RADIOTHERAPY IN THYMOMAS : INDICATIONS, CONTROVERSIES AND MODERN TECHNIQUES

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ANATOMY OF THYMUS

Location

- Primary lymphoepithelial organ in the anterior superior mediastinum
- Extends from the lower neck to the level of the 4th costal cartilage
- Usually lies behind the sternum and anterior to the great vessels

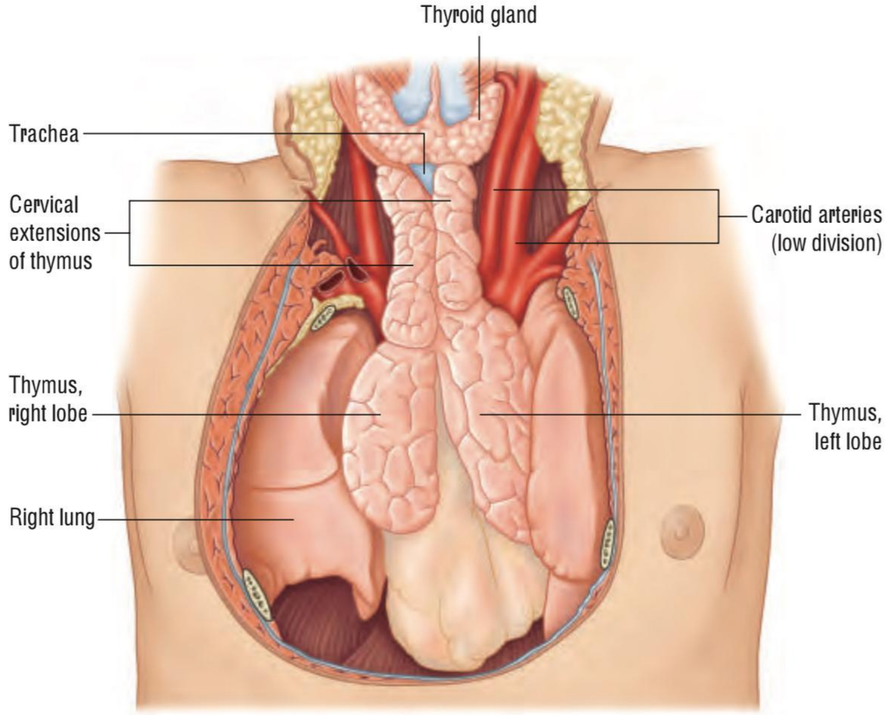
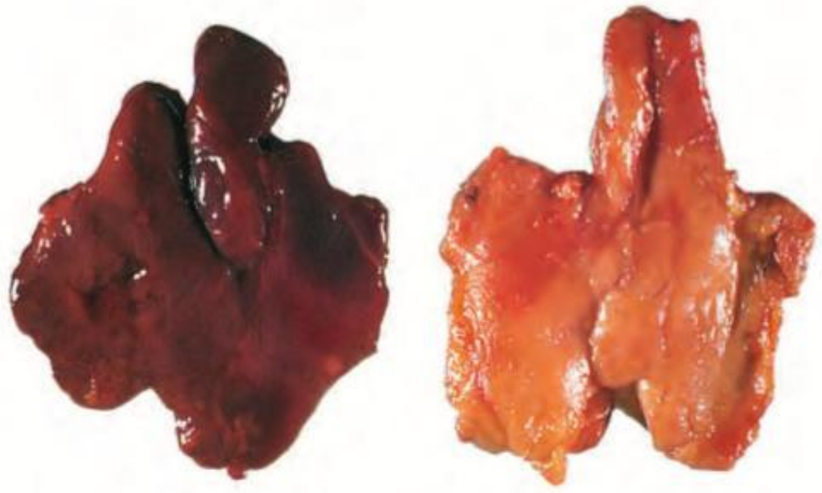


Fig. 56.8 The neonatal thymus.

- Bilobed encapsulated organ located in the superior mediastinum and anterior part of inferior mediastinum
- Two lobes are joined in the midline by connective tissue that merges with capsule of each lobe
- Largest around puberty and persists into old age, but with considerable fibrofatty infiltration



RELATIONS

		Ant	Post	Lat
Superior		Manubrium sterni	T1-T4	pleurae
Inferior	Ant	Sternum	Pericardium	pleurae
	Middle	Sterno - pericardial lig	Esophagus, aorta	pleurae
	Post	Pericardium	T5-T12	pleurae

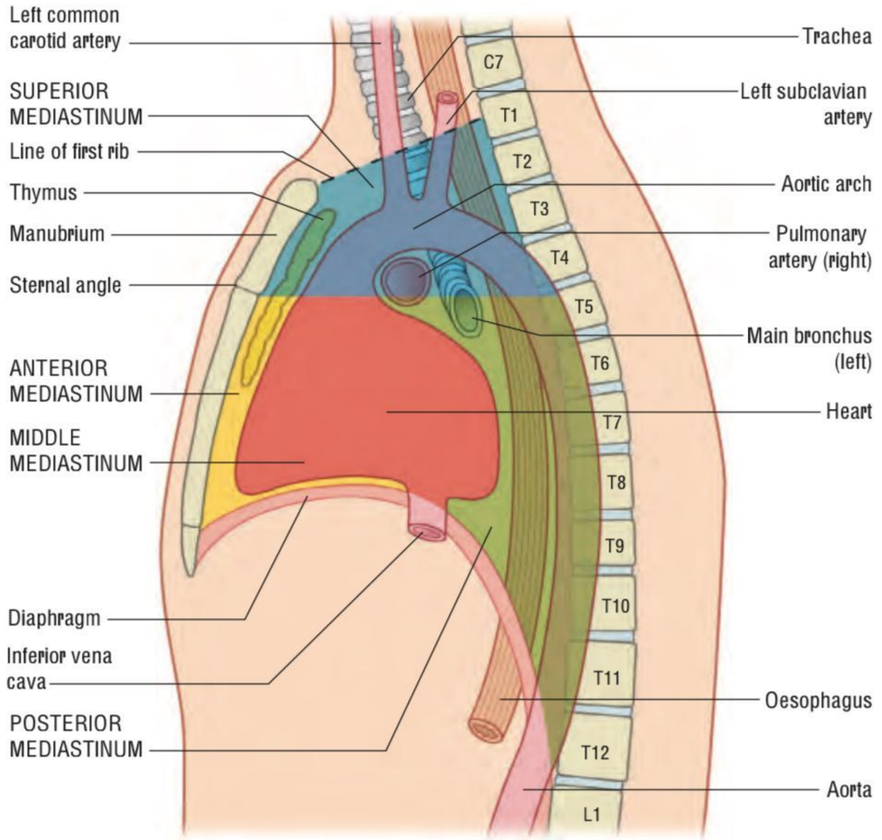


Fig. 56.1 The mediastinal divisions.

Bailey & Love's Short Practice of Surgery. 28th ed. CRC Press; Thoracic Anatomy chapter — Mediastinal divisions

- The thymus is an incompletely understood lymphoepithelial organ that functions in T-lymphocyte maturation.
- Embryologically, derived from the endoderm of the lower portion of the third pharyngeal pouch
- Involutes during adulthood, gradually being replaced by adipose tissue.
- Blood supply- internal mammary arteries
- Venous drainage -innominate and internal thoracic veins
- Lymphatics -lower cervical, internal mammary, and hilar lymph nodes.

HISTOLOGY

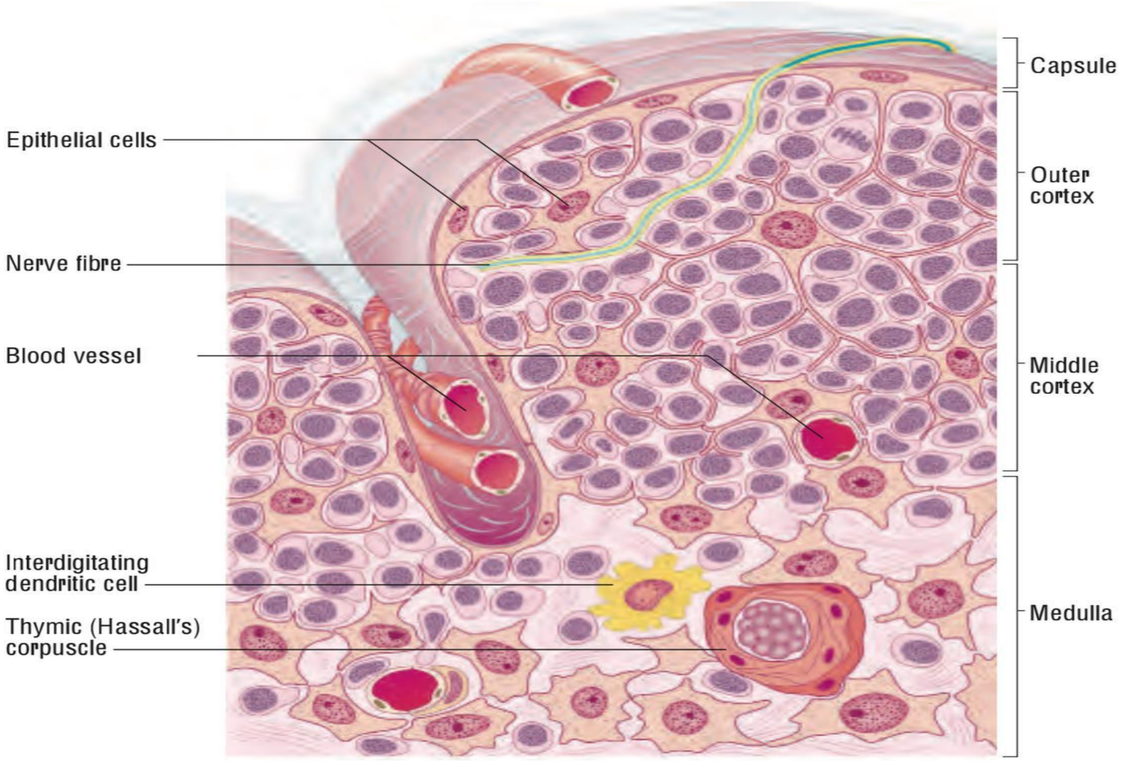
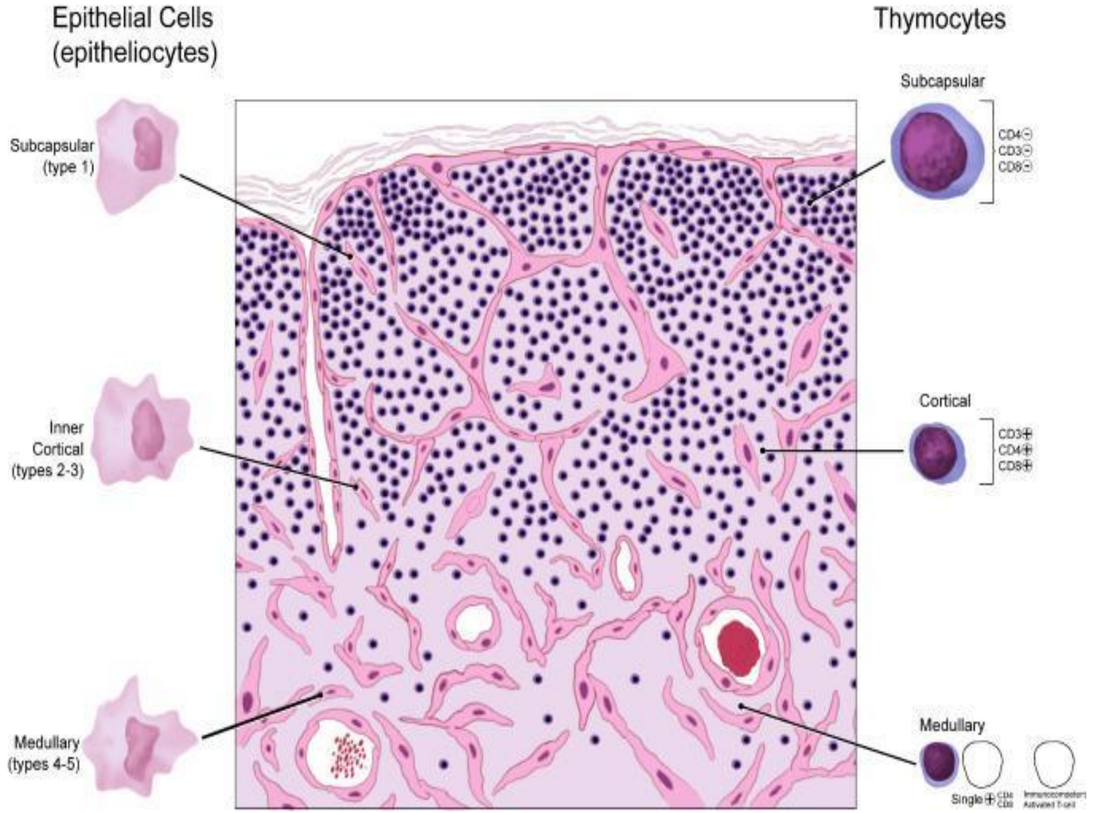


Fig. 56.10 Thymic structure and cellular organization, showing an interlobular septum, the cortical circulation and thymocytes within an epithelial framework.



- HASSAL'S CORPUSCLES: Whorls of flattened concentrically layered epithelial cells.
  - They characterise the THYMIC MEDULLA

Ellis H, Mahadevan V. *Clinical Anatomy: Applied Anatomy for Students and Junior Doctors*. 14th ed. Hoboken, NJ: Wiley-Blackwell; 2019.

THYMOMA

Thymomas are the most common tumors found in anterior mediastinum, accounting for 30% of anterior mediastinal tumours and 20% of all mediastinal tumours in adults.

- Over 90% of all thymomas occur in the anterior mediastinum with the remainder arising in the neck or other areas of the mediastinum and chest, including rarely, the heart
- Typical age at presentation is between 40 and 85 years old
- Equal prevalence between men and women.

EPIDEMIOLOGY

- **SEER data:** incidence approximately **1.3–2.6 cases per million person-years**
- Incidence increases with age:
  - **~4.2 per million person-years** at age 18
  - **~10.6 per million person-years** at age 80
- Peak incidence in the **5th–7th decades**
- No strong gender predilection (slight variations across series)
- **Rare in children and adolescents**
- Represent the most common primary tumors of the anterior mediastinum in adults

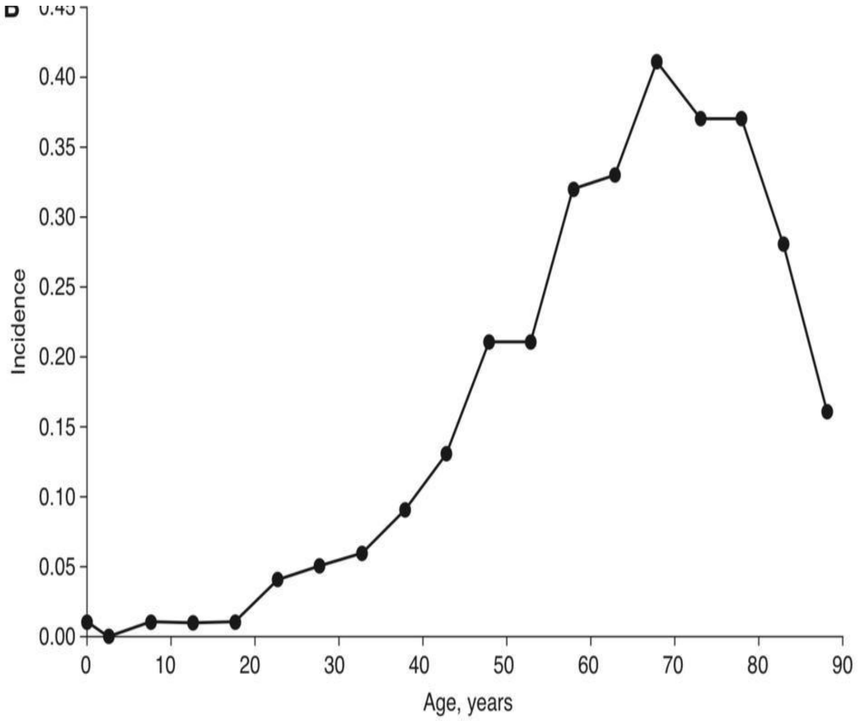


Figure 32.1 Epidemiology of tl epithelial tumors. Panel A show incidence of thymomas over time approximately 1970 to 2005 with ations due to unclear factors but sibly changes in reporting and p ogy classification. Panel B show incidence by age peaking in th decade of life and possibly decre thereafter. (Used with permission Engels EA. Epidemiology of thym and associated malignancies. *J T Oncol.* 2010;5(10 Suppl 4):S26

Engels EA. Epidemiology of thymoma and associated malignancies. *J Thorac Oncol.* 2010;5(10 Suppl 4):S260-S265.

ETIOLOGY AND RISK FACTORS

- The etiology of thymic epithelial tumors (TETs) remains largely unknown, and no specific environmental, lifestyle, or hereditary risk factors have been consistently identified. However, several paraneoplastic and syndromic associations are well recognized:

- Myasthenia gravis (MG) – the most common association, occurring in approximately 30–50% of patients with thymoma.

- Pure red cell aplasia (PRCA).

- Hypogammaglobulinemia (Good syndrome).

- Neuroendocrine tumors of the thymus (NETTs) are associated with Multiple Endocrine Neoplasia type 1 (MEN1) syndrome.

- Molecular aberrations in thymoma are not clearly understood.
- Several studies shown an elevated expression of EGFR, But rarely been associated with mutations.
- VEGF, IGF-1R, KIT pathways – Other signalling pathways shown over expression.

NATURAL HISTORY

Characterized by an indolent growth pattern that can be locally invasive

One-third of thymomas are asymptomatic and found incidentally on chest x-rays.

40% of cases present with symptoms relating to impingement by the intrathoracic mass

Symptoms due to paraneoplastic syndromes

- **THORACIC MANIFESTATIONS:**
- Due to anterior mediastinal mass related to its size and effect on adjacent organs:
    - Chest pain
    - Shortness of breath
    - Cough
    - Phrenic nerve palsy
    - hoarseness,
    - superior vena cava obstruction
    - tumor hemorrhage.
- Pleural and pericardial effusions: Most common manifestations of more disseminated disease

- **PARANEOPLASTIC DISORDERS**:
- 70 % of thymomas are proposed to be associated with paraneoplastic syndromes.
- Myasthenia gravis has the highest incidence among the vast array of paraneoplastic syndromes associated with thymoma: upto 50%
- Conversely only 10% to 15% of patients with myasthenia gravis have a thymoma

Table 6 Paraneoplastic/autoimmune syndromes associated with thymomas.

Condition	Findings	Treatments
Myasthenia gravis	Fatigable weakness with variable extension (from ocular to generalized)	Steroids, pyridostigmine, immunosuppression, IVIG, plasmapheresis
Pure red cell aplasia	Anemia	Steroids, immunosuppression
Hypogammaglobulinemia	Recurrent, severe infections	IVIG
Lambert Eaton syndrome	Fatigable weakness, autonomic symptoms	3,4-Diaminopyridine steroids, IVIG, plasmapheresis
Myositis	Muscle pain, weakness, elevated CK	Steroids
Acquired neuromyotonia	Diffuse fasciculations, cramps, hyperhydrosis	Sodium channel blockers (phenytoin), IVIG, plasmapheresis, steroids
Encephalitis	Memory impairment, behavioral changes, hallucinations, seizures, altered level of consciousness	Steroids, IVIG, rituximab, cyclophosphamide
Morvan's syndrome	Neuromyotonia and encephalitis, often with sleep disorder	Steroids, IVIG, rituximab, cyclophosphamide
Autoimmune Autonomic Neuropathy	Orthostatic hypotension, dry mouth, impaired pupillary responses, sexual dysfunction, urinary retention	Pyridostigmine, symptomatic therapies, IVIG, plasmapheresis, steroids, immunosuppression
Paraneoplastic cerebellar degeneration	Nystagmus, vertigo, dysarthria, ataxia	Steroids, IVIG, rituximab, cyclophosphamide

David S. Schrump et al. **Thymoma and Thymic Carcinoma: An Update.** *Journal of Thoracic Oncology*. 2014.

- Second primary malignancies occur in approximately 15% of patients with thymoma, possibly due to underlying immune dysregulation.
  - Most common: Non-Hodgkin lymphoma
  - Followed by gastrointestinal malignancies and soft tissue sarcomas
  - Risk is highest in patients with high-grade histology and advanced-stage disease.

Pattern of Spread

- Most thymomas are slow-growing and indolent.
- When they spread, the most common pattern is local and pleural dissemination:
  - Tumor implants on pleural surfaces ("drop metastases")
  - May progress to malignant pleural effusion
- Lymphatic spread is uncommon (~1.8%):
  - About 90% of involved lymph nodes are in the anterior mediastinum
- Hematogenous metastasis is rare:

EVALUATION AND WORKUP

- **HISTORY AND PHYSICAL EXAMINATION**

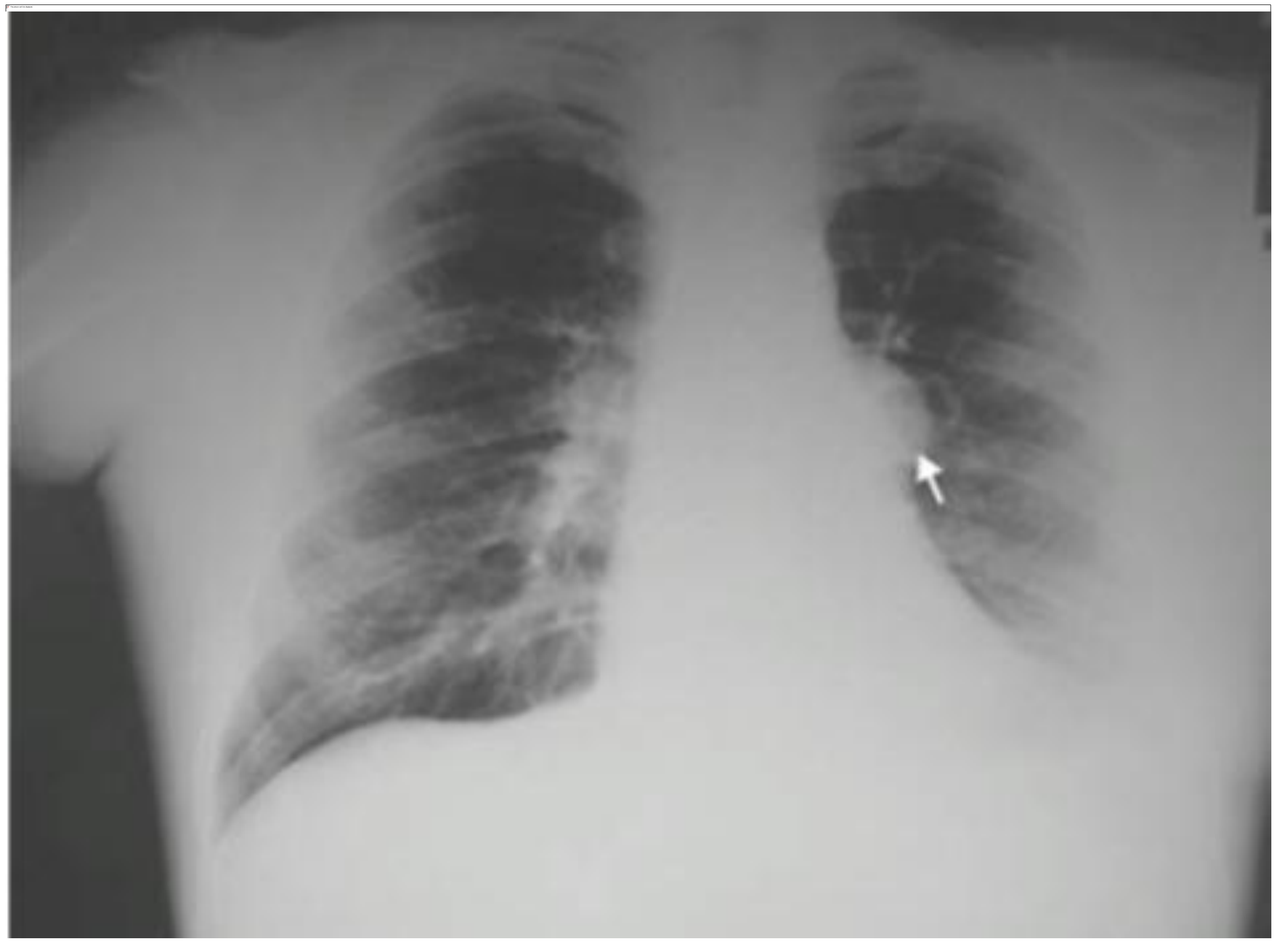
For the primary	Paraneoplastic syndromes	To rule out DDs
Examine for signs and symptoms suggestive of thoracic mass: cough, chest pain, breathlessness	Focus on signs and symptoms s/o paraneoplastic syndromes especially Myasthenia: Fatigue, diplopia ,ptosis and dysarthria Cushing's syndrome: Cushingoid habits	Ask for constitutional symptoms : such as fever, chills and weight loss - may suggest the presence of a MEDIASTINAL LYMPHOMA

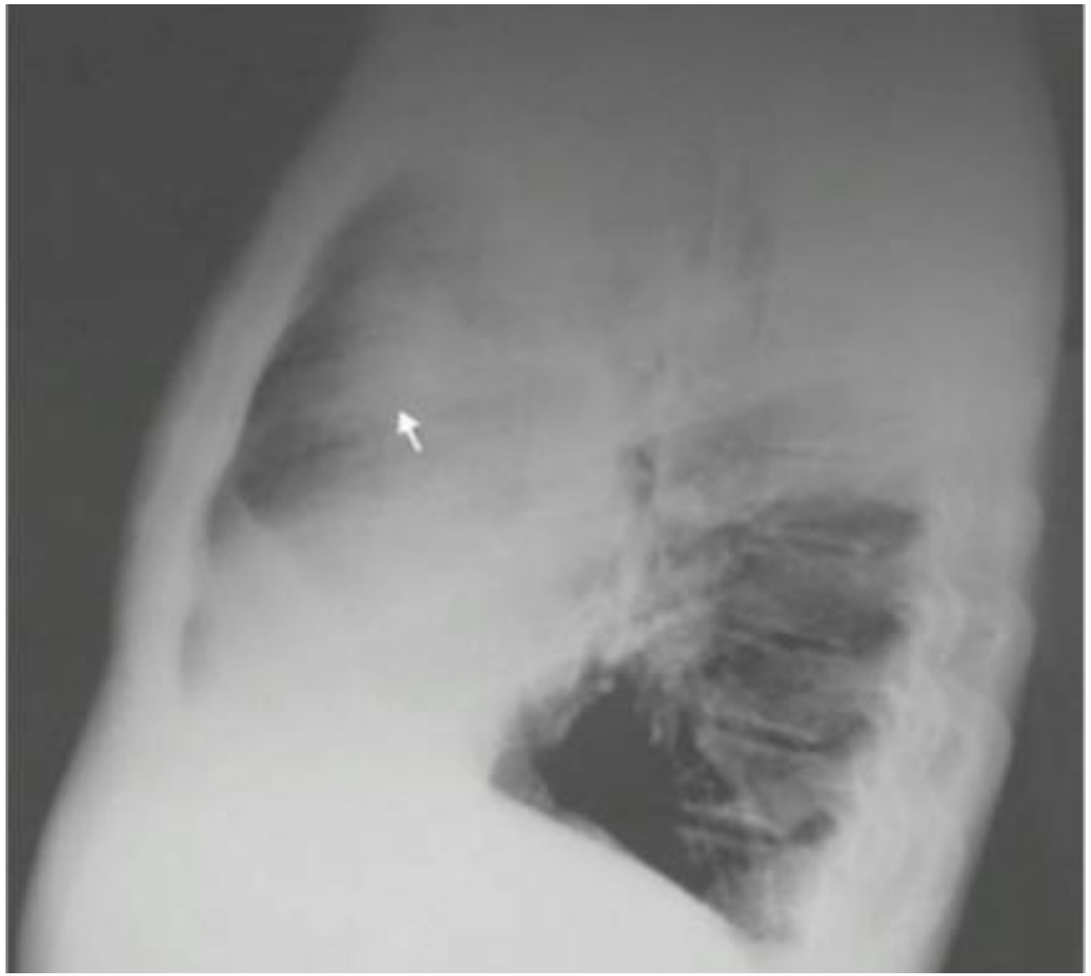
- **BIOCHEMICAL INVESTIGATIONS:**

Routine investigations	Paraneoplastic syndromes	To rule out DDs
• Blood urea, creatinine • Electrolytes • Complete hemogram with peripheral smear	Anti-acetylcholine receptor (anti-AchR) antibody levels should be checked in all patients with suspected thymoma •i/c/o suspected Cushings Syndrome: Dexamethasone suppression test and urinary cortisol	• Serum AFP and beta HCG in young men to assess for non seminomatous germ cell tumour

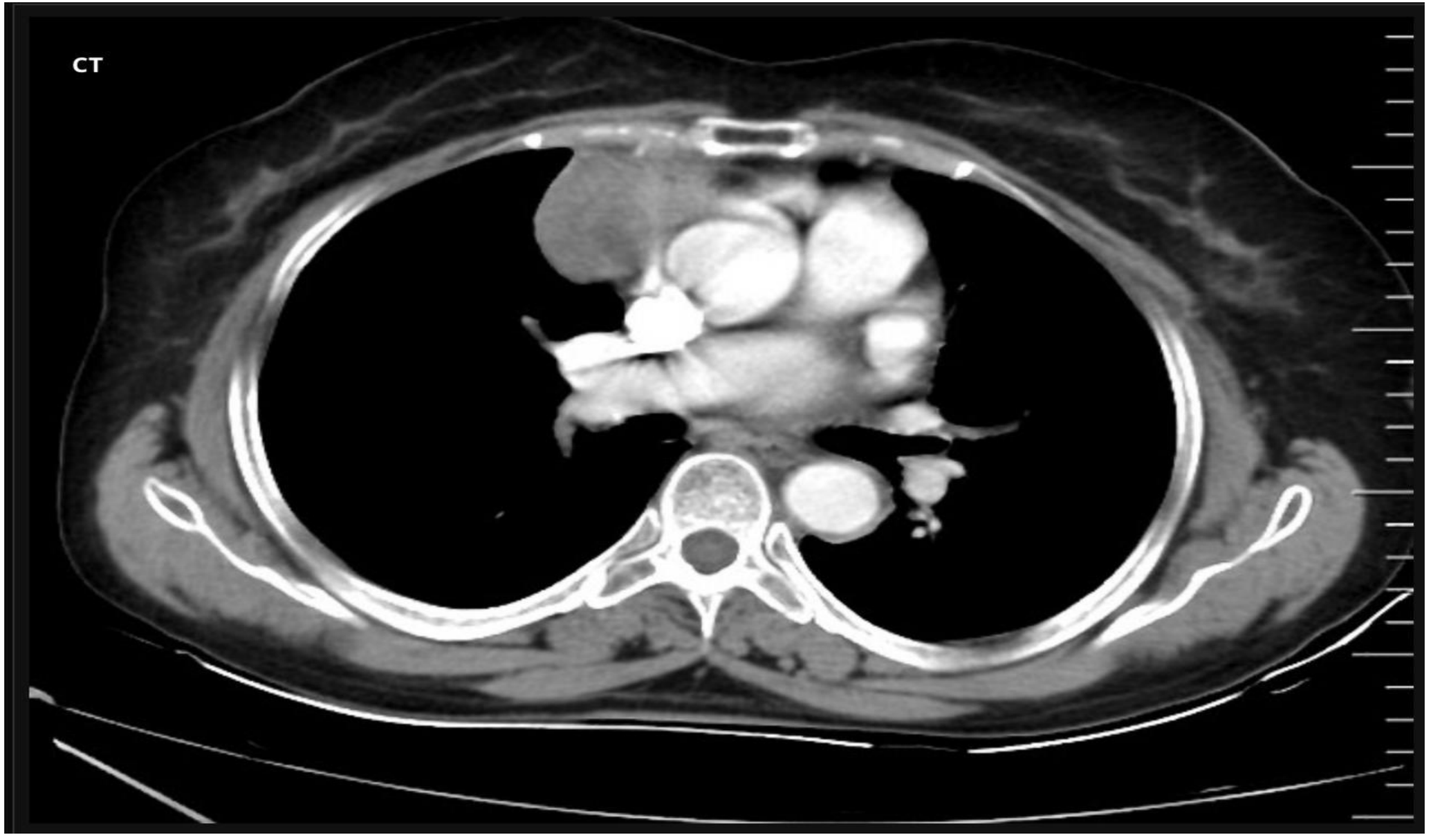
THORACIC IMAGING:

- CT > MRI
- Contrast-enhanced computed tomography (CECT) of the thorax is the preferred investigation for thymic neoplasms.
- Establishes the presence of anterior mediastinal mass
- Provides initial information to surgeon whether the mass is resectable or not
- Can show whether thymoma is well circumscribed or of it is infiltrating surrounding structures
- Assess the nature of the lesion (cystic versus solid), detect fat and calcium.





Frontal view shows a soft tissue shadow silhouetting the left heart border.
On lateral view an oval soft tissue shadow is appearing anterior to the heart.


CT

- MRI is superior to CT in defining vascular involvement and can detect subtle differences in tumor contour, capsule clarity, and intra- tumoral signal, which correlate with the WHO classification of thymomas.

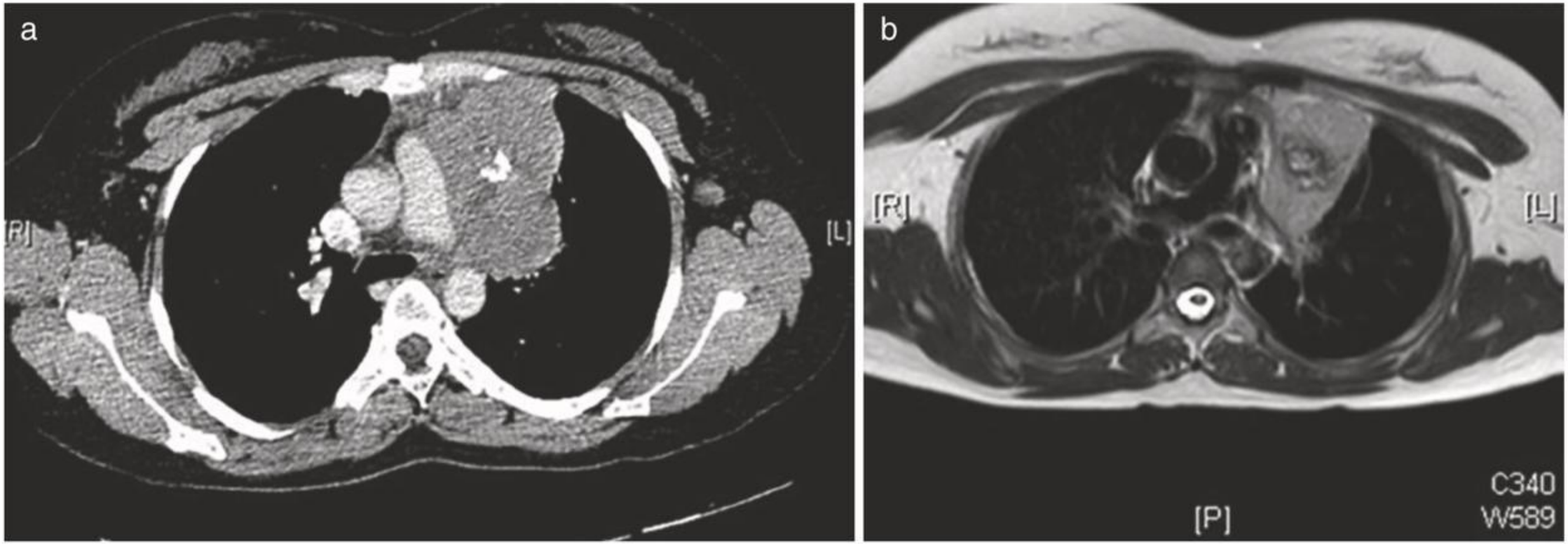
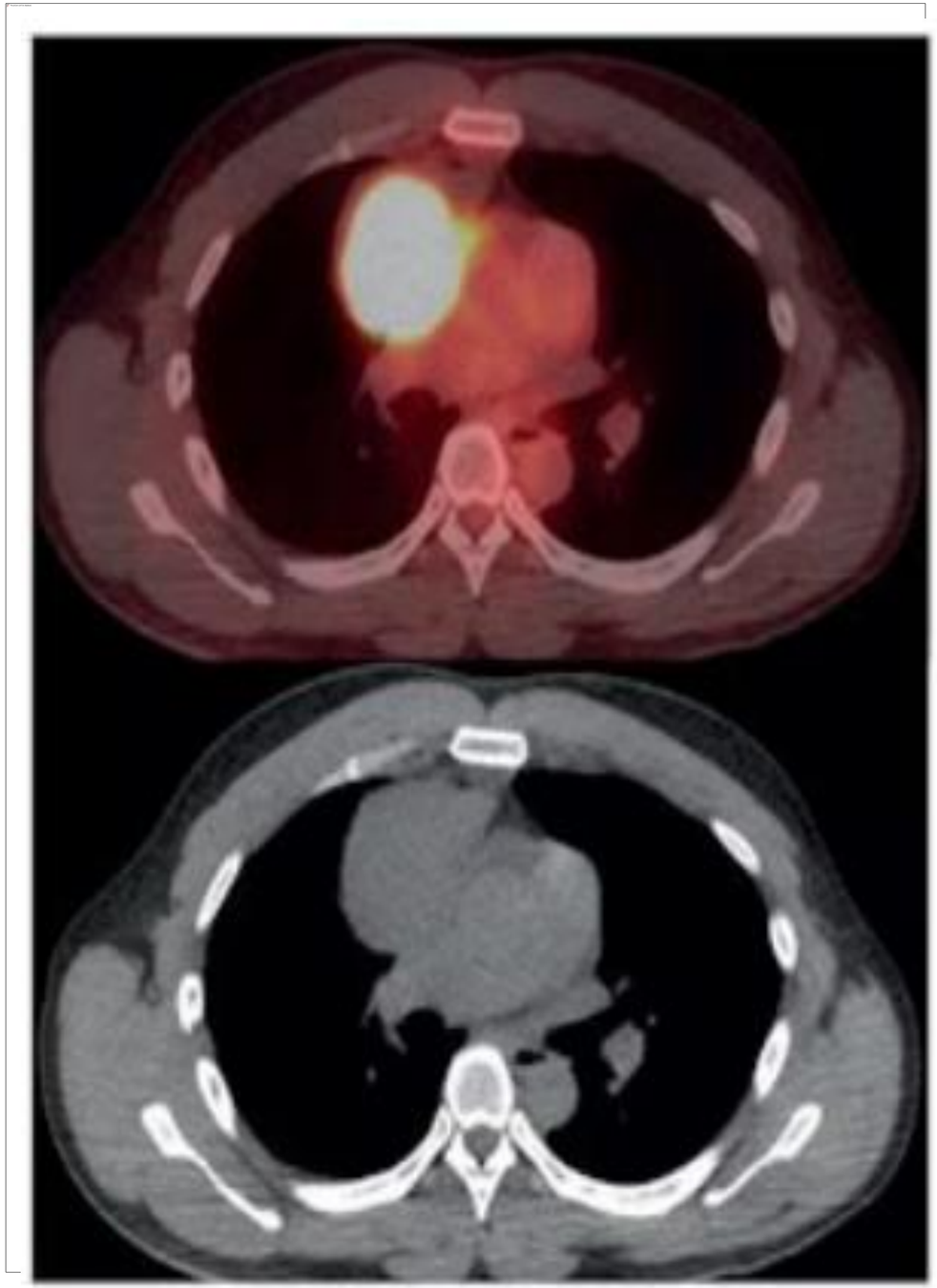


Fig. 4 (**a**) CT scan of thymoma with suspected infiltration of pulmonary conus. (**b**) MRI shows no evidence of infiltration of pulmonary artery

Marom EM. Imaging thymoma. *J Thorac Oncol*. 2010;5(10 Suppl 4):S296-S303

- PET-CT scans repeatedly have been shown to distinguish thymomas from thymic carcinomas, correlate with WHO tumor grade, and predict Masaoka-Koga stage. similarly reported to have correlation of SUVmax with low-risk thymomas (3.43), high-risk thymomas (4.42), and thymic carcinoma (8.23, P <.001)



- **Need for biopsy**

- Pretreatment biopsy is not required if the diagnosis of thymic tumour is highly probable and upfront surgical resection is achievable.

- Biopsy is required in all other clinical situations approaches may consist of

    - percutaneous core-needle biopsy

    - incisional surgical biopsy through mediastinotomy or mini thoracotomy, with sensitivity rates ranging from 40% to 93%

- Pleural spaces should be respected to avoid tumour cell seeding.

STAGING AND CLASSIFICATION

Numerous classification systems have been developed for thymomas over the years Most of them are of historical value and have little clinical significance

- The World Health Organization (WHO) attempted to organize the pathological classification of thymic tumors and introduced a new nomenclature which subclassified thymomas

  1999 WHO: A/AB/B1/B2/B3 / other rare histology

  Updated WHO 2004———> 2015———> 2021 (5th edition)

Current concept is that all thymomas except micronodular thymoma and nearly all TET'sare aggressive and considered malignant.

Thymoma Subtype	Obligatory Criteria	Optional Criteria
Type A	Occurrence of bland, spindle-shaped epithelial cells (at least focally); paucity[a] 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 (>4/2 mm^2); nuclear crowding	Polygonal epithelial cells; CD20+ epithelial cells
Type AB	Occurrence of bland, spindle-shaped epithelial cells (at least focally); abundance[a] 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[b]	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[b]		

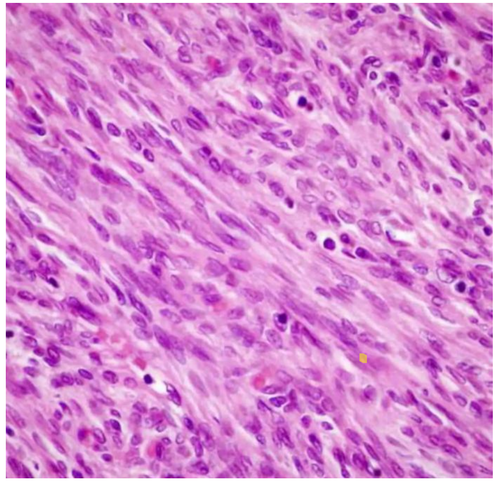
The atypical type A thymoma variant (in bold) is the only new addition to the "historic" list of thymoma subtypes.[1]

[a]Paucity versus abundance: any area of crowded immature T cells or moderate numbers of immature T cells in more than 10% of the investigated tumor are indicative of "abundance."

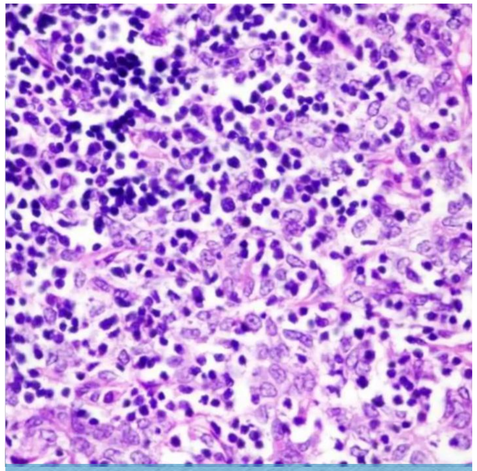
[b]Microscopic thymoma, sclerosing thymoma, lipofibroadenoma.

WHO, World Health Organization; MNT, micronodular thymoma with lymphoid stroma.

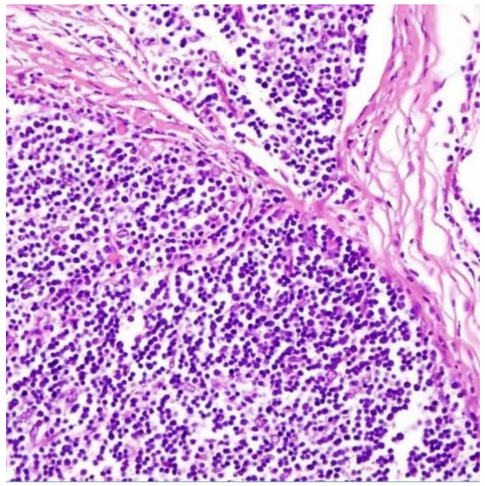
Marx A, Chan JKC, Coindre JM, Detterbeck F, Girard N, Harris NL, Jaffe ES, Kurrer MO, Marom EM, Moreira AL, Mukai K, Orazi A, Ströbel P. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. *J Thorac Oncol*. 2015;10(10):1383-1395.



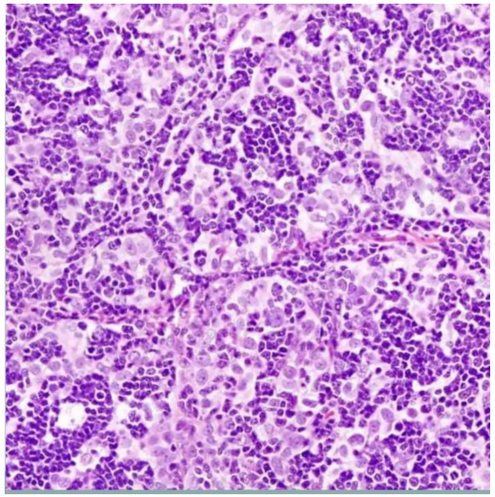
Type A



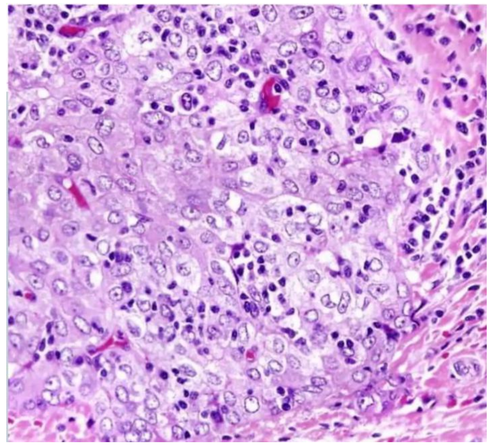
Type AB



Type B1



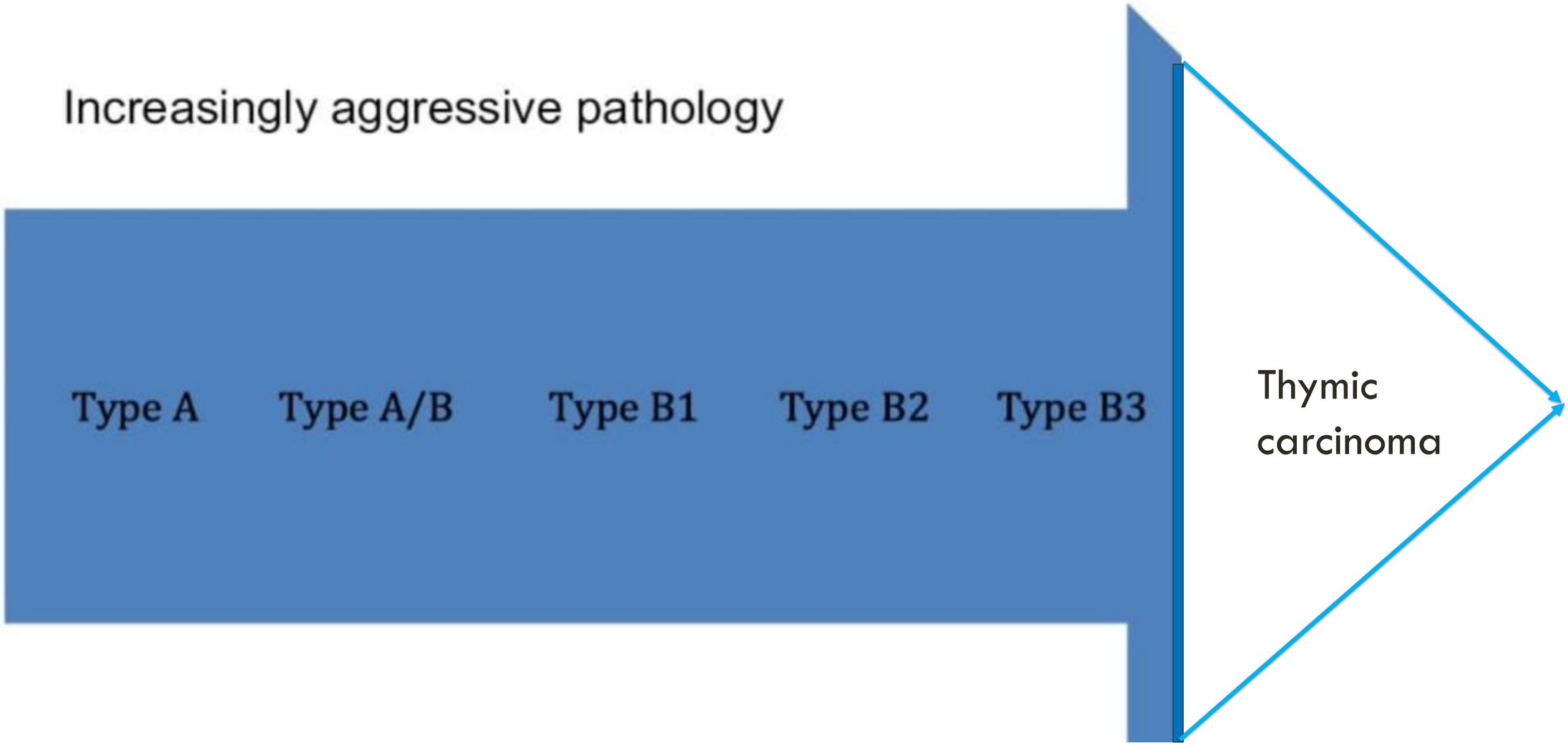
Type B2



Type B3

Typ
e

Classification and Subtypes



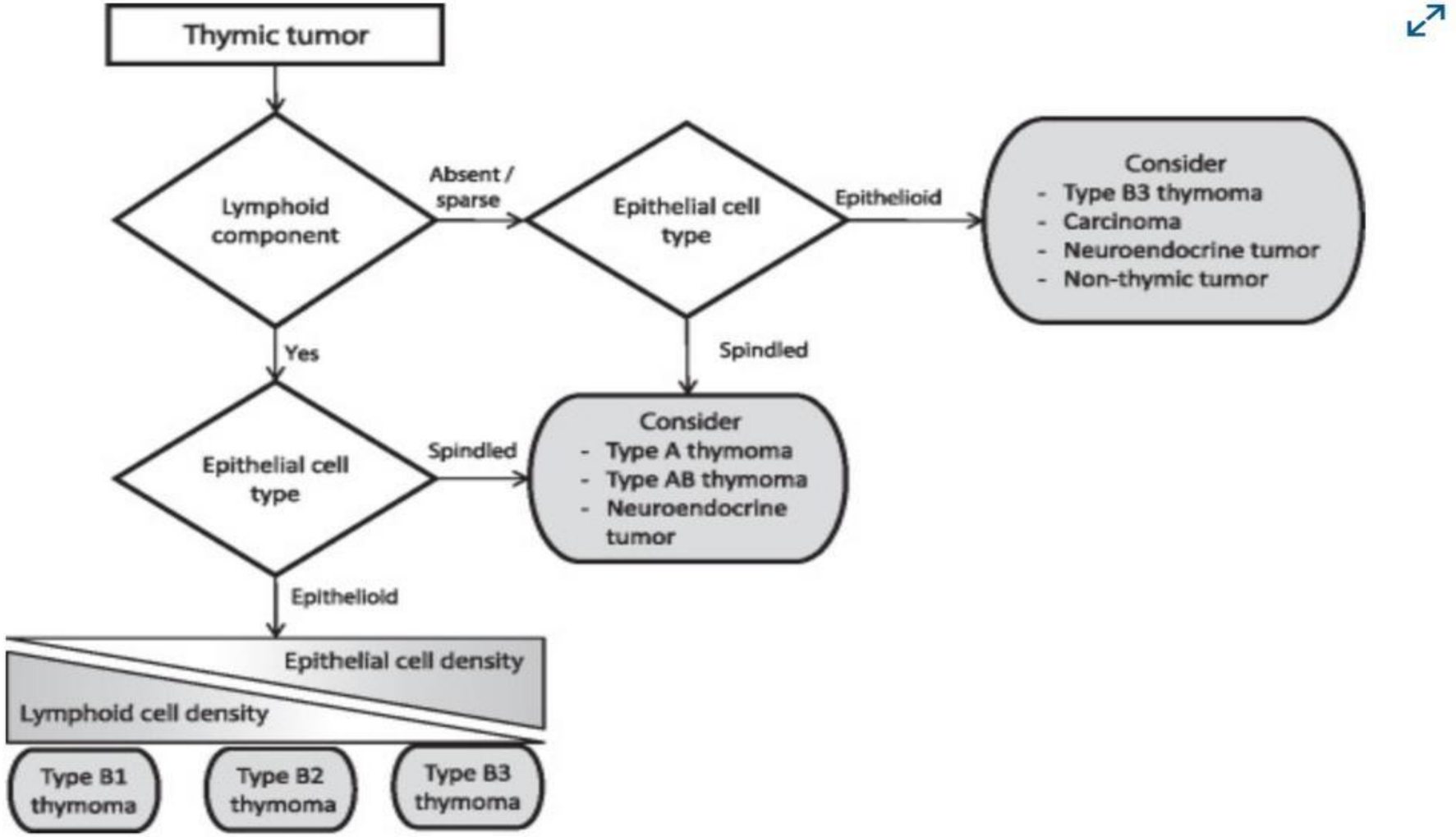


FIGURE 2 Flowchart for initial hematoxylin and eosin-based subtyping of thymoma; final subtyping must take all criteria into account as described in the

MASOKA STAGING

- The four-tiered Masaoka staging system was proposed in 1981 and a modification of this classification was suggested by Koga et al. in 1994.

Stage	Definition
I	Grossly and microscopically completely encapsulated tumor
IIa	Microscopic transcapsular invasion
b	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organ (i.e., pericardium, great vessel, or lung)
IVa	Pleural or pericardial metastases
b	Lymphogenous or hematogenous metastasis

Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. *Cancer*. 1981;48(11):2485-2492.

Table 4. Proposed Tumour–Node–Metastasis staging (International Association for the Study of Lung Cancer Prognostic Factors Committee- International Thymic Malignancy Interest Group) [30] and corresponding Masaoka-Koga stage

Stage		Descriptors
Tumour		
T1	T1a	Encapsulated or unencapsulated, with or without extension into the mediastinal fat
	T1b	Extension into the mediastinal pleura
T2		Direct invasion of the pericardium (partial or full-thickness)
T3		Direct invasion of the lung, the brachiocephalic vein, the superior vena cava, the chest wall, the phrenic nerve and/or hilar (extrapericardial) pulmonary vessels
T4		Direct invasion of the aorta, arch vessels, the main pulmonary artery, the myocardium, the trachea or the oesophagus
Node		
N0		N0 No nodal involvement
N1		N1 Anterior (perithymic) nodes (IASLC levels 1, 3a, 6 and/or supradiaphragmatic/inferior phrenics/
N2		
Metastasis		
M0		
M1	M1a	
	M1b	

Stage grouping		Corresponding Masaoka-Koga stage
I	T1N0M0	I, IIA, IIB, III
II	T2N0M0	III
IIIA	T3N0M0	III
IIIB	T4N0M0	III
IVA	T any N0,1 M0,1a	IVA, IVB
IVB	T any N0-2 M0-1b	IVB

TNM unified Masaoka stages I-III in stage I
Pericardial invasion – masaoka stage III ⊚ TNM II

MANAGEMENT OF THE THYMOMA

Surgery

- Complete (R0) surgical resection is the mainstay of therapy for stage I/II thymomas
- Complete thymectomy including the tumour, the residual thymus gland and perithymic fat is preferred
- Thymomectomy—leaving residual thymic tissue and perithymic fat behind—alone is an option in stage I tumours in non-myasthenic patients
- Minimally invasive surgery is an option for in the hands of appropriately trained thoracic surgeons

R0 Resectability rates – Stage I (100%), Stage II (85%)

- 5 year local recurrence rate - < 5% for stage I tumors, 10% for stage II.

- Lymphnode sampling is +/-

- Incidence of lymph node metastases, in thymoma is infrequent (2.8% to 5.6%)

- ITMIG group advocates locoregional lymphadenectomy concomitant with thymectomy (N1 nodes- ant mediastinal & ant cervical)

Masoka stage III/IVA-resectable

Complete resection is deemed to be achievable upfront, surgery represents the first step of the treatment

- ➢ Extended total thymectomy
  - ➢ all tissue anterior to the pericardium from the diaphragm to the neck and laterally from one phrenic nerve to the other
- En bloc resection of the thymoma and all involved structures is recommended for locally advanced disease (Stage III/IV). May include resection of lung, pericardium, great vessels, nerves, and pleural implants. Involvement of the innominate vein or superior vena cava may require: Partial resection with primary repair, or
- Complete resection with vascular reconstruction using a prosthetic graft.

Surgical clips are placed at close or uncertain margins to facilitate accurate postoperative radiotherapy planning.

Therapy for Thymic Epithelial Tumors: A Clinical Study of 1,320 Patients From Japan

Kazuya Kondo, MD, PhD, and Yasumasa Monden, MD, PhD

Department of Oncological and Regenerative Surgery, School of Medicine, University of Tokushima, Tokushima, Japan

Complete surgical resection (R0) is the strongest predictor of survival in thymic epithelial tumors.

•Survival is significantly better after complete resection than after incomplete resection or biopsy alone.

•Completeness of surgery outweighs stage and adjuvant therapy as a prognostic factor.

•Treatment should focus on maximizing R0 resection, including induction therapy when needed to improve resectability.

Kondo K, Monden Y. *Ann Thorac Surg*. 2003;76:878-884.

The role of postoperative radiotherapy for thymomas: a multicentric retrospective evaluation from three Italian centers and review of the literature

Alessio Bruni[1], Alessandro Stefani[2], Marco Perna[3], Paolo Borghetti[4], Niccolò Giaj Levra[5,6], Elisa D'Angelo[1], Alessandra D'Onofrio[4], Laura Rubino[1], Luca Frassinelli[1], Viola Salvestrini[3], Matteo Mariotti[3], Filippo Alongi[5,6], Alessandro Gonfiotti[7], Lorenzo Livi[3], Vieri Scotti[3]

Complete surgical resection (R0) remains the cornerstone of thymoma treatment; PORT is mainly guided by stage and margin status.

•Extent of resection is an independent prognostic factor and strongly influences survival.
•Most common recurrence after surgery – local recurrence

•Stage and margin status (R0/R1/R2) are the key determinants for considering postoperative radiotherapy.
•PORT is strongly recommended after incomplete resection (R1/R2), whereas its benefit after completely resected early-stage thymoma remains controversial.

•Type of Thymoma histology – an important prognostic factor

Bruni A et al. *J Thorac Dis*. 2019;11(Suppl 15):S1882-S1890

Role of PORT

- **Stage I**
  - If complete resection (R0): no postoperative radiotherapy
  - If incomplete resection (R1): postoperative radiotherapy(50–54 Gy)

Clinical Trial > Chin Med J (Engl). 1999 Feb;112(2):136-8.

Postoperative radiotherapy for stage I thymoma: a prospective randomized trial in 29 cases

H Zhang [1], N Lu, M Wang, X Gu, D Zhang

Stage I thymoma: Complete surgery alone is generally sufficient; PORT did not improve outcomes

Zhang H et al. *Chin Med J (Engl)*. 1999;112(2):136-138.

Outcome of Multimodality Treatment for 188 Cases of Type B3 Thymoma

Lanting Gao, MD, Changlu Wang, MD,* Wentao Fang, MD, PhD,† Jie Zhang, MD,‡ Changxing Lv, MD, PHD,* and Shen Fu, MD, PhD§*

Adjuvant radiotherapy is not usually recommended after a totally resected stage I thymoma. In this study, adjuvant radiotherapy had no impact on the OS, FFR, and TTP in multivariate analyses. Although the patients were stratified based on Masaoka stage, adjuvant radiotherapy improved the OS for stage III to IV patients in multivariate analyses.

Gao L, Wang C, Fang W, Zhang J, Lv C, Fu S. Outcome of multimodality treatment for 188 cases of type B3 thymoma. *J Thorac Oncol*. 2013;8(10):1329-1334. doi:10.1097/JTO.0b013e31829ceb50

Original Article

The role of postoperative radiotherapy for stage I/II/III thymic tumor—results of the ChART retrospective database

Qianwen Liu[1*], Zhitao Gu[2*], Fu Yang[3], Jianhua Fu[1], Yi Shen[4], Yucheng Wei[4], Lijie Tan[5], Peng Zhang[6], Yongtao Han[7], Chun Chen[8], Renquan Zhang[9], Yin Li[10], Keneng Chen[11], Hezhong Chen[12], Yongyu Liu[13], Youbing Cui[14], Yun Wang[15], Liewen Pang[16], Zhentao Yu[17], Xinming Zhou[18], Yangchun Liu[19], Jin Xiang[20], Yuan Liu[2], Wentao Fang[2]; Members of the Chinese Alliance for Research in Thymomas[a]

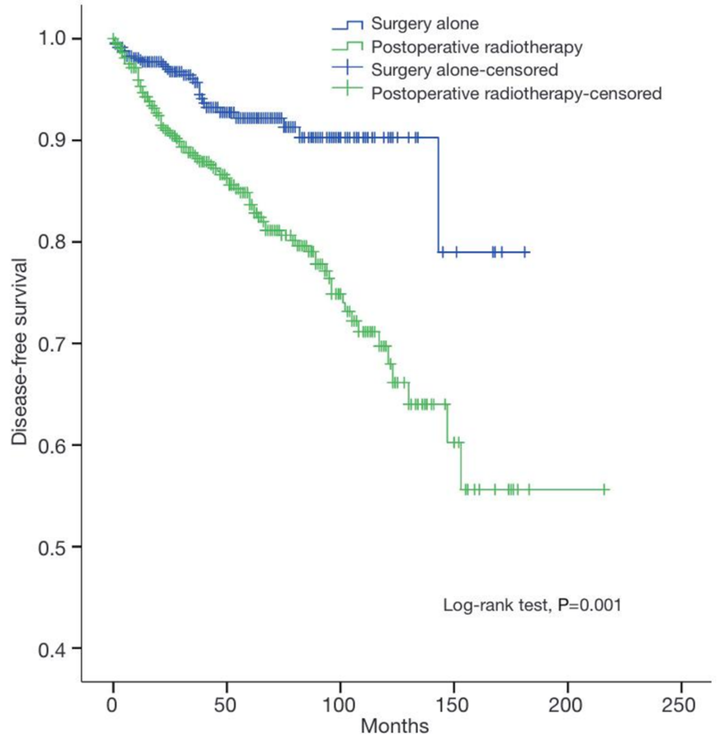


Figure 2 Kaplan-Meir disease-free survival curve of patients treated with surgery alone, and those treated with PORT. PORT decreased DFS of stage I/II/III thymic epithelial tumor (P<0.001).

Conclusions:

The current retrospective study indicates that PORT after incomplete resection could improve OS and DFS for patients with stage I to III thymic tumors. However for those after complete resection, PORT does not seem to have any survival benefit on the whole.

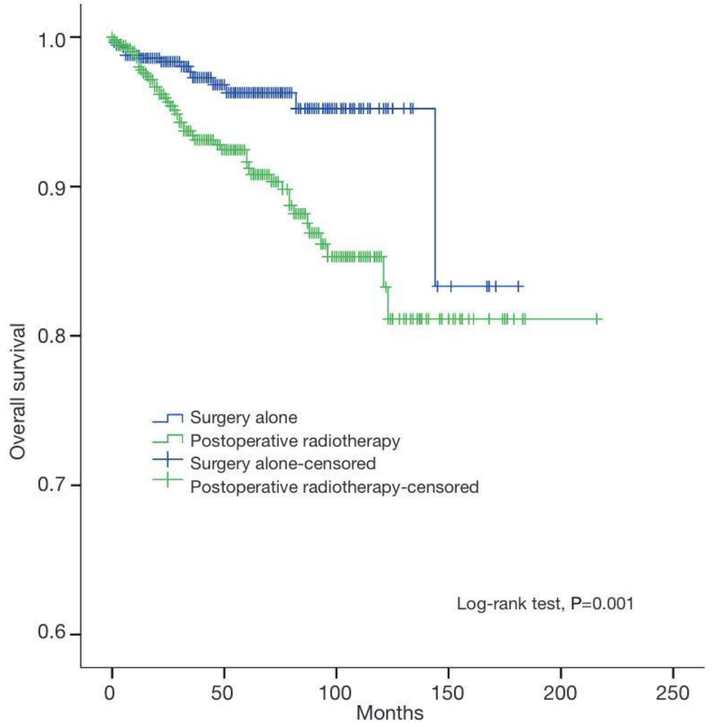
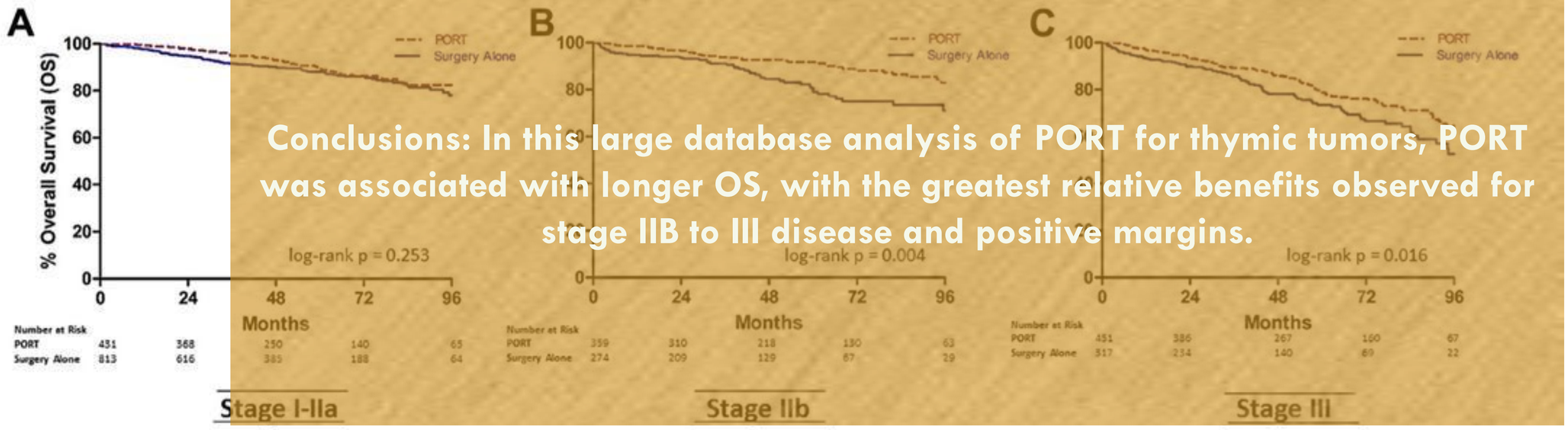


Figure 1 Kaplan-Meir overall survival curve of patients treated with surgery alone, and those treated with PORT. PORT decreased OS of stage I/II/III thymic epithelial tumor (P=0.001).

Liu Q et al. *J Thorac Dis*. 2016;8(4):687-695.

The Impact of Postoperative Radiotherapy for Thymoma and Thymic Carcinoma

Matthew W. Jackson, MD,[a,*] David A. Palma, MD, MsC, PhD,[b]
D. Ross Camidge, MD, PhD,[c] Bernard L. Jones, PhD,[a] Tyler P. Robin, MD, PhD,[a]
David J. Sher, MD, MPH,[d] Matthew Koshy, MD,[e] Brian D. Kavanagh, MD, MPH,[a]
Laurie E. Gaspar, MD, MBA,[a] Chad G. Rusthoven, MD[a]



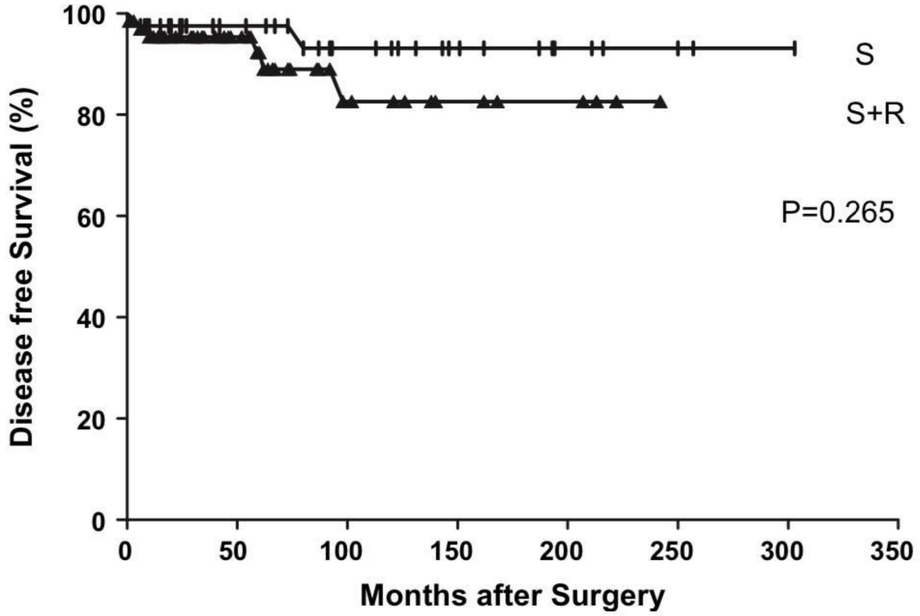
Conclusions: In this large database analysis of PORT for thymic tumors, PORT was associated with longer OS, with the greatest relative benefits observed for stage IIB to III disease and positive margins.

Jackson MW et al. *J Thorac Oncol.* 2017;12(4):734-744.

ROLE OF ADJUVANT RADIOTHERAPY FOR STAGE II THYMOMA AFTER COMPLETE TUMOR RESECTION

YI-DONG CHEN, M.D.,* QIN-FU FENG, M.D.,* HAI-ZHEN LU, M.D.,† YOU-SHENG MAO, M.D.,‡ ZONG-MEI ZHOU, M.D.,* GUANG-FEI OU, M.D.,* MEI WANG, M.D.,* JUN ZHAO, M.D.,‡ HONG-XING ZHANG, M.D.,* ZE-FEN XIAO, M.D.,* DONG-FU CHEN, M.D.,* JUN LIANG, M.D.,* YI-RUI ZHAI, M.D.,* LU-HUA WANG, M.D.,* AND JIE HE, M.D.‡

Departments of *Radiation Oncology, †Pathology, and ‡Thorax Surgery, Cancer Hospital/Institute, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China



CONCLUSIONS

In conclusion, pathologic type (type B3) thymoma was an independent prognostic factor for patients with stage II thymoma. The addition of adjuvant radiotherapy for patients with stage II thymoma who had undergone a complete tumor resection did not significantly alter survival and recurrence rates. However, this was a retrospective

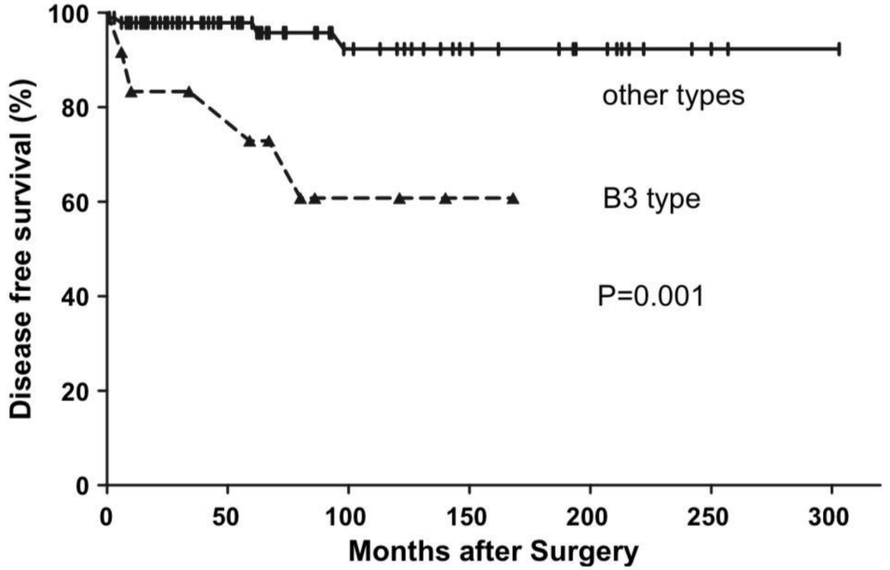


Fig. 3. Influence of histological type on DFS rates in stage II thymoma patients.

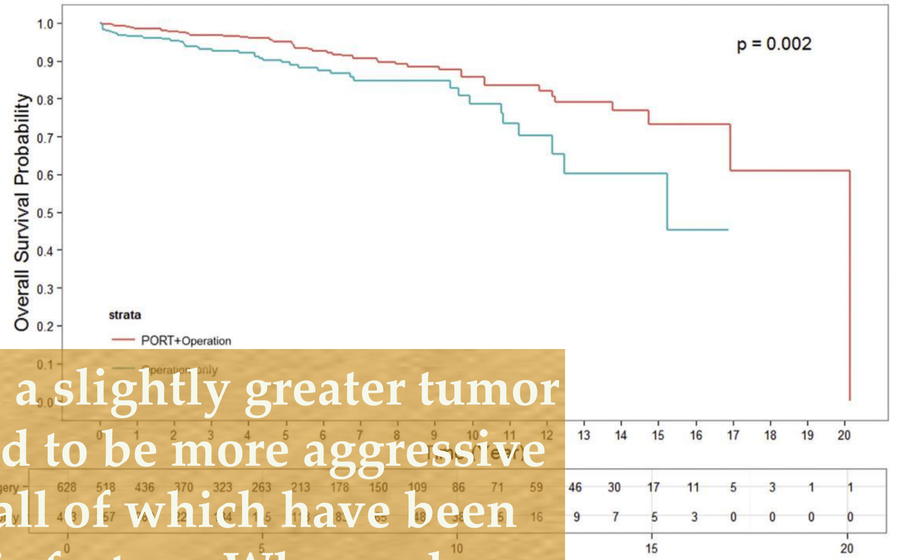
Chen YD et al. *Int J Radiat Oncol Biol Phys.* 2010;78(5):1400-1406.

ORIGINAL ARTICLE

Postoperative Radiation Therapy Is Associated with Longer Overall Survival in Completely Resected Stage II and III Thymoma—An Analysis of the International Thymic Malignancies Interest Group Retrospective Database

Andreas Rimner, MD,[a,*] Xiaopan Yao, PhD,[b] James Huang, MD,[c] Alberto Antonicelli, MD,[d] Usman Ahmad, MD,[c] Robert J. Korst, MD,[e] Frank Detterbeck, MD,[d] Daniel R. Gomez, MD[f]

- Conclusions: We observed an OS benefit with the use of PORT in completely resected stage II and III thymoma. In the absence of a randomized trial, this represents the most comprehensive analysis of individual patient data and strong evidence in favor of PORT in this patient population.



III combined.

In this data set we found that patients receiving PORT had a slightly greater tumor diameter, greater proportion of histologic subtypes deemed to be more aggressive (B1 to B3), and higher rate of paraneoplastic syndromes, all of which have been previously reported to be potentially adverse prognostic factors. When sub-groups with different histologic subtypes were analyzed, the patient group with stage III, WHO type B1, B2, or B3, thymomas had the greatest benefit with PORT.

Rimner A et al. *J Thorac Oncol*. 2016;11(10):1785-1792.

Table 2 Summary of National Guidelines Regarding Adjuvant Radiation in Resected Thymus Cancers

		Thymomas				Thymic Carcinomas			
		Stage I	Stage IIA	Stage IIB	Stage III-IV	Stage I	Stage IIA	Stage IIB	Stage III-IV
R0	NCCN[6]	No PORT	Consider	Consider	Consider	No PORT	Consider	Consider	Consider
	ESMO[7]	No PORT	Consider for B3 histology	Consider for B2-3 histology	PORT	PORT	PORT	PORT	PORT
	GOECP/SEOR[8]	No PORT	Consider for B3 histology	Consider for B2-3 histology	PORT	No PORT	Consider PORT	Consider PORT	PORT
	TYME[9]	No PORT	No PORT	Consider for B2-3 histology	PORT	No PORT	No PORT	Consider PORT	PORT
R1/2	NCCN[6]	PORT	PORT	PORT	PORT	PORT	PORT	PORT	PORT
	ESMO[7]	PORT	PORT	PORT	PORT	PORT	PORT	PORT	PORT
	GOECP/SEOR[8]	PORT	PORT	PORT	PORT	PORT	PORT	PORT	PORT
	TYME[9]	PORT	PORT	PORT	PORT	PORT	PORT	PORT	PORT

Adapted from Gomez DR, Komaki R. *J Thorac Oncol*. 2014;9(Suppl 2):S174-S179.

For Stage II

- The role of PORT is controversial
- Postoperative radiotherapy is not recommended after complete resection of stage II thymoma
- In the ITMIG data- base, cumulative incidence of mediastinal or extramediastinal recurrence was only 8% at 10 years
- Postoperative radiotherapy may be considered in case of aggressive histology (type B2, B3) or extensive transcapsular invasion (stage IIB)

However, this indication is not absolute as the evidence to support this approach is limited and the reported results are sometimes contradictory

able 1 **Summary of Studies Examining Adjuvant Radiation in Resected Thymus Cancers**

Author, Y	Level of Evidence	Study Design	Masaoka Stages	Radiation Details	Results	Interpretation
Zhang, 1999[15]	1	Prospective randomized study of 29 Masaoka stage I thymomas treated with and without PORT	Stage I (100%)	Linac based, 50 Gy for Type A and 60 Gy for Type B in 2 Gy per fraction using 3D technique	10-y LF 0% with or without PORT 10-y OS 92% without PORT versus 88% with PORT	PORT does not reduce LF for completely resected Masaoka stage I thymomas
Lim, 2016[16]	3	Metanalysis of 7 retrospective studies including 1724 Masaoka stage II-IV thymomas treated with and without PORT	Stage II (66%) Stage III (30%) Stage IV (4%)	Not reported	Masaoka stage II – no OS benefit with PORT (HR 1.45, 95% CI 0.83-2.55) Masaoka stage III-IV – OS benefit with PORT (HR 0.63, 95% CI 0.40-0.99)	PORT is associated with improved OS for completely resected Masaoka stage III-IV thymomas, but not Masaoka stage II thymomas. The benefit of PORT for Masaoka stage II thymomas remains controversial
Tateishi, 2021[17]	3	Metanalysis of 5 large database studies including 4746 Masaoka stage II-III thymomas treated with and without PORT	Not reported	Not reported	Masaoka stage II – OS benefit with PORT (HR 0.63, 95% CI 0.44-0.91) Masaoka stage III – OS benefit with PORT (HR 0.72, 95% CI 0.55-0.95)	PORT is associated with improved OS for completely resected Masaoka stage II-III thymomas. The benefit of PORT for Masaoka stage II thymomas remains controversial
Hamaji, 2017[18]	3	Metanalysis of 7 studies including 973 Masaoka stage II-III thymic carcinomas treated with and without PORT	Not reported	Not reported	RFS benefit with PORT (HR 0.54, 95% CI 0.41-0.71) and OS benefit with PORT (HR 0.66, 95% CI 0.54-0.80)	PORT is associated with improved RFS and OS for completely resected Masaoka stage II-III thymic carcinomas
Curran, 1988[19]	4	Retrospective review of 103 Masaoka stage I-IV thymomas treated with and without PORT	Stage I (42%) Stage II (20%) Stage III (35%) Stage IV (3%)	Cobalt-60 source, 32-60 Gy with a median dose of 50 Gy in 1.8-2 Gy per fraction using 2D technique	5-y LF R0 Masaoka stage I – 0% with and without PORT R0 Masaoka stage II-III – 50% without PORT and 0% with PORT R1-2 Masaoka stage I – 25% without PORT and 5% with PORT R1-2 Masaoka stage II-III – 80% without PORT and 20% with PORT	PORT improves LC for completely resected Masaoka stage II-III thymomas and incompletely resected thymomas of all stages. There is no benefit with PORT for completely resected Masaoka stage I thymomas

Table 1 (*continued*)

Author, Y	Level of Evidence	Study Design	Masaoka Stages	Radiation Details	Results	Interpretation
Rimner, 2016[20]	4	ITMIG retrospective review of 1263 Masaoka stage II-III thymomas treated with and without PORT	Stage II (69%) Stage III (31%)	Not reported	10-y OS Masaoka stage II – 83% without PORT and 91% with PORT Masaoka stage III – 64% without PORT and 79% with PORT	PORT is associated with improved OS for completely resected Masaoka stage II-III thymomas. The benefit of PORT for Masaoka stage II thymomas remains controversial
Jackson, 2017[21]	4	NCDB analysis of 4056 Masaoka stage I-IV thymomas and thymic carcinomas treated with and without PORT	Stage I-IIA (39%) Stage IIB (18%) Stage III (30%) Stage IV (13%)	Not reported	OS benefit with PORT (HR 0.72, 95% CI 0.59-0.87) Greatest benefit for stage III and positive margins No benefit for stage I-IIA	PORT is associated with improved OS for completely resected Masaoka stage IIB-IV thymus cancers but not Masaoka stage I-IIA thymus cancers
Mangi, 2002[22]	4	Retrospective review of 35 Masaoka stage II thymomas treated with and without PORT	Stage II (100%)	Linac based, 30-61 Gy with a median dose of 45 Gy in 1.8-2 Gy per fraction using 3D technique	10-y OS was 100% without PORT and 84% with PORT	PORT may not benefit completely resected Masaoka stage II thymomas. Likely underpowered to detect any difference
Chen, 2010[23]	4	Retrospective review of 107 Masaoka stage II thymomas treated with and without PORT	Stage II (100%)	Linac based, 22-60 Gy with a median dose of 60 Gy in 2 Gy per fraction using 3D technique	10-y LF 5% without PORT and 10% with PORT (ns) and 10-y RFS 93% without PORT and 83% with PORT	PORT may not benefit completely resected Masaoka stage II thymomas. Possible selection bias accounting for discrepancy
Omasa, 2015[28]	4	Retrospective review of 2835 Masaoka stage II-III thymomas and thymic carcinomas treated with and without PORT	Stage II (71%) Stage III (29%)	Not reported	No RFS benefit with PORT for Masaoka stage II-III thymomas (HR 0.94, 95% CI 0.51-1.75) RFS benefit with PORT for Masaoka stage II-III thymic carcinomas (HR 0.48, 95% CI 0.30-0.78)	PORT is associated with improved RFS for Masaoka stage II-III thymic carcinomas, but not Masaoka stage II-III thymomas
Forquer, 2009[29]	4	SEER analysis of 901 Masaoka stage I-III thymomas and thymic carcinomas treated with and without PORT	Stage I (31%) Stage II-III (69%)	Not reported	Masaoka stage I – 5-y OS was 87% without PORT and 81% with PORT Masaoka stage II-III – 5-y OS was 66% without PORT and 76% with PORT	PORT is associated with improved OS for completely resected Masaoka stage II-III thymomas and thymic carcinomas, but not Masaoka stage I

Current Trial Report

RADIORYTHMIC: Phase III, Opened, Randomized Study of Postoperative Radiotherapy Versus Surveillance in Stage IIb/III of Masaoka Koga Thymoma after Complete Surgical Resection

C. Basse [1 #], A. Botticella [2 #], T.J. Molina [3], P.E. Falcoz [4], Y. Oulkhouir [5], M. Kerjouan [6], E. Pichon [7], V. Westeel [8], L. Thiberville [9], X. Quantin [10], C. Clément-Duchêne [11], J. Khalifa [12], F. Le Tinier [13], M. Ginoux [14], F. Thillays [15], P. Mordant [16], B. Besse [17], P.A. Thomas [18 ##], C. Le Péchoux [19 ##], Nicolas Girard [20 ##]

Show more

https://doi.org/10.1016/j.cllc.2021.01.020

Ongoing trial –Final results awaited in 2028

Basse C et al. *Clin Lung Cancer*. 2021;22(5):469-472

ZHANG ET AL. (THYPORT TRIAL)

- **Study type:** Multi-institutional randomized Phase III trial
- **Population:** Completely resected **Masaoka stage II–III WHO B-type thymoma**
- **Arms:**
  - Surgery alone
  - Surgery + conformal postoperative radiotherapy (PORT)
- **Primary objective:** Determine whether PORT improves disease control and survival after R0 resection.

An Open-label, Multi-center, Randomized Phase III Study of Adjuvant Radiotherapy for Stage II/III Thymoma After Complete Resection

Dr. Kailiang (K.L.) Wu

- Open-label, multicenter, randomized Phase III trial.
- Population: Completely resected **Stage II–III thymoma**.
- Comparison:
  - Observation/surveillance
  - Postoperative radiotherapy (PORT)
- Planned enrollment: ~238 patients.
- Objective: Determine whether PORT improves survival and recurrence outcomes after R0 resection.

This is one of the most important ongoing studies addressing the long-standing controversy regarding PORT in stage II/III thymoma.

Li X et al. An Open-label, Multi-center, Randomized Phase III Study of Adjuvant Radiotherapy for Stage II/III Thymoma After Complete Resection. ClinicalTrials.gov Identifier: NCT02633553

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v40–v55, 2015
doi:10.1093/annonc/mdv277

Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

N. Girard[1], E. Ruffini[2], A. Marx[3], C. Faivre-Finn[4] & S. Peters[5], on behalf of the ESMO Guidelines Committee*

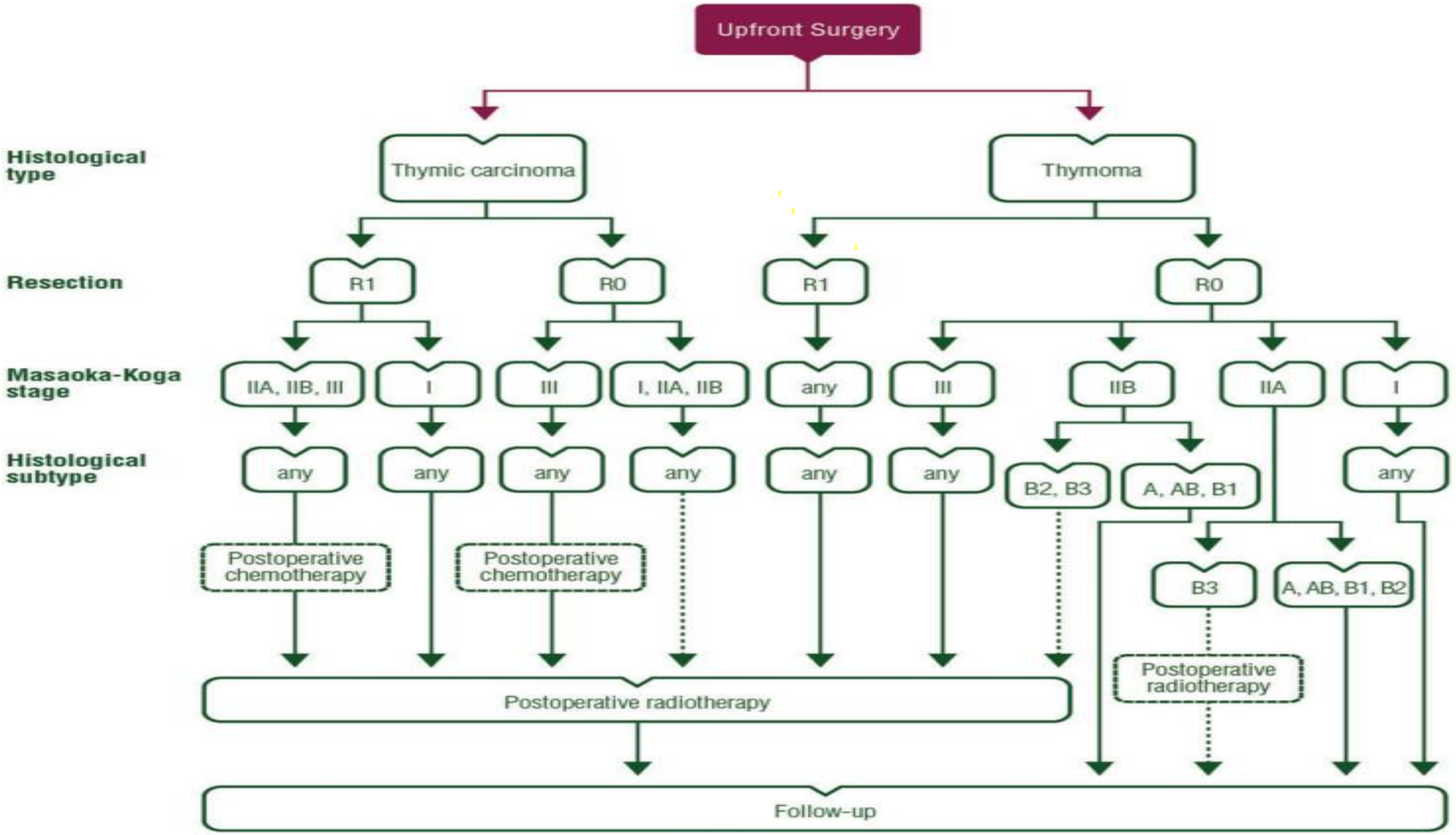
[1]Department of Respiratory Medicine, Expert Centre for Thymic Malignancies, Reference Centre for Orphan Pulmonary Diseases, Hôpital Louis Pradel, Hospices Civils de Lyon, Lyon, France; [2]Department of Thoracic Surgery, University of Torino, Turin, Italy; [3]Institute of Pathology, University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany; [4]Institute of Cancer Sciences, The University of Manchester, Manchester Academic Health Science Centre, The Christie NHS Foundation Trust, Manchester, UK; [5]Department of Medical Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

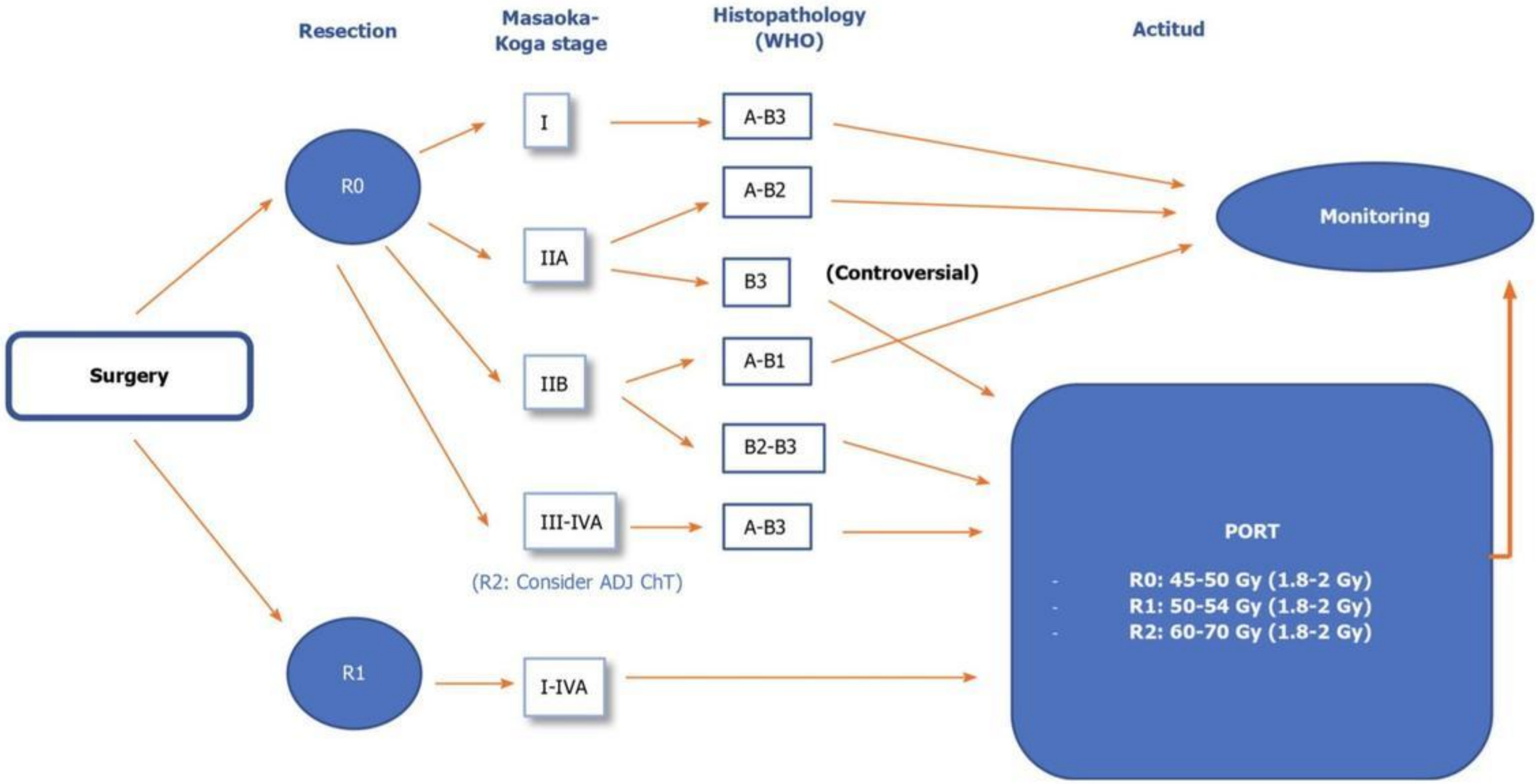
GUIDELINES

GOECP/SEOR radiotherapy guidelines for thymic epithelial tumours

Mikel Rico, Sonia Flamarique, Cristina Casares, Tamara García, Miriam López, Maribel Martínez, Javier Serrano, Manuel Blanco, Raúl Hernanz, Lourdes de Ingunza-Barón, Francisco José Marcos, Felipe Couñago

ESMO GUIDELINES- FOR RESECTABLE THYMIC TUMORS





Adapted from ESMO/RYTHMIC guidelines.

LOCALLY ADVANCED THYMOMAS

Thymus cancers may be unresectable for a variety of reasons: A) locally unresectable, B) medically inoperable, or C) distant metastases

The preferred management for locally unresectable thymus cancers is induction therapy (Induction chemotherapy / Induction chemoradiotherapy) followed by curative intent resection if feasible followed by PORT

. If disease remains unresectable after induction therapy, the next best option is definitive non-surgical treatment.

INDUCTION CHEMOTHERAPY - EVIDENCE

Author, Y	Level of Evidence	Study Design	Masaoka Stages	Radiation Details	Results	Interpretation
Lucchi, 2001[31]	2	Prospective study of 7 unresectable thymic carcinomas treated with induction cisplatin, epirubicin, and etoposide followed by surgery and PORT	Stage III (100%)	Linac based, 45 Gy for complete resection and 60 Gy for incomplete resection in 1.8-2 Gy per fraction using 3D technique	OR 100% and CR 14% All patients underwent surgery R0 57% and R2 43% Median OS not reached after a median follow up of 85 mo	Induction chemo is able to convert unresectable thymic carcinomas into resectable disease effectively with long term survival in patients able to complete trimodality therapy
Venuta, 2003[32]	2	Prospective study of 15 unresectable thymomas and thymic carcinomas treated with induction cisplatin, epirubicin, and etoposide followed by surgery and PORT	Stage III (53%) Stage IV (47%)	Not reported	OR 66% All patients underwent surgery Thymoma – R0 91%, LF 20%, 10-y OS 88% Thymic carcinoma – R0 82%, LF 27%, 10-y OS 56%	Induction chemo is able to convert unresectable thymomas and thymic carcinomas into resectable disease effectively with long term survival in patients able to complete trimodality therapy
Kim, 2004[33]	2	Prospective study of 22 unresectable thymomas treated with induction cyclophosphamide, doxorubicin, cisplatin, and prednisone followed by surgery and PORT and consolidative chemo	Stage III (50%) Stage IVA (45%) Stage IVB (5%)	Linac based, 50 Gy for complete resection and 60 Gy for incomplete resection in 2 Gy per fraction using 3D technique	OR 77% and CR 14% All but 1 patient underwent surgery R0 76% and R2 24% 5-y OS 95%, 7-y OS 77% Grade 3+ toxicity 41% (heme, GI)	Induction chemo is able to convert unresectable thymic carcinomas into resectable disease effectively with long term survival in patients able to complete trimodality therapy
Kunitoh, 2010[34]	2	Prospective study of 23 unresectable thymomas treated with induction cisplatin, vincristine, doxorubicin, and etoposide followed by surgery and PORT	Stage III (100%)	Linac based, 48 Gy for complete resection and 60 Gy for incomplete resection and unresectable disease in 2 Gy per fraction using 3D technique	OR 62% and CR 0% 13/23 patients underwent surgery R0 69% and R2 31% 5-y PFS 43%, 8-y OS 69%	Induction chemo is able to convert unresectable thymic carcinomas into resectable disease effectively with long term survival in patients able to complete trimodality therapy

Yom SS, Liu AK. Role of Radiation Therapy in the Management of Thymic Malignancies. Hematol Oncol Clin North Am. 2015;29(3):471–482. Adapted from published prospective induction therapy studies (Lucchi 2001, Venuta 2003, Kim 2004, Kunitoh 2010).

INDUCTION CHEMOTHERAPY

- Standard treatment for unresectable locally advanced thymic epithelial tumors (TETs) including advanced thymoma and thymic carcinoma. Goals: Downstage tumor
- Improve resectability and achieve R0 resection
- Control micrometastatic disease
- Improve long-term outcomes
- Cisplatin-based combination chemotherapy is recommended. CAP/PAC: Cisplatin + Doxorubicin + Cyclophosphamide (preferred for thymoma)
- EP: Cisplatin + Etoposide (commonly used for thymic carcinoma)
- ADOC: Cisplatin + Doxorubicin + Vincristine + Cyclophosphamide

Table 6. Selected chemotherapy regimens for advanced thymic epithelial tumours assessed in phase II trials (adapted from [60] with permission of Informa Healthcare)

Regimen	Agents	Doses
ADOC	Doxorubicin	40 mg/m^2/3 weeks
	Cisplatin	50 mg/m^2/3 weeks
	Vincristine	0.6 mg/m^2/3 weeks
	Cyclophosphamide	700 mg/m^2/3 weeks
CAP	Cisplatin	50 mg/m^2/3 weeks
	Doxorubicin	50 mg/m^2/3 weeks
	Cyclophosphamide	500 mg/m^2/3 weeks
PE	Cisplatin	60 mg/m^2/3 weeks
	Etoposide	120 mg/m^2 × 3 days/3 weeks
VIP	Etoposide	75 mg/m^2 × 4 days/3 weeks
	Ifosfamide	1.2 g/m^2 × 4 days/3 weeks
	Cisplatin	20 mg/m^2 × 4 days/3 weeks
CODE	Cisplatin	25 mg/m^2/1 week
	Vincristin	1 mg/m^2/2 weeks
	Doxorubicin	40 mg/m^2/2 weeks
	Etoposide	80 mg/m^2 × 3 days/2 weeks
Carbo-Px	Carboplatin	AUC 5–6/3 weeks
	Paclitaxel	200–225 mg/m^2/3 weeks
CAP-GEM	Capecitabine	650 mg/m^2 b.i.d. 14 days/3 weeks
	Gemcitabine	1000 mg/m^2 × 2 days/3 weeks

- 2–4 cycles are usually administered before reassessment.
- Response evaluation with CT/MRI after induction therapy to determine resectability.
- If complete resection (R0) becomes feasible: Proceed to surgery
- Follow with postoperative radiotherapy as indicated

ROLE OF INDUCTION CHEMORADIOTHERAPY

- Induction chemoradiotherapy may be considered in patients unable to tolerate anthracycline-based regimens.
- Radiotherapy: 45 Gy in 30 fractions (1.5 Gy BID) using 3D conformal RT
- . Cisplatin-etoposide alone: ORR 40%.
- Addition of radiotherapy: ORR increased to 100%. Improved outcomes with chemoradiotherapy: Median PFS: 52 vs 31 months
- Median OS: 171 vs 41 months

Conclusion: Cisplatin-etoposide–based chemoradiotherapy is an effective alternative induction strategy for patients unsuitable for anthracycline-based chemotherapy.

INDUCTION CHEMORT - EVIDENCE

Author, Y	Level of Evidence	Study Design	Masaoka Stages	Radiation Details	Results	Interpretation
Tamiya, 2014[35]	2	Prospective study of 11 patients with unresectable thymoma treated with induction cisplatin and etoposide ± radiation followed by surgery	Stage III (27%) Stage IVA (55%) Stage IVB (18%)	Linac based, 45 Gy in 1.5 Gy per fraction twice daily using 3D technique	Chemo alone – OR 40%, median PFS 31 mo, median OS 41 mo Chemoradiation – OR 100%, median PFS 52 mo, median OS 171 mo All underwent surgery	Induction cisplatin and etoposide appears to be inferior to historical controls of anthracycline-based induction chemo. In patients unable to tolerate anthracycline-based induction chemo, adding radiation to induction cisplatin and etoposide improves outcomes
Wright, 2008[36]	2	Retrospective review of 10 unresectable thymomas treated with induction chemoradiation using cisplatin and etoposide followed by surgery	Stage III (70%) Stage IVA (30%)	Linac based, 40-45 Gy in 1.8-2 Gy per fraction using 3D technique	OR 40% and CR 0% All patients underwent surgery R0 80% and R1 20% 5-y OS 70%	Induction chemoradiation using cisplatin and etoposide is safe and effective. Useful for patients who are unable to undergo anthracycline-based induction chemo
Korst, 2014[37]	2	Prospective study of 22 unresectable thymomas and thymic carcinomas treated with induction chemoradiation using cisplatin and etoposide	Stage III (71%) Stage IV (29%)	Linac based, 45 Gy in 1.8 Gy per fraction using 3D or IMRT technique	OR 48% and CR 0% All patients underwent surgery R0 77%, R1 14%, R2 5% 5-y PFS 83% 5-y OS 71%	Induction chemoradiation using cisplatin and etoposide is safe and effective. Useful for patients who are unable to undergo anthracycline-based induction chemo

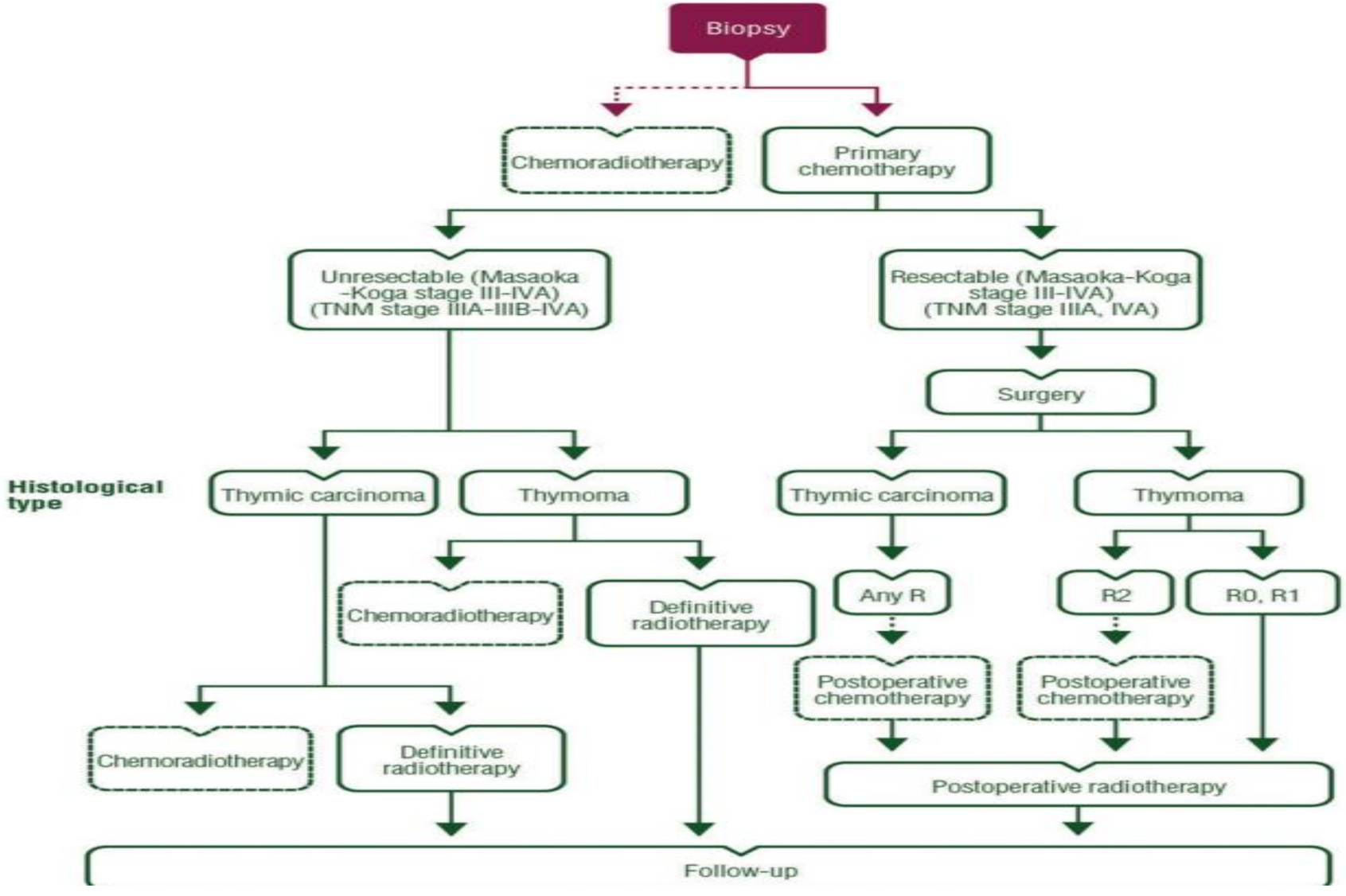
Grade 3+ Toxicity 41% (Name, CI)

Yom SS, Liu AK. Role of Radiation Therapy in the Management of Thymic Malignancies. Hematol Oncol Clin North Am. 2015;29(3):471–482. Adapted from published prospective induction therapy studies (Lucchi 2001, Venuta 2003, Kim 2004, Kunitoh 2010).

MEDICALLY INOPERABLE THYMOMAS-EVIDENCE

Author, Y	Level of Evidence	Study Design	Masaoka Stages	Radiation Details	Results	Interpretation
Loehrer, 1997[38]	2	Prospective study of 23 unresectable thymomas treated with definitive chemoradiation using cisplatin, doxorubicin, and cyclophosphamide	Stage III (96%) Stage IVA (4%)	Mega-voltage source, 54 Gy in 1.8 Gy per fraction using 2D technique	OR 70% and CR 22% 5-y PFS 67% 5-y OS 70% Grade 3+ toxicity 61% (heme, GI)	Definitive chemoradiation for unresectable thymomas is a safe and effective option for patients with unresectable disease after induction therapy
Fan, 2020[39]	2	Prospective study of 56 unresectable thymomas and thymic carcinomas treated with definitive chemoradiation using cisplatin and etoposide	Stage III (14%) Stage IVA (11%) Stage IVB (75%)	Linac based, 60 Gy in 2 Gy per fraction using IMRT technique	OR 86% and CR 0% 5-y PFS 30% 5-y OS 56% Grade 3+ toxicity 43% (heme, GI)	Definitive chemoradiation for unresectable thymomas and thymic carcinomas is a safe and effective option for patients with unresectable disease after induction therapy

ESMO GUIDELINES- LOCALLY ADVANCED THYMOMAS



RT DOSING

Resection Status	ESMO	NCCN	GEOSP	Bruni et al. (2020)
R0 (Complete resection)	45–50 Gy	45–50 Gy	45-50 Gy	45–50 Gy
R1 (Microscopic residual disease)	50–54 Gy	54 Gy	50 -54 Gy	50–54 Gy
R2 (Gross residual disease)	60–66 Gy	60–70 Gy	60-70 Gy	60–70 Gy
Definitive RT (Unresectable disease)	60–66 Gy	60–70 Gy	60-66 Gy	60–70 Gy

Gomez DR, Komaki R, Yu JB, et al. *Radiation Therapy Definitions and Reporting Guidelines for Thymic Malignancies. J Thorac Oncol.* 2011;6(Suppl 3):S1743–S1748. (ITMIG/RTOG Consensus Guideline)

RT DOSING- INDUCTION RT

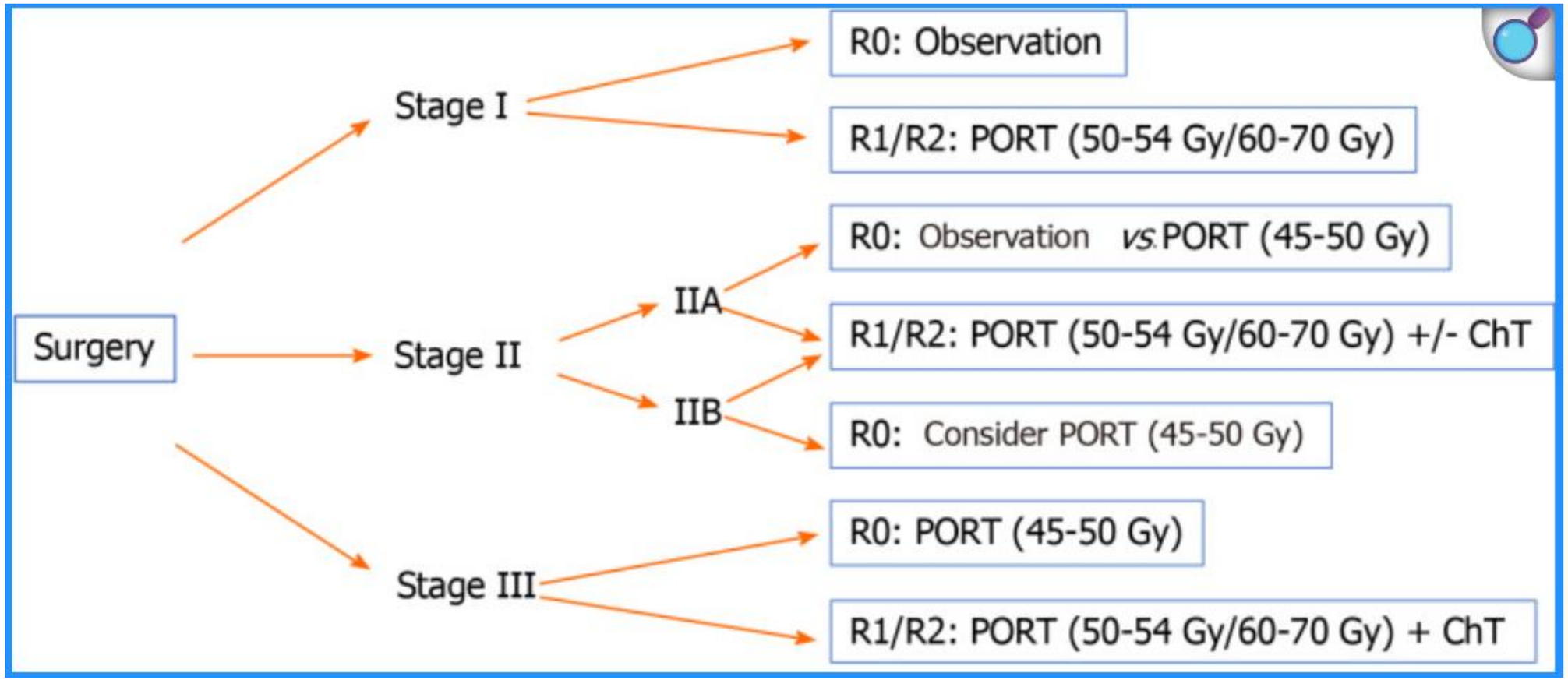
- Recommended induction RT doses are consistent across major guidelines (NCCN, ESMO, ITMIG).
- Standard dose: 45–50 Gy in 1.8–2 Gy per fraction. According to ITMIG: CTV = Gross tumor volume (GTV) + 5–10 mm margin.
- PTV = CTV + additional 5–10 mm margin (with daily kV image guidance).

Target volume focuses on the gross tumor and areas of microscopic extension. Elective nodal irradiation is generally not recommended.

Elective treatment of mediastinal or nodal regions may be considered in selected patients with a perceived high risk of regional recurrence.

Modern planning techniques (IMRT/VMAT with IGRT) are preferred to minimize cardiac and pulmonary toxicity.

GOECP/SEOR RADIOTHERAPY GUIDELINES FOR THYMIC EPITHELIAL TUMOURS



RT PLANNING

Patient Positioning & Simulation

- Supine position with neck slightly extended
- Arms above head whenever feasible
- Allows optimal coplanar and non-coplanar beam arrangements
- CT simulation with 3–5 mm slice thickness
- IV contrast recommended to improve target/OAR delineation
- 4D-CT simulation preferred to assess respiratory motion
- If 4D-CT unavailable:
  - Slow CT acquisition through entire respiratory cycle, or
  - Inspiratory and expiratory CT scans
- FDG-PET/CT fusion may aid target delineation

TMIG/RTOG Consensus Contouring Guideline

RT TECHNIQUES

Rimner et al. / Modern adjuvant RT series

- In Stage III thymoma after R0 resection, modern RT techniques (3D-CRT/IMRT) improved overall survival compared with surgery alone.
- Conventional RT was associated with more cardiac and pulmonary complications.

IMRT vs 3DCRT

- Superior target conformity compared with 3D-CRT.
- Reduces dose to lungs, heart, esophagus, and spinal cord.
- Better sparing of normal tissues allows safer dose escalation for definitive RT.

VMAT VS IMRT

- VMAT achieves dosimetry comparable to or better than IMRT while maintaining target coverage.

- Particularly useful for large mediastinal targets with complex geometry.

- Most evidence is dosimetric and retrospective; no randomized trials specifically comparing VMAT versus IMRT in thymoma

PROTON THERAPY

Physical Advantage

- Presence of **Bragg peak.**
- Virtually no exit dose.
- Markedly reduces integral dose to OARS

Zhu et al., 2018

- Proton therapy achieved superior sparing of the heart, lungs, and esophagus compared with IMRT for thymic malignancies.

Vogel et al., 2016 (Prospective Proton Study)

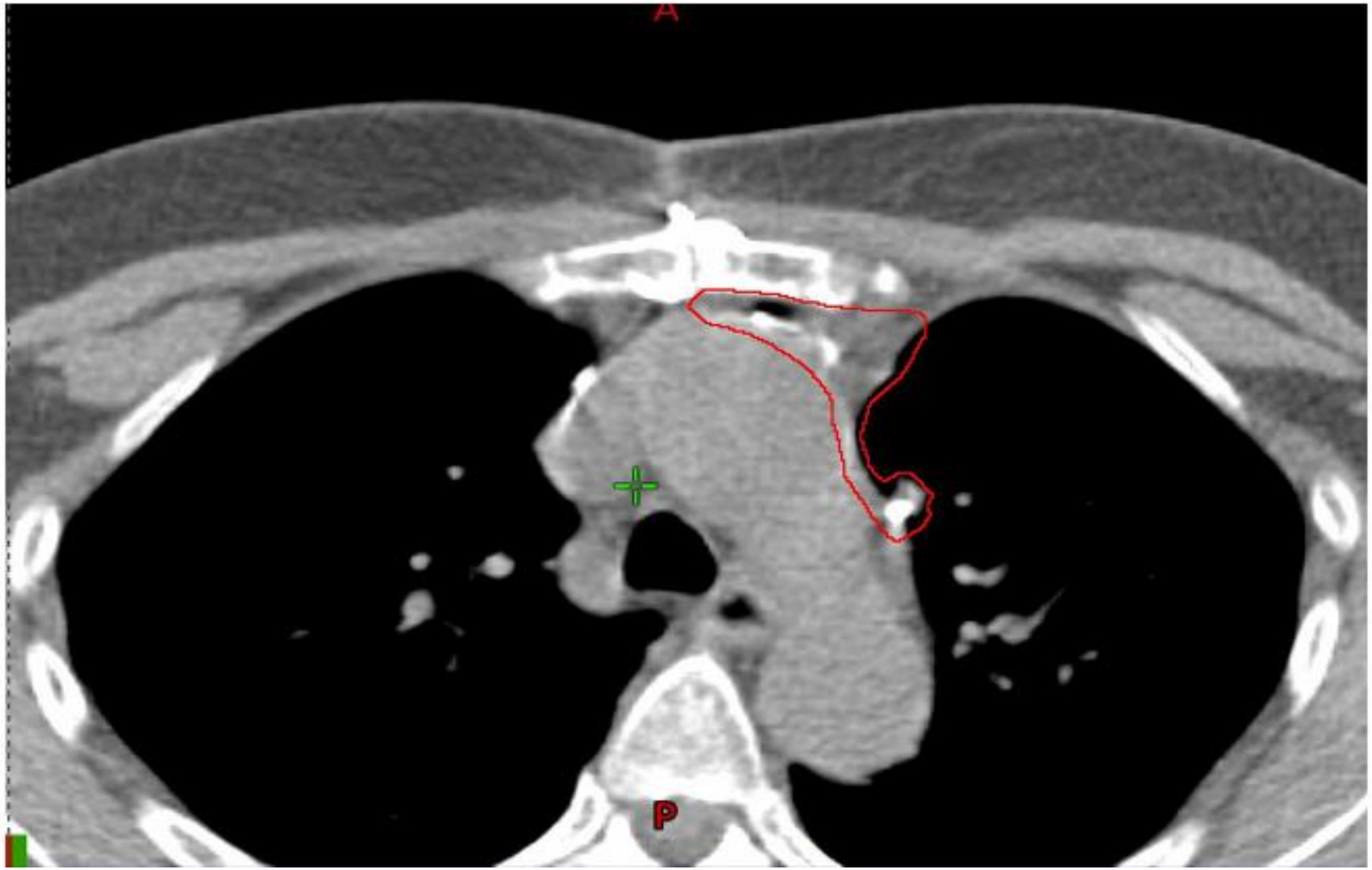
- 27 patients with thymoma/thymic carcinoma.
- Median dose: 61.2 Gy(RBE).
- 100% local control.
- No Grade ≥3 toxicity.
- Acute Grade 2 toxicities:
  - Dermatitis 37%
  - Fatigue 11%
  - Esophagitis 7%
  - Pneumonitis 4%

POSTOPERATIVE CTV DELINEATION

- Use both **preoperative and postoperative imaging**
- Include:
  - Tumor bed
  - Preoperative extent of disease
  - Surgical clips
  - Areas at high risk for microscopic residual disease
- Routine coverage of the **entire mediastinum is no longer recommended**

RECOMMENDED MARGINS

Margin	Recommendation
GTV → CTV	0.5–1.0 cm
CTV → PTV (No 4DCT, No daily IGRT)	1.0–1.5 cm
ITV → PTV (4DCT, No daily IGRT)	0.5–1.0 cm
ITV → PTV (4DCT + Daily IGRT/kV imaging)	0.5 cm



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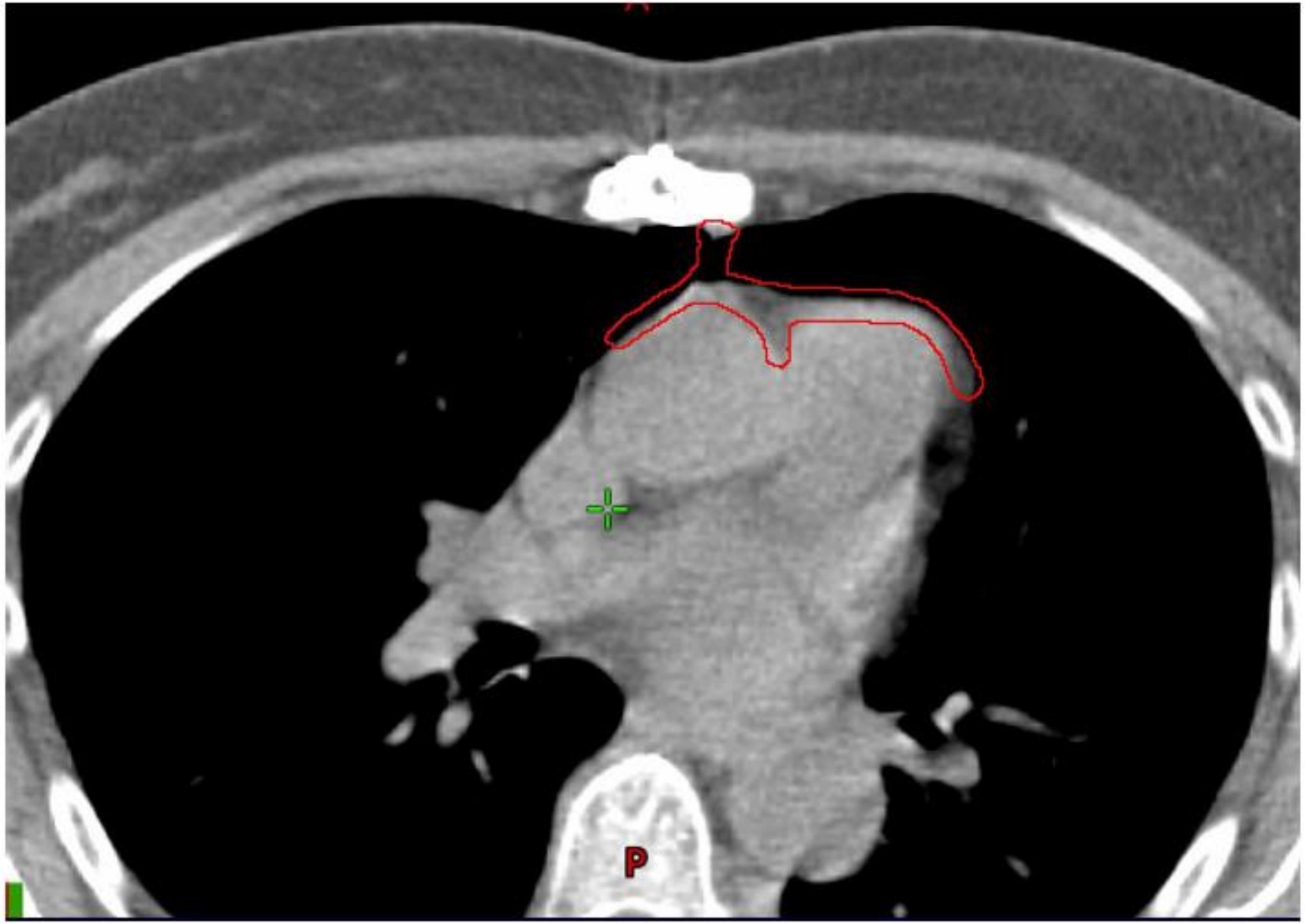

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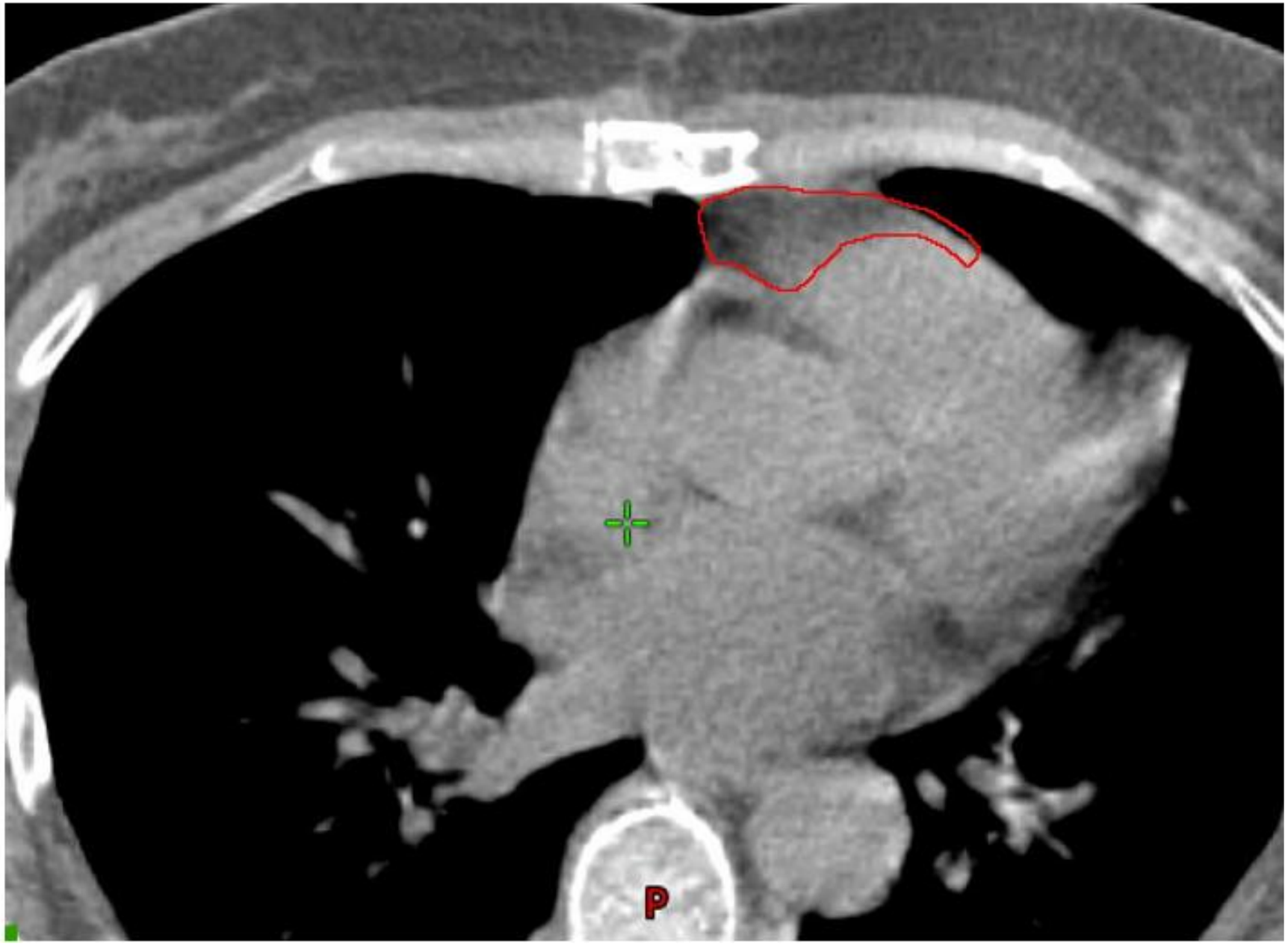
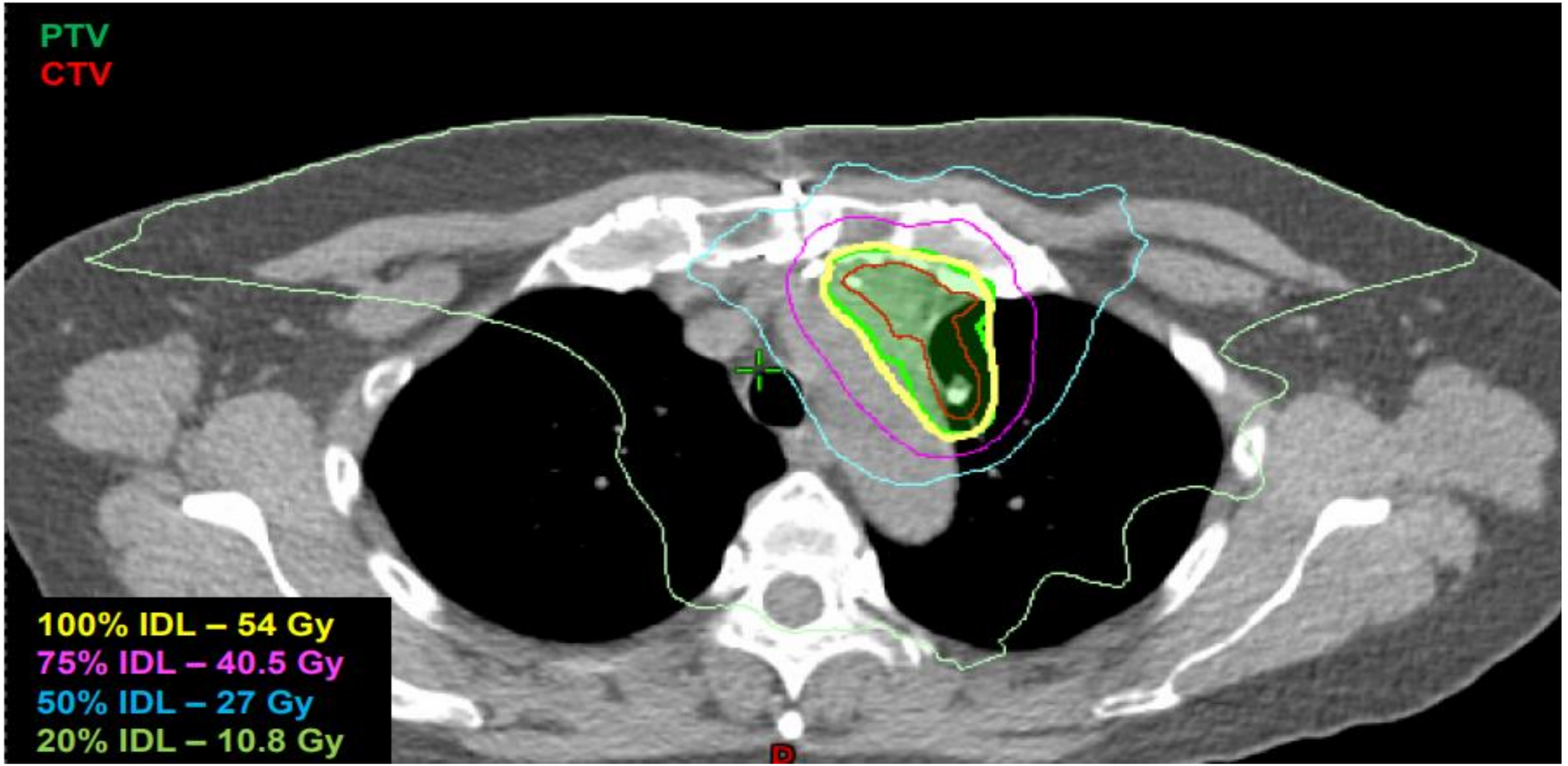


Courtesy - ARRO

PLAN DISTRIBUTION



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DOSE CONSTRAINTS

Spinal cord	Dmax < 45 Gy		
	Dmax < 40 Gy if 3 Gy/fraction		
Lung (total lung minus GTV; solely total lung for postoperative cases without GTV)	Mean dose < 20 Gy		
	Mean dose < 8 Gy if post-pneumonectomy		
	RT alone	RT with chemotherapy	Neoadjuvant treatment before surgery
	V20 ≤ 40%	V20 ≤ 35%	V20 ≤ 30%
		V10 ≤ 45%	V10 ≤ 40%
		V5 ≤ 65%	V5 ≤ 55%
	V20 < 10% and V5 < 60% if post-pneumonectomy		
Heart	Mean dose < 26 Gy		
	V30 ≤ 45%		
Esophagus	Mean dose < 34 Gy		
	Dmax ≤ 80 Gy		
	V70 < 20%		
	V50 < 50%		
Kidney	20 Gy < 32% bilateral kidney		
Liver	Mean dose < 30 Gy		
	V30 ≤ 40%		

International Thymic Malignancy Interest Group
Gomez D, Komaki R, Yu J, Ikushima H, Bezjak A, et al. "Radiation Therapy Definitions and Reporting Guidelines for Thymic Malignancies."
Journal of Thoracic Oncology. 2011;6(7 Suppl 3):S1743–S1748.

PALLIATIVE RADIOTHERAPY

Study	Patients	RT Dose	Key Results
Mornex et al., 1995	Advanced/ recurrent thymoma	Various palliative schedules	Demonstrated significant tumor regression and symptom relief, confirming thymoma radiosensitivity
Urgesi et al., 1990	Metastatic/ recurrent thymoma	30–60 Gy	Objective responses observed in irradiated lesions; durable local control in many patients
Owen et al., ITMIG review	Recurrent/ metastatic TETs	Various	RT effective for palliation of pain, dyspnea, cough, and mediastinal compression symptoms
ESMO Guidelines 2021	Advanced TETs	Individualized	Recommend palliative RT for symptomatic local or metastatic disease
NCCN Guidelines	Recurrent/metastatic TETs	Individualized	RT recommended for symptom control and local control in unresectable recurrence

ACUTE TOXICITIES

Esophagitis

Radiation Dermatitis

Fatigue

Cough

Dyspnea

Nausea

Hematologic toxicity

Acute Radiation Pneumonitis

CHRONIC TOXICITIES

Pulmonary fibrosis

Radiation pneumonitis → fibrosis

Cardiac toxicity

Constrictive pericarditis

Esophageal stricture

Spinal cord injury

Brachial plexopathy

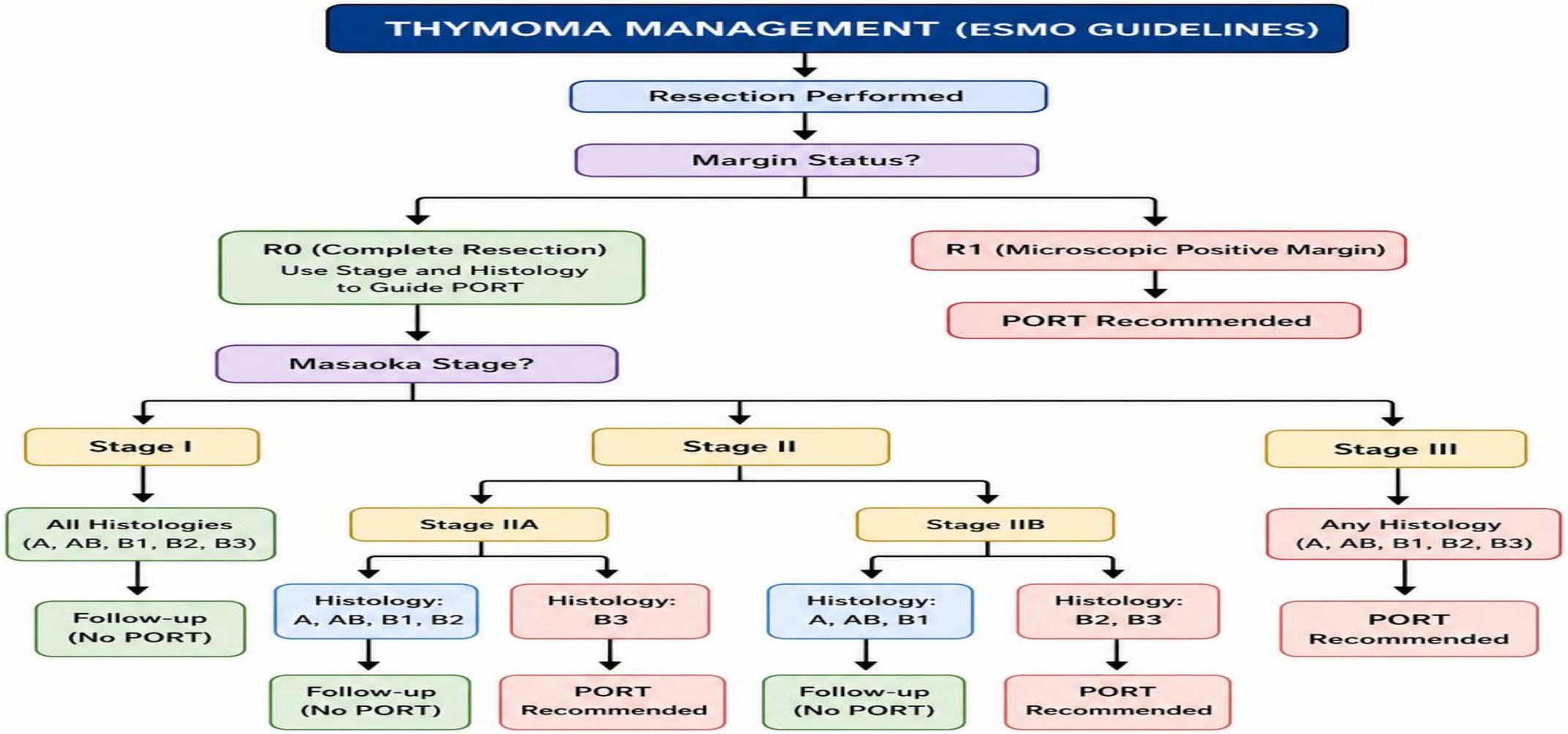
Hypothyroidism

Secondary malignancies

FOLLOW UP

- Baseline thoracic CT scan 3–4 months after surgery
- For completely resected stage I/II thymomas: CT scan every year for 5 years, then every 2 years
- For stage III/IV thymomas, thymic carcinoma or after R1–2 resection: CT scan every 6 months for 2 years, then annually
- Continuation of follow-up for 10–15 years

NCCN Guidelines for Thymomas and Thymic Carcinomas ,



SUMMARY TABLE

Masaoka Stage	WHO Histology	Recommendation
Stage I	All (A, AB, B1, B2, B3)	Follow-up (No PORT)
Stage IIA	A, AB, B1, B2	Follow-up (No PORT)
Stage IIA	B3	PORT Recommended
Stage IIB	A, AB, B1	Follow-up (No PORT)
Stage IIB	B2, B3	PORT Recommended
Stage III	All (A, AB, B1, B2, B3)	PORT Recommended
R1 (Any Stage)	Any Histology	PORT Recommended

KEY POINTS

- PORT → Stage III disease, particularly WHO type B2 and above.
- R1 (positive margin) → PORT recommended.

THANK YOU