

Postgraduate Course Medical Oncology

Work-up, anatomy, staging and surgical aspects
of thymoma and thymic carcinoma

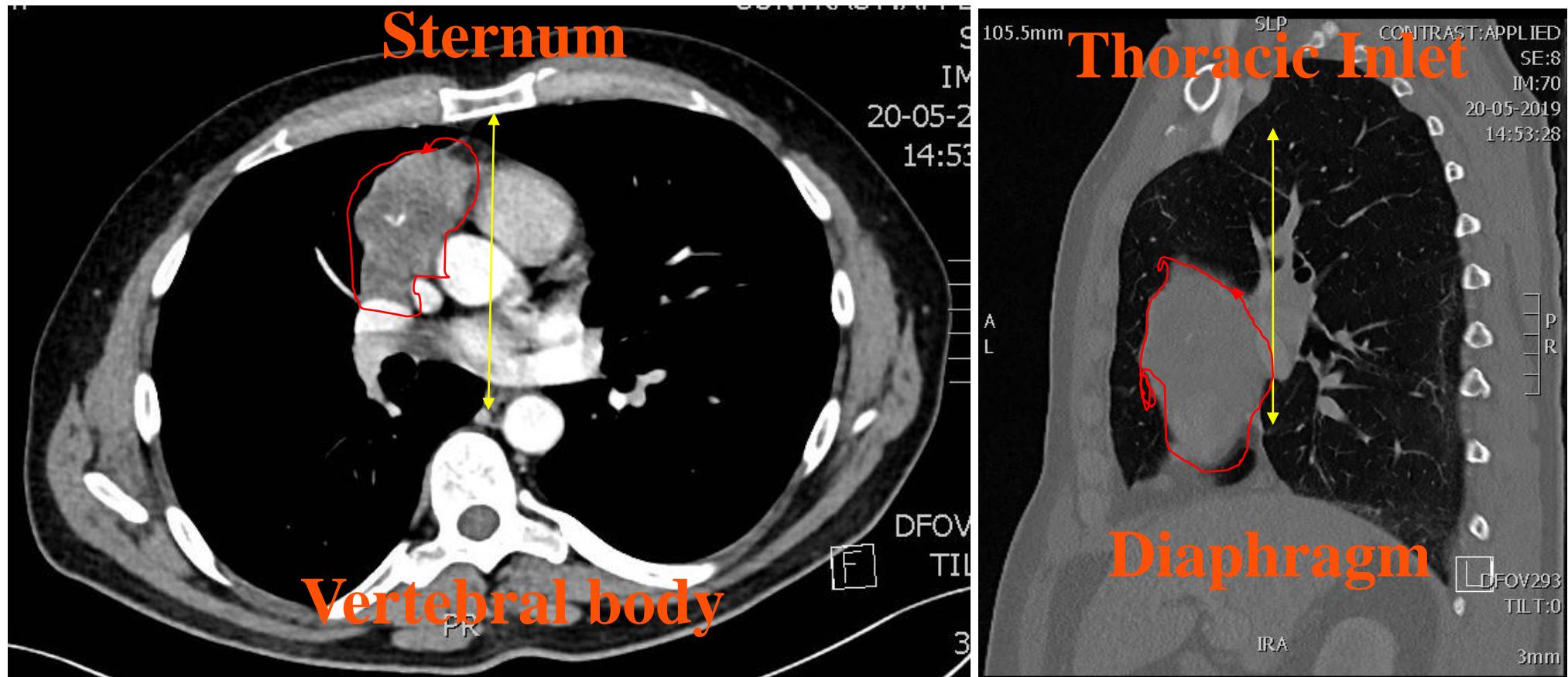
Dirk Van Raemdonck

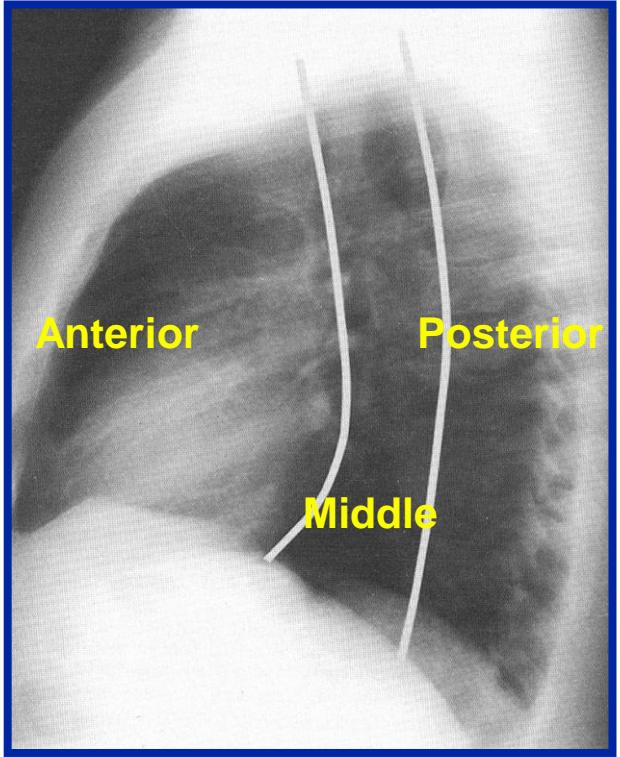
MD, PhD, FEBTS, FERS



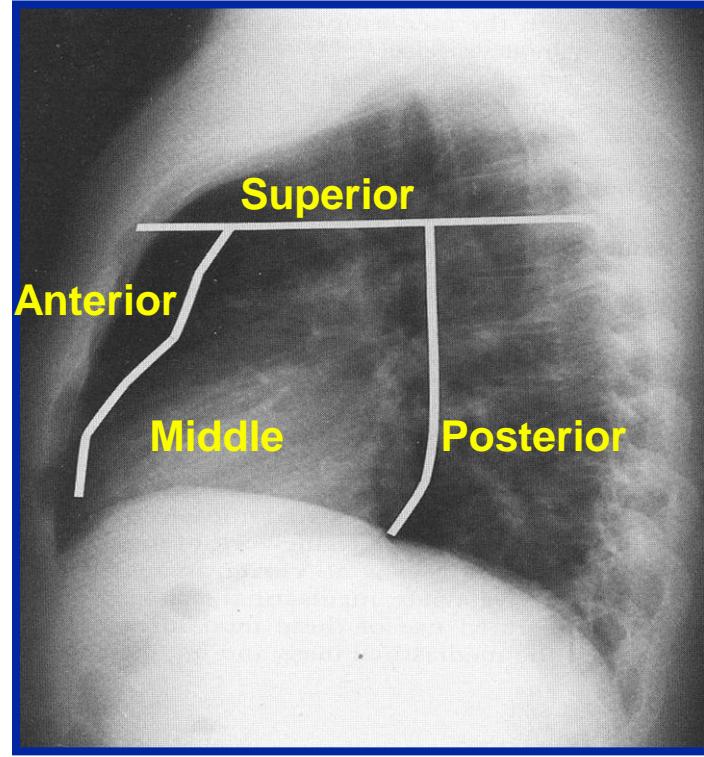
Mediastinum

space in between both pleural cavities





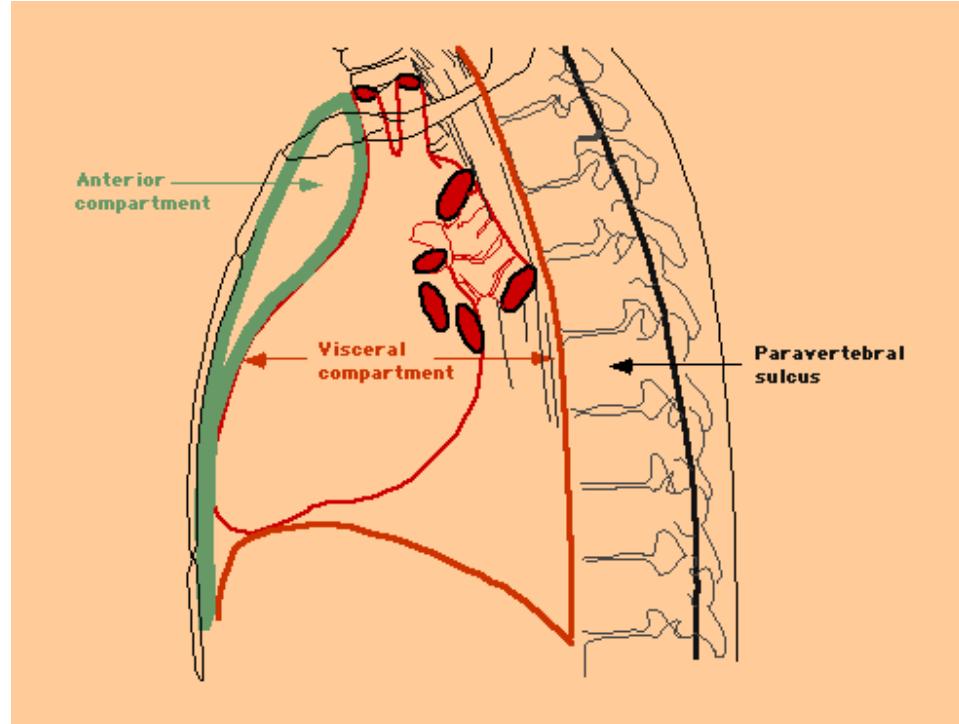
3 compartments



4 compartments

3 compartments

- Anterior
- Visceral
- Paravertebral



Shields 1972

Textbook Thoracic Surgery



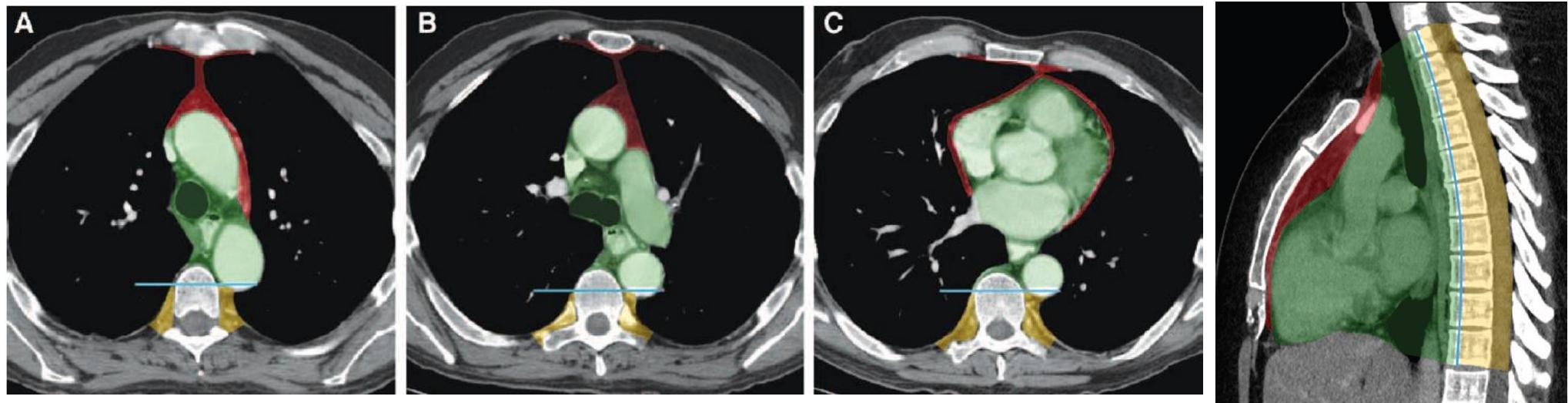
International
Thymic
Malignancy
Interest Group

ITMIG DEFINITIONS AND POLICIES

A Modern Definition of Mediastinal Compartments

Brett W. Carter, MD, Noriyuki Tomiyama, MD, † Faiz Y. Bhora, MD,‡
Melissa L. Rosado de Christenson, MD,§ Jun Nakajima, MD,|| Phillip M. Boiselle, MD,¶
Frank C. Detterbeck, MD,# and Edith M. Marom, MD**

- Pre-vascular
- Visceral
- Paravertebral



EDITORIAL COMMENTARY

What comes out of Pandora's box?

Dirk Van Raemdonck, MD, PhD



J Thorac Cardiovasc Surg 2015; 149: 110-1

Mediastinal Structures

Pre-vascular

- Thymus
- Mammary vessels
- Ectopic (para)thyroid
- Lymph nodes
- Fatty tissue

Visceral

- Pericardium
- Heart
- Great vessel
- Trachea & bronchi
- Lymph nodes
- Fatty tissue

Paravertebral

- Descendens aorta
- Azygos vein
- Oesophagus
- Vagal nerve
- Sympatetic chain
- Thoracic duct
- Lymph nodes
- Fatty tissue

Mediastinal Mass

- infections
- tumors

Mediastinal Mass

- infections
- tumors

Mediastinal infections

- **post-operative**

- sternotomy (LIMA / RIMA – diabetes - steroids)
- mediastinoscopy
- oesophageal fistula / leak gastric tube

- **post-traumatic**

- instrumental perforation (gastro, EUS, EBUS, TEE)
- sharp trauma (knife)
- corpus alienum (chicken bone, dental prothesis)
- barogenic rupture (Boerhaave's syndrome)

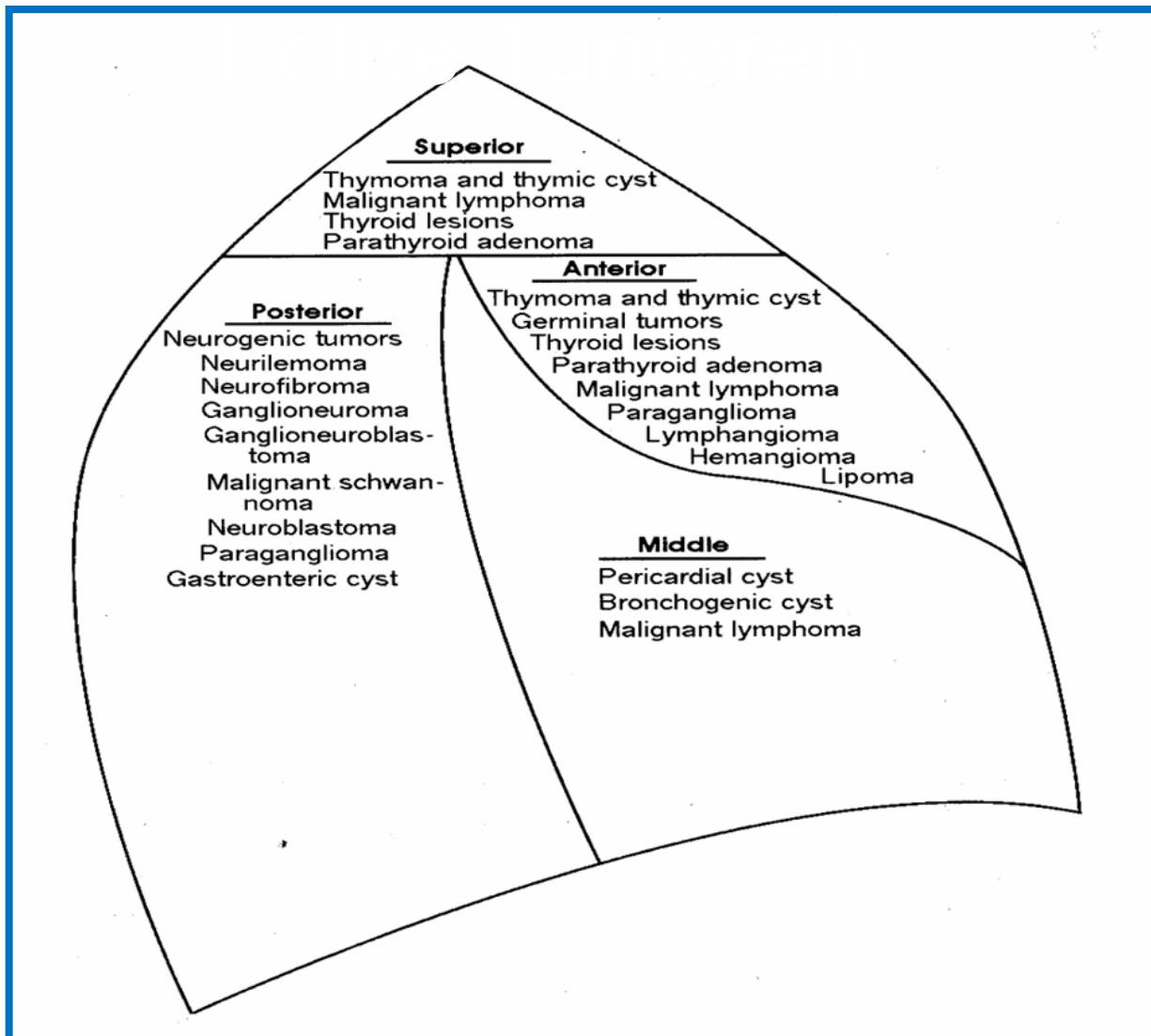
- **descending infection**

- dental abcess
- Ludwig's angina
- osteosynthesis cervical spine

Mediastinal Mass

- infections
- tumors

Real tumors & cysts



False tumors

<i>Previsceral Compartment (Anterior)</i>	<i>Visceral Compartment</i>	<i>Paravertebral Sulci (Posterior)</i>
Aneurysm of ascending aorta, innominate artery, or subclavian artery Abnormal dilatation of superior vena cava or azygos vein Sternal or chondrosternal tumors Lymphangiomas	Aneurysm of the heart or aortic arch Pericarditis Enlarged lymph nodes Mediastinitis Aneurysm of pulmonary artery	Diaphragmatic hernias Aneurysm of descending aorta Tumor of the esophagus Megaesophagus Extralobar sequestration Pott's abscess Meningocele Extramedullary hematopoiesis

Age

	<i>Pediatric</i>	<i>Adult</i>
Neurogenic	35%	21%
Thymoma	Rare	19%
Lymphoma	25%	13%
Cysts	16%	18%
Germ cell	10%	10%
Mesenchymal	10%	6%
Endocrine	Rare	6%

Pre-vascular

	<i>Children</i> <i>(n = 702)</i>	<i>Adults</i> <i>(n = 179)</i>
Thymic	17%	47%
Germ cell	25%	15%
Lymphoma	45%	23%
Mesenchymal	15%	—
Endocrine	—	16%

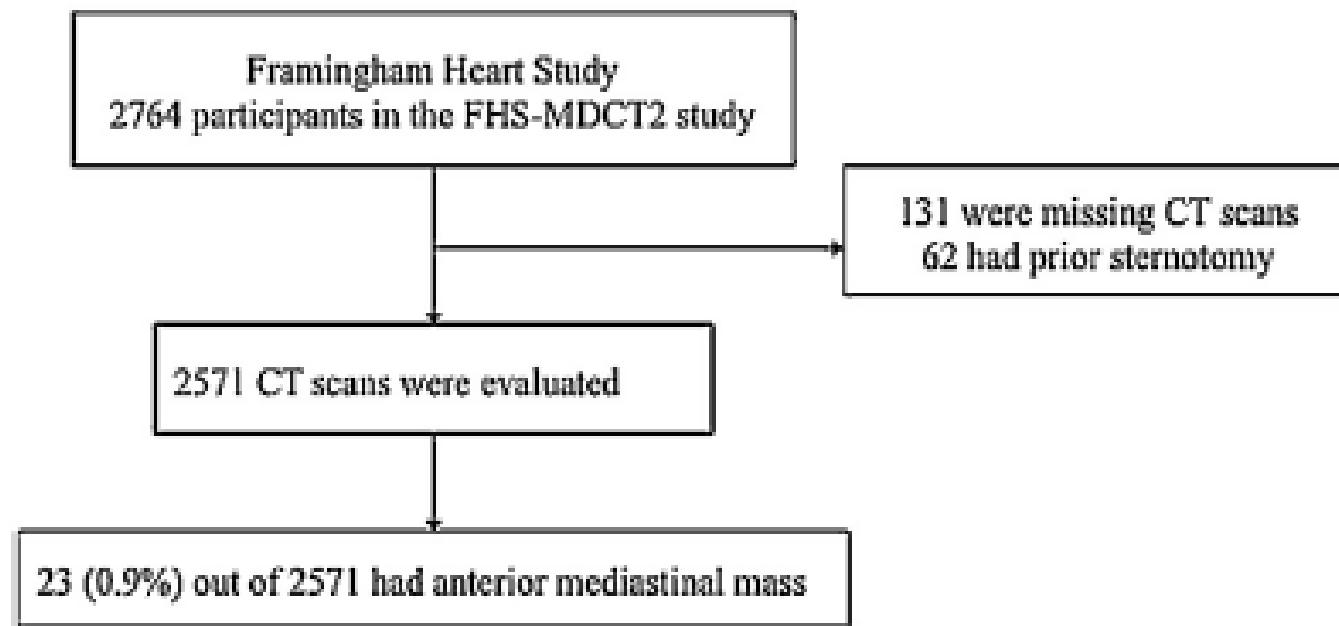
Symptoms

- ✓ incidental finding
- ✓ systemic symptoms
- ✓ local symptoms
- ✓ paraneoplastic symptoms

Incidental finding

Prevalence of Anterior Mediastinal Masses?

- Framingham Heart Study
- 2571 patients with chest CT scans



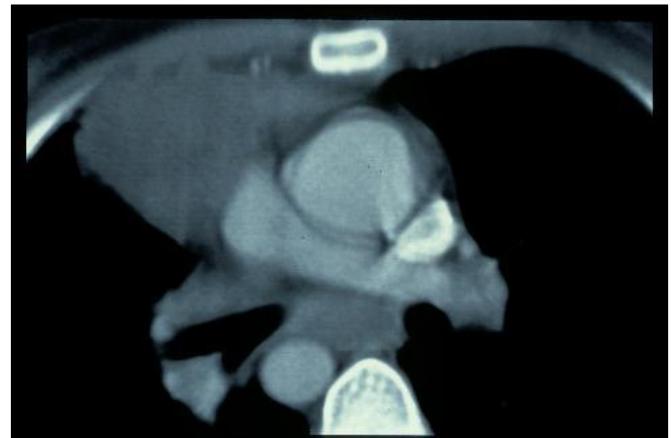
23 (0.9%) out of 2571 had anterior mediastinal mass

1% of the population had anterior mediastinal mass

Systemic Symptoms

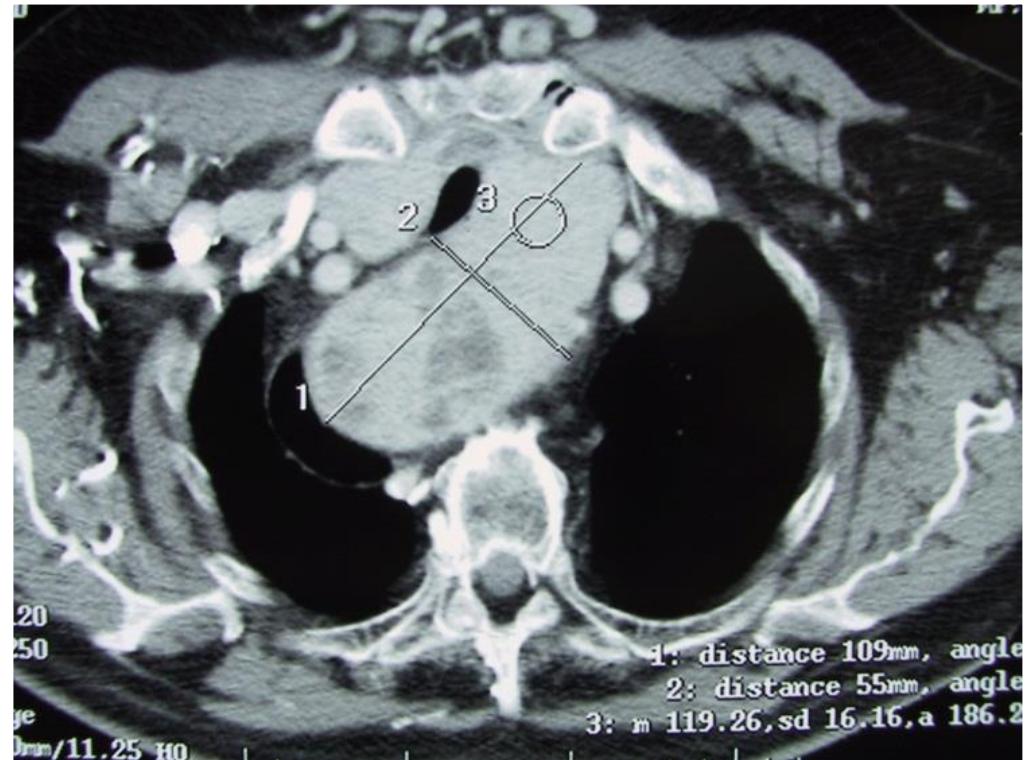
(B-symptoms)

- ✓ anorexia
- ✓ weight loss
- ✓ fever
- ✓ (night) sweating



Local Symptoms

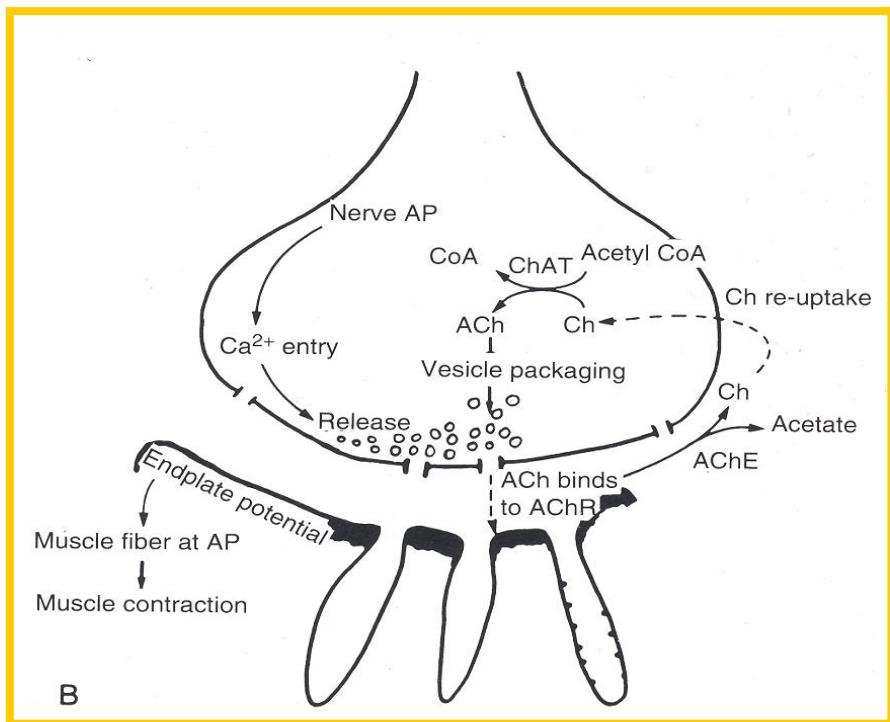
- ✓ **chest pain**
- ✓ **cough**
- ✓ **dyspnea**
- ✓ **hemoptysis**
- ✓ **stridor**
- ✓ **hoarsness**
- ✓ **dysphagia**



Paraneoplastic Symptoms

- ✓ **Neuromuscular**
(**myasthenia gravis, Lambert-Eaton, myositis**)
- ✓ **Immunologic**
(**hypogammaglobulinemia, T-cell dysfunction**)
- ✓ **Hematologic**
(**red blood cell aplasia, pancytopenia**)
- ✓ **Dermatologic**
(**pemphigus, mucocutaneous candidiasis**)
- ✓ **Auto-immune**
(**lupus, Sjögren, polymyositis, scleroderma**)
- ✓ **Osteogenic**
(**hypertrophic osteo-artropathy**)
- ✓ **Endocrine**
(**cushing, hyper(para)thyroidism, hypoglycemia, SIADH**)

Myasthenia Gravis (MG)



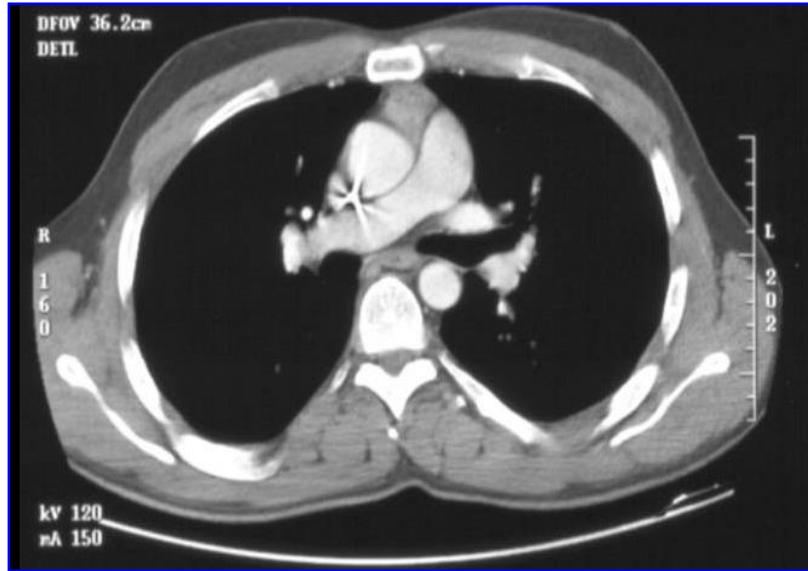
neuromuscular & auto-immune disorder (ACh receptor AB):

- **Ocular:** ptosis – diplopia
- **Bulbar:** dysphagia – dysarthria
- **Respiratory:** dyspnea

medical treatment:

- **cholinesterase blocker**
(pyridostigmine: Mestinon®)
- **Steroids**
- **Immunosuppressants**
- **Plasmapheresis**

MG & thymoma



- In 15% of patients with MG, a thymoma is found
- In thymomatous patients with MG, thym(om)ectomy is advised
- In selected non-thymomatous MG patients, thymectomy is beneficial to control symptoms
(MGTX – RCT: N Engl J Med. 2016;375(6):511-22)

Physical Exam



- ✓ **normal**
- ✓ **facial oedema**
- ✓ **dilated veins**
- ✓ **hoarsness**
- ✓ **stridor, cough**
- ✓ **Horner's syndrome**
- ✓ **cervical lymphadenopathy**

Laboratory Testing

- ✓ Tumor markers
- ✓ Hormones
- ✓ Antibodies
- ✓ Bone marrow cells (lymphoma)

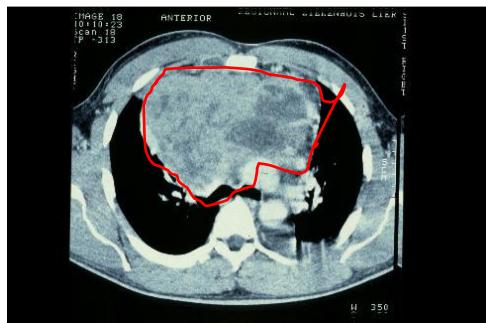
Tumor markers



- CEA (NSCLC e.g. TxN2M0)



- NSE (neuro-endocrine e.g. SCLC)



- α -FP – β -HCG (germ cell)

Hormones

- insuline
- T3 – T4
- PTH
- calcitonine
- ACTH
- catecholamines

Antibodies

- Anti-ACh receptor Ab (myasthenia gravis)
- Anti-muscle Ab (myositis)
- T-cell antigens (lymphoma)
- B-cell antigens (lymphoma)

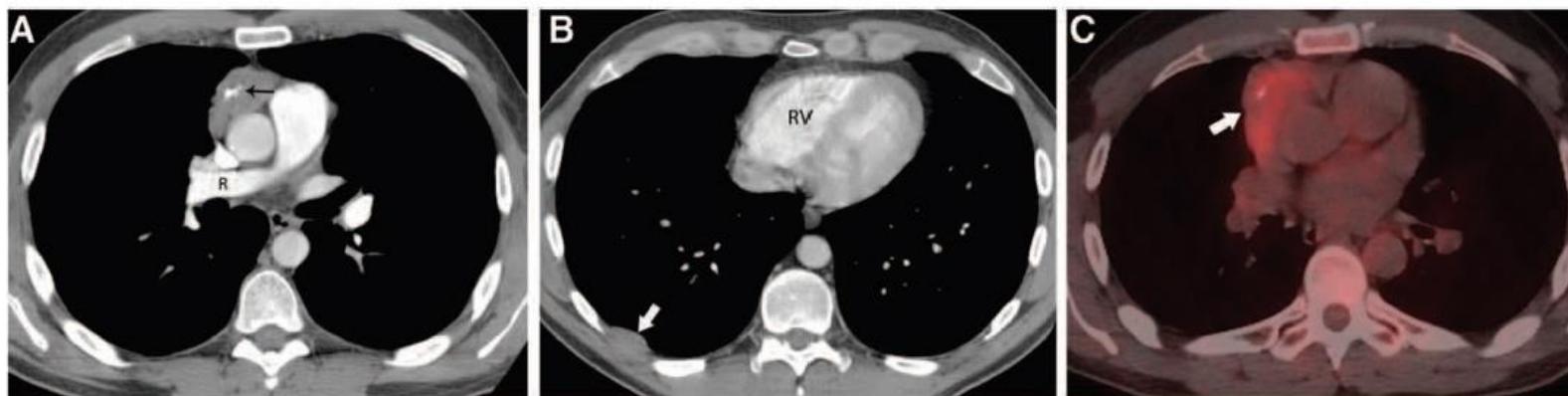
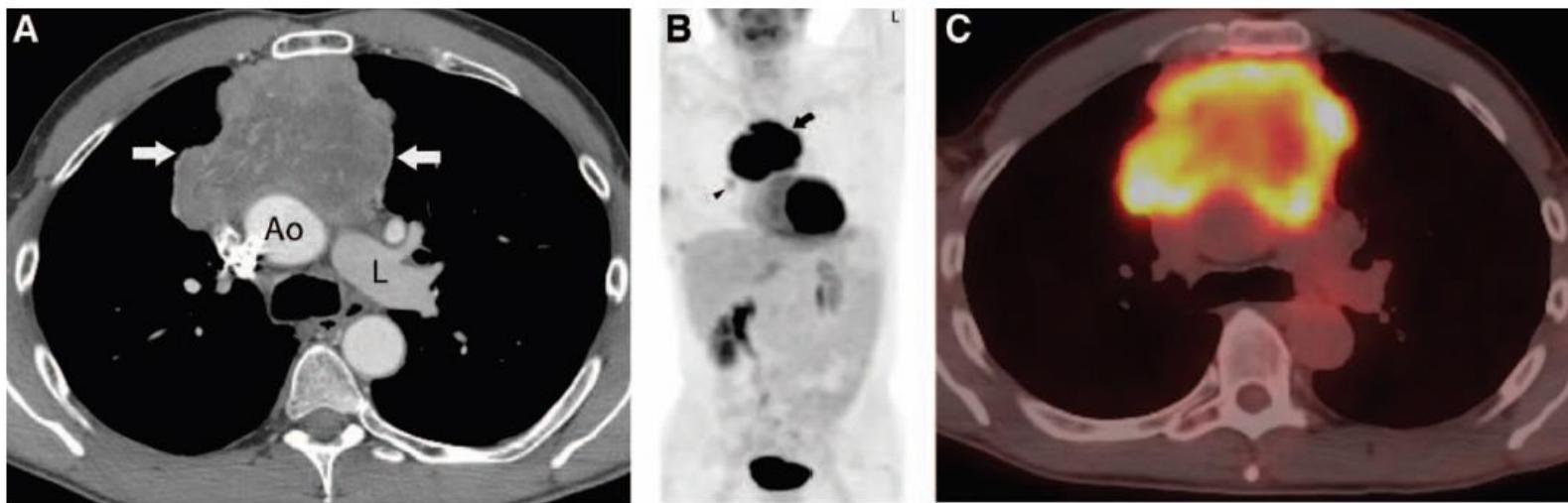
Radiographic Imaging

- ✓ **Chest X-ray**
- ✓ **CT chest**
- ✓ **MRI chest**
- ✓ **angiography**
- ✓ **barium swallow**
- ✓ **(echo abdomen)**
- ✓ **(CT abdomen)**
- ✓ **(echo testes)**

Nuclear Imaging

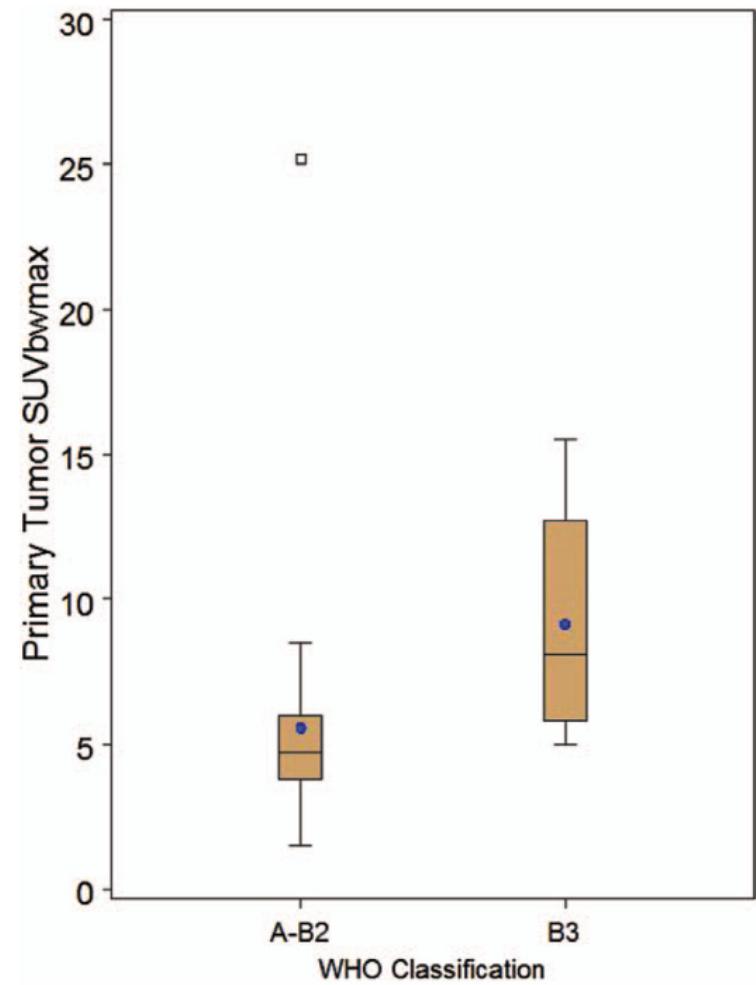
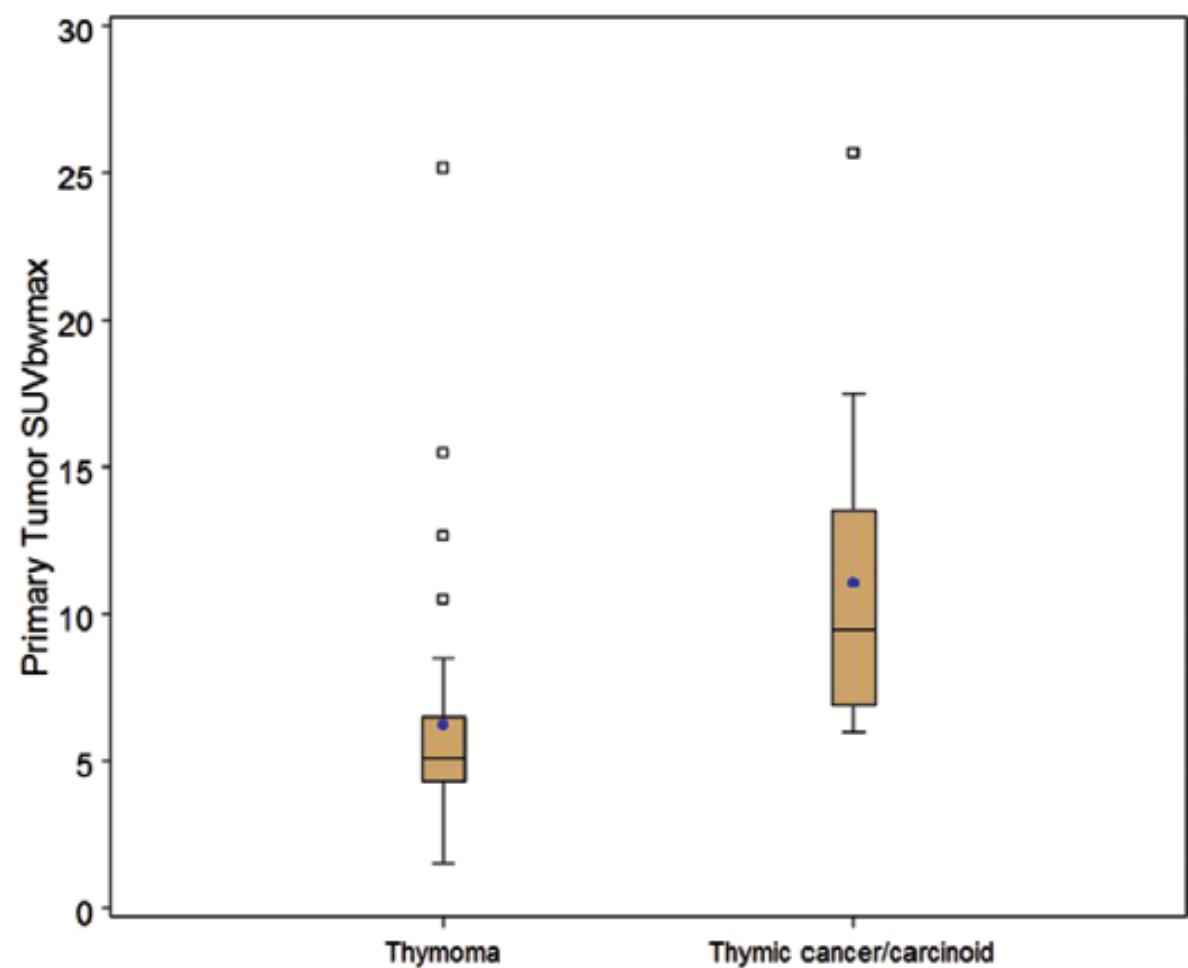
- ✓ thyroid scan (^{123}I , ^{131}I , $^{99\text{m}}\text{Tc}$)
- ✓ parathyroid scan (^{201}Tl)
- ✓ MIBG scan (^{131}I -metaiodobenzylguanidine)
 - pheochromocytoma
 - neuroblastoma
- ✓ PET scan (18-FluoroDeoxyGlucose, octreotide)

FDG PET scan in differential diagnosis



Benviste et al. J Thorac Oncol 2013;8: 502-510

FDG PET scan in differential diagnosis



Benviste et al. J Thorac Oncol 2013;8: 502-510

Endoscopy

✓ bronchoscopy

- extrinsic compression
- endoluminal invasion

✓ oesophagoscopy

- extrinsic compression
- endoluminal invasion

✓ EUS - EBUS

- transbronchial biopsy
- transoesophageal biopsy

NCCN guidelines: work up

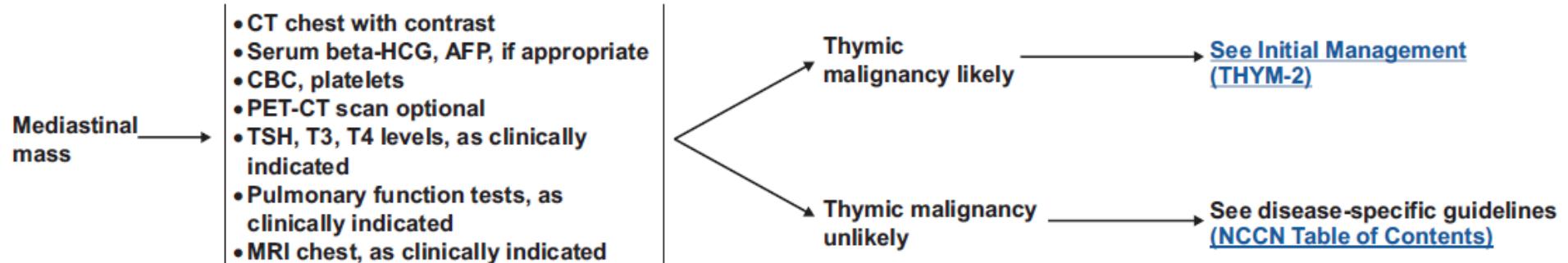


National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2013 Thymomas and Thymic Carcinomas

[NCCN Guidelines Index](#)
[Thymic Table of Contents](#)
[Discussion](#)

INITIAL EVALUATION



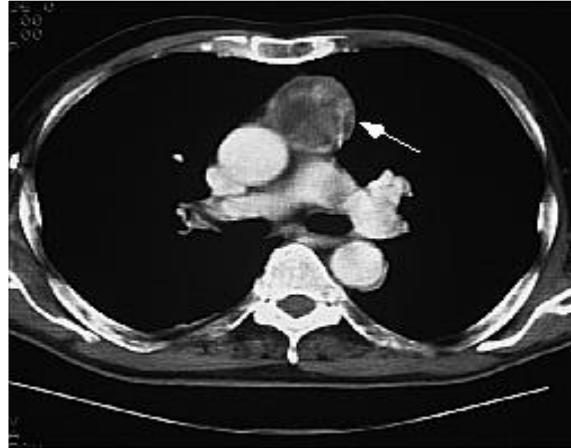
Biopsy: non-invasive to invasive

- Endoscopic biopsy (EBUS – EUS)
- CT-guided: FNA – Tru-cut Bx
- Cervical mediastinoscopy
- Anterior mediastinotomy (Chamberlain)
- VATS Thoracoscopy

When to perform surgical biopsy?

- **"encapsulated" tumors**

- solitary anterior mass
- primary resectable
- non-invasive on CT scan
- negative tumor markers (α -FP/ β -HCG)



NO

- **"invasive" tumors**

- differential diagnosis: tissue needed
- induction chemotherapy



YES

NCCN guidelines: initial management

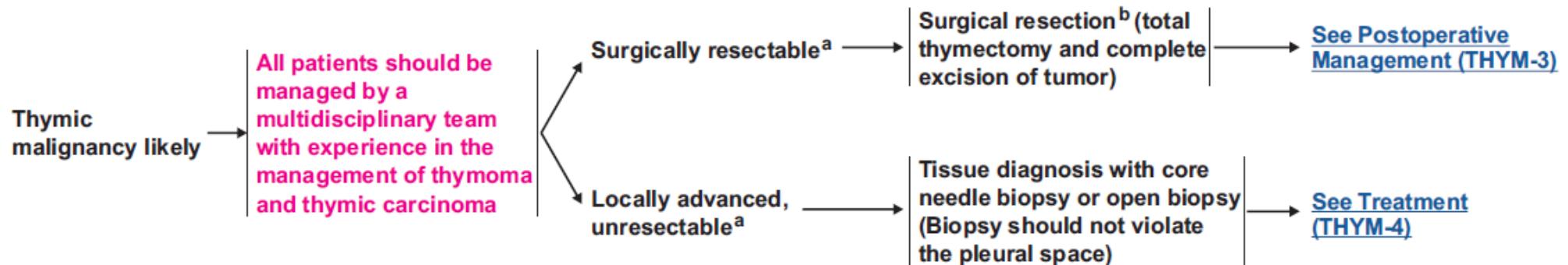
NCCN

National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2013 Thymomas and Thymic Carcinomas

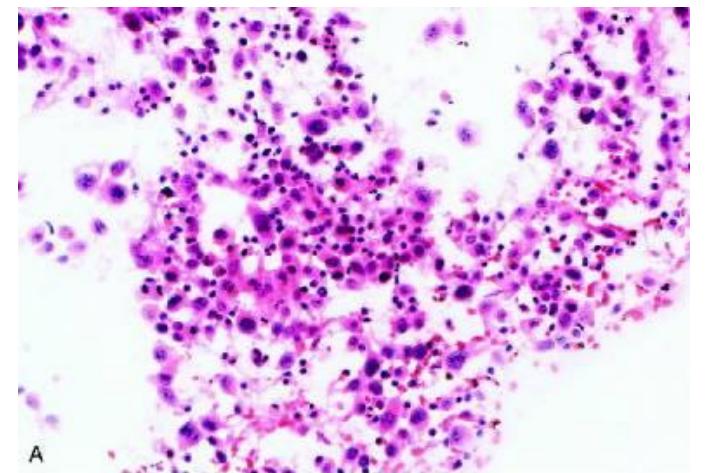
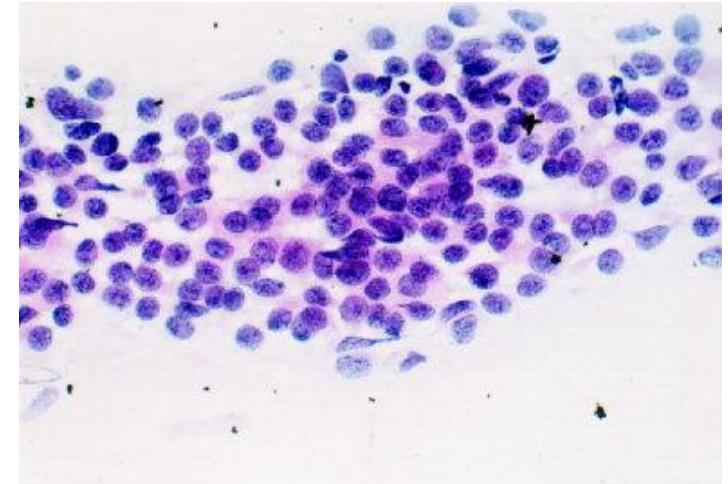
[NCCN Guidelines Index](#)
[Thymic Table of Contents](#)
[Discussion](#)

INITIAL MANAGEMENT



adequate tissue?

- Fine Needle Aspiration Biopsy
- Tru-cut Biopsy
- Surgical Biopsy



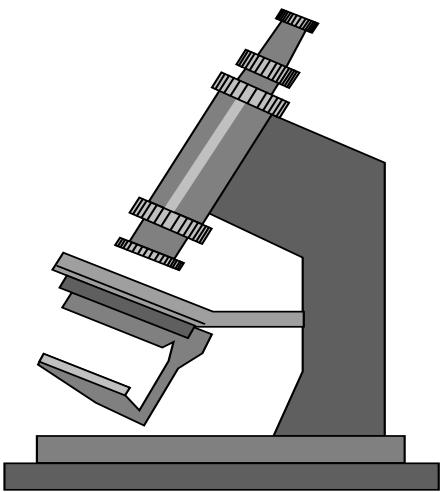
Accuracy of Needle Biopsy of Mediastinal Lesions

- *Table 2 Diagnostic accuracy according to type of needle*

	No. of procedures	Sensitivity (%)	Specificity (%)	Accuracy (%)
Overall				
Fine needle	60	90	100	77
Tru-Cut	34	96	100	94
Carcinomas				
Fine needle	25	96	-	88
Tru-Cut	5	100	-	100
Non-carcinomas				
Fine needle	35	81	100	69
Tru-Cut	29	96	100	94

Morrissey et. al. Thorax 1993, 48: 632-637

Role of Frozen Section



- ✓ **to check quality of biopsy**
- ✓ **not for definitive diagnosis**
- ✓ **final results to be awaited**

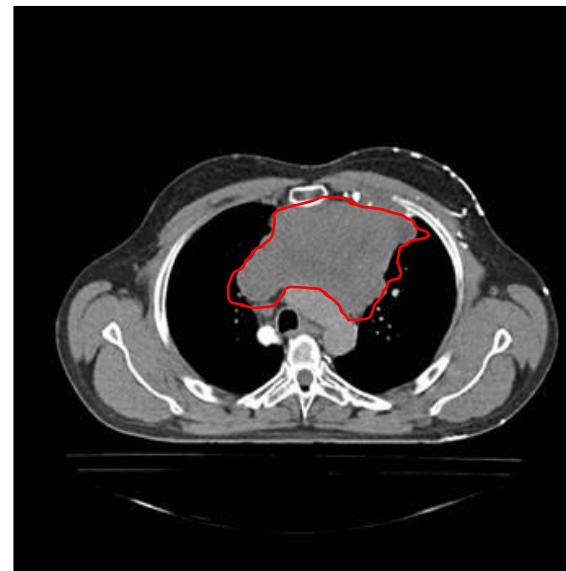
de Montpreville et al. Eur J Cardiothorac Surg 1998;13:190-195

“... frozen section is less effective for a precise diagnosis of some primary mediastinal lesions, which may have close histologic appearance.”

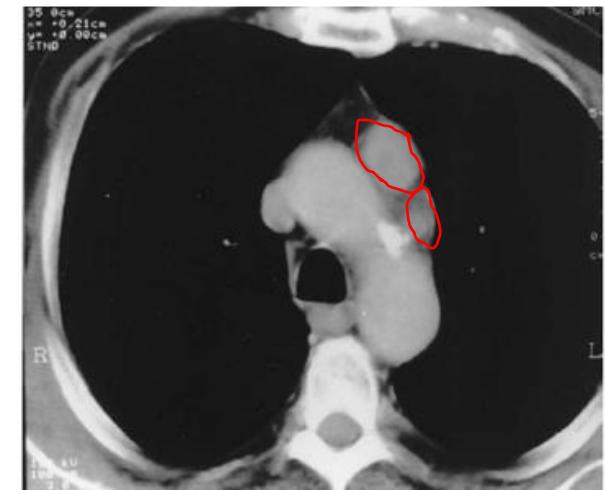
Invasive Biopsy



cervical
mediastinoscopy

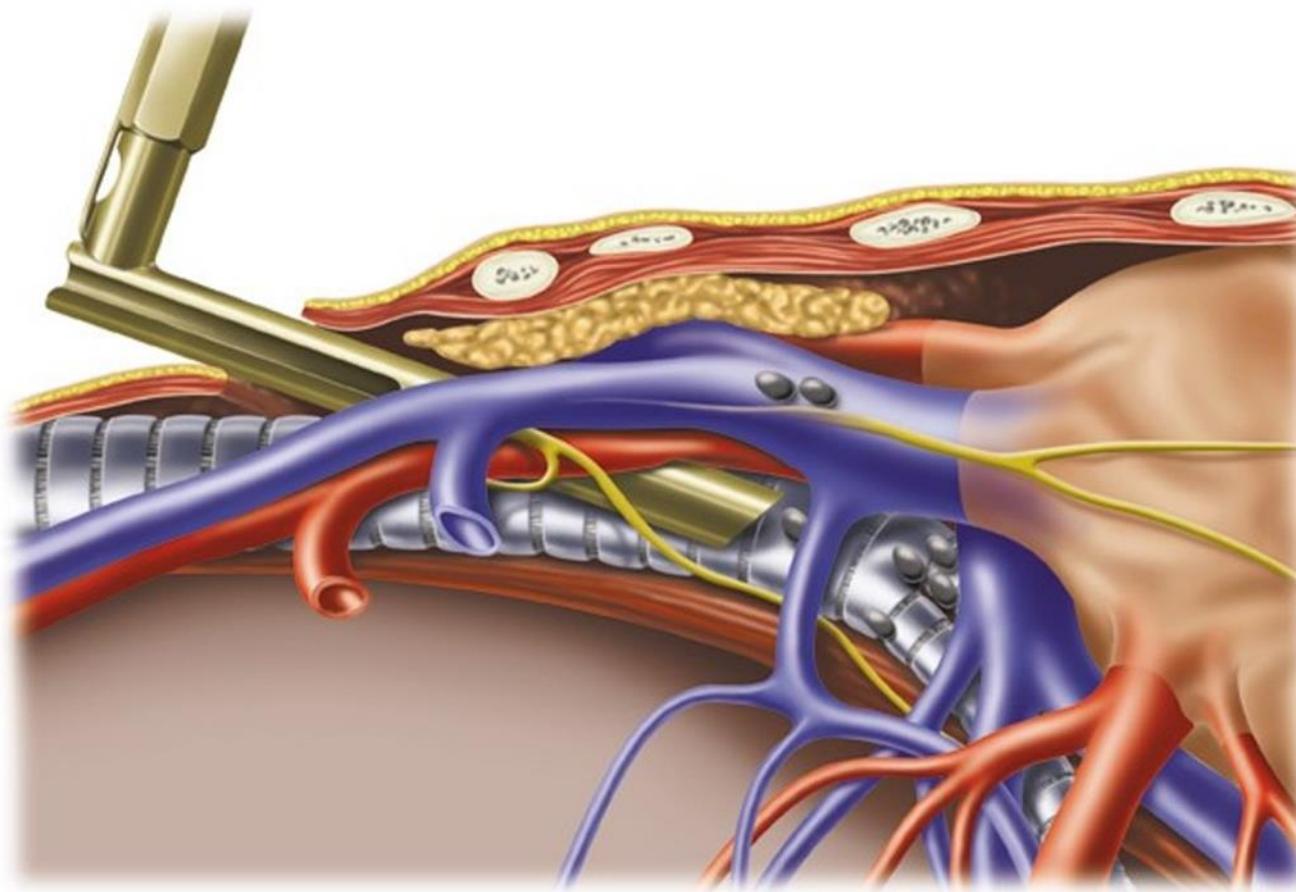


left anterior
mediastinotomy

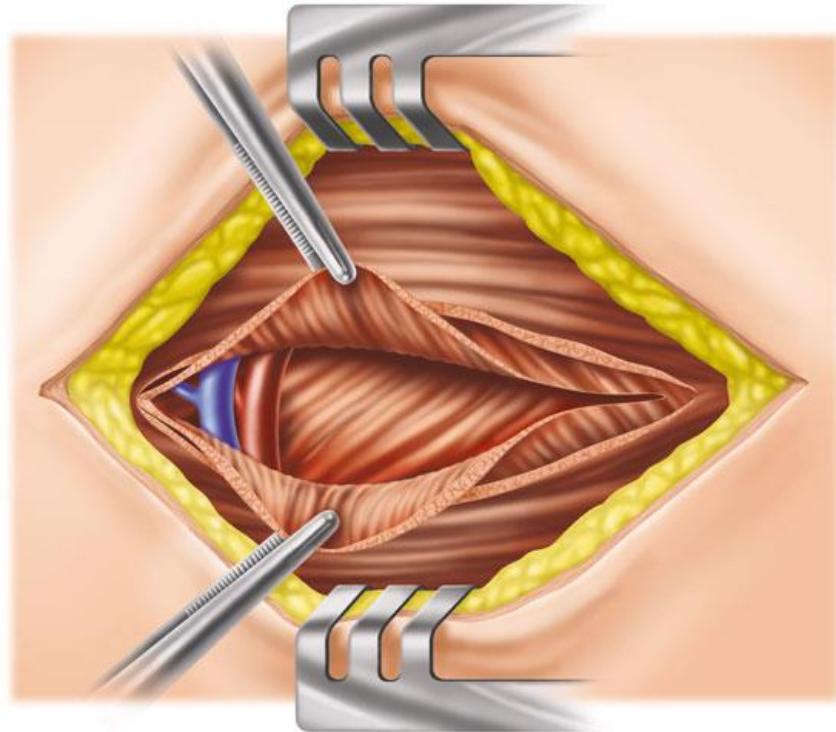
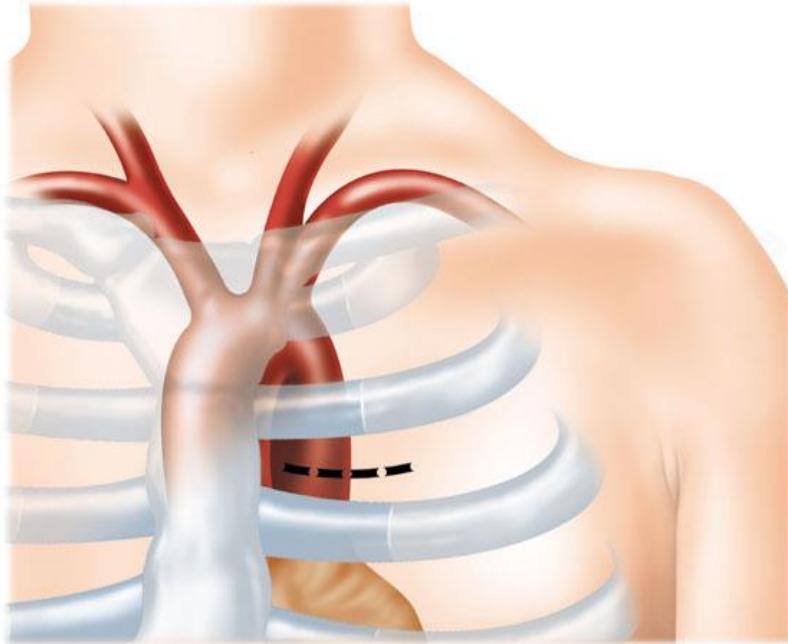


left
thoracoscopy

Cervical (Video) Mediastinoscopy



Anterior Mediastinotomy (Chamberlain)



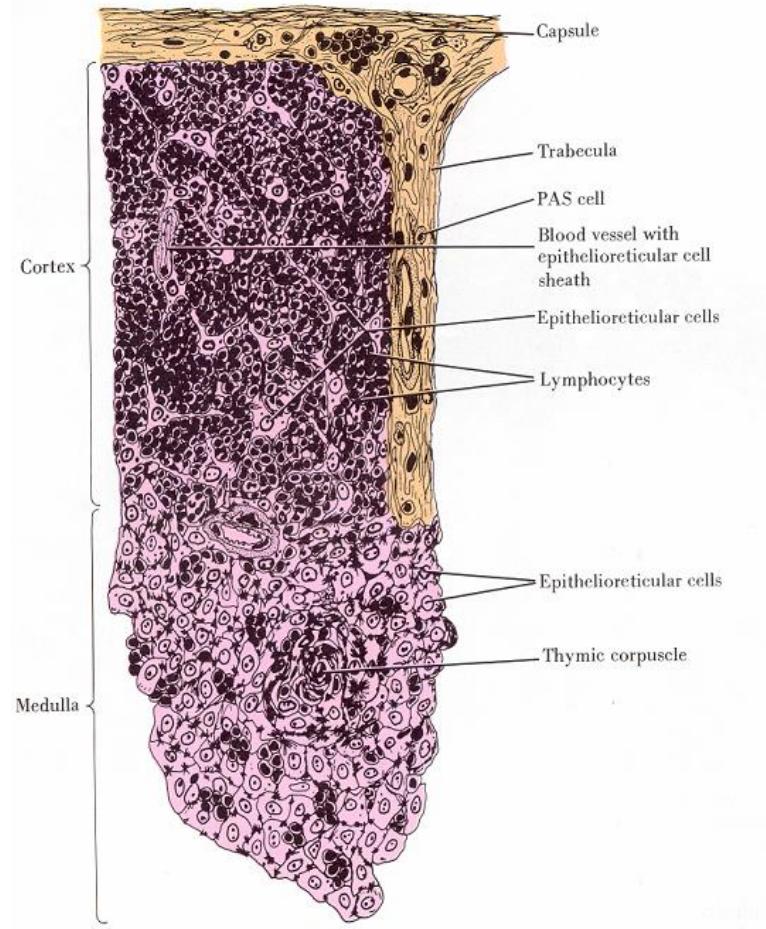
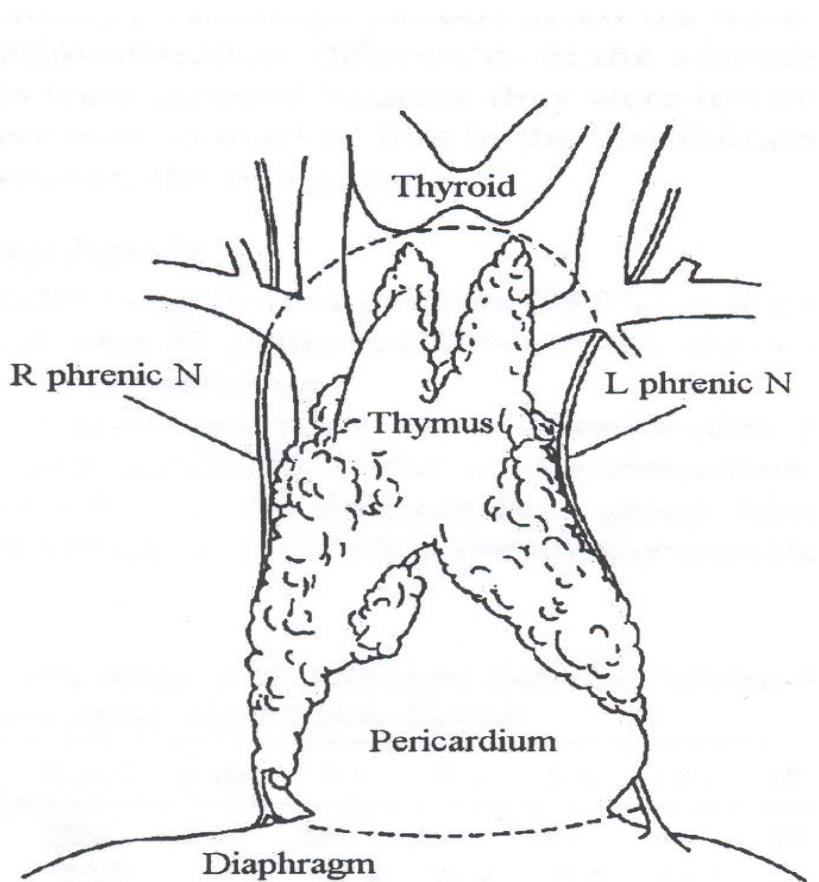
“Surgical” Tumors

- Thymic Epithelial Tumors
- Germ Cell Tumors
- Thyroid & Parathyroid
- Neurogenic Tumors
- Cystic Lesions

“Surgical” Tumors

- Thymic Epithelial Tumors (TETs)
- Germ Cell Tumors
- Thyroid & Parathyroid
- Neurogenic Tumors
- Cystic Lesions

Thymus: Anatomy & Morphology



- **capsule**
- **cortex**
- **medulla**

Histology: cell lines

- epithelium → thymoma
- lymphocytes → lymphoma
- neuroendocrine cells → neuroendocrine tumor
- germ cells → germ cell tumors
- fat → thymolipoma

TET - Epidemiology

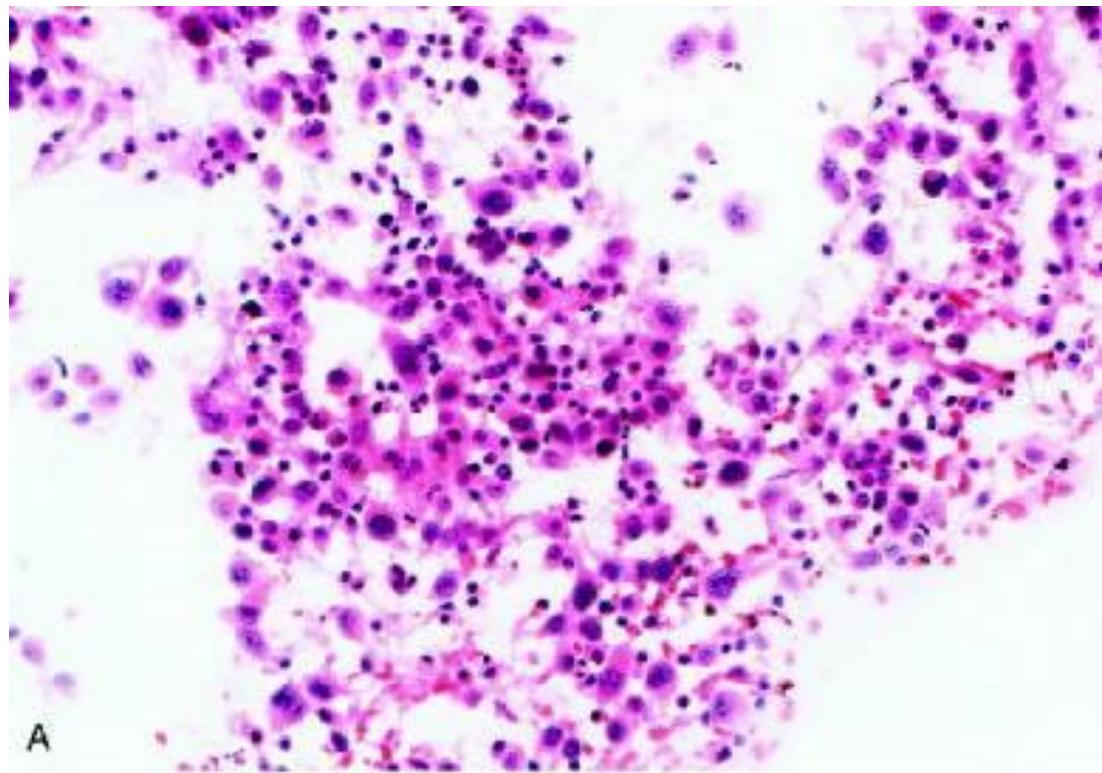
- **20 % all mediastinal tumors**
- **47% all tumors anterior mediastinum**
- **90% in all tumors in antero-superior mediastinum**

TET - Types

- Thymoma (A – AB – B1 – B2 – B3)
- Thymic carcinoma (C)
- Thymic neuroendocrine tumor (NET)
- Thymolipoma

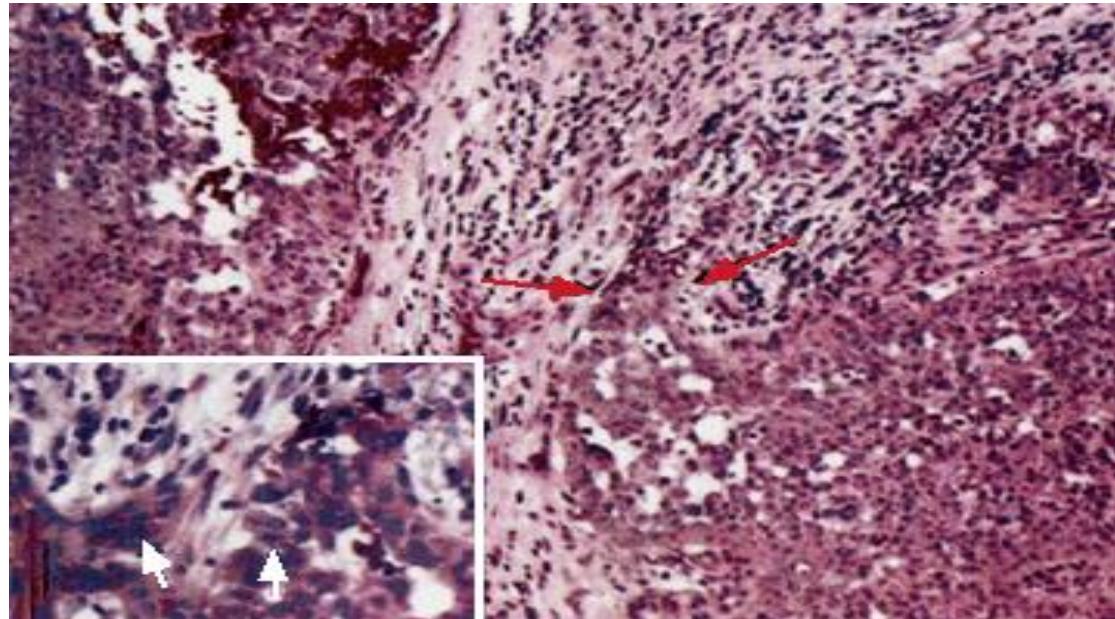
Thymoma

- epithelial tumour
- 85-90% of all TETs
- Cytology: “non-malignant cells”
- Morphologic
 - well encapsulated (“benign”)
 - locally invasive (“malignant”)



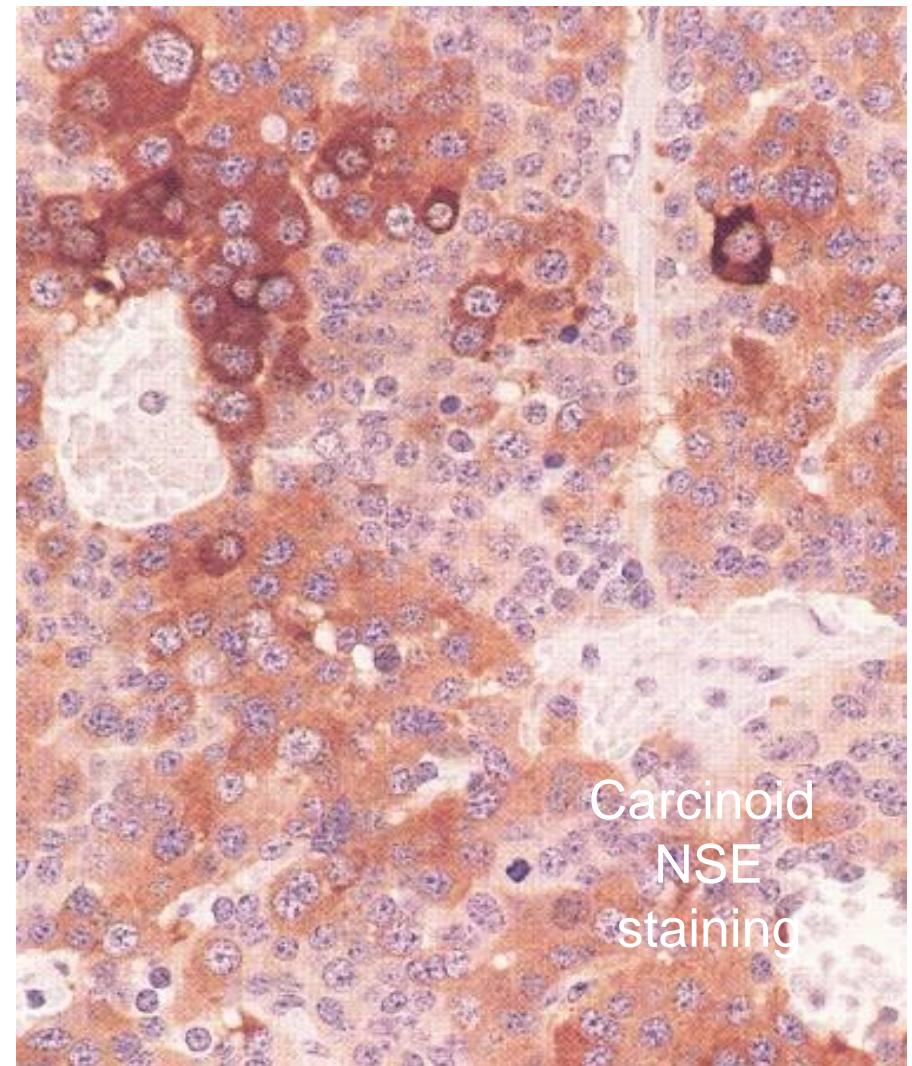
Thymic Carcinoma

- epithelial tumour
- 5 – 10% all TETs
- cytologic: mitoses (malignant)
- morphologic: locally invasive (malignant)
- lymphatic & hematogenous metastases
- subtypes (squamous cell, small cel carcinoma)

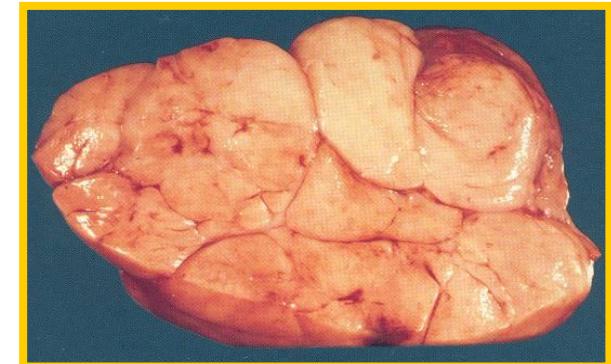
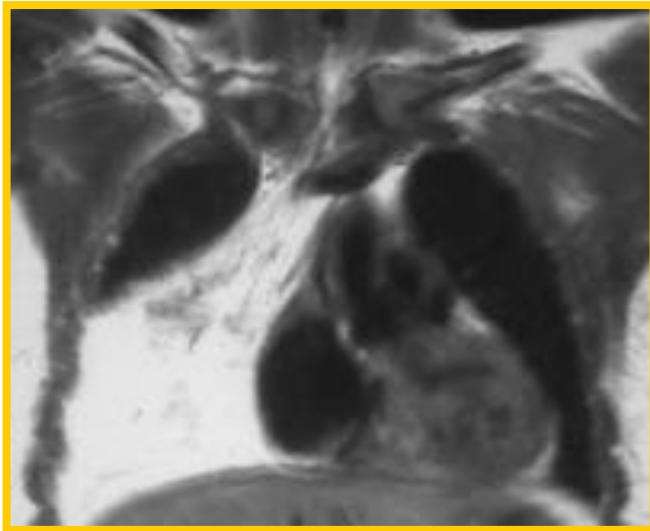


Thymic Carcinoid (NET)

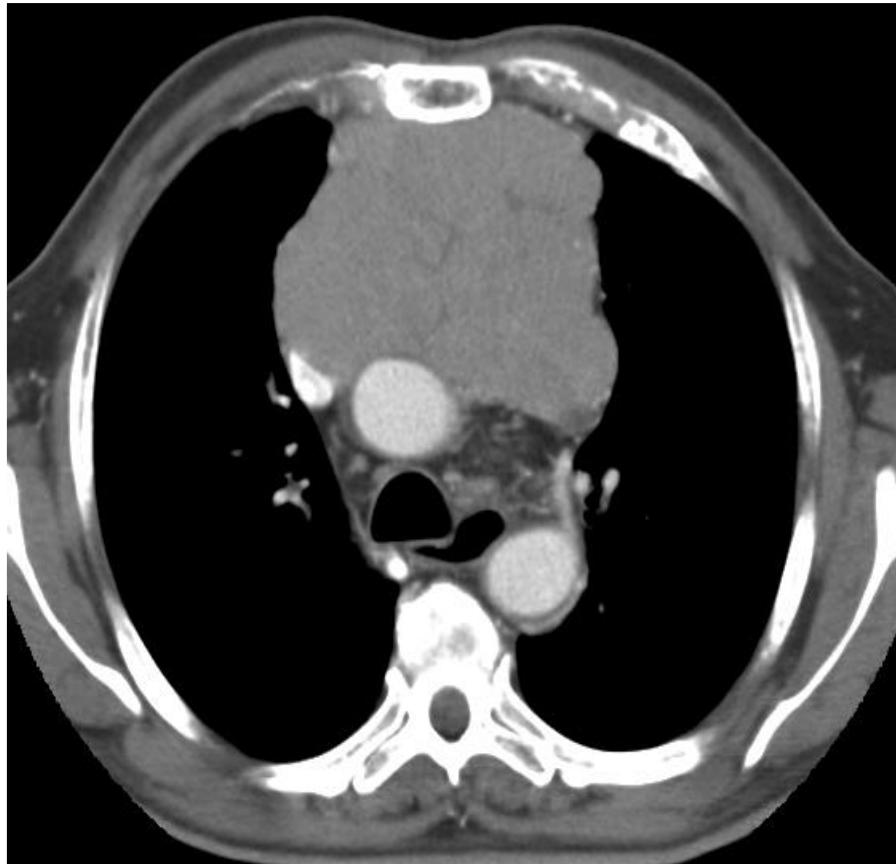
- epithelial tumour
- 5% of all TETs
- 25% associated with MEN-1 syndrome
- 1/3 carcinoid syndrome
- lymphatic & hematogenous metastases
- subtypes neuroendocrine tumours



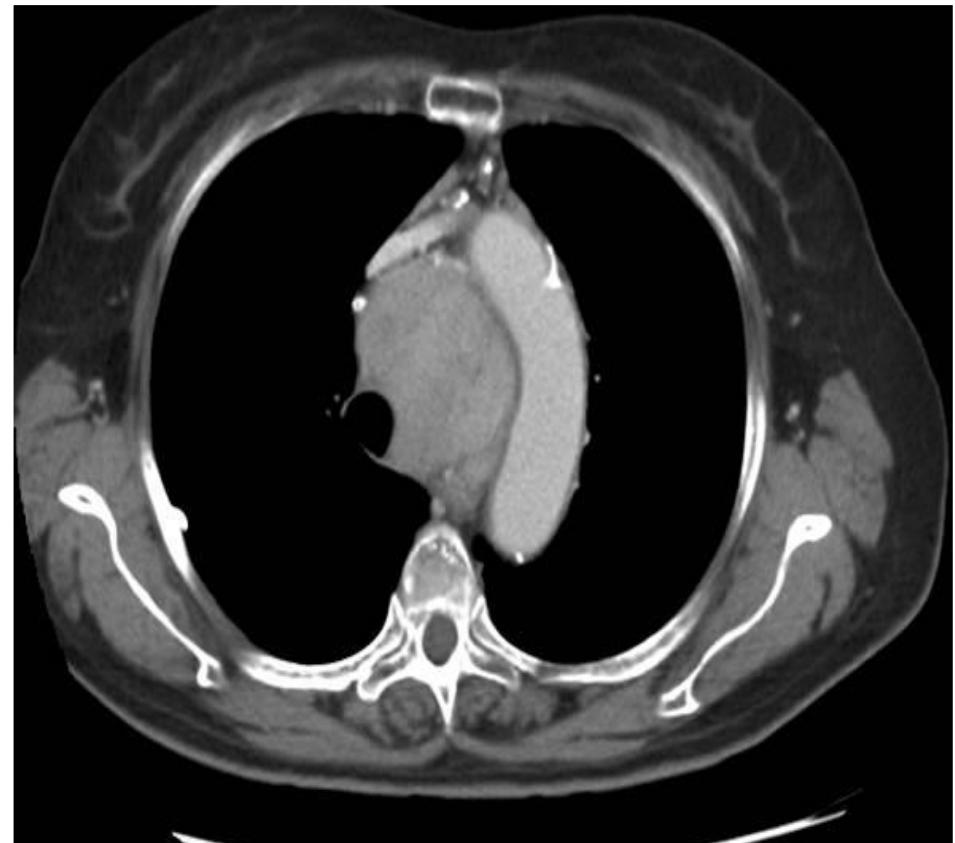
Thymic Lipoma



Mediastinal Compartment

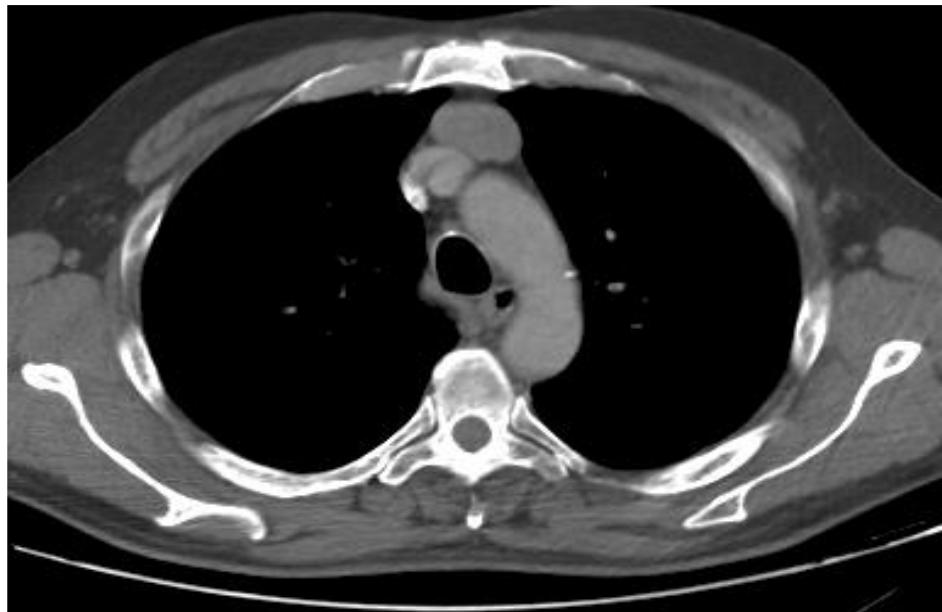


Prevascular (90%)

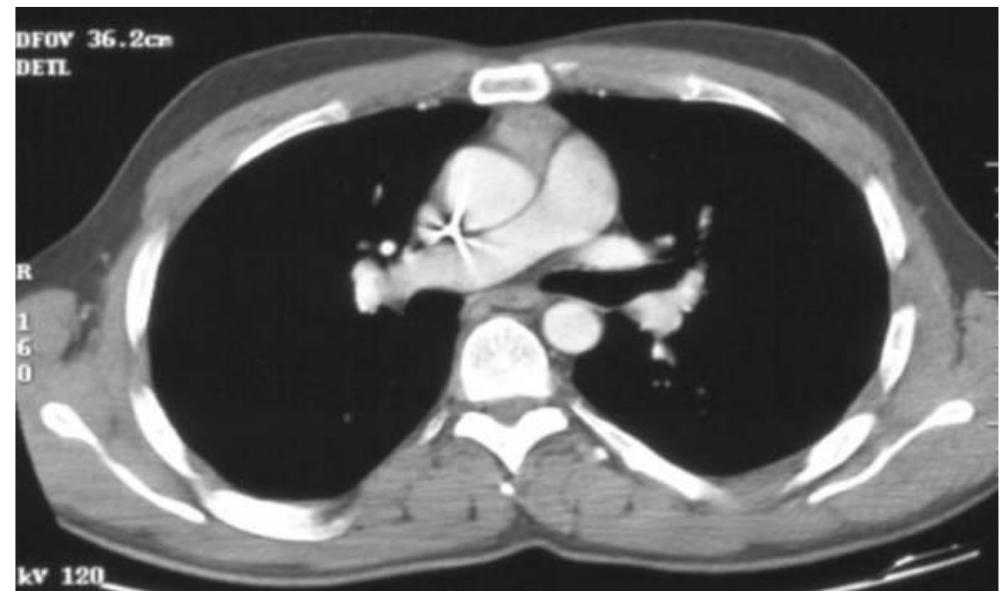


Visceral (10%)

Differential Diagnosis



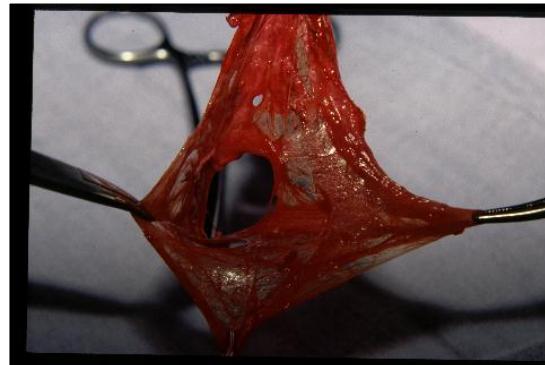
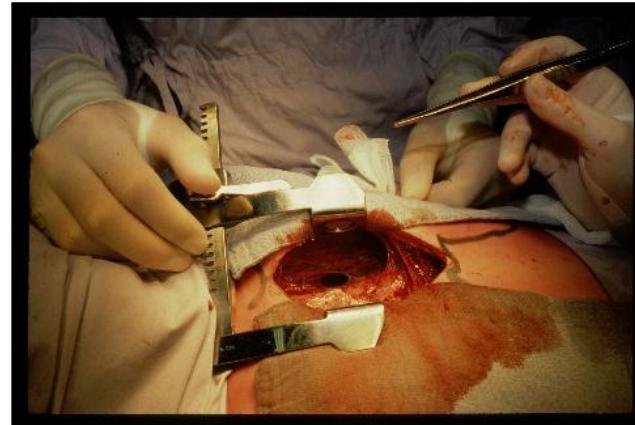
THYMOMA



HYPERPLASIA

sometimes difficult

Thymic Cyst



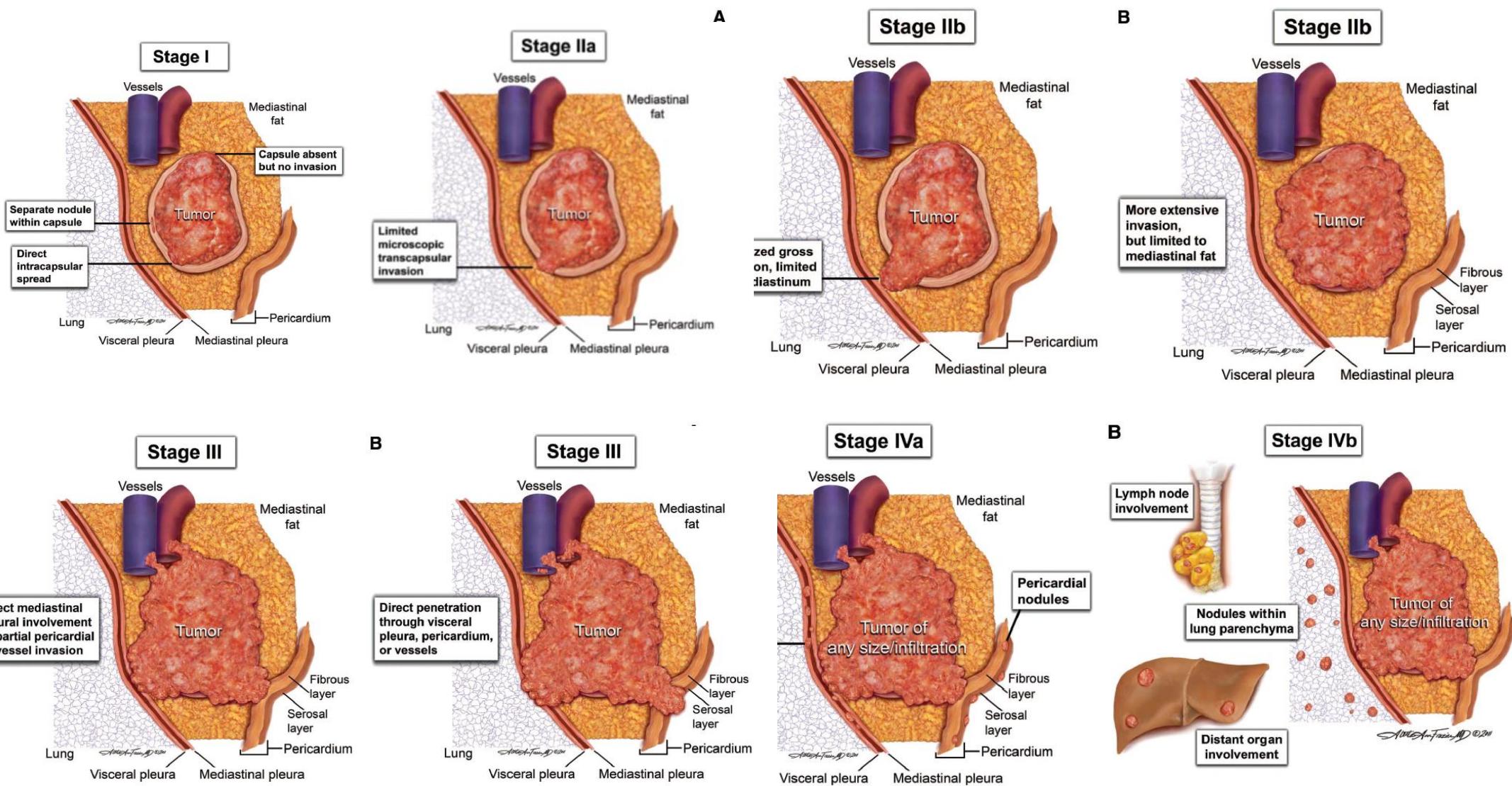
Staging Systems

- MASAOKA-KOGA resectability
- WHO classification histology
- TNM classification tumour – nodes - metastases

MASAOKA-KOGA Staging

- Stage I:
 - *macroscopically completely encapsulated.*
 - *microscopically no capsular invasion.*
- Stage IIa:
 - *microscopic invasion into capsule*
- Stage IIb:
 - *macroscopic invasion into surrounding fatty tissue or mediastinal pleura.*
- Stage III:
 - *macroscopic invasion into neighboring organs (lung, phrenic nerve, vein).*
- Stage IVa:
 - *pleural or pericardial dissemination.*
- Stage IVb:
 - *lymphatic or hematogenous metastasis.*

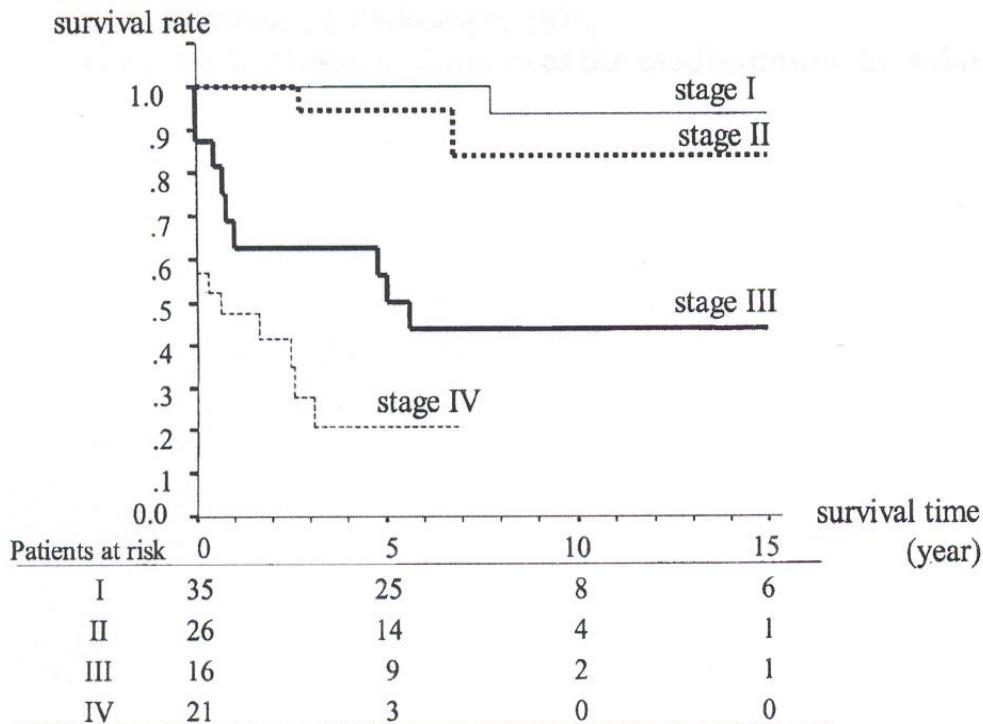
MASAOKA-KOGA Staging



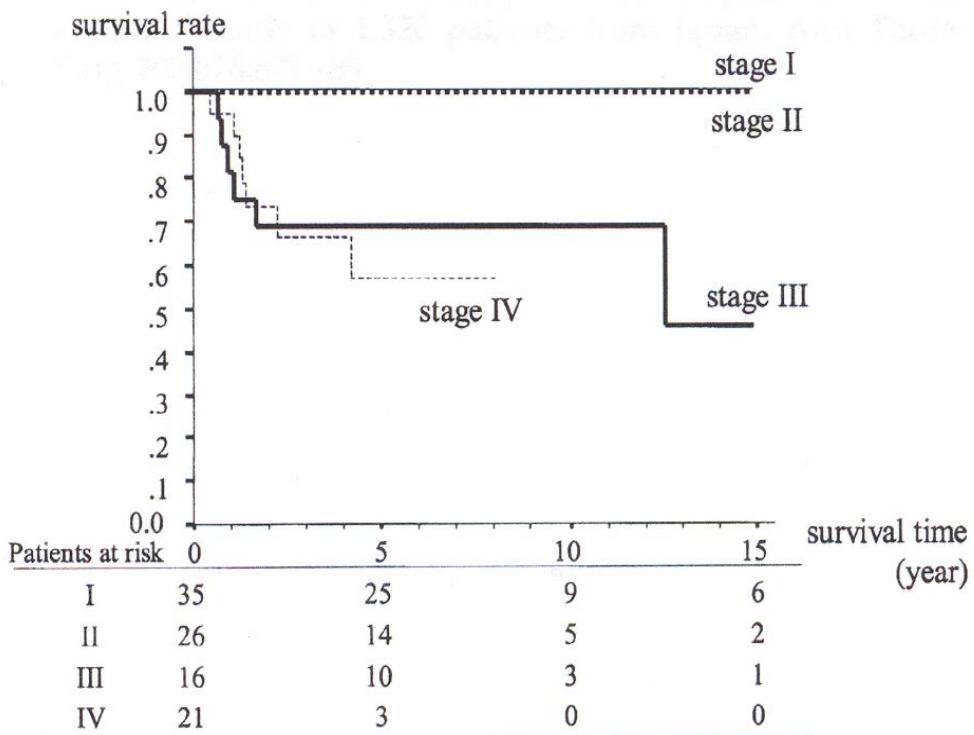
Thymoma

MASAOKA - KOGA

DISEASE-FREE SURVIVAL



OVERALL SURVIVAL



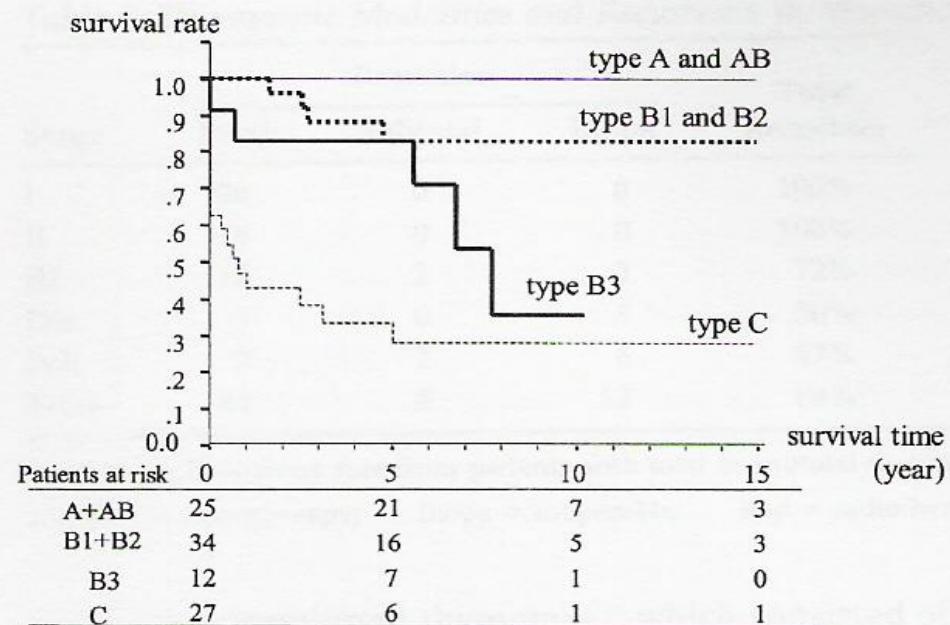
WHO Classification (old)

Type A	Spindle cell, medullary
Type AB	Mixed
Type B1	Predominantly cortical, lymphocyte rich
Type B2	Cortical
Type B3	Well-differentiated thymic carcinoma
Type C	Thymic carcinoma

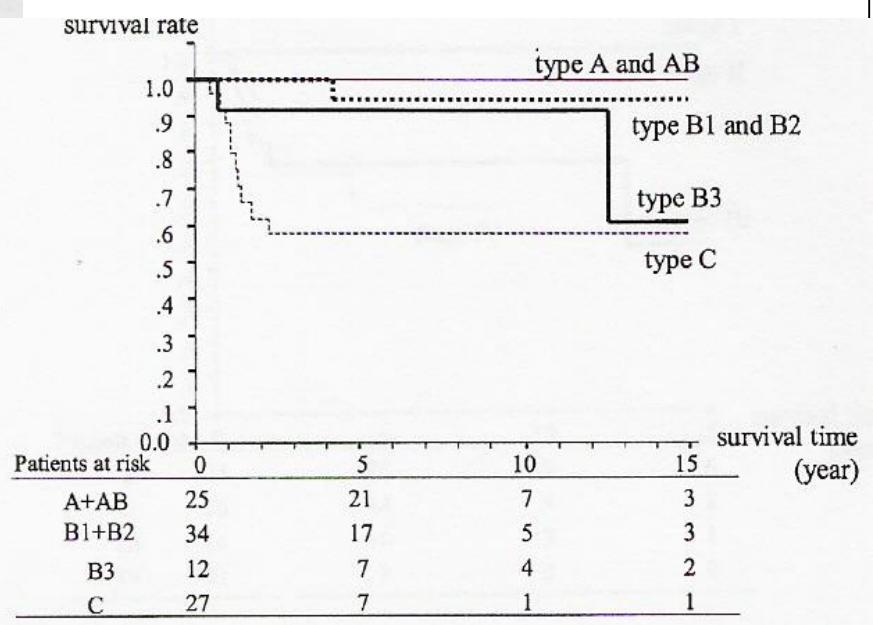
Thymoma

WHO Classification

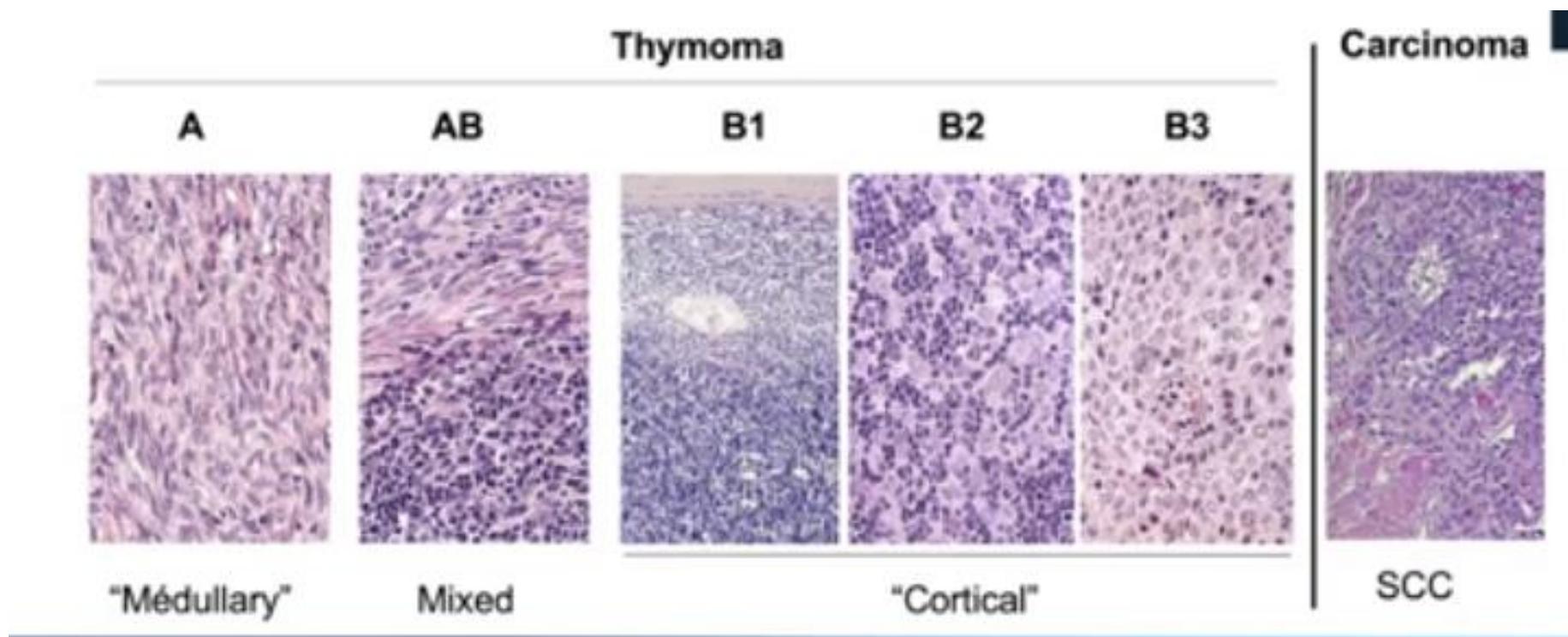
Disease-free survival curve



Survival curve



ITMIG Consensus Statement on the Use of the WHO Histological Classification of Thymoma and Thymic Carcinoma: Refined Definitions, Histological Criteria, and Reporting



TNM Classification

- T (T1 – T2 – T3 – T4)
 - local invasion
 - pericardium – pleura - lung
 - prognostic factor
- N (N1 – N2 – N3)
 - thymic carcinoma > thymoma
 - skip metastases possible
 - prognostic factor N+ versus N-
- M (M0 – M1)
 - liver – spleen – bone – kidney
 - thymic carcinoma > thymoma
 - prognostic factor M+ versus M-

TNM 8th Edition (based on ITMIG proposal)

TABLE 1. T Categories and Descriptors

T	Descriptors
T1	A tumor that either is limited to the thymus with or without encapsulation, directly invades into the mediastinum only or directly invades the mediastinal pleura but does not involve any other mediastinal structure For further testing, T1 is subdivided into T1a (no mediastinal pleural involvement) and T1b (direct invasion of the mediastinal pleura) <i>(Level 1 structures—thymus, anterior mediastinal fat, mediastinal pleura)</i>
T2	A tumor with direct invasion of the pericardium (either partial or full-thickness) <i>(Level 2 structures—pericardium)</i>
T3	A tumor with direct invasion into any of the following: lung, brachiocephalic vein, SVC, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins <i>(Level 3 structures—lung, brachiocephalic vein, SVC, phrenic nerve, chest wall, hilar pulmonary vessels)</i>
T4	A tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus <i>(Level 4 structures—aorta [ascending, arch, or descending], arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus)</i>

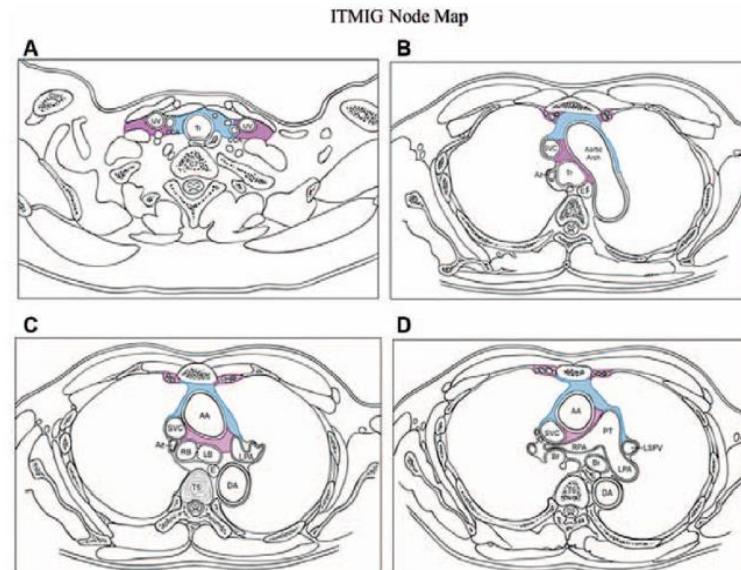
T categories are defined by “levels” of invasion; they reflect the highest degree of invasion regardless of how many other (lower level) structures are invaded.

SVC, superior vena cava.

TABLE 1. N, M Descriptors

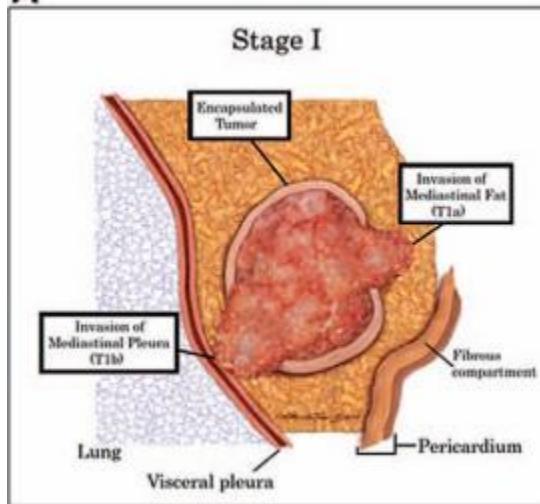
Category	Definition (Involvement of) ^a
N0	No nodal involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes
M0	No metastatic pleural, pericardial, or distant sites
M1	
a	Separate pleural or pericardial nodule(s)
b	Pulmonary intraparenchymal nodule or distant organ metastasis

^aInvolvement must be pathologically proven in pathologic staging.

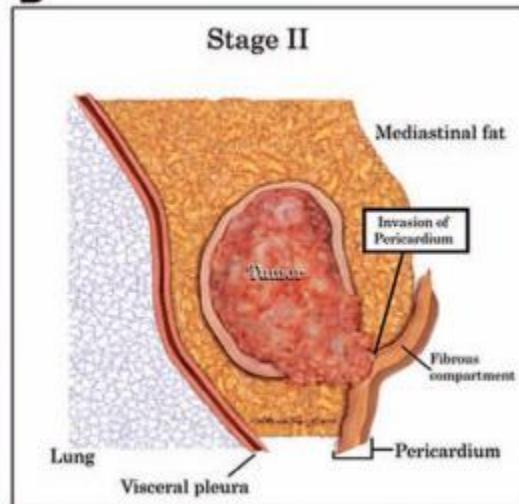


TNM 8th Edition

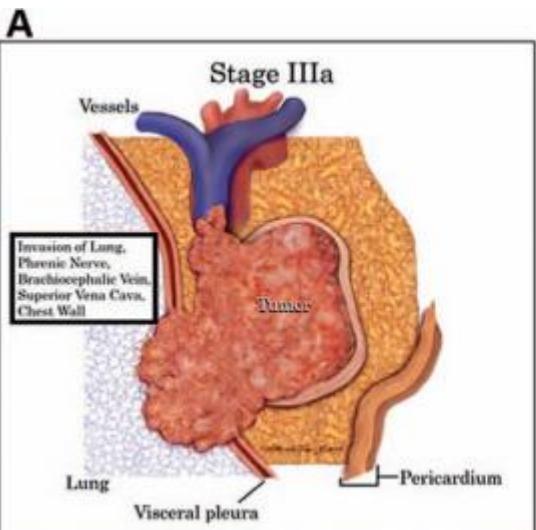
A



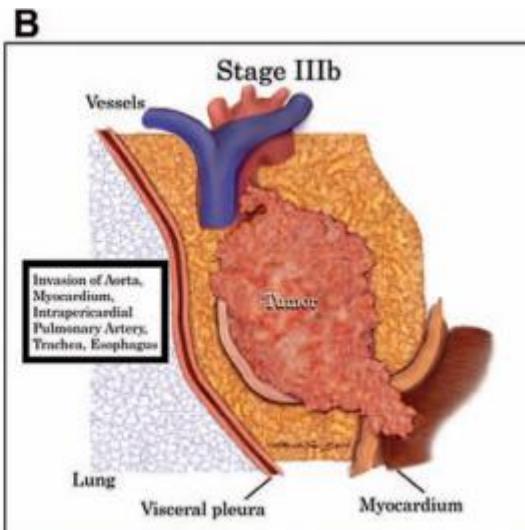
B



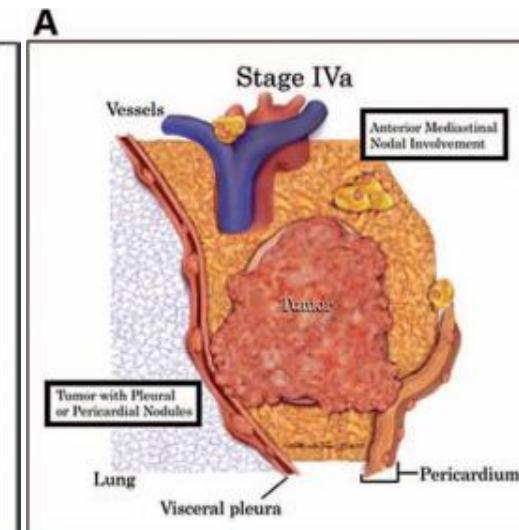
A



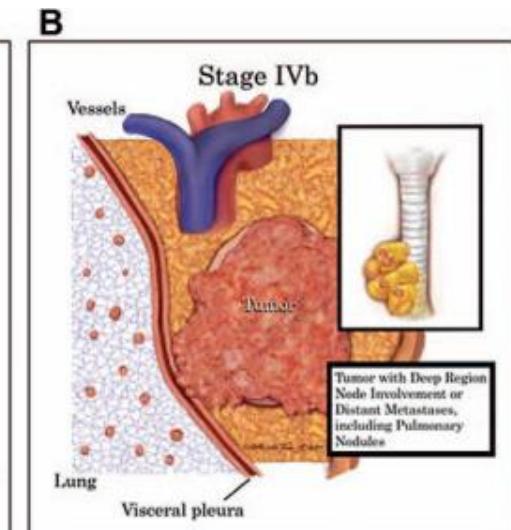
B



A



B

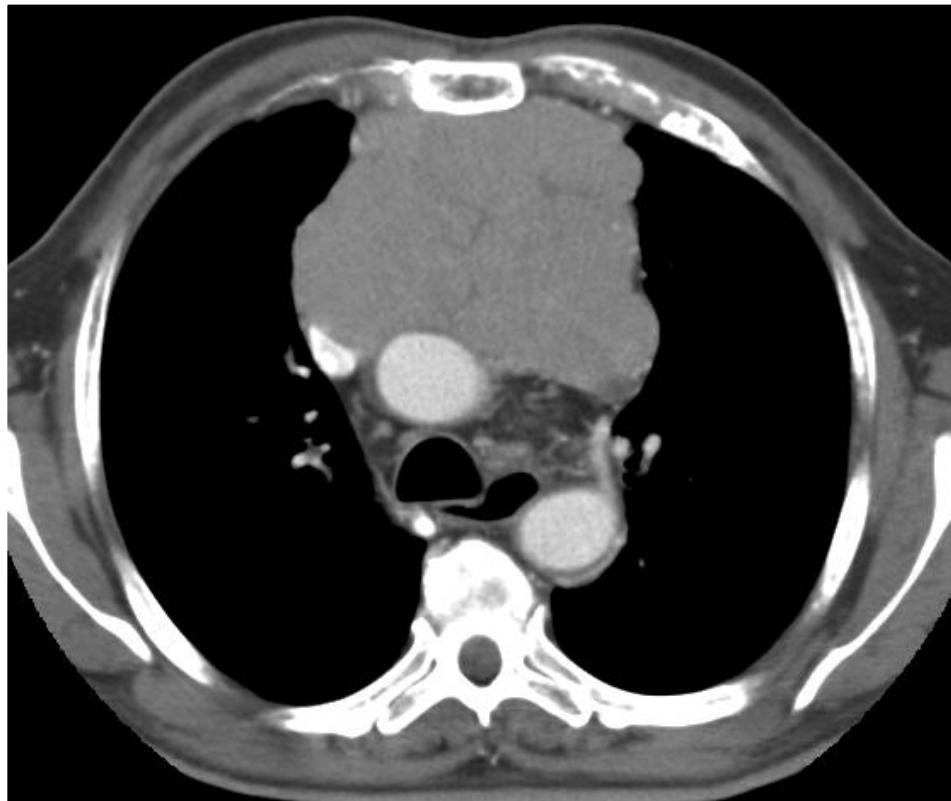


Treatment Algorithm

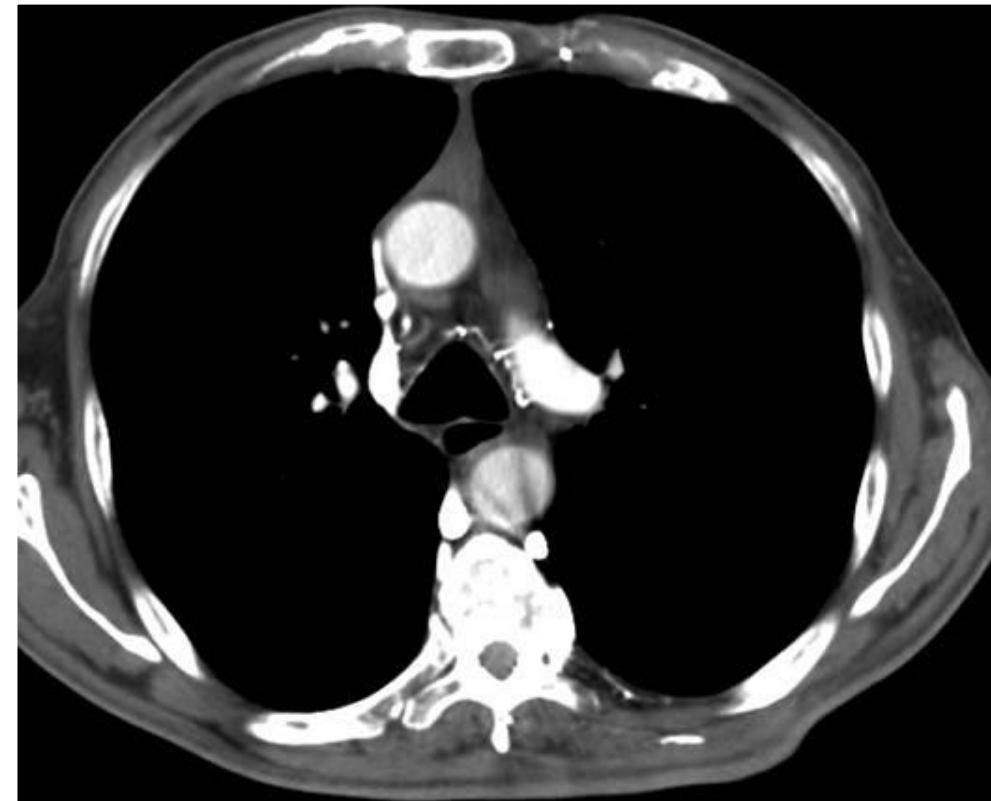
- TNM stage I
SURGERY
- TNM stage II - III
SURGERY + PORT (limited to R1-R2 only?)
- TNM stage III & IV:
MULTIMODAL THERAPY

Note: level 1 evidence is lacking!

Induction Chemotherapy ADOC - CAP



Pre



Post

NCCN guidelines: surgical principles

Complete excision!



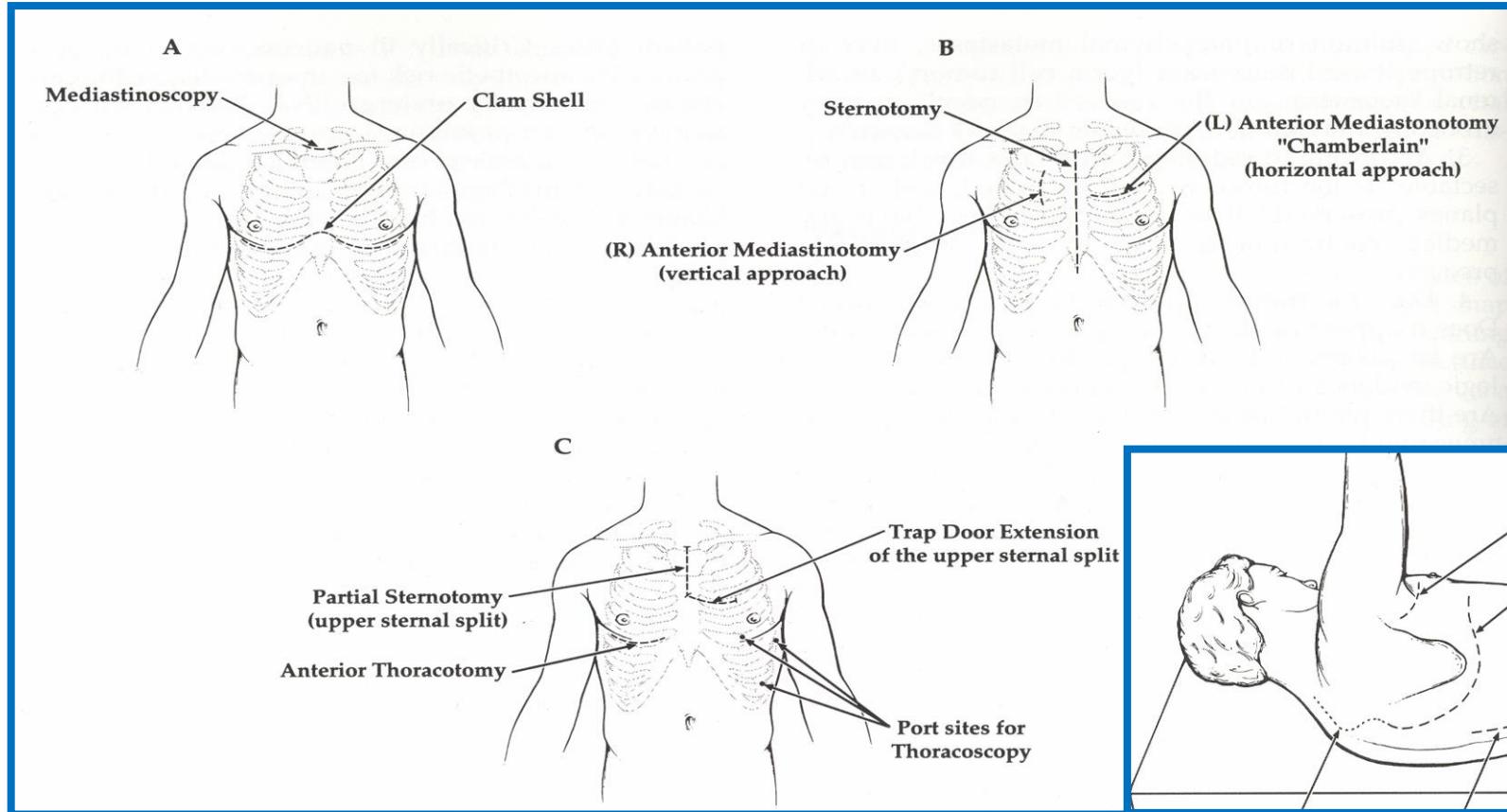
NCCN Guidelines Version 1.2013 Thymomas and Thymic Carcinomas

[NCCN Guidelines Index](#)
[Thymic Table of Contents](#)
[Discussion](#)

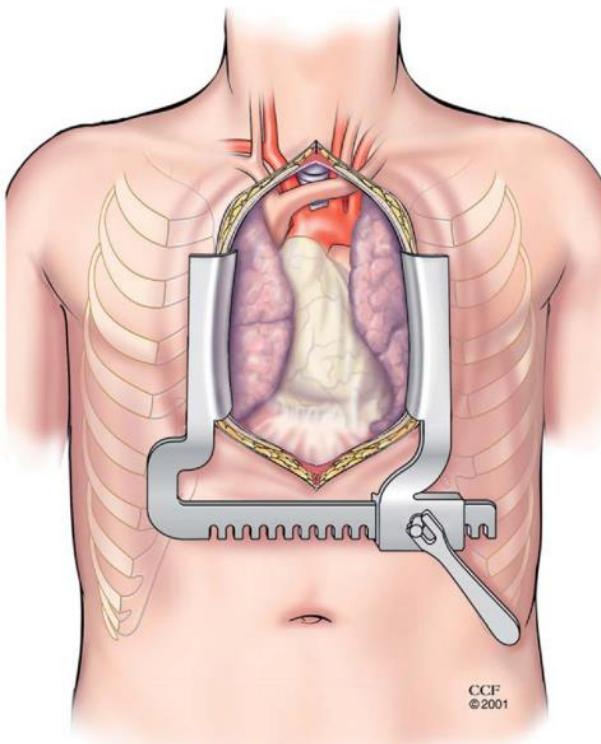
PRINCIPLES OF SURGICAL RESECTION

- Surgical resection should be performed on carefully evaluated patients by board-certified thoracic surgeons. Locally advanced (unresectable) and resectable stage \geq II cases should be discussed and evaluated by a multidisciplinary team.
- Surgical biopsy should be avoided if a resectable thymoma is strongly suspected based on clinical and radiologic features.
- Biopsy of a possible thymoma should avoid a transpleural approach.
- Prior to surgery, patients should be evaluated for signs and symptoms of myasthenia gravis and should be medically controlled prior to undergoing surgical resection.
- Goal of surgery is complete excision of the lesion with total thymectomy and complete resection of contiguous and noncontiguous disease.
- Complete resection may require the resection of adjacent structures, including the pericardium, phrenic nerve, pleura, lung, and even major vascular structures. Bilateral phrenic nerve resection should be avoided due to severe respiratory morbidity.
- During thymectomy, the pleural surfaces should be examined for pleural metastases. In some cases, resection of pleural metastases to achieve complete gross resection may be appropriate.
- Minimally invasive procedures are not routinely recommended due to the lack of long-term data. However, minimally invasive procedures may be considered in select patients if done all oncologic goals can be met as in standard procedures, and if performed in specialized centers by surgeons with experience in these techniques.¹

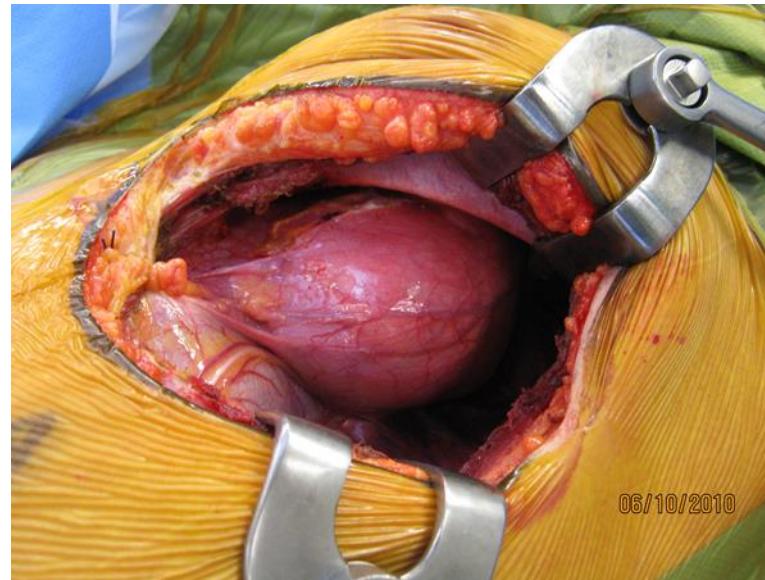
Surgical Approach to Intrathoracic Tumours



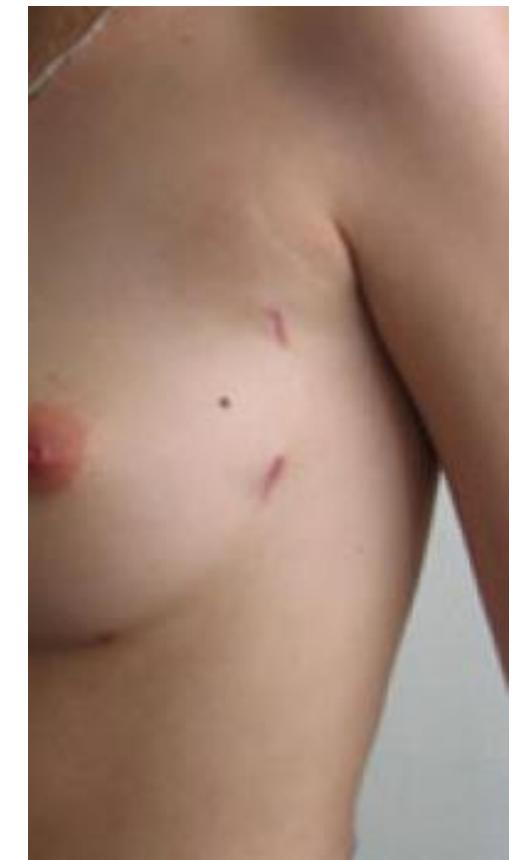
Sternotomy



Thoracotomy



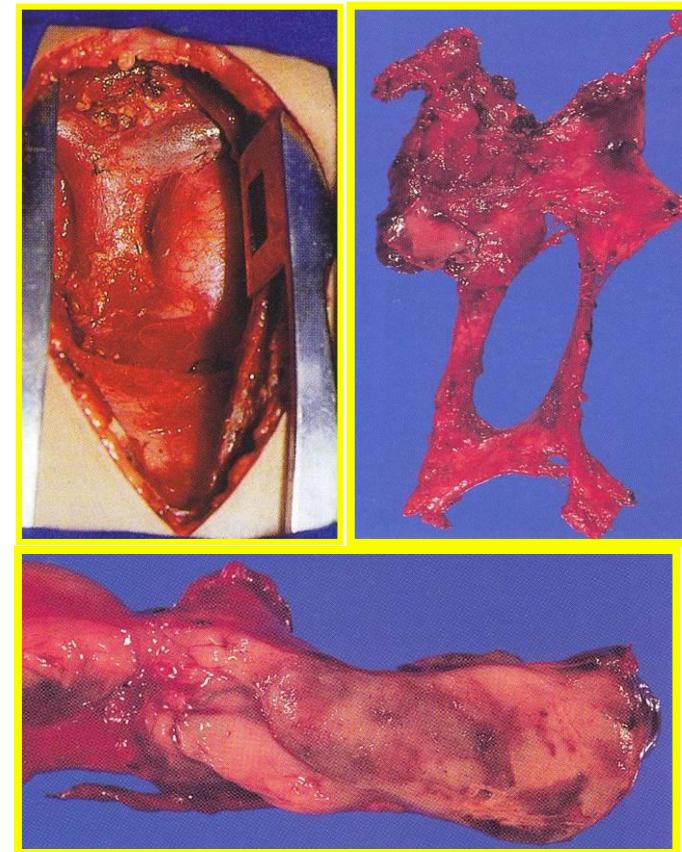
VATS



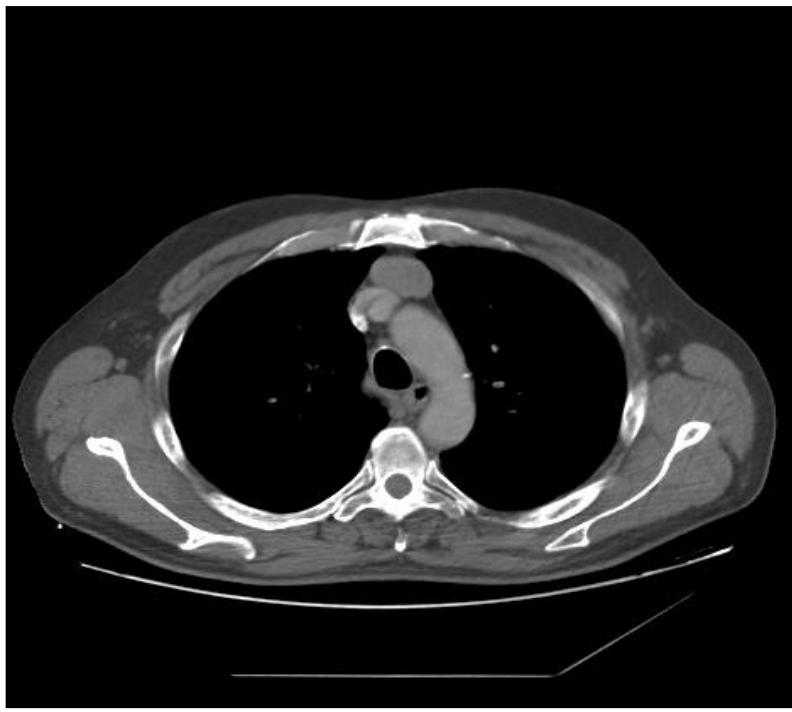


SURGERY

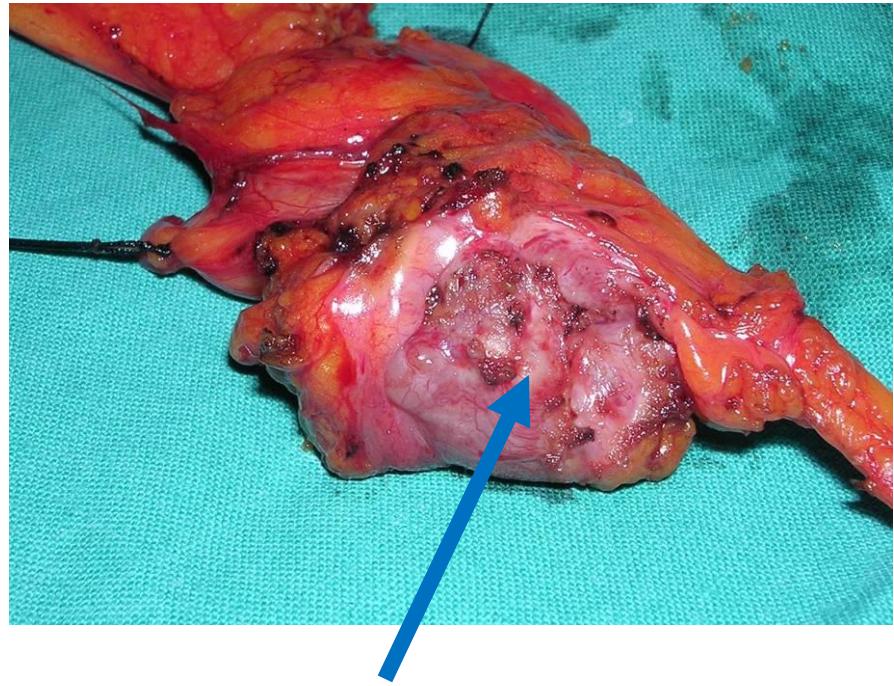
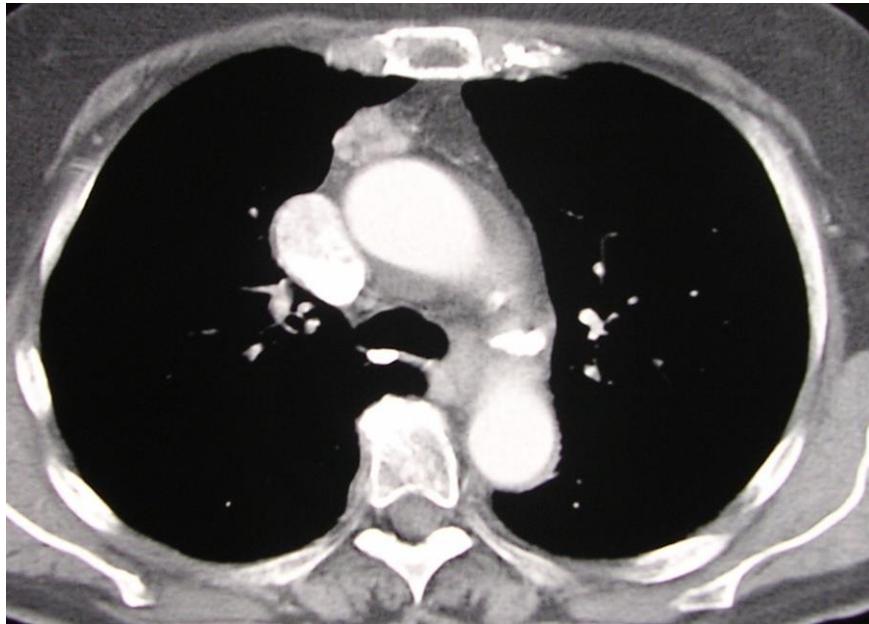
- **Complete Resection !**
en bloc total thymectomy + mediastinal fat
+ vital structures (when invaded):
 - pericardium – pleura
 - phrenic nerve – innominate vein
 - lung (wedge – lobe – pneumonectomy)



Stage I



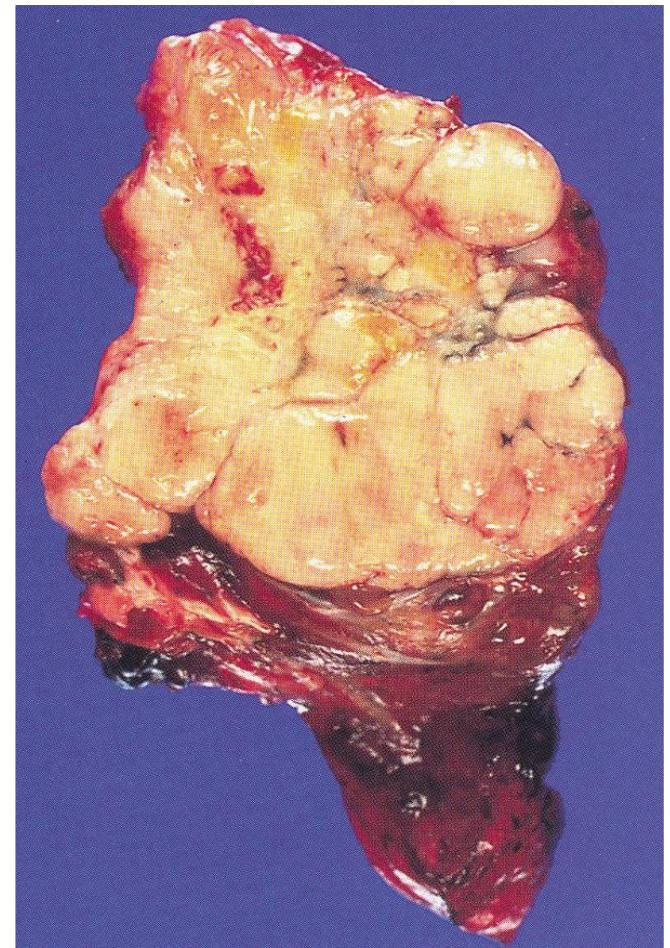
Stage II



Pericardium

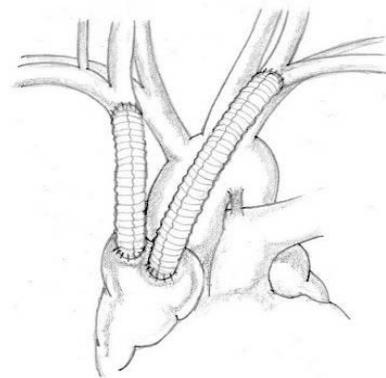
Stage IIIa

lung invasion

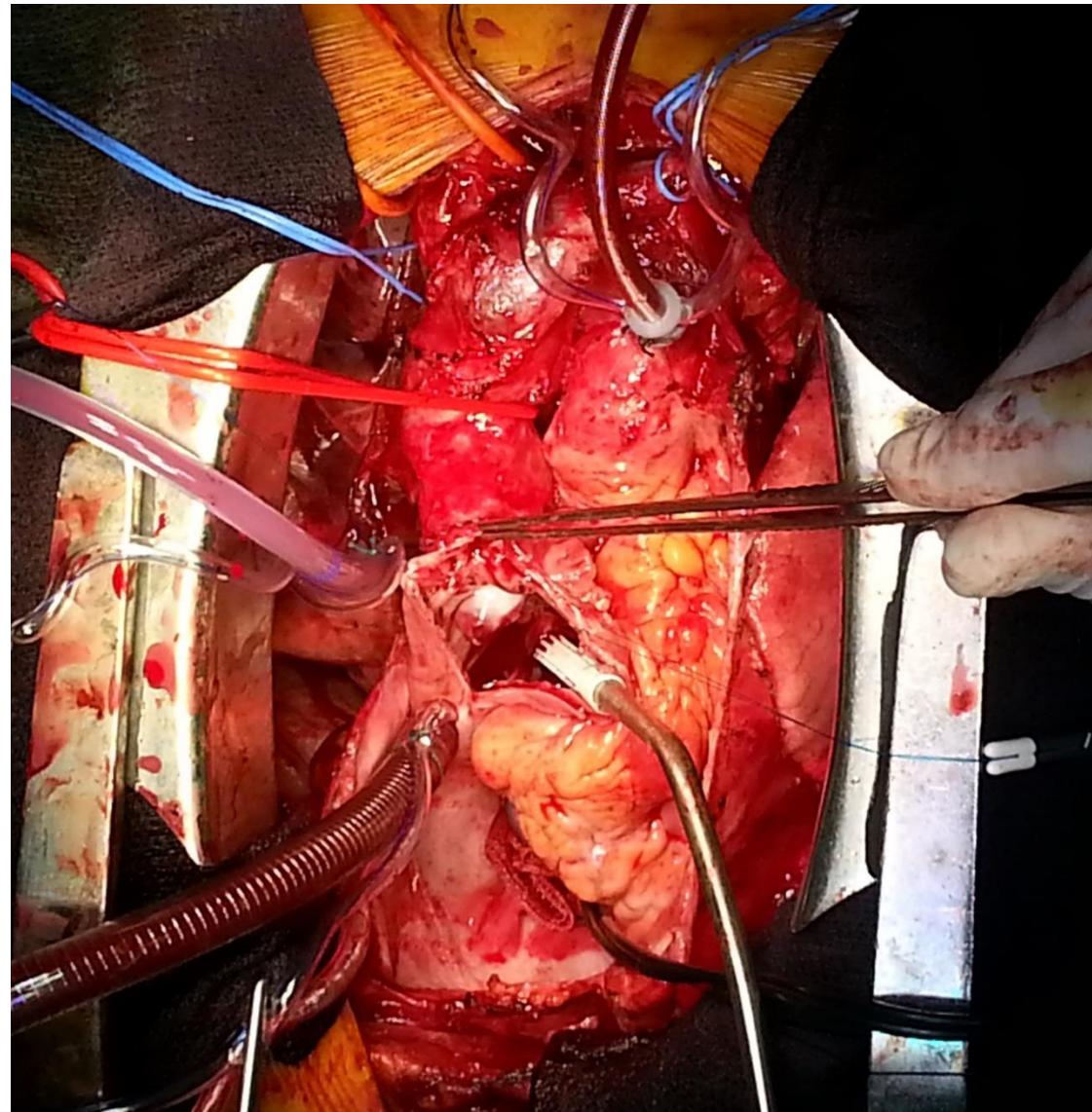


Stage IIIa

venous invasion



Stage IIIb

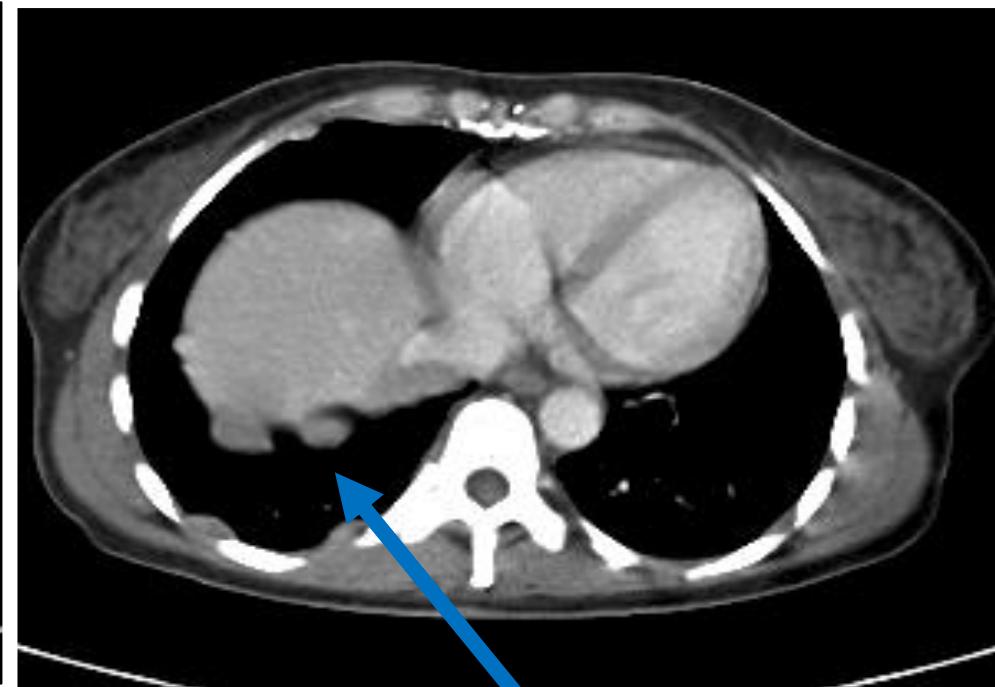


invasion

intrapericardial

vessels

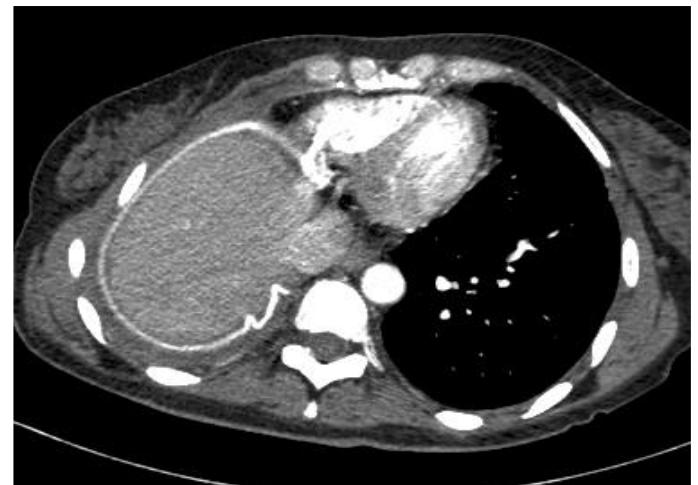
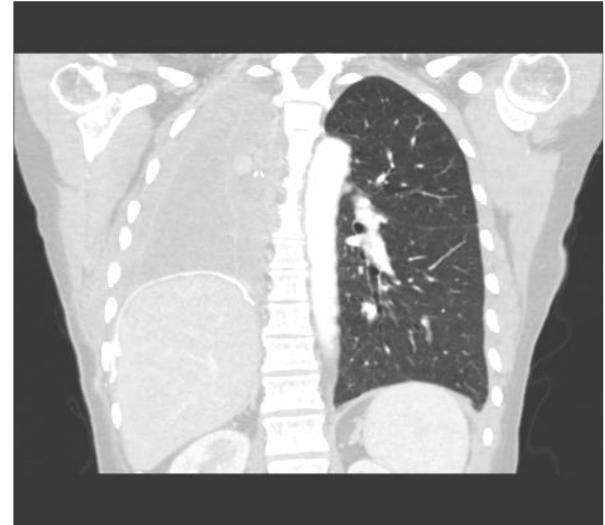
Stage IVa



pleural droplet metastases

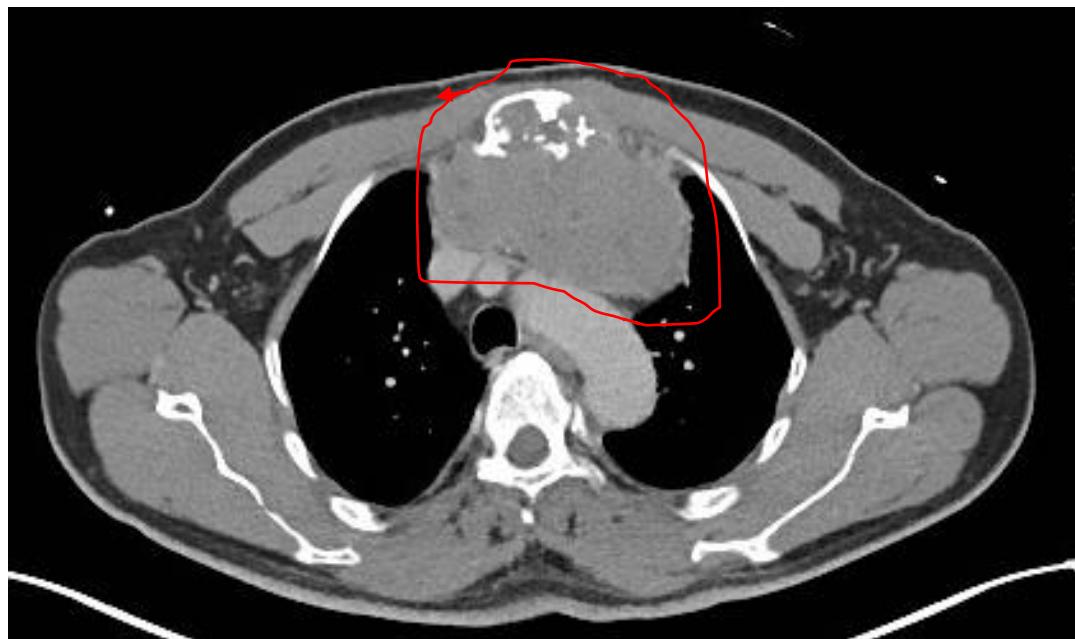
Stage IVa

- local pleural resection (debulking)
- pleurectomy & decortication?
- Intrapleural heated chemotherapy?
- extrapleural-pneumonectomy?

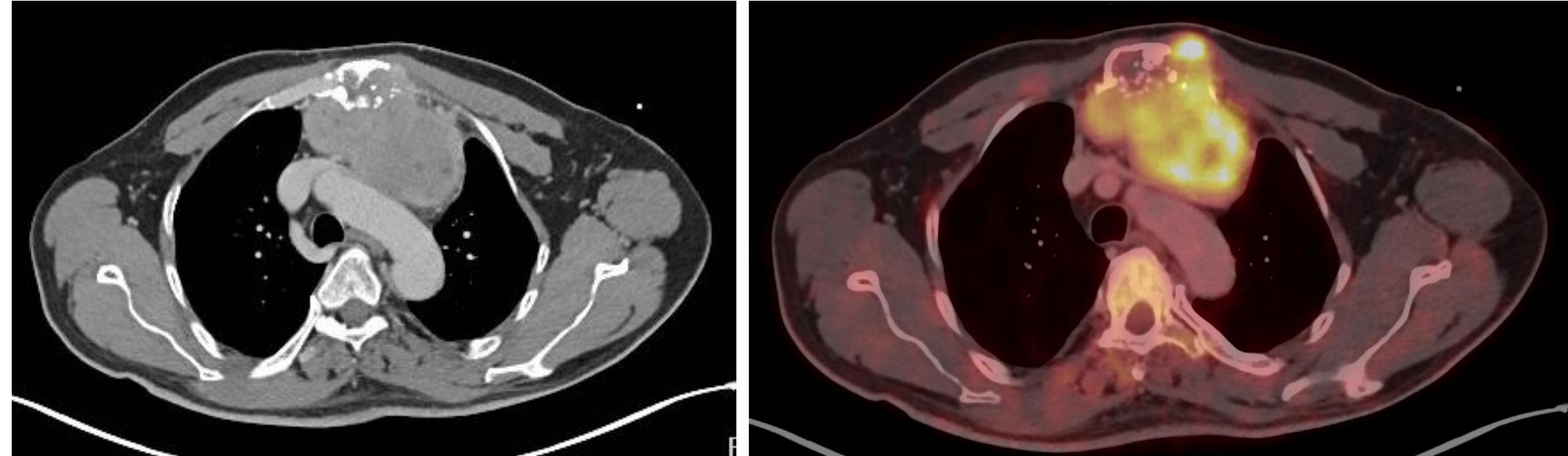


Thymic Carcinoma

- * 61-year male
- * Interscapular pain
- * Palpable mass sternum



Thymic Carcinoma



- **Induction chemotherapy 4 x CAP**
- En bloc resection & reconstruction
- Adjuvant radiotherapy

Thymic Carcinoma



- Induction chemotherapy 4 x CAP
- En bloc resection & reconstruction
- Adjuvant radiotherapy

NCCN guidelines: follow up



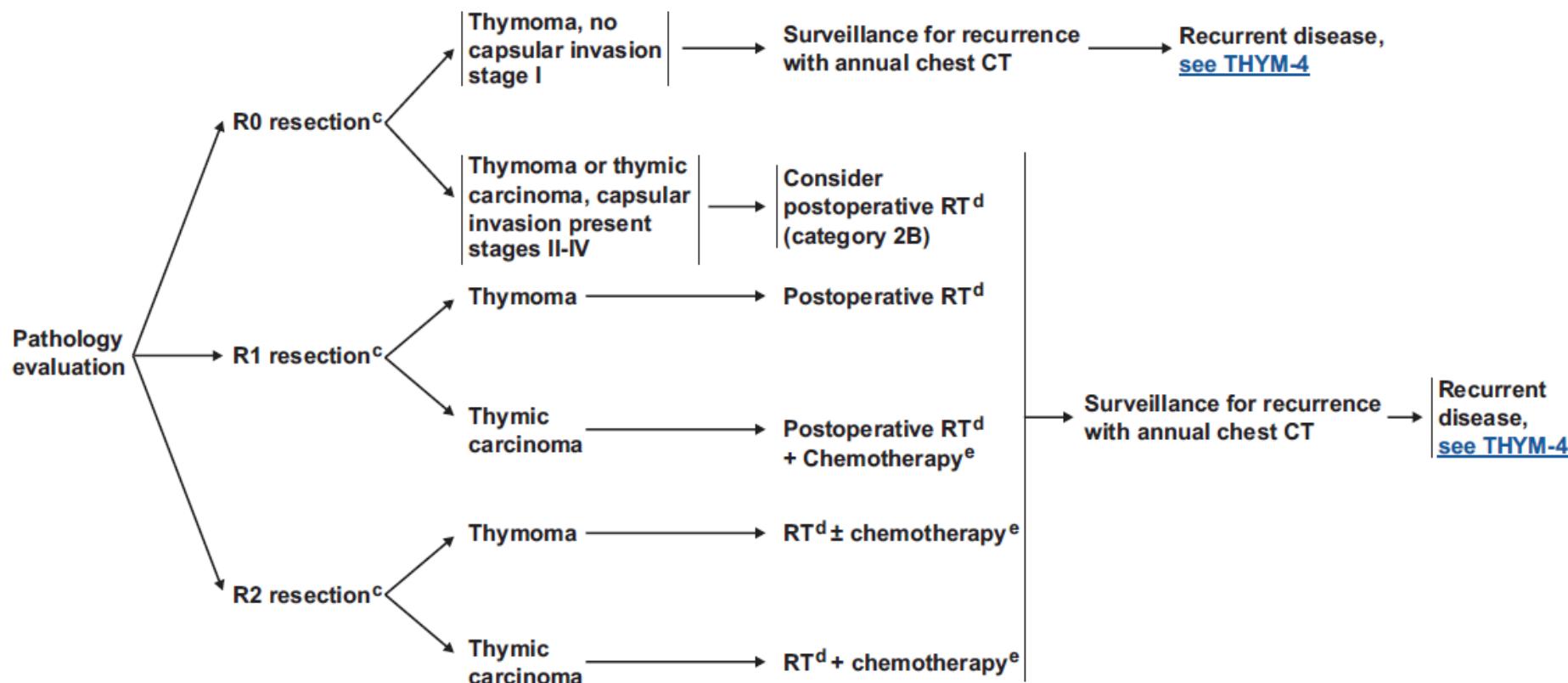
National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2013 Thymomas and Thymic Carcinomas

[NCCN Guidelines Index](#)
[Thymic Table of Contents](#)
[Discussion](#)

RESECTABLE DISEASE^b

POSTOPERATIVE MANAGEMENT



Conclusions

- ❖ good knowledge of anatomy – mediastinal compartments
- ❖ differential diagnosis: age - symptoms
- ❖ non-invasive diagnostic tests (markers, scans)
- ❖ do not biopsy well encapsulated tumour!
- ❖ complete resection is most important prognosticator
- ❖ thoracoscopic resection for non-invasive lesions
- ❖ thoracotomy / sternotomy for invasive lesions