in association with UKEPS UK Endocrine Pathology Society

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CASE 4

Single 2.2 cm thyroid nodule of the left lobe in a 67 year old woman. Preoperative FNA Thy3f (Bethesda IV)

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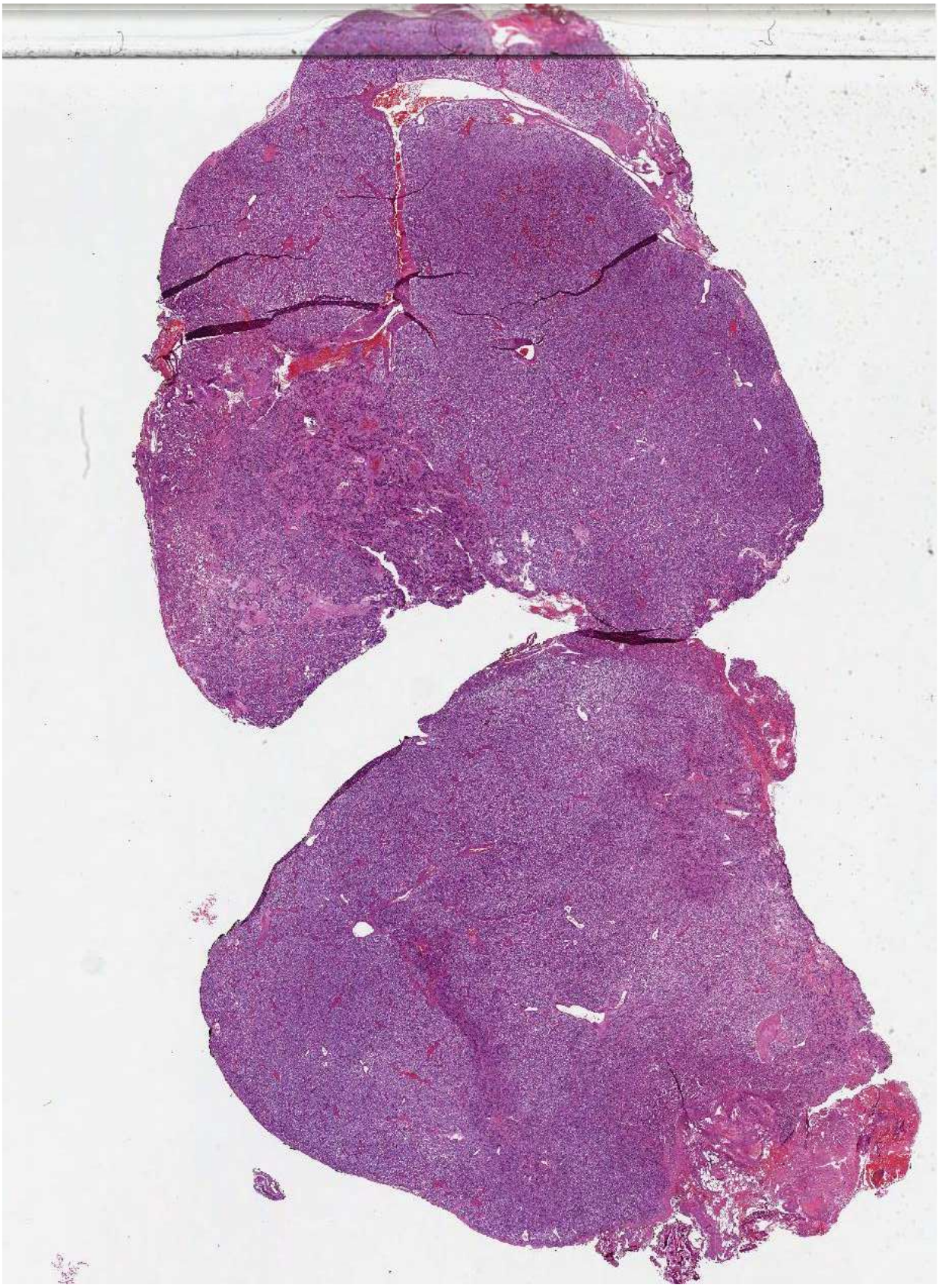
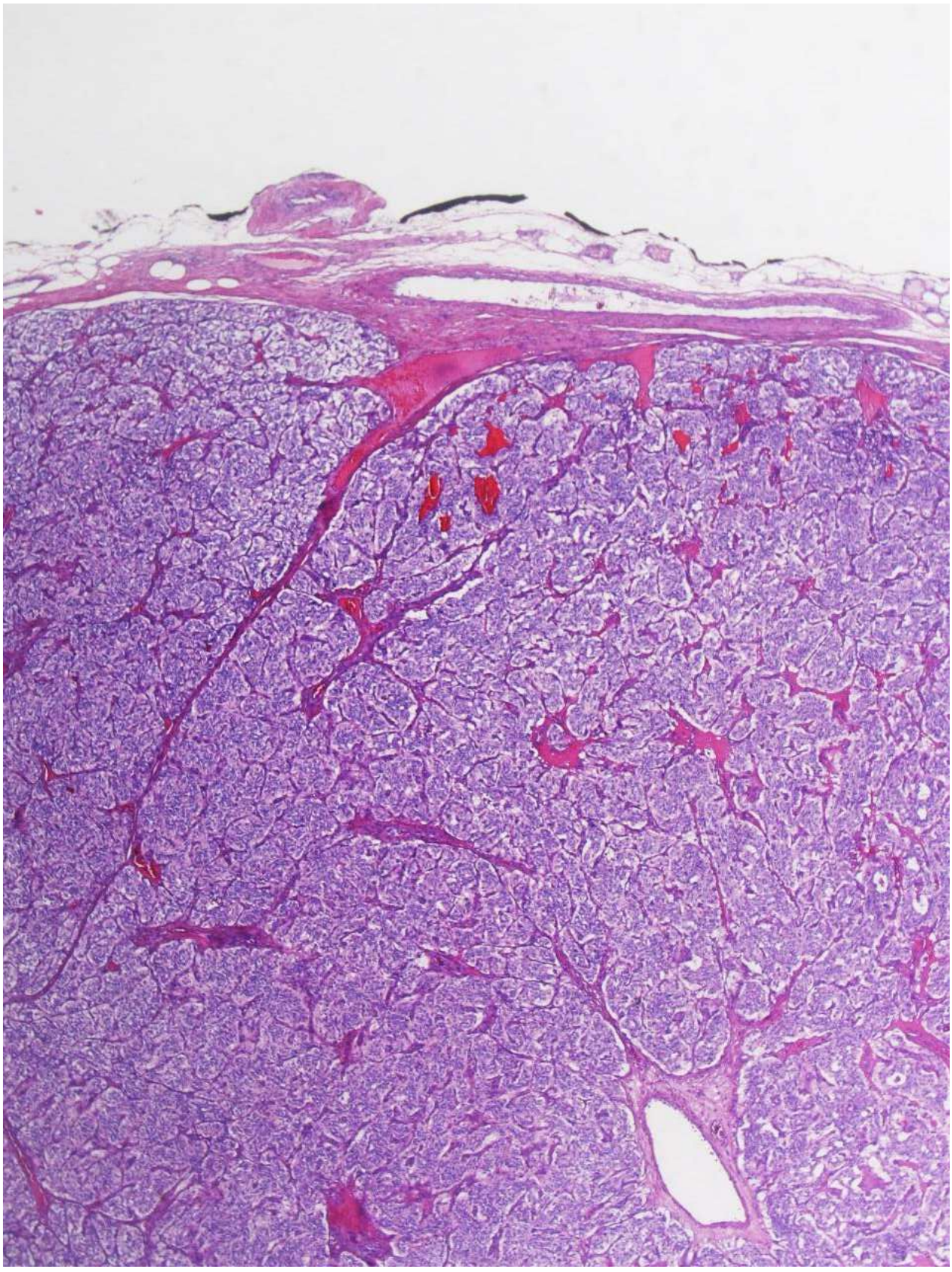
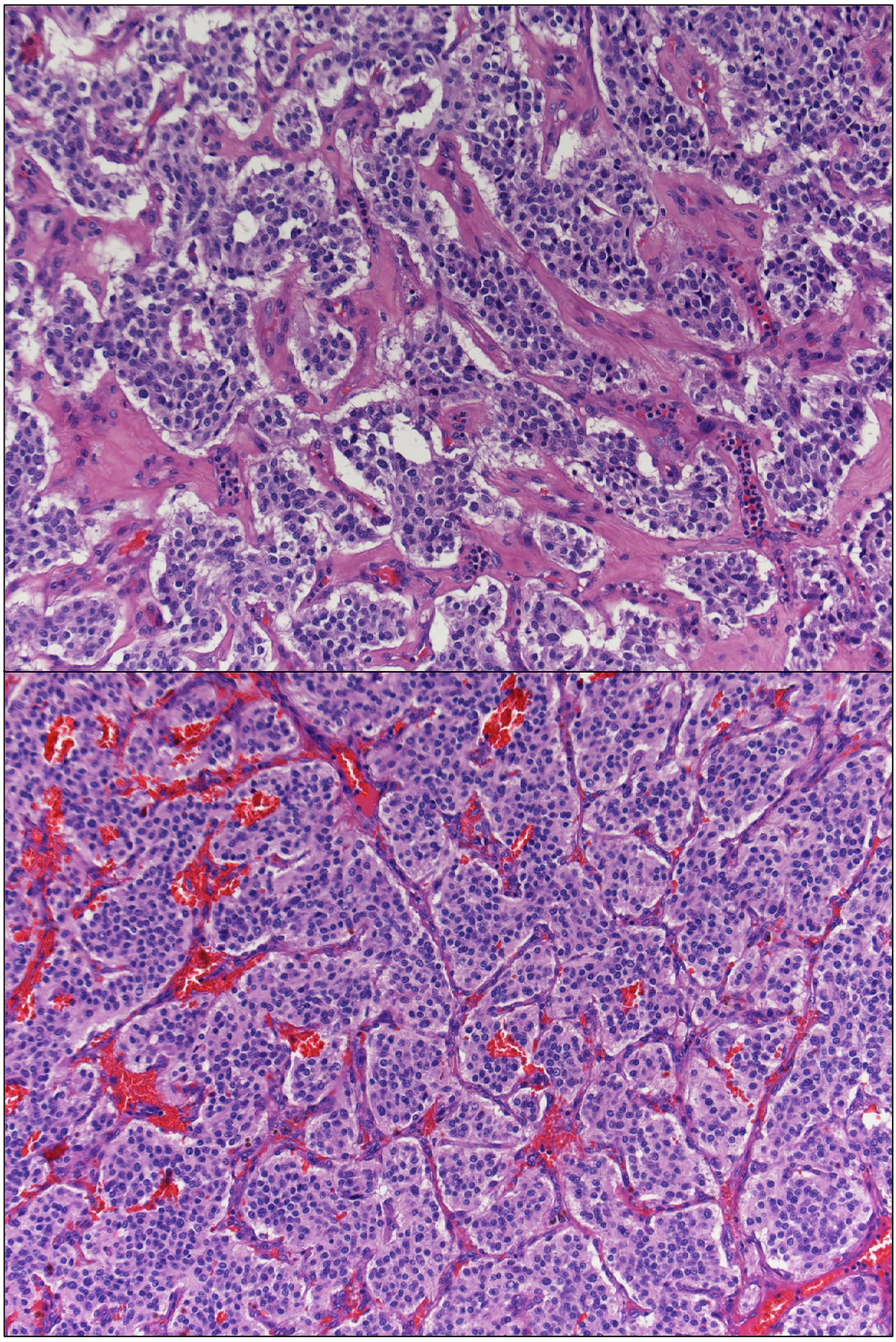
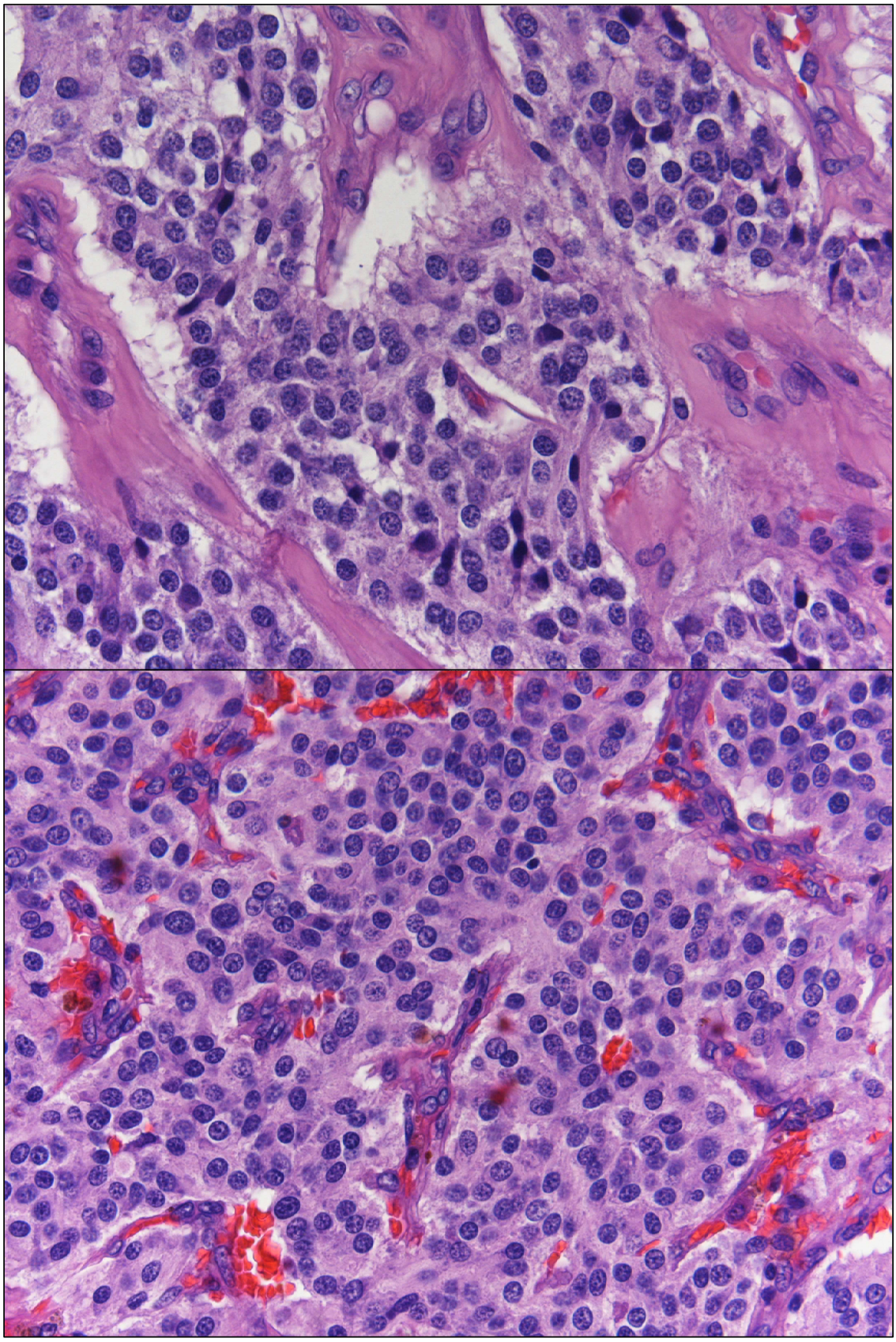
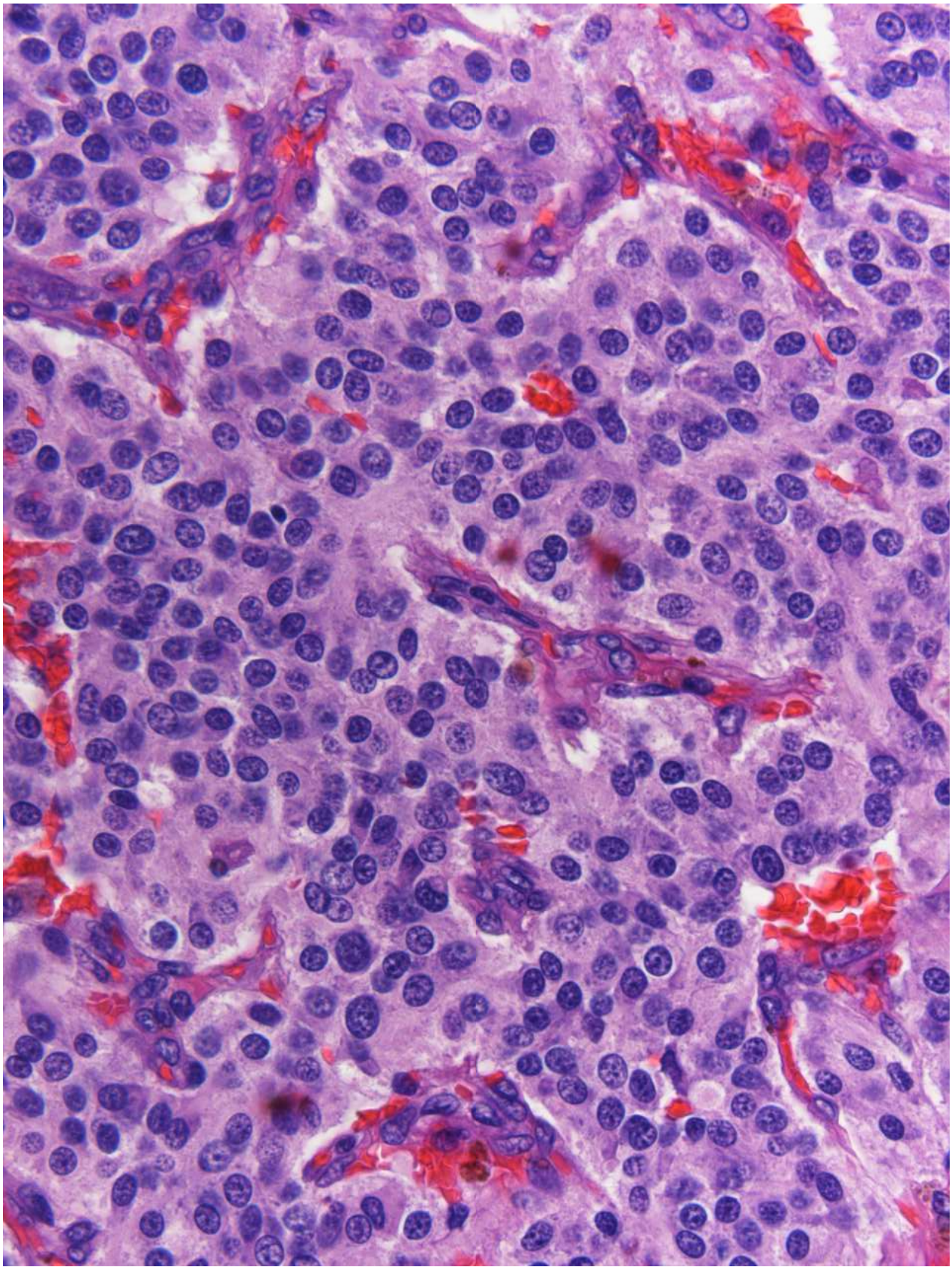
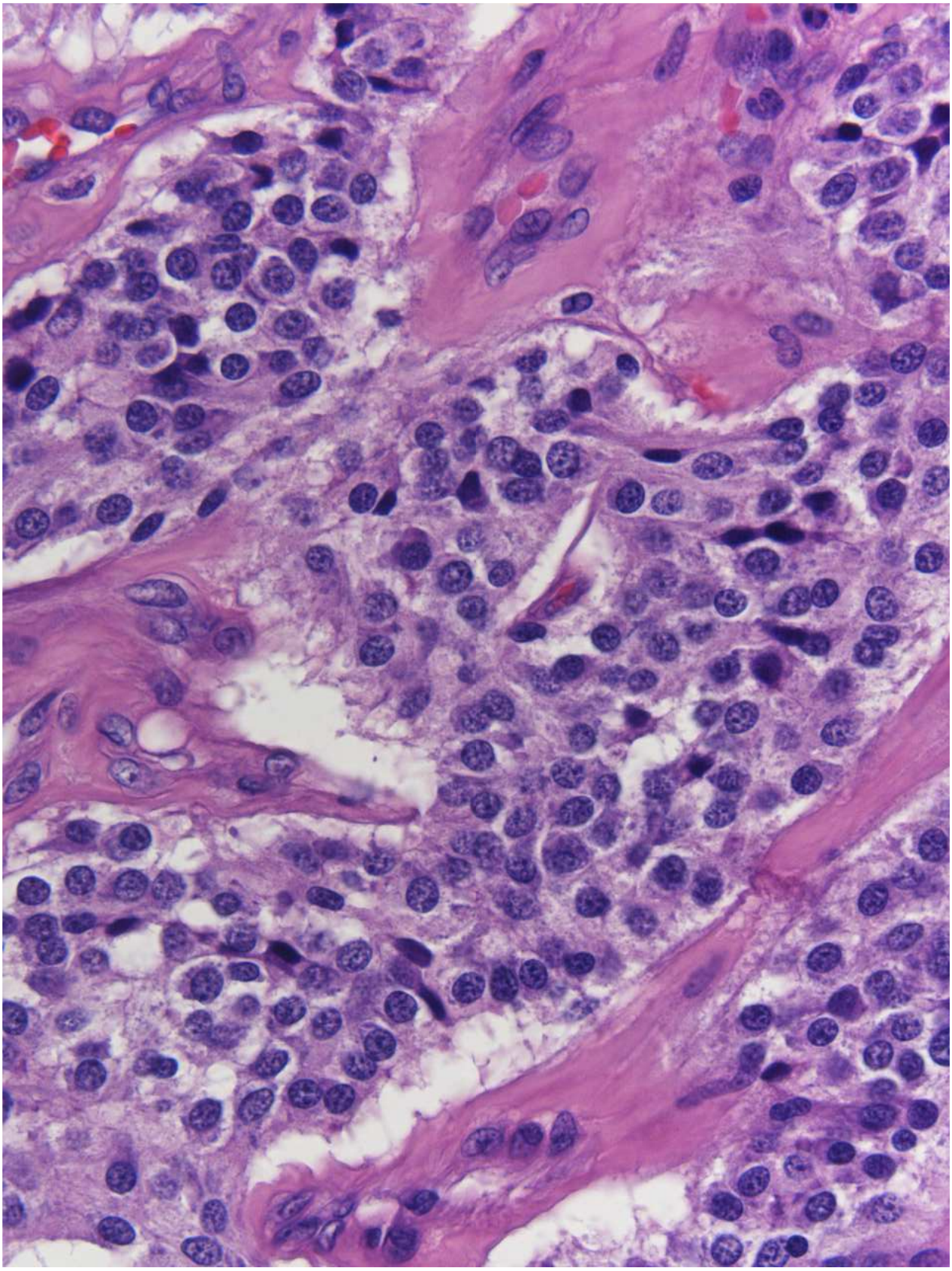


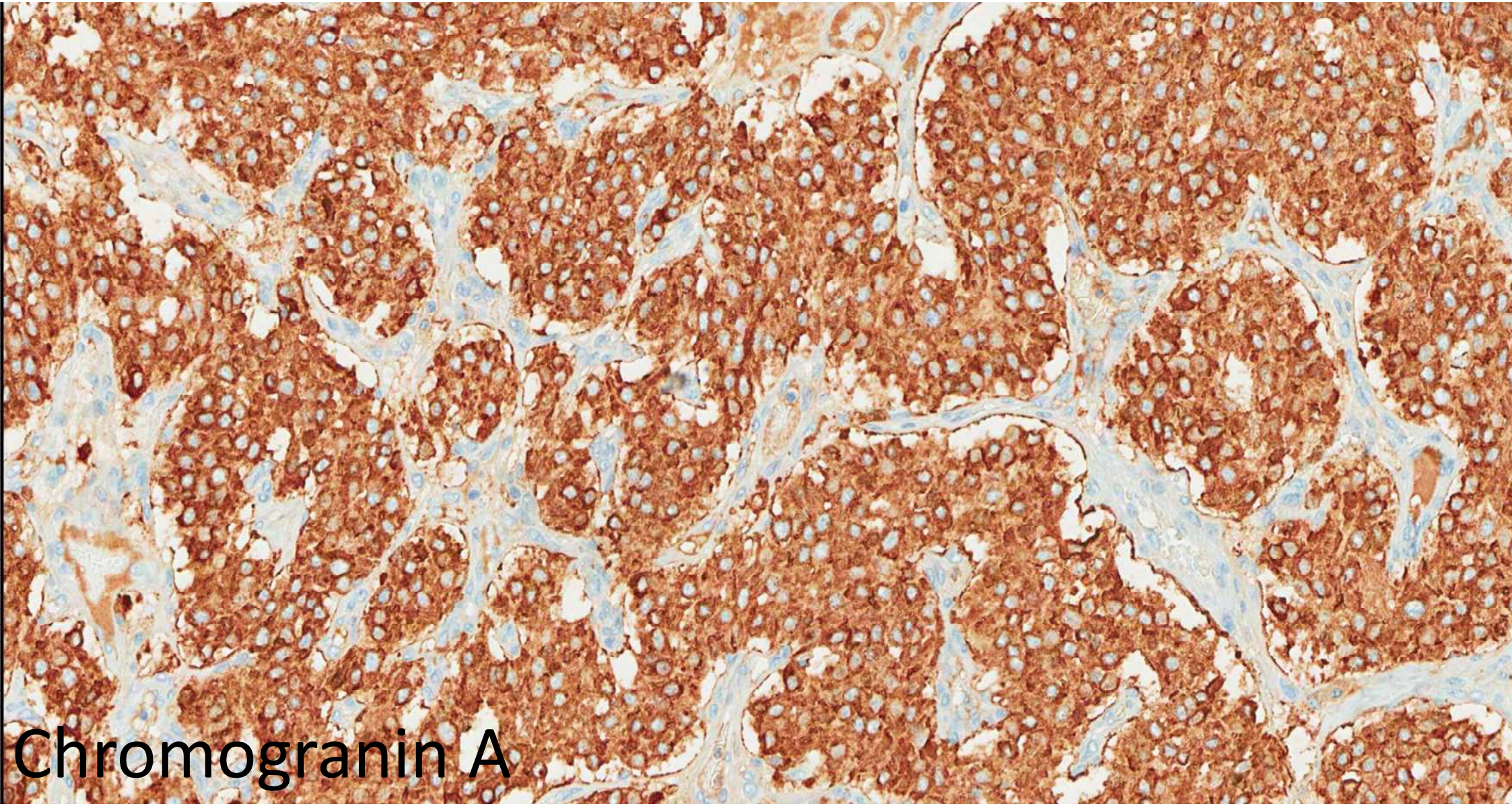


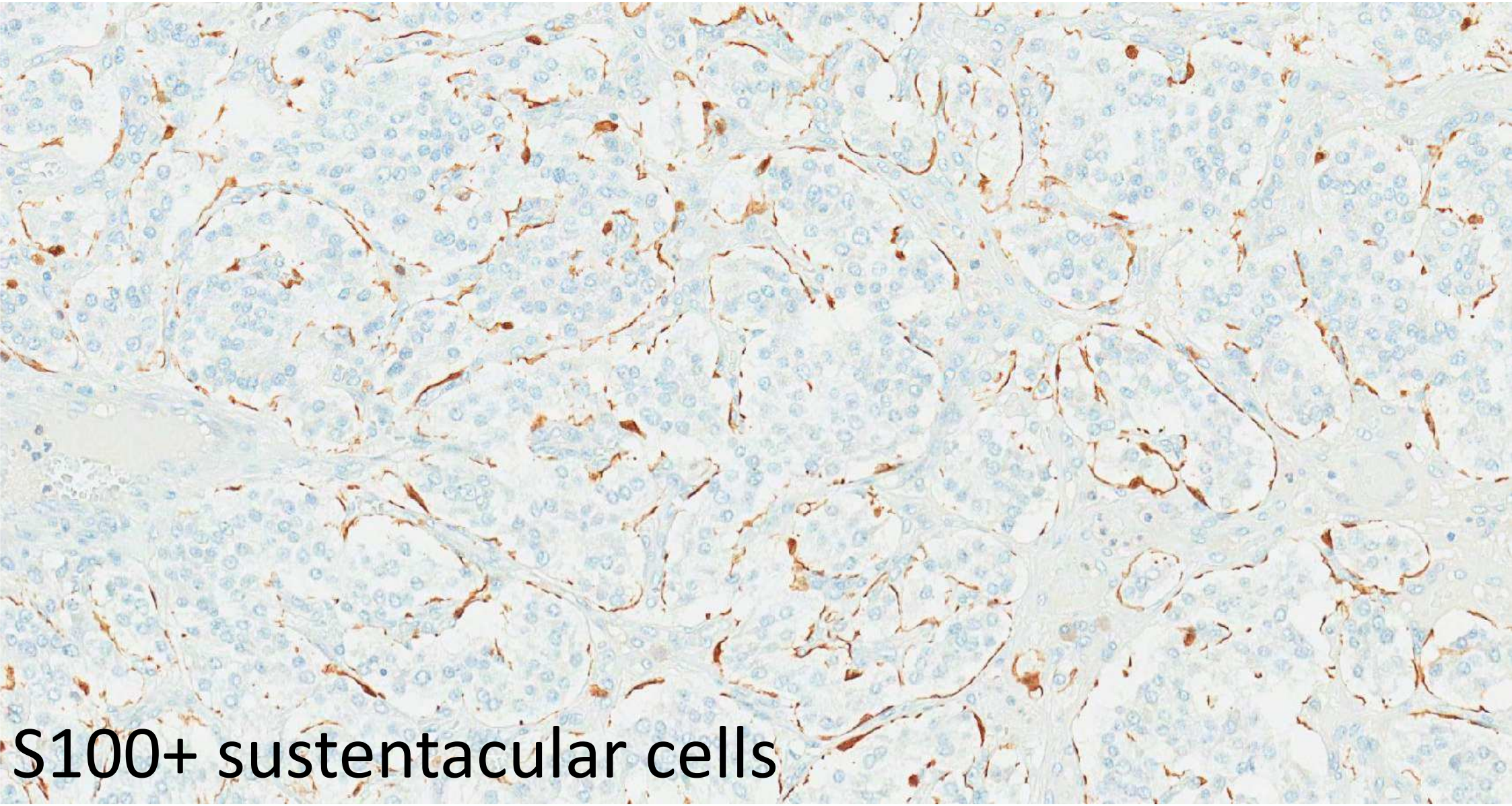


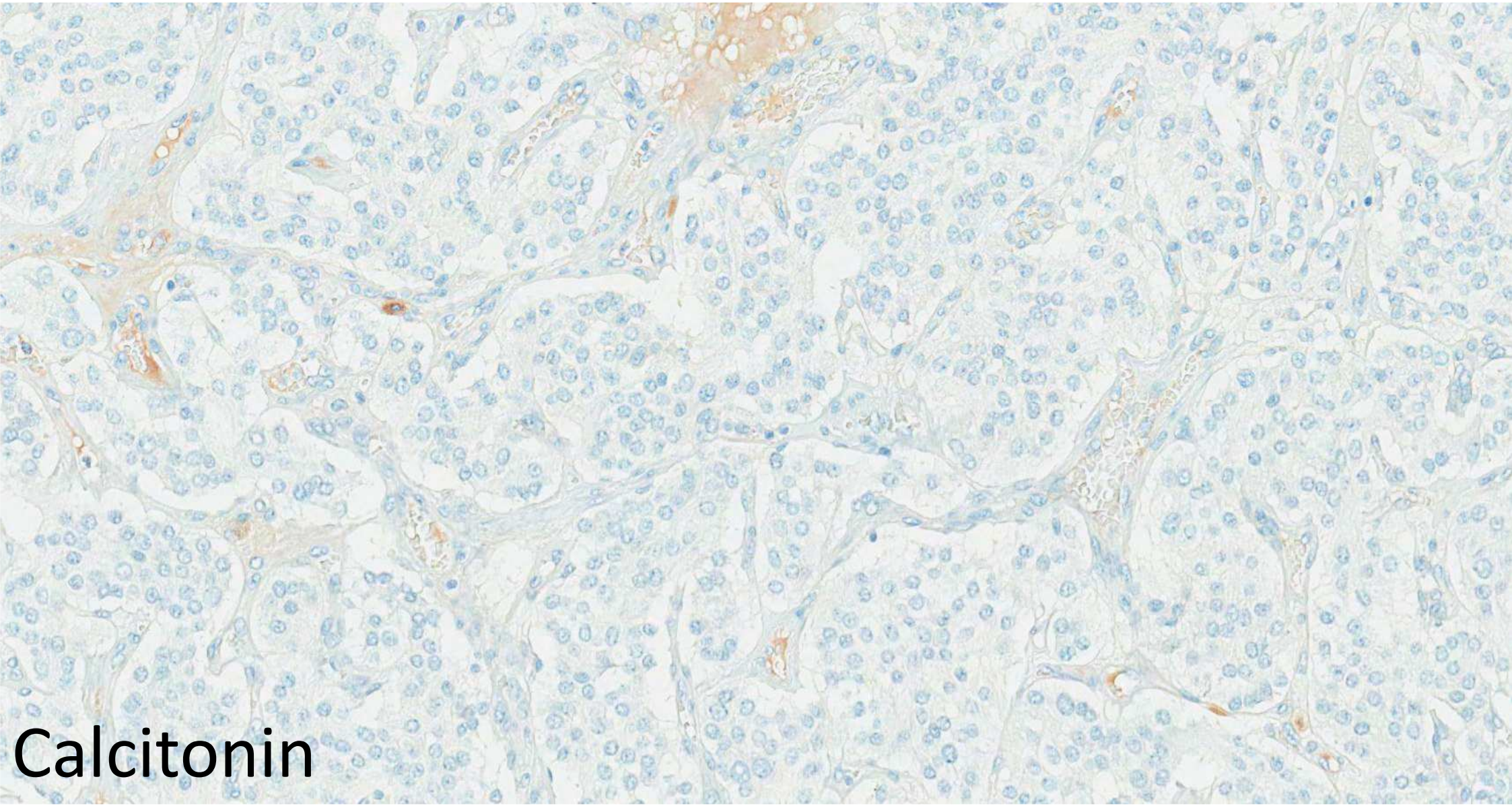


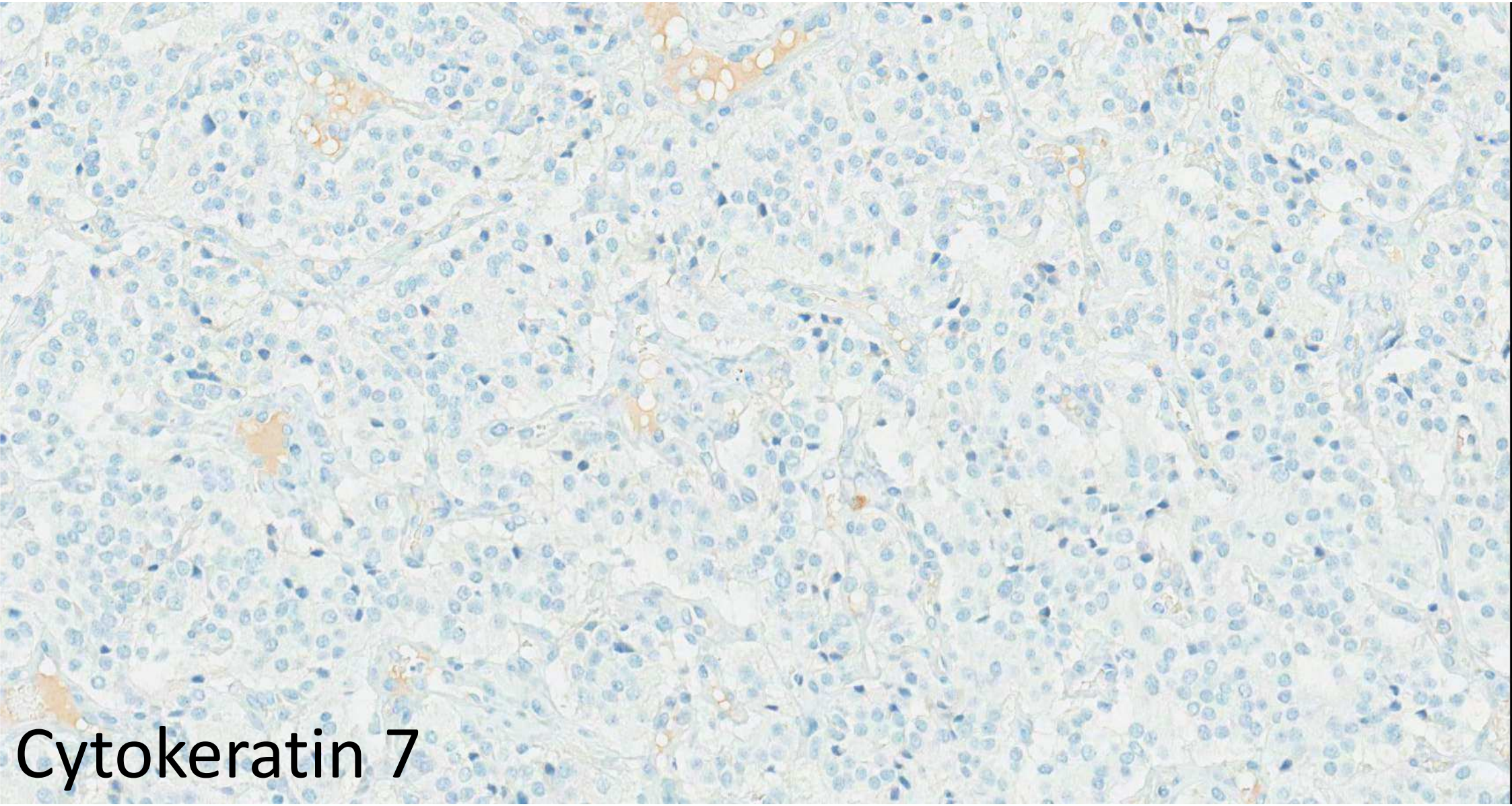


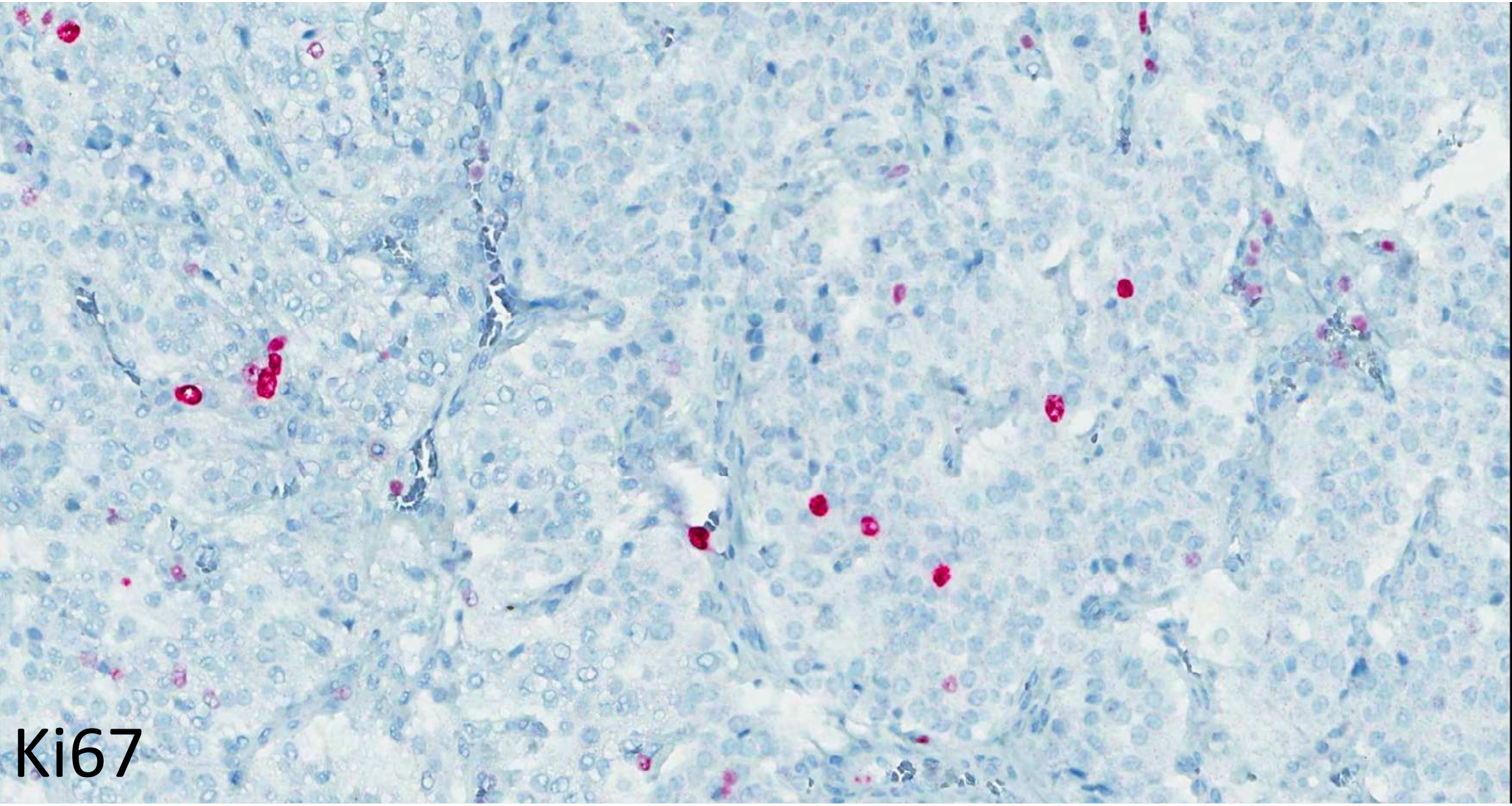


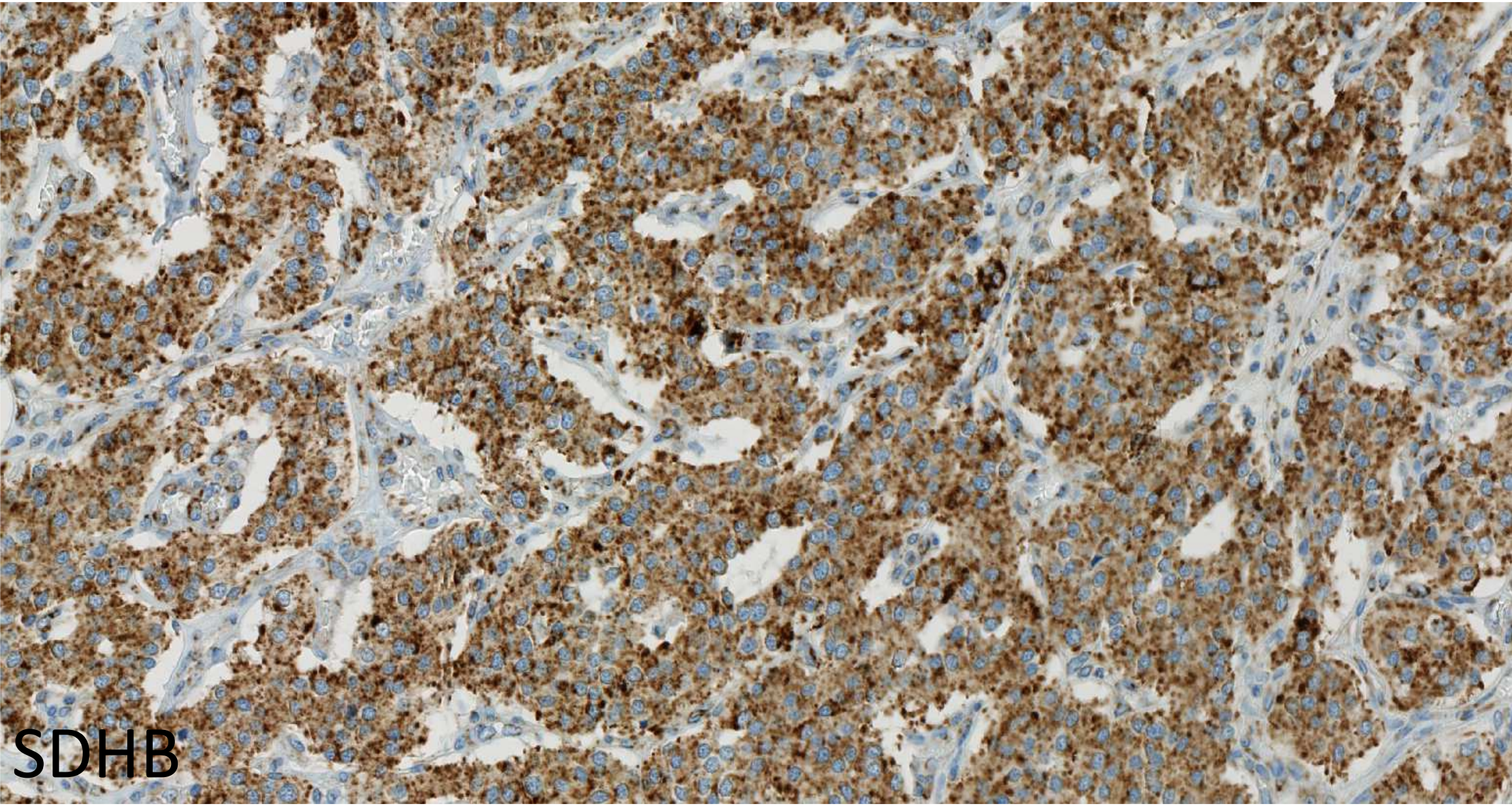

Chromogranin A


S100+ sustentacular cells


Calcitonin


Cytokeratin 7


Ki67


SDHB

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CASE 4
Thyroid paraganglioma

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The patient underwent left lobectomy: the surgen was surprised to see the nodule «pop out» from the thyroid in the operating room. Patient free of disease at last follow up, six years after the diagnosis

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CASE 4

Points for discussion

- What is a thyroid paraganglioma?
- How do you handle thyroid paragangliomas?

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Paraganglioma of the thyroid gland

- Thyroid paraganglioma develop from parasympathetic paraganglia in or immediately beneath the thyroid capsule → Parasympathetic paragangliomas
- Rare: ~75 cases reported worldwide
- Mean age 40-50, mostly female
- Asymptomatic thyroid nodule, in a euthyroid patient, incidenally discovered after ultrasound examination
- Encapsulated and composed of nests (“Zellballen”) of chromogranin-positive tumor cells, surrounded by S-100 positive sustentacular cells, indistinguishable from paragangliomas at other sites
- Clinically indolent, but potential for malignancy has documented in rare cases

References

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- Buss DH, Marshall RB, Baird FG, Myers RT. Paraganglioma of the thyroid gland. Am J Surg Pathol. 1980 Dec;4(6):589-93
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- González Poggioli N, López Amado M, Pimentel MT. Paraganglioma of the thyroid gland: a rare entity. Endocr Pathol 2009;20:62-5.

Paraganglioma of the thyroid gland

Differential diagnosis

- Paraganglioma of the carotid body or other cervical paraganglia developing in close proximity or extending into the thyroid, distinction based on surgical findings and imaging
- Medullary thyroid carcinoma
- Hyalinizing trabecular tumor with nesting pattern resulting in a paraganglioma-like appearance (indeed term paraganglioma-like adenoma of the thyroid was originally proposed fo hyalinizing trabecular adenoma) and other tumors of follicular cells with nested patterns
- Intrathyroidal parathyroid adenoma
- Metastatic tumors: neuroendocrine tumors (e.g. carcinoid from the lung), renal cell carcinoma, other carcinomas with nested paraganglioma-like pattern

Paraganglioma of the thyroid gland: differential diagnosis

	Thyroid transcription factors	Keratin	Neuroendocrine markers (Chromogranin, synaptophysin)	S-100 + sustentacular cells	Tumor specific markers
Paraganglioma	–	–	+	+	Choline acetyl transferase + Tyrosine hydroxylase +/–[a] Dopamine βHydroxylase +/–[a]
Medullary carcinoma	TTF-1 + (weak) PAX8 – (weak/focal+ if antibody is polyclonal)	+	+	–	Calcitonin +, CEA +, Calcitonin gene-related peptide (CGRP) +
Tumors of follicular cells with nesting pattern (e.g. Hyalinizing trabecular tumor)	TTF1 + Pax8 +	+	–	–	Thyroglobulin
Intrathyroidal parathyroid adenoma	–	+	+	–	Parathormone
Metastatic carcinoma	TTF1 – (+ in neuroendocrine lung tumors) PAX8 –	+	– (+ if tumor is neuroendocrine)	–	Expression depending on tumor type

[a]Tyrosine hydroxylase (cathecolamine biosynthesis) and Tyrosine βhydroxylase (norepinephrine) positivity may be weak and variable, since most tumors in the thyroid are parasympathetic paragangliomas

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Pheochromocytoma-Paraganglioma: SDH immunohistochemistry for genetic screening

- **Up to 40% of paragangliomas have a germline mutation**: 14 known genes: MEN1, NF1, RET, von Hippel–Lindau [VHL], SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, EGLN1, HIF2A, KIF1Bb, and MAX

✓ **Highest heritability among human neoplasms**

- **Familial disease in the head and neck paraganglioma is typically associated with SDHD, SDHC, SDHB, and SDHAF2 mutations (Pheochromocytoma-Paraganglioma syndromes)**
- **Need to do SDHB and SDHA immunohistochemistry to screen for genetic testing**
  - SDHB, but not SDHA protein expression lost in paragangliomas with germline SDHB, SDHC, SDHD or SDHAF2 mutation **(IHC: SDHB-, SDHA+)**
  - SDHA and SDHB protein expression lost in paragangliomas with germline SDHA mutation **(IHC: SDHB-, SDHA+)**

✓ **SDHB negative immunoreactivity correlates with malignant behavior because these syndromic tumors are more aggressive**

References

- van Nederveen FH, …,Dinjens WN. An immunohistochemical procedure to detect patients with paraganglioma and phaeochromocytoma with germline SDHB, SDHC, or SDHD gene mutations: a retrospective and prospective analysis. Lancet Oncol. 2009 Aug;10(8):764-71
- Favier J, Amar L, Gimenez-Roqueplo AP. Paraganglioma and phaeochromocytoma: from genetics to personalized medicine. Nat Rev Endocrinol. 2015 Feb;11(2):101-11. doi: 10.1038/nrendo.2014.188. Epub 2014 Nov 11. PMID: 25385035.
- Papathomas TG,…,de Krijger RR. SDHB/SDHA immunohistochemistry in pheochromocytomas and paragangliomas: a multicenter interobserver variation analysis using virtual microscopy: a Multinational Study of the European Network for the Study of Adrenal Tumors (ENS@T). Mod Pathol. 2015 Jun;28(6):807-21

Pheochromocytoma-Paraganglioma: SDH immunohistochemistry for genetic screening

		Immunohistohemistry	
	Gene	SDHA	SDHB
Germline mutation	SDHA	Negative	Negative
	SDHB	Positive (granular mitochondrial staining)	Negative
	SDHC		
	SDHD		
	SDHAF2		

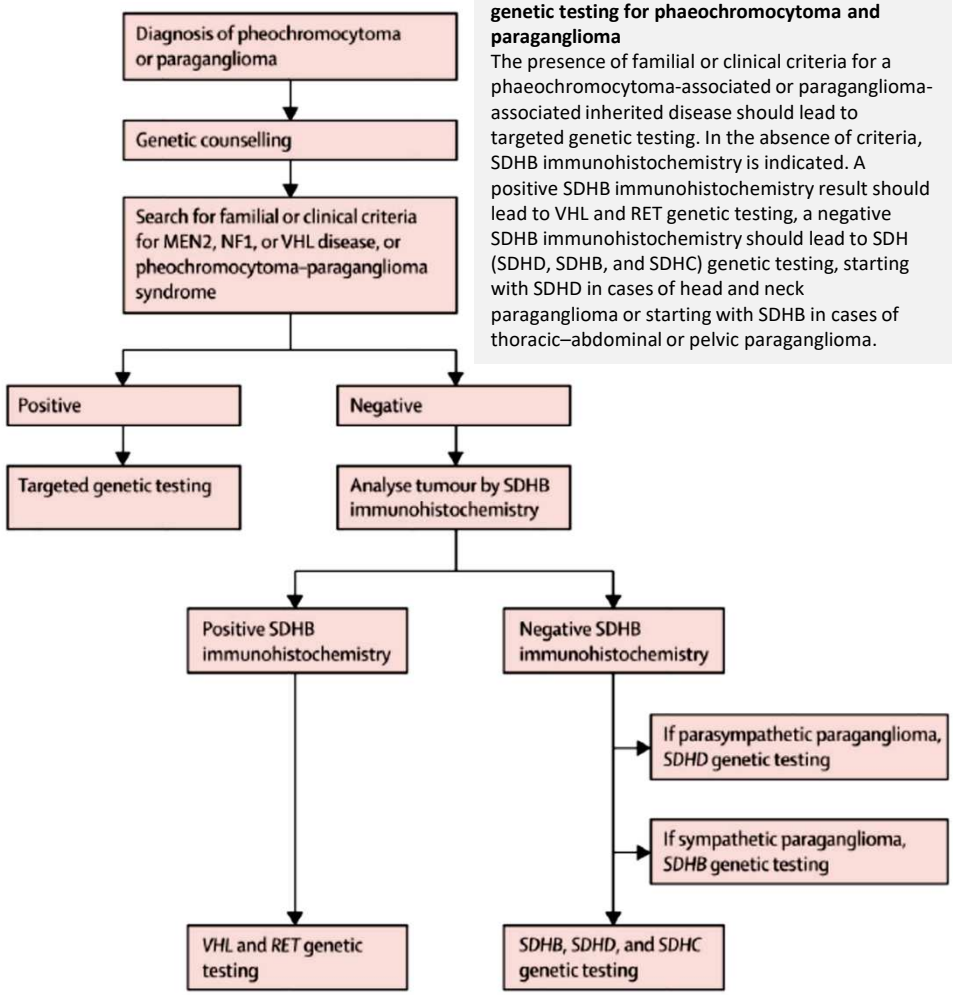

Figure 3. Suggested algorithm for molecular genetic testing for phaeochromocytoma and paraganglioma
The presence of familial or clinical criteria for a phaeochromocytoma-associated or paraganglioma-associated inherited disease should lead to targeted genetic testing. In the absence of criteria, SDHB immunohistochemistry is indicated. A positive SDHB immunohistochemistry result should lead to VHL and RET genetic testing, a negative SDHB immunohistochemistry should lead to SDH (SDHD, SDHB, and SDHC) genetic testing, starting with SDHD in cases of head and neck paraganglioma or starting with SDHB in cases of thoracic–abdominal or pelvic paraganglioma.

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Pheochromocytoma-Paraganglioma: SDH immunohistochemistry for genetic screening

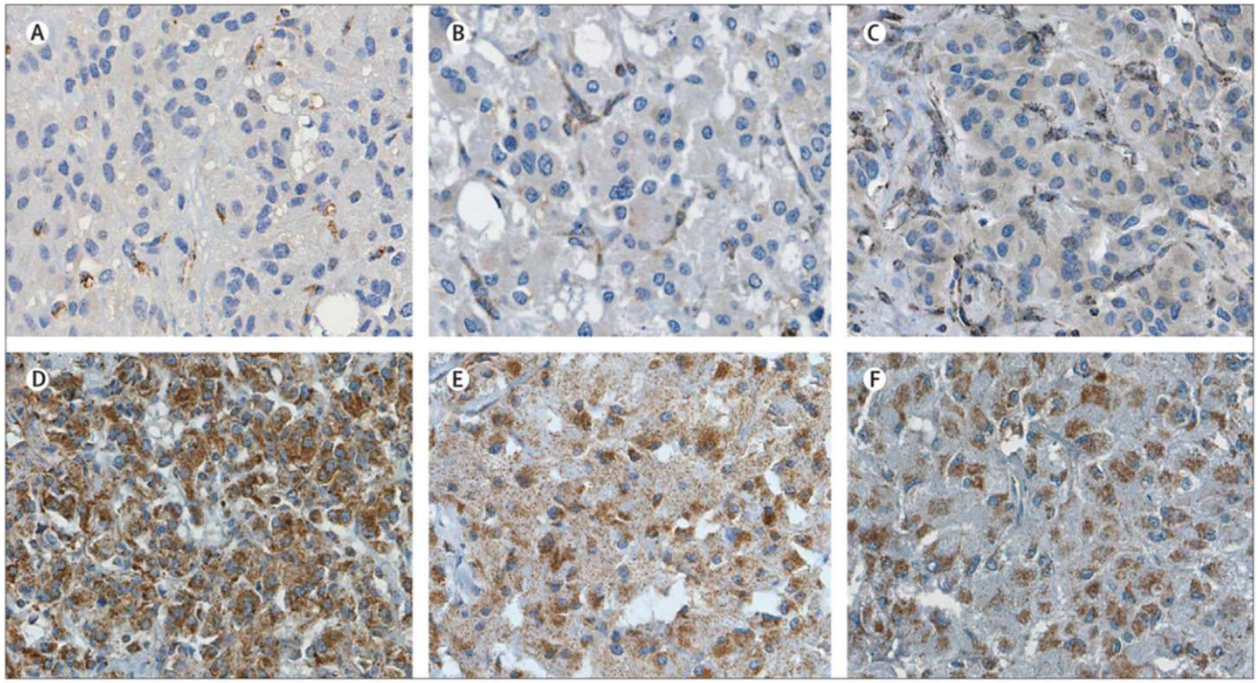
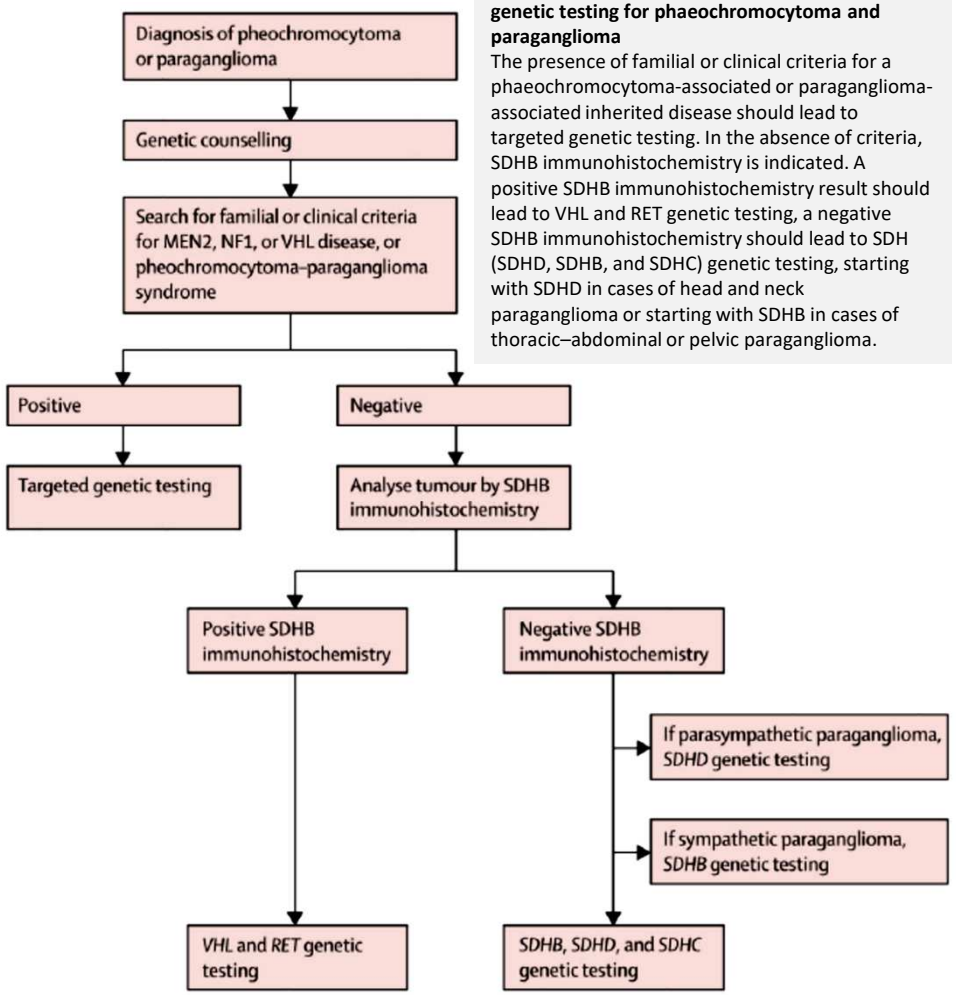


Figure 1. Phaeochromocytoma and paraganglioma SDHB immunohistochemistry.
(A) Phaeochromocytoma with SDHB mutation. (B) Paraganglioma with SDHC mutation. (C) Paraganglioma with SDHD mutation. (D) Phaeochromocytoma with VHL mutation. (E) Phaeochromocytoma with RET mutation. (F) Phaeochromocytoma from a patients with NF1 (clinical diagnosis). Note: Strong speckled SDHB immunostaining in non-SDH mutated tumours (D, E, and F). Absence of SDHB immunostaining in the tumour cells of SDHB, SDHC, and SDHD-mutated tumours, with positive staining in the normal cells of the intratumoral fibrovascular network (A, B, and C). In the SDHD-mutated tumour (C) diffuse cytoplasmic background staining is seen, clearly distinct from the staining of the intratumoral fibrovascular network.



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Paraganglioma of the thyroid gland: germline mutations

Table 3: Molecular genetics in thyroid paragangliomas reported in the literature

Author [reference]	Age/gender	IHC	SDH mutation analysis	Additional genetic testing	Course
Phitayakorn *et al.*[2]	73/female	NA	Negative	RET negative	Disease free
González Poggioli *et al.*[32]	31/female	SDHB +	Negative	RET negative	Disease free
Yu *et al.*[33]	30/female	ND	Negative	RET negative	Disease free
Waise and Jogai[34]	50/male	NA	Negative	TMEM127 and VHL negative	Not described
Castelblanco *et al.*[35]	59/female	SDHB +	Negative	RET negative	NA
Castelblanco *et al.*[35]	78/female	SDHB +	Negative	RET negative	NA
Castelblanco *et al.*[35]	51/female	SDHB +	Negative	RET negative	NA
Schmit *et al.*[21]	33/male	NA	NA	NA	NA
Costinean *et al.*[36]	32/female	NA	Multiple homozygous and heterozygous SNP in SDH B, C, D subunits	Heterozygous SNP and extra genetic mutation in the NNMT gene at PGL1 locus	Disease free
von Dobschuetz *et al.*[7]	27/male	ND	SDHB +	ND	B/L phaeochromocytoma
von Dobschuetz *et al.*[7]	32/male	ND	SDHB +	ND	ND
von Dobschuetz *et al.*[7]	36/female	ND	SDHA +	ND	ND
von Dobschuetz *et al.*[7]	37/female	ND	SDHA +	ND	ND
Zantour *et al.*[1]	32/female	ND	SDHB +	ND	ND
Pelizzo *et al.*[4]	67/female	SDHA and SDHB +	ND	ND	ND

IHC=Molecular study by immunohistochemistry, SDH=Succinate dehydrogenase, A, B, C, D=Subunits of SDH enzyme, NA=Not available, +=Positive, ND=Not done, SNP=Single nucleotide polymorphisms, NNMT=Nicotinamide N-methyl transferase, PGL=Paraganglioma, VHL=Von Hippel–Lindau, B/L=Bilateral

Mishra P, Padhi S, Behera G. Thyroid paraganglioma: A case-based systematic review of literature. J Cancer Res Ther. 2020 Dec;16(Supplement):S11-S21. doi: 10.4103/jcrt.JCRT_713_18