in association with UKEPS UK Endocrine Pathology Society

London Endocrine Pathology Update

Monday February 10th and Tuesday February 11th, 2025 - The Gordon Museum of Pathology, Guy's Campus, London, UK

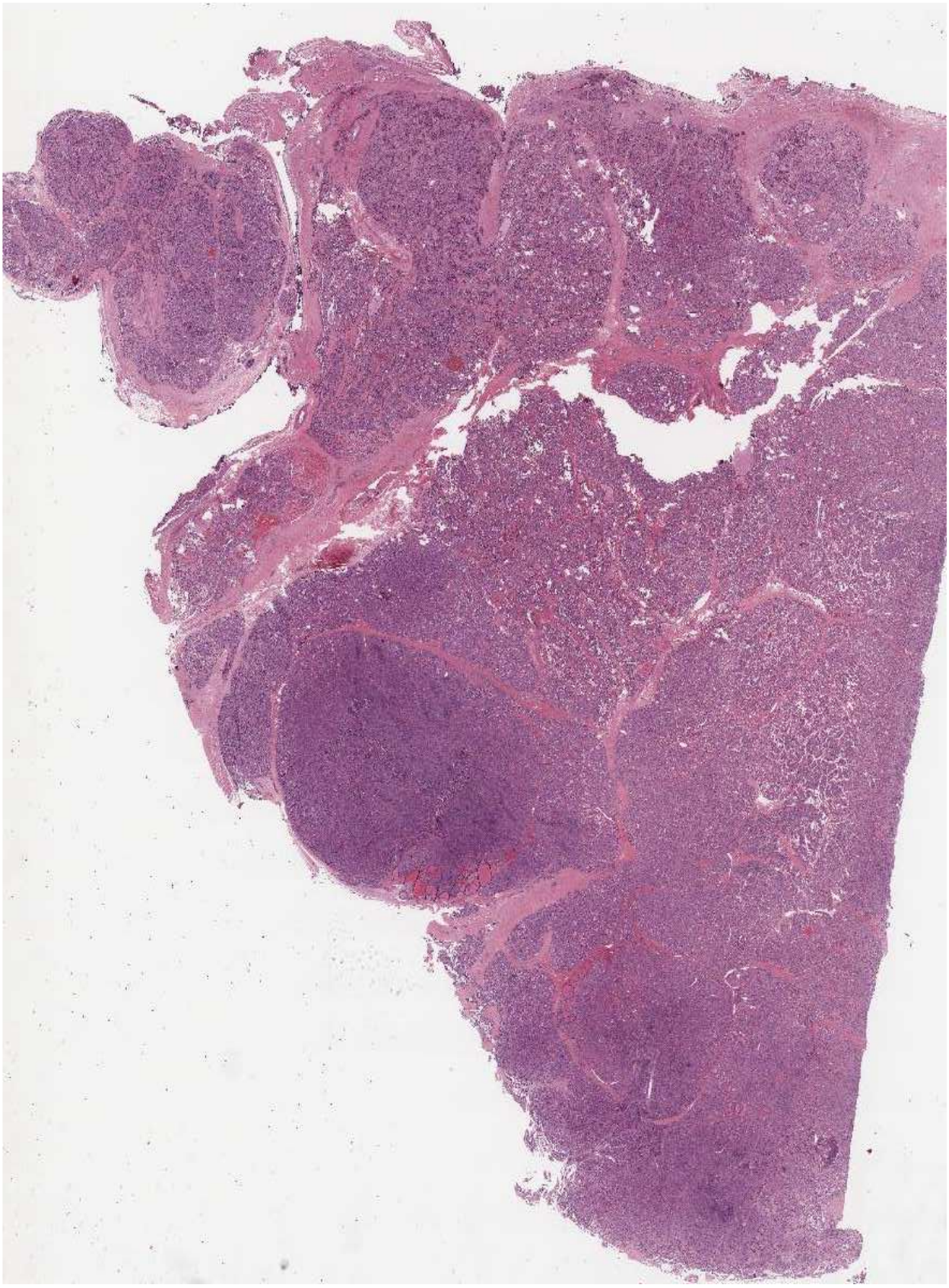
CASE 2

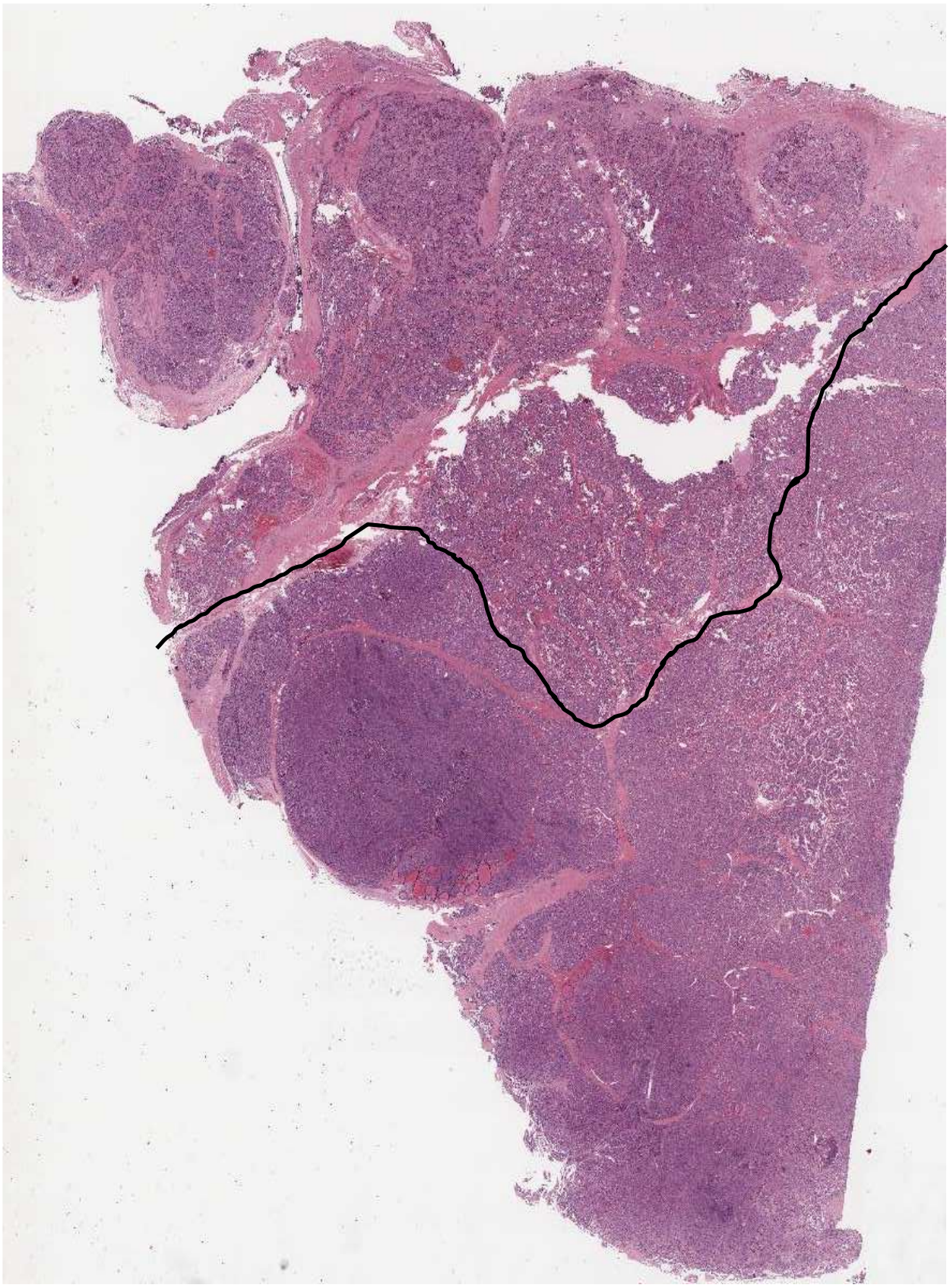
Multinodular 6X3X3 cm right thyroid lobe lesion extending to the isthmus in a 72 years old man

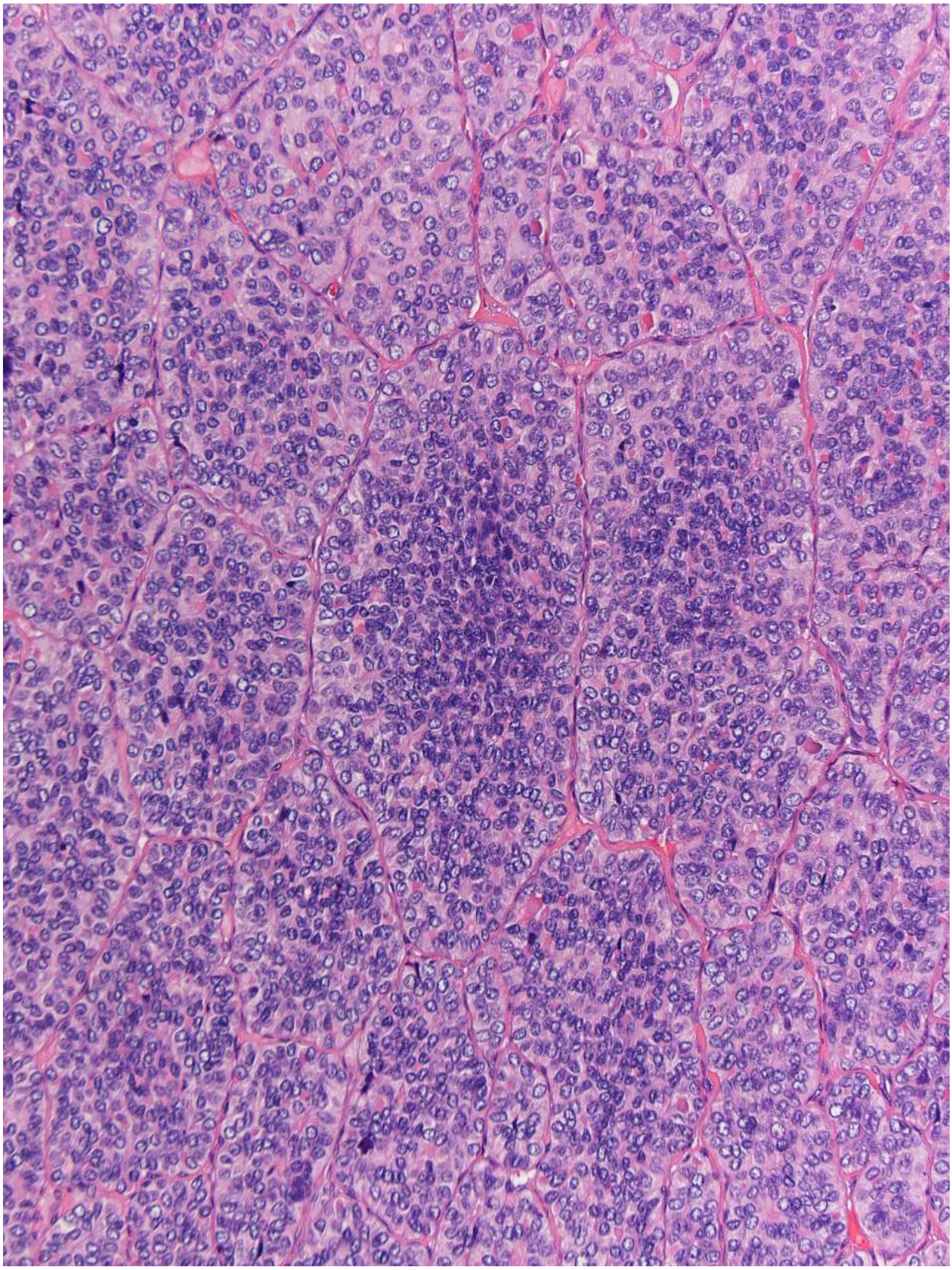
Giovanni Tallini, MD

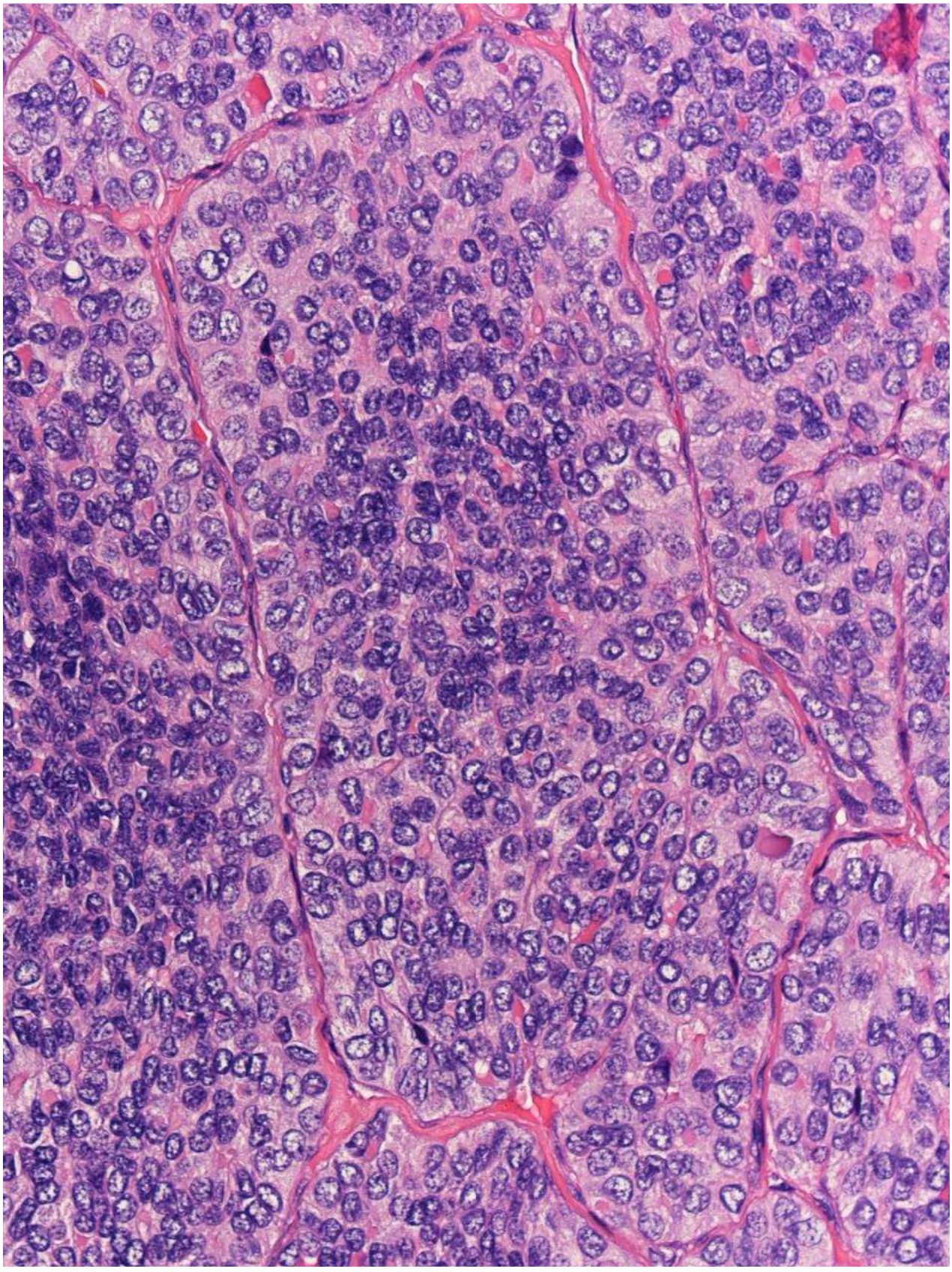
Anatomic Pathology, University of Bologna Medical Center

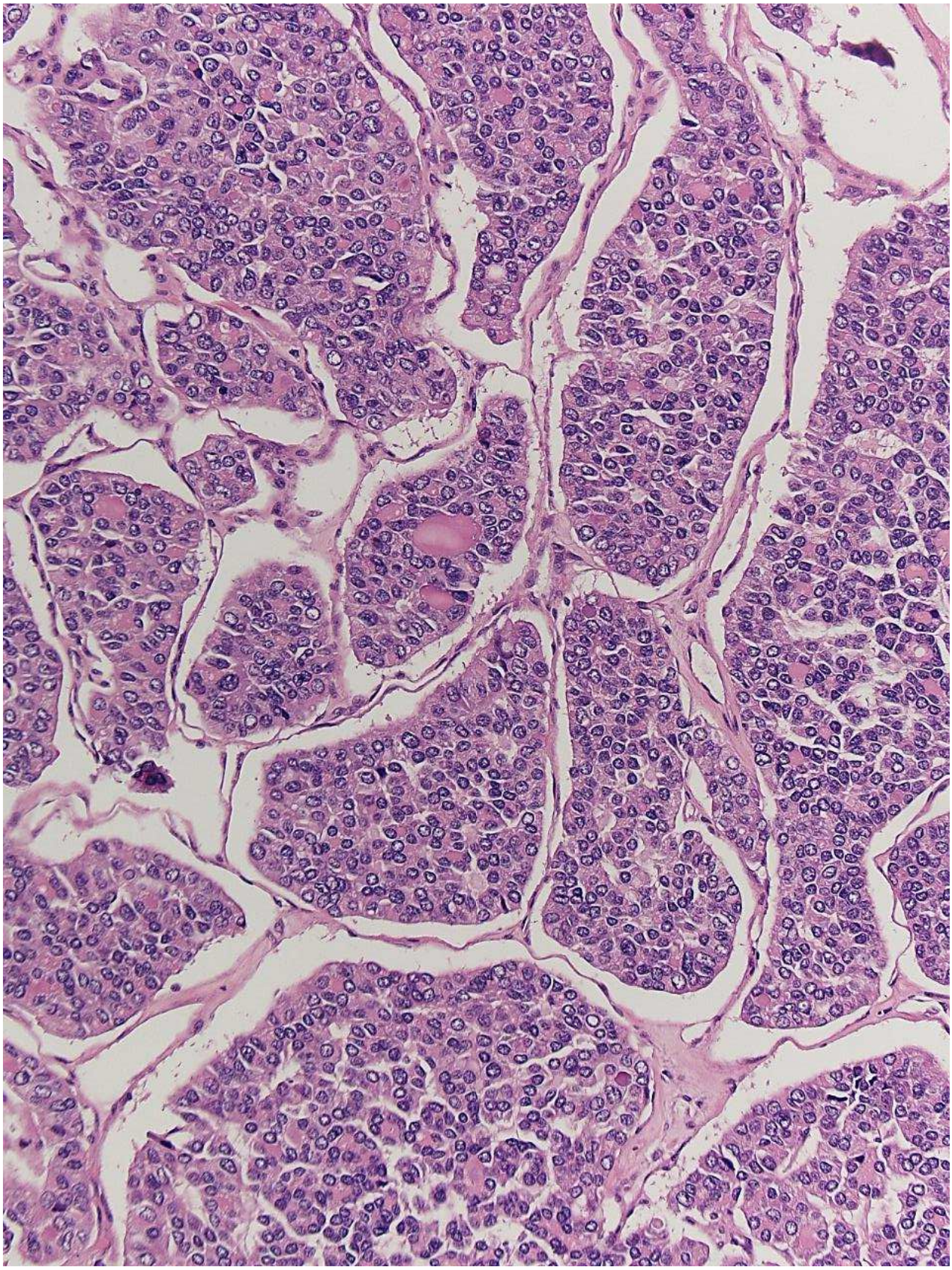
giovanni.tallini@unibo.it

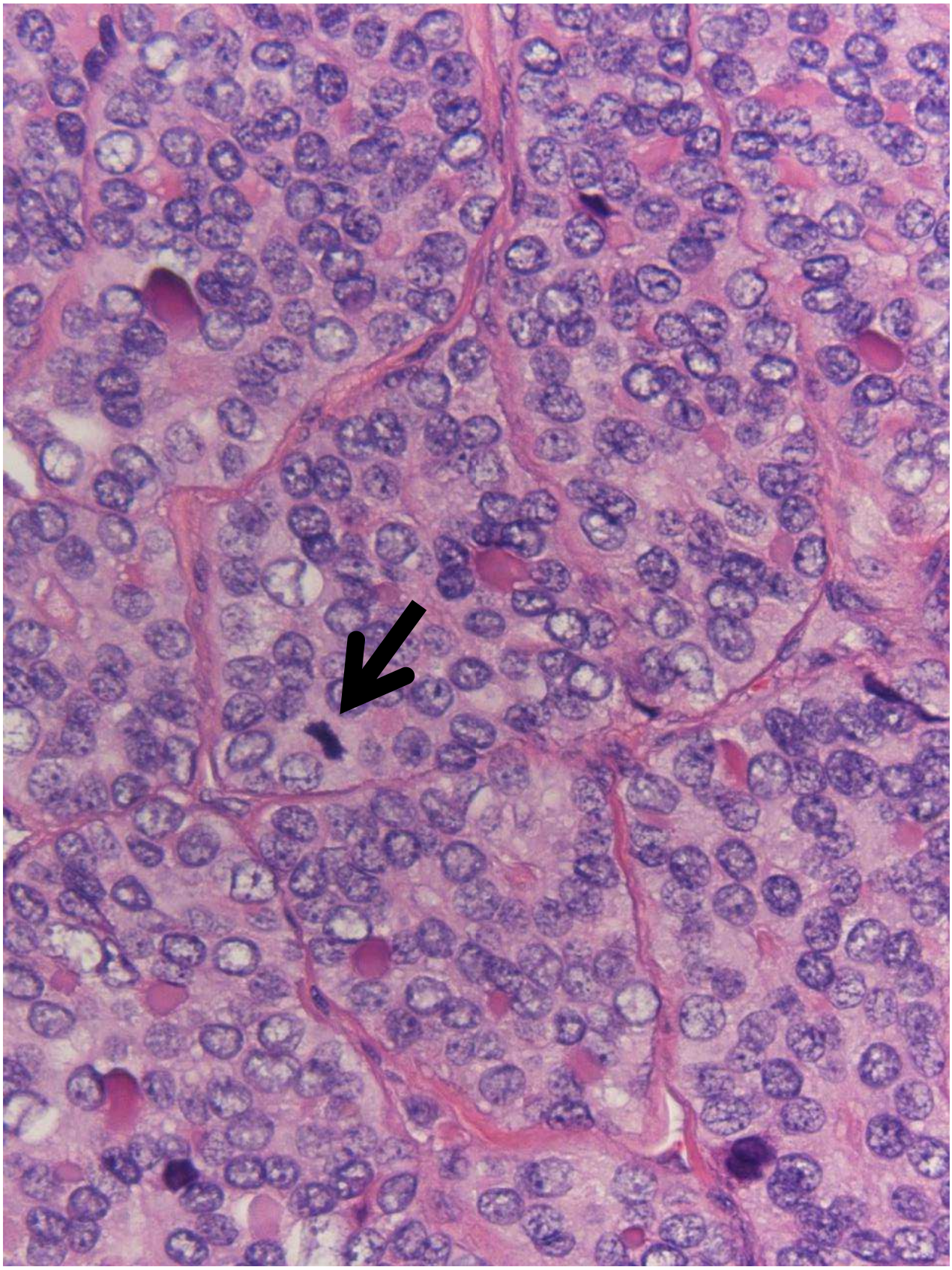


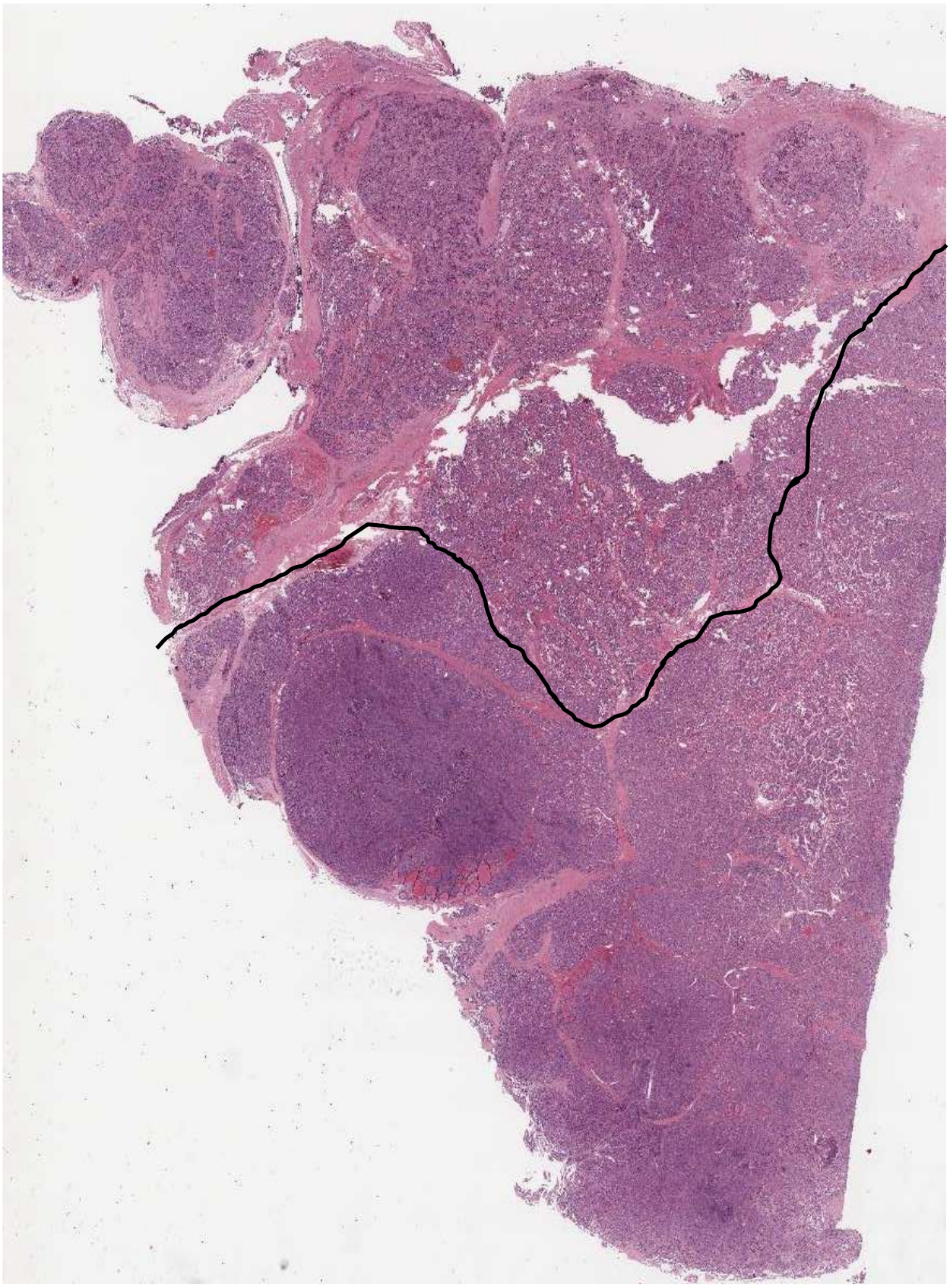


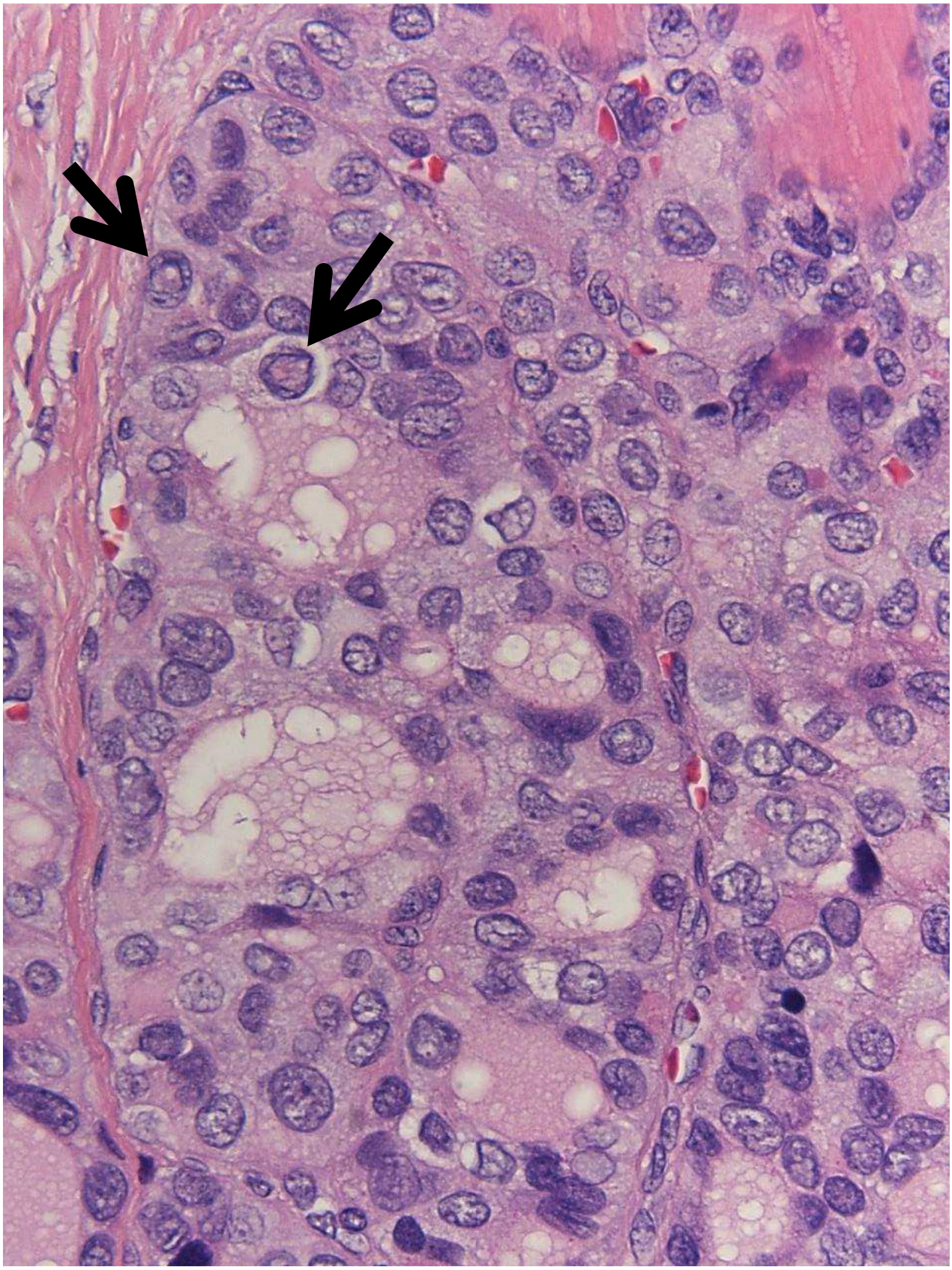


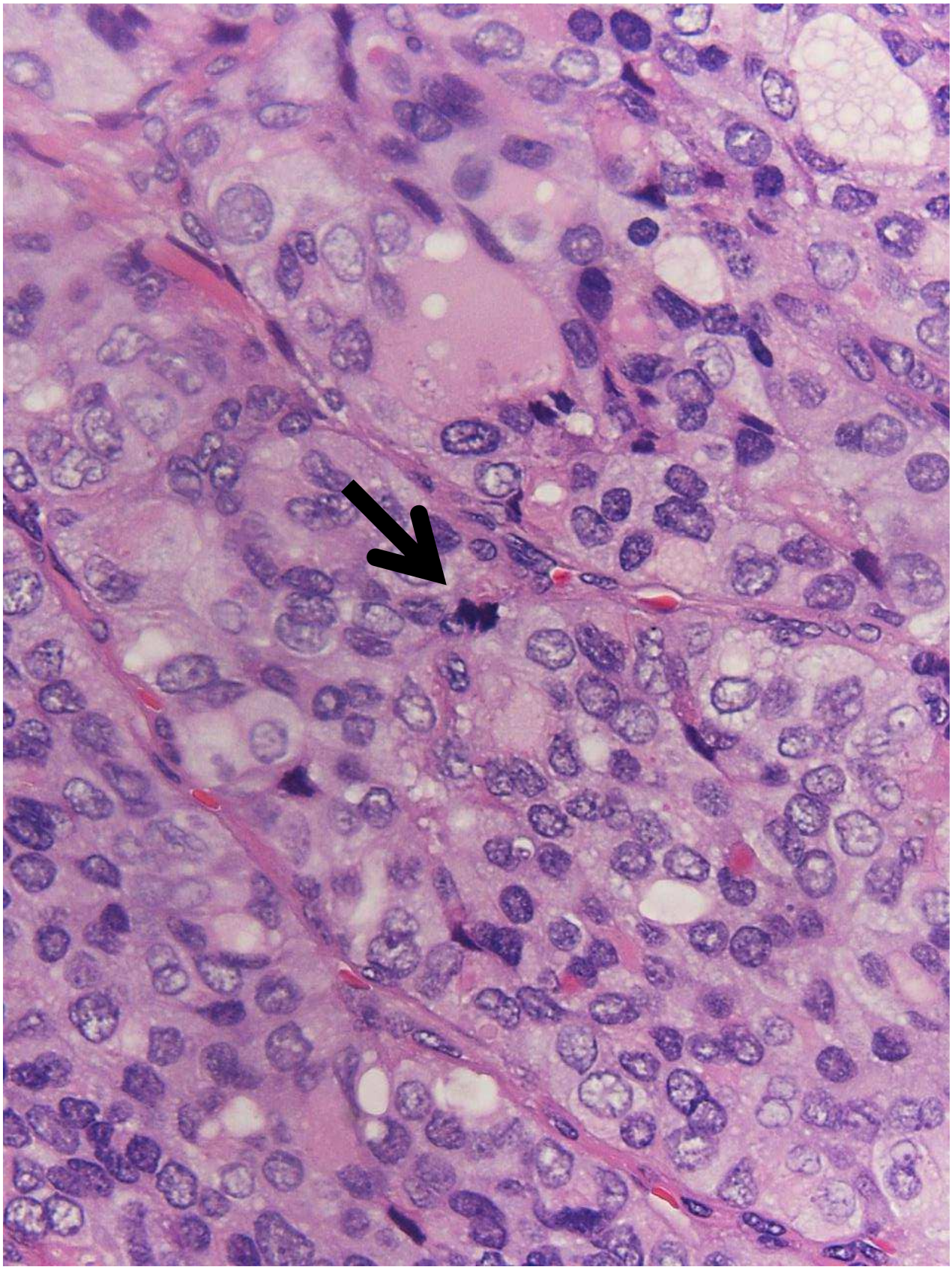


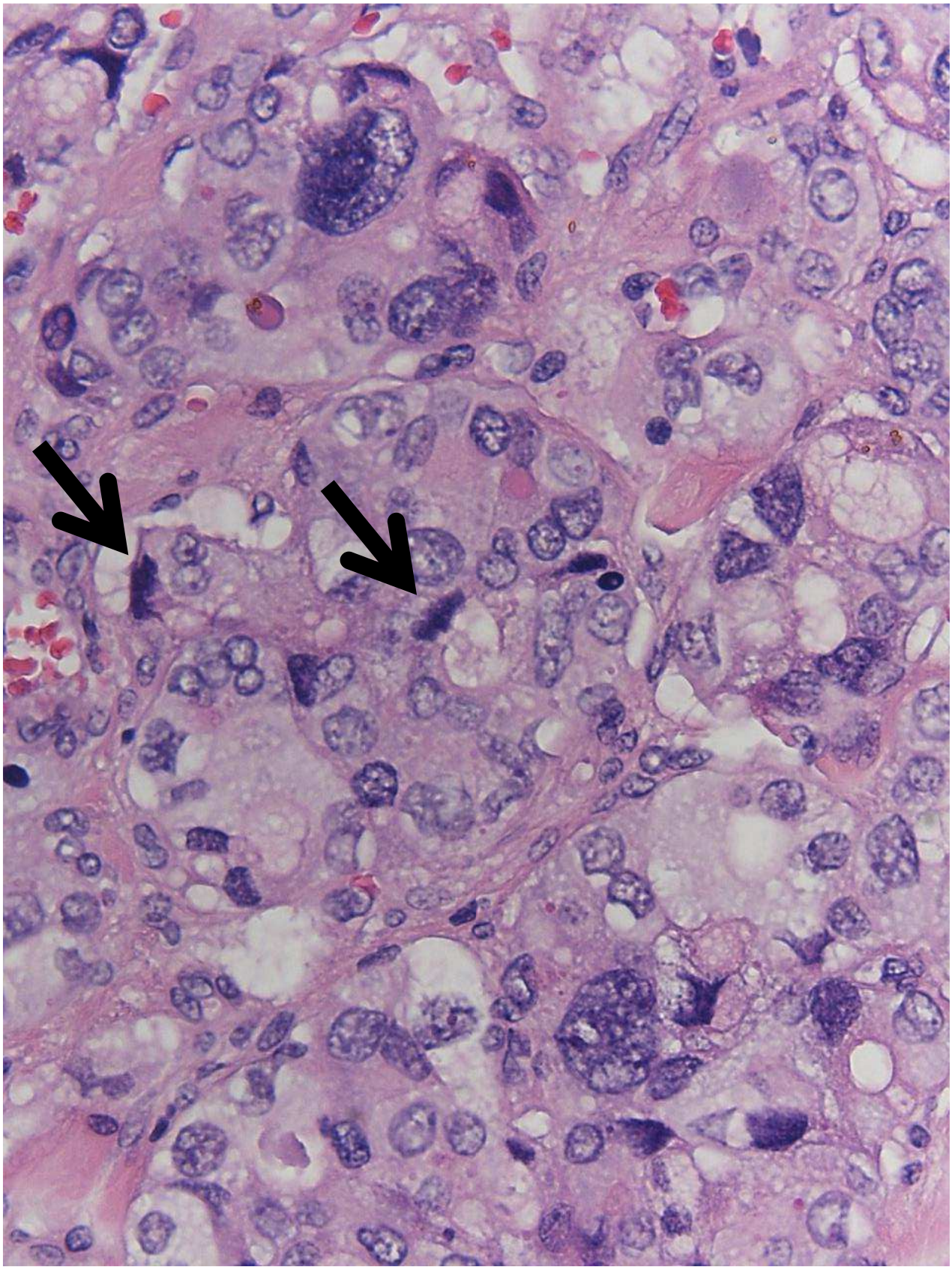


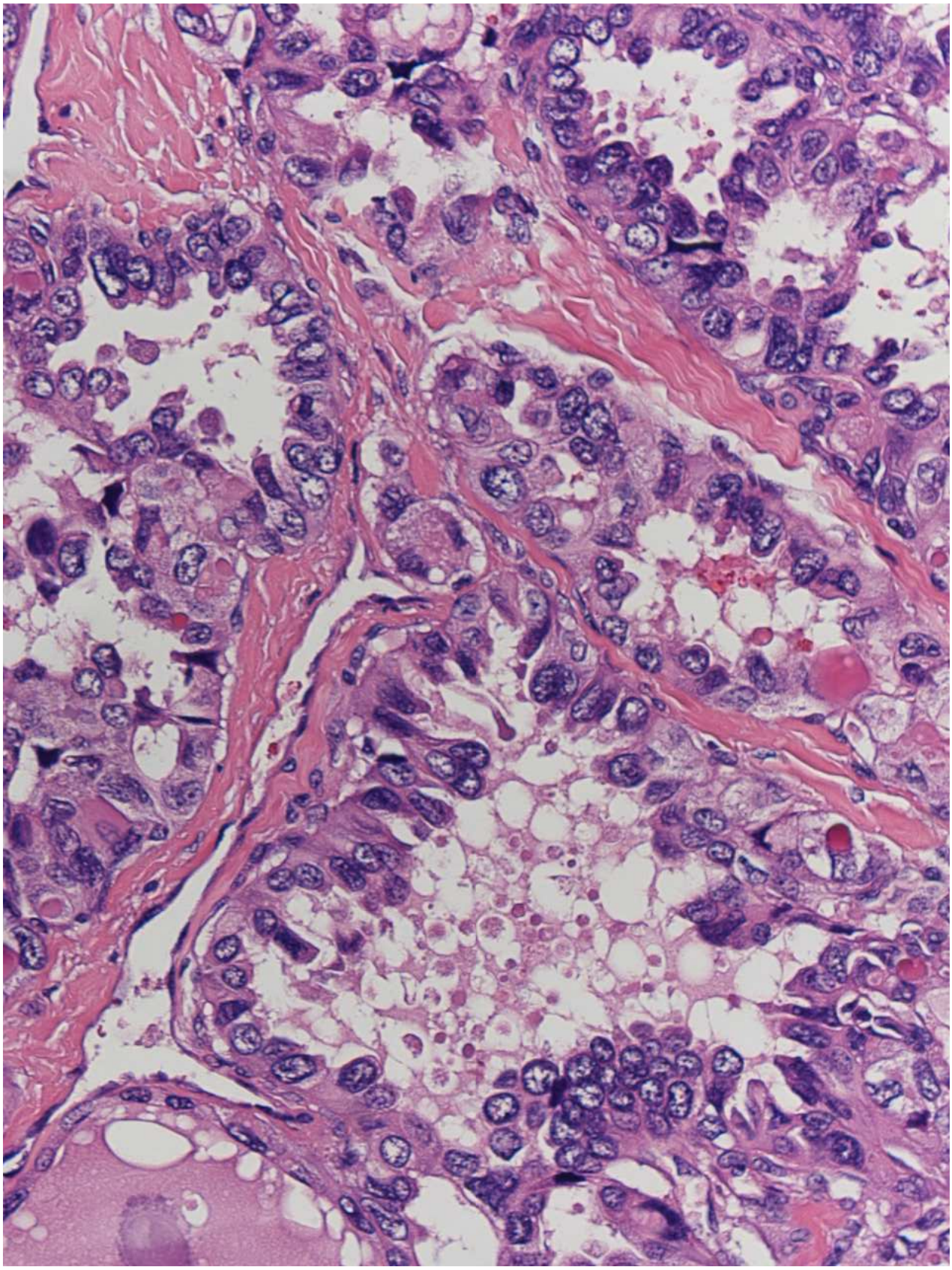


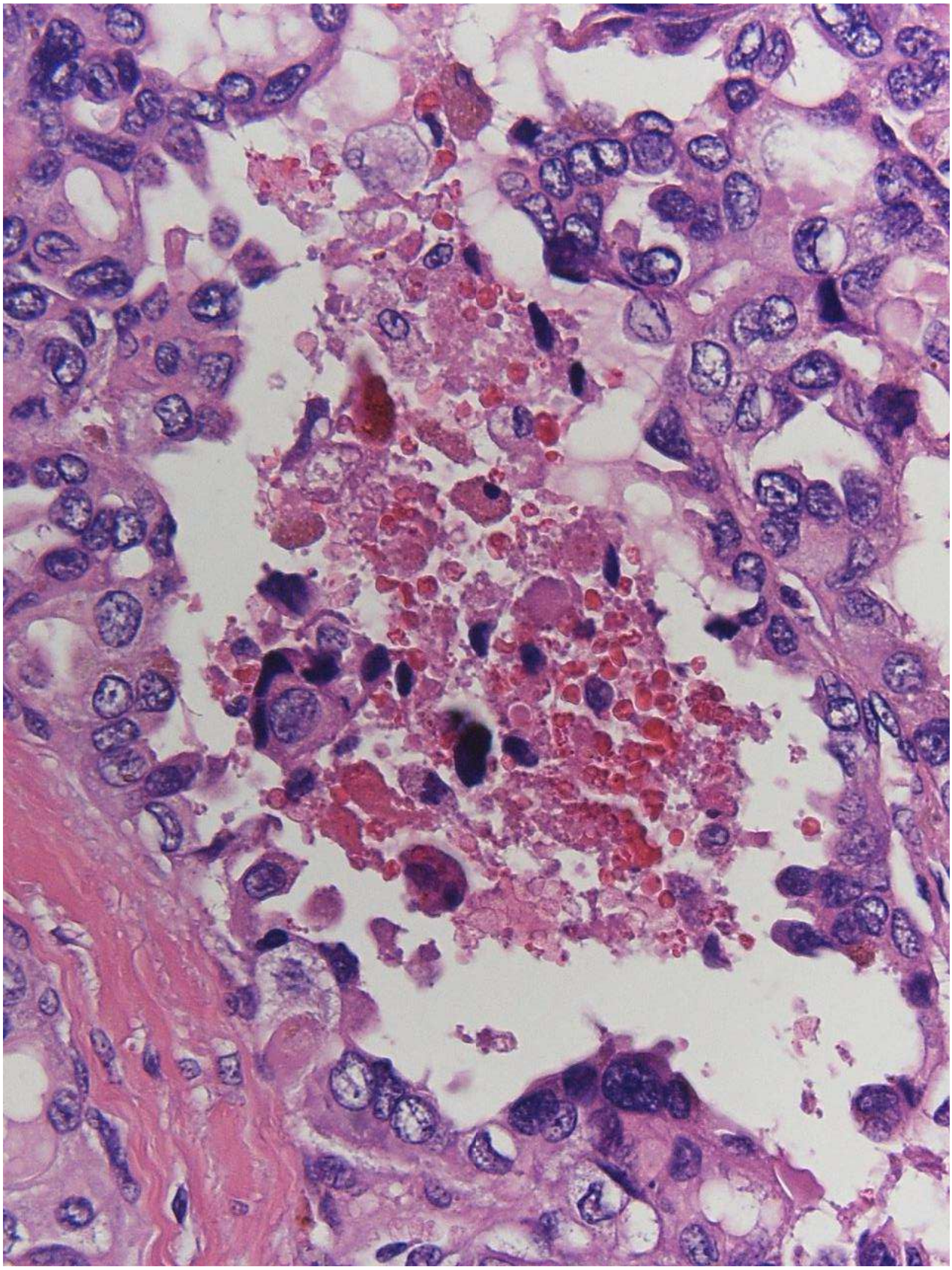


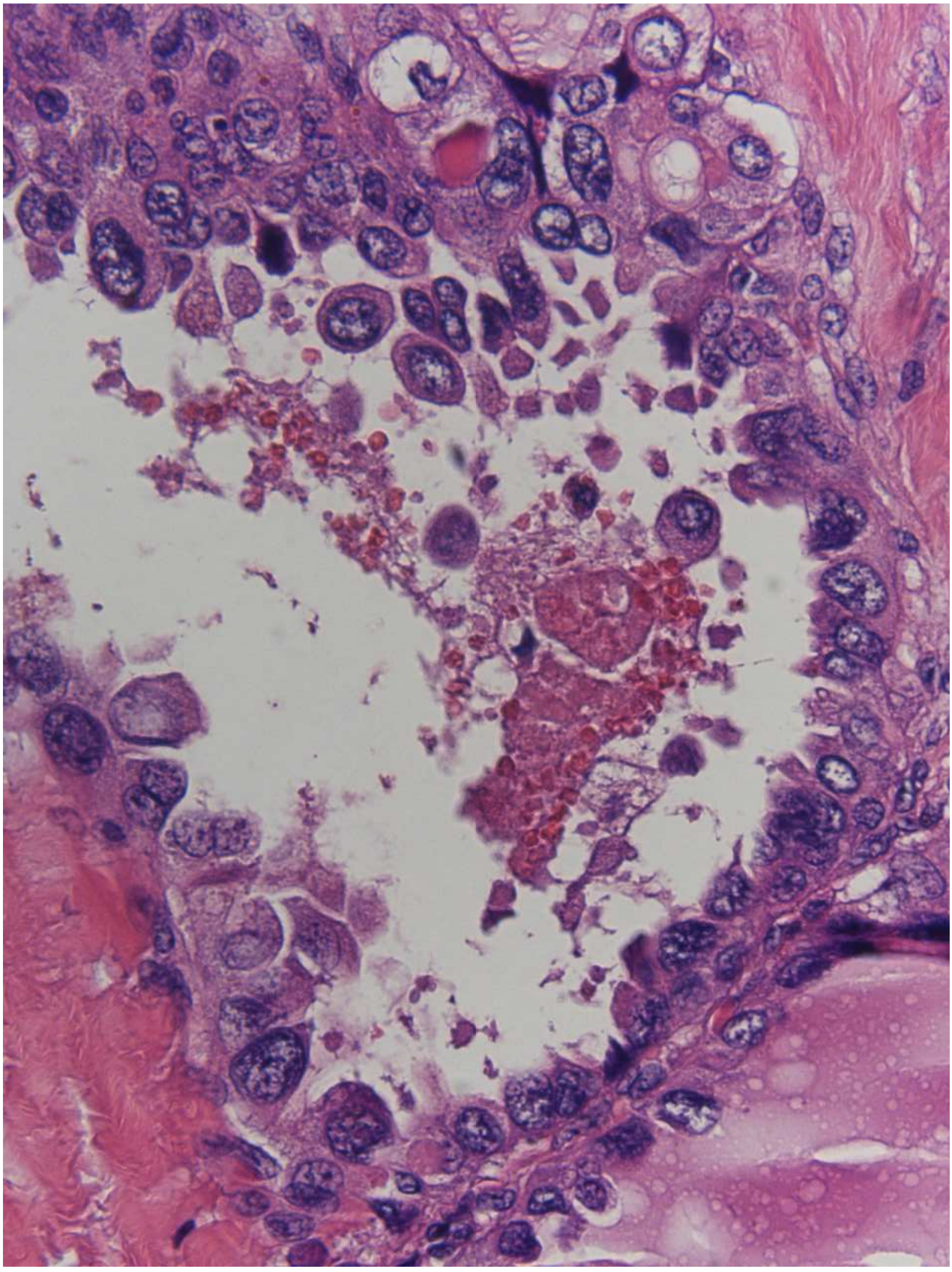












in association with UKEPS UK Endocrine Pathology Society

London Endocrine Pathology Update

Monday February 10th and Tuesday February 11th, 2025 - The Gordon Museum of Pathology, Guy's Campus, London, UK

CASE 2

Poorly differentiated thyroid carcinoma originating from follicular variant papillary carcinoma with «hobnail» component

Giovanni Tallini, MD

Anatomic Pathology, University of Bologna Medical Center

giovanni.tallini@unibo.it

in association with UKEPS UK Endocrine Pathology Society

London Endocrine Pathology Update

Monday February 10th and Tuesday February 11th, 2025 - The Gordon Museum of Pathology, Guy's Campus, London, UK

CASE 2

The patient developed bone and lung metastases 7 months after total thyroidectomy followed by radioactive iodine ablation, and died with disease 3 years after the diagnosis

Giovanni Tallini, MD

Anatomic Pathology, University of Bologna Medical Center

giovanni.tallini@unibo.it

in association with UKEPS UK Endocrine Pathology Society

London Endocrine Pathology Update

Monday February 10th and Tuesday February 11th, 2025 - The Gordon Museum of Pathology, Guy's Campus, London, UK

CASE 2

Points for discussion

- When to diagnose Hobnail papillary carcinoma?
- What is a poorly differentiated thyroid carcinoma?

Giovanni Tallini, MD

Anatomic Pathology, University of Bologna Medical Center

giovanni.tallini@unibo.it

in association with UKEPS UK Endocrine Pathology Society

London Endocrine Pathology Update

Monday February 10th and Tuesday February 11th, 2025 - The Gordon Museum of Pathology, Guy's Campus, London, UK

CASE 2

Points for discussion

- When to diagnose Hobnail papillary carcinoma?
- What is a poorly differentiated thyroid carcinoma?

Giovanni Tallini, MD

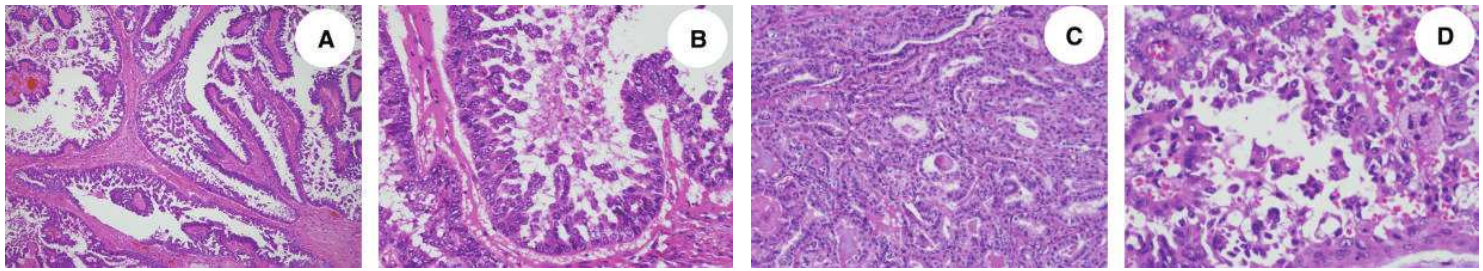
Anatomic Pathology, University of Bologna Medical Center

giovanni.tallini@unibo.it

Thyroid papillary carcinoma with micropapillary and hobnail growth pattern: a histological variant with intermediate malignancy?

Utaroh Motosugi, Shin-Ichi Murata, Kohji Nagata, Masanori Yasuda, Michio Shimizu

Letter to the editor - Thyroid. 2009 May;19(5):535-7



(A, B) Hematoxylineosin staining of the recurrent tumor, specimen of current admission, showed papillary carcinoma with predominant micropapillary features in which papillary tufts lacked a central fibrovascular core. (C) The primary tumor that was resected 10 years ago mainly revealed an ordinary papillary carcinoma. (D) The primary tumor resected 10 years ago also demonstrated micropapillary features at its periphery

Papillary thyroid carcinoma with prominent hobnail features: a new aggressive variant of moderately differentiated papillary carcinoma. A clinicopathologic, immunohistochemical, and molecular study of eight cases.

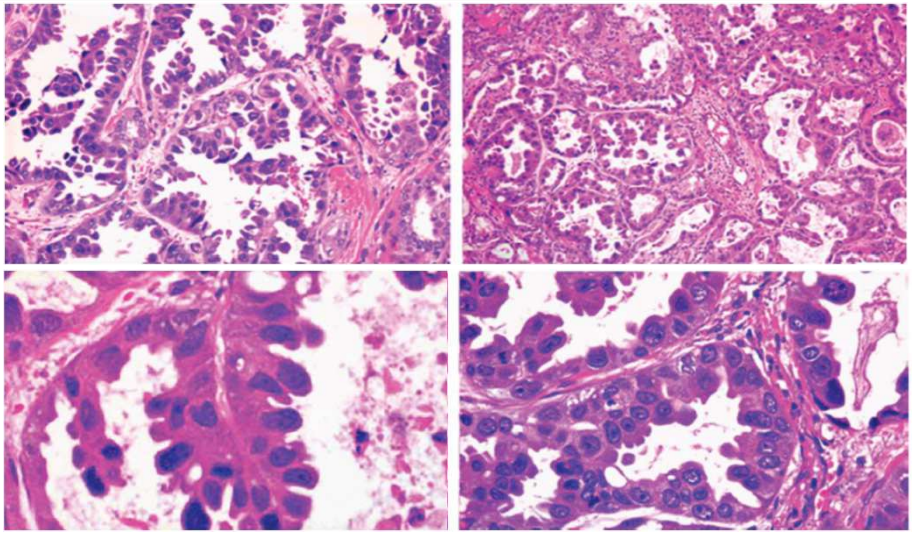
Asioli S, Erickson LA, Sebo TJ, Zhang J, Jin L, Thompson GB, Lloyd RV

Am J Surg Pathol. 2010 Jan;34(1):44-52

TABLE 1. Clinicopathologic Features of Eight Cases of Papillary Thyroid Carcinoma With Prominent Hobnail Feature

Case	Age/ Sex	Size	Vascular Invasion	Nuclear Atypia	Mitoses (Atypical Mitoses)	% Hobnail Features	Post Surgical RT	Recurrence	Lymph Nodes MTS	Distant MTS (Sites)	pTNM	BRAF Status	FU (mo)
1	51/F	2.0	Yes	Severe	9 (1)	75	Yes*	No	NA	Liver, lung, bone, brain, spinal cord	T1 (m) Nx M1	WT	DOD (6)
2	78/F	4.0	Yes	Moderate	4	100	Yes†	Yes	Yes	No	T3 (m) N1 M0	NA	DOD (10)
3	63/F	1.0	Yes	Moderate	3	60	No	No	Yes	Lung	T1 N1 M1	MUT	DOD (31)
4	28/F	1.2	No	Moderate	3	30	Yes	Yes	Yes	No	T3 (m) N0 M0	WT	AND (120)
5	58/M	1.8	Yes	Moderate	4	75	Yes	Yes	Yes	Shoulder, Lung, bone, muscle, pancreas	T3 (m) N1 M1	MUT	AWD (87)
6	53/F	3.5	Yes	Severe	5 (1)	75	Yes	No	No	No	T2 N0 M0	MUT	AND (236)
7	65/F	2.8	Yes	Moderate	6	50	Yes†	No	Yes	Brain, lung	T3 (m) N1 M1	MUT	DOD (124)
8	65/M	4.0	Yes	Severe	3	75	Yes*†	No	Yes	Epiglottis, larynx, nasopharynx, base of tounge, tonsils	T3 (m) N1 M1	WT	AWD (4)

Tumors with > 30% hobnail/micropapillary features very aggressive



Papillary thyroid carcinomas with prominent hobnail features. The main patterns of growth showed papillary (A) and follicular (B) architecture. In case 1, papillary pattern included variably sized complex papillary structures with prominent vascular cores (C). The follicular pattern showed variably sized follicles lined by thick neoplastic epithelium (2 to 4-cells thick) (D).

Prevalence of a hobnail pattern in papillary, poorly differentiated, and anaplastic thyroid carcinoma: a possible manifestation of high-grade transformation

Amacher AM, Goyal B, Lewis JS Jr, El-Mofty SK, Chernock RD

Am J Surg Pathol. 2015 Feb;39(2):260-5. doi: 10.1097/PAS.0000000000000329. PubMed PMID: 25321328

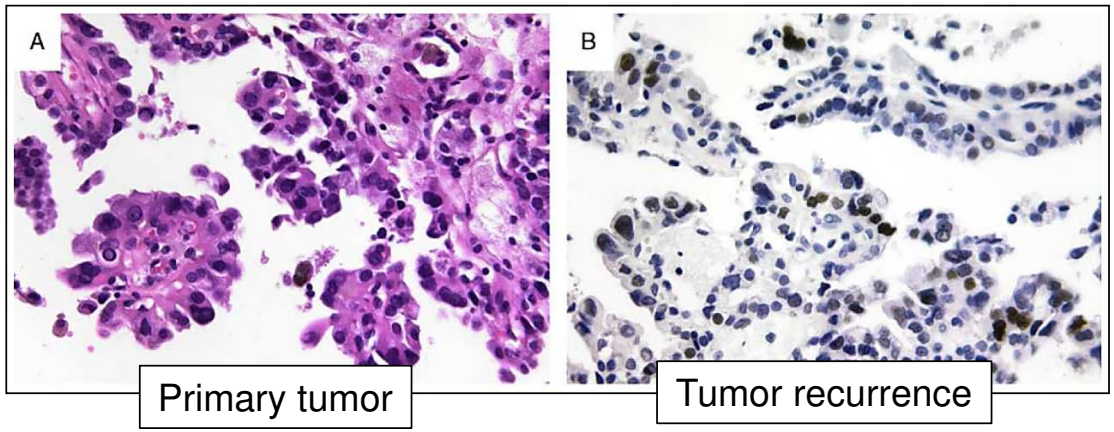
TABLE 3. Clinical and Pathologic Features of Poorly Differentiated and Anaplastic Thyroid Carcinoma Cases With Hobnail Features

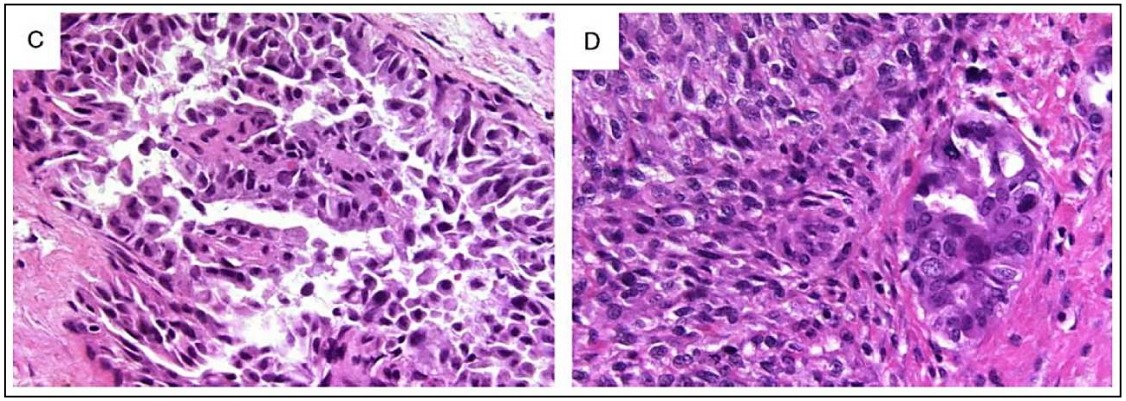
Case	Age	Sex	Tumor Type	Primary (% HOB)	Metastasis (% HOB)	Nuclear Features of HOB Component
1	62	F	PDCa	> 90	Present* (LN)	Similar to PDCa
2	76	F	PDCa with focal classical PTC	NA	10 (Larynx)	Similar to PDCa
3	50	M	Classical (primary), PDCa and PTC with tall/ columnar cell and focal ATC (metastases)†	0	10† (LN)	Similar to PTC and PDCa
4	76	M	PDCa	NA	50-60 (LN)	Similar to PTC
5	46	M	ATC	Present*	10 (LN)	Similar to ATC

Hobnail Variant of Papillary Thyroid Carcinoma: Clinicopathologic and Molecular Evidence of Progression to Undifferentiated Carcinoma in 2 Cases

Cameselle-Teijeiro JM, Rodríguez-Pérez I, Celestino R, Eloy C, Piso-Neira M, Abdulkader-Nallib I, Soares P, Sobrinho-Simões M

Am J Surg Pathol. 2017 Jun;41(6):854-860. doi: 10.1097/PAS.0000000000000793. PubMed PMID: 28009606





A potential diagnostic pitfall for hobnail variant of papillary thyroid carcinoma

Wong KS, Chen TY, Higgins SE, Howitt BE, Lorch JH, Alexander EK, Marqusee E, Cho NL, Nehs MA, Doherty GM, Barletta JA

Histopathology. 2020 Apr;76(5):707-713

Table 1. Clinicopathological characteristics of 'hobnail–like' PTC versus true hobnail variant

	'Hobnail-like' PTC* (n = 36)	True hobnail PTC (n = 7)	P-value
Sex, n (%)			
Female	21 (58)	5 (71)	0.68
Male	15 (42)	2 (29)	
Age (years)			
Mean	40	68	<0.001
Range	19–71	48–92	
Surgery, n (%)			
Total thyroidectomy	34 (94)	6 (86)	0.42
Hemi–thyroidectomy	2 (6)	1 (14)	
Tumour size (cm)			
Mean	2.1	4.4	<0.001
Range	0.7–5.8	2.5–8.0	
Gross extrathyroidal extension, n (%)	0 (0)	5 (71)	<0.001
Positive surgical resection margin, n (%)	4 (11)	3 (43)	0.072
Lymph node metastasis at diagnosis, n (%)†	17 (63)	6 (86)	0.38
Mitotic index ≥3 per 10 HPF, n (%)	0 (0)	5 (71)	<0.001
Tall cell morphology in >30% of the tumour	3 (8)	6 (86)	<0.001
Focal de-differentiation, n (%)	0 (0)	5 (71)	<0.001

PTC, Papillary thyroid carcinoma; HPF, High-power fields.
*From cohorts 1 and 2.
†Including only patients with lymph nodes taken at the time of thyroid resection.

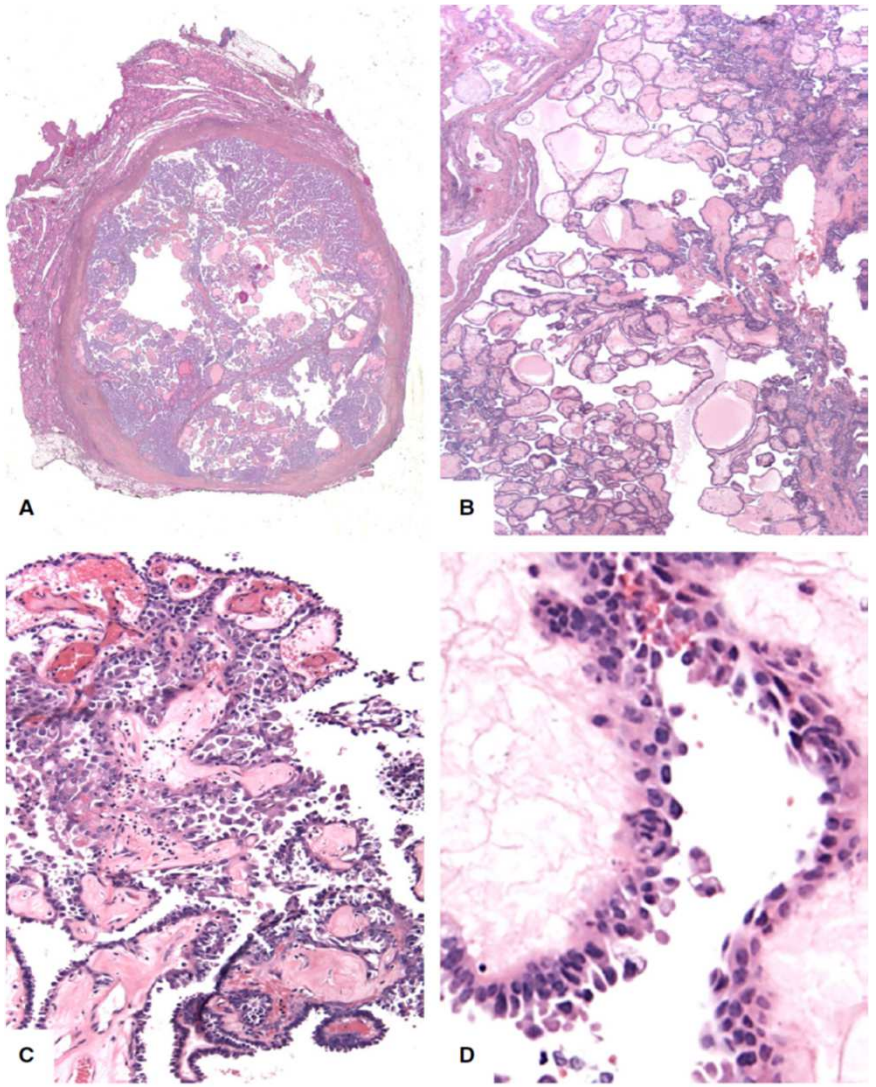


Figure 1. A–D, Examples of classic papillary thyroid carcinoma with 'hobnail-like' morphology. Many tumours were at least partially encapsulated and showed cystic change, and all tumours in this group were grossly confined to the thyroid. The papillae were thick, hyalinized and variably oedematous. Hobnailing and nuclear pseudo-stratification warranting characterisation as 'hobnail-like' can be appreciated at higher power.

A potential diagnostic pitfall for hobnail variant of papillary thyroid carcinoma

Wong KS, Chen TY, Higgins SE, Howitt BE, Lorch JH, Alexander EK, Marqusee E, Cho NL, Nehs MA, Doherty GM, Barletta JA

Histopathology. 2020 Apr;76(5):707-713

Table 1. Clinicopathological characteristics of 'hobnail–like' PTC versus true hobnail variant

	'Hobnail-like' PTC* (n = 36)	True hobnail PTC (n = 7)	P-value
Sex, n (%)			
Female	21 (58)	5 (71)	0.68
Male	15 (42)	2 (29)	
Age (years)			
Mean	40	68	<0.001
Range	19–71	48–92	
Surgery, n (%)			
Total thyroidectomy	34 (94)	6 (86)	0.42
Hemi–thyroidectomy	2 (6)	1 (14)	
Tumour size (cm)			
Mean	2.1	4.4	<0.001
Range	0.7–5.8	2.5–8.0	
Gross extrathyroidal extension, n (%)	0 (0)	5 (71)	<0.001
Positive surgical resection margin, n (%)	4 (11)	3 (43)	0.072
Lymph node metastasis at diagnosis, n (%)†	17 (63)	6 (86)	0.38
Mitotic index ≥3 per 10 HPF, n (%)	0 (0)	5 (71)	<0.001
Tall cell morphology in >30% of the tumour	3 (8)	6 (86)	<0.001
Focal de-differentiation, n (%)	0 (0)	5 (71)	<0.001

PTC, Papillary thyroid carcinoma; HPF, High-power fields.
*From cohorts 1 and 2.
†Including only patients with lymph nodes taken at the time of thyroid resection.

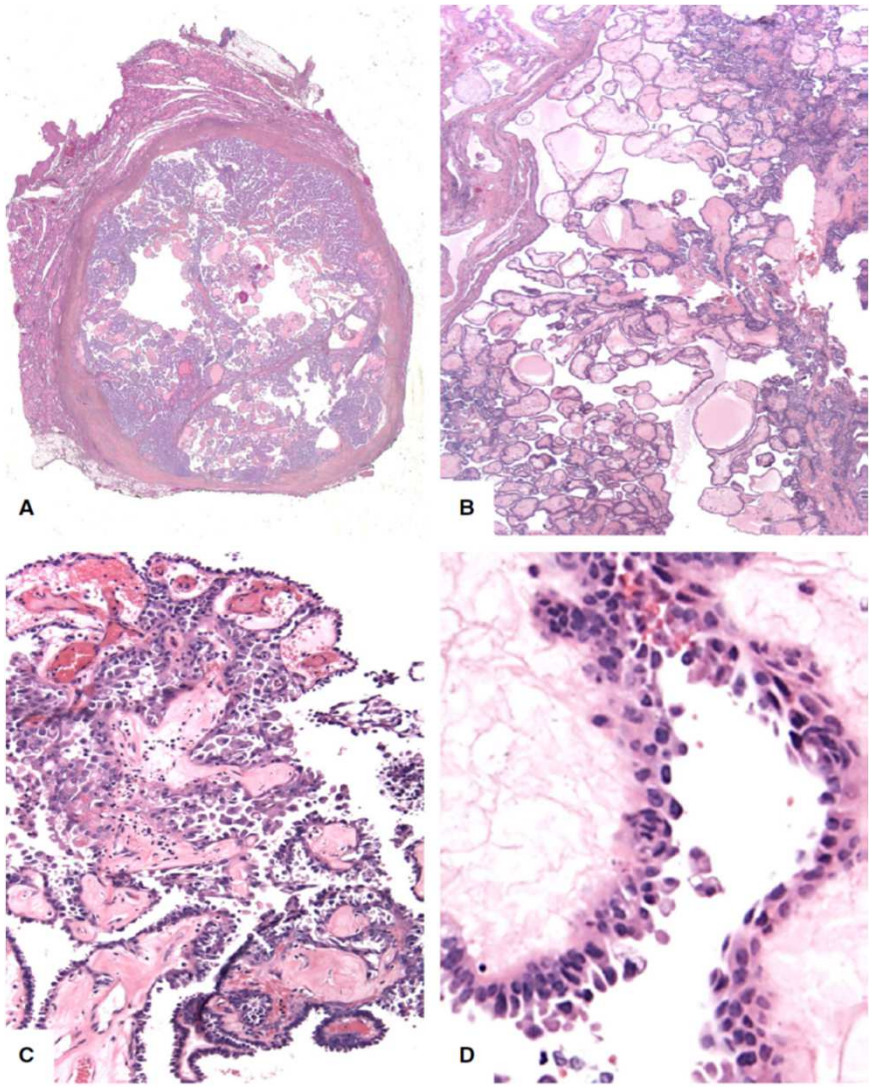


Figure 1. A–D, Examples of classic papillary thyroid carcinoma with 'hobnail-like' morphology. Many tumours were at least partially encapsulated and showed cystic change, and all tumours in this group were grossly confined to the thyroid. The papillae were thick, hyalinized and variably oedematous. Hobnailing and nuclear pseudo-stratification warranting characterisation as 'hobnail-like' can be appreciated at higher power.

A potential diagnostic pitfall for hobnail variant of papillary thyroid carcinoma

Wong KS, Chen TY, Higgins SE, Howitt BE, Lorch JH, Alexander EK, Marqusee E, Cho NL, Nehs MA, Doherty GM, Barletta JA

Histopathology. 2020 Apr;76(5):707-713

Table 2. IHC and molecular characteristics of 'hobnail-like' PTC versus true hobnail variant

	'Hobnail-like' PTC* (n = 16)	True hobnail PTC (n = 7)	P-value
Ki67 PI ≥ 5%, n (%)	0 (0)	6 (86)	<0.001
Mutant p53 staining by IHC, n (%)	0 (0)	1 (14)	0.30
BRAF V600E mutation, n (%)†	7 (88)	3 (100)	1.0
Secondary mutation, n (%)†	0 (0)	3 (100)	0.0061

PTC, Papillary thyroid carcinoma; PI, Proliferative index; IHC, Immunohistochemistry.

*From cohort 1.

†Of cases with molecular data available ('hobnail-like': n = 8; true hobnail: n = 3); secondary mutations included those involving the *TERT* promoter, *AKT2*, *ATM* and *ARID2*.

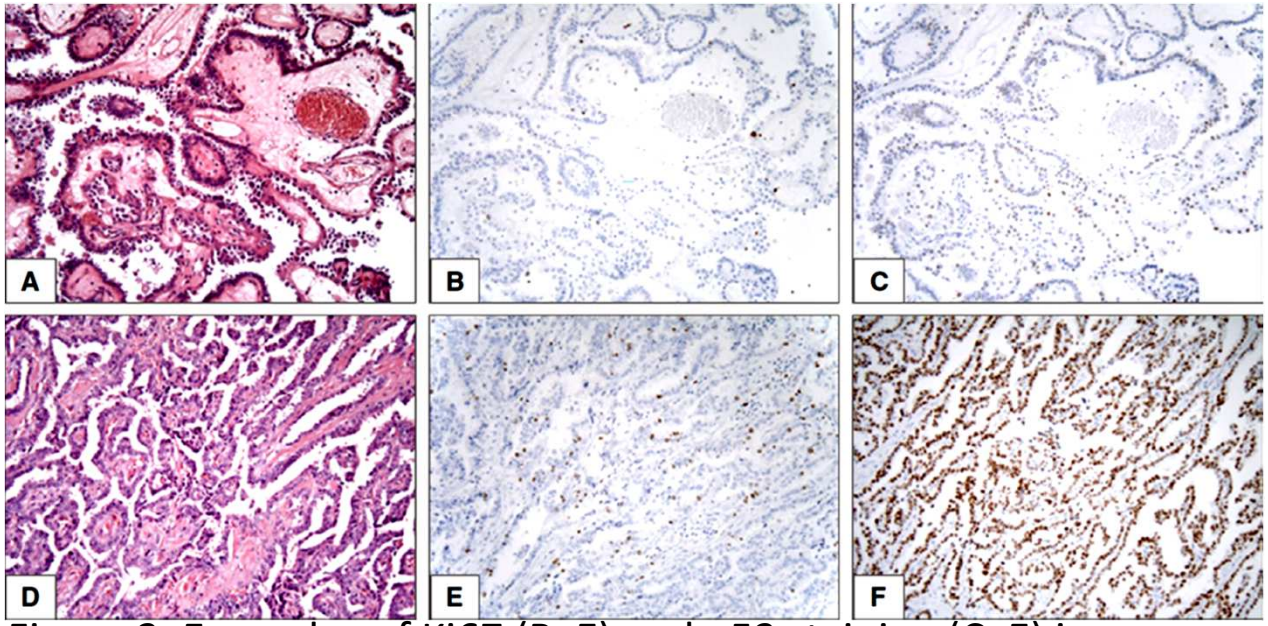


Figure 3. Examples of Ki67 (B, E) and p53 staining (C, E) in 'hobnail-like' classic papillary thyroid carcinoma (PTC) (A–C) and true hobnail variant of PTC (D–F). All 'hobnail-like' tumours demonstrated a Ki67 proliferative index of <5% and wild-type p53 expression. In contrast, the Ki67 was elevated (≥5%) in the majority of true hobnail variant. Secondary mutations present only in cases with "true hobnail" features (*TERT* promoter, *AKT2 ATM*, *ARID2)*.

A potential diagnostic pitfall for hobnail variant of papillary thyroid carcinoma

Wong KS, Chen TY, Higgins SE, Howitt BE, Lorch JH, Alexander EK, Marqusee E, Cho NL, Nehs MA, Doherty GM, Barletta JA

Histopathology. 2020 Apr;76(5):707-713

Table 2. IHC and molecular characteristics of 'hobnail-like' PTC versus true hobnail variant

	'Hobnail-like' PTC* (n = 16)	True hobnail PTC (n = 7)	P-value
Ki67 PI ≥ 5%, n (%)	0 (0)	6 (86)	<0.001
Mutant p53 staining by IHC, n (%)	0 (0)	1 (14)	0.30
BRAF V600E mutation, n (%)†	7 (88)	3 (100)	1.0
Secondary mutation, n (%)†	0 (0)	3 (100)	0.0061

PTC, Papillary thyroid carcinoma; PI, Proliferative index; IHC, Immunohistochemistry.

*From cohort 1.

†Of cases with molecular data available ('hobnail-like': n = 8; true hobnail: n = 3); secondary mutations included those involving the *TERT* promoter, *AKT2*, *ATM* and *ARID2*.

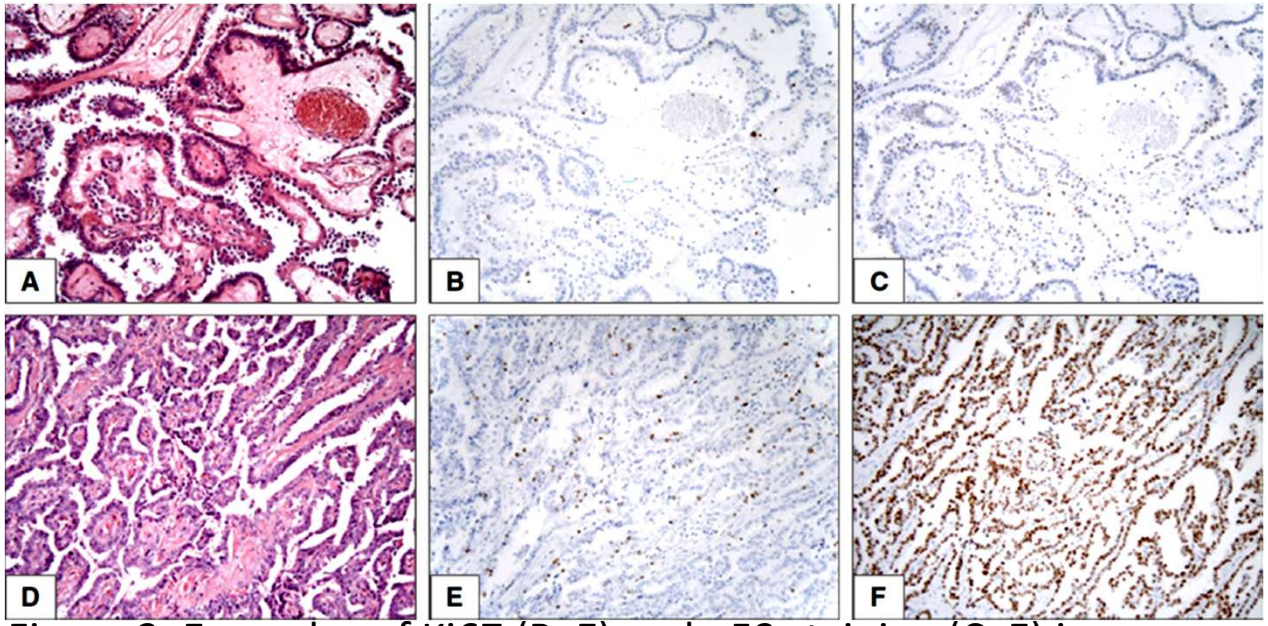


Figure 3. Examples of Ki67 (B, E) and p53 staining (C, E) in 'hobnail-like' classic papillary thyroid carcinoma (PTC) (A–C) and true hobnail variant of PTC (D–F). All 'hobnail-like' tumours demonstrated a Ki67 proliferative index of <5% and wild-type p53 expression. In contrast, the Ki67 was elevated (≥5%) in the majority of true hobnail variant. Secondary mutations present only in cases with "true hobnail" features (*TERT* promoter, *AKT2 ATM*, *ARID2)*.

in association with UKEPS UK Endocrine Pathology Society

London Endocrine Pathology Update

Monday February 10th and Tuesday February 11th, 2025 - The Gordon Museum of Pathology, Guy's Campus, London, UK

CASE 2

Points for discussion

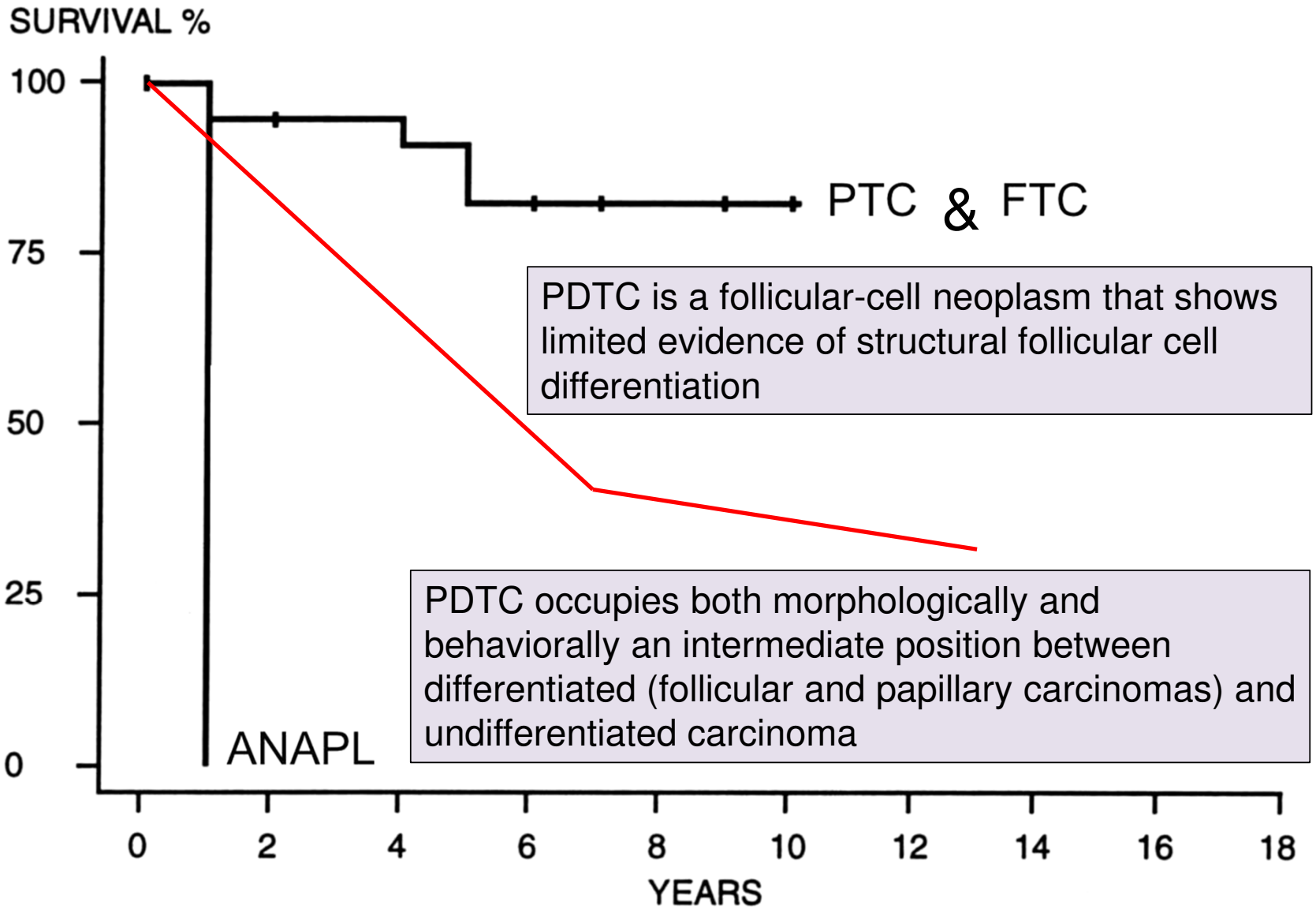
- When to diagnose Hobnail papillary carcinoma?
- What is a poorly differentiated thyroid carcinoma?

Giovanni Tallini, MD

Anatomic Pathology, University of Bologna Medical Center

giovanni.tallini@unibo.it

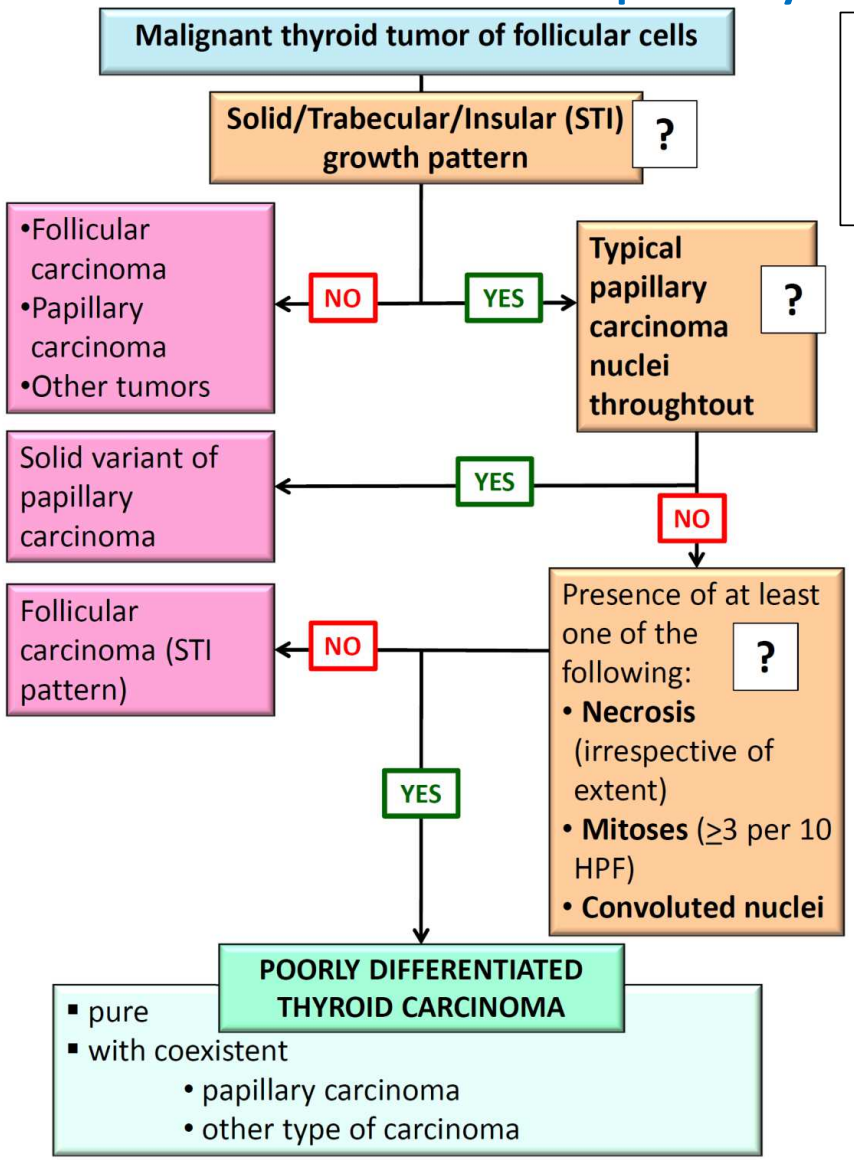
What is a poorly differentiated thyroid carcinoma?



PDTC is a follicular-cell neoplasm that shows limited evidence of structural follicular cell differentiation

PDTC occupies both morphologically and behaviorally an intermediate position between differentiated (follicular and papillary carcinomas) and undifferentiated carcinoma

What is a poorly differentiated thyroid carcinoma?



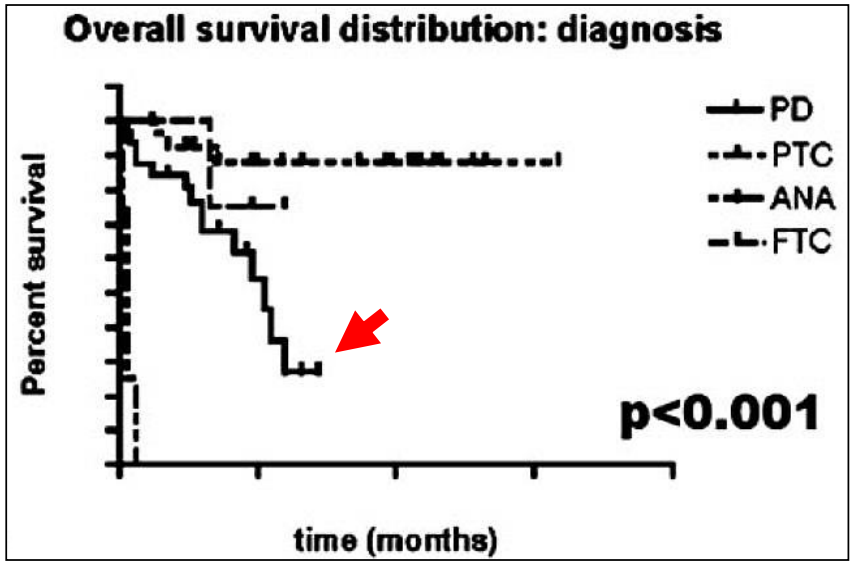
Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach

Volante M, Collini P, Nikiforov YE, Sakamoto A, Kakudo K, Katoh R, Lloyd RV, LiVolsi VA, Papotti M, Sobrinho-Simoes M, Bussolati G, Rosai J

Am J Surg Pathol. 2007 Aug;31(8):1256-64

Consistent with WHO criteria:

- **Differentiation loss**
- **High grade features**
- **Prognosis intermediate between PTC/FTC and undifferentiated ca.**



What is a poorly differentiated thyroid carcinoma?

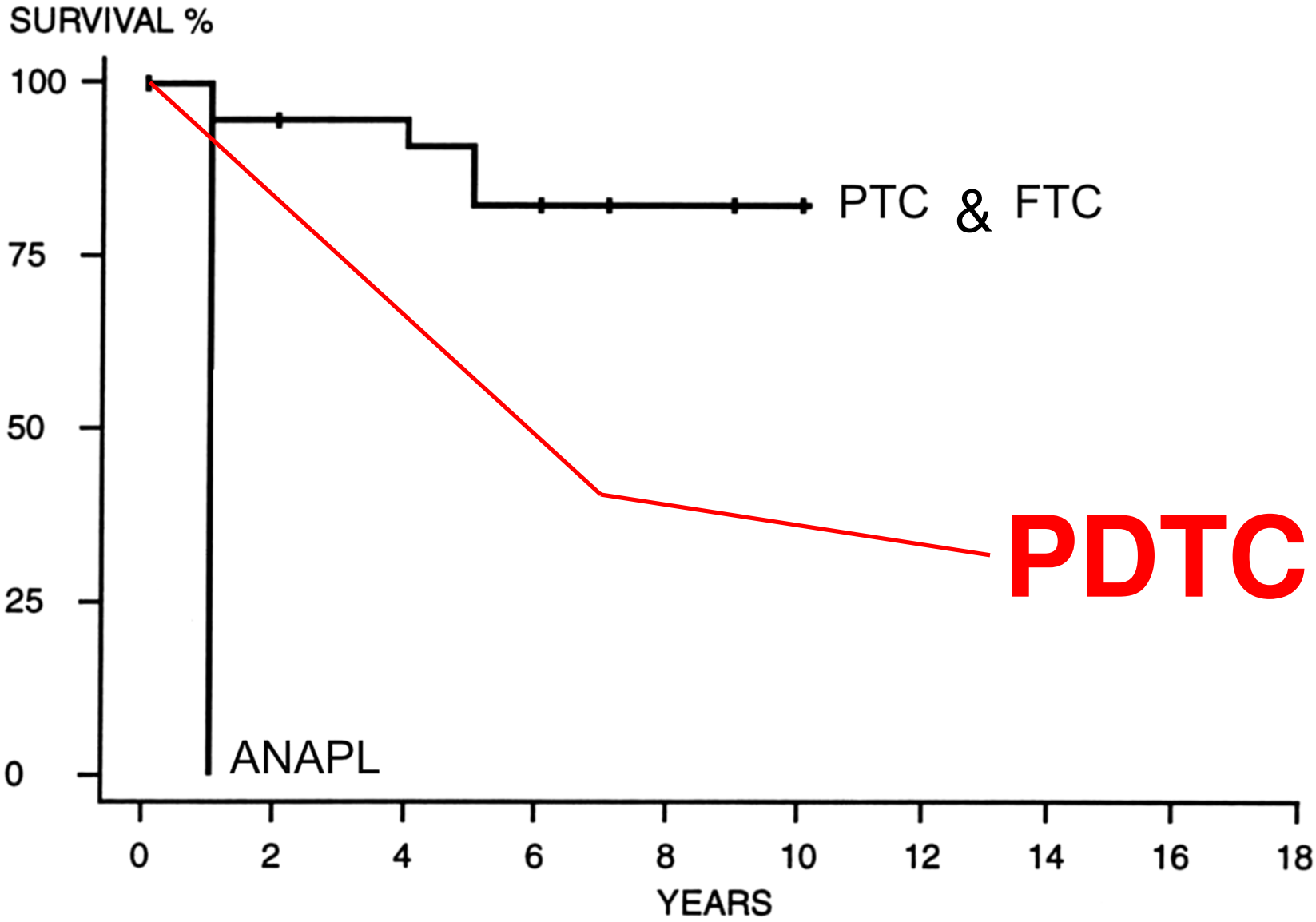
Immunohistochemistry

- ↑Ki67
- P53+ *but no marker is specific*
- TG+, TTF1+, PAX8+

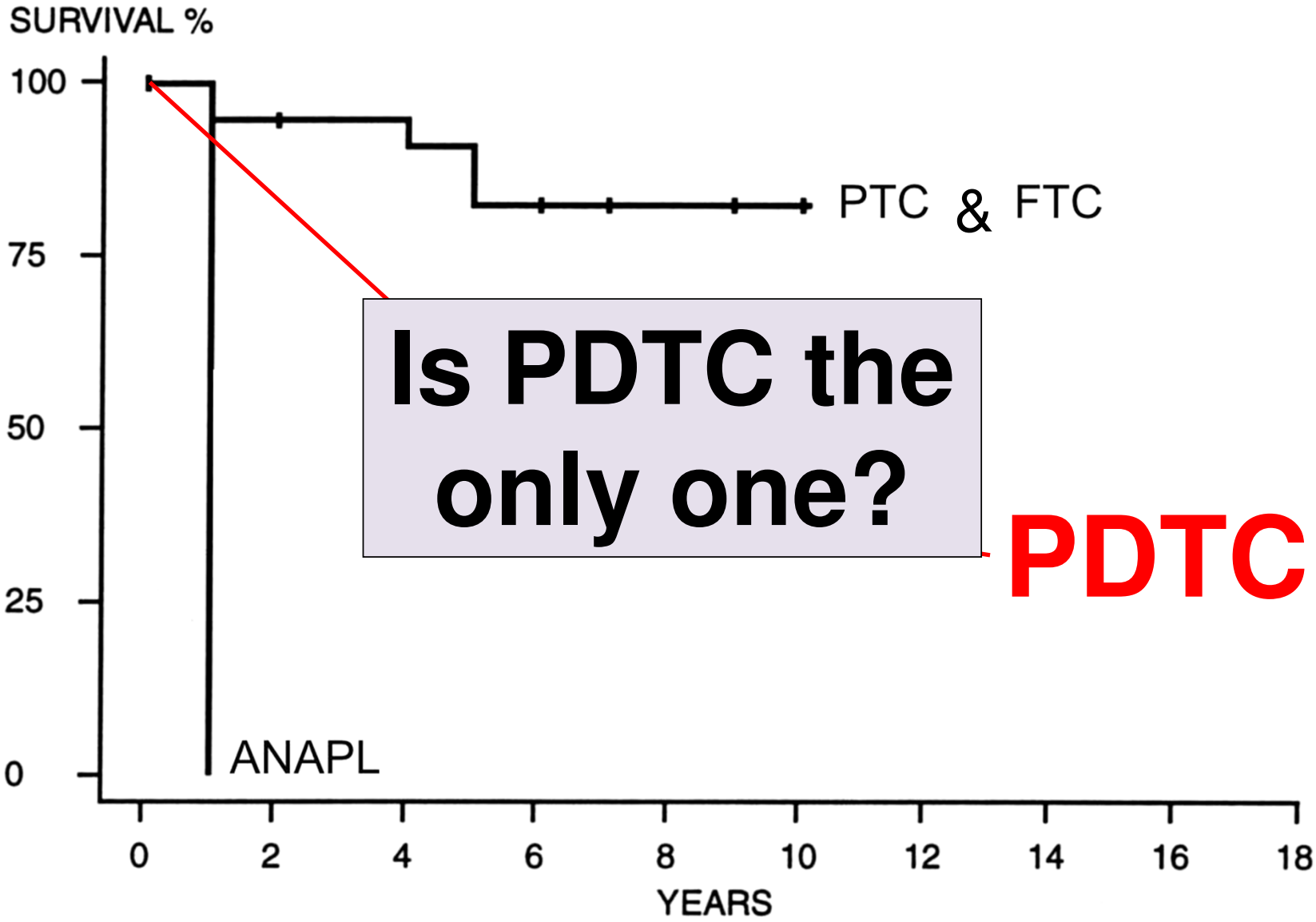
Rule Out

- **Medullary carcinoma**
  (calcitonin+, neuroendocrine markers+)
- **PTH carcinoma**
  (parathormone+, neuroendocrine markers+)
- **Anaplastic carcinoma**
  (TG-, TTF1-, PAX8+)
- **Lymphoma (Large cell)**
- **Tumors metastatic to the thyroid**

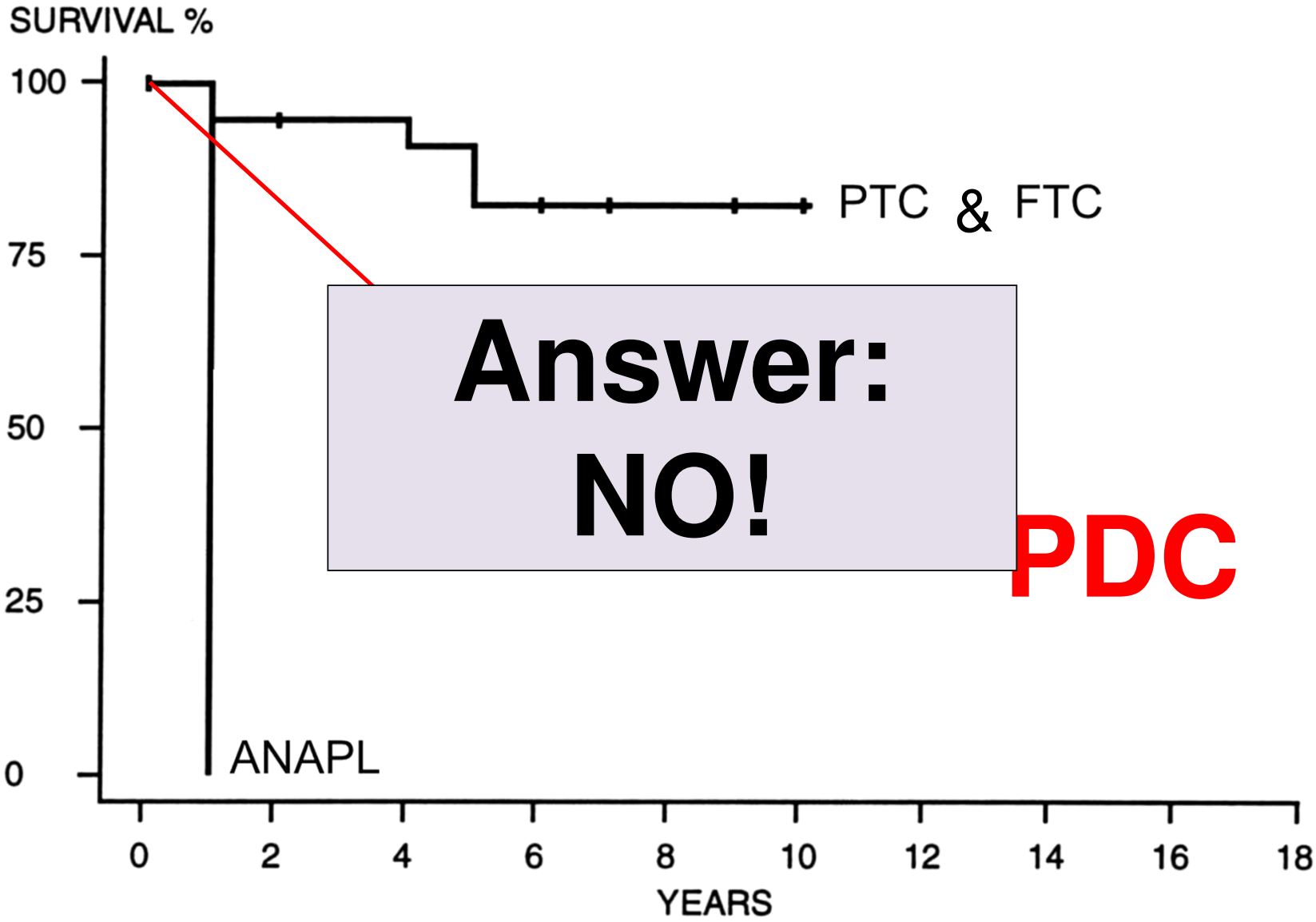
What is a poorly differentiated thyroid carcinoma?



What is a poorly differentiated thyroid carcinoma?



What is a poorly differentiated thyroid carcinoma?



What is a poorly differentiated thyroid carcinoma?

Total No. Fatal Cases	67 (100%)
Papillary carcinoma*	29 (43.2)
Anaplastic carcinoma	17 (25.3)
Poorly differentiated CA	9 (13.4)
Medullary carcinoma	6 (8.9)
Hürthle cell CA	2 (2.9)
Follicular carcinoma, widely invasive	3 (4.4)
Mucoepidermoid carcinoma with eosinophilia	1 (1.4)
All categories listed in Table 1†	0 (0)

*No follicular variant papillary carcinoma

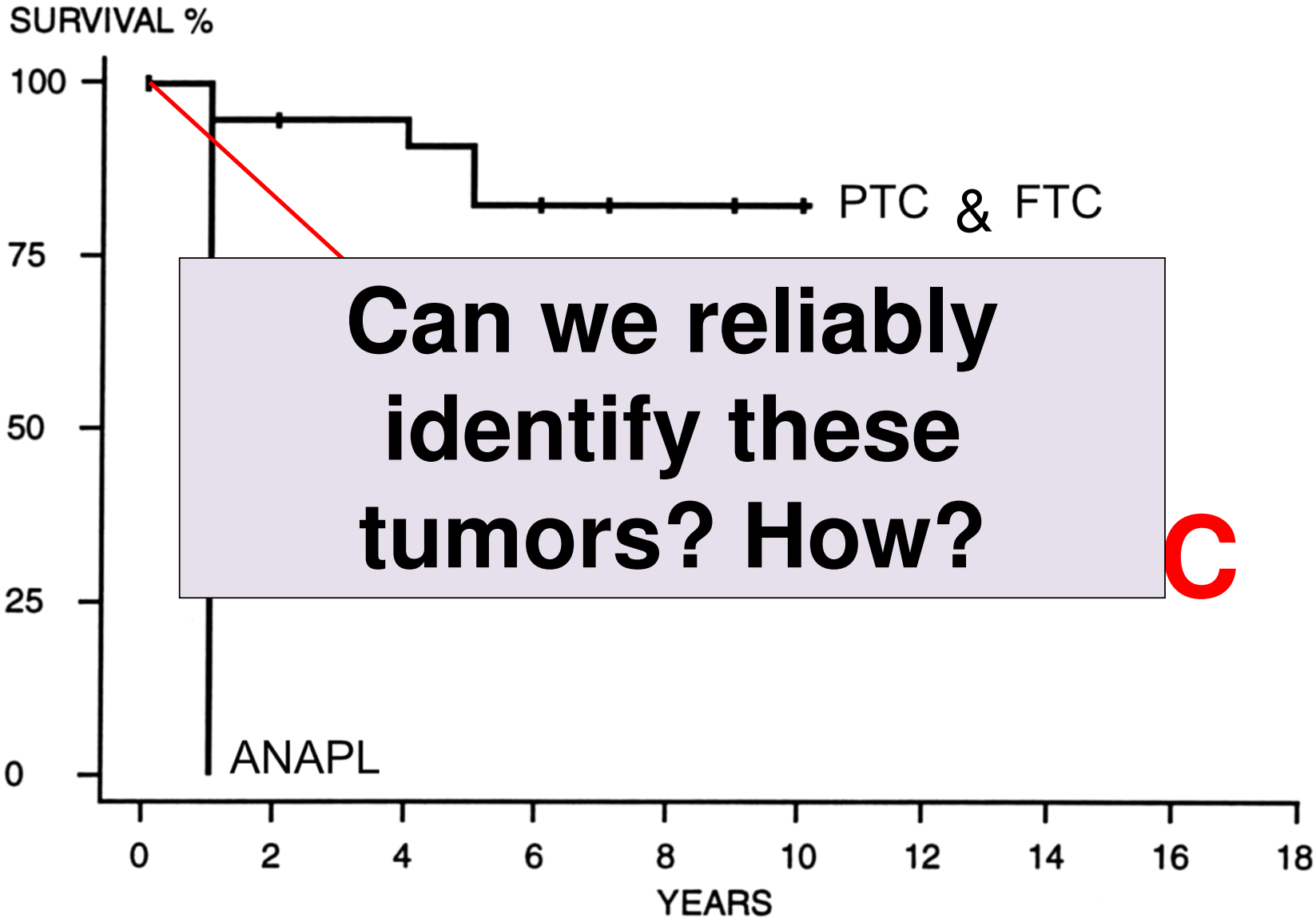
Piana et al Am J Surg Pathol 34:868-72, 2010

44 fatal tumors, after the exclusion of anaplastic and medullary cancers[a]

- PTC 29/44 (66%)
- PDTC 9/44 (20%)
- FTC 5/44 (3 widely invasive, 2 oncocytic) (12%)
- 1/44 mucoepidermoid carcinoma (2%)

[a]1039 consecutive cases of thyroid carcinoma treated at a single institution and followed for an average of 11.9 years or until death

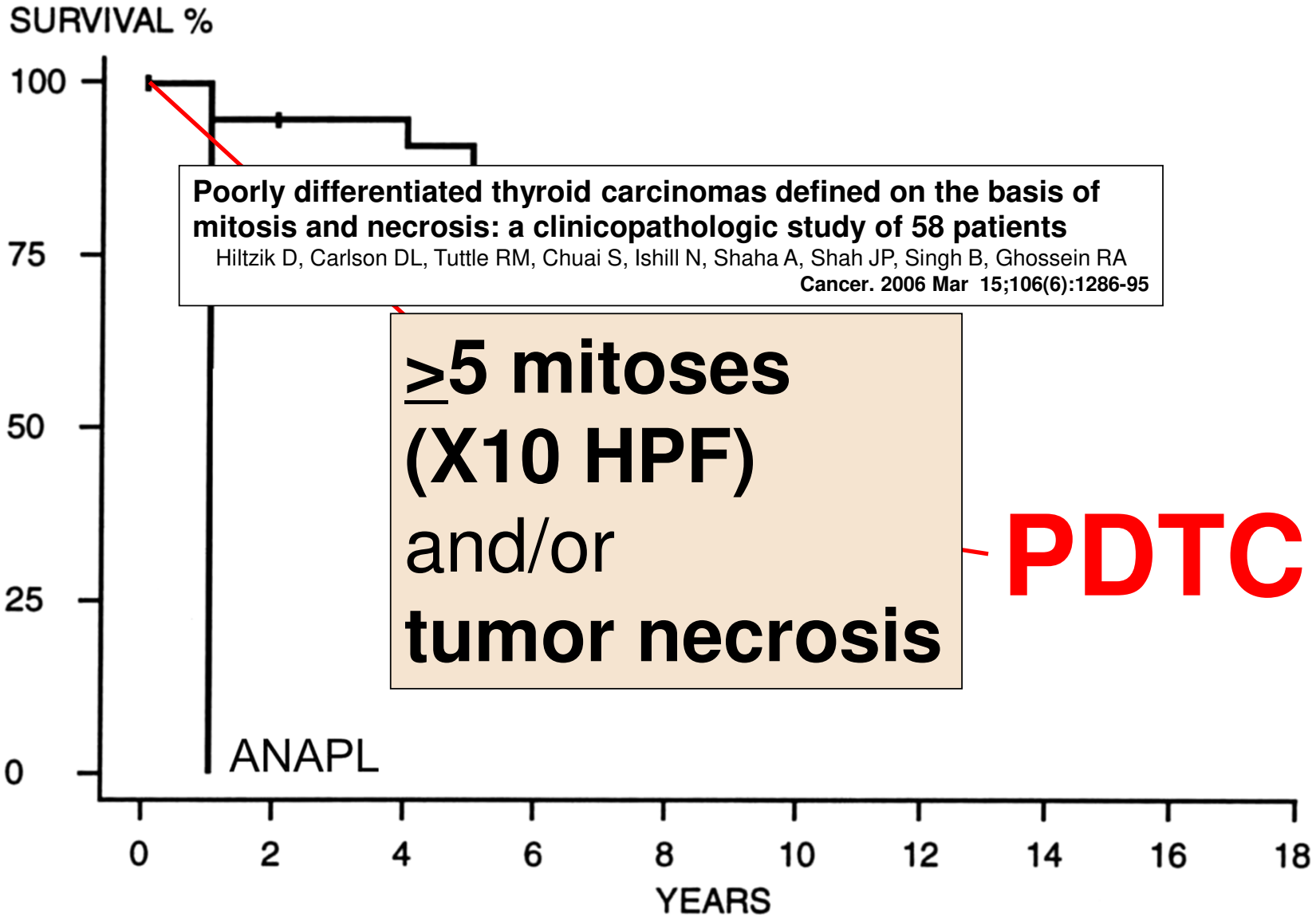
What is a poorly differentiated thyroid carcinoma?



Can we reliably identify these tumors? How?

C

What is a poorly differentiated thyroid carcinoma?



Poorly differentiated thyroid carcinomas defined on the basis of mitosis and necrosis: a clinicopathologic study of 58 patients

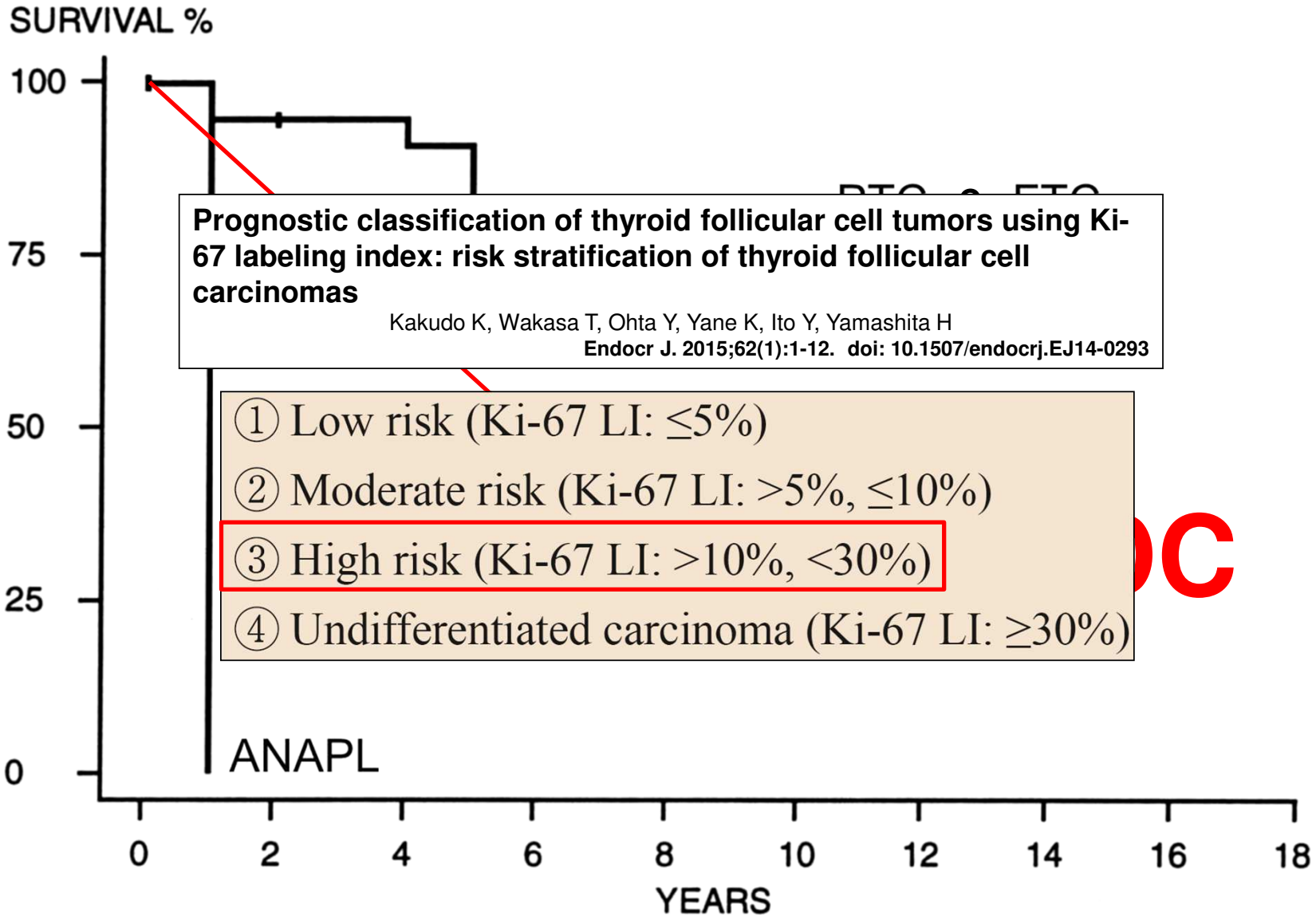
Hiltzik D, Carlson DL, Tuttle RM, Chuai S, Ishill N, Shaha A, Shah JP, Singh B, Ghossein RA

Cancer. 2006 Mar 15;106(6):1286-95

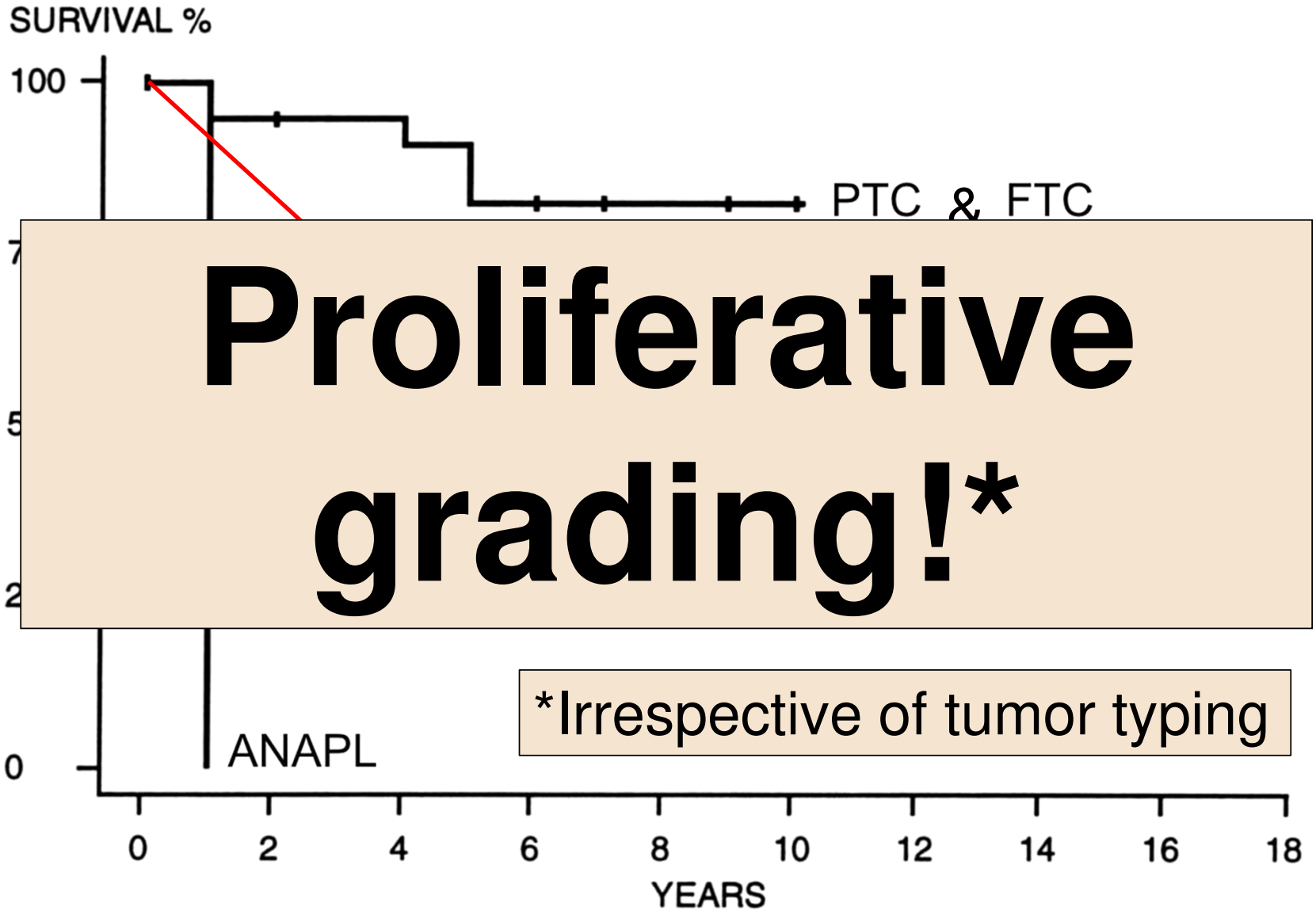
≥5 mitoses (X10 HPF)
and/or
tumor necrosis

PDTC

What is a poorly differentiated thyroid carcinoma?



What is a poorly differentiated thyroid carcinoma?



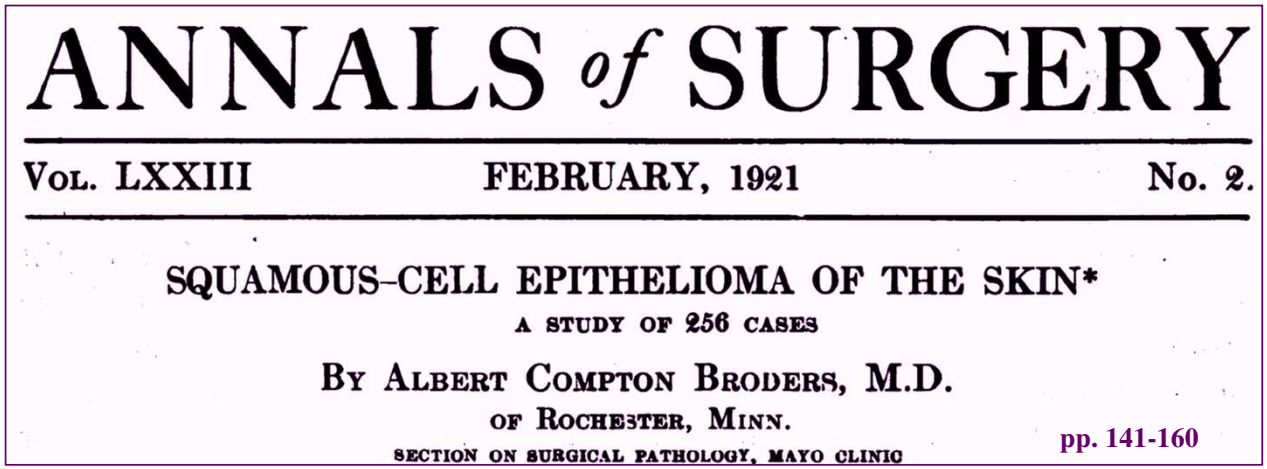
Proliferative grading!*

*Irrespective of tumor typing

Tumor prognostication

Host factors: Age, Sex, Genetic background

Tumor factors: Diagnosis (Histotype), Stage (tumor burden), Grade



ANNALS of SURGERY

VOL. LXXIII FEBRUARY, 1921 No. 2.

SQUAMOUS-CELL EPITHELIOMA OF THE SKIN*

A STUDY OF 256 CASES

BY ALBERT COMPTON BRODERS, M.D.

OF ROCHESTER, MINN.

SECTION ON SURGICAL PATHOLOGY, MAYO CLINIC

pp. 141-160

Tumor grade:

- "Cytologic": cellularity, atipia, mitoses, necrosis (Proliferative grading)
- "Architectural": differentiation-how much the tumor has departed from the normal reference tissue

Tumor prognostication

Histologic tumor typing and grading provide different, complementary, information

- **Grading:** extremely (cost-)effective tool to predict prognosis
- **Typing:** defines tumors with distinct clinicopathologic profiles and biologically relevant features (e.g. FV-PTC: *RAS*-like profile; PTC: *BRAF* V600E-like)

Prognostic risk-based classification of follicular cell derived carcinomas of the thyroid gland

Grade (mitoses, tumor necrosis)	**Histologic differentiation** (architecture: papillae, follicles, solid/trabecular/insular patterns)	**Histotype**	**Outcome**
Low	Present, good	Papillary carcinoma	Favorable
		Follicular carcinoma	
		Oncocytic carcinoma	
High		Differentiated high grade thyroid carcinoma: papillary, follicular, oncocytic	Intermediate
	Present, poor	Poorly differentiated thyroid carcinoma	
	Absent	Anaplastic thyroid carcinoma	Poor

Prognostic risk-based classification of follicular cell derived carcinomas of the thyroid gland

Grade (mitoses, tumor necrosis)	Histologic differentiation (architecture: papillae, follicles, solid/trabecular/insular patterns)	Histotype	Outcome
Low	Present, good	Papillary carcinoma	Favorable
		Follicular carcinoma	
		Oncocytic carcinoma	
High		**Differentiated high grade thyroid carcinoma: papillary, follicular, oncocytic**	Intermediate
	Pres	**Poorly differentiated thyroid carcinoma**	
	Absent	Anaplastic thyroid carcinoma	Poor

High grade non-anaplastic thyroid carcinoma

Diagnostic criteria for high grade follicular cell - derived thyroid carcinomas

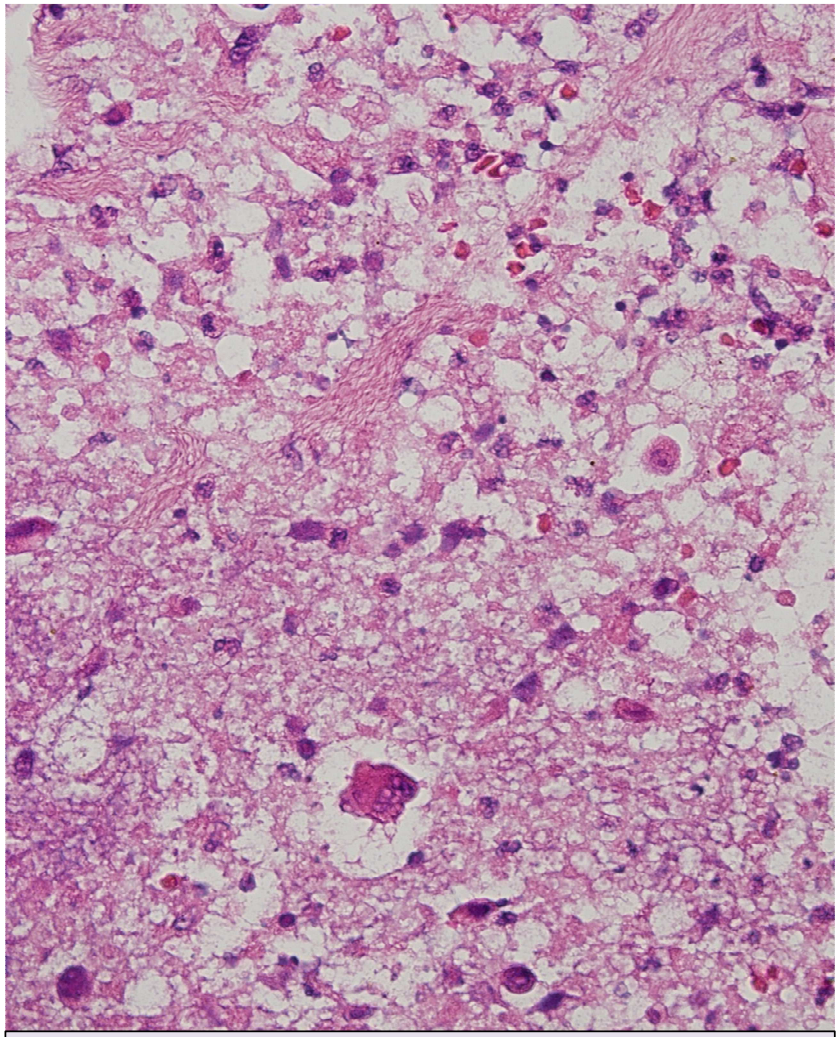
	Poorly differentiated thyroid carcinoma	Differentiated high grade thyroid carcinoma
Growth pattern	Required: solid/trabecular/insular	Papillary, follicular, solid[a]
Nuclear Cytology	Required: no features of PTC	Any
Other features: tumor necrosis, mitosis and convoluted nuclei	Minimum requirement: one of the following three features: •Mitotic count ≥ 3/2 mm^{2}, [b] •Tumor necrosis •Convoluted nuclei	Minimum requirement: one of the following two features: •Mitotic count ≥ 5/2 mm^{2} •Tumor necrosis
Anaplastic features	Absent	Absent

[a]Tumors with solid growth and PTC nuclear features are classified as high-grade differentiated thyroid carcinoma

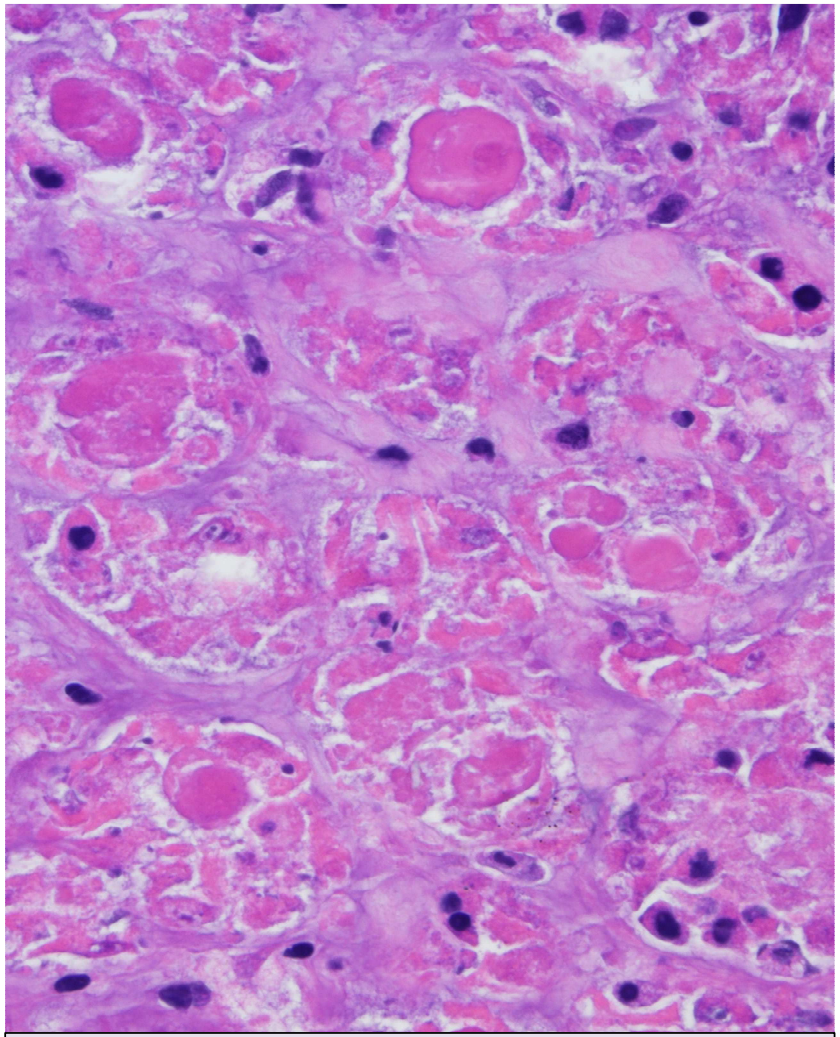
[b]Eight high power fields (X400) with most microscopes

Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, LiVolsi VA, Papotti MG, Sobrinho-Simões M, Tallini G, Mete O. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol. 2022 Mar;33(1):27-63. doi: 10.1007/s12022-022-09707-3. PMID: 35288841

Tumor necrosis vs. ischemic necrosis



Tumor necrosis: «dirty», like that of Colonic adenocarcinoma



Ischemic necrosis: «clean», like that of Myocardial infarction

Counting mitoses

- **Follow standard international (SI) units**

OLYMPUS MICROSCOPE BX51

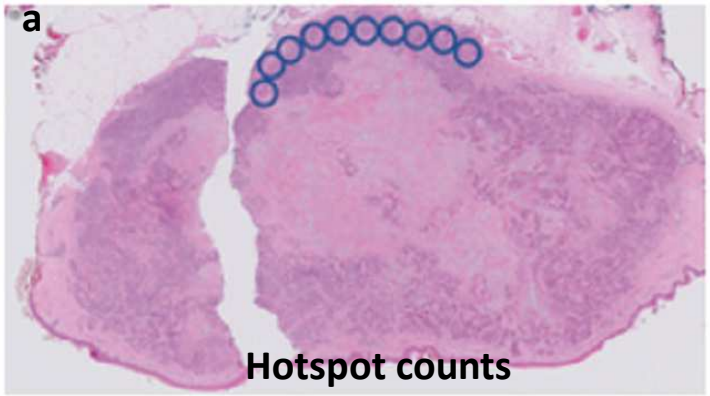
2X>>**field diameter** 22:2 =**11** mm. **Field area**=~**94.9** mm^2
4X>>**field diameter** 22:4 =**5.5** mm. **Field area**=~**23.7** mm^2
10X>**field diameter** 22:10=**2.2** mm. **Field area**=~**3.8** mm^2
20X>**field diameter** 22:20=**1.1** mm. **Field area**=~**0.95** mm^2
40X>**field diameter** 22:40=**0.55** mm. **Field area**=~**0.24** mm^2
60X>**field diameter** 22:60=**0.36** mm. **Field area**=~**0.10** mm^2

Field diameter (mm) [Endocr Pathol. 2022 Mar;33(1):3-5]	Field area (mm^2)	Approximate number of fields per 1 mm^2
0.40	0.126	8
0.41	0.132	8
0.42	0.138	7
0.43	0.145	7
0.44	0.152	7
0.45	0.159	6
0.51	0.204	5
0.52	0.212	5
0.53	0.221	5
0.55	0.237	4
0.57	0.255	4
0.58	0.264	4
0.59	0.273	4
0.60	0.283	4
0.61	0.292	3
0.62	0.302	3
0.63	0.312	3
0.64	0.322	3
0.65	0.332	3
0.66	0.342	3
0.67	0.352	3
0.68	0.363	3
0.69	0.374	3

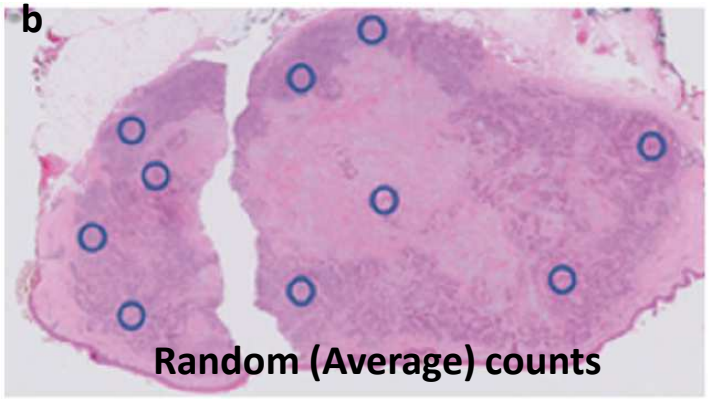
10 HPF (X400) = 2.4 mm^2
2.0 mm^2 = 8 HPF (X400)

Circular field area calculated using the formula $\pi \times r^2$, where 'r' is the radius

- **Methods: Hotspot vs. Random (or Average) counts**, until a specified area (usually 2 mm^2) or a specific number of cells have been assessed - for specific tumor types check original reference manuscript



Hotspots
Assess all slides from the tumor at relatively low power to find the region containing more mitoses ("hotspots")→count mitoses in the initial HPF and adjacent non-overlapping fields



Randomly selected High power fields

Fig. 2 Hotspot counting based on square tiles or round microscope fields. Random counting (a) should use a randomization method to avoid bias, while hotspot counts (b) are usually linear or serpentine. It should be noted that contiguous round fields miss some areas of tumor which may contain mitoses. The method used should be clearly specified [Cree IA, Tan PH, Travis WD, Wesseling P, Yagi Y, White VA, Lokuhetty D, Scolyer RA. Counting mitoses: SI(ze) matters! Mod Pathol. 2021 Sep;34(9):1651-1657]