomas who have capsular invasion after an R0 resection, postoperative RT can be considered (see *Postoperative Treatment and Management* in the algorithm).^{99,104,121-123} Adjuvant therapy is not recommended for completely resected (R0) stage I thymic carcinomas.^{68,98,99}

Six first-line chemotherapy regimens are recommended in the NCCN Guidelines. Unfortunately, thymic carcinomas respond poorly to chemotherapy. The NCCN Panel has preference stratified the first-line regimens for patients with thymic carcinomas. The NCCN Panel voted that carboplatin/paclitaxel is preferred for first-line therapy, because it



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has the highest response rate in patients with thymic carcinomas in clinical trials (overall response rate, 22%–36%).^{149,154,185-194} Data suggest that the CAP and ADOC regimens are also effective for thymic carcinomas, but these regimens are more toxic than carboplatin/paclitaxel.^{7,192} The NCCN Panel voted that the following are “other recommended” regimens for patients with thymic carcinomas: CAP with or without prednisone, ADOC, PE, and

etoposide/ifosfamide/cisplatin.^{136,142,143,145,146} 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 *Postoperative Treatment and Management* in the algorithm).¹¹ 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. If patients cannot tolerate first-line combination regimens, consider second-line systemic therapy options. 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.³³ However, the duration, frequency, or type of imaging for surveillance for thymic carcinomas has not been established in published studies.

For thymic carcinomas, there are little data regarding second-line systemic therapy.¹³⁹ Second-line systemic therapy for thymic carcinomas includes sunitinib, pemetrexed, everolimus, paclitaxel, gemcitabine with or without capecitabine, 5-FU, etoposide, ifosfamide, lenvatinib, and pembrolizumab (see *Principles of Systemic Therapy for Thymic Malignancies* in the algorithm).^{7,139,140,158,168,195} For thymic carcinomas, response rates for subsequent systemic therapy range from 4% to 21%.⁷ Sunitinib is recommended for patients with thymic carcinoma regardless of *c-Kit* mutation status (these mutations occur in <10% of patients).^{84,140,162,196-202} Patients with thymomas do not have *c-Kit*

mutations.¹⁷² With lenvatinib, there is a high risk for side effects and frequent dose reductions may be needed.¹⁹⁵ For the 2022 update (Version 1), panel members removed octreotide (including LAR) with or without prednisone as a second-line therapy option for patients with thymic carcinoma. Octreotide and prednisone are not effective in thymic carcinoma as shown in multiple studies in which no responses were seen.^{165,203}

Pembrolizumab is active (response rate, 22.5%; 95% CI, 10.8%–38.5%) as second-line therapy in patients with thymic carcinomas but is associated with a high rate of severe immune-related adverse events (15%).^{204,205} For example, grade 3–4 myocarditis has been reported in 5% to 9% of patients with thymic carcinomas receiving pembrolizumab, which is a higher adverse rate than seen in patients with other malignancies who receive pembrolizumab.^{171,205} The NCCN Panel recommends pembrolizumab as second-line systemic therapy for patients with thymic carcinomas based on the clinical data. Capecitabine may be added to gemcitabine based on clinical trial data.^{159,166} There were three partial responses in eight patients with thymic carcinomas receiving gemcitabine/capecitabine. In a phase 2 study assessing everolimus, median overall survival was approximately 14 months in patients with thymic carcinomas (n = 19); one patient had a complete response.¹⁶¹ However, there was a high risk of fatal pneumonitis.¹⁶¹ The NCCN Panel has preference stratified the second-line regimens for patients with thymic carcinoma. The panel voted that the following agents are other recommended including everolimus, 5-FU, gemcitabine with or without capecitabine, lenvatinib, paclitaxel, pembrolizumab, pemetrexed, and sunitinib. Etoposide and ifosfamide are useful in certain circumstances.

Summary

These NCCN Guidelines focus on thymomas and thymic carcinomas and outline the evaluation, treatment, and management of these mediastinal



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tumors. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2022, which are described in greater detail in this revised Discussion text; references have been added. For the 2022 update (Version 1), panel members removed octreotide (including LAR) with or without prednisone as a second-line therapy option for patients with thymic carcinoma. Octreotide and prednisone are not effective in patients with thymic carcinoma as shown in multiple studies in which no responses were seen.^{165,203}



Discussion
update in
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Discussion
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