台北榮總胸腺癌診療共識

V.1.0 2025

台北榮總肺癌團隊

Revised on 2025/2/24

TNM classification

AJCC 9th edition

T (Tumor) Categories

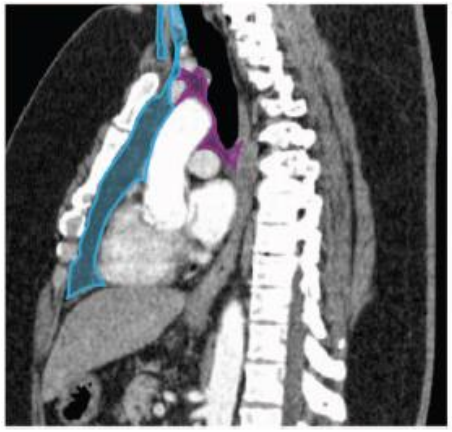
- **T1:** Tumor is limited to the thymus or mediastinum only
  - **T1a:** Tumor ≤5 cm in greatest dimension
  - **T1b:** Tumor >5 cm in greatest dimension
- **T2:** Tumor directly invades the pericardium (partial or full thickness), lung, or phrenic nerve
- **T3:** Tumor directly invades one or more of the following:
  - Brachiocephalic vein
  - Superior vena cava
  - Chest wall
  - Extrapericardial pulmonary arteries or veins
- **T4:** Tumor directly invades one or more of the following:
  - Aorta (ascending, arch, or descending)
  - Arch vessels
  - Intrapericardial pulmonary arteries or veins
  - Myocardium
  - Trachea
  - Esophagus

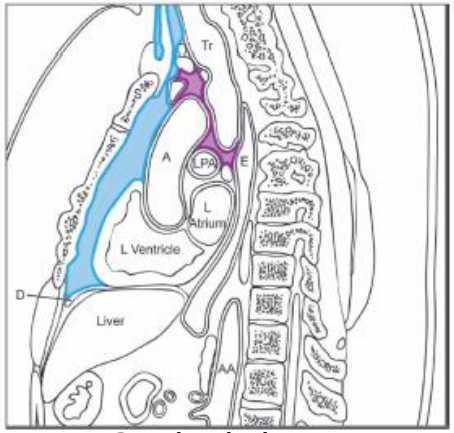
TNM classification

AJCC 9th edition

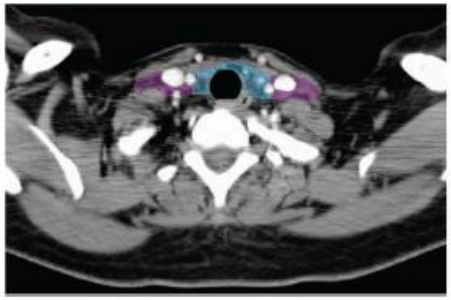
N (Lymph Node) Categories
• **N0**: No regional lymph node metastasis • **N1**: Metastasis in anterior (perithymic) lymph nodes • **N2**: Metastasis in deep intrathoracic or cervical lymph nodes (e.g., paratracheal, subcarinal, aortopulmonary window, hilar, jugular, or supraclavicular nodes)
Definition of distant metastasis (M)
• **M0:** No distant metastasis • **M1a:** Presence of separate pleural or pericardial nodule(s) (droplet metastases) • **M1b:** Presence of pulmonary intraparenchymal nodules or distant organ metastasis

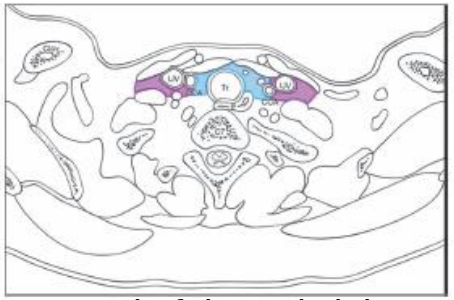
ITMIG/IASLC node compartments for thymic malignancies. Graphic depiction of N1 (anterior region, blue) and N2 (deep region, purple) node compartments



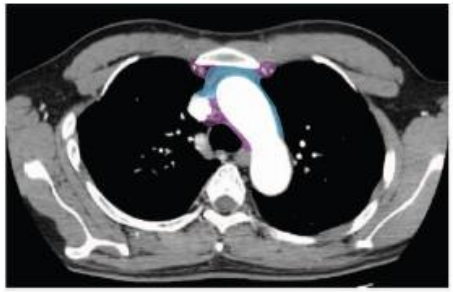


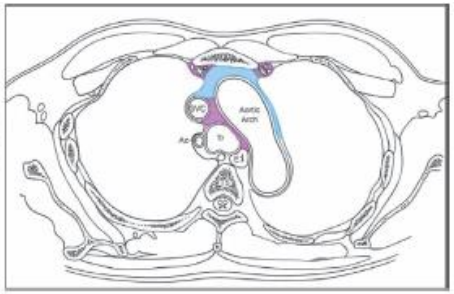
Sagittal view

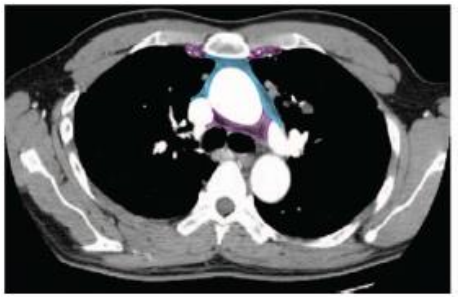


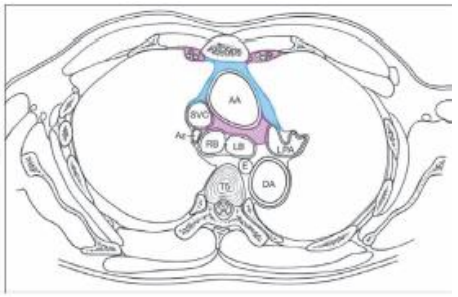


Level of thoracic inlet

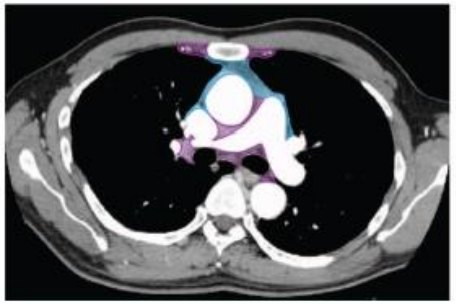


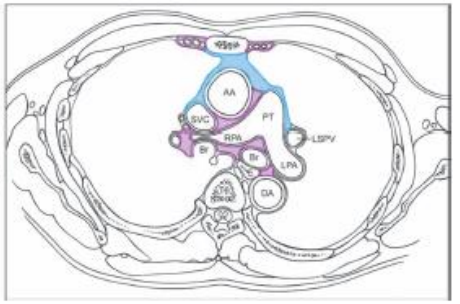


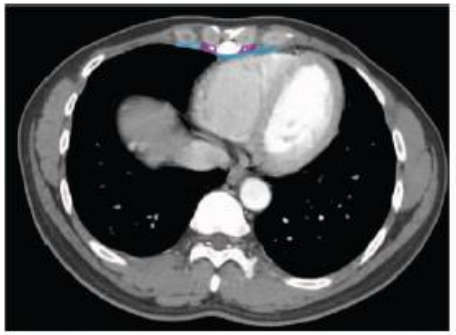


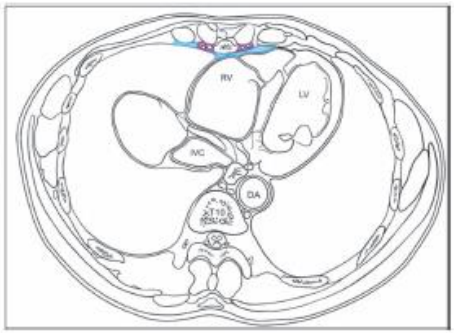


Level of aortopulmonary window









J Thorac Oncol. 2014 Sep;9(9 Suppl 2):S81-7

Table 35.1 Lymph node regions for thymic malignancies

	Region Boundaries	Node Groups*
N1: Anterior Region	*Superior:* hyoid bone *Lateral (neck):* medial border of carotid sheaths *Lateral (chest):* mediastinal pleura *Anterior:* Sternum *Posterior (medially):* great vessels, pericardium *Posterior (laterally):* phrenic nerve *Inferior:* Xiphoid, diaphragm	Low anterior cervical: pretracheal, paratracheal, peri-thyroid, precricoid/delphian Peri-Thymic Prevascular Para-aortic, Ascending Aorta, Superior Phrenics Supradiaphragmatic / Inferior Phrenics / Pericardial
N2: Deep Region	*Superior:* Level of lower border of cricoid cartilage *Anteromedial (neck):* lateral border of sternohyoid, medial border of carotid sheath *Posterolateral (neck):* anterior border of trapezius *Anterior (chest): Right* – Anterior Border of SVC; *Left* – aortic arch, aortopulmonary window *Posterior (Chest):* Esophagus *Lateral (chest):* pulmonary hila *Inferior:* Diaphragm	Lower Jugular Supraclavicular/venous angle: confluence of internal jugular & subclavian vein Internal Mammary nodes Upper Paratracheal Lower Paratracheal Subaortic / Aortopulmonary Window Subcarinal Hilar

*Region and node group boundaries match those established by the American Academy of Otolaryngology - Head and Neck Surgery, American Society for Head and Neck Surgery, and the International Association for the Study of Lung Cancer where applicable.
SVC, superior vena cava

TNM classification

AJCC 9th edition

- **Stage grouping**

Stage	T	N	M
I	**T1**	N0	M0
II	**T2**	N0	M0
IIIa	**T3**	N0	M0
IIIb	**T4**	N0	M0
IVa	T any	**N1**	M0
	T any	N0, 1	**M1a**
IVb	T any	**N2**	M0, 1a
	T any	N any	**M1b**

Modified Masaoka Staging

Staging

Table 1. Modified Masaoka clinical staging of thymoma[1-3]

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

[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] Detterbeck 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.

WHO Histologic Classification

WORLD HEALTH ORGANIZATION HISTOLOGIC CLASSIFICATION[1]

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.

• Footnote d modified: ~~Microscopic thymoma; sclerosing thymoma,~~ Lipofibroadenoma.

[1] Marx A, Detterback 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).

WHO Histologic Classification

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**

Thymic Carcinoma Subtypes

- **Squamous carcinomas**
  - Squamous cell carcinoma, NOS
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  - Lymphoepithelial carcinoma
- **Adenocarcinomas**
  - Adenocarcinoma, NOS
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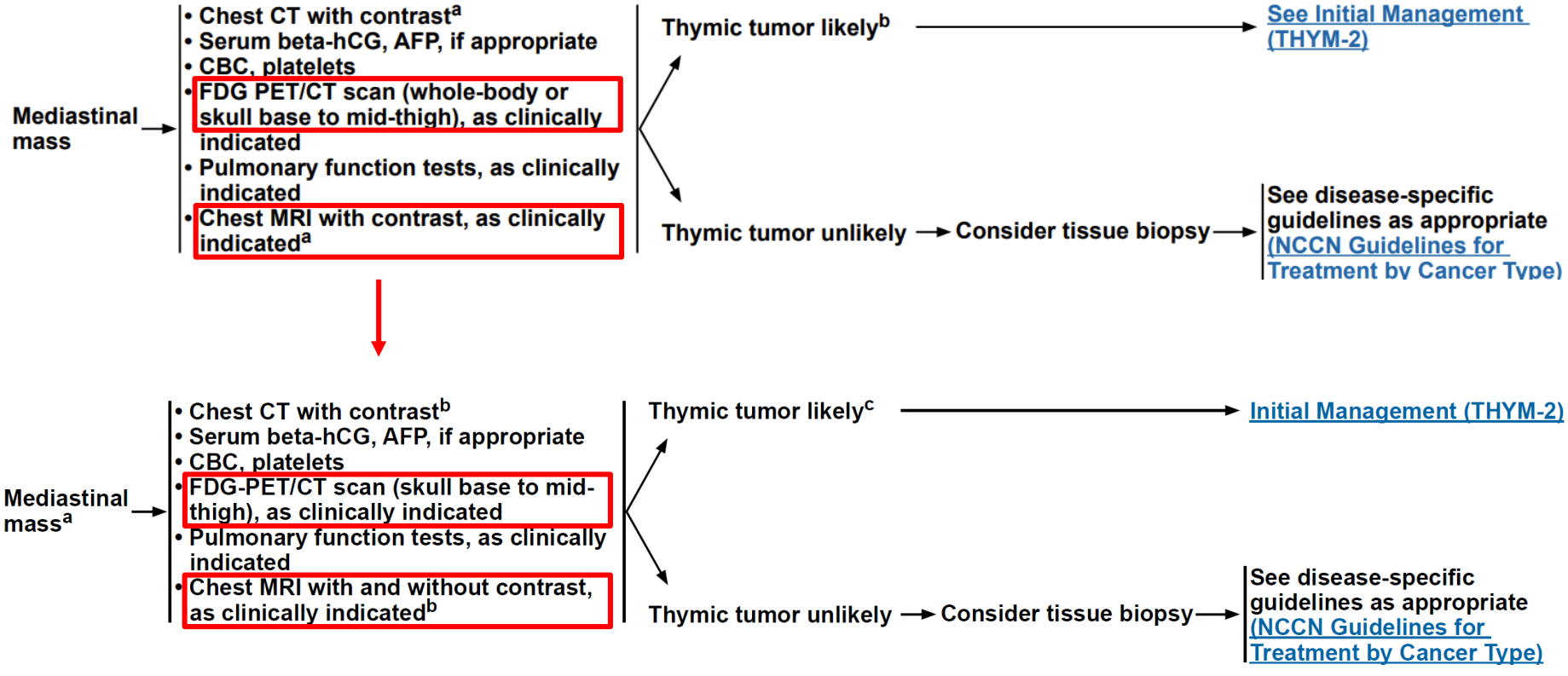
- **Adenosquamous carcinoma**
- **NUT carcinomas**
- **Salivary gland-like carcinomas**
  - Mucoepidermoid carcinoma
  - Clear cell carcinoma
  - Sarcomatoid carcinoma
  - Carcinosarcoma
- **Carcinoma, undifferentiated, NOS**
- **Thymic Carcinoma, NOS**
- **Neuroendocrine tumors**
  - Carcinoid tumor, 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

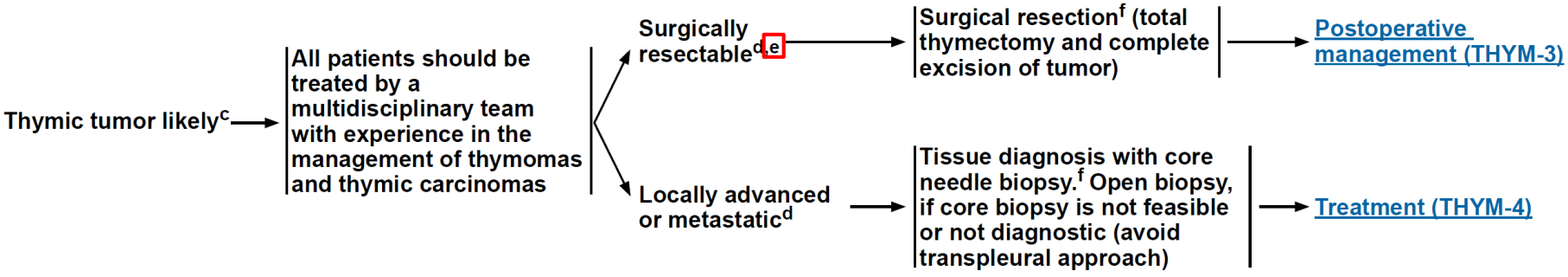
[1] Marx A, Detterback F, Marom EM, et al. Tumours of the thymus. In: WHO Classification of Tumours Editorial Board. Thoracic tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2021 [2021 9 12]. (WHO classification of tumours series, 5th ed.; vol. 5).

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.

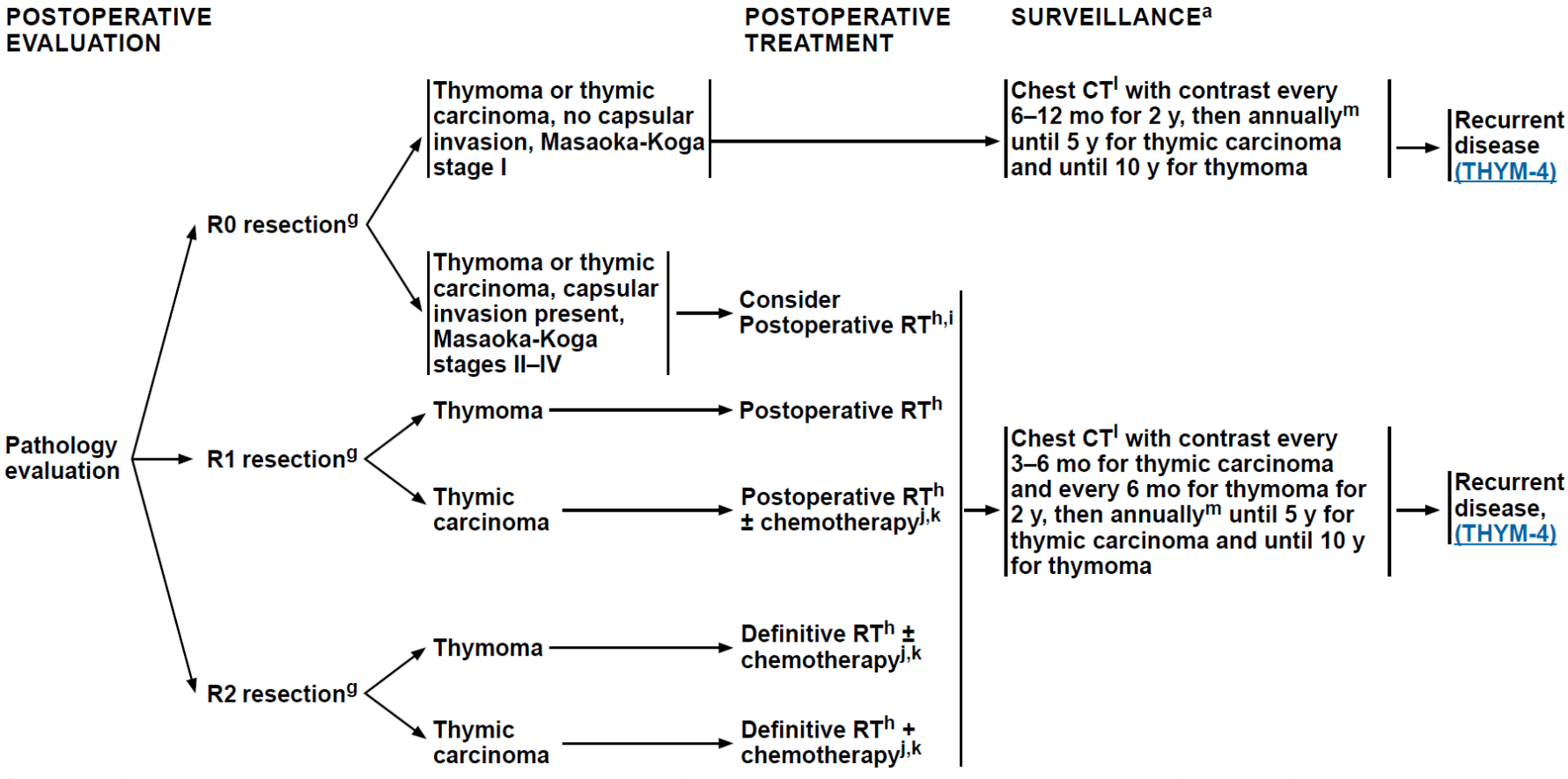
Initial management



[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 with medical oncology as needed. Resectability is defined as complete (R0) resection.

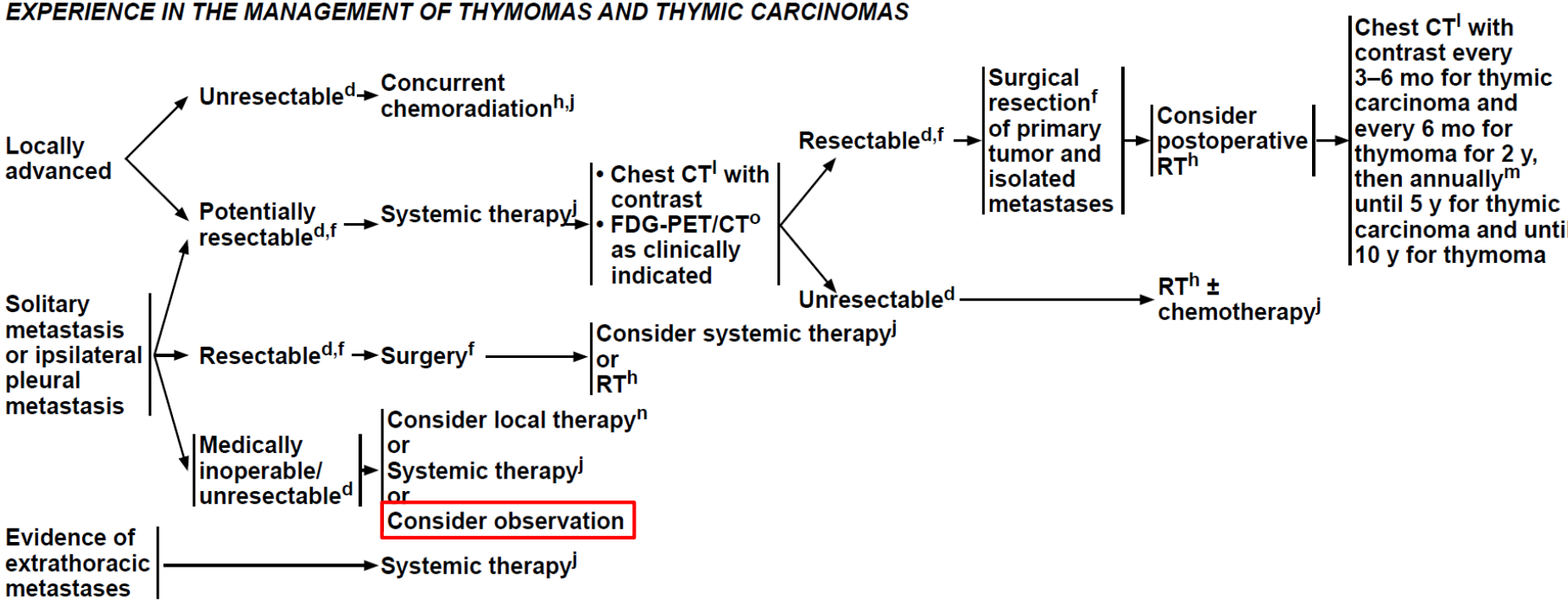
[e] If R0 resection considered uncertain, preoperative systemic therapy should be considered. See Principles of Systemic Therapy (THYM-C).



[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.

RECURRENT, ADVANCED, OR METASTATIC DISEASE | **TREATMENT** | **SURVEILLANCE[a]**

ALL PATIENTS SHOULD BE TREATED BY A MULTIDISCIPLINARY TEAM WITH EXPERIENCE IN THE MANAGEMENT OF THYMOMAS 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 with medical oncology 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.

Principles of surgical resection (I)

- 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 ≥ 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 thymomas 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.
- Goal of surgery is complete excision of the lesion with total thymectomy and complete resection of contiguous and noncontiguous disease

Principles of surgical resection (II)

- 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 radiation therapy 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.

Rationale of Radiotherapy for Invasive thymoma and thymic carcinoma

- Thymoma is the most common tumor of the anterior mediastinum, accounting for approximate 20% of all mediastinal tumors in adults.
- Complete surgical resection is the treatment of choice for all thymomas regardless of invasiveness.
- Radiotherapy is excellent adjuvant therapy for invasive thymomas, which are generally radio-responsive.
- RT should be given for unresectable or incomplete resection patients with invasive thymoma or thymic carcinoma.

Rationale of Radiotherapy for Invasive thymoma and thymic carcinoma

General Principles

- Recommendations regarding RT should be made by a board-certified radiation oncologist.
- RT should be given for patients with unresectable (if disease progresses on induction chemotherapy) or incompletely resected invasive thymoma or thymic carcinoma.
- Radiation oncologists need to communicate with the surgeon to review the operative findings and to help determine the target volume at risk. They also need to communicate with the pathologist regarding the detailed pathology on histology, disease extent such as extracapsular extension, and surgical margins.
- Acronyms and abbreviations for RT are the same as listed in 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 60-70 Gy should be given to patients with unresectable disease.
- For adjuvant treatment, the radiation dose consists of 45-50 Gy for clear/close margins and 54 Gy for microscopically positive resection margins. A total dose of 60 Gy and above should be given to patients with gross residual disease (similar to patients with unresectable disease),[3,4] when conventional fractionation (1.8 to 2.0 Gy per daily fraction) is applied.

For unresectable disease: 60-70 Gy (with daily fraction between 1.8 to 2 Gy)

For post-operative status: 45-50 Gy for radical surgery

54 Gy for close margin and 60 Gy for gross residual lesions.

Radiation dose less than 40 Gy possess higher relapse incidence.

For large, invasive thymoma, neoadjuvant RT has been advocated.

Rationale of Radiotherapy for Invasive thymoma and thymic carcinoma

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.

GTV: gross visible tumor volume

CTV: encompassing the entire thymus, surgical clips and potential site with residual disease.

PTV: including target motion and setup error.

Post-operative radiotherapy will be arranged within 4-6 weeks after surgical intervention.

Rationale of Radiotherapy for Invasive thymoma and thymic carcinoma

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 dose to the total heart should be limited to ≤30 Gy.

Radiotherapy technique: including IMRT, VMAT and Tomotherapy

Carbon ion radiotherapy(CIRT) may be considered after case-specific discussion at MDT and CIRT tumor board.

Modern RT techniques can help to reduce the dose of normal tissues, including heart and lung.

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.

Masaoka stage II and III thymoma

- Post-OP RT for Masaoka stage II and III thymoma remains controversial and should be discussed in MDT.

Chemotherapy/others

PRINCIPLES OF SYSTEMIC THERAPY

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS[a]

THYMOMA

Preferred (Other Recommended for Thymic Carcinoma)

- **CAP**[1]
  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**[6,7][b]
  Carboplatin AUC 6
  Paclitaxel 200 mg/m²
  Administered every 3 weeks

Other Recommended for Thymic Carcinoma and Thymoma

- **CAP with prednisone**[2]
  Cyclophosphamide 500 mg/m² IV on day 1;
  Doxorubicin, 20 mg/m²/day IV continuous infusion on days 1–3;
  Cisplatin 30 mg/m² days 1–3;
  Prednisone 100 mg/day days 1–5;
  Administered every 3 weeks

- **ADOC**[3]
  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**[4,b]
  Cisplatin 60 mg/m² IV day 1; Etoposide 120 mg/m²/day IV days 1–3;
  Administered every 3 weeks

- **Etoposide/ifosfamide/cisplatin**[5]
  Etoposide 75 mg/m² on days 1–4; Ifosfamide 1.2 g/m² on days 1–4;
  Cisplatin 20 mg/m² on days 1–4
  Administered every 3 weeks

[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.

Chemotherapy/others

PRINCIPLES OF SYSTEMIC THERAPY

SECOND-LINE SYSTEMIC THERAPY

THYMOMA
Other Recommended
- Etoposide[4,8,9]
- Everolimus[10]
- 5-FU and leucovorin[11]
- Gemcitabine ± capecitabine[12,13]
- Ifosfamide[14]
- Octreotide[b] (including LAR) +/- prednisone[15,16]
- Paclitaxel[17]
- Pemetrexed[18]

THYMIC CARCINOMA
Other Recommended
- Everolimus[10]
- 5-FU and leucovorin[11]
- Gemcitabine ± capecitabine[12,13]
- Lenvatinib[c,19]
- Paclitaxel[17]
- Pembrolizumab[d,20,21]
- Pemetrexed[18]
- Sunitinib[22]

Useful in Certain Circumstances
- Etoposide[4,8,9]
- Ifosfamide[14]

THYMOMA
Other Recommended
- Etoposide[4,8]
- Everolimus[9]
- 5-FU and leucovorin[10]
- Gemcitabine ± capecitabine[11,12]
- Ifosfamide[13]
- Octreotide[c] (including LAR) (if octreotide scan or dotatate PET/CT positive) +/- prednisone[14,15]
- Paclitaxel[16]
- Pemetrexed[17]

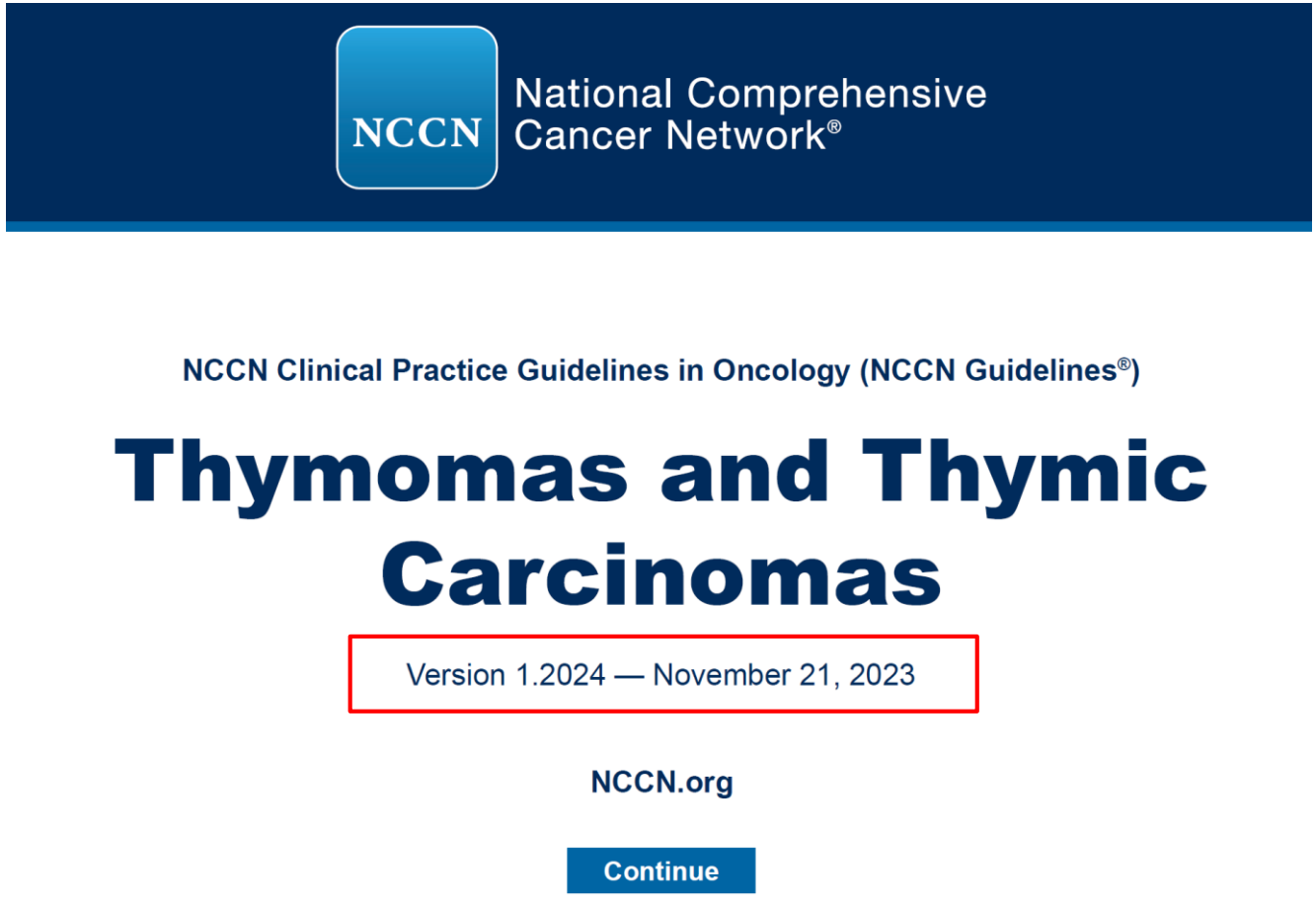
THYMIC CARCINOMA
Preferred
- Pembrolizumab[d,18,19]
- Sunitinib[20]
- Lenvatinib[e,21]
- Gemcitabine ± capecitabine[11,12]

Other Recommended
- Everolimus[9]
- 5-FU and leucovorin[10]
- Paclitaxel[16]
- Pemetrexed[17]

Useful in Certain Circumstances
- Etoposide[4,8]
- Ifosfamide[13]

[c] Nuclear medicine scan (octreotide scan or dotatate PET/CT [dotatate PET/CT preferred if available]) to assess for octreotide-avid disease.
[d] 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.
[e] There is a high risk for side effects and frequent dose reductions may be needed.

台北榮總胸腺癌診療共識
主要依據- NCCN v1. 2024



其他參考文獻:
Yen-Han Tseng,Yi-Hsuan Lin,Yen-Chiang Tseng,Yu-Chin Lee,Yu-Chung Wu,Wen-Hu Hsu,Sang-Hue Yen,Jacqueline Whang-Peng,Yuh-Min Chen, Adjuvant Therapy for Thymic Carcinoma--A Decade of Experience i a Taiwan National Teaching Hospital. PLoS One. 2016 Jan 12;11(1)

Pleural Mesothelioma
AJCC 9th T staging

Table 2. Distribution by Clinical T (cT) and Pathologic T (pT) Descriptors for the Proposed Ninth Edition T Category for Pleural Mesothelioma

Primary Tumor (T)

Category	Clinical T (cT)	Pathologic T (pT)
Tx	Tumor cannot be assessed	
T0	No tumor is present	
T1	Tumor limited to the ipsilateral pleura with **Psum**[a] **≤ 12 mm** with no involvement of the fissure (**Fmax**[b] **≤ 5 mm**)	Tumor limited to the ipsilateral pleura with no involvement of the fissure
T2	Tumor involving the ipsilateral pleura with **Psum**[a] **≤ 12 mm** and with any of the following: • involvement of the fissure (**Fmax**[b] **> 5 mm**) • mediastinal fat invasion • solitary area of chest wall soft tissue invasion; or Tumor involving the ipsilateral pleura with **Psum**[a] **> 12 mm but ≤30 mm**, with or without: • involvement of the fissure (**Fmax**[b] **> 5 mm**) • mediastinal fat invasion • solitary area of chest wall soft tissue invasion	Tumor involving the ipsilateral pleura and with any of the following: • involvement of the fissure • ipsilateral lung parenchyma invasion • diaphragm (nontransmural) invasion
T3	Tumor involving the ipsilateral pleura with **Psum**[a] **> 30 mm**; with or without: • involvement of the fissure (**Fmax**[b] **> 5 mm**) • mediastinal fat invasion • solitary area of chest wall soft tissue invasion	Tumor limited to the ipsilateral pleura (with or without fissure involvement) and with invasion of any of the following: • mediastinal fat • surface of pericardium • endothoracic fascia • solitary area of chest wall soft tissue
T4	Tumor with invasion of any of the following (any **Psum**[a]): • chest wall bony invasion (rib) • mediastinal organs (heart, spine, esophagus, trachea, great vessels) • diffuse chest wall invasion • direct tumor extension through the diaphragm or pericardium • direct extension to the contralateral pleura • presence of malignant pericardial effusion	Tumor with invasion of any of the following: • chest wall bony invasion (rib) • mediastinal organs (heart, spine, esophagus, trachea, great vessels) • diffuse chest wall invasion • transmural invasion of the diaphragm or pericardium • direct extension to the contralateral pleura • presence of malignant pericardial effusion

[a]Psum = pmax1 + pmax2 + pmax3 (sum of three measurements of maximal pleural thickness measured on axial images along the chest wall or mediastinum in each of the three divisions of the chest—upper, middle, and lower divided by two lines; one at the top of the aortic arch and the second drawn at the top the left atrium).

[b]Fmax = maximal thickness of pleural tumor along the fissures measured on sagittal images.

Pleural Mesothelioma
AJCC 9th T staging: Measurement of pleural thickness

- Division of Upper- Middle- Lower by aortic arch and top of Left atrium
- Psum = Pmax1+Pmax2+Pmax3
- Fmax = maximal fissure thickness

- T1: Psum ≤ 12mm + Fmax ≤ 5mm
- T2: Psum ≤ 30mm + Fmax >5mm
- T3: Psum ≥ 30mm
- T4: chest wall, mediastinal organ, diaphragm, pericardium/pericardial effusion, contralateral pleura

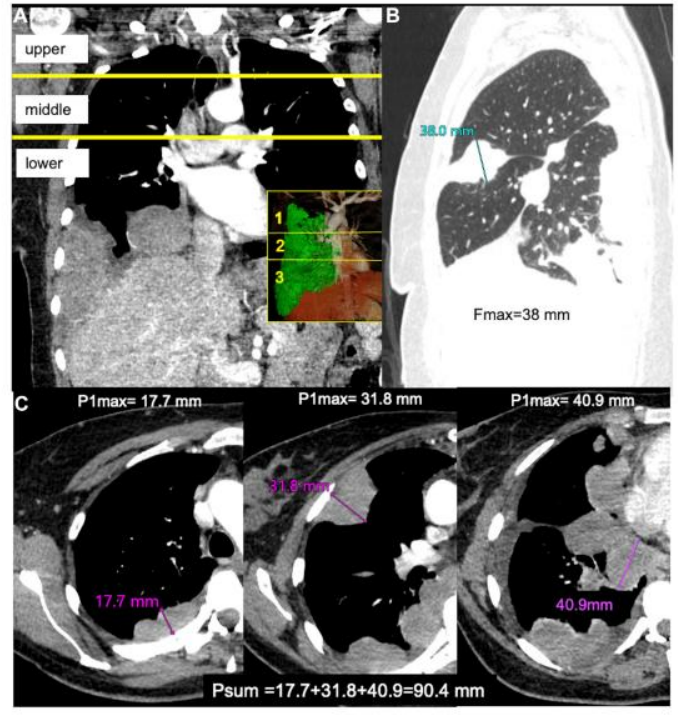


Figure 2. (*A*) Coronal and sagittal images of patients with pleural mesothelioma illustrating division of the chest into approximate thirds by a line drawn at the level of the aortic arch and a second line at the top of the left atrium, dividing the chest into three relatively equal parts of upper, middle, and lower levels. The maximum pleural thickness on each of these levels (pmax1, pmax2, and pmax3) is measured and combined to derive a sum of maximum pleural thickness (Psum = pmax1 + pmax2 + pmax3). (*B*) Sagittal image revealing fissure involvement by tumor; maximal fissure thickness Fmax = 38 mm. (*C*) Axial images with maximal pleural thickness measurement at each of the three levels; p1max = 17.7 mm; p2max = 31.8 mm and p3max = 40.9 mm, and Psum = 17.7 + 31.8 + 40.9 = 90.4 mm.

Pleural Mesothelioma
AJCC 9th N staging and M staging

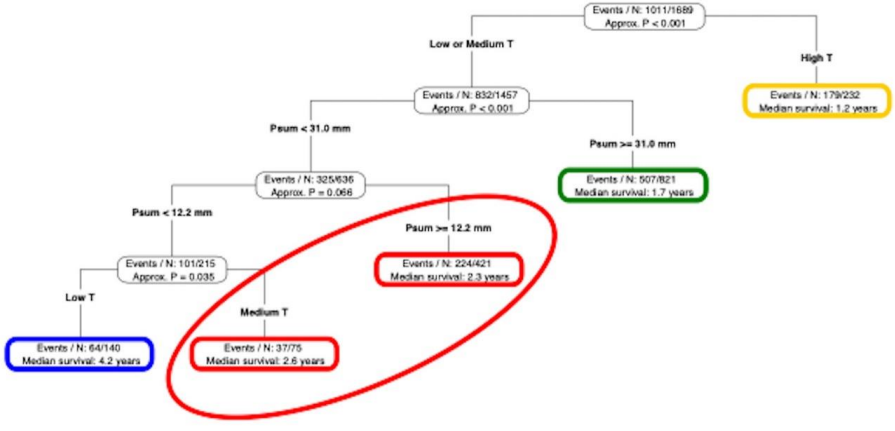
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases to ipsilateral intrathoracic lymph nodes (includes ipsilateral bronchopulmonary, hilar, subcarinal, paratracheal, aortopulmonary, paraoesophageal, peridiaphragmatic, pericardial, intercostal and internal mammary nodes)
N2	Metastases to contralateral intrathoracic lymph nodes. Metastases to ipsilateral or contralateral supraclavicular lymph nodes

M0	No distant metastases
M1	Distant metastases present

International Association for the Study of Lung Cancer (IASLC) Staging Project

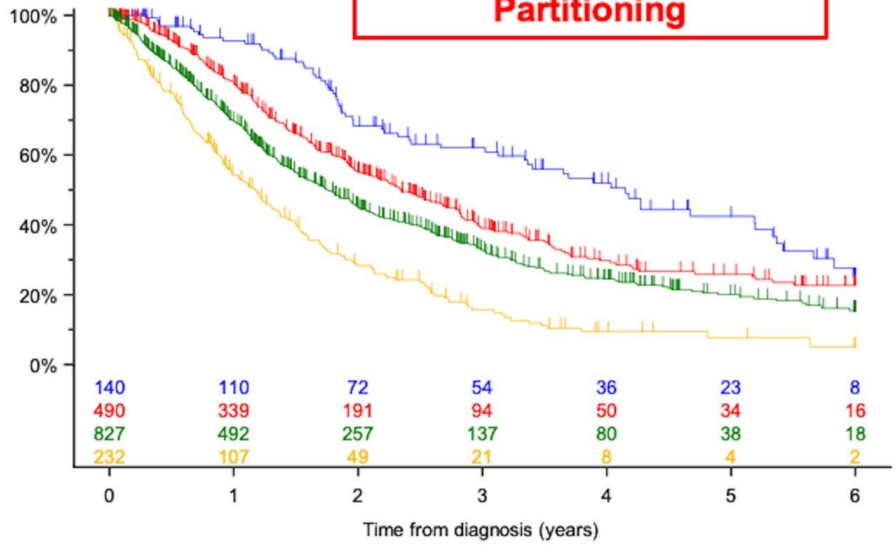
A

Recursive Partitioning agnostically identifies potential cutpoints for separation by prognosis Clinical T category , 9th ed Database



B

Overall Survival of cohorts identified by Recursive Partitioning



	Deaths / N	Median in Months	3-Year Estimate
Low T Psum<=12	64 / 140	49.8 (40, 62.4)	62% (53, 71)
Low T 12>Psum<=30 + Medium T Psum<=30	259 / 490	28.1 (24.3, 33.4)	39% (34, 44)
Low/Medium T Psum>30	501 / 827	21.1 (18.8, 23.5)	33% (29, 37)
High T	178 / 232	14.2 (11.3, 16.5)	16% (10, 21)

C

Survival is statistically different between cohorts identified by Recursive Partitioning

Comparison	P-value
Low T and Psum<= 12 mm vs Low T and Psum > 12mm and <= 30 mm or Medium T and Psum <=30 mm	0.0005
Low T and Psum> 12 mm and <= 30 mm Medium T and Psum <=30 mm vs Low- MediumT and Psum >30 mm	0.0002
Low-Medium T and Psum >30 mm vs High T	<0.0001

Pleural Mesothelioma
Clinical staging

AJCC 8th

TNM staging system for malignant pleural mesothelioma				
Stage	**T**	**N**	**M**	
Stage IA	T1	N0	M0	Most resectable
Stage IB	T2 or 3	N0	M0	
Stage II	T1 or 2	N1	M0	
Stage IIIA	T3	N1	M0	Some resectable
Stage IIIB	T1-3	N2	M0	
	T4	Any N	M0	Unresectable
Stage IV	Any T	Any N	M1	

American Joint Committee on Cancer, 8th edition

AJCC 9th

Clinical Stage Groupings	N0	N1	N2
Proposed T1	I	II	IIIA
Proposed T2	II	IIIA	IIIA
Proposed T3	IIIA	IIIA	IIIA
Proposed T4	IIIB	IIIB	IIIB
M1	IV	IV	IV

References

1.Malignancies. August 20-21, 2009. Bethesda, Maryland, USA. J ThoracOncol 2010;5:S259-370.

2. Strollo DC, Rosado de Christenson ML, Jett JR. Primary mediastinaltumors. Part 1: tumors of the anterior mediastinum. Chest 1997;112:511-522.

3. Engels EA, Pfeiffer RM. Malignant thymoma in the United States:demographic patterns in incidence and associations with subsequent malignancies. Int J Cancer 2003;105:546-551.

4. Masaoka A. Staging system of thymoma. J Thorac Oncol 2010;5:S304-312.

5. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878-884;discussion 884-875

6. Eng TY, Fuller CD, Jagirdar J, et al. Thymic carcinoma: state of the art review. Int J Radiat Oncol Biol Phys 2004;59:654-664.

7. Marchevsky A, Marx A, Strobel P, et al. Policies and reporting guidelines for small biopsy specimens of mediastinal masses. J Thorac Oncol 2011;6:S1724-1729.

8. Strollo DC, Rosado-de-Christenson ML, Jett JR. Primary mediastinal tumors: part II. Tumors of the middle and posterior mediastinum. Chest 1997;112:1344-1357.

9. Rashid OM, Cassano AD, Takabe K. Thymic neoplasm: a rare disease with a complex clinical presentation. J Thorac Dis 2013;5:173-183

10. Detterbeck FC, Parsons AM. Management of stage I and II thymoma. Thorac Surg Clin 2011;21:59-67, vi-vii.

11. Detterbeck FC, Zeeshan A. Thymoma: current diagnosis and treatment. Chin Med J (Engl) 2013;126:2186-2191.

12. Barth TFE, Leithäuser F, Joos S, et al. Mediastinal (thymic) large Bcell lymphoma: where do we stand? Lancet Oncol 2002;3:229-234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12067685.

13. Ferolla P, Falchetti A, Filosso P, et al. Thymic neuroendocrine carcinoma (carcinoid) in multiple endocrine neoplasia type 1 syndrome: the Italian series. J Clin Endocrinol Metab 2005;90:2603-2609.

14. Teh BT. Thymic carcinoids in multiple endocrine neoplasia type 1. J Intern Med 1998;243:501-504.

15. Benveniste MF, Rosado-de-Christenson ML, Sabloff BS, et al. Role of imaging in the diagnosis, staging, and treatment of thymoma. Radiographics 2011;31:1847-1861; discussion 1861-1843.

16. Marom EM. Advances in thymoma imaging. J Thorac Imaging2013;28:69-80; quiz 81-63

17. Marom EM. Imaging thymoma. J Thorac Oncol 2010;5:S296-303.

18. Rosado-de-Christenson ML, Strollo DC, Marom EM. Imaging of thymic epithelial neoplasms. Hematol Oncol Clin North Am 2008;22:409-431

19. Sadohara J, Fujimoto K, Muller NL, et al. Thymic epithelial tumors:comparison of CT and MR imaging findings of low-risk thymomas, highriskthymomas, and thymic carcinomas. Eur J Radiol 2006;60:70-79.Available at: http://www.ncbi.nlm.nih.gov/pubmed/16766154.

20. Marom EM, Rosado-de-Christenson ML, Bruzzi JF, et al. Standard report terms for chest computed tomography reports of anterior mediastinal masses suspicious for thymoma. J Thorac Oncol 2011;6:S1717-1723.

References

21. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409
22. Sung YM, Lee KS, Kim BT, et al. 18F-FDG PET/CT of thymic epithelial tumors: usefulness for distinguishing and staging tumor subgroups. J Nucl Med 2006;47:1628-1634
23. Ruffini E, Van Raemdonck D, Detterbeck F, et al. Management of thymic tumors: a survey of current practice among members of the European Society of Thoracic Surgeons. J Thorac Oncol 2011;6:614-623
24. Kondo K. Optimal therapy for thymoma. J Med Invest 2008;55:17-28..
25. Detterbeck FC, Parsons AM. Thymic tumors. Ann Thorac Surg 2004;77:1860-1869.
26. Wright CD. Stage IVA thymoma: patterns of spread and surgical management. Thorac Surg Clin 2011;21:93-97, vii.
27. Wright CD. Extended resections for thymic malignancies. J Thorac Oncol 2010;5:S344-347.
28. Huang J, Rizk NP, Travis WD, et al. Feasibility of multimodality therapy including extended resections in stage IVA thymoma. J Thorac Cardiovasc Surg 2007;134:1477-1483; discussion 1483-1474
29. Kimura T, Inoue M, Kadota Y, et al. The oncological feasibility and limitations of video-assisted thoracoscopic thymectomy for early-stage thymomas. Eur J Cardiothorac Surg 2013.
30. Odaka M, Akiba T, Mori S, et al. Oncological outcomes of thoracoscopic thymectomy for the treatment of stages I-III thymomas. Interact Cardiovasc Thorac Surg 2013;17:285-290.
31. Toker A, Sonett J, Zielinski M, et al. Standard terms, definitions, and policies for minimally invasive resection of thymoma. J Thorac Oncol 2011;6:S1739-1742.
32. Pennathur A, Qureshi I, Schuchert MJ, et al. Comparison of surgical techniques for early-stage thymoma: feasibility of minimally invasivethymectomy and comparison with open resection. J Thorac Cardiovasc Surg 2011;141:694-701.
33. Komanapalli CB, Cohen JI, Sukumar MS. Extended transcervical video-assisted thymectomy. Thorac Surg Clin 2010;20:235-243..
34. Limmer KK, Kernstine KH. Minimally invasive and robotic-assisted thymus resection. Thorac Surg Clin 2011;21:69-83, vii.
35. Detterbeck 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:S1710-1716
36. Huang J, Detterbeck FC, Wang Z, Loehrer PJ, Sr. Standardoutcome measures for thymic malignancies. J Thorac Oncol 2011;6:S1691-1697.
37. Moran CA, Walsh G, Suster S, Kaiser L. Thymomas II: aclinicopathologic correlation of 250 cases with a proposed staging system with emphasis on pathologic assessment. Am J Clin Pathol2012;137:451-461.
38. Kondo K. Tumor-node metastasis staging system for thymicepithelial tumors. J Thorac Oncol 2010;5:S352-356.
39. Lee HS, Kim ST, Lee J, et al. A single institutional experience of thymic epithelial tumours over 11 years: clinical features and outcome and implications for future management. Br J Cancer 2007;97:22-28.

References

40. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485-2492.
41. Wright CD. Management of thymomas. Crit Rev Oncol Hematol 2008;65:109-120.
42. Detterbeck FC. The international thymic malignancy interest group. J Natl Compr Canc Netw 2013;11:589-593.
43. Travis W, Brambilla E, Muller-Hermelink H, Harris C. Pathology and genetics of tumours of the lung, pleura, thymus and heart. WHO Classification of Tumors, 3rd ed. Lyon: IARC Press; 2004:145-197.
44. Lewis JE, Wick MR, Scheithauer BW, et al. Thymoma. A clinicopathologic review. Cancer 1987;60:2727-2743.
45. Park HS, Shin DM, Lee JS, et al. Thymoma. A retrospective study of 87 cases. Cancer 1994;73:2491-2498.
46. Kondo K, Yoshizawa K, Tsuyuguchi M, et al. WHO histologic classification is a prognostic indicator in thymoma. Ann Thorac Surg 2004;77:1183-1188.
47. Moran CA, Weissferdt A, Kalhor N, et al. Thymomas I: aclinicopathologic correlation of 250 cases with emphasis on the World Health Organization schema. Am J Clin Pathol 2012;137:444-450.
48. Marx A, Rieker R, Toker A, et al. Thymic carcinoma: is it a separate entity? From molecular to clinical evidence. Thorac Surg Clin 2011;21:25-31 v-vi.
49. Margaritora S, Cesario A, Cusumano G, et al. Thirty-five-year follow-up analysis of clinical and pathologic outcomes of thymoma surgery. Ann Thorac Surg 2010;89:245-252; discussion 252.
50. Regnard JF, Magdeleinat P, Dromer C, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. J Thorac Cardiovasc Surg 1996;112:376-384.
51. Yano M, Sasaki H, Yokoyama T, et al. Thymic carcinoma: 30 cases at a single institution. J Thorac Oncol 2008;3:265-269.
52. Ogawa K, Toita T, Uno T, et al. Treatment and prognosis of thymic carcinoma: a retrospective analysis of 40 cases. Cancer 2002;94:3115-3119.
53. Okereke IC, Kesler KA, Freeman RK, et al. Thymic carcinoma: outcomes after surgical resection. Ann Thorac Surg 2012;93:1668-1672; discussion 1672-1663.
54. Ried M, Potzger T, Sziklavari Z, et al. Extended Surgical Resections of Advanced Thymoma Masaoka Stages III and IVa Facilitate Outcome.Thorac Cardiovasc Surg 2013.
55. Detterbeck F, Youssef S, Ruffini E, Okumura M. A review of prognostic factors in thymic malignancies. J Thorac Oncol2011;6:S1698-1704.
56. Mehran R, Ghosh R, Maziak D, et al. Surgical treatment of thymoma. Can J Surg 2002;45:25-30.
57. Murakawa T, Nakajima J, Kohno T, et al. Results from surgical treatment for thymoma. 43 years of experience. Jpn J ThoracCardiovasc Surg 2000;48:89-95.
58. Wakely PE, Jr. Fine needle aspiration in the diagnosis of thymic epithelial neoplasms. Hematol Oncol Clin North Am 2008;22:433-442.

References

59. Detterbeck FC, Moran C, Huang J, et al. Which way is up? Policies and procedures for surgeons and pathologists regarding resection specimens of thymic malignancy. J Thorac Oncol 2011;6:S1730-1738.
60. Gilhus NE, Owe JF, Hoff JM, et al. Myasthenia gravis: a review of available treatment approaches. Autoimmune Dis 2011;2011:847393.
61. Autoantibodies to acetylcholine receptors in myasthenia gravis. N Engl J Med 1983;308:402-403.
62. Howard FM, Lennon VA, Finley J, et al. Clinical correlations of antibodies that bind, block, or modulate human acetylcholine receptors in myasthenia gravis. Ann N Y Acad Sci 1987;505:526-538.
63. Utsumi T, Shiono H, Kadota Y, et al. Postoperative radiation therapy after complete resection of thymoma has little impact on survival. Cancer 2009;115:5413-5420.
64. Korst RJ, Kansler AL, Christos PJ, Mandal S. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. Ann Thorac Surg 2009;87:1641-1647.
65. Forquer JA, Rong N, Fakiris AJ, et al. Postoperative radiotherapy after surgical resection of thymoma: differing roles in localized and regional disease. Int J Radiat Oncol Biol Phys 2010;76:440-445.
66. 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.
67. Gomez D, Komaki R, Yu J, et al. Radiation therapy definitions and reporting guidelines for thymic malignancies. J Thorac Oncol 2011;6:S1743-1748.
68. Gomez D, Komaki R. Technical advances of radiation therapy for thymic malignancies. J Thorac Oncol 2010;5:S336-343.
69. 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.
70. Moran JM, Dempsey M, Eisbruch A, et al. Safety considerations for IMRT: executive summary. Med Phys 2011;38:5067-5072.
71. Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). Cancer Radiother 2011;15:555-559.
72. Holmes T, Das R, Low D, et al. American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments. Int J Radiat Oncol Biol Phys 2009;74:1311-1318.
73. ICRU Report 83: Prescribing, Recording, and Reporting Intensity Modulated Photon Beam Therapy (IMRT). Journal of the ICRU 2010;10.
74. Kong FM, Pan C, Eisbruch A, Ten Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity. Semin Radiat Oncol 2007;17:108-120.
75. Milano MT, Constine LS, Okunieff P. Normal tissue tolerance dose metrics for radiation therapy of major organs. Semin Radiat Oncol 2007;17:131-140.
76. Myojin M, Choi NC, Wright CD, et al. Stage III thymoma: pattern of failure after surgery and postoperative radiotherapy and its implicationfor future study. Int J Radiat Oncol Biol Phys 2000;46:927-933.

References

77. 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 Phys1995;32:651-659.
78. Singhal S, Shrager JB, Rosenthal DI, et al. Comparison of stages III thymoma treated by complete resection with or without adjuvant radiation. Ann Thorac Surg 2003;76:1635-1641; discussion 1641-1632.
79. Rena O, Papalia E, Oliaro A, et al. Does adjuvant radiation therapy improve disease-free survival in completely resected Masaoka stage II thymoma? Eur J Cardiothorac Surg 2007;31:109-113.
80. Mangi AA, Wright CD, Allan JS, et al. Adjuvant radiation therapy for stage II thymoma. Ann Thorac Surg 2002;74:1033-1037.
81. Sugie C, Shibamoto Y, Ikeya-Hashizume C, et al. Invasive thymoma: postoperative mediastinal irradiation, and low-dose entire hemithorax irradiation in patients with pleural dissemination. J ThoracOncol 2008;3:75-81.
82. Ogawa K, Uno T, Toita T, et al. Postoperative radiotherapy for patients with completely resected thymoma: a multi-institutional, retrospective review of 103 patients. Cancer 2002;94:1405-1413.
83. Cowen D, Richaud P, Mornex F, et al. Thymoma: results of a multicentric retrospective series of 149 non-metastatic irradiated patients and review of the literature. FNCLCC trialists. Federation Nationale des Centres de Lutte Contre le Cancer. Radiother Oncol 1995;34:9-16.
84. Girard N, Lal R, Wakelee H, et al. Chemotherapy definitions and policies for thymic malignancies. J Thorac Oncol 2011;6:S1749-1755.
85. Girard N. Chemotherapy and targeted agents for thymic malignancies. Expert Rev Anticancer Ther 2012;12:685-695.
86. Loehrer PJ, Sr., Chen M, Kim K, et al. Cisplatin, doxorubicin, and cyclophosphamide plus thoracic radiation therapy for limited-stage unresectable thymoma: an intergroup trial. J Clin Oncol 1997;15:3093-3099.
87. Loehrer PJ, 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.
88. 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 Oncol1996;14:814-820.
89. Shin DM, Walsh GL, Komaki R, et al. A multidisciplinary approach to therapy for unresectable malignant thymoma. Ann Intem Med 1998;129:100-104.
90. Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy for invasive thymoma. A 13-year experience. Cancer 1991;68:30-33.
91. Loehrer PJ, 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. Cancer2001;91:2010-2015.
92. 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.

References

93. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stageIII and IVA thymomas: a single-institution experience with a long followup.J Thorac Oncol 2006;1:308-313.
94. Yokoi K, Matsuguma H, Nakahara R, et al. Multidisciplinary treatment for advanced invasive thymoma with cisplatin, doxorubicin, and methylprednisolone. J Thorac Oncol 2007;2:73-78.
95. Lemma GL, Loehrer PJ, Sr., Lee JW, et al. A phase II study of carboplatin plus paclitaxel in advanced thymoma or thymic carcinoma: E1C99 [abstract]. J Clin Oncol 2008;26(Suppl 15):Abstract 8018.
96. Venuta F, Rendina EA, Longo F, et al. Long-term outcome after multimodality treatment for stage III thymic tumors. Ann Thorac Surg 2003;76:1866-1872; discussion 1872.
97. Rajan A, Giaccone G. Chemotherapy for thymic tumors: induction,consolidation, palliation. Thorac Surg Clin 2011;21:107-114, viii.
98. Schmitt J, Loehrer PJ, Sr. The role of chemotherapy in advanced thymoma. J Thorac Oncol 2010;5:S357-360.
99. 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.
100. Furugen M, Sekine I, Tsuta K, et al. Combination chemotherapy with carboplatin and paclitaxel for advanced thymic cancer. Jpn J Clin Oncol 2011;41:1013-1016.
101. Riely GJ, Huang J. Induction therapy for locally advanced thymoma. J Thorac Oncol 2010;5:S323-326.
102. Wright CD, Choi NC, Wain JC, et al. Induction chemoradiotherapy followed by resection for locally advanced Masaoka stage III and IVA thymic tumors. Ann Thorac Surg 2008;85:385-389.
103. Longo F, De Filippis L, Zivi A, et al. Efficacy and tolerability of longacting octreotide in the treatment of thymic tumors: results of a pilot trial.Am J Clin Oncol 2012;35:105-109.
104. 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. JClin Oncol 2004;22:293-299.
105. 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 Oncol2010;21:1168-1172.
106. Highley MS, Underhill CR, Parnis FX, et al. Treatment of invasive thymoma with single-agent ifosfamide. J Clin Oncol 1999;17:2737-2744.
107. Pan CC, Chen PC, Wang LS, et al. Thymoma is associated with an increased risk of second malignancy. Cancer 2001;92:2406-2411.
108. Suster S, Rosai J. Thymic carcinoma. A clinicopathologic study of 60 cases. Cancer 1991;67:1025-1032.
109. Huang J, Rizk NP, Travis WD, et al. Comparison of patterns of relapse in thymic carcinoma and thymoma. J Thorac Cardiovasc Surg 2009;138:26-31.
110. Strobel P, Hohenberger P, Marx A. Thymoma and thymic carcinoma: molecular pathology and targeted therapy. J Thorac Oncol 2010;5:S286-290.

References

111. Moran CA, Suster S. Thymic carcinoma: current concepts and histologic features. Hematol Oncol Clin North Am 2008;22:393-407.
112. Hosaka Y, Tsuchida M, Toyabe S, et al. Masaoka stage and histologic grade predict prognosis in patients with thymic carcinoma. Ann Thorac Surg 2010;89:912-917.
113. Blumberg D, Burt ME, Bains MS, et al. Thymic carcinoma: current staging does not predict prognosis. J Thorac Cardiovasc Surg 1998;115:303-308; discussion 308-309.
114. Sakai M, Onuki T, Inagaki M, et al. Early-stage thymic carcinoma: is adjuvant therapy required? J Thorac Dis 2013;5:161-164.
115. Maruyama R, Suemitsu R, Okamoto T, et al. Persistent and aggressive treatment for thymic carcinoma. Results of a single-institute experience with 25 patients. Oncology 2006;70:325-329.
116. Weide LG, Ulbright TM, Loehrer PJ, Williams SD. Thymic carcinoma. A distinct clinical entity responsive to chemotherapy. Cancer 1993;71:1219-1223.
117. Lucchi M, Mussi A, Ambrogi M, et al. Thymic carcinoma: a report of 13 cases. Eur J Surg Oncol 2001;27:636-640.
118. Yoh K, Goto K, Ishii G-i, et al. Weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide is an effective treatment for advanced thymic carcinoma. Cancer 2003;98:926-931.
119. Igawa S, Murakami H, Takahashi T, et al. Efficacy of chemotherapy with carboplatin and paclitaxel for unresectable thymic carcinoma. Lung Cancer 2010;67:194-197.
120. Koizumi T, Takabayashi Y, Yamagishi S, et al. Chemotherapy for advanced thymic carcinoma: clinical response to cisplatin, doxorubicin,vincristine, and cyclophosphamide (ADOC chemotherapy). Am J ClinOncol 2002;25:266-268.
121. Kanda S, Koizumi T, Komatsu Y, et al. Second-line chemotherapyof platinum compound plus CPT-11 following ADOC chemotherapy inadvanced thymic carcinoma: analysis of seven cases. Anticancer Res2007;27:3005-3008.
122. Komatsu Y, Koizumi T, Tanabe T, et al. Salvage chemotherapy with carboplatin and paclitaxel for cisplatin-resistant thymic carcinoma--three cases. Anticancer Res 2006;26:4851-4855.
123. Okuma Y, Shimokawa T, Takagi Y, et al. S-1 is an active anticancer agent for advanced thymic carcinoma. Lung Cancer 2010;70:357-363
124. Koizumi T, Agatsuma T, Komatsu Y, Kubo K. Successful S-1monotherapy for chemorefractory thymic carcinoma. Anticancer Res 2011;31:299-301.
125. Kelly RJ, Petrini I, Rajan A, et al. Thymic malignancies: from clinical management to targeted therapies. J Clin Oncol 2011;29:4820-4827.
126. Strobel P, Bargou R, Wolff A, et al. Sunitinib in metastatic thymic carcinomas: laboratory findings and initial clinical experience. Br J Cancer 2010;103:196-200.
127. Bisagni G, Rossi G, Cavazza A, et al. Long lasting response to the multikinase inhibitor bay 43-9006 (Sorafenib) in a heavily pretreated metastatic thymic carcinoma. J Thorac Oncol 2009;4:773-775.

References

128.Yen-Han Tseng,Yi-Hsuan Lin,Yen-Chiang Tseng,Yu-Chin Lee,Yu-Chung Wu,Wen-Hu Hsu,Sang-Hue Yen,Jacqueline Whang-Peng,Yuh-Min Chen, Adjuvant Therapy for Thymic Carcinoma--A Decade of Experience i a Taiwan National Teaching Hospital. **PLoS One.** 2016 Jan 12;11(1).

129. Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. Lancet Oncol 2018;19:347-355.

130. Cho J, Kim HS, Ku BM, et al. Pembrolizumab for patients with refractory or relapsed thymic epithelial tumor: An open-label phase II trial. J Clin Oncol 2019;37:2162-2170.

131. Ruffini E, Guerrera F, Brunelli A, et al. Report from the European Society of Thoracic Surgeons prospective thymic database 2017: a powerful resource for a collaborative global effort to manage thymic tumors. Eur J Cardiothorac Surg 2019;55:601-609.

132. Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. Lancet Oncol. 2020;21(6):843-850.

133. Hirai F, Yamanaka T, Taguchi K, et al A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L. Ann Oncol 2015;26:363-8.

134. Loap P, Scher N, Goudjil F, et al. Proton Beam Therapy for Thymic Carcinoma with Pericardial Involvement. Int J Part Ther 2021;7:65-70.

135. Tateishi Y, Horita N, Namkoong H, et al. Postoperative Radiotherapy for Completely Resected Masaoka/Masaoka-Koga Stage II/III Thymoma Improves Overall Survival: An Updated Meta-Analysis of 4746 Patients. J Thorac Oncol 2021;16:677-685.

136. Schneider F, Roden AC, Dacic S. Protocol for the examination of specimens from patients with thymic tumors: College of American Pathologists; 2021.

137. Benveniste MFK, Betancourt Cuellar SL, Carter BW, et al. Thymic Epithelial Neoplasms: Tumor-Node-Metastasis Staging. Radiol Clin North Am 2021;59:183-192.

138. 133. Giaccone G, Kim C. Durable Response in Patients With Thymic Carcinoma Treated With Pembrolizumab After Prolonged Follow-Up. J Thorac Oncol 2021;16:483-485.

139. Chen, Liu, et al. "The value of postoperative radiotherapy in thymoma patients with myasthenia gravis." Radiotherapy and Oncology 183 (2023): 109644.

140. Zhou, Dong, et al. "Postoperative radiotherapy for completely resected thymoma: Differing roles in masaoka stage II and stage III disease." Asian Journal of Surgery 45.12 (2022): 2670-2675.

141.Tateishi, Yudai, et al. "Postoperative radiotherapy for completely resected Masaoka/Masaoka-Koga Stage II/III thymoma improves overall survival: an updated meta-analysis of 4746 patients." Journal of Thoracic Oncology 16.4 (2021): 677-685.

142. Song, Seung Hwan, et al. "The role of postoperative radiotherapy in stage II and III thymoma: a Korean multicenter database study." Journal of Thoracic Disease 12.11 (2020): 6680.

References

143. Omasa, Mitsugu, et al. "Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: The Japanese Association for Research on the Thymus Database Study." Cancer 121.7 (2015): 1008-1016.

144.. Chen, Liu, et al. "The value of postoperative radiotherapy in thymoma patients with myasthenia gravis." *Radiotherapy and Oncology* 183 (2023): 109644.

145. Zhou, Dong, et al. "Postoperative radiotherapy for completely resected thymoma: Differing roles in masaoka stage II and stage III disease." *Asian Journal of Surgery* 45.12 (2022): 2670-2675.

146.Tateishi, Yudai, et al. "Postoperative radiotherapy for completely resected Masaoka/Masaoka-Koga Stage II/III thymoma improves overall survival: an updated meta-analysis of 4746 patients." *Journal of Thoracic Oncology* 16.4 (2021): 677-685.

147. Song, Seung Hwan, et al. "The role of postoperative radiotherapy in stage II and III thymoma: a Korean multicenter database study." *Journal of Thoracic Disease* 12.11 (2020): 6680.

148. Omasa, Mitsugu, et al. "Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: The Japanese Association for Research on the Thymus Database Study." *Cancer* 121.7 (2015): 1008-1016.

149. J Thorac Oncol. 2024 Sep;19(9):1310-1325.

150. J Thorac Oncol. 2024 Sep;19(9):1326-1338.

151. J Thorac Oncol. 2024 Nov;19(11):1564-1577.

152. J Thorac Oncol. 2024;19:1339-1351.

153. J Thorac Oncol. 2023;18(12):1655–1671.

154. J Thorac Oncol. 2024;19(1):52–70.

155. J Thorac Oncol. 2023;18(12):1672–1688.

156. J Thorac Oncol. 2023;18(12):1638-1654.

157. Radiographics. 2024;44(9):e240196.