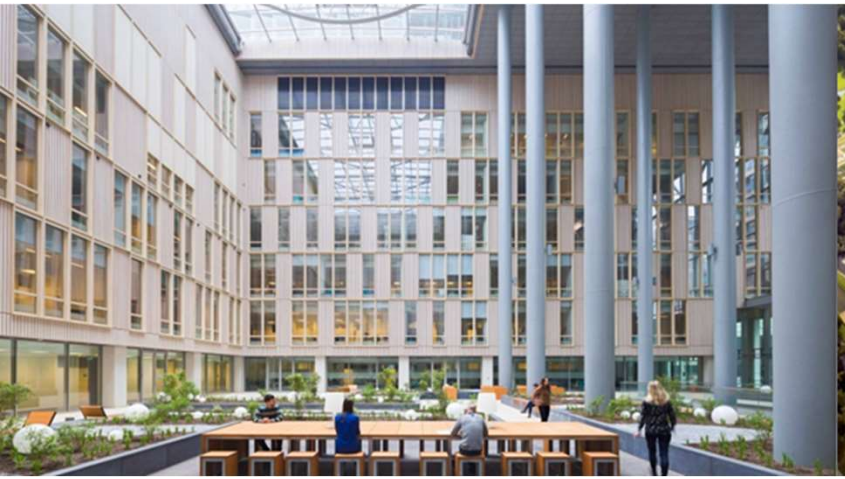
Classification of thymic tumors



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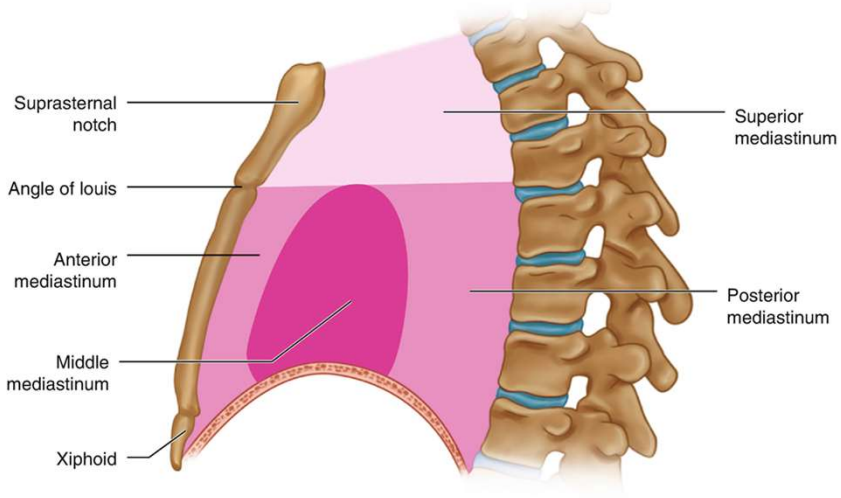
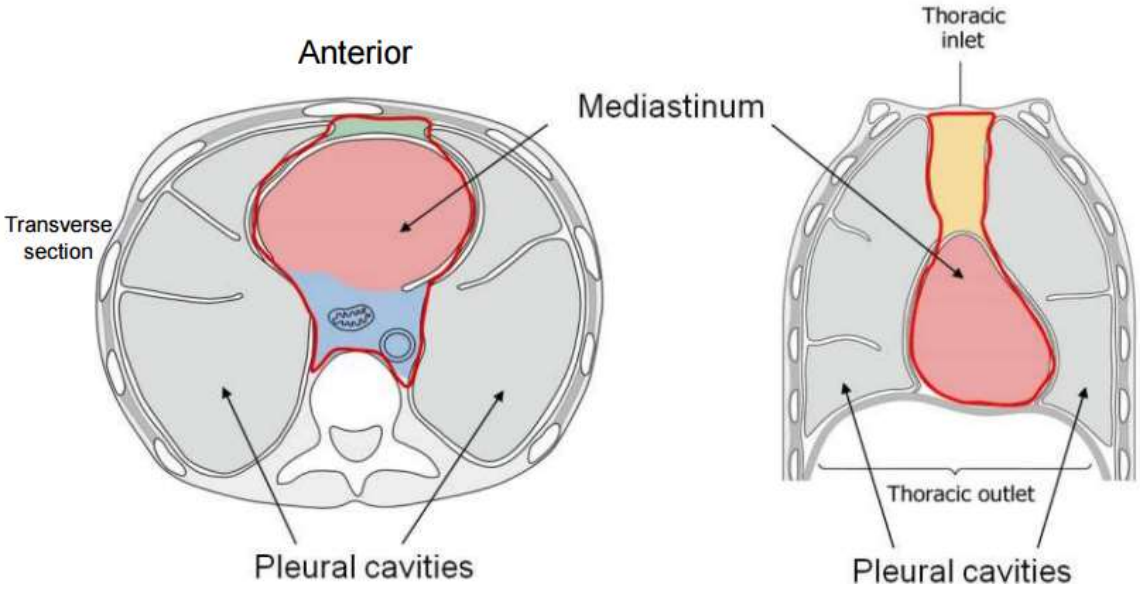
University Medical Center Rotterdam

Mediastinum





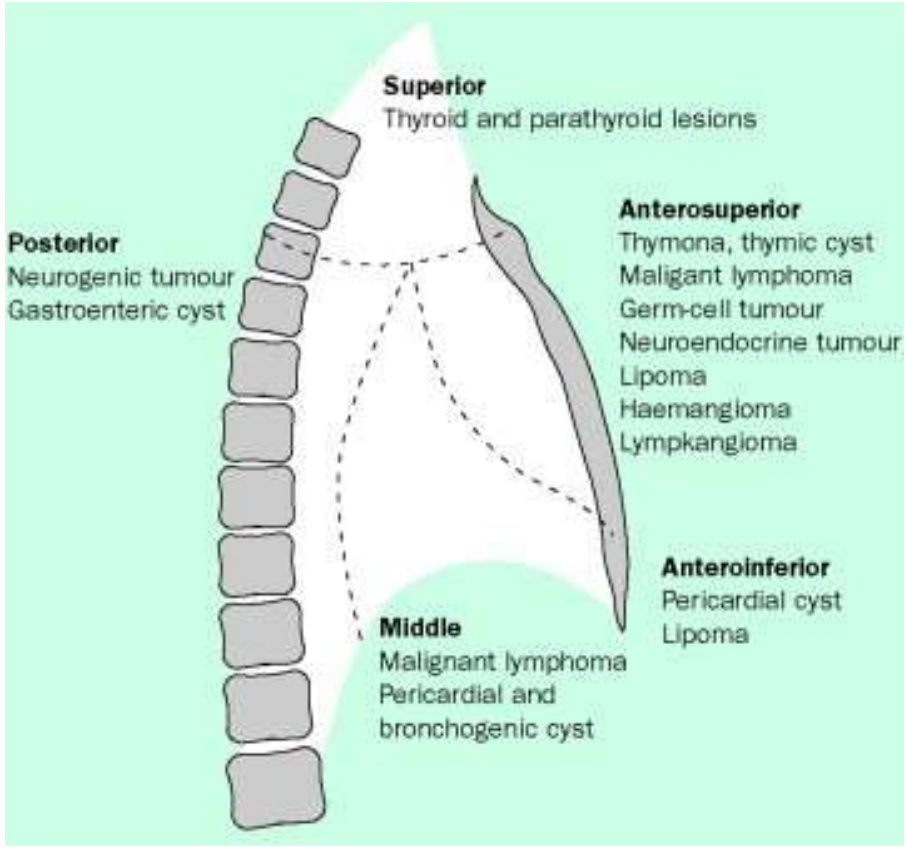
Mediastinal tumours

Children:

- Posterior mediastinum
- Usually benign
- 2/3 symptomatic

Adults:

- Anterior mediastinum
- Often malignant
- 30-50 years
- 1/3 symptomatic



Mediastinal tumours

Malignant tumours:

- 25% of total
  - Antero-superior 59%
  - Posterior 16%
  - Middle 16%

Epidemiology

- Prevalence of mediastinal tumours: 0.73-0.9%
- Esp. in prevascular/anterior compartiment
- TETs most frequent mediastinal tumor (27.8%) followed by benign cysts (20%) and primary mediastinal lymphomas (16.1%).
- 10-15% of mediastinal tumours are germ cell tumours (60-70% non-seminoma)
- Mediastinum most common location of extragonadal germ cell tumour (4%)
- Median age mediastinal germ cell tumours: 25-35 year

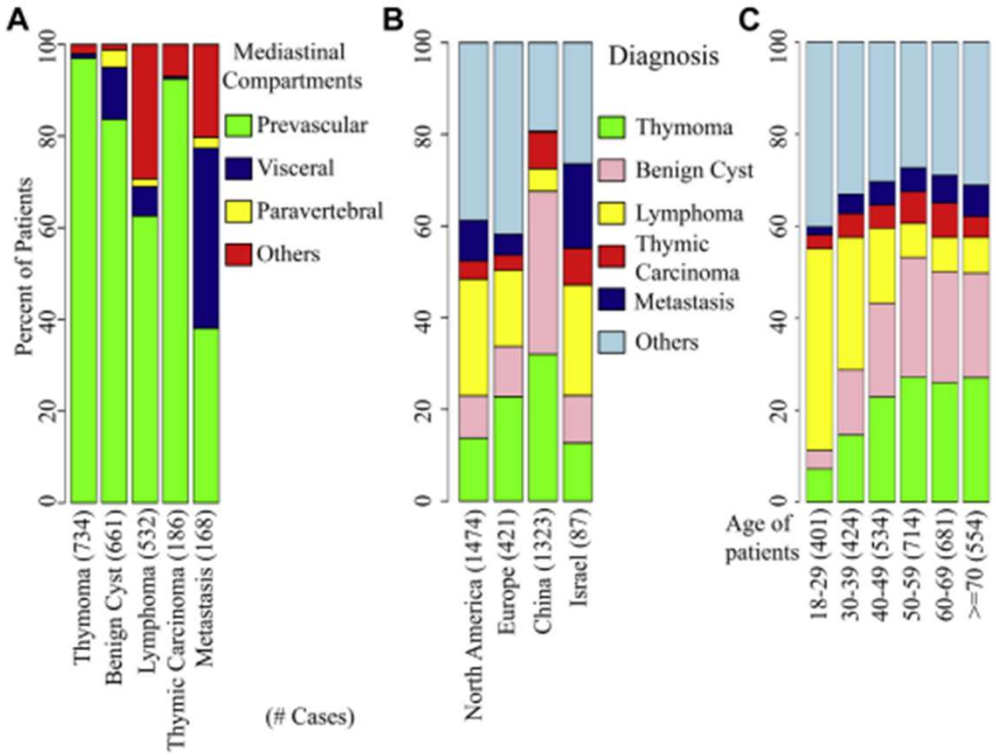


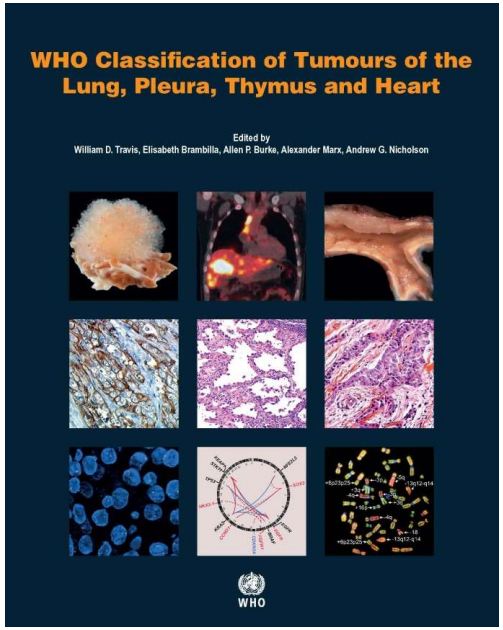
Figure 1. *(A)* Distribution of the most common mediastinal lesions throughout the different compartments. "Other" compartments include lesions that were located in more than one compartment including prevascular and visceral, visceral and paravertebral, prevascular, visceral and paravertebral, and prevascular and paravertebral. Distribution of the most common mediastinal lesions based on geographic areas *(B)* and age *(C)*. Other diagnoses include all diagnoses that are listed in Table 3, with the exception of thymoma, benign cyst, lymphoma, thymic carcinoma, and metastasis.

Distribution of Mediastinal Lesions Across Multi-Institutional, International, Radiology Databases (jto.org)

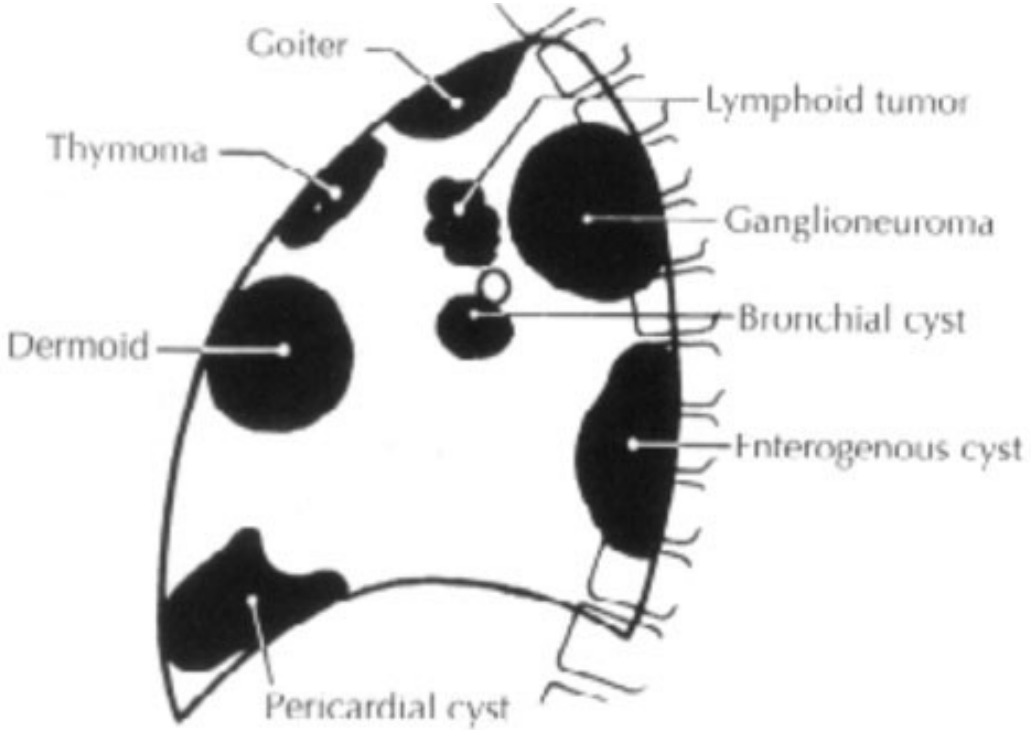
Mediastinal tumours

WHO Classification:

- Thymoma
- Thymic carcinoma
- Neuroendocrine tumours of the thymus
- Combined thymic carcinomas
- Germ cell tumours
- Lymphomas
- Histiocytic and dendritic cell neoplasms
- Myeloid sarcoma and acute myeloid leukemia
- Soft tissue tumours
- Ectopic tumours
- Metastases



Tumours of the mediastinum

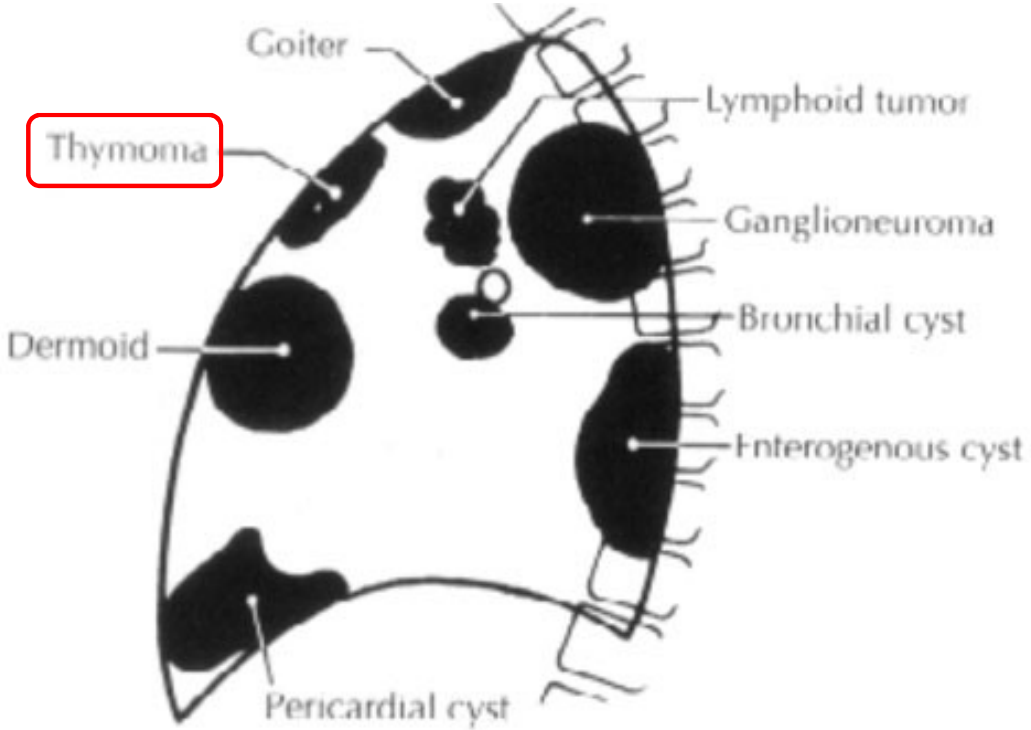


Differential diagnosis of mediastinal mass

Anterior compartment	Middle compartment	Posterior compartment
Thymus ▪ Thymoma ▪ Thymic cyst ▪ Thymic hyperplasia ▪ Thymic carcinoma	Bronchogenic cyst	Neurogenic tumors ▪ Neurofibroma ▪ Neurilemmoma ▪ Neurosarcoma ▪ Ganglioneuroma ▪ Ganglioneuroblastoma ▪ Neuroblastoma ▪ Chemodectoma ▪ Pheochromocytoma
Lymphoma	Pericardial cyst	Meningoceles
Germ cell tumor ▪ Teratoma/dermoid cyst ▪ Seminoma ▪ Non-seminoma - Yolk sac tumor - Embryonal carcinoma - Choriocarcinoma	Lymphadenopathy ▪ Lymphoma ▪ Sarcoid ▪ Metastatic lung cancer	Thoracic spine lesions (eg, Pott's disease)
Intrathoracic thyroid ▪ Substernal goiter ▪ Ectopic thyroid tissue	Enteric cyst	
Parathyroid adenoma	Esophageal tumors	
Hemangioma	Vascular masses and enlargement	
Lipoma		
Liposarcoma		
Fibroma		
Fibrosarcoma		
Foramen of Morgagni hernia		

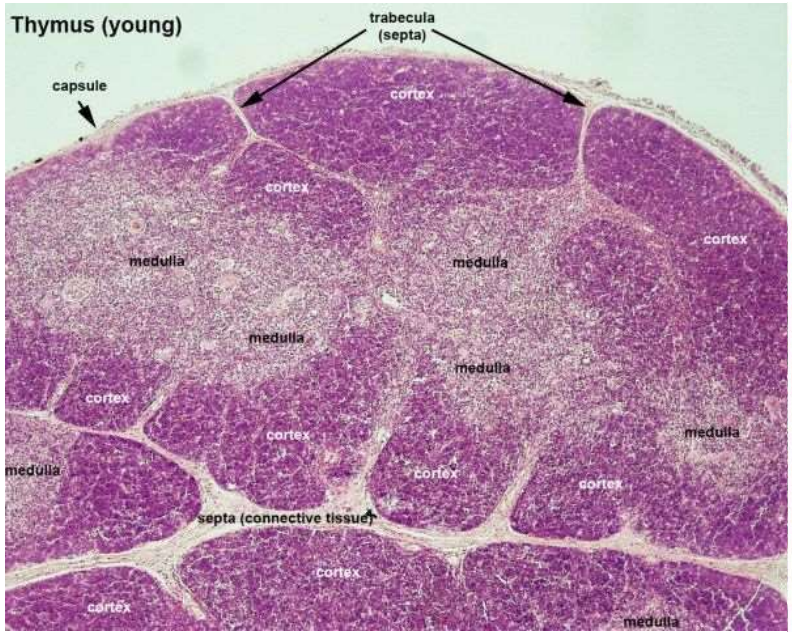
UpToDate®

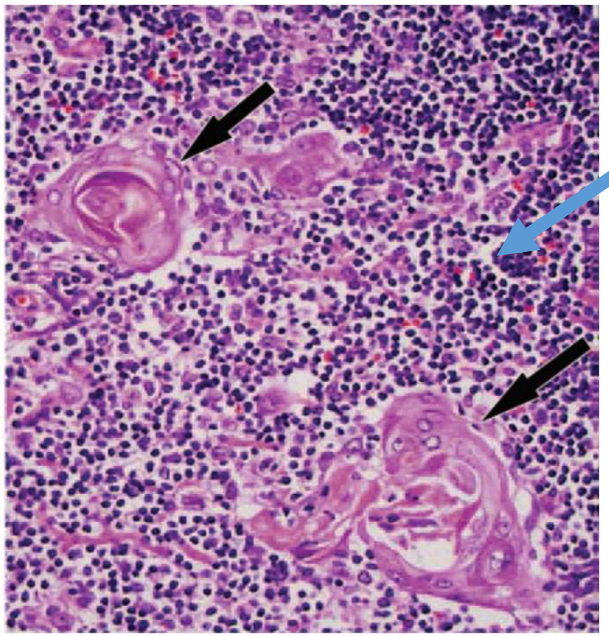
Tumours of the mediastinum



Normal thymus

- Thymus first described as such by Galen of Pergamum (130–200 AD)



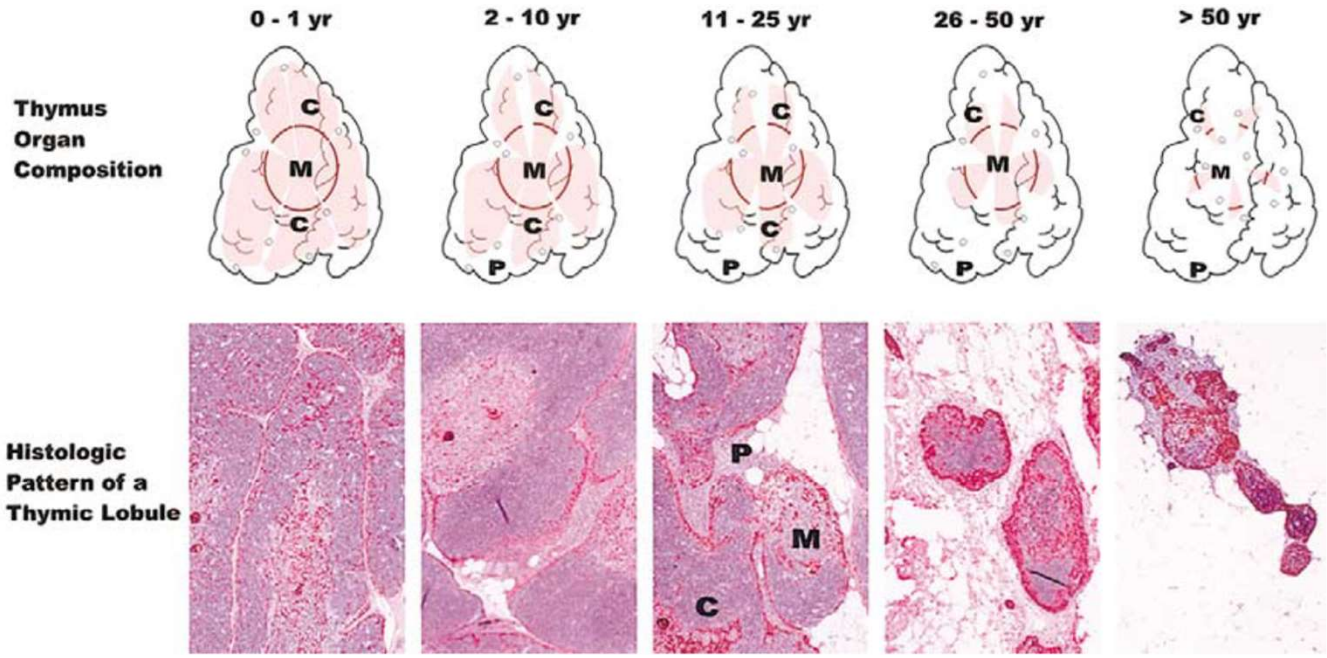


- Epithelial cells
- Lymphocytes
- Role in immune tolerance

Ishino et al. Radiographics, 2006

Normal thymus

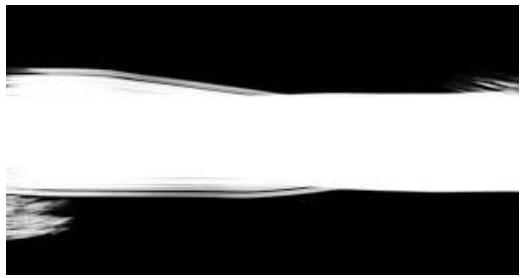
- The thymus reaches its maximum weight in puberty and subsequently undergoes involution



Hale. Ann Diagn Pathol 2004;8:50-60.

Thymoma

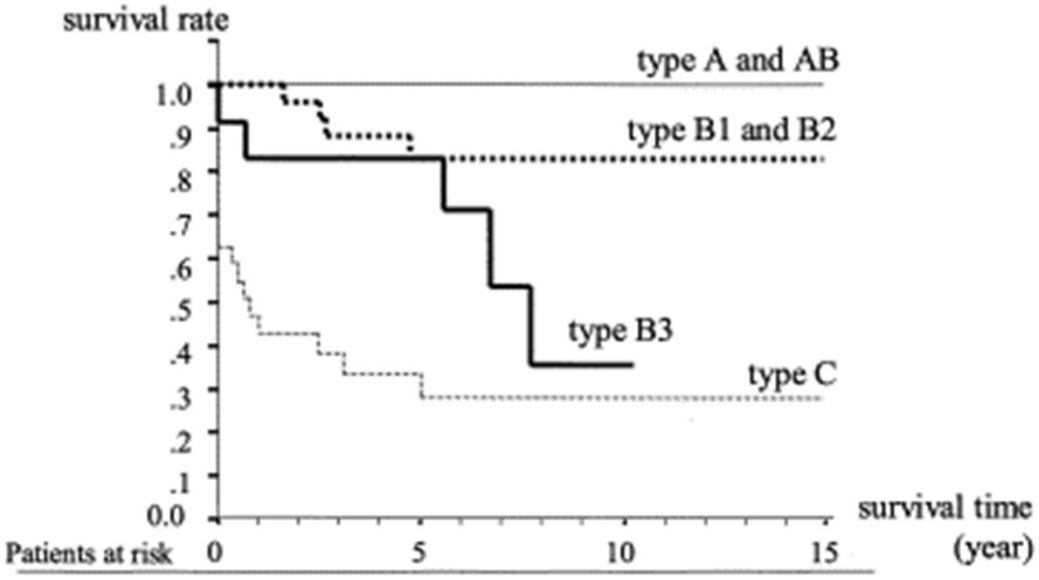
- The term “thymoma” was first introduced by F. Grandhomme in 1900. At that time, it was applied to all *malignant tumors* arising in the thymic gland.
- In 1906 E. T. Bell first described tumors of the thymus that were associated with myasthenia gravis (MG) and used the term “thymoma” meaning *non-malignant tumors*.



Marino and Roden. Mediastinum 2018;2:9; Kondo et al. Ann Thorac. Surg 2004.

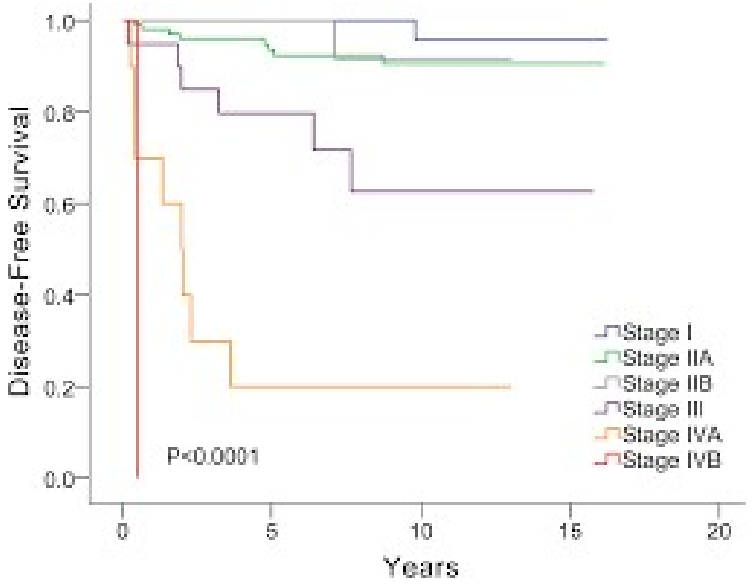
Thymoma prognosis

Histological type



Kondo et al. Ann Thorac Surg. 2004;77(4):1183-1188.

Extent of disease



Tseng et al. PLoS One. 2017;12(6):e0179527.

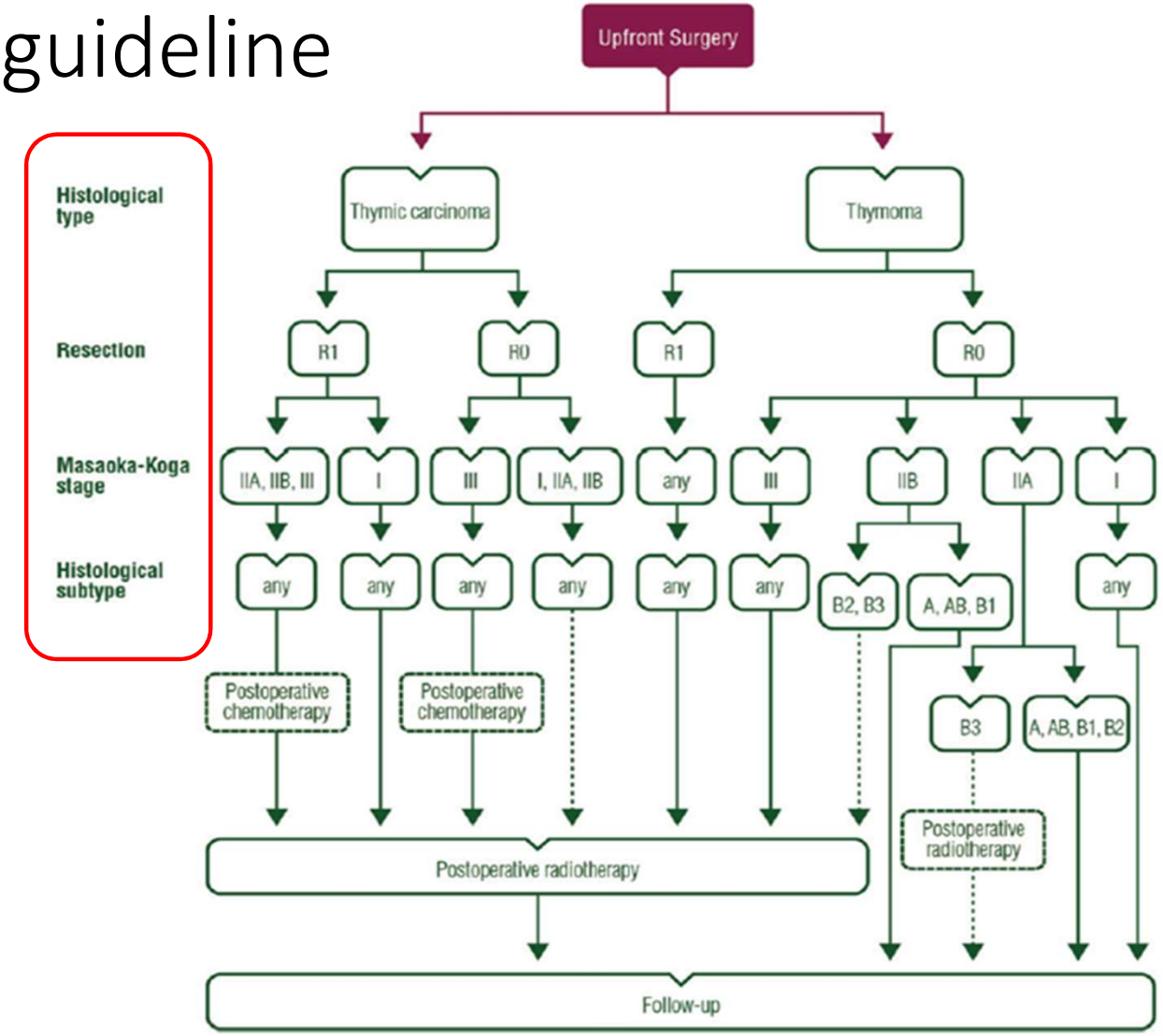
Not 1 disease!

Grading and staging

- **Grading**: Tumor grade is the description of a tumor based on how abnormal the tumor cells and the tumor tissue look under a microscope. It is an indicator of how quickly a tumor is likely to grow and spread. => Thymoma types
- **Staging**: Stage refers to the extent of your cancer, such as how large the tumor is, and if it has spread.

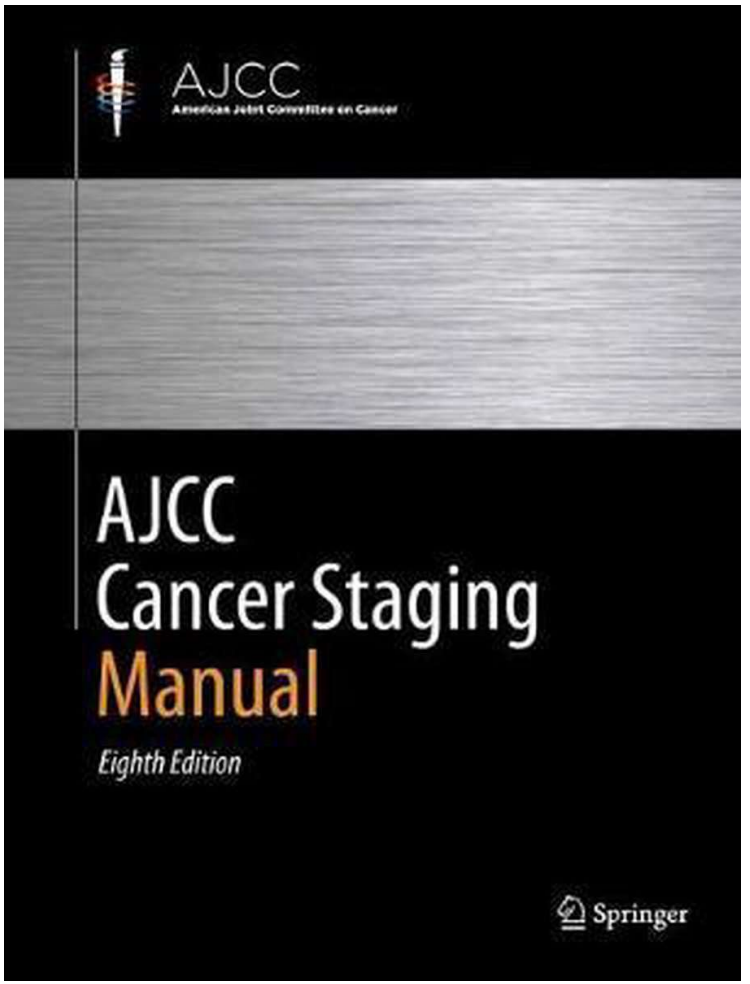
https://www.cancer.gov/about-cancer/diagnosis-staging/prognosis

ESMO guideline



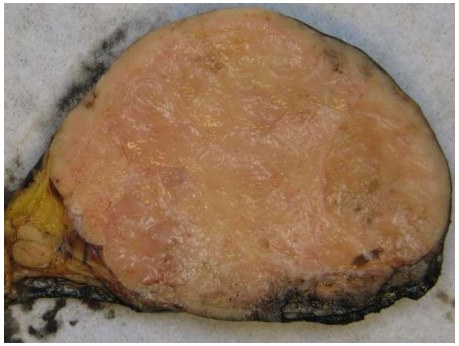
Grading

Staging

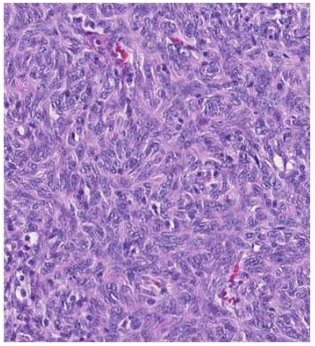


The pathologist's toolbox

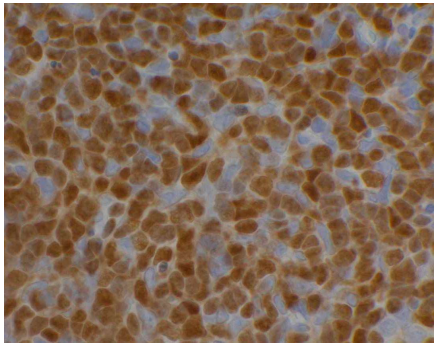
Macroscopy



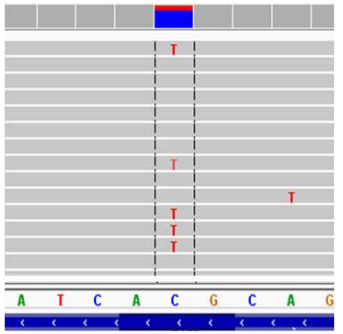
Microscopy



Ancillary stains

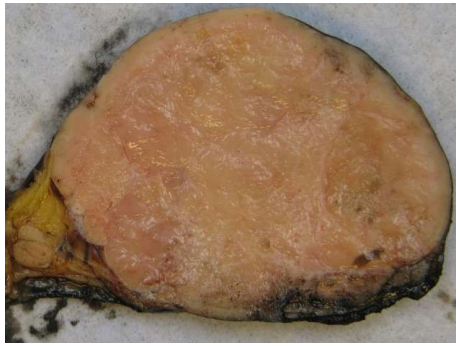


Molecular diagnostics



The pathologist's toolbox

Macroscopy

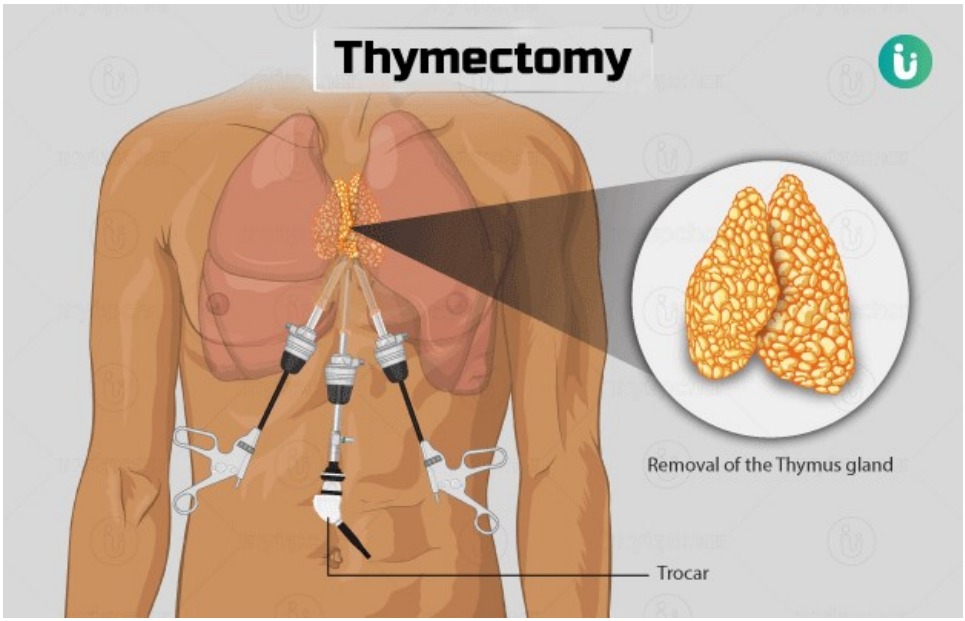


Microscopy

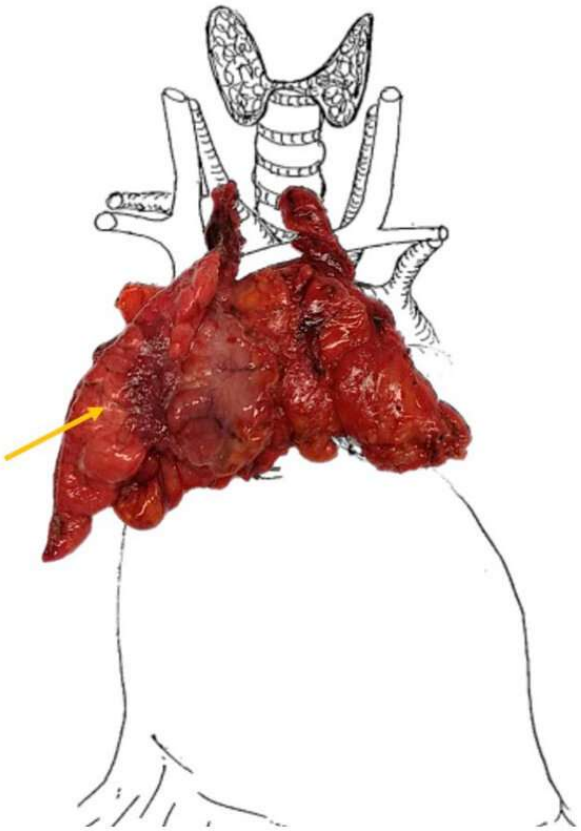
Ancillary stains

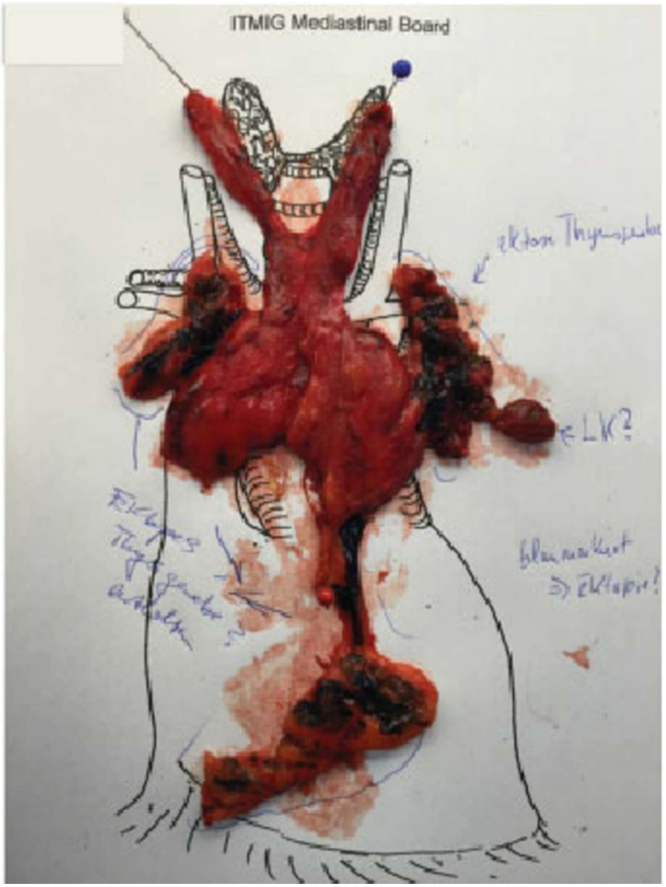
Molecular diagnostics

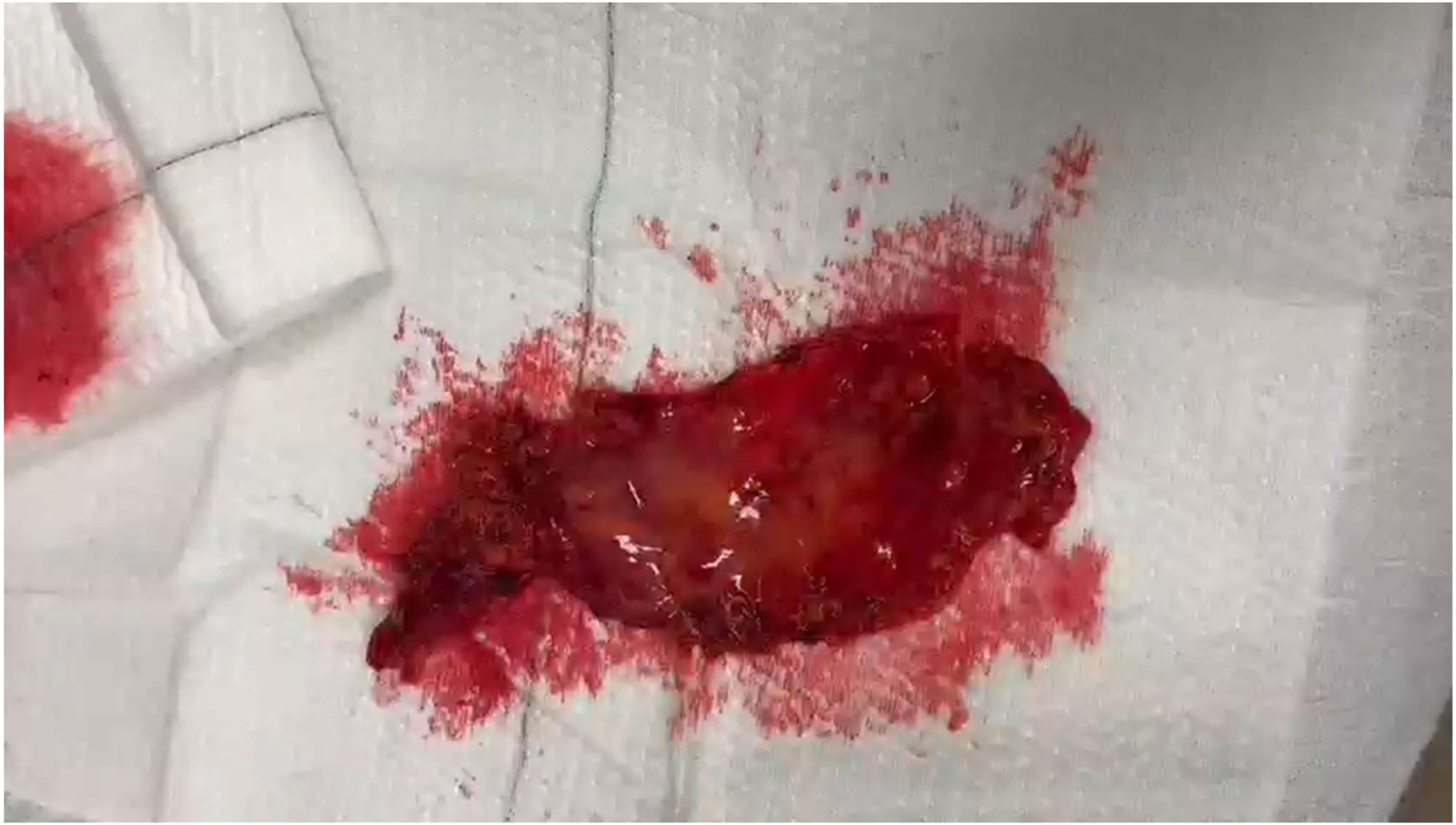
VATS / RATS thymectomy



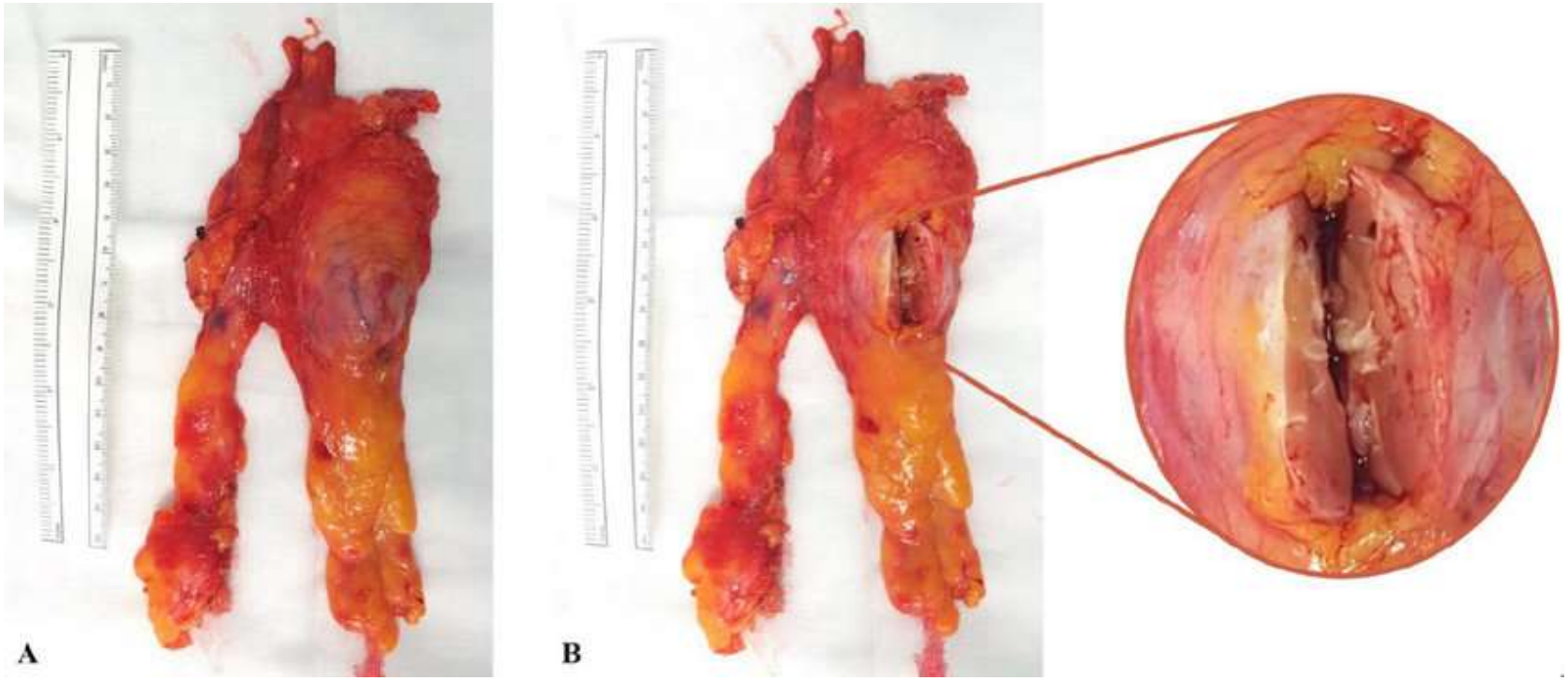
VATS / RATS thymectomy specimen



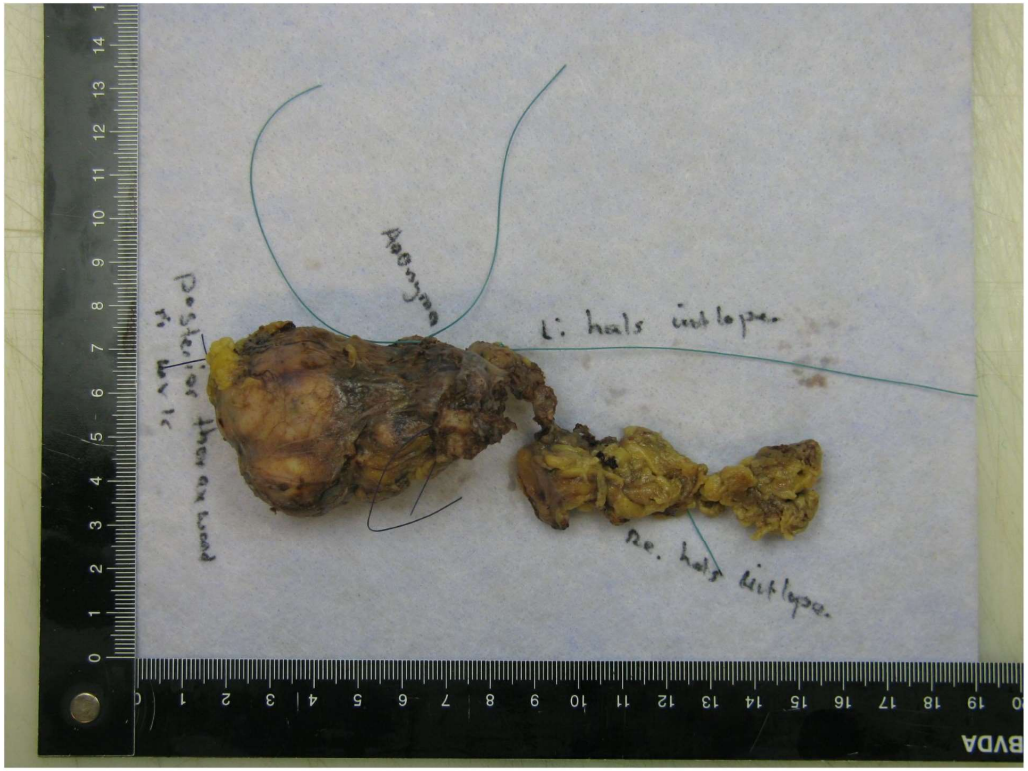




VATS / RATS thymectomy specimen



VATS / RATS thymectomy specimen



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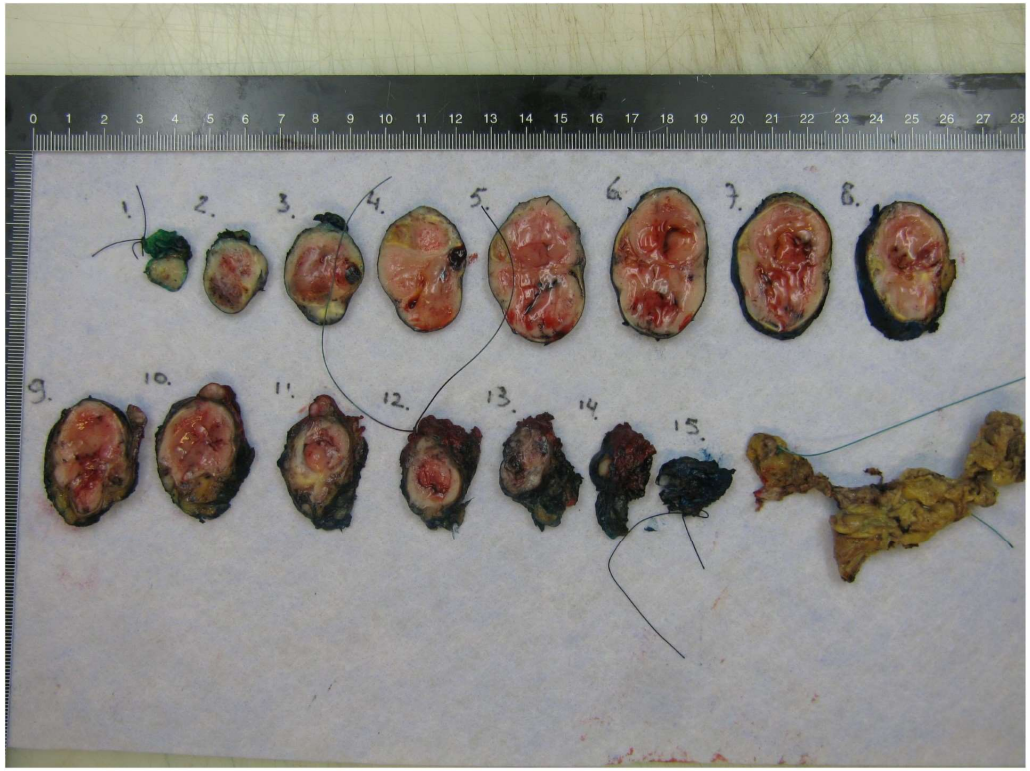

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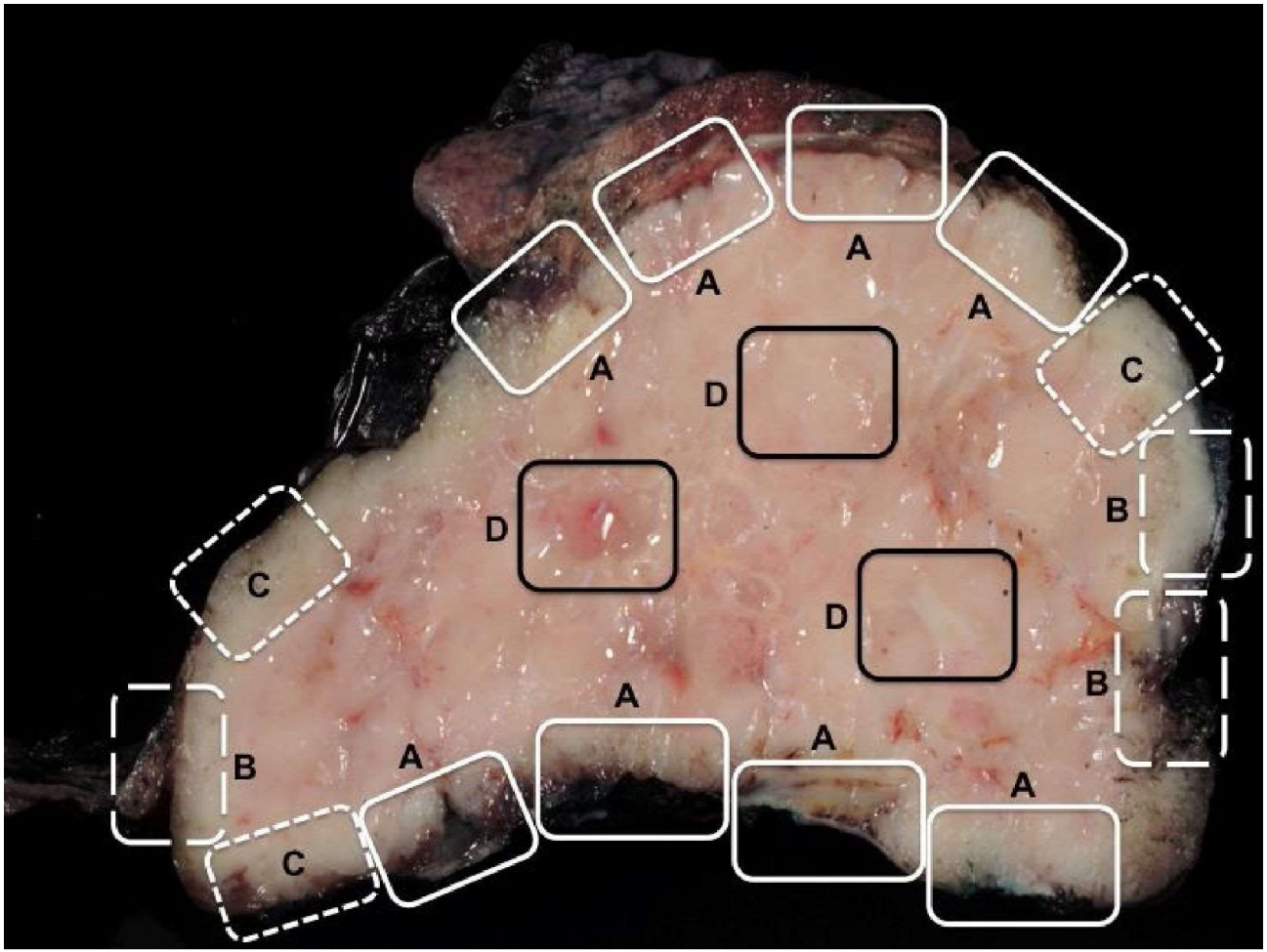
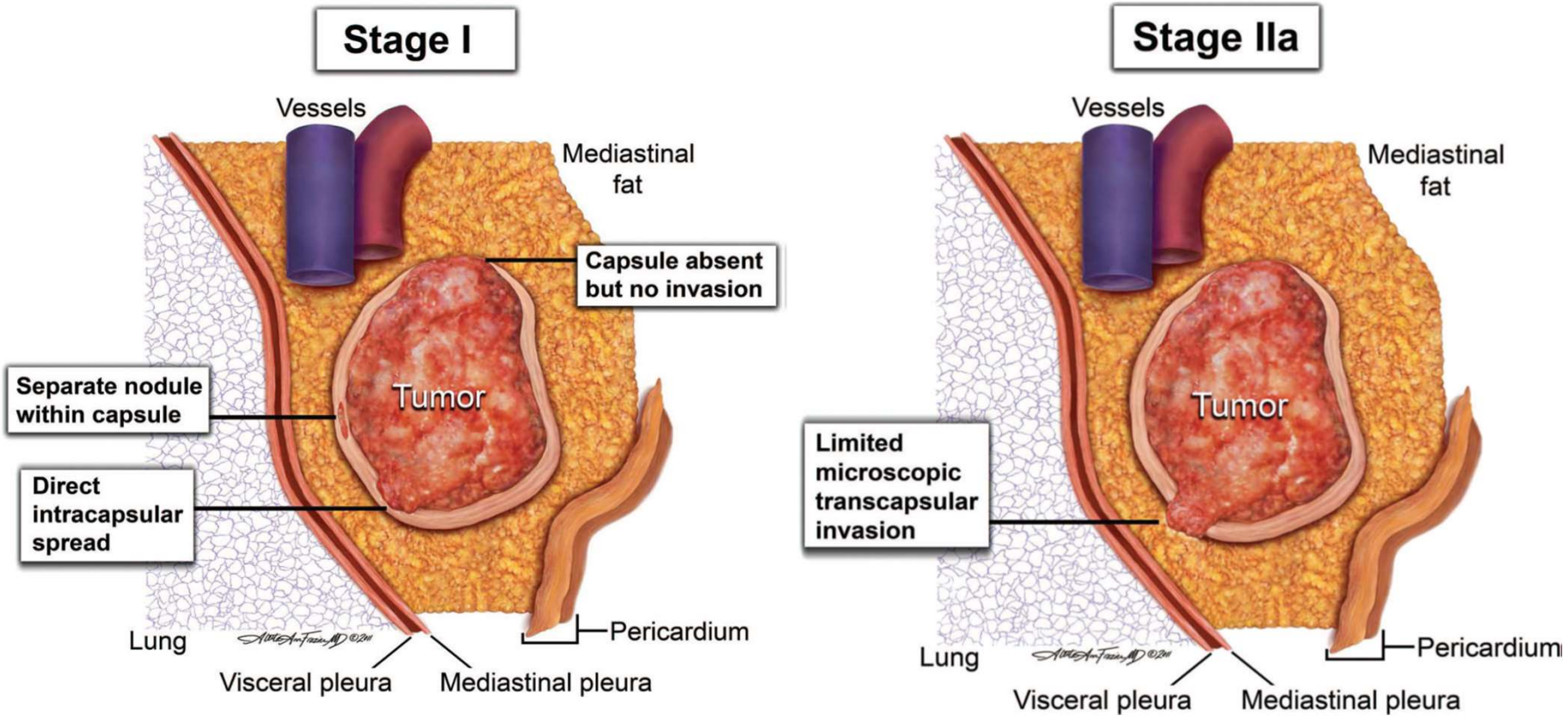
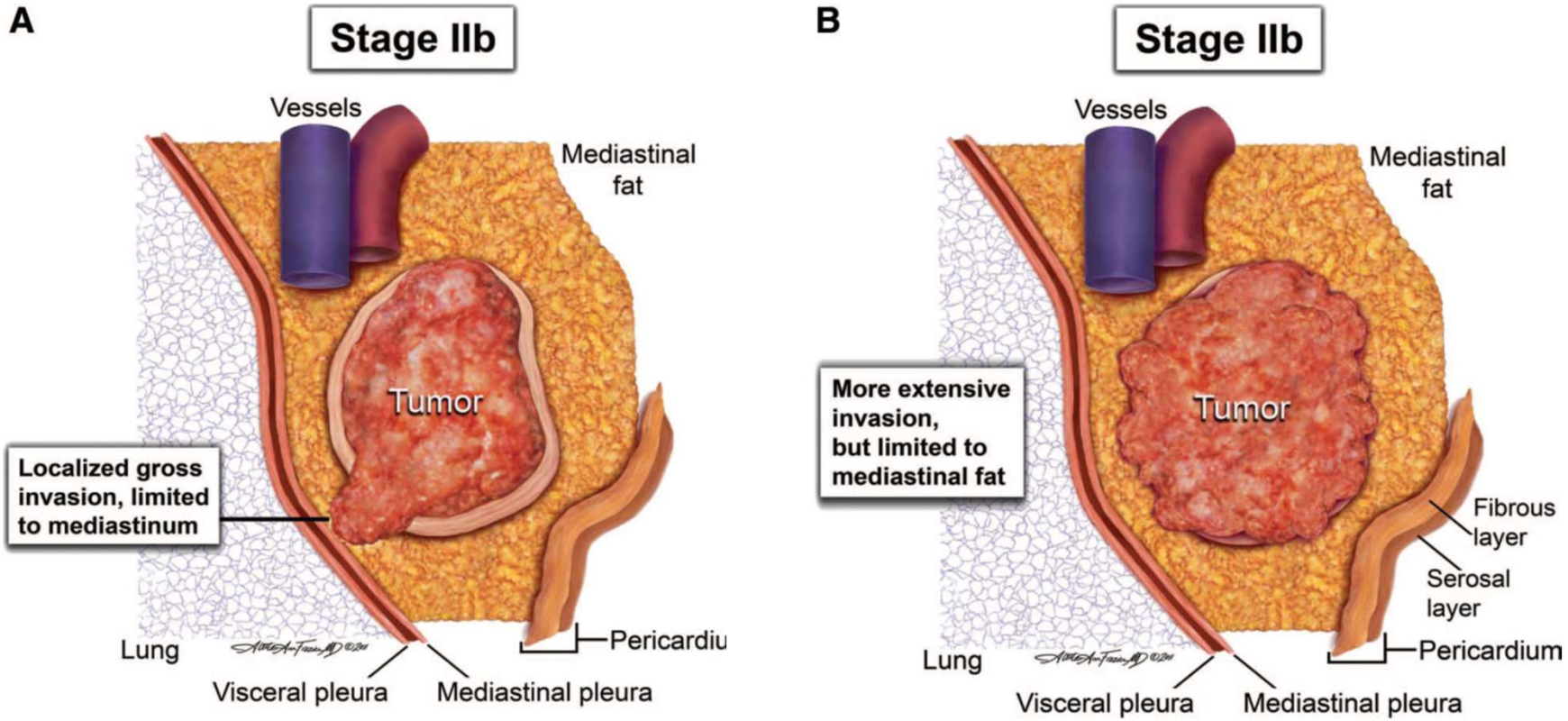
VATS / RATS thymectomy specimen



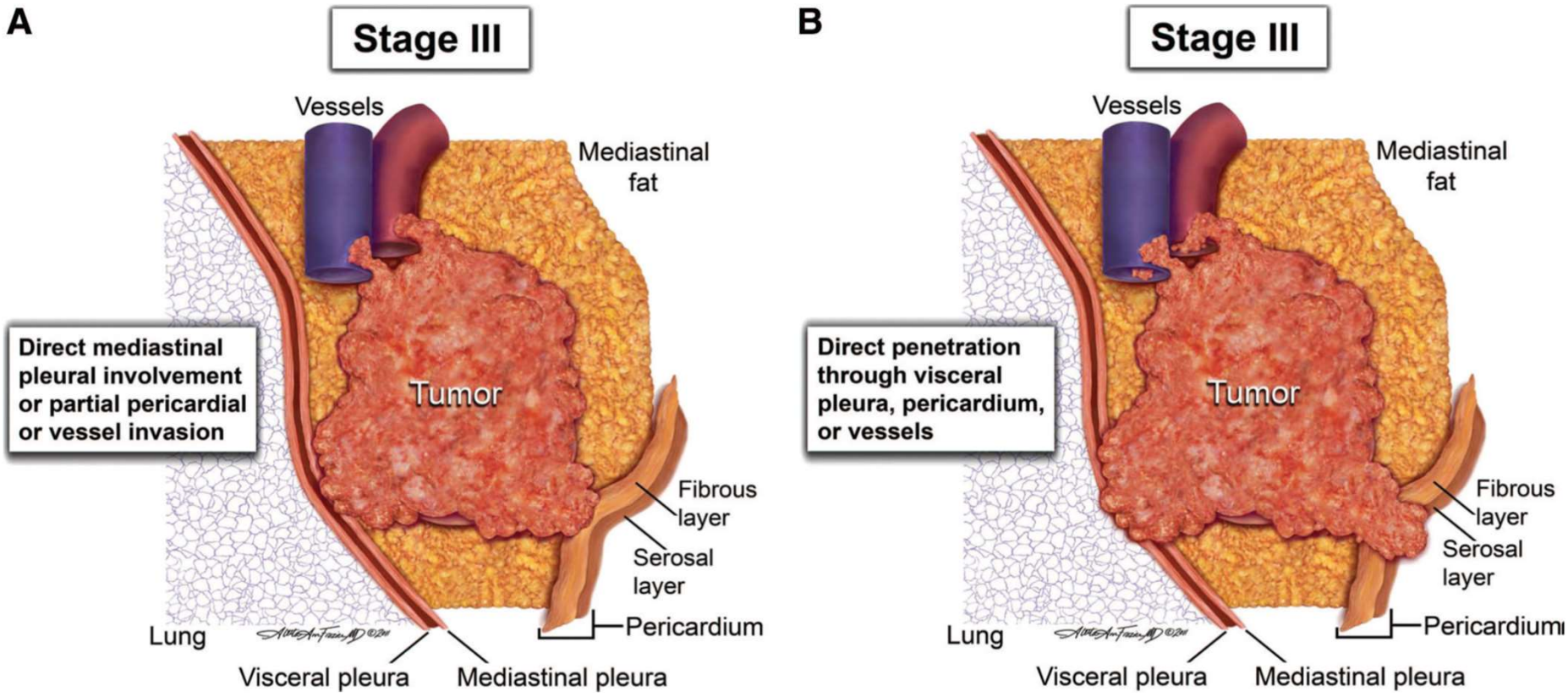
Masaoka-Koga staging



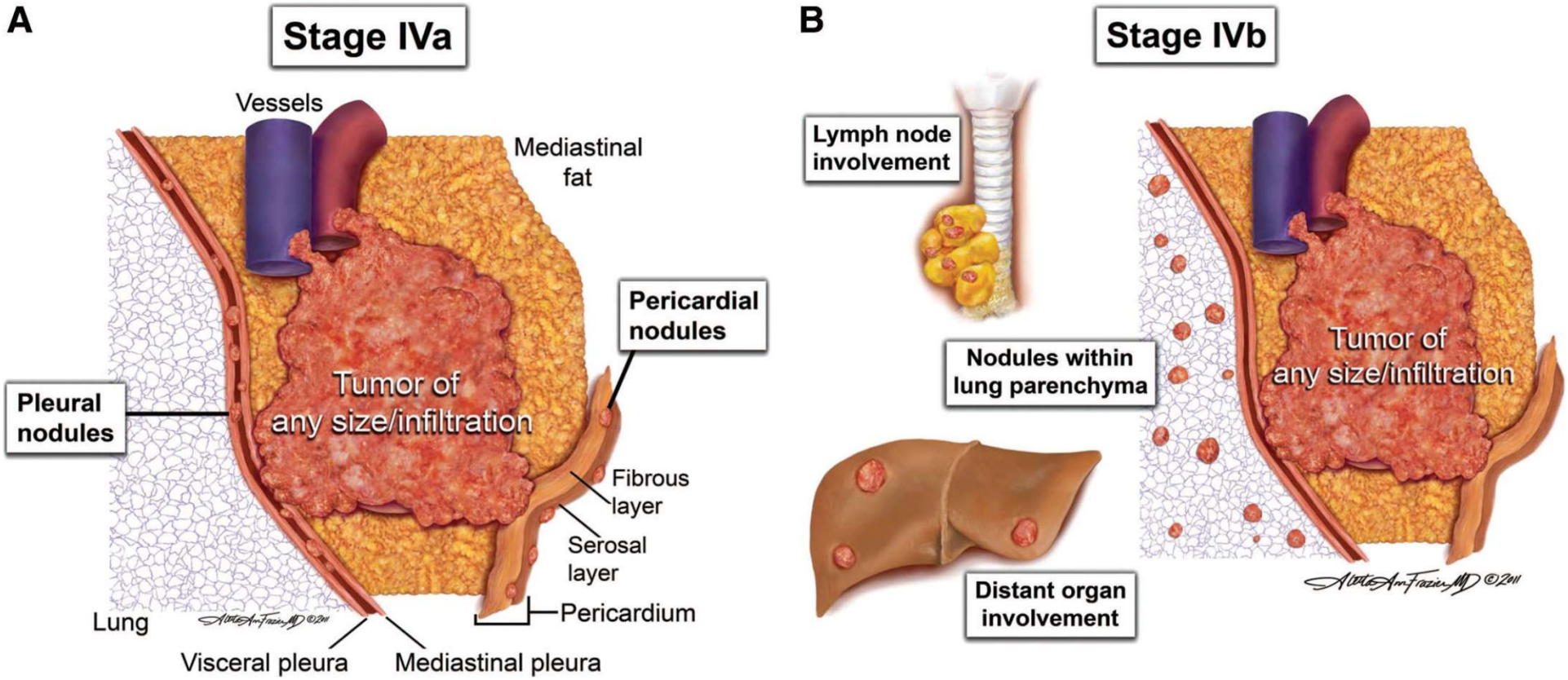
Masaoka-Koga staging



Masaoka-Koga staging



Masaoka-Koga staging



Detterbeck et al. J Thorac Oncol. 2011;6: S1710–S1716.

TNM classification

Clinical staging

Table 1 **The IASLC/ITMIG Thymic Epithelial Tumors Staging Project**

T Descriptors (6, 7)

Category	Definition (Involvement of)*a,b*
T1	
a	Encapsulated or unencapsulated, with or without extension into mediastinal fat
b	Extension into mediastinal pleura
T2	Pericardium
T3	Lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels
T4	Aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus

a Involvement must be pathologically proven in pathologic staging.
b A tumor is classified according to the highest T level of involvement that is present with or without any invasion of structures of lower T levels.

N and M Descriptors (6, 8, 9)

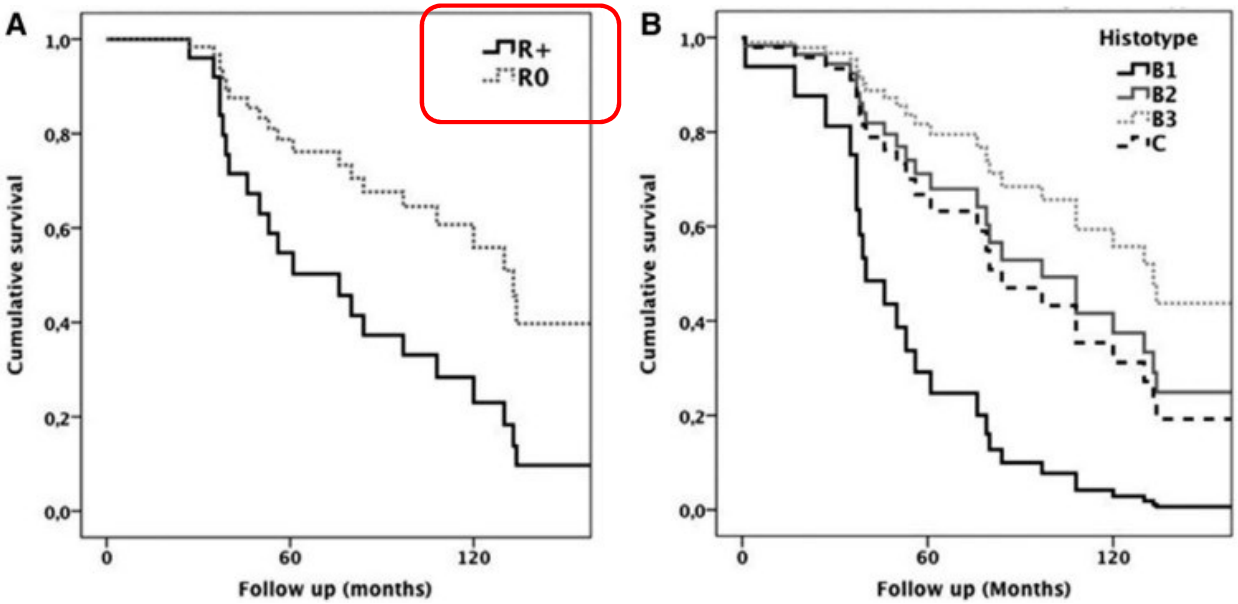
Category	Definition (Involvement of)*a*
N0	No nodal involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes
M0	No metastatic pleural, pericardial, or distant sites
M1	
a	Separate pleural or pericardial nodule(s)
b	Pulmonary intraparenchymal nodule or distant organ metastasis

a Involvement must be pathologically proven in pathologic staging.

Table 2. **The IASLC/ITMIG Thymic Epithelial Tumors Staging Project**

Stage Grouping (6-9)

Stage	**T**	**N**	**M**
I	**T1**	N0	M0
II	**T2**	N0	M0
IIIa	**T3**	N0	M0
IIIb	**T4**	N0	M0
IVa	T any	**N1**	M0
	T any	N0,1	**M1a**
IVb	T any	**N2**	M0, 1a
T any	N any	**M1**	

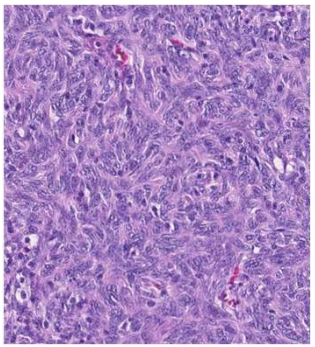


Sandri et al. J Thor Oncol. 2014; 9(12): 1796-1804.

The pathologist's toolbox

Macroscopy

Microscopy



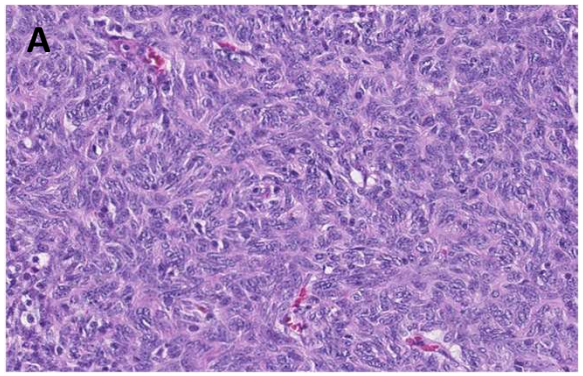
Ancillary stains

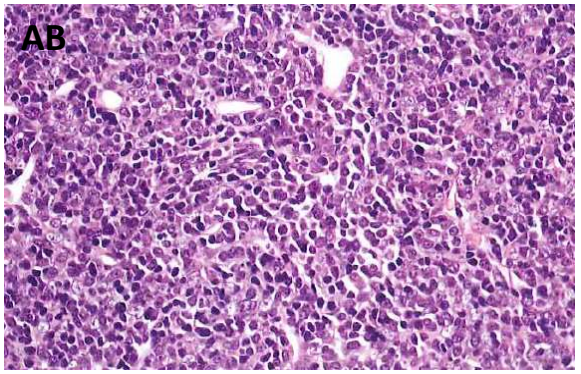
Molecular diagnostics

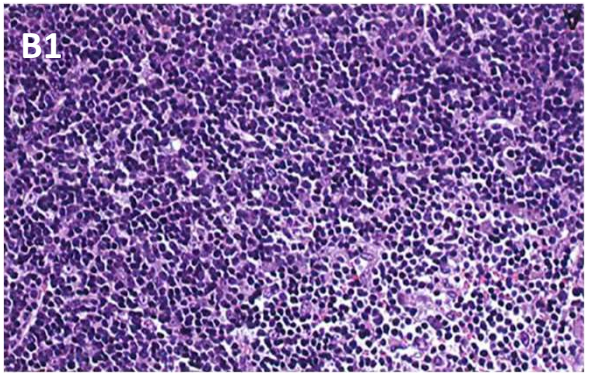
WHO Classification

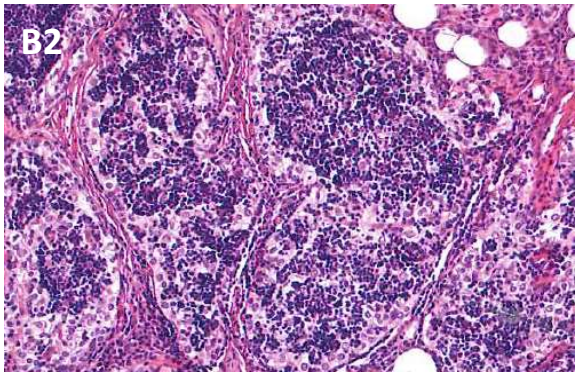
‘Epithelial tumours of the thymus’

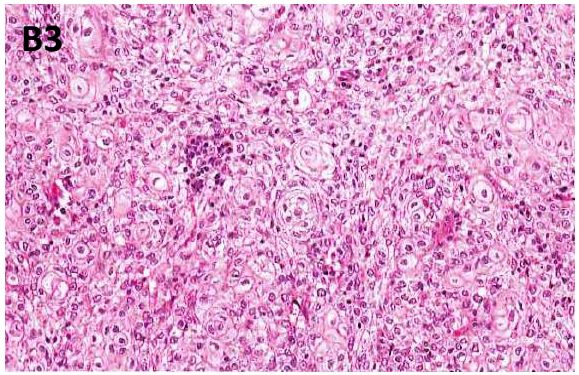
Epithelial tumours	
Thymoma	
Type A thymoma, including atypical variant	8581/3*
Type AB thymoma	8582/3*
Type B1 thymoma	8583/3*
Type B2 thymoma	8584/3*
Type B3 thymoma	8585/3*
Micronodular thymoma with lymphoid stroma	8580/1*
Metaplastic thymoma	8580/3
Other rare thymomas	
Microscopic thymoma	8580/0
Sclerosing thymoma	8580/3
Lipofibroadenoma	9010/0*
Thymic carcinoma	
Squamous cell carcinoma	8070/3
Basaloid carcinoma	8123/3
Mucoepidermoid carcinoma	8430/3
Lymphoepithelioma-like carcinoma	8082/3
Clear cell carcinoma	8310/3
Sarcomatoid carcinoma	8033/3
Adenocarcinomas	
Papillary adenocarcinoma	8260/3
Thymic carcinoma with adenoid cystic carcinoma-like features	8200/3*
Mucinous adenocarcinoma	8480/3
Adenocarcinoma, NOS	8140/3
NUT carcinoma	8023/3*
Undifferentiated carcinoma	8020/3
Other rare thymic carcinomas	
Adenosquamous carcinoma	8560/3
Hepatoid carcinoma	8576/3
Thymic carcinoma, NOS	8586/3
Thymic neuroendocrine tumours	
Carcinoid tumours	
Typical carcinoid	8240/3
Atypical carcinoid	8249/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Combined thymic carcinomas	

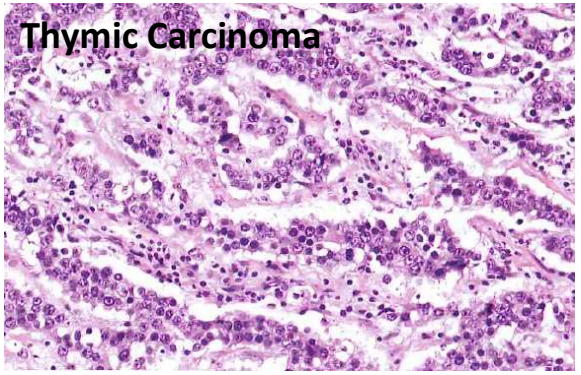












Thymoma

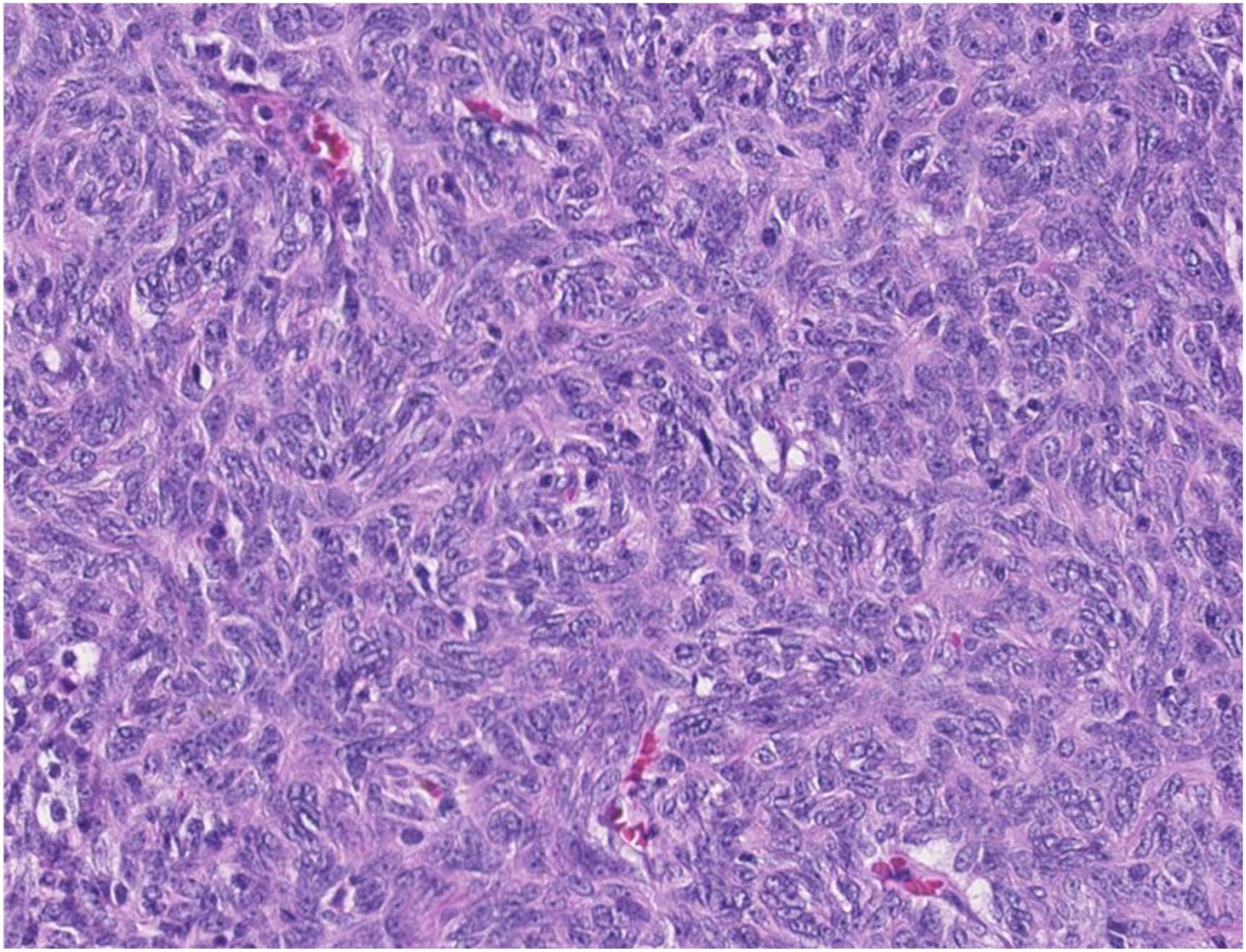
- Type A thymoma (medullary thymoma)
  - Spindled to epithelioid
- Type B thymoma
  - Resembles normal thymus
  - Increased epithelial / lymphocytic ratio
- Type B1 thymoma
  - Resembles normal thymus
  - Lymphocyte rich
  - Neoplastic epithelial cells appear benign

Thymoma

- Type B2 thymoma (cortical thymoma)
  - As B1, but larger epithelial component (clusters of >3 epithelial cells)
  - Epithelial elements more evidently neoplastic with enlarged vesicular nuclei and nucleoli
- Type B3 thymoma
  - "Sheet-like" pattern of epithelial cells with few or no lymphocytes
  - Moderate nuclear atypia
  - Type AB thymoma
  - Mixture of type A and B, usually with sharp distinction

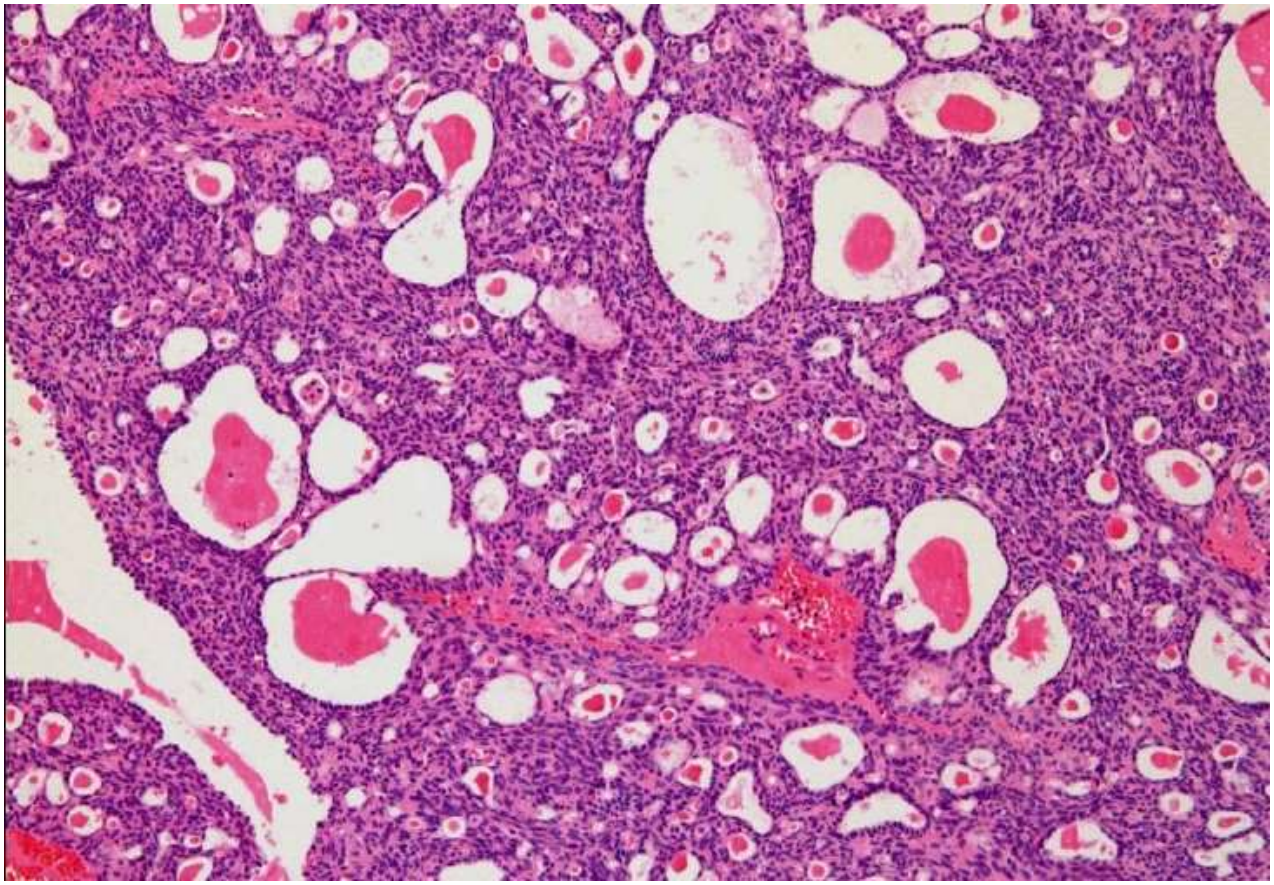
Thymoma

- Thymic carcinoma
  - Evident cellular atypia
  - Resembles carcinoma, no thymus recognisable

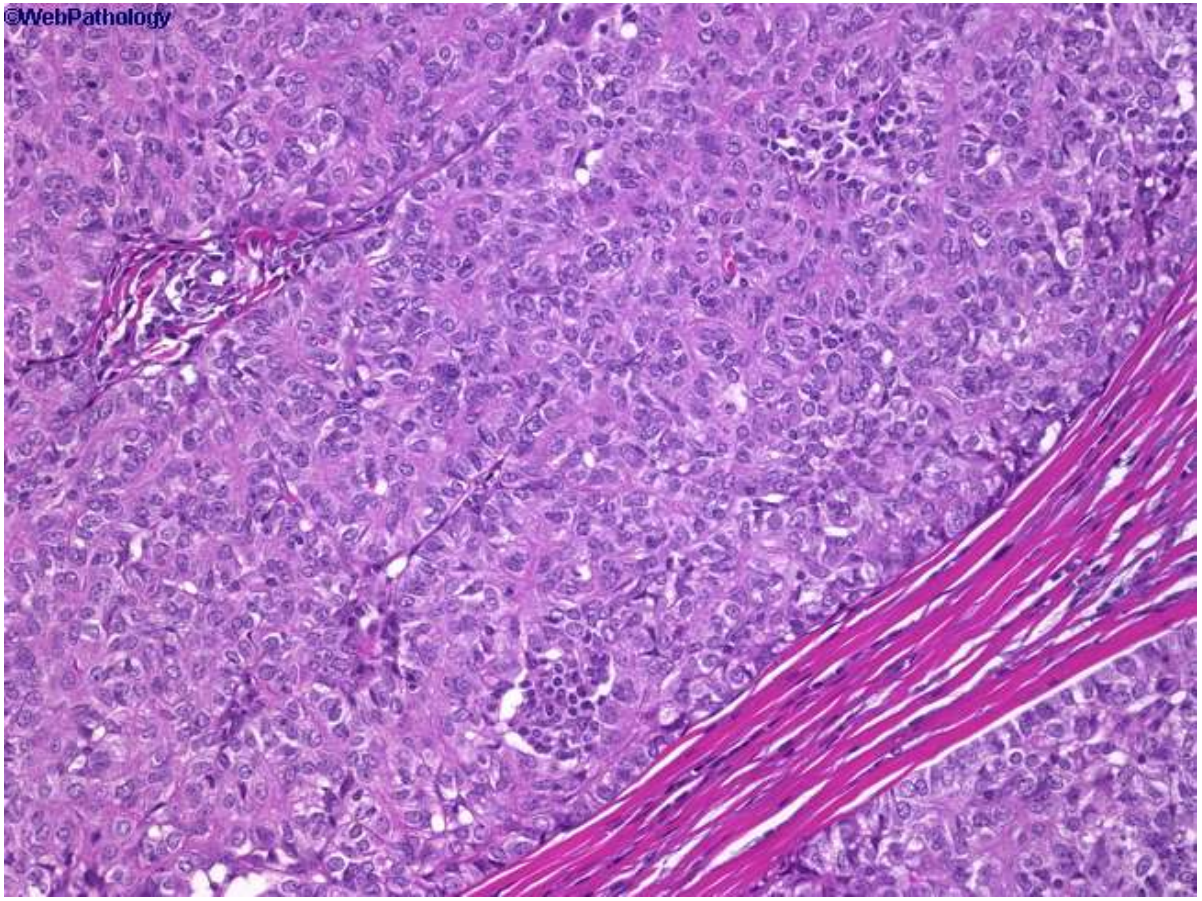


Type A Thymoma

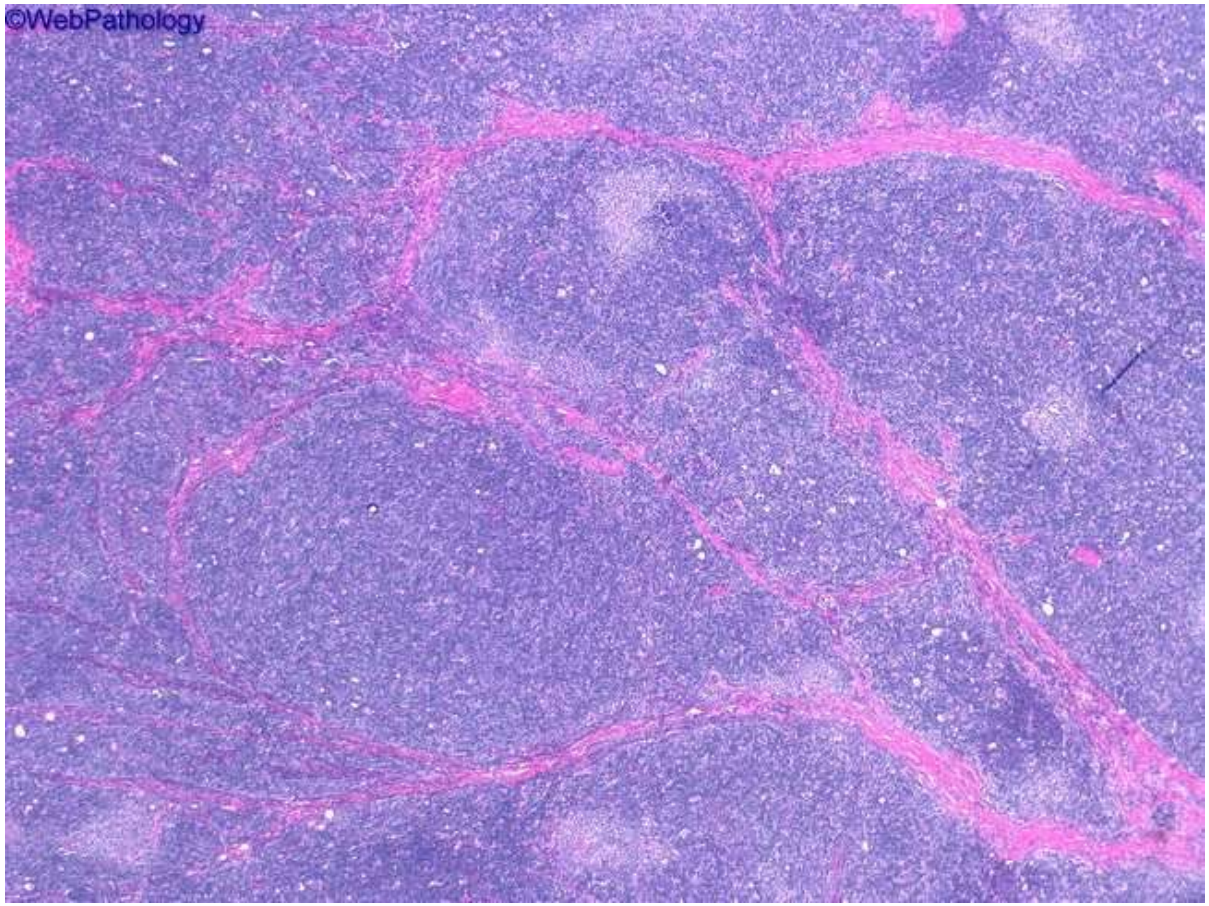
Thymoma type A



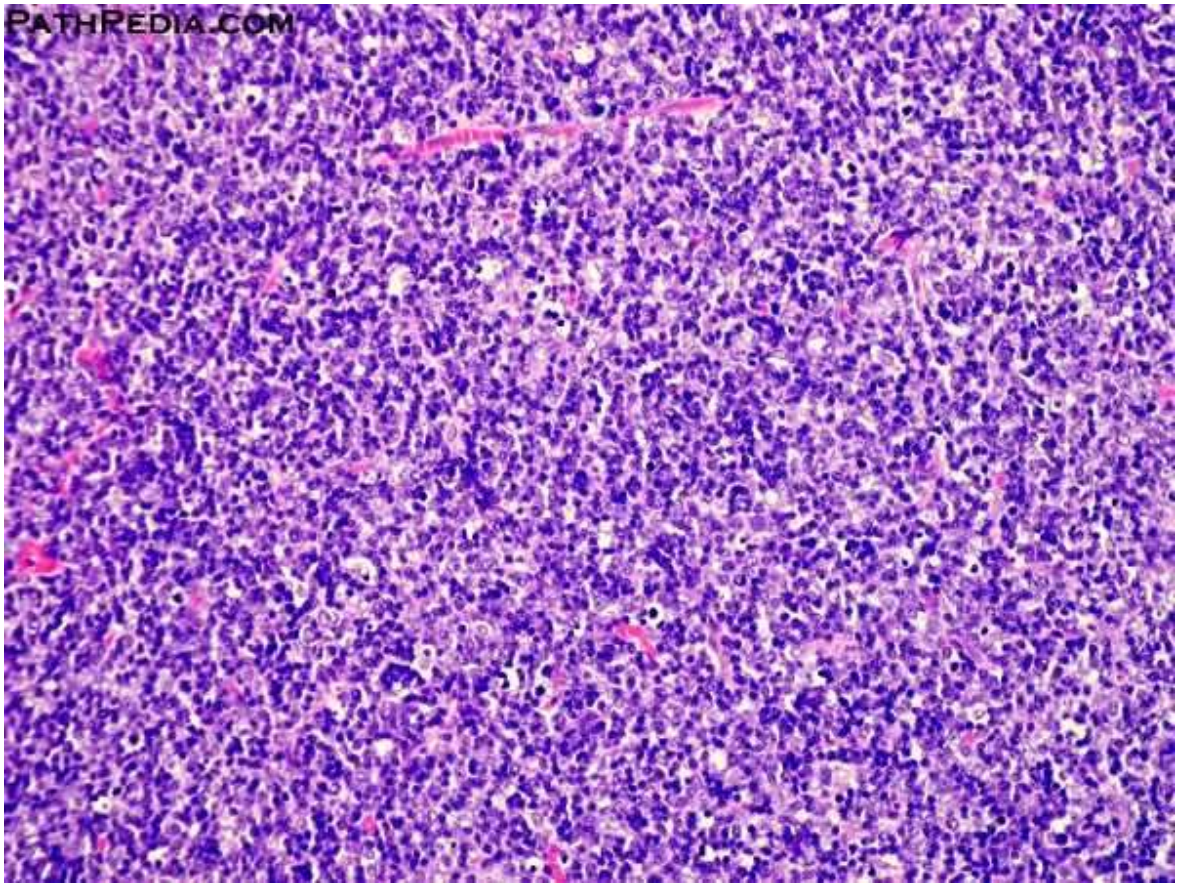
Thymoma type A



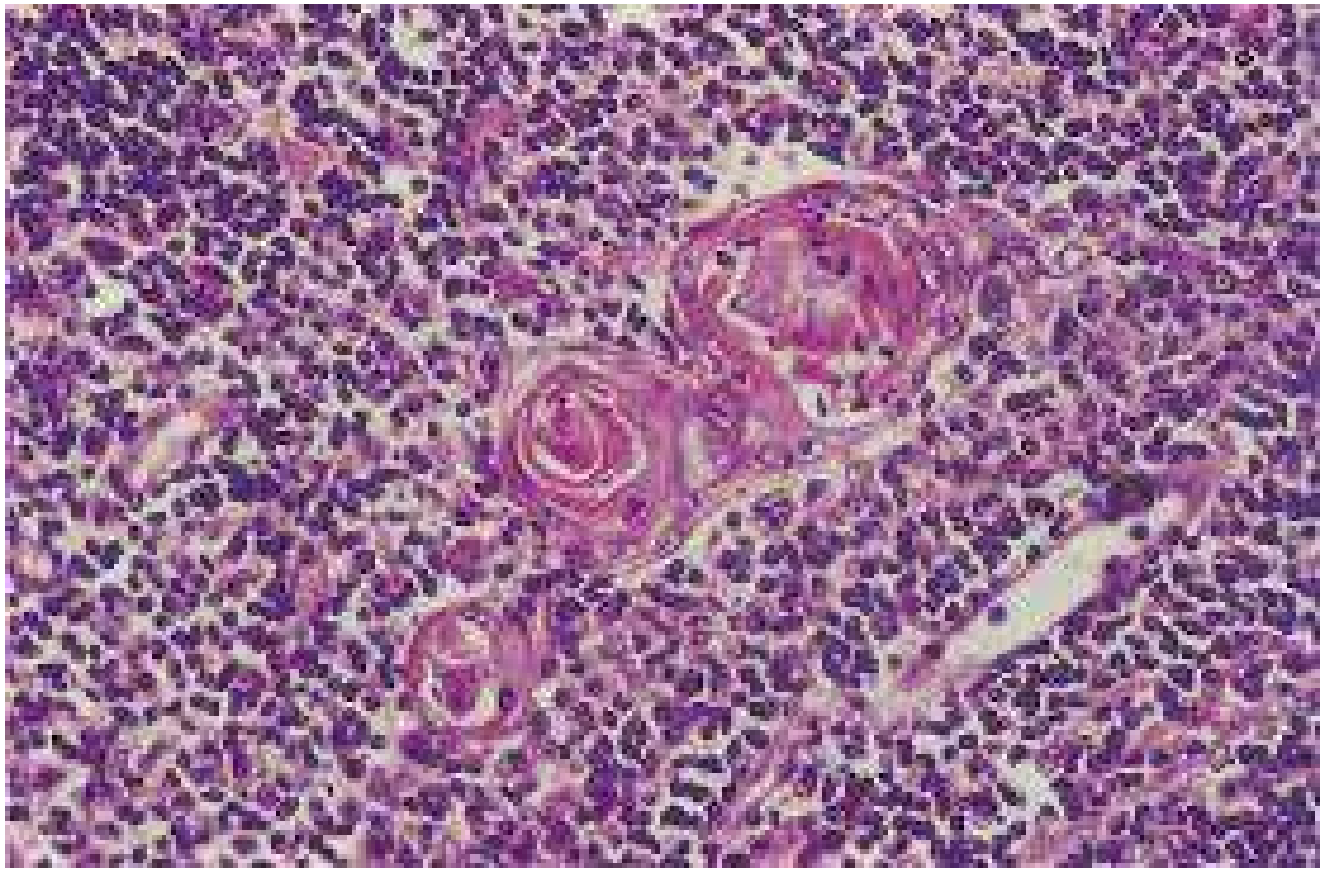
Thymoma type B1

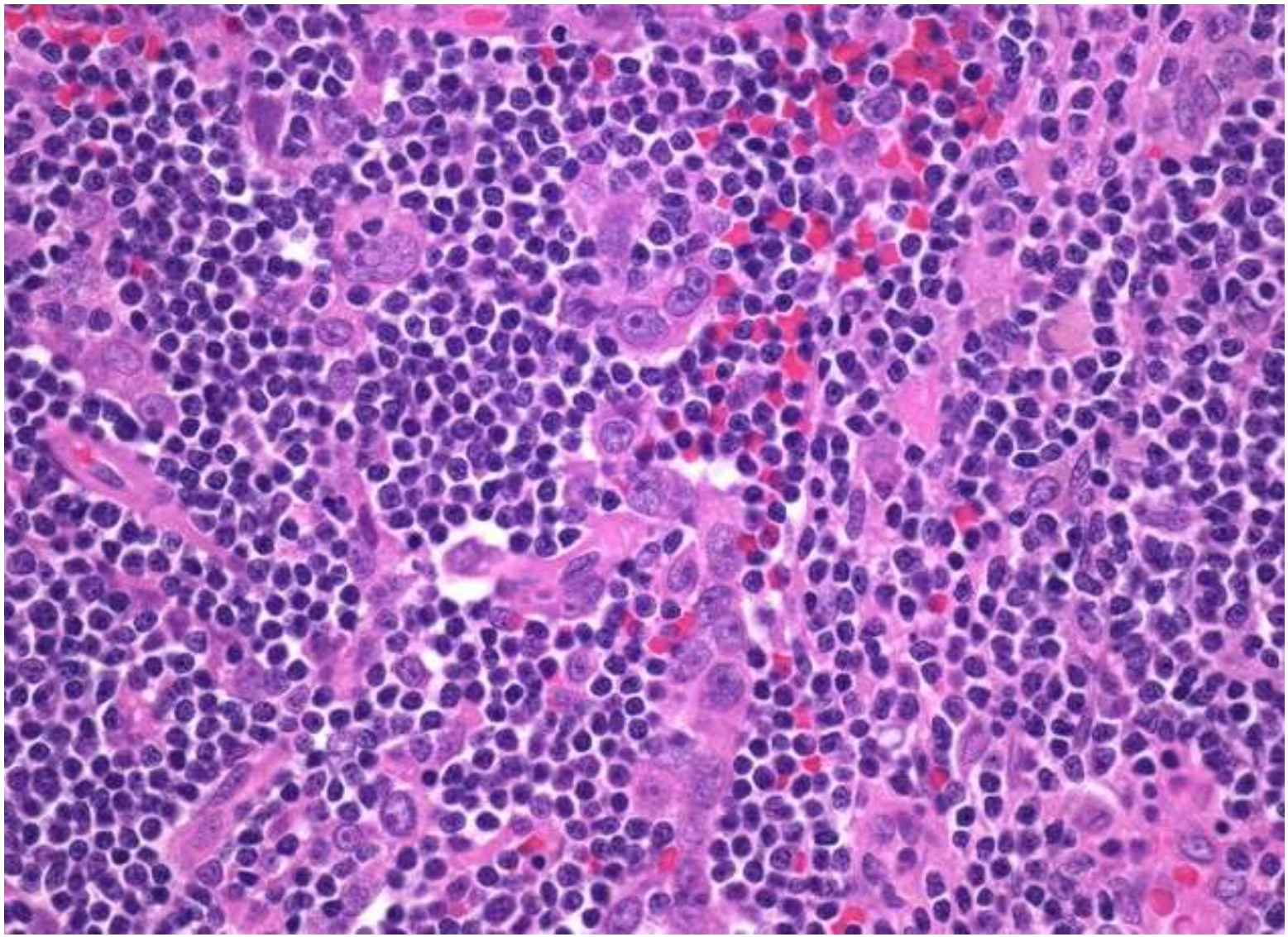


Thymoma type B1



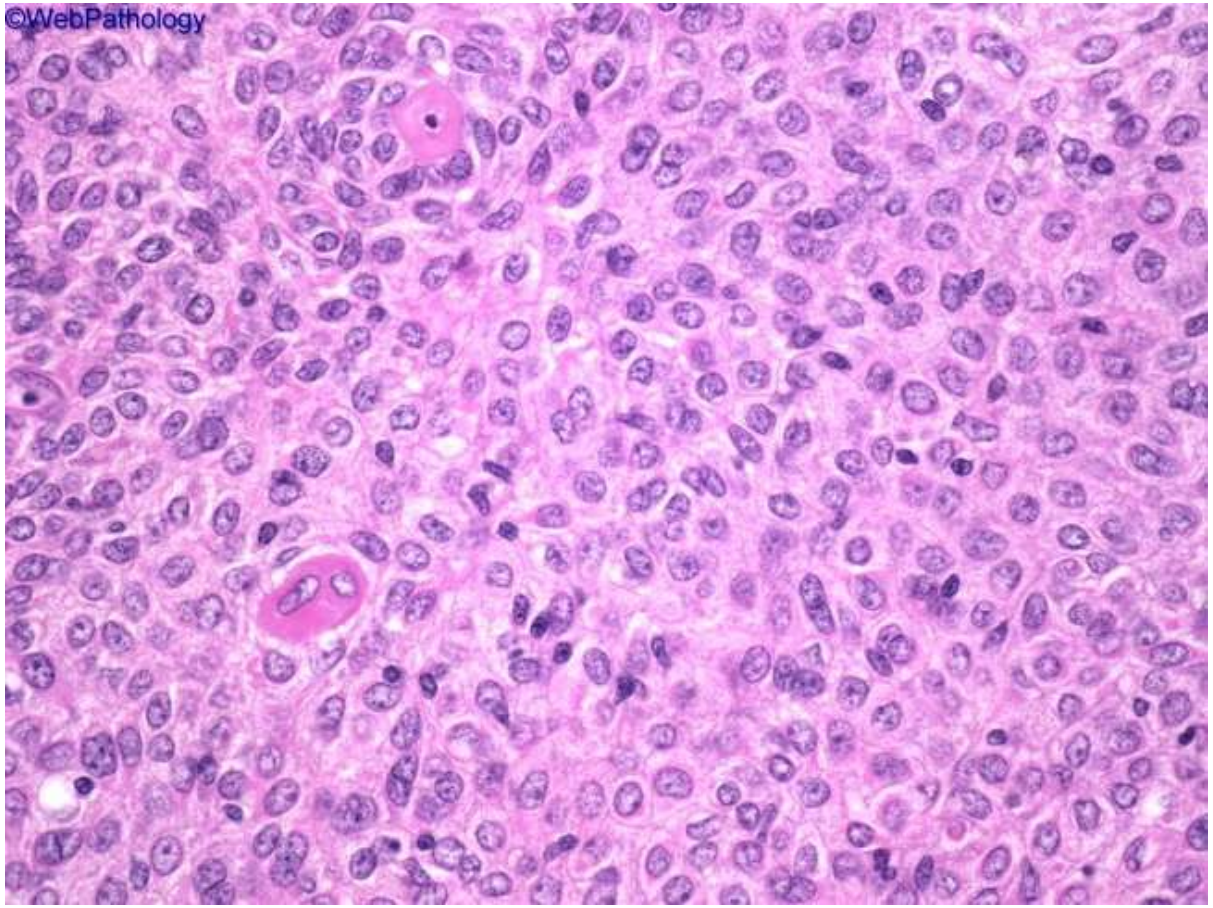
Thymoma type B1

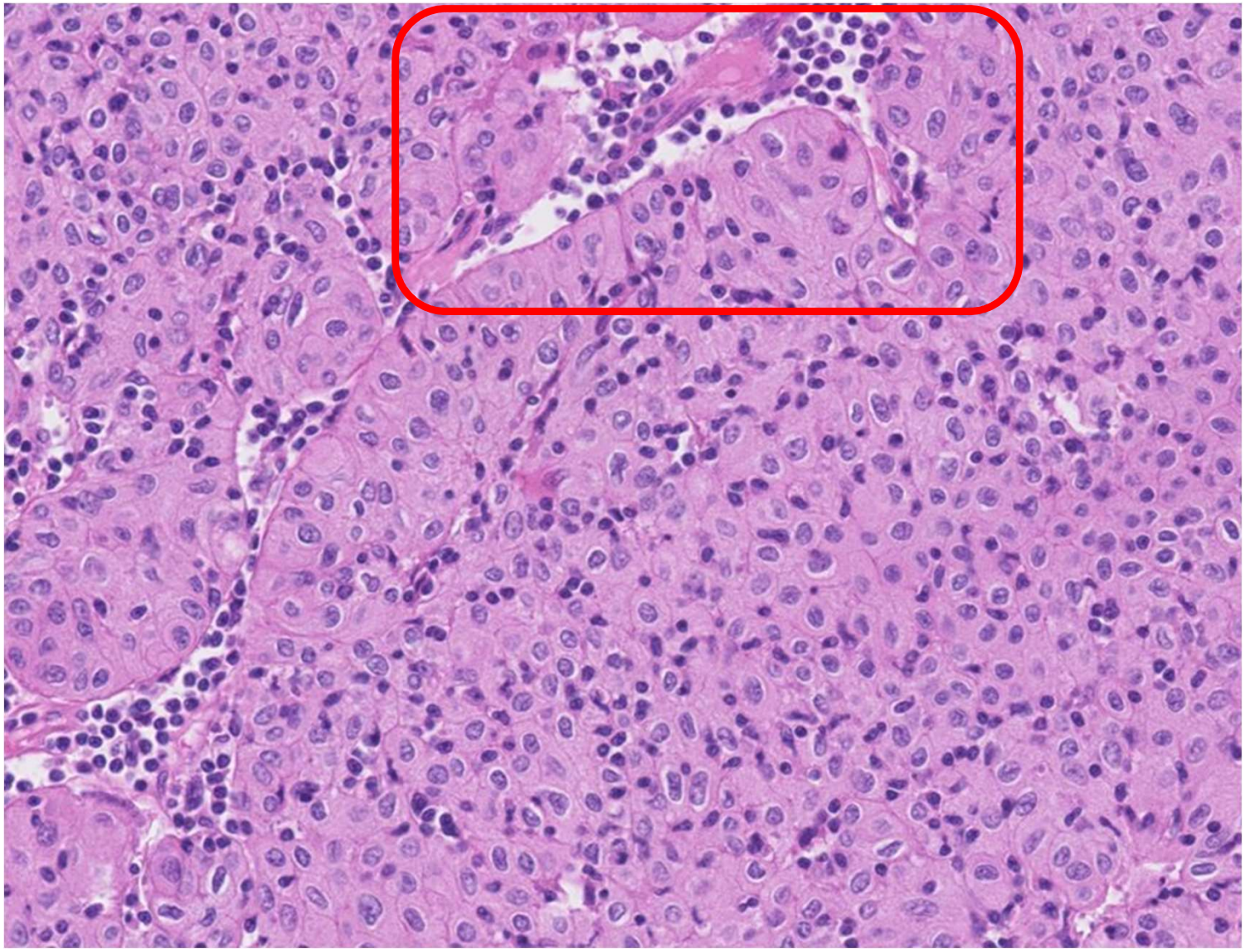




Type B2 Thymoma

Thymoma type B3

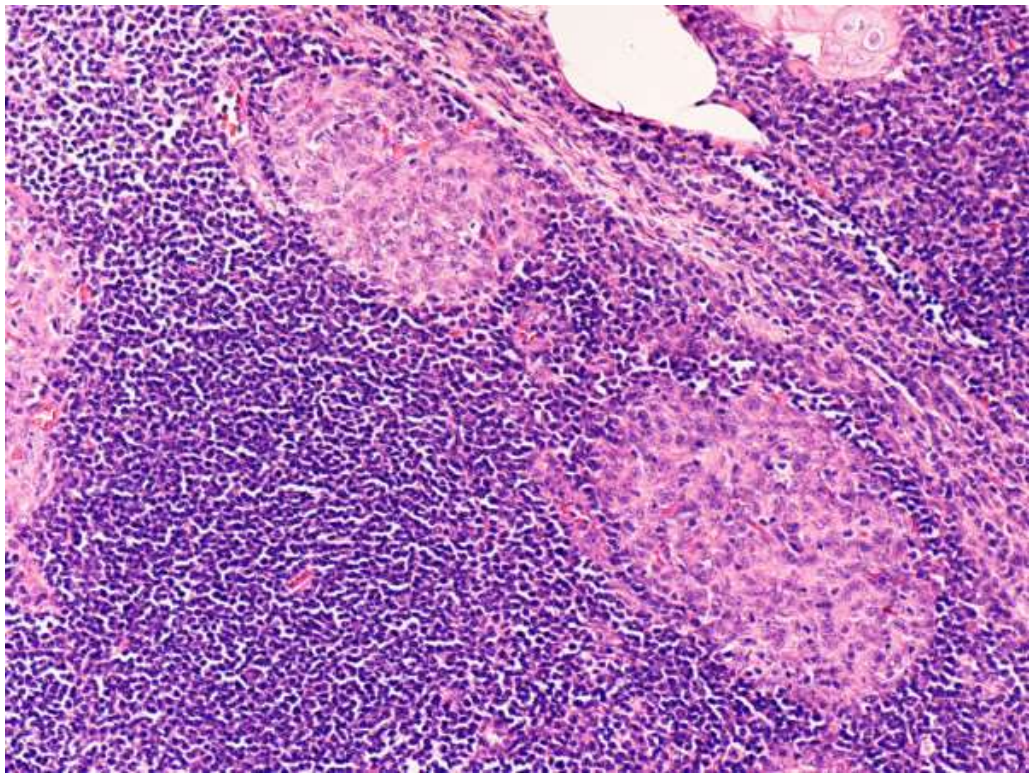


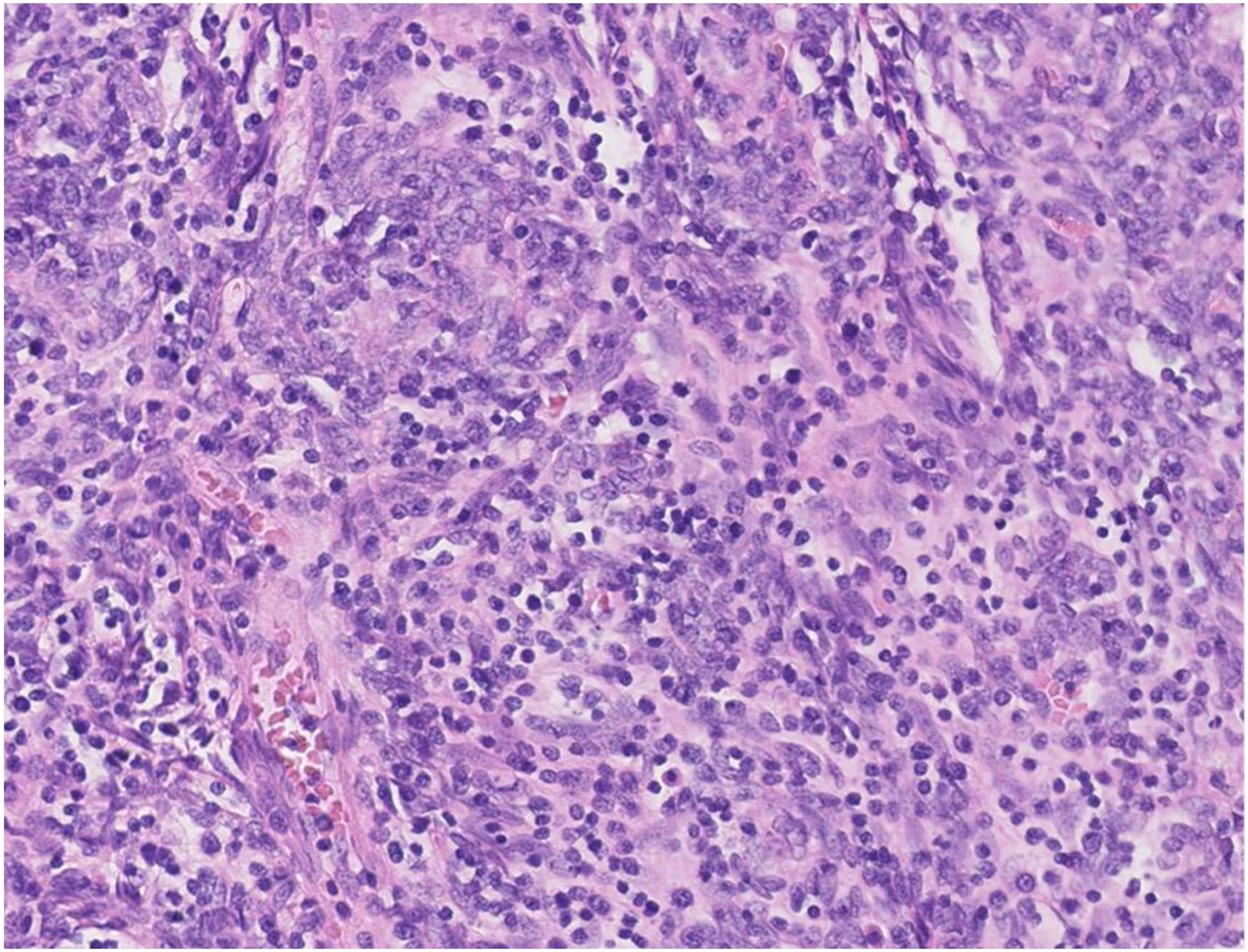


Type B3 Thymoma

Other thymomas

- Micronodular thymoma with lymphocyte-rich stroma (=> **mature** lymphocytes, no epithelium)





Type AB Thymoma

Other thymomas

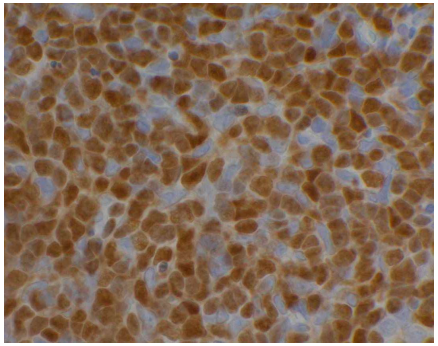
- Metaplastic thymoma (=> biphasic with distinct demarcation between spindled and solid polygonal component, few lymphocytes)
- Sclerosing thymoma
- Lipofibroadenoma (resembles breast FA)

The pathologist's toolbox

Macroscopy

Microscopy

Ancillary stains



Molecular diagnostics

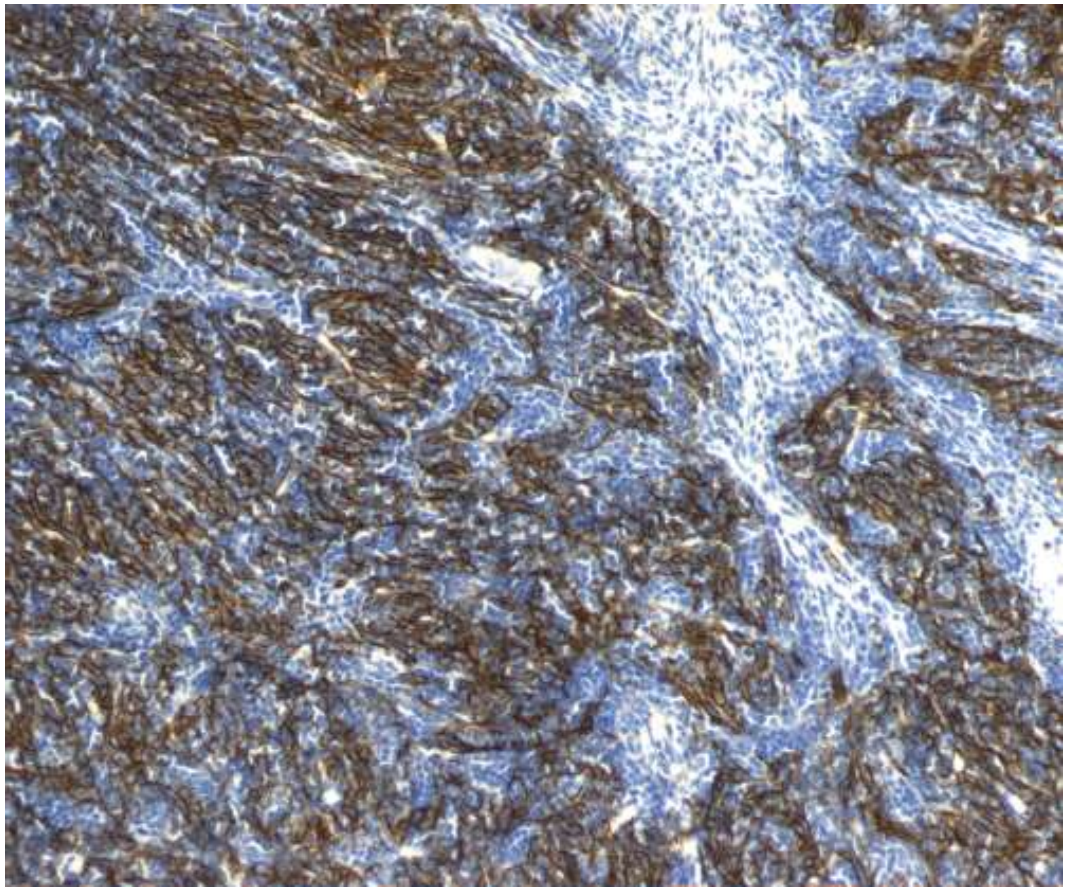
Thymoma type A

- IHC usually not necessary
  - Positive for pankeratin, other keratines, P63, PAX8, CD20
  - Negative for CK20, CD5, CD117
  - TdT positive lymphocytes absent or rare
- DD:
  - Type AB thymoma
  - Spindled variant of type B3 (perivascular spaces in B3 vs. acinar, rozetting or pericytomatous pattern in type A)
  - Thymic carcinoma => morphology and thymic ca. positive for CD5 and CD117
  - Carcinoid => IHC

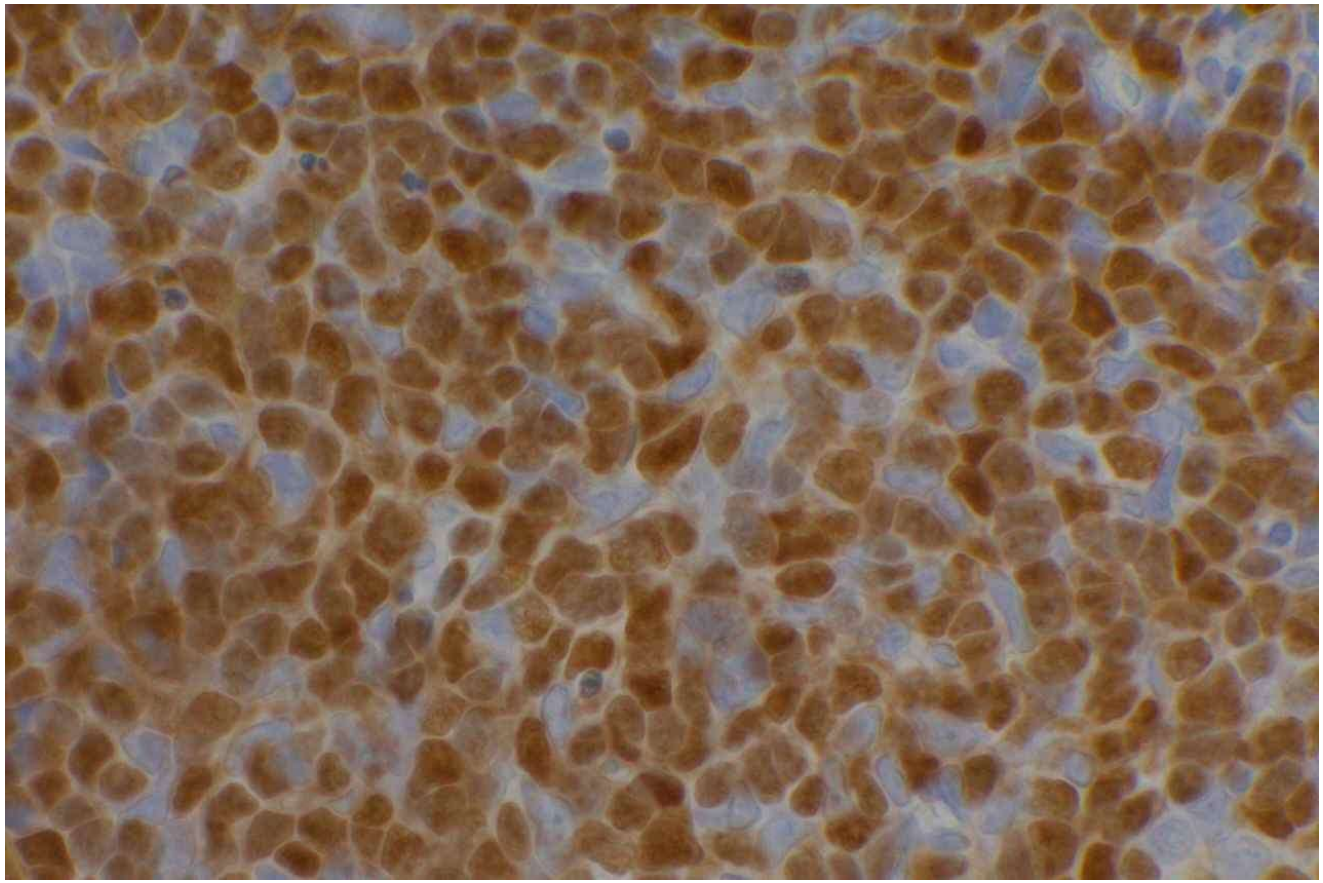
Thymoma type B1

- IHC:
  - Epithelial network positive for pankeratin, other keratins (e.g. CK19), P63, PAX8
  - Negative for CK20, CD5, CD117
  - TdT / CD1a positive lymphocytes present
- DD:
  - Hyperplastic thymus (type B1 larger lobules, fibrous capsule, septa, predomniant cortical differentiation, few to no Hassall's bodies)
  - Type AB thymoma => morphology and CD20
  - T-lymphoblastic lymphoma => morphology (T-LBL atypical lymphocytes) and keratins

Thymoma type B1 - pankeratin



Thymoma type B1 - TdT



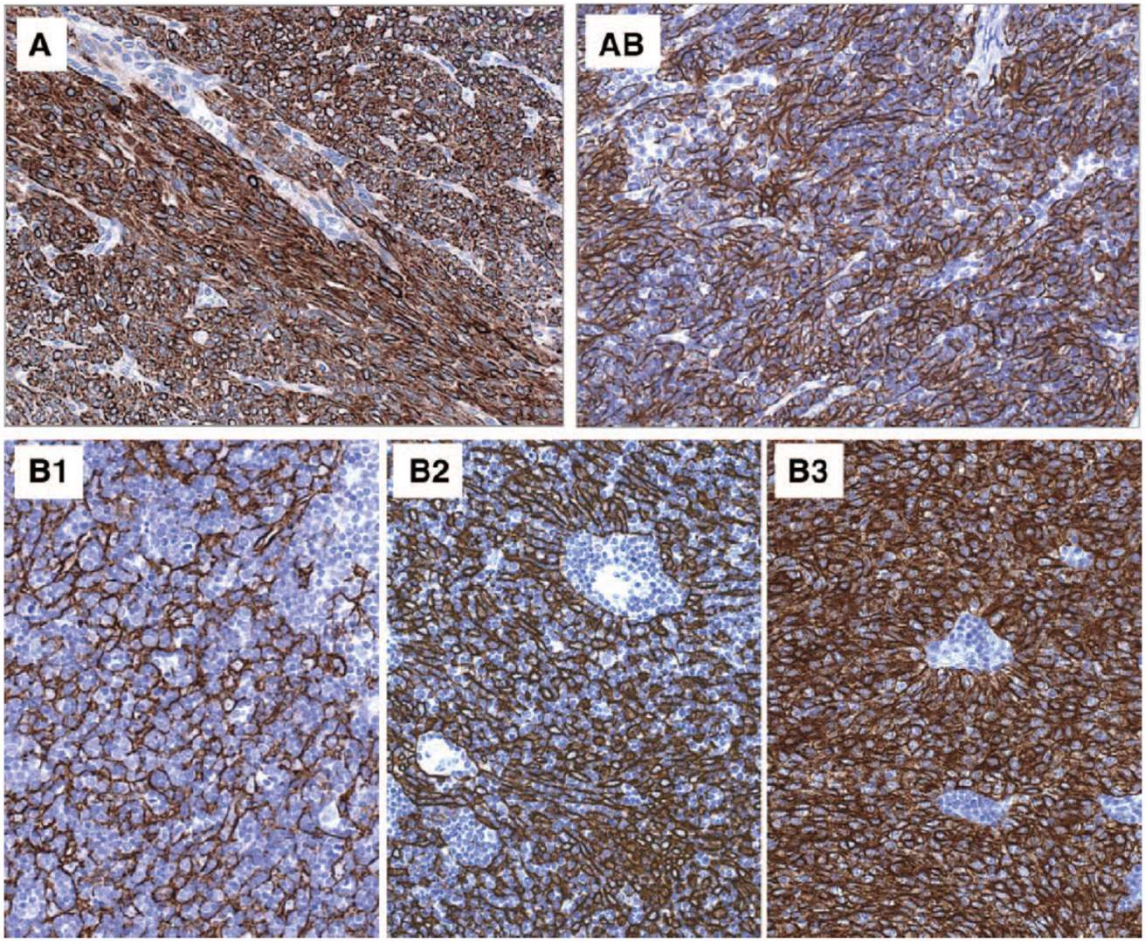
Thymoma type B2

- IHC:
  - Dense epithelial network with keratins
  - TdT positive cells
- DD:
  - Type B1 => resembles normal thymus with fewer epithelial cells
  - Type B3 => fewer lymphocytes

Thymoma type B3

- IHC:
  - Positive for keratins, except CK20
  - Positive for P63, PAX8
  - Negative for CD5 and CD117
  - TdT positive cells in >95%
- DD:
  - Type B2 => more lymphocytes (‘blue’ vs. ‘pink’)
  - Thymic carcinoma (TSQCC)
    - => morphology: no lobular pattern, infiltrative growth, desmoplasia, no perivascular spaces, more atypia, hemidesmosomes
    - => IHC: TSQCC: positive for CD5, CD117, GLUT1, MUC1, negative for TdT

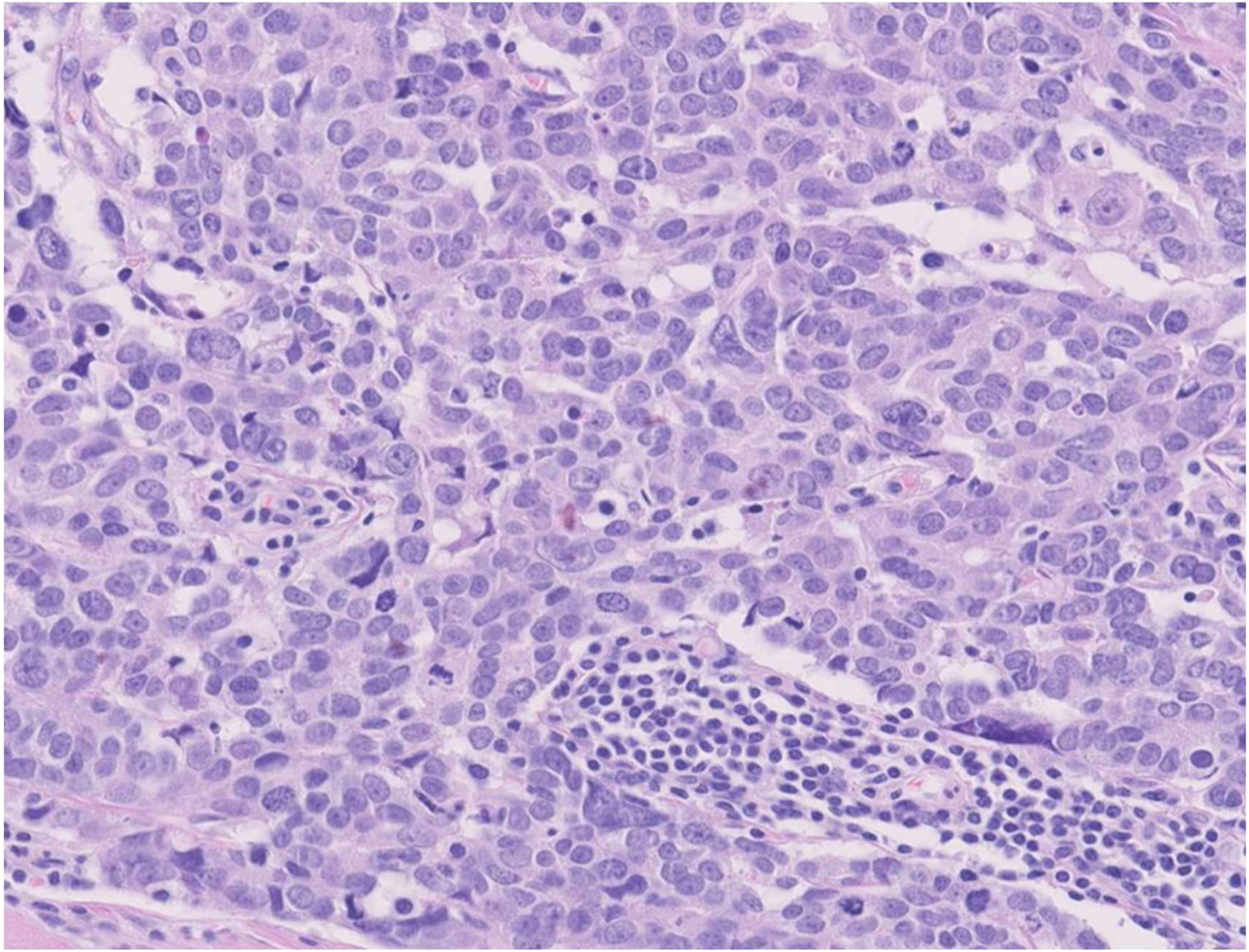
Thymoma types – pankeratin



Thymic carcinoma

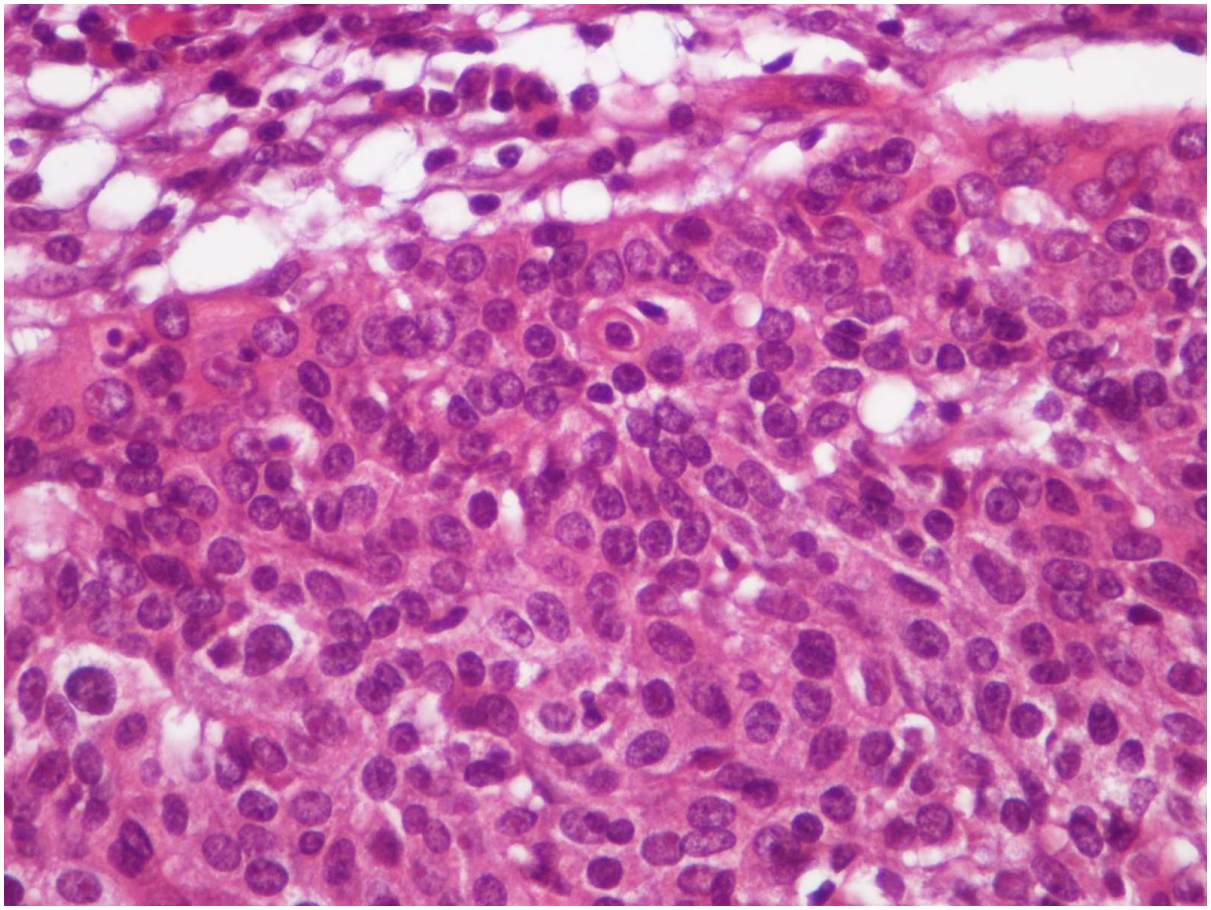
- **Squamous cell carcinoma**
- Basaloid carcinoma
- Mucoepidermoid carcinoma
- Lymphoepithelioma-like carcinoma
- Clear cell carcinoma
- Sarcomatoid carcinoma
- Adenocarcinoma
  - Papillary
  - Adenoid cystic
  - Mucinous
  - NOS
- NUT carcinoma
- Undifferentiated carcinoma
- Adenosquamous carcinoma
- Hepatoid carcinoma
- Thymic carcinoma NOS
- Combined thymic carcinomas

	CD5	CD117	GLUT1	MUC1
Thymic carcinoma	62%	78%	83%	69%
- TSQCC	74%	84%	89%	88%
- Other ca.	32%	35%	-	100%
Thymoma	3%	3%	47%	0%



Thymic carcinoma

Thymic carcinoma - TSQCC



Neuro-endocrine thymic tumours

- Carcinoid
  - Typical
  - Atypical
- Large cell neuro-endocrine carcinoma
- Small cell carcinoma

=> Analogous to pulmonary tumours, incl. grading and IHC

Interobserver variation

- The Dutch national thymoma panel was set up in 2009
- It consists of 13 pathologists from Europe (The Netherlands, Germany, Great Britain) and the USA
- The panel offers as service typing / classification and if possible, staging of the received cases within two weeks according to the WHO classification.
- The assessment takes place on a virtual platform where all cases are deposited
- The diagnoses of the panel members are bundled and a consensus diagnosis is established and reported to the submitter.
- The panel functions as a national reference panel for primary epithelial tumours of the thymus.

Study - Materials and Methods

- H&E sections as well as immunohistochemical stains from mediastinal masses of more than 45 hospitals in the Netherlands and Belgium were sent to the panel between January 2011 until December of 2018.
- The data of all scoring pathologists was subjected to statistical analysis and interobserver concordance (Fleiss Kappa) was calculated.

Results

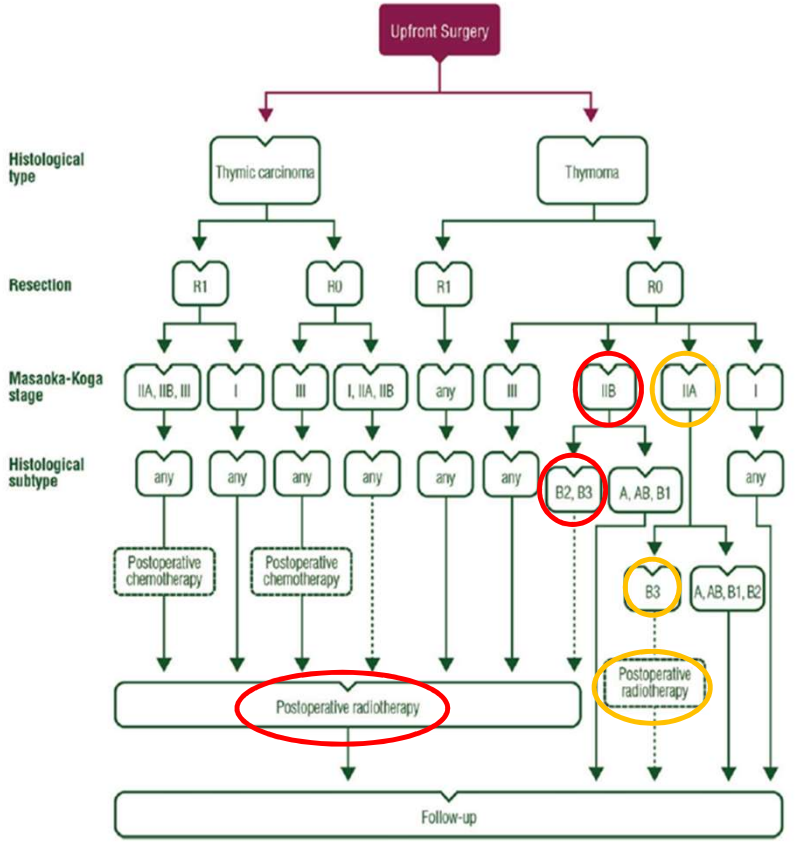
Characteristic	N=305 (%)
Gender	
Female	140 (45,9%)
Male	165 (54,1%)
Age at diagnosis (median, range)	61 (16-88)
Diagnostic procedure	
Biopsy	90 (29,5%)
Resection specimen	215 (70,5%)
Number of pathologists diagnosing a case (mode, range)	9 (7-12)

WHO type	No	Percent
A	36	11,80%
AB	80	26,20%
B1	34	11,10%
B2	41	13,40%
B3	27	8,90%
MNT-LS	18	5,90%
Other thymoma	3	1,00%
Thymic CA	33	10,80%
Carcinoid	1	0,30%
Germ cell tumour	2	0,70%
Lymfoma	1	0,30%
Metastasis	7	2,30%
Benign leasion	14	4,60%
No consenus diagnosis	8	2,60%

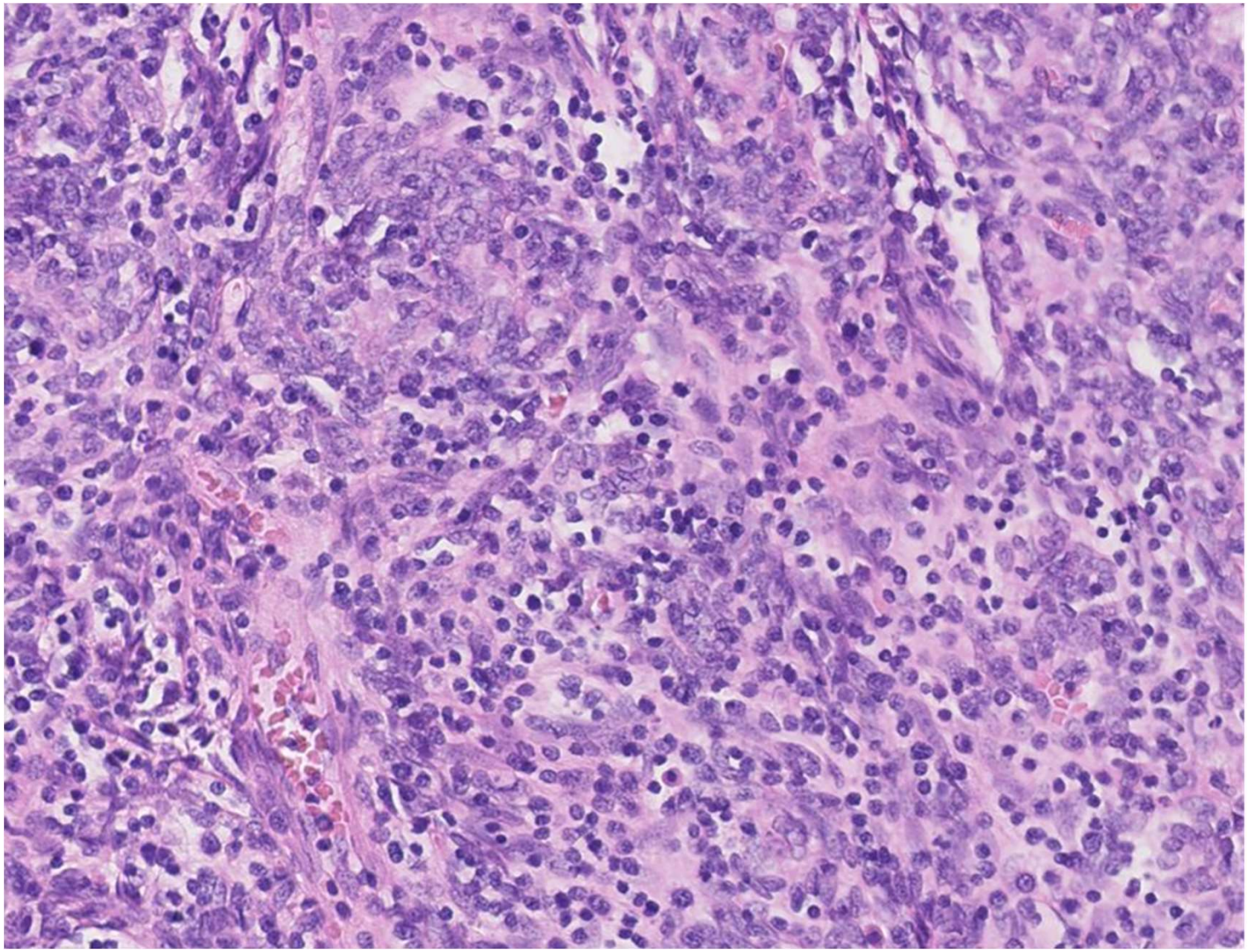
78,3%

Results

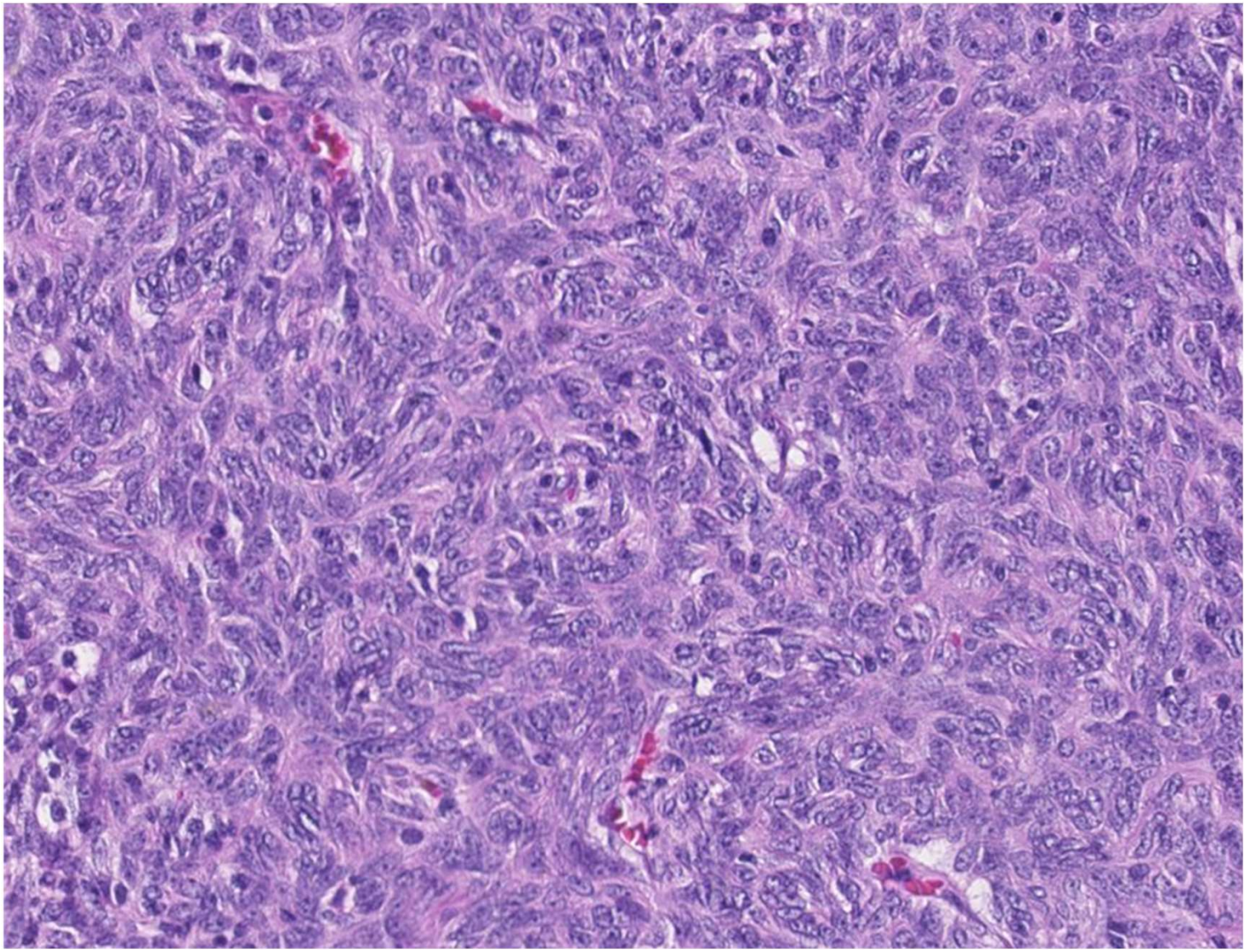
		Percent Agreement (p_a)	Percent Chance Agreement (p_e)	κ (Coefficient) [CI]
All diagnosis	combined	0,8855	0,6466	0,6762 [0,6416; 0,7108]
	biopsy	0,7945	0,492	0,5955 [0,5381; 0,6530]
	resection	0,9224	0,7147	0,7281 [0,6615; 0,7946]
A/AB/B1 vs B2/B3	combined	0,7877	0,5275	0,5506 [0,5134; 0,5879]
	biopsy	0,682	0,4919	0,374 [0,2933; 0,4547]
	resection	0,824	0,5413	0,6163 [0,5754; 0,6573]
A/AB/B1/ B2 vs B3	combined	0,7877	0,6951	0,4929 [0,4352; 0,5506]
	biopsy	0,7749	0,6578	0,3423 [0,2348; 0,4497]
	resection	0,8695	0,7092	0,5512 [0,4940; 0,6083]



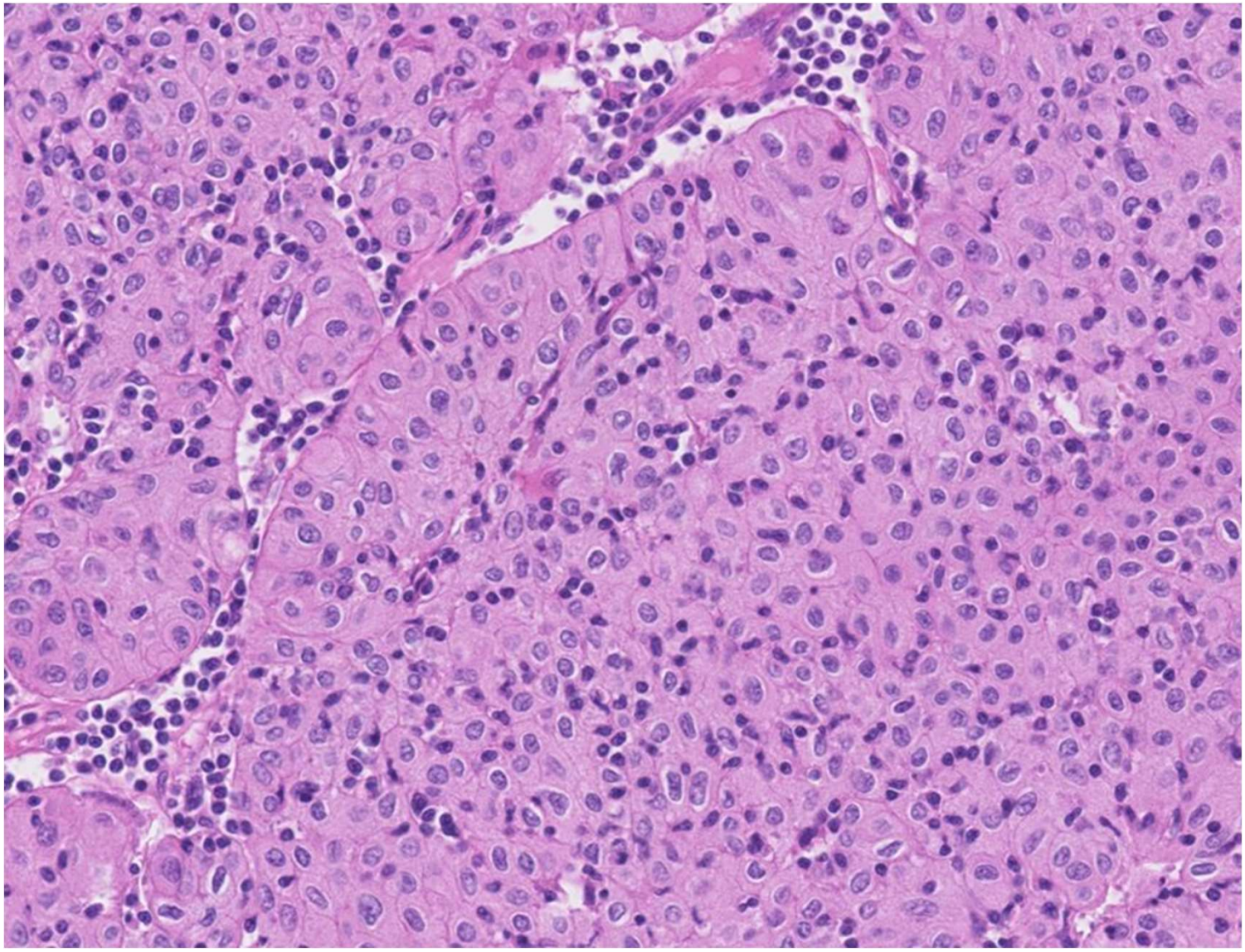
		No of scoring pathologists	Biopsy	No of scoring pathologists	Resection specimen
Case 1	79 year, male	9	**65% MNT** (25% AB, 10%A)	10	**72.22%MNT** (16.66%A, 11.11%AB)
Case 2	45 year, male	7	**92.85%B1** (7.15%B2)	7	**51.43%B1** (22.86%AB, 25.71%B2)
Case 3	55 year, male	7	**47.77%B2** (30%B1, 22.22%AB)	9	**100%AB**
Case 4	66 year, female	5	**80%B1** (20%B2)	9	**64%B2** (36%B1)
Case 5	55 year, male	8	**84.29%ThymicCA** (15.71%B3)	7	**88.75%ThymicCA** (11.25%B3)
Case 6	49 year, male	8	**76.66%B1** (22.22%NOS, 1.11%NTT)	9	**66.25%B1** (33.75%B2)
Case 7	68 year, male	8	**78.5%A** (21.5%AB)	7	**100%A**
Case 8	64 year, female	8	**66.66%B1** (22.22%NOS, 11.11%B2)	9	**36.25%B1** (25%AB, 20%B2, 12.5%other, 6.25%B3)
Case 9	41 year, male	10	**56.25%B2** (18.75%B3, 12.5%NOS, 12.5%AB)	8	**88%B2** (12%B1)
Case 10	70 year, male	8	**88.88%A** (11.11%NOS)	9	**92.5%A** (7.5%B3)
Case 11	73 year, male	8	**68.18%MNT** (22.72%A, 9.09%Normaal)	11	**100%MNT**
Case 12	53 year, female	8	**68.75%B1** (25%NOS, 6.25%B2)	8	**66.25%B2** (17.5%B1, 12.5%AB, 3.75%)
Case 13	78 year, male	10	**94.44%A** (5.56%AB)	9	**100%A**
Case 14	58 year, female	8	**95%A** (5%AB)	10	**43.75%A** (12.5%AB vs NTT vs other, 10%B3, 7.5%NOS, 1.25%B2)
Case 15	61 year, female	6	**40%MNT vs NOS** (20%AB)	5	**65%AB** (30%MNT, 5%B1)



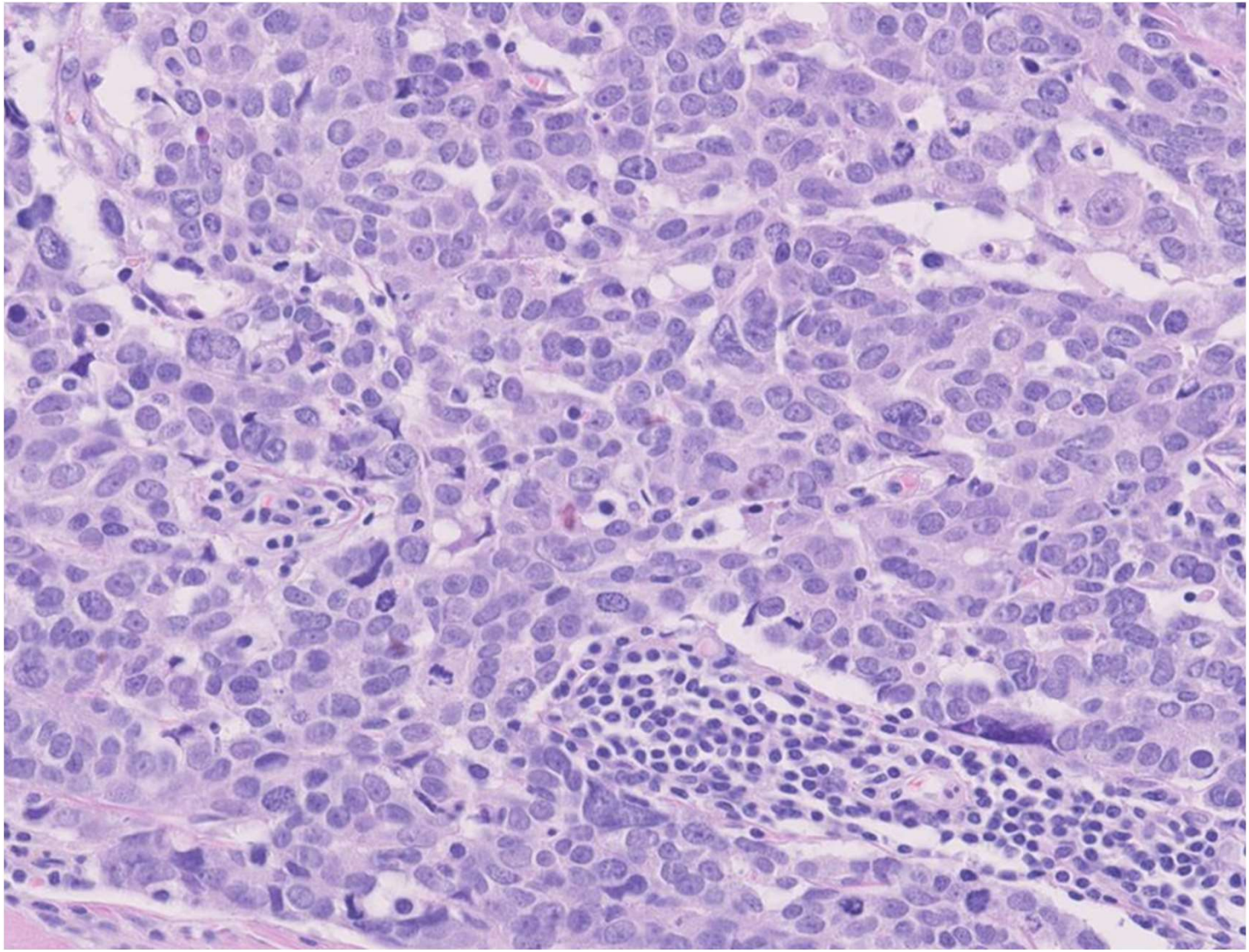
AB Thymoma
100% consensus
n=7



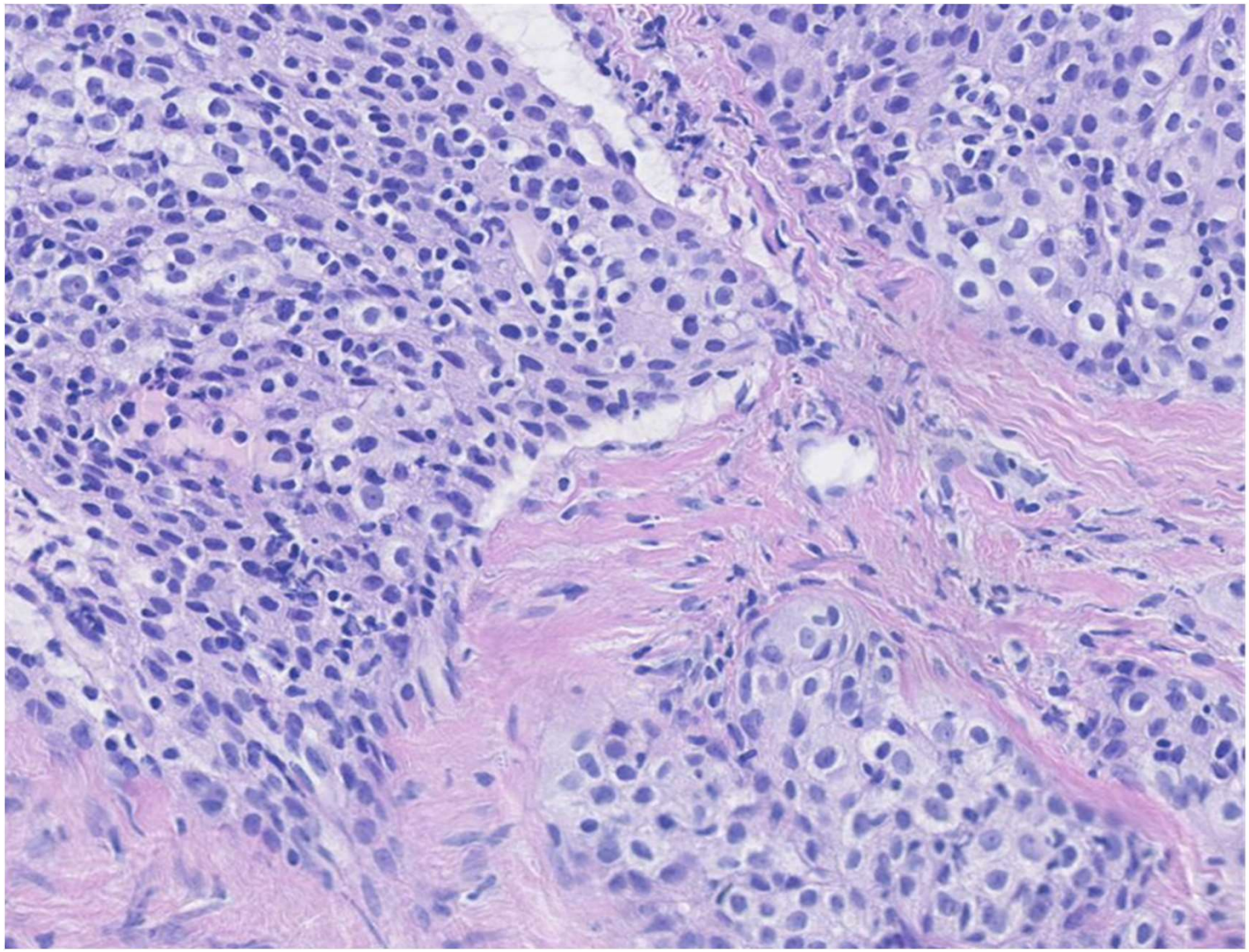
A Thymoma
100% consensus
n=10



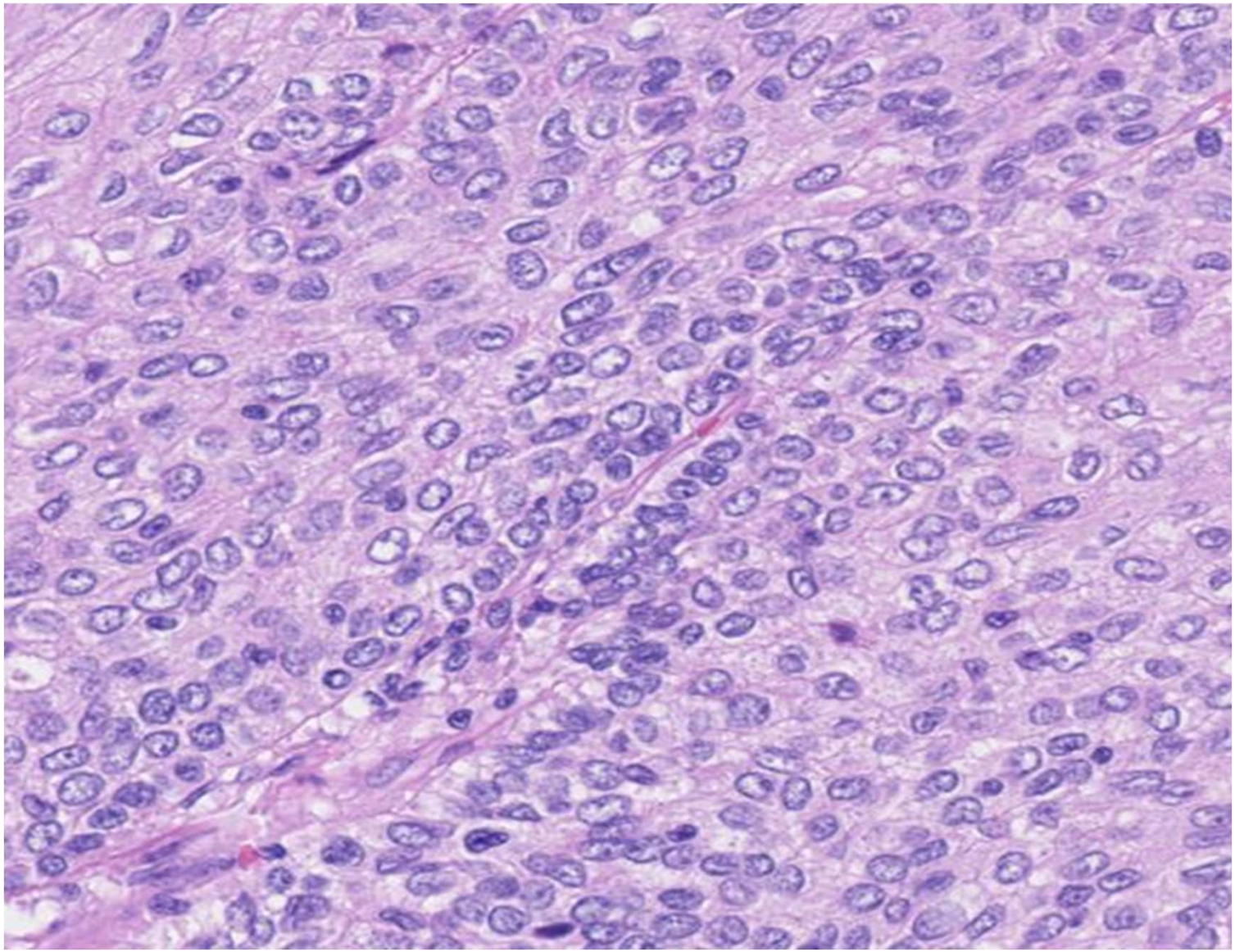
B3 Thymoma
99% consensus
n=7



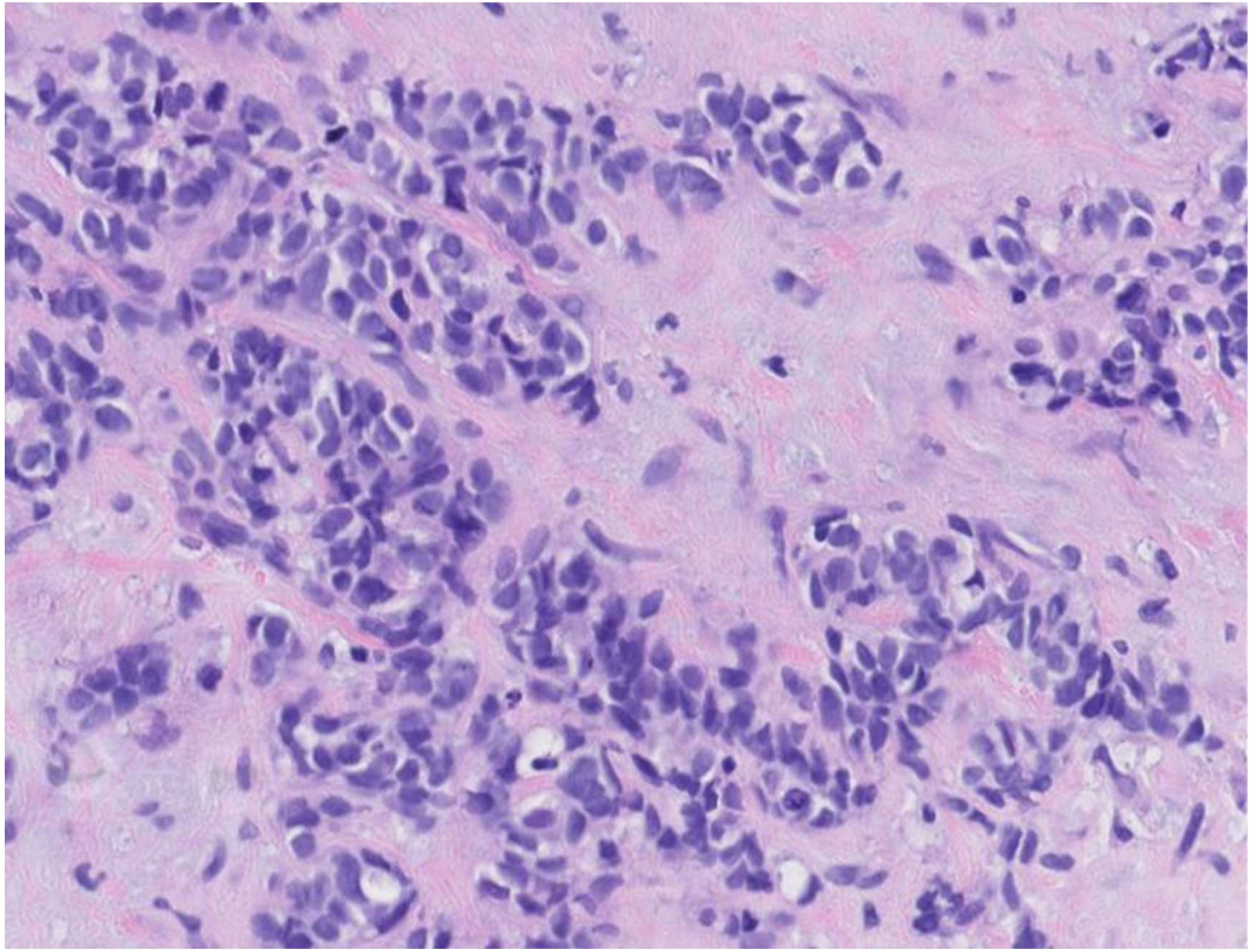
Thymic CA
100% consensus
n=7



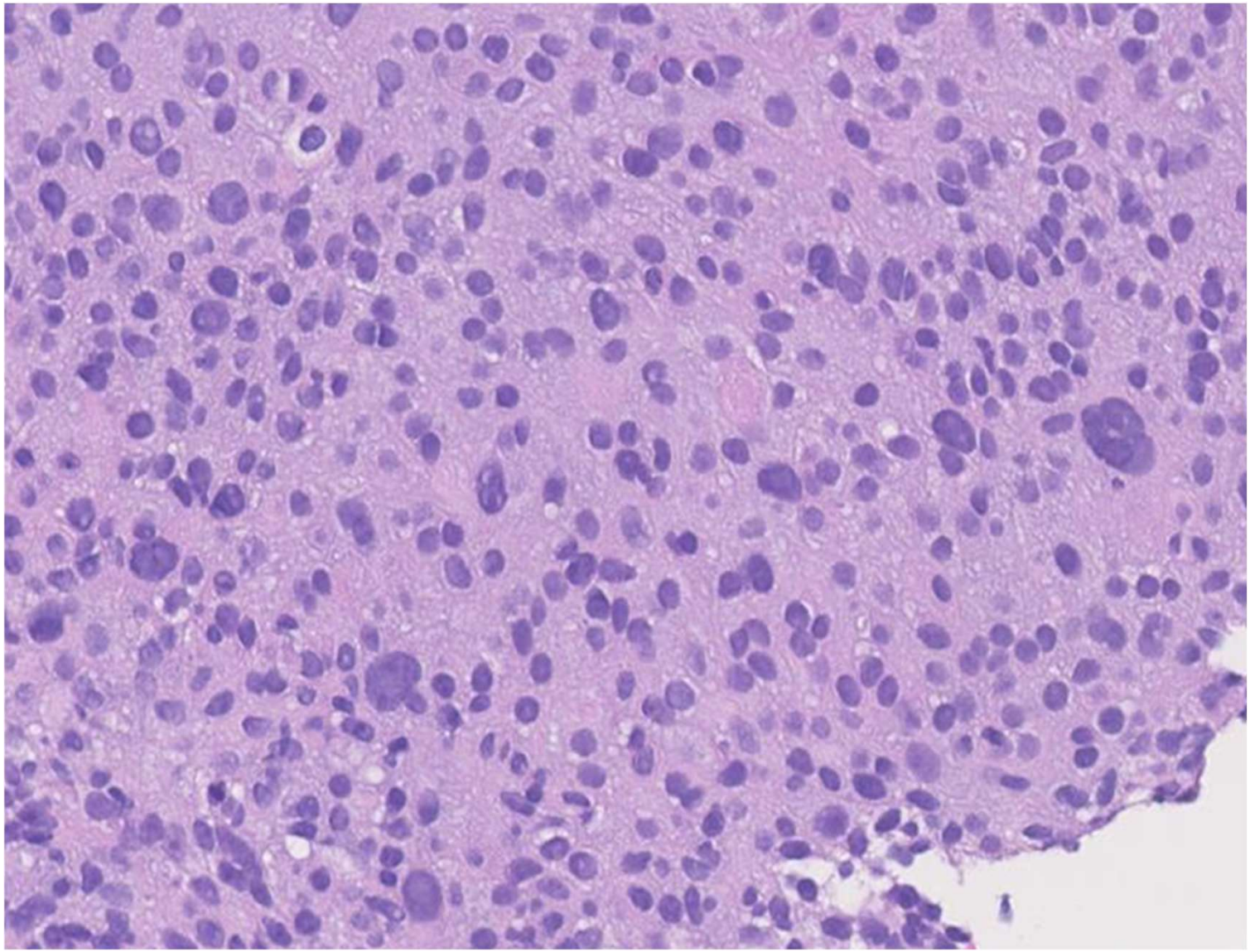
55% B3,
45% Thymic CA
n=9



66,66% B3
22,22% Thymic CA
3,33% B2
n=9



77,77% Thymic CA
22,23% A
n=9



62,5% Thymic CA
25% thymic lesion NOS
12,5% metastasis
n=4

Conclusions

- Main difficulties arose between type A thymoma vs B3 and thymic carcinoma.
- Lower κ values were seen between different B-type [B1, B2, B3)] thymomas.
- The difference between the B subgroup is clinically important because of different therapeutic approaches in Masaoka-Koga stage II A and II B.

Conclusions

- Lower κ values in biopsies might be explained by the low amount of available tissue and the lack of sufficient typing.
- The biopsy diagnosis of a thymic tumour can provide a good indication of the underlying pathology.
- Whole-slide imaging gives experts around the world access to rare (thymic) lesions and, in the context of a virtual panel, offers a good template for dealing with rare tumours where expertise is sparse.

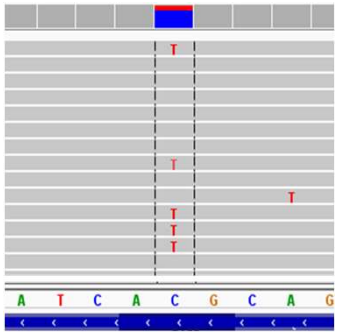
The pathologist's toolbox

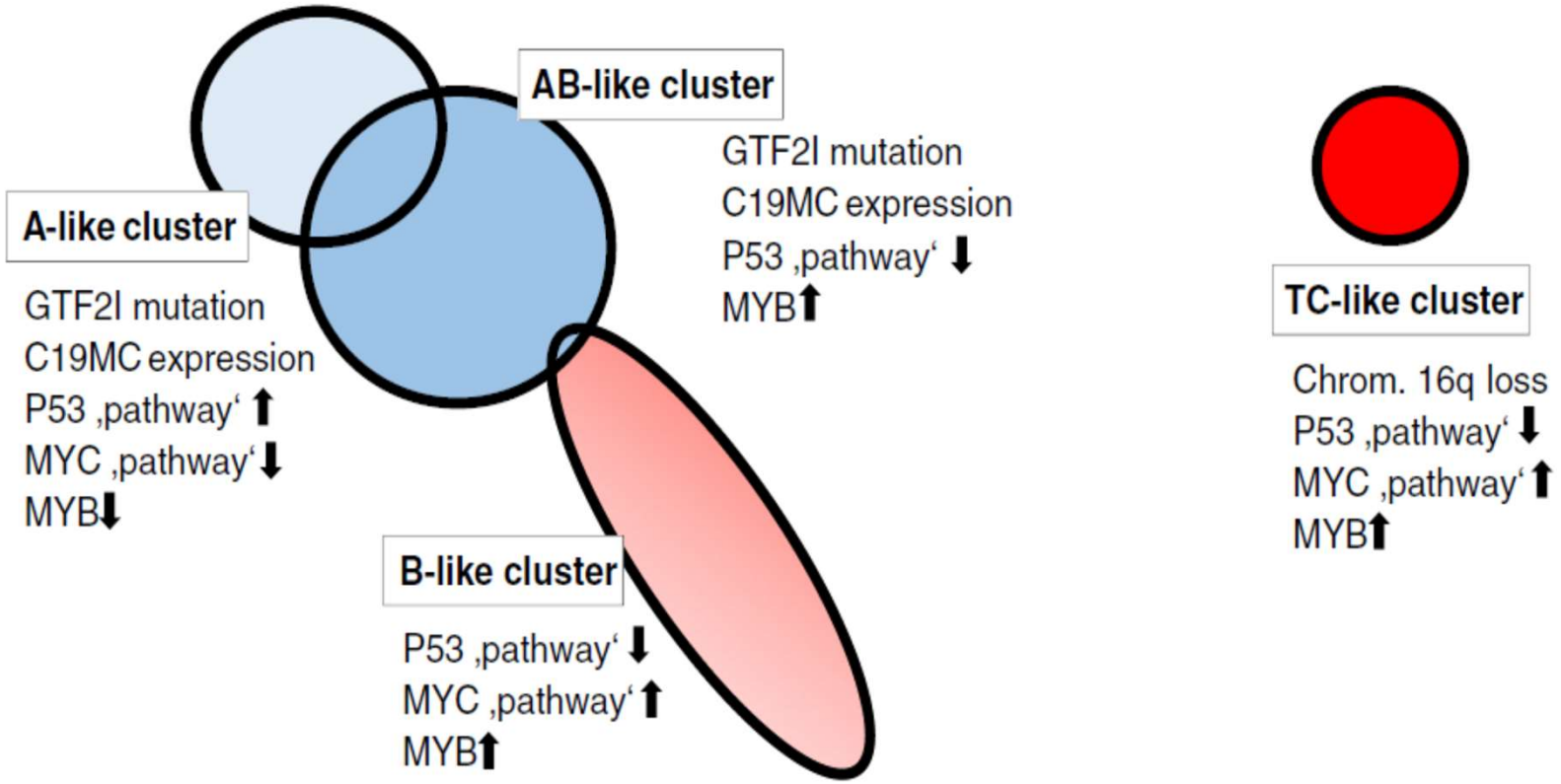
Macroscopy

Microscopy

Ancillary stains

Molecular diagnostics





Marx et al. Virchows Archiv 2021;478:101–110.

Table 1 Recurrent molecular alterations with potential differential diagnostic relevance in TETs. Radovich et al. 2018 [10]; Feng et al. 2017 [39]; Petrini et al. 2015 [12]; Viviero et al. 2020 [45]; Massoth et al. 2020 [46]

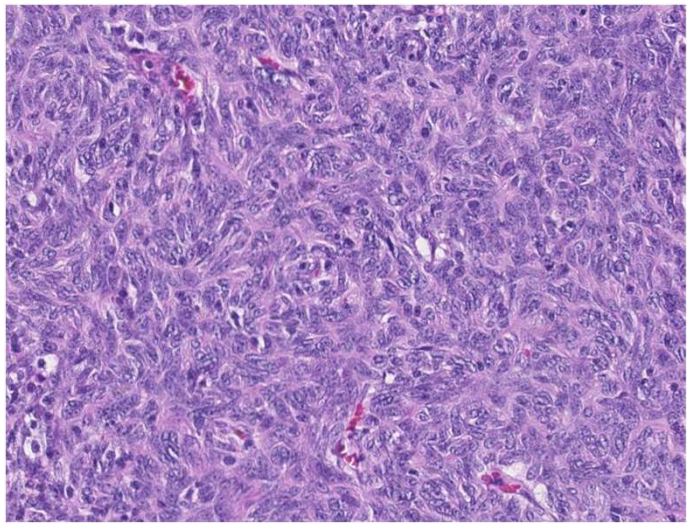
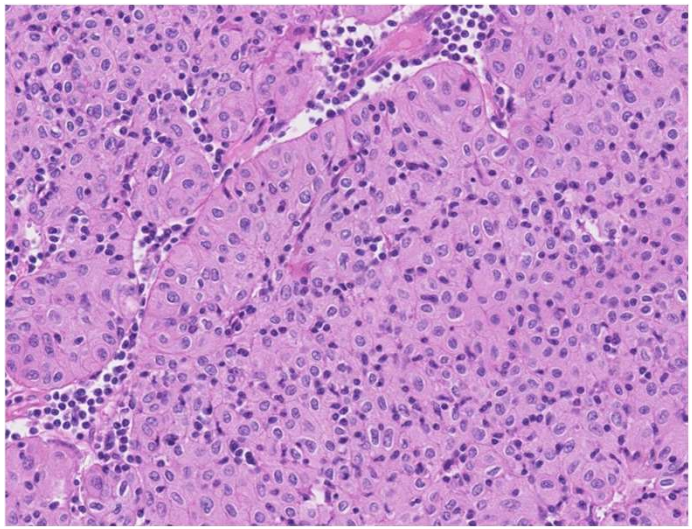
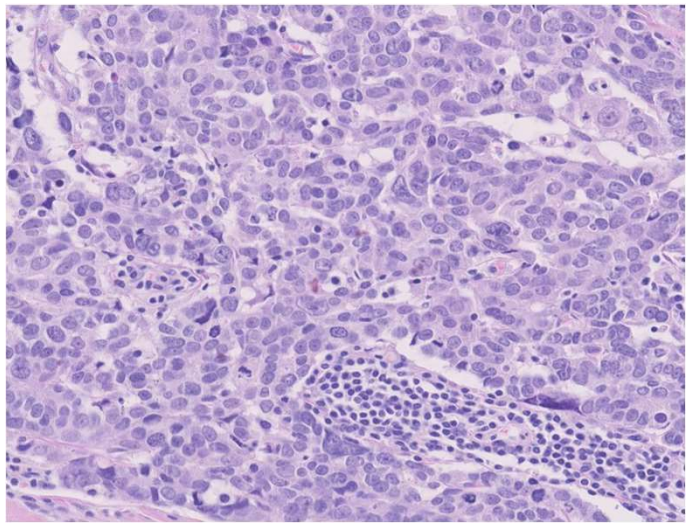
Genetic alteration	Type A thymoma	Type AB thymoma	Type B1 thymoma	Type B2 thymoma	Type B3 thymoma	MNT*	Metaplastic thymoma	Thymic carcinoma
GTF2A, p.L424H	82–100*%	71*–79%	0*–32%	0*–22%	10*–21%	50% (1 of 2*)	n.t.	0*–8%
YAP1-MAML2 translocation	(–-)	(---)	(–-)	(---)	(---)	(---)	100%	n.k.
KMT2A-MAML2 translocation	(–-)	(---)	(–-)	<10%	<10%	n.k.	n.k.	(–-)
16q loss	(–-)	(---)	(–-)	(---)	(---)	(---)	n.t.	80%*

*Results obtained by the TCGA THYM consortium [10]

TETs, thymic epithelial tumors; *(—)*, 0%; *n.k.*, not known; *n.t.*, not tested

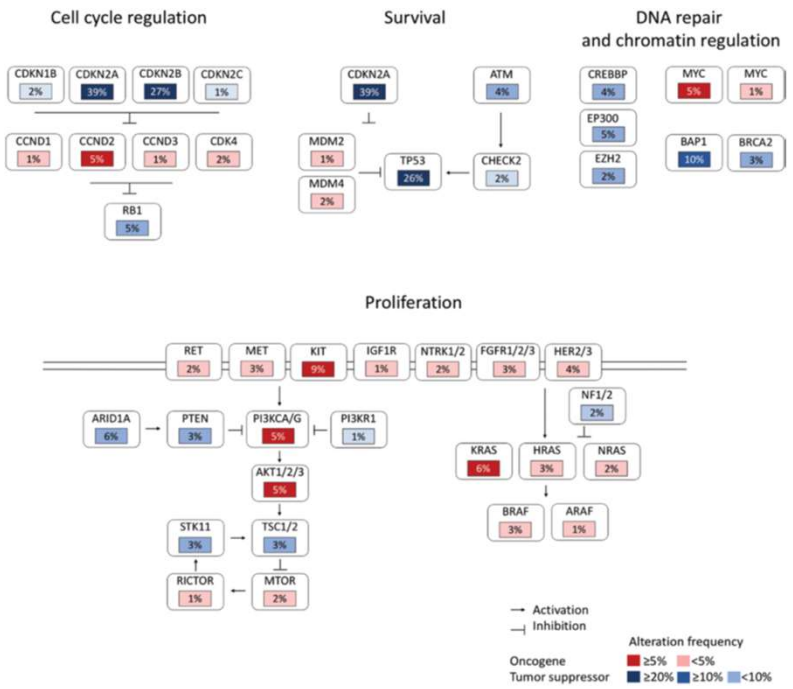
Marx et al. Virchows Archiv 2021;478:101–110.

Thymoma type A vs. type B3 vs. thymic carcinoma

- Thymoma type A:
  - Few genomic alterations
  - GTF2AI mutations
  - In contrast to thymic ca. no *APC*, *RB1* and *TP53* mutations

Comprehensive genomic profiling in TETs



Thymomas:

- low frequency of genomic alterations (average of 1.8)
- low levels of TMB
- >10% of cases in CDKN2A/B and TP53 genes

Unresectable, stage III, type B3 thymoma:

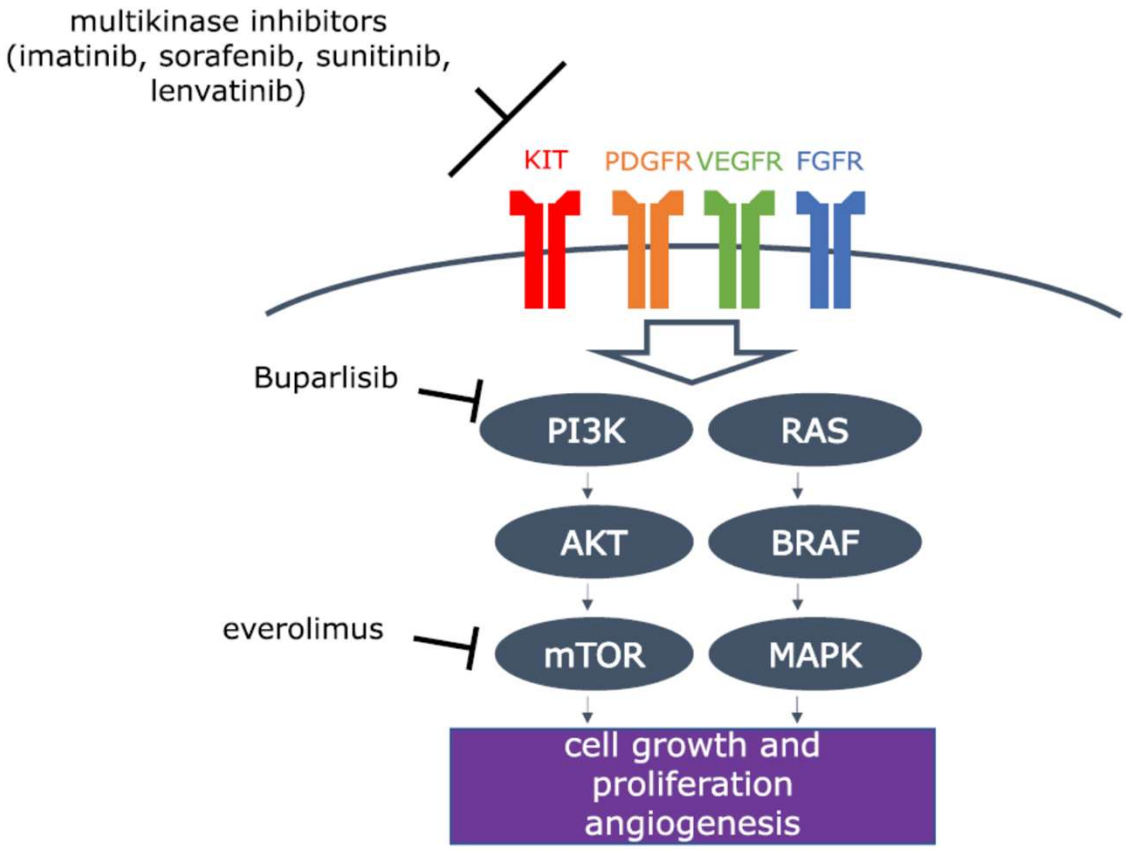
- amplification of NTRK1

Thymic carcinomas:

- higher frequency of alterations (4.0 ($P < .0001$)
- clinically relevant genomic alterations in CDKN2A, KIT, and PTEN/PI3K/MTOR pathways

Girard et al. The Oncologist, 2022, doi: 10.1093/oncolo/oyac115.

⇒ Targeted treatment?



Muto and Okuma. Expert Review of Anticancer Therapy, 2022; 22:4,401-413.

Immunotherapy for TETs

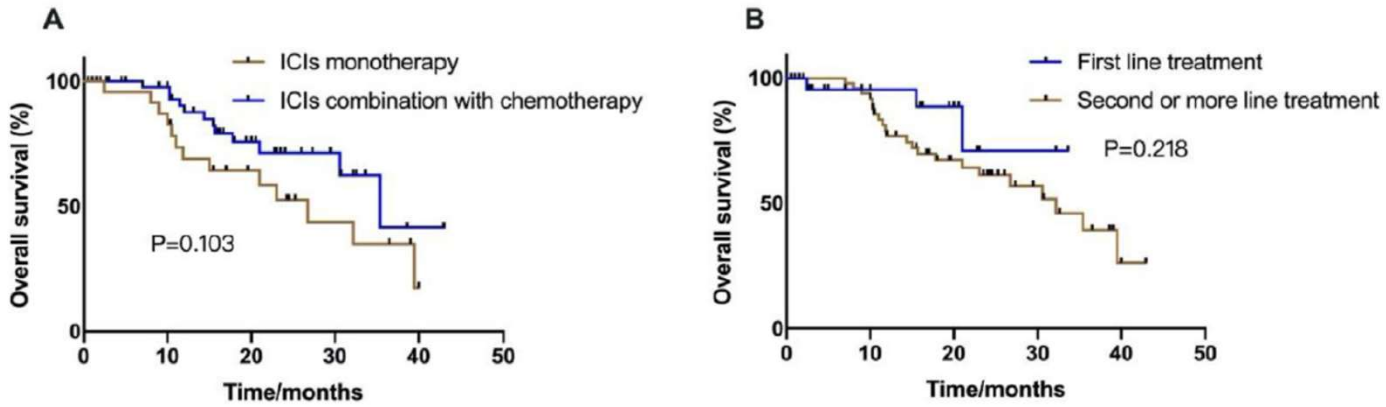


Fig. 5. Kaplan–Meier estimates of OS according to treatment lines and ICIs treatment regimens in all patients. (A) OS in patients with ICI monotherapy and ICIs combined with chemotherapy (P = 0.103). (B) OS in patients receiving ICIs as first-line treatment and as second- or posterior-line treatment (P = 0.218).

Wang et al. European Journal of Cancer 174 (2022) 21e30.

- A retrospective analysis of thymic malignancies revealed that PD-L1 is more highly expressed in thymic carcinomas (36-100%%) than in thymomas (23-92%)[1,2]
  - Unclear if this is of prognostic significance
  - Possible correlation with outcome in IO?[3,4]

1. Katsuya Yet al. Lung Cancer 2015; 88: 154–59.
2. Jovanovic et al. J Thorac Dis 2020;12(12):7561-7570.
3. Giaccone et al. Lancet Oncol 2018;19:347-55.
4. Cho et al. J Clin Oncol 2019;37:2162-70.

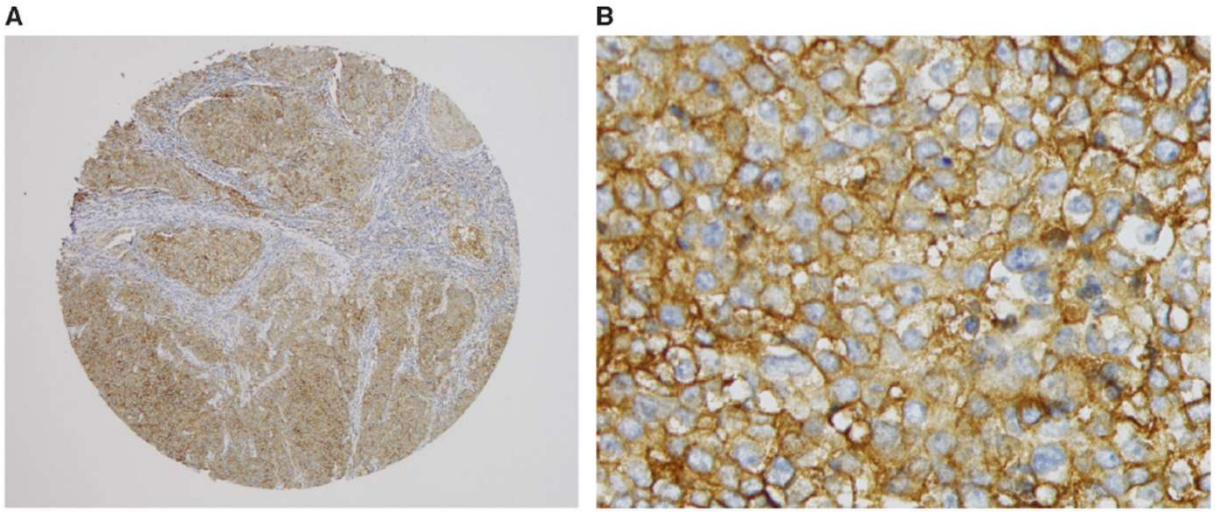


Fig. 2 **a** Tissue microarray showing strong membranous staining of PD-L1 in a high percentage of tumor cells. **b** High-power view of membranous staining pattern for PD-L1

Table 2 Percentage of PD-L1 staining in 21 cases of poorly differentiated non-keratinizing squamous cell carcinoma of the thymus

Case no.	PD-L1 staining percent staining	Stromal pattern
1	>50%	Lymphoepithelioma-like
2	0	Desmoplastic
3	>50%	Lymphoepithelioma-like
4	>50%	Lymphoepithelioma-like
5	<50%	Desmoplastic
6	0	Desmoplastic
7	>50%	Lymphoepithelioma-like
8	<50%	Lymphoepithelioma-like
9	>50%	Lymphoepithelioma-like
10	>50%	Lymphoepithelioma-like
11	<50%	Desmoplastic
12	0	Desmoplastic
13	0	Desmoplastic
14	<50%	Lymphoepithelioma-like
15	>50%	Lymphoepithelioma-like
16	>50%	Lymphoepithelioma-like
17	0	Desmoplastic
18	>50%	Lymphoepithelioma-like
19	<50%	Lymphoepithelioma-like
20	>50%	Lymphoepithelioma-like
21	0	Desmoplastic

Lymphoepithelioma-like: cores were characterized by dense lymphoplasmacytic stroma; Desmoplastic: cores showed a lymphoid cell-poor stroma

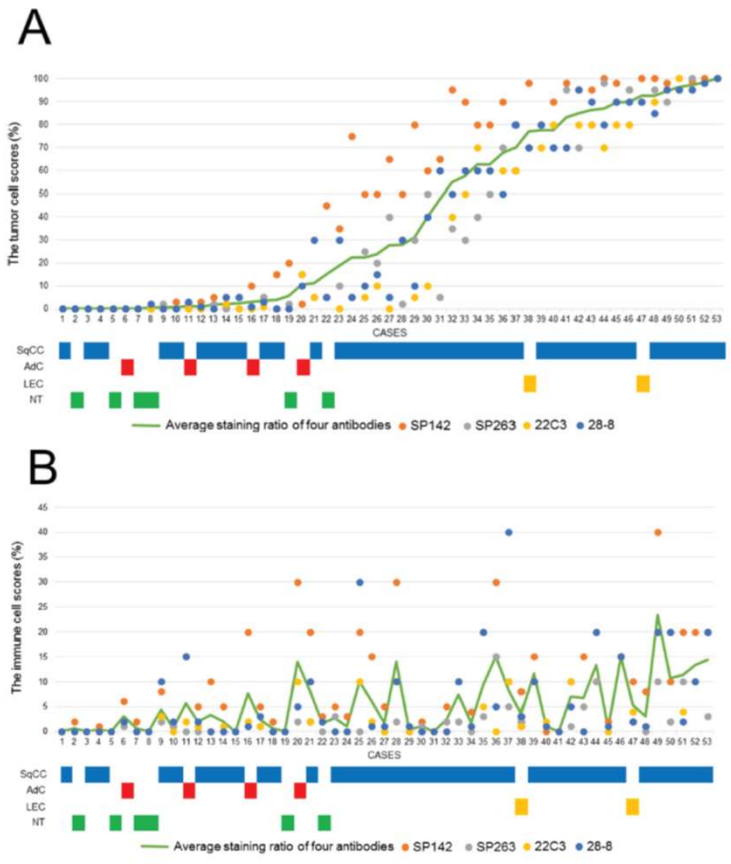
Suster et al. Modern Pathology 2018;31:1801–1806.

Table 4. Reagents and scoring criteria used for the assessment of PD-L1.

Clone of PD-L1 AntiBody	Company, City, Country	Definition of Scoring Criteria
22C3	Dako North America, Carpinteria, CA, USA	PD-L1 expression was classified as "high" if at least 50% of the tumor cells, inflammatory cells, or stroma cells stained positive. PD-L1 expression in 0% to 49% of cells was classified as "low" expression.
28-8	Abcam, Tokyo, Japan	PD-L1 $\geq$ 1% was defined as "positive".
22C3	Agilent Technologies, Santa Clara, CA, USA	PD-L1 expression was classified as "high" if at least 50% of the tumor cells stained positive. PD-L1 expression in 1–49% of cells was classified as "low" expression.

Abbreviation: PD-L1, programmed death ligand-1.

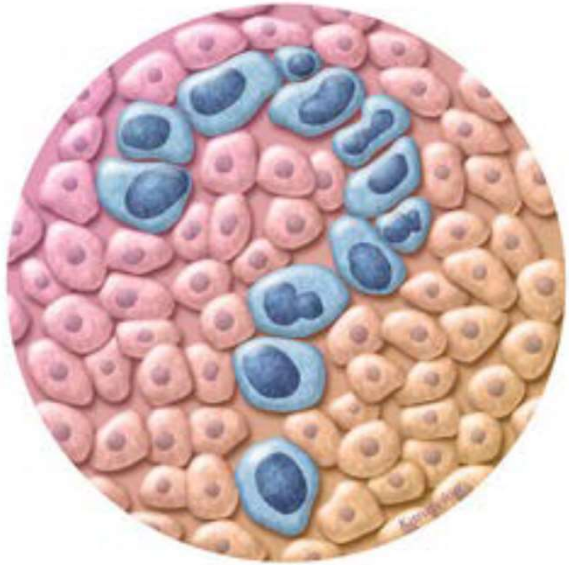
Kaira et al. Cancers 2021;13:1065.
Cho et al. J. Clin. Oncol. 2019;37:2162–2170.
Ak et al. J. Oncol. Pharm. Pract. 2020.
Giaccone et al. Lancet Oncol. 2018;19:347–355.



Sakane et al. Oncotarget, 2018;9(6):6993-7009.

Summary

- In TETs, macroscopy is important for staging
- Most differential diagnoses can be resolved by H&E and IHC alone
- MD can be an option
- Some entities remain difficult => cases welcome in our panel
- **Join the TMWG of the ESP ☺!**



Thank you for your attention!