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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 5

68 year-old woman with goiter and a widely invasive multinodular 6 cm mass

Giovanni Tallini, MD
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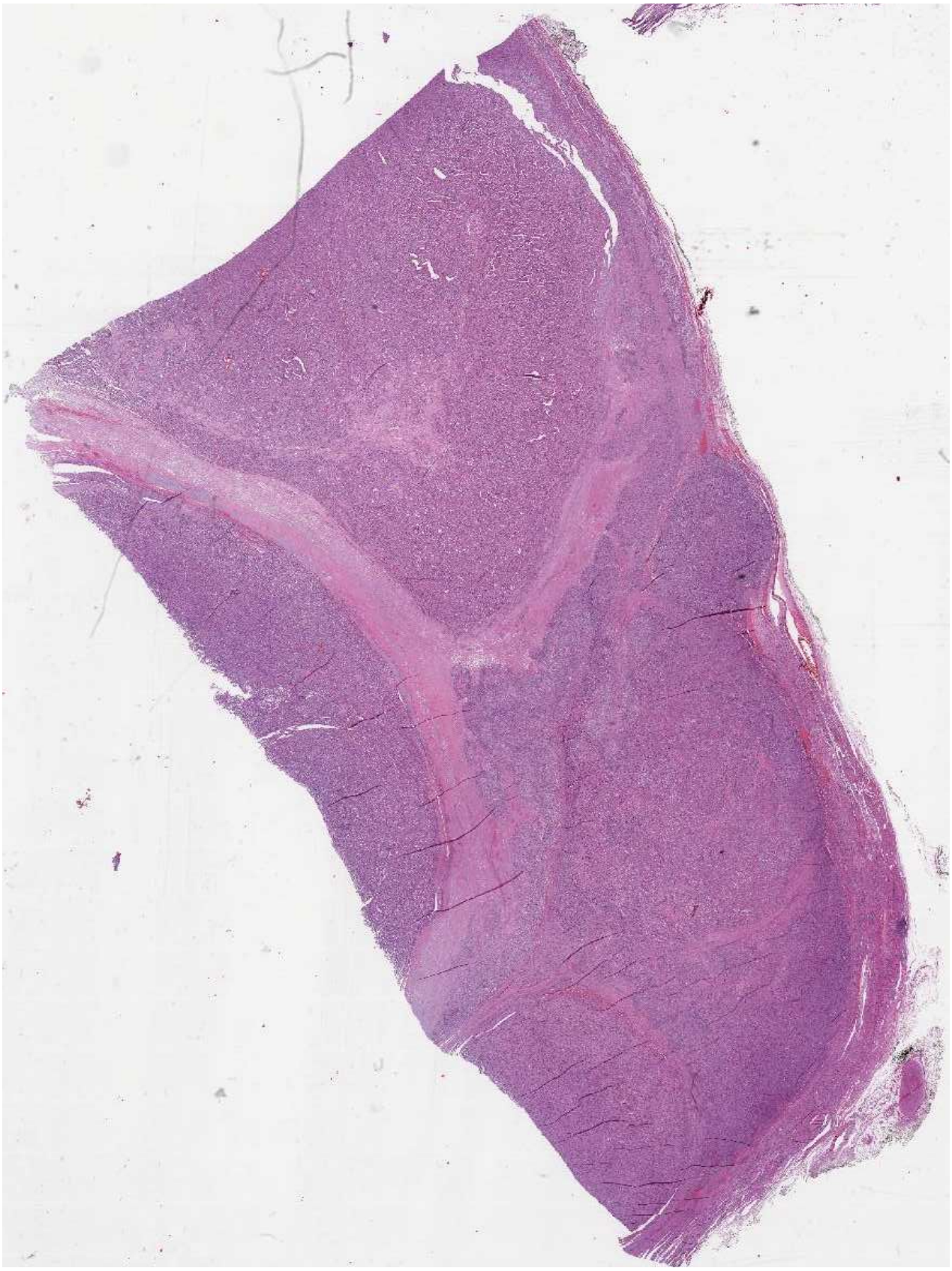

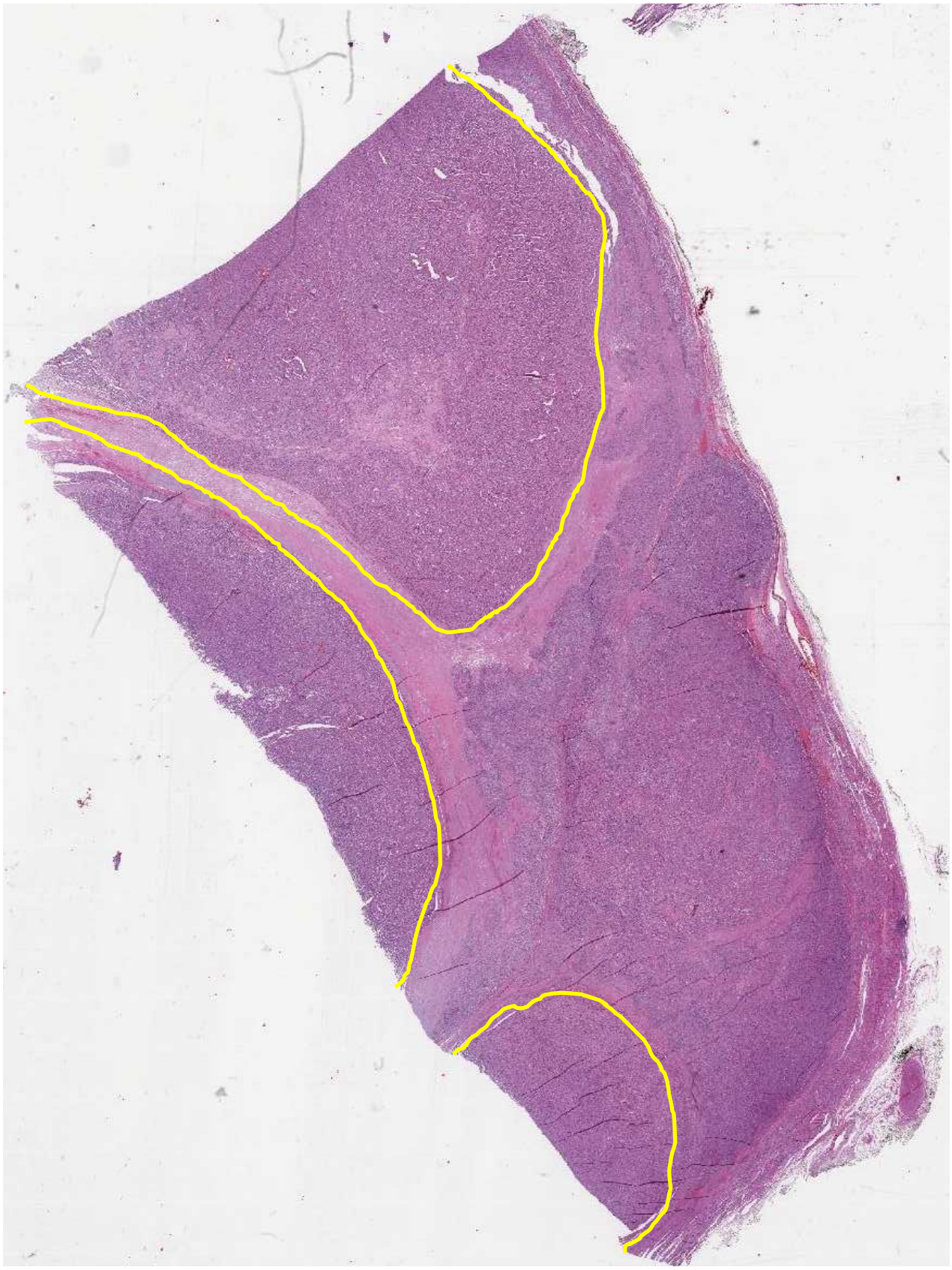

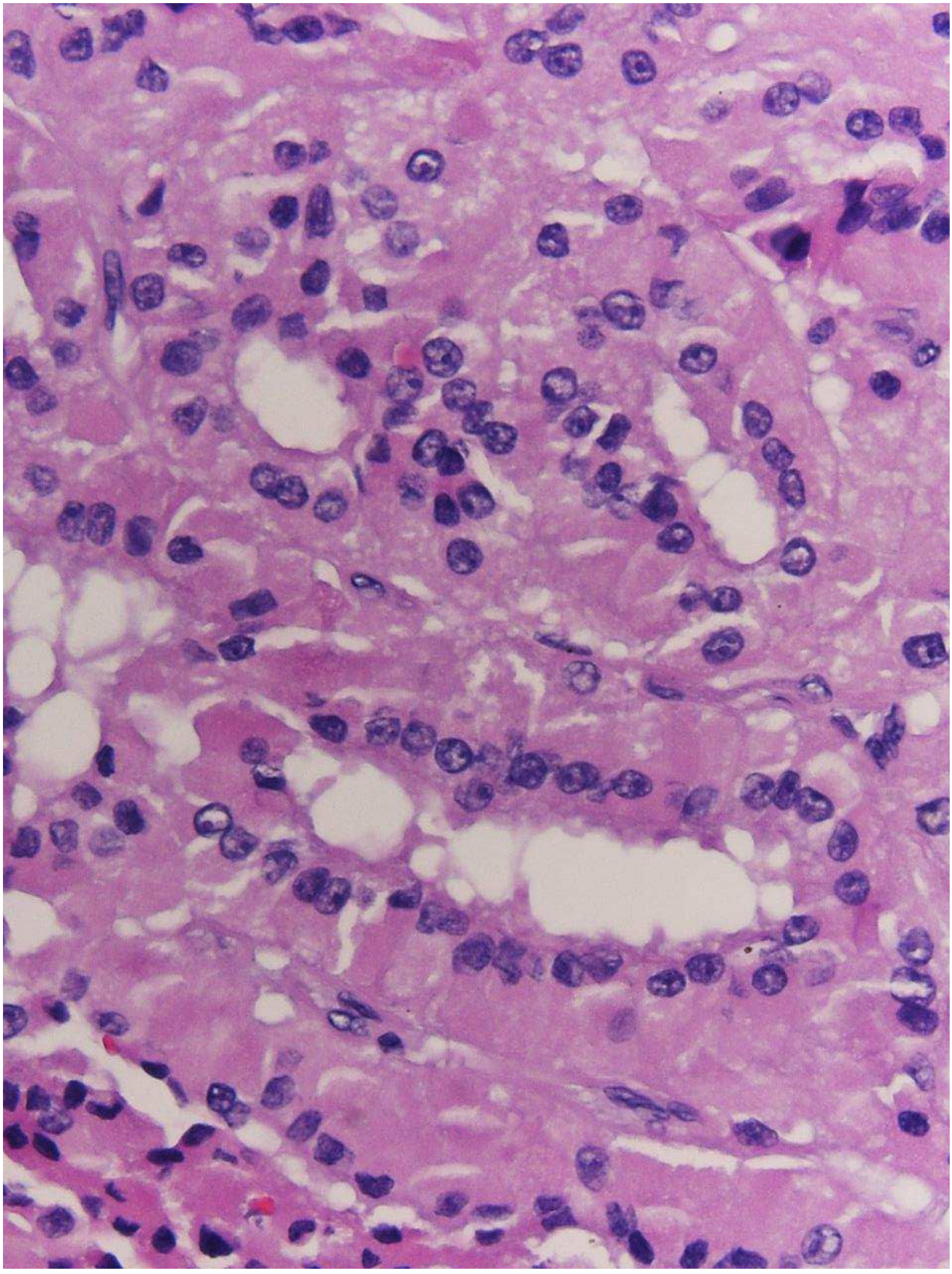

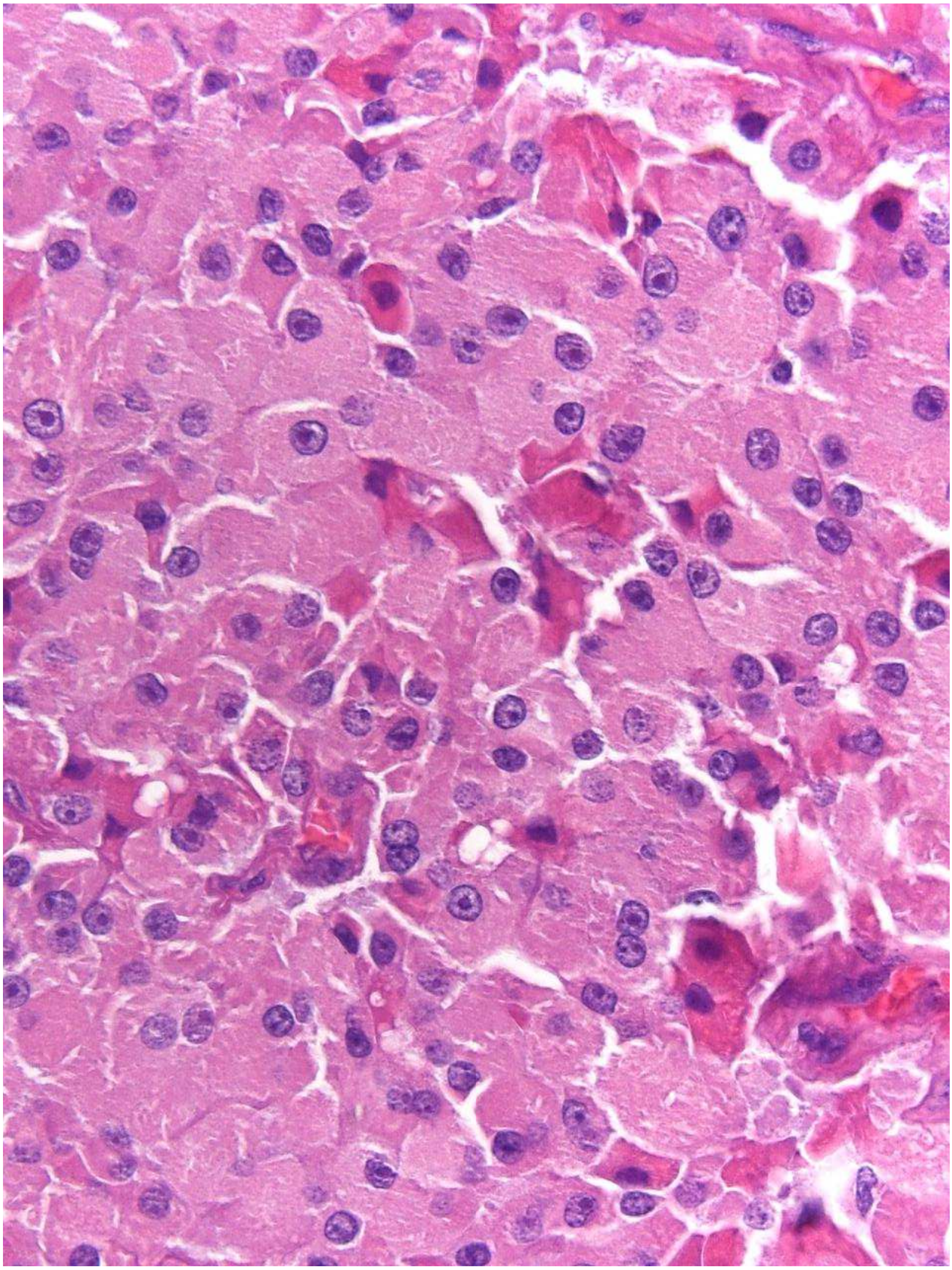

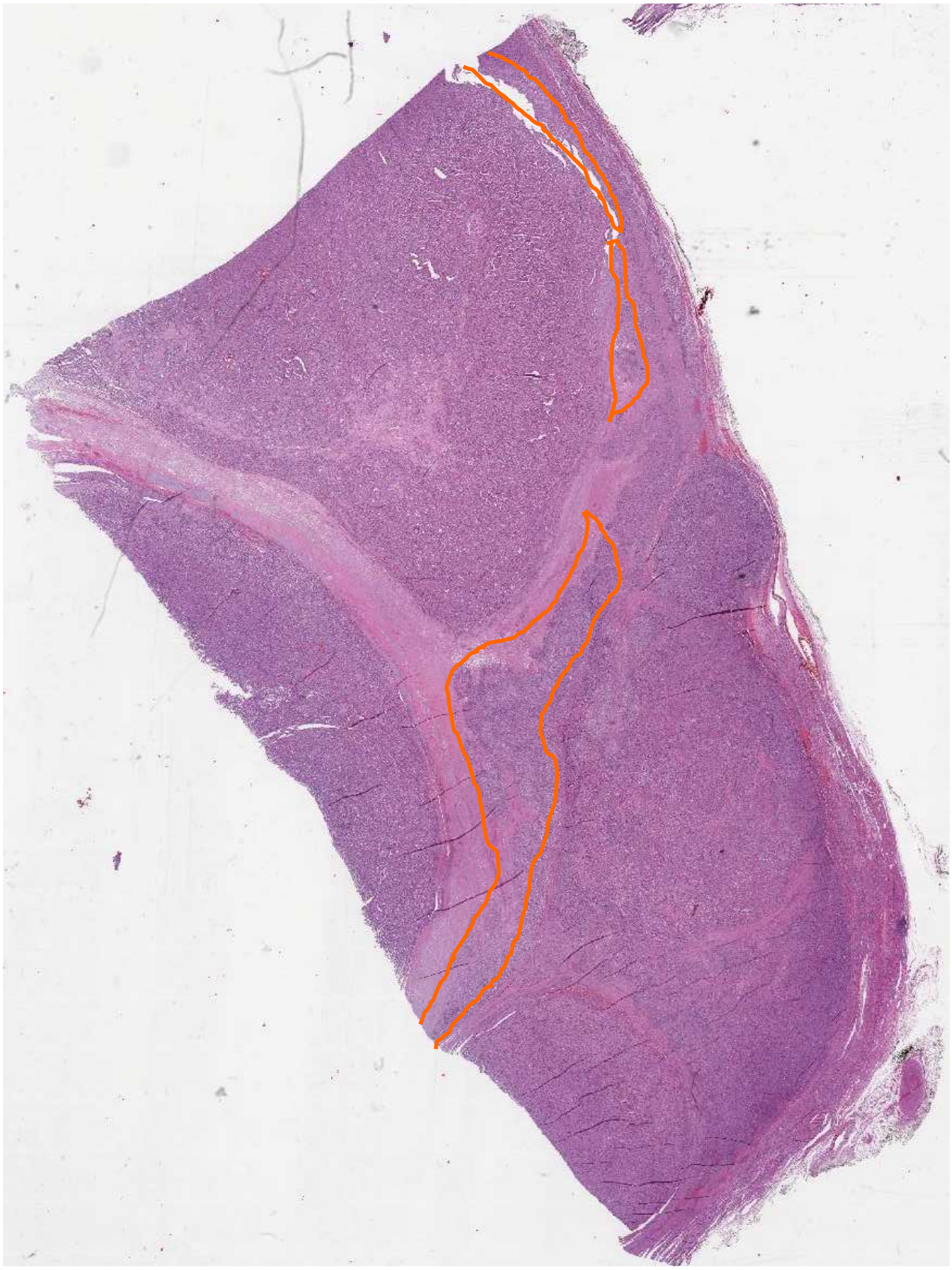

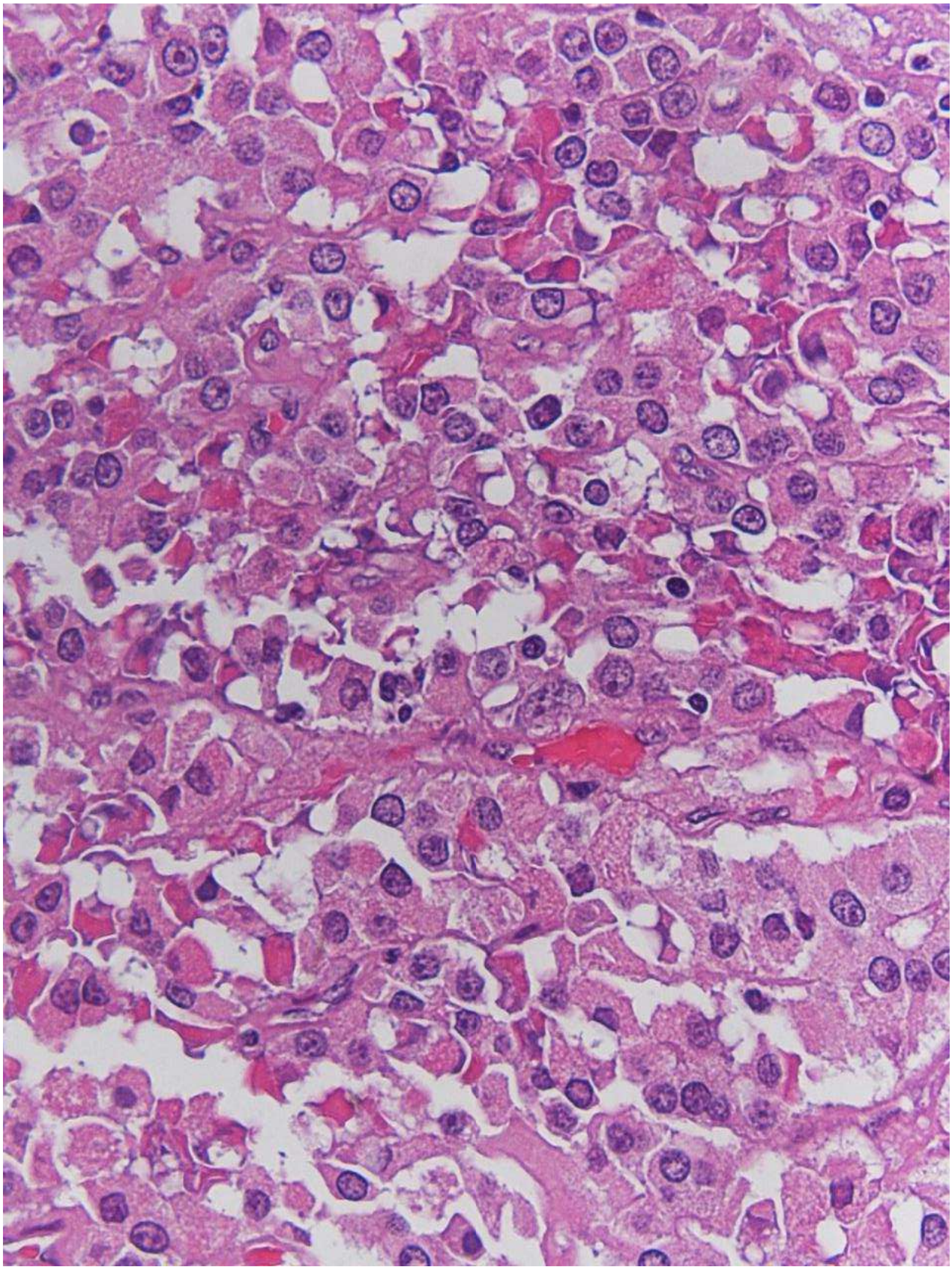

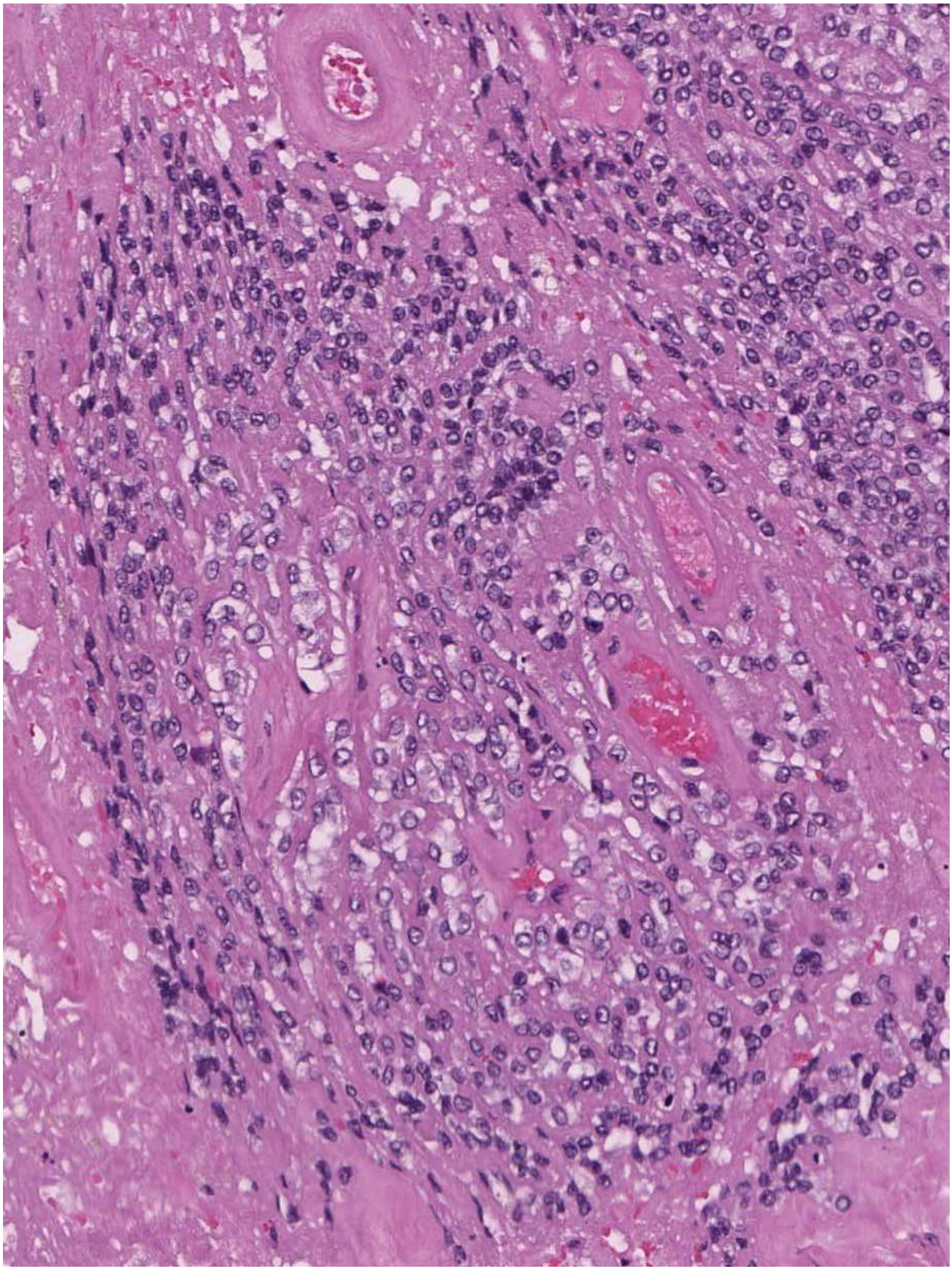

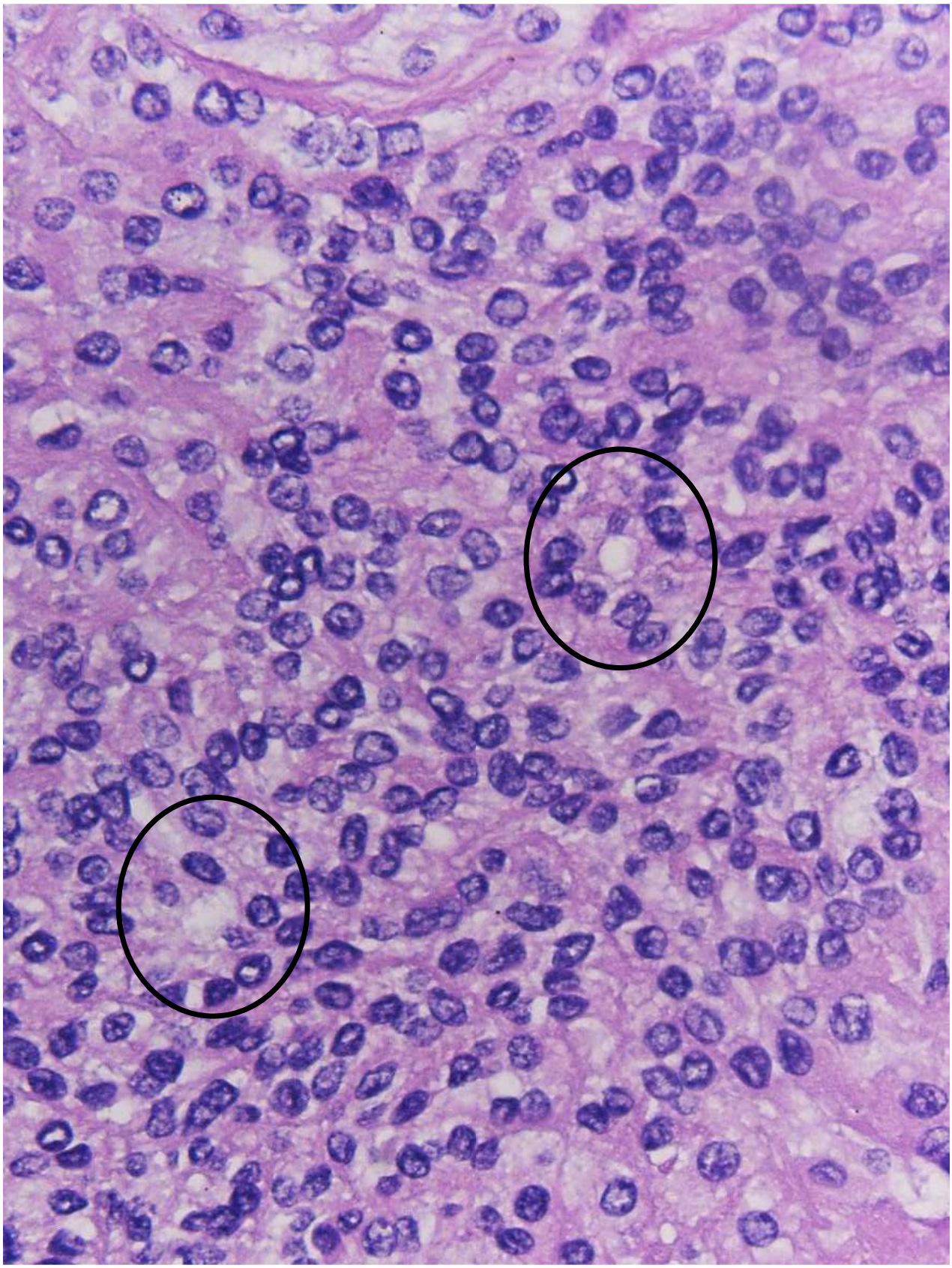

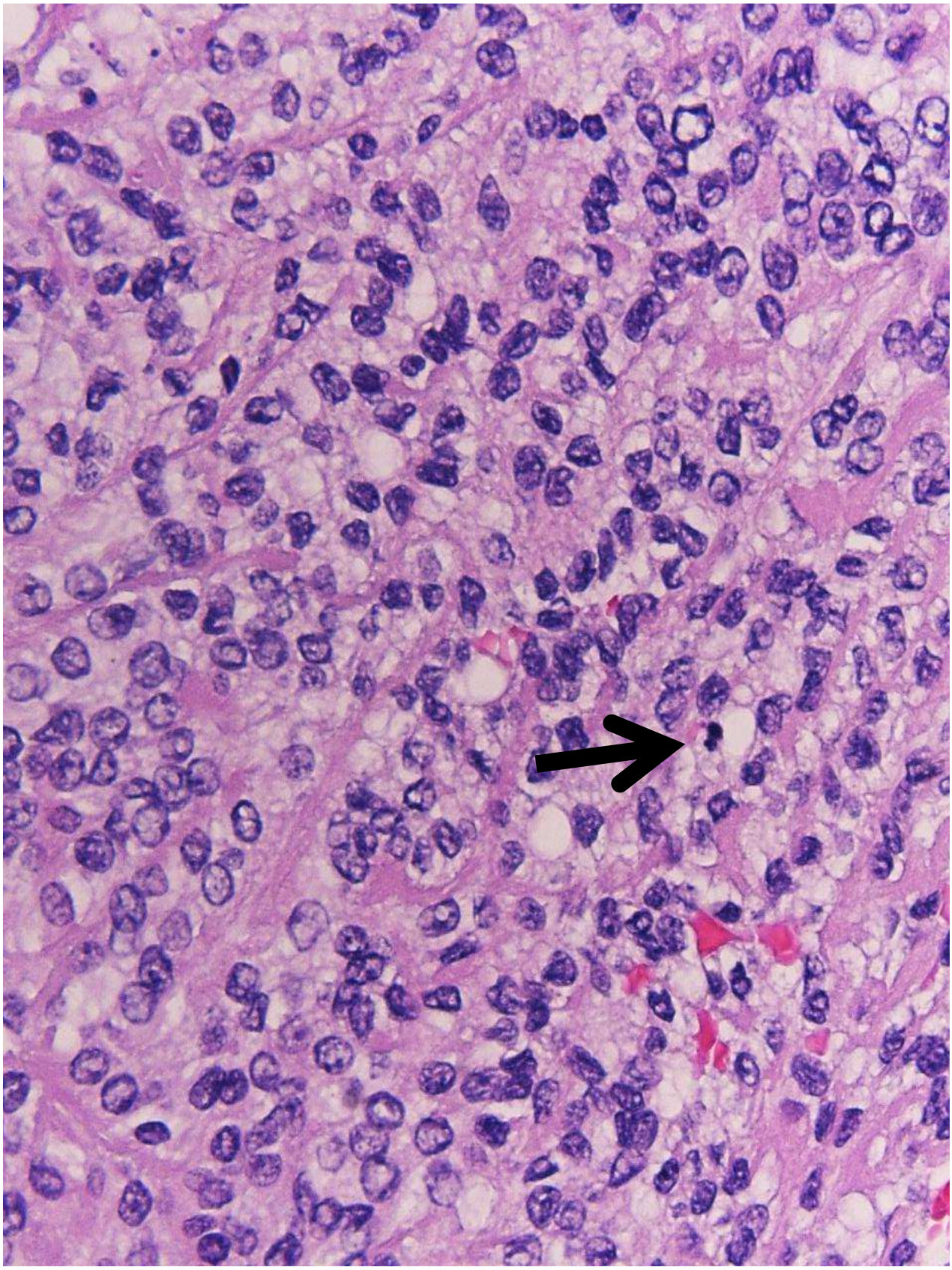

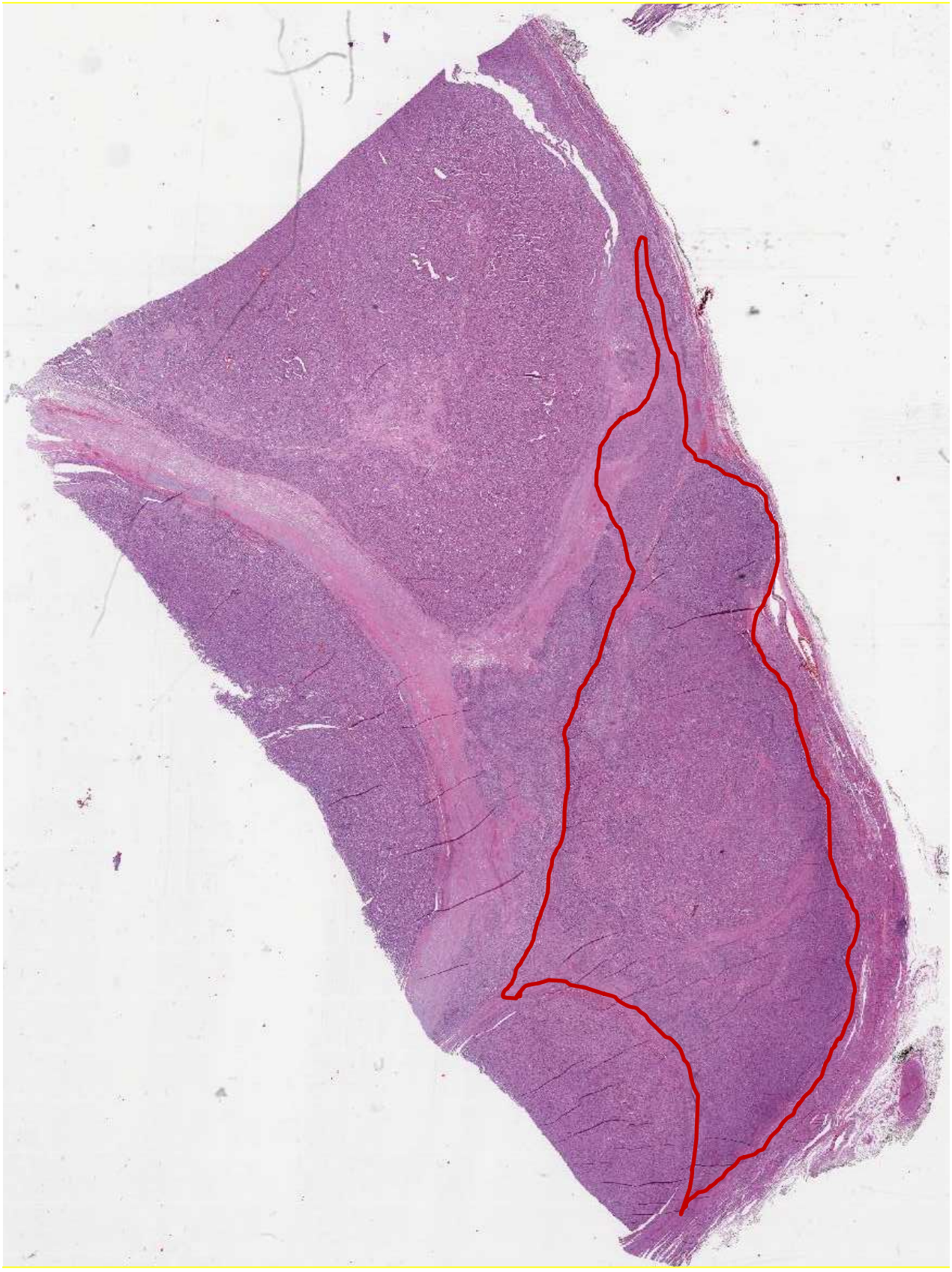

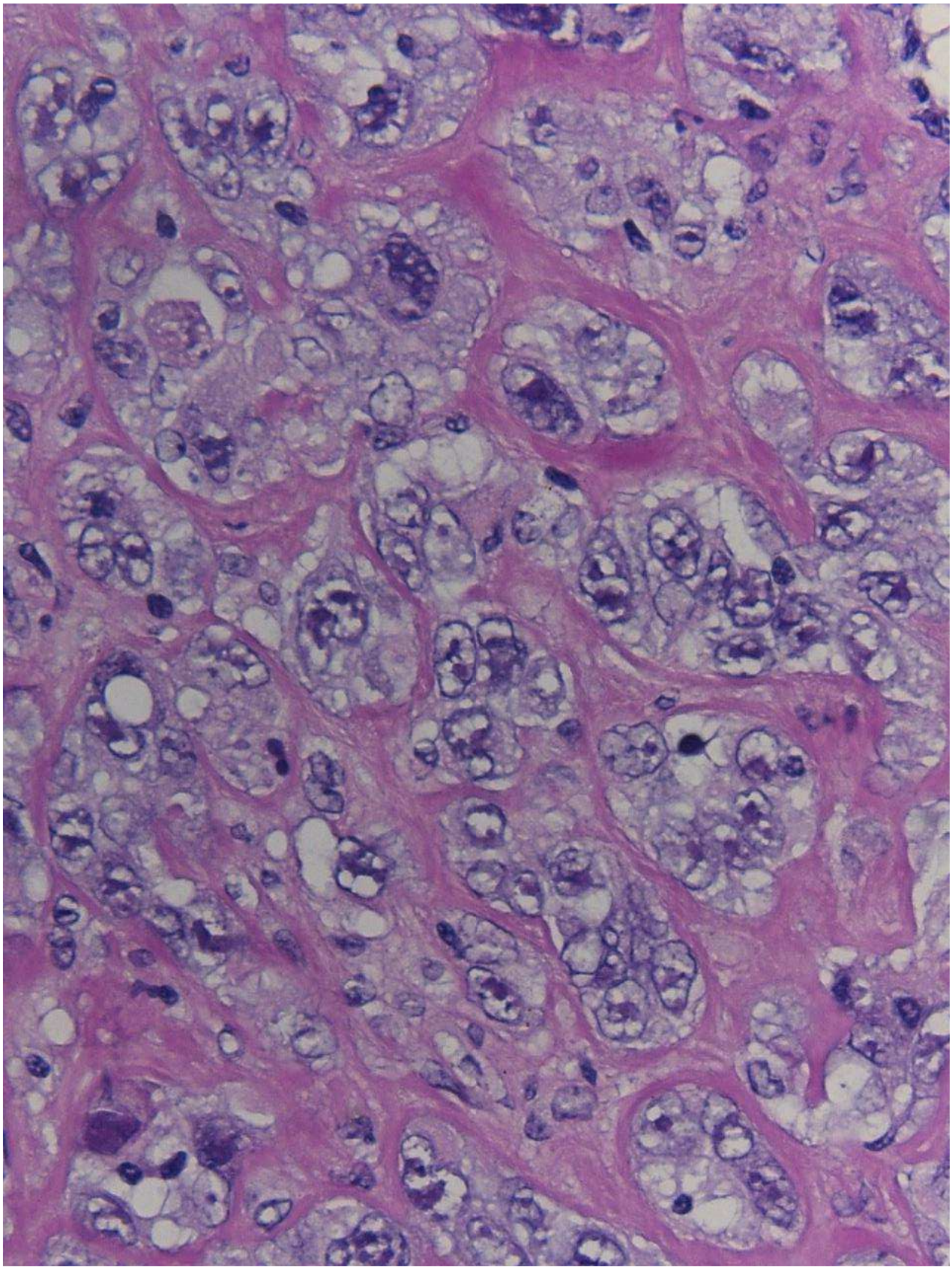

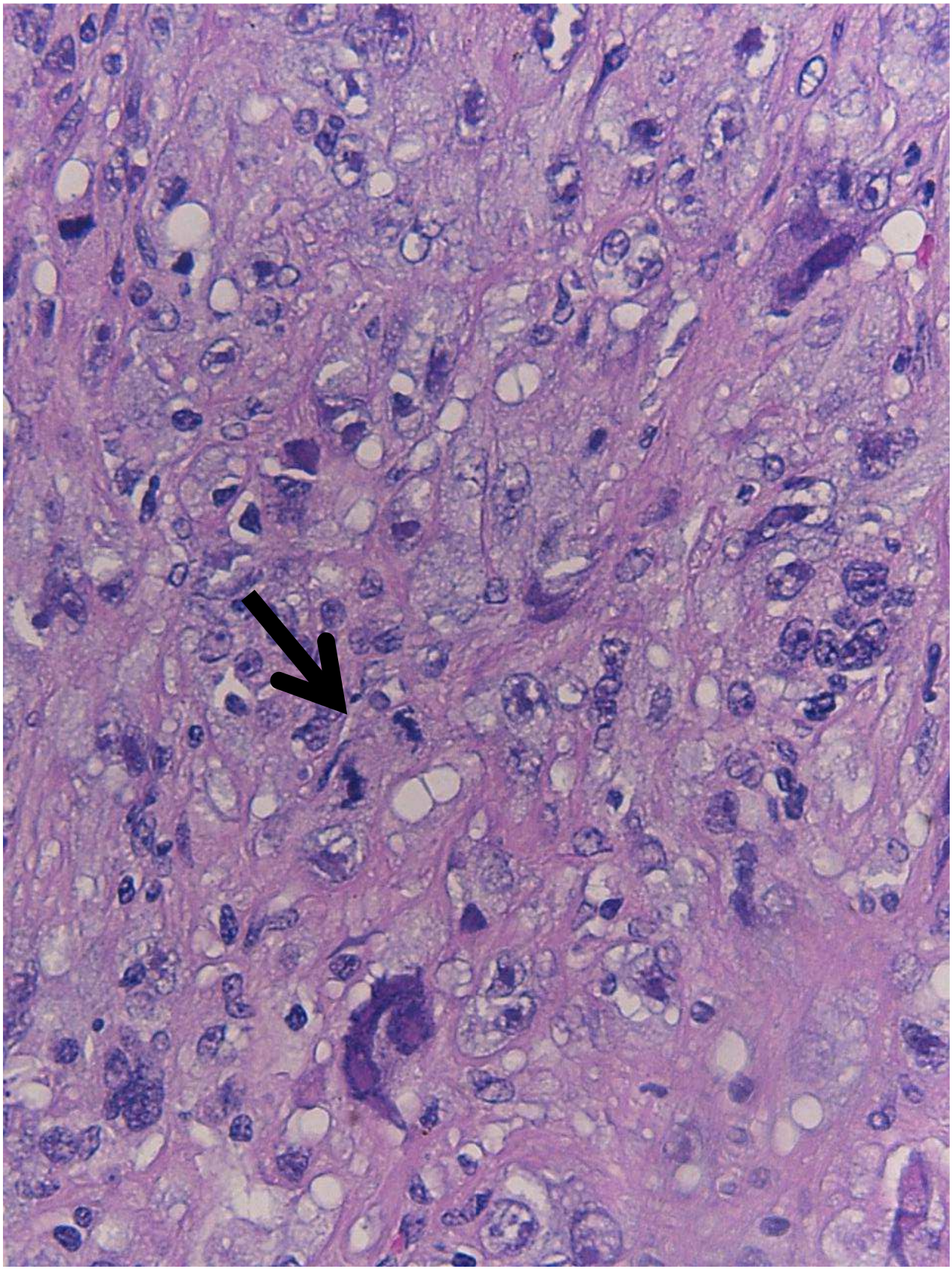

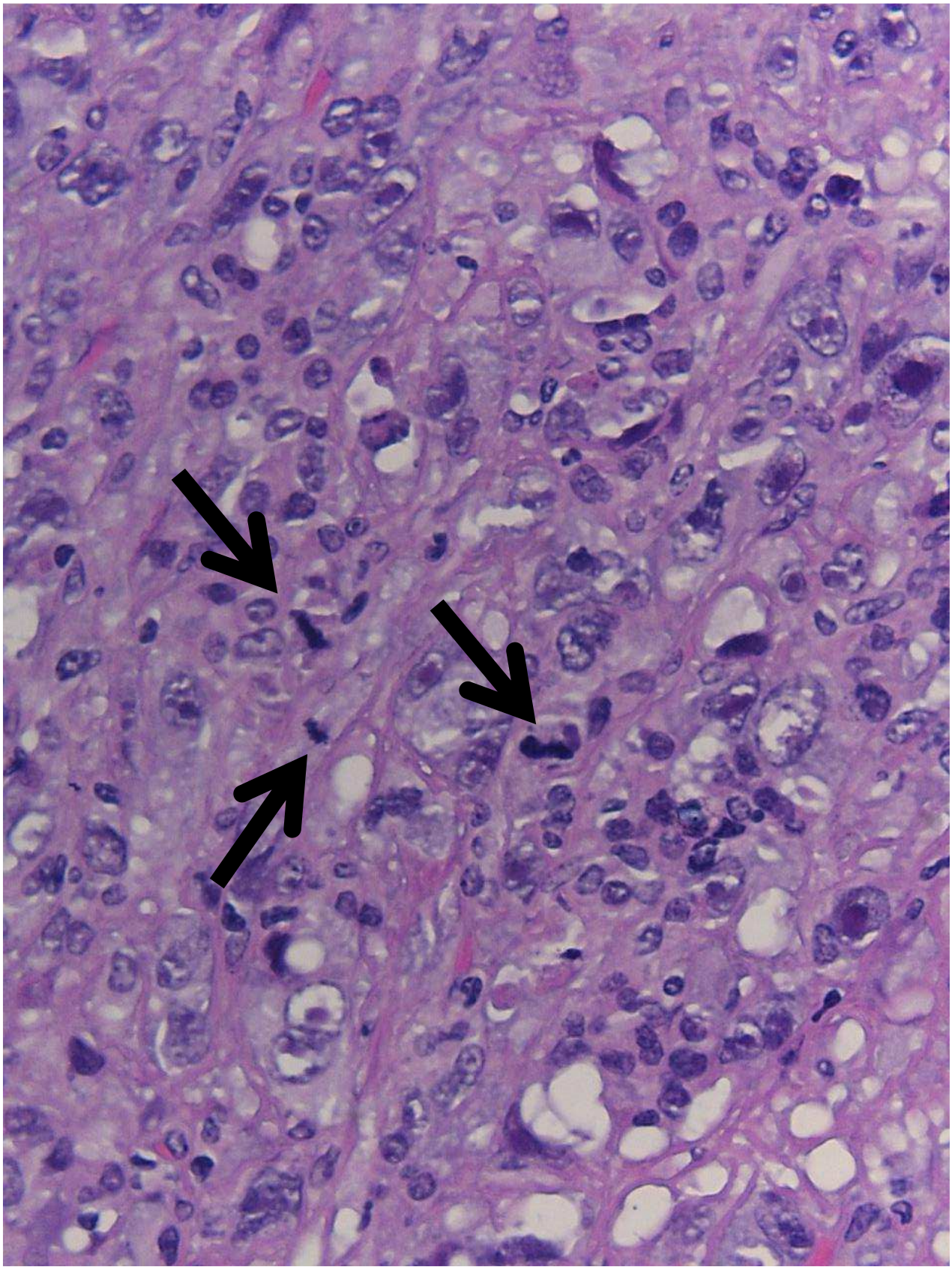

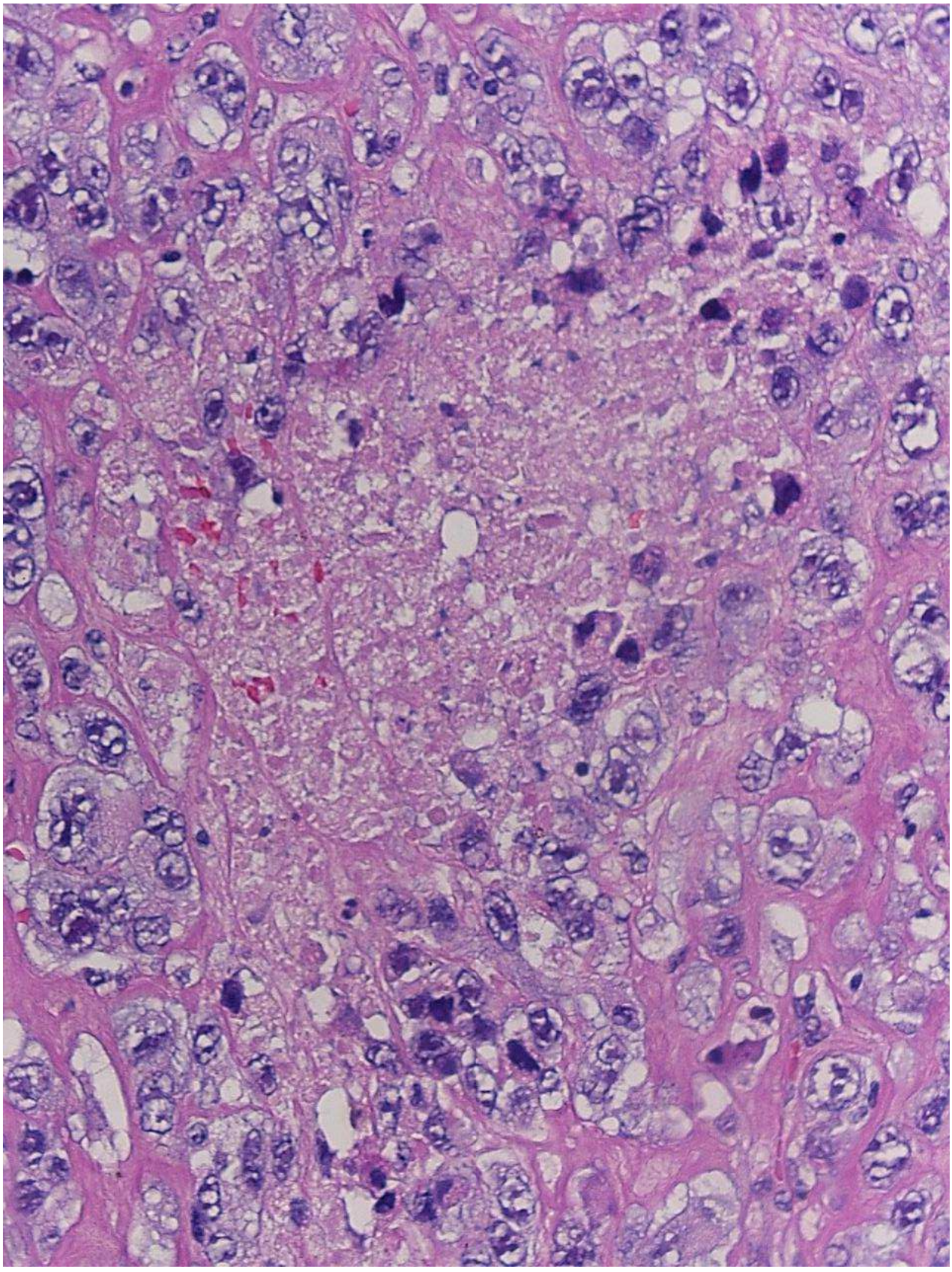

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CASE 5

Undifferentiated carcinoma arising in a widely invasive oncocytic carcinoma with poorly differentiated areas

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CASE 5

Treatement: thyroidectomy followed by radioactive iodine ablation. Oucome: patient died of disease after mutiple recurrences and locoregional RT, 3.5 years after the initial diagnosis

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CASE 5

Points for discussion

- Prognosis of tumors with focal anaplastic carcinoma
- Oncocytic tumors and vascular invasion

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CASE 5

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- Oncocytic tumors and vascular invasion

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Prognosis of tumors with focal anaplastic carcinoma

Anaplastic thyroid carcinomas incidentally found on postoperative pathological examination

Yoshida A, Sugino K, Sugitani I, Miyauchi A

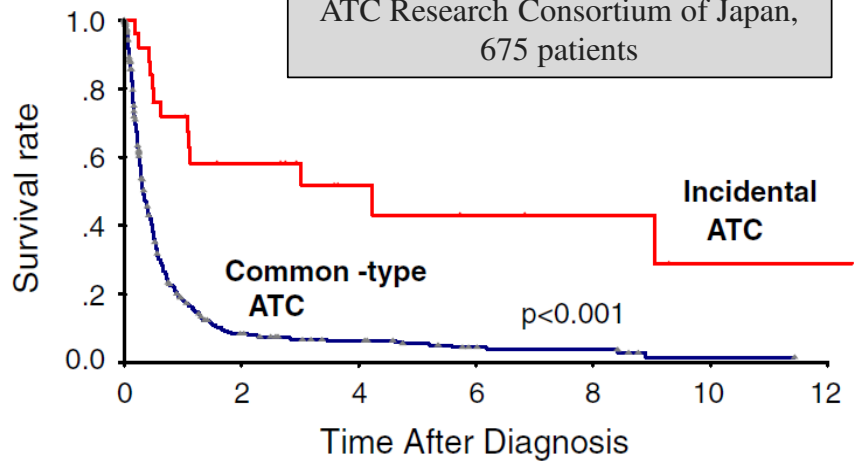
World J Surg. 2014 Sep;38(9):2311-6. doi: 10.1007/s00268-014-2536-9

Table 1 Clinicopathological factors in incidental and common-type anaplastic thyroid carcinoma

	Incidental ATC ($n = 25$)	Common-type ATC ($n = 546$)	p value
Age (years)	66.6 ± 11.3	68.7 ± 11.0	0.734
Male:female ratio	3:22 (1:7.3)	208:338 (1:1.6)	0.010
Tumor size, cm (mean ± SD)	2.1 ± 2.1	6.5 ± 2.6	0.000
Extrathyroid invasion	13/25 (52.0 %)	426/536 (79.5 %)	0.004
Distant metastasis	3/21 (12.5 %)	215/525 (41.0 %)	0.005
Coexisting papillary carcinoma	24/25 (96.0 %)	123/476 (24.9 %)	0.000

ATC anaplastic thyroid carcinoma, *SD* standard deviation

ATC Research Consortium of Japan, 675 patients



	Incidental ATC (n=25)	Common-type ATC (n=546)
Disease-related death	12 (48.0%)	478 (84.9%)
1-year survival rate	71.8%	18.6%
2-year survival rate	58.3%	8.5%

Incidental anaplastic carcinoma is more common in women, has smaller size, is more often confined to the thyroid, has fewer distant metastases, typically arises in PTC, has better prognosis

Prognosis of tumors with focal anaplastic carcinoma

Changes of Clinicopathologic Characteristics and Survival Outcomes of Anaplastic and Poorly Differentiated Thyroid Carcinoma

Lee DY, Won JK, Lee SH, Park DJ, Jung KC, Sung MW, Wu HG, Kim KH, Park YJ, Hah JH

Thyroid. 2016 Mar;26(3):404-13. doi: 10.1089/thy.2015.0316

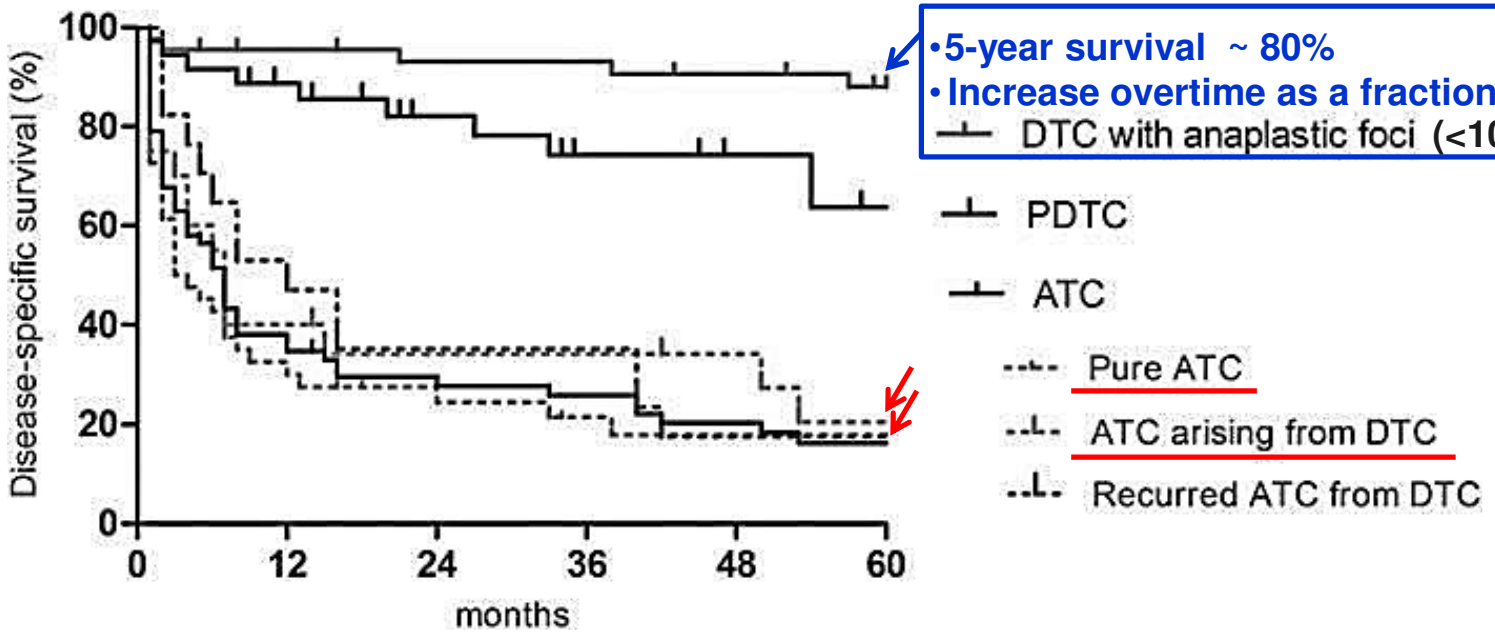


FIG. 1. Comparison of disease specific survival according to diagnosis. DTC, differentiated thyroid cancer; PDTC, poorly differentiated thyroid cancer; ATC, anaplastic thyroid cancer

- **Anaplastic thyroid cancer T category in the AJCC 8th edition follows the same definitions used for differentiated thyroid carcinoma (not anymore T4 by definition)**
- **The proportion (%) of anaplastic carcinoma incidentally found in differentiated thyroid tumors must be indicated in the pathology report**

Prognosis of tumors with focal anaplastic carcinoma

Dissecting Anaplastic Thyroid Carcinoma: A Comprehensive Clinical, Histologic, Immunophenotypic, and Molecular Study of 360 Cases

Xu B, Fuchs T, Dogan S, Landa I, Katabi N, Fagin JA, Tuttle RM, Sherman E, Gill AJ, Ghossein R

Thyroid. 2020 Oct;30(10):1505-1517

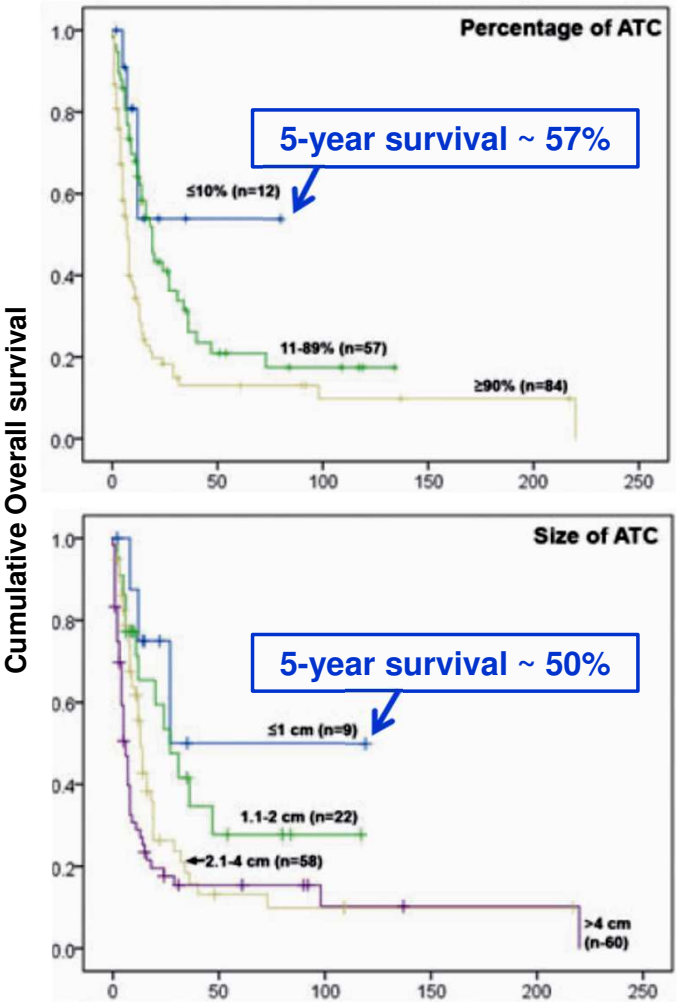


TABLE 4. CLINICAL AND PATHOLOGIC PROGNOSTIC PARAMETERS IN ANAPLASTIC THYROID CARCINOMA

	Univariate			*Multivariate*		
	HR	*CI*	p	*HR*	*CI*	p
All patients						
Age at ATC diagnosis	1.871	1.453–2.410	**<0.001**	1.671	1.276–2.188	**<0.001**
Resectability	0.680	0.529–0.875	**0.003**	0.510	0.389–0.670	**<0.001**
Chemotherapy	0.587	0.453–0.761	**<0.001**	0.697	0.493–0.985	**0.041**
Radiation therapy	0.650	0.497–0.850	**0.002**	0.863	0.607–1.228	0.863
Primary resection						
Encapsulation	0.312	0.115–0.851	**0.023**	0.699	0.238–2.052	0.514
Percentage of ATC	1.847	1.321–2.583	**<0.001**	0.768	0.238–2.476	0.659
Size of ATC	1.596	1.255–2.031	**<0.001**	1.451	0.620–3.398	0.391
Margin status	2.359	1.398–3.982	**0.001**	1.391	0.516–3.748	0.514
Gross residual disease	2.718	1.515–4.874	**0.001**	2.391	1.141–5.010	**0.021**
Gross ETE	4.678	1.133–19.319	**0.033**	2.109	0.479–9.286	0.324

Bold values indicate significant *p*-values.
CI, 95% confidence interval; HR, hazard ratio.

Overall survival (entire cohort)

On **univariate analysis**, age, resectability, chemotherapy, radiotherapy, margin status, encapsulation, gross residual disease, gross extrathyroidal extension, **percentage, and size of ATC in the primary tumor** predicted OS ($p < 0.05$). Age, resectability, chemotherapy, and gross residual disease were independent prognostic factors in the entire cohort, while gross residual disease was the only independent predictor of OS in patients who had resection of their tumor

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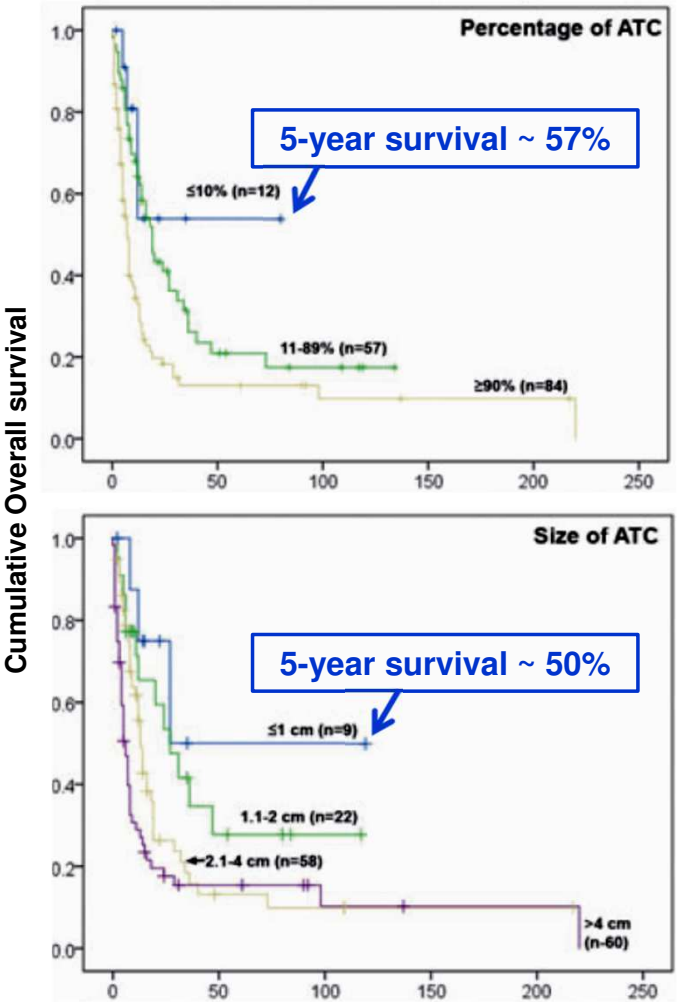

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Factors associated with survival in Anaplastic thyroid carcinoma ("common" type)

Prognostic factors	Univariate analysis				Multivariate analysis		
	Median survival (days)	6-Month survival rate (%)	1-Year survival rate (%)	*p*	HR	95% CI	P
Pretreatment factors							
Age (years)							
≥70 ($n = 284$)	94	33	17	**0.015**	1.28	1.04–1.58	**0.020**
<70 ($n = 263$)	118	40	21				
Sex							
Male ($n = 208$)	106	35	18	0.53	1.09	0.88–1.36	0.42
Female ($n = 339$)	112	37	19				
Acute symptoms							
Absent ($n = 218$)	176	52	27	**<0.0001**			
Present ($n = 325$)	85	26	13		1.34	1.06–1.69	**0.0014**
Leukocytosis							
Absent ($n = 326$)	144	44	22	**<0.0001**			
Present ($n = 181$)	62	19	11		1.48	1.18–1.87	**0.0008**
Hypercalcemia							
Absent ($n = 505$)	110	37	19	0.13			
Present ($n = 26$)	94	21	4		1.29	0.81–2.05	0.29
Tumor size							
>5 cm ($n = 348$)	103	30	14	**0.0001**	1.42	1.12–1.81	**0.0037**
≤5 cm ($n = 174$)	133	49	26				
T status							
4a ($n = 109$)	171	49	30	**0.0005**			
4b ($n = 429$)	104	34	16		1.47	1.11–1.96	**0.0079**
N status							
0 ($n = 161$)	149	46	24	**0.0031**			
1 ($n = 319$)	98	34	17		1.17	0.93–1.47	0.19
M status							
0 ($n = 312$)	157	48	25	**<0.0001**			
1 ($n = 223$)	74	21	10		1.83	1.48–2.27	**<0.0001**

Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients

Sugitani I, Miyauchi A, Sugino K, Okamoto T, Yoshida A, Suzuki S

World J Surg. 2012 Jun;36(6):1247-54. doi: 10.1007/s00268-012-1437-z

Favorable prognostic factors:

- Younger age
- Tumor limited to the thyroid

Unfavorable prognostic factors:

- Acute symptoms at presentation (sudden appearance of dysphonia, dysphagia, dyspnea, and rapid growth of the tumor)
- Leukocytosis (due to the release of leucocyte colony-stimulating factors by the tumor)
- Large tumors
- Distant metastases

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- Large tumors
- Distant metastases

Prolonged survival of anaplastic thyroid carcinoma is associated with resectability, low tumor-infiltrating neutrophils/myeloid-derived suppressor cells, and low peripheral neutrophil-to-lymphocyte ratio

Xu B, Zhang L, Setoodeh R, Mohanty AS, Landa I, Balzer B, Tiedje V, Ganly I, Dogan S, Fagin JA, Ghossein R

Endocrine. 2022 Jun;76(3):612-619. doi: 10.1007/s12020-022-03008-9. Epub 2022 Feb 11. PMID: 35149932

Table 1 Comparison of clinicopathologic features, outcomes, and immune microenvironment between ATC long term survivor (ATC LTS) and ATC control group

	ATC LTS ($n=46$)	ATC control ($n=75$)	P values
Outcome			
Median OS (95% confidence interval), months	120 (86–153)	6 (5–7)	**<0.001**
Median DMFS (95% confidence interval), months	41 (22–59)	1 (0–2)	**<0.001**
Clinicopathologic features			
Female: male ratio	26:20 (1.3:1)	40:35 (1.1:1)	0.439
Age	62 (29–85)	67 (33–88)	**0.045**
Specimen type			
Cytology/biopsy/incision/excision	5/46 (11%)	34/75 (45%)	**0.043**
Resection	41/46 (89%)	41/75 (55%)	
Predominant cytologic features of ATC			
Epithelioid	14/46 (30%)	22/75 (29%)	0.804
Spindle	13/46 (28%)	18/75 (24%)	
Squamous	6/46 (13%)	15/75 (20%)	
Pleomorphic	7/46 (15%)	11/75 (15%)	
Rhabdoid	3/46 (7%)	7/75 (9%)	
Osteoclast giant cell-rich	3/46 (7%)	2/75 (3%)	
Mitotic index, per 10 high power fields, median (range)	8 (1–42)	9 (0–45)	0.934
Necrosis	29/46 (63%)	60/75 (81%)	**0.034**
Atypical mitosis	38/46 (84%)	65/75 (88%)	0.593
Prior/co-existing DTC	28/46 (61%)	36/75 (48%)	
FTC	0	2	
HCC	3	2	
PDTC	4	8	0.077
PDTC, HCC	3	0	
PDTC, PTC	5	6	
PTC	13	18	
Distant metastasis at presentation	1/43 (2%)	42/75 (56%)	**<0.001**
Chemotherapy	29/41 (71%)	49/74 (66%)	0.151
Radiation therapy	36/40 (90%)	64/74 (86%)	0.138
Kinase inhibitors	7/40 (18%)	26/74 (35%)	0.054
Immunotherapy	1/40 (3%)	14/74 (19%)	**0.018**
Resection for thyroid ATC	**$n=37$ (80%)**	**$n=32$ (43%)**	**<0.001**
Size of the primary tumor (cm), median (range)[a]	4.3 (2.2–11.2)	6.0 (3.0–11.2)	**0.003**
Percentage of ATC in the primary tumor, median (range)	60% (2–100%)	100% (10–100%)	**0.007**
Maximal dimension of ATC (cm), median (range)	2.2 (0.4–8.5)	5.4 (0.9–9.5)	**<0.001**
Encapsulation: Encapsulated	8/37 (22%)	0/32 (0%)	**0.006**
Encapsulation: Infiltrative	29/37 (78%)	32/32 (100%)	
Vascular invasion	28/36 (78%)	28/31 (90%)	**0.202**
Pathologic evidence of extrathyroidal extension	23/31 (74%)	32/32 (100%)	**0.002**
Positive margin	19/36 (53%)	29/31 (94%)	**<0.001**
Nodal metastasis	11/36 (31%)	19/30 (63%)	**0.013**
Gross residual disease	2/16 (13%)	14/27 (52%)	**0.021**
Gross extrathyroidal extension	11/16 (69%)	24/25 (96%)	**0.026**
Peripheral blood at the time of ATC diagnosis	**$n=38$**	**$n=75$**	
Absolute neutrophil count (K/mcL), mean ± SEM	4.2 ± 0.5	8.3 ± 0.8	**<0.001**
Neutrophil-to-lymphocyte ratio, mean ± SEM	2.9 ± 0.5	6.9 ± 0.8	**<0.001**
Peripheral blood at the time of ATC diagnosis in patients without DM at presentation	$n=35$	$n=33$	
Absolute neutrophil count (K/mcL), mean ± SEM	4.3 ± 0.5	8.0 ± 0.7	**<0.001**
Neutrophil-to-lymphocyte ratio, mean ± SEM	2.9 ± 0.5	5.5 ± 0.9	**0.006**
Tumor-associated immune microenvironment	**$n=13$**	**$n=12$**	
CD15-positive neutrophils, mean ± SEM	55 ± 15	155 ± 34	**0.012**
PD-L1 Positivity	11 (85%)	8 (67%)	0.378
PD-L1 CPS score	49 ± 11	42 ± 11	0.656
PRAME	4 (31%)	1 (8%)	0.322
MHC-I on tumor cells			
<25%	3 (23%)	0 (0%)	0.200
25–75%	3 (23%)	3 (25%)	
>75%	7 (54%)	9 (75%)	
CD68-positive macrophages, per high power field, mean ± SEM	293 ± 47	190 ± 33	0.090
CD163-positive macrophages, mean ± SEM	312 ± 38	273 ± 39	0.476
CD4-positive helper T cells, mean ± SEM	79 ± 22	95 ± 16	0.551
CD8-positive cytotoxic T cells, mean ± SEM	163 ± 39	190 ± 27	0.573
PD-1-positive immune cells, mean ± SEM	70 ± 26	60 ± 14	0.745
FOXP3-positive regulatory T cells, mean ± SEM	54 ± 10	67 ± 18	0.524

P values were obtained using log-rank test for survival, Fisher's exact test or Chi-square test for categorical variables, and two-tailed Student's t test for continuous variable. Bold p values: significant p values. OS: overall survival, DMFS: distant metastasis-free survival, SEM: standard error of mean, DTC: differentiated thyroid carcinoma, FTC: follicular thyroid carcinoma, HCC: Hurthle cell carcinoma, PDTC: poorly differentiated thyroid carcinoma, CPS: combined positive score

[a]Refer to size of the entire tumor (ATC and DTC)

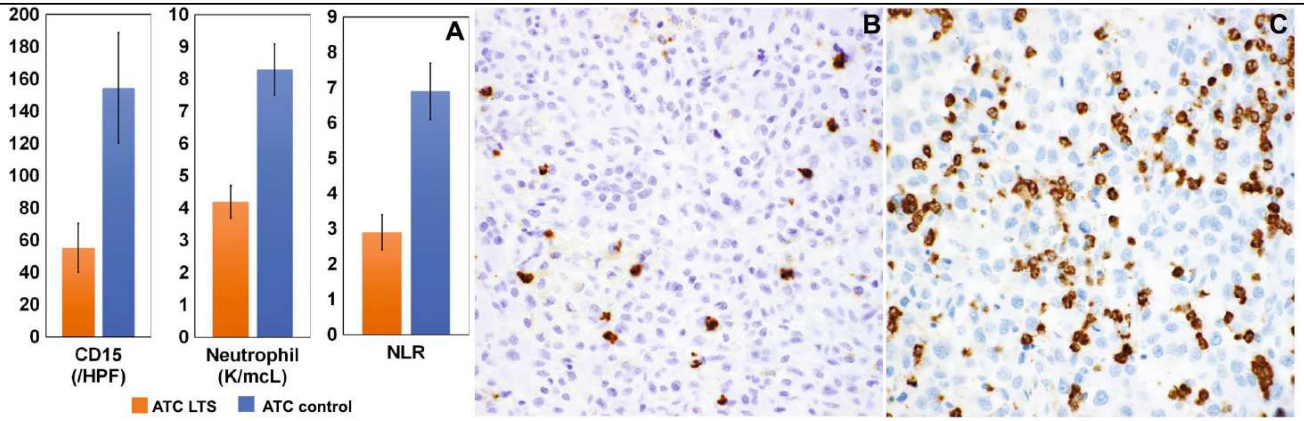


Fig. 1 ATC long-term survivor is characterized with low CD15- positive tumor-infiltrating myeloid-derived suppressor cells (MDSC)/neutrophils, low peripheral neutrophil count, and low peripheral neutrophil-to lymphocyte ratio (NLR). **A** The histograms showing the average CD15-MDSC per high power field (HPF), peripheral neutrophil count (K/mcL), and NLR differ significantly between ATC Long term survival and ATC control patients. Error bars represent standard errors of means. CD15 immunohistochemistry in an ATC LTS (**B**) and an ATC control patient (**C**)

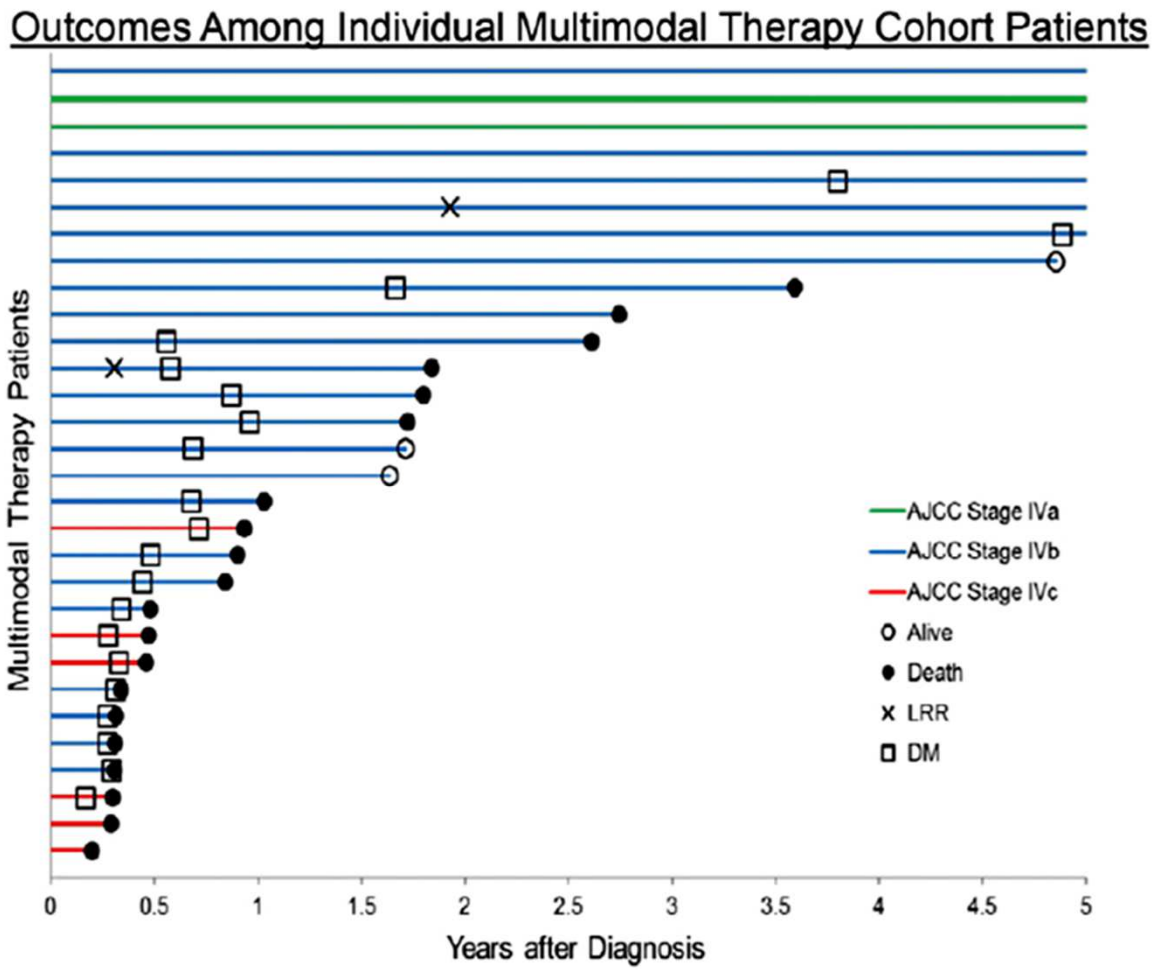
46 ATC long term survivors and 75 ATC control patients: compared with ATC control patients, **ATC long term survivors** are characterized by **1) higher frequency of (primary) resection** as well as clinicopathologic parameters attributed to **resectability**, **2)** peripheral blood with **lower neutrophil counts** and **lower neutrophil-to-lymphocyte ratio** and **3) lower number of tumor-infiltrating neutrophils/myeloid-derived suppressor cells (MDSC) by immunohistochemistry**. Survival benefits of low peripheral neutrophil counts and low NLR persist even when controlling for distant metastasis status at presentation

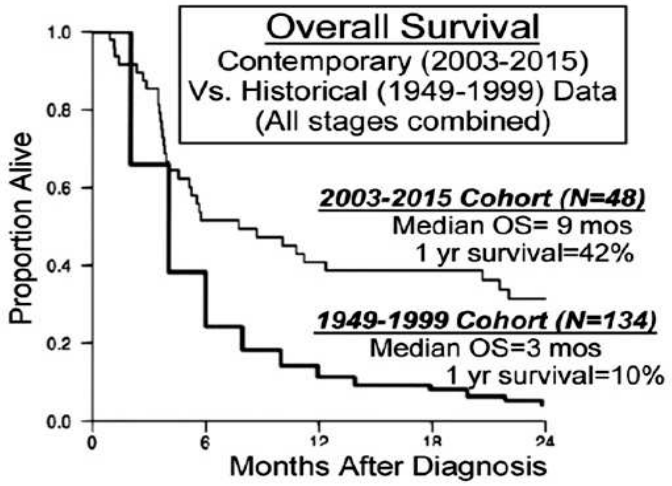
Factors associated with survival in Anaplastic thyroid carcinoma

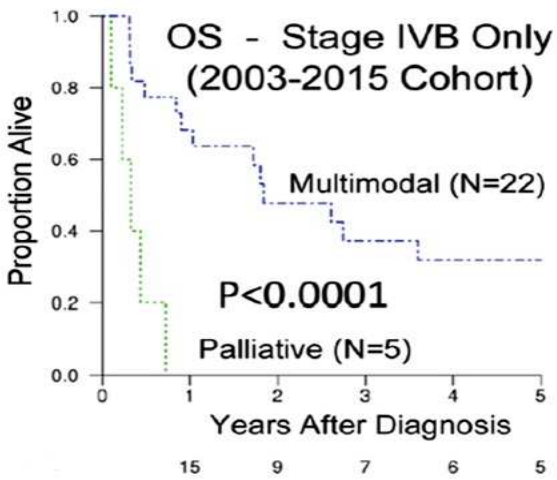
Survival in Response to Multimodal Therapy in Anaplastic Thyroid Cancer

Prasongsook N, Kumar A, Chintakuntlawar AV, Foote RL, Kasperbauer J, Molina J, Garces Y, Ma D, Wittich MAN, Rubin J, Richardson R, Morris J, Hay I, Fatourechi V, McIver B, Ryder M, Thompson G, Grant C, Richards M, Sebo TJ, Rivera M, Suman V, Jenkins SM, Smallridge RC, Bible KC

J Clin Endocrinol Metab. 2017 Dec 1;102(12):4506-4514. doi: 10.1210/jc.2017-01180







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 5

Points for discussion

- Prognosis of tumors with focal anaplastic carcinoma
- Oncocytic tumors and vascular invasion

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Anatomic Pathology, University of Bologna Medical Center
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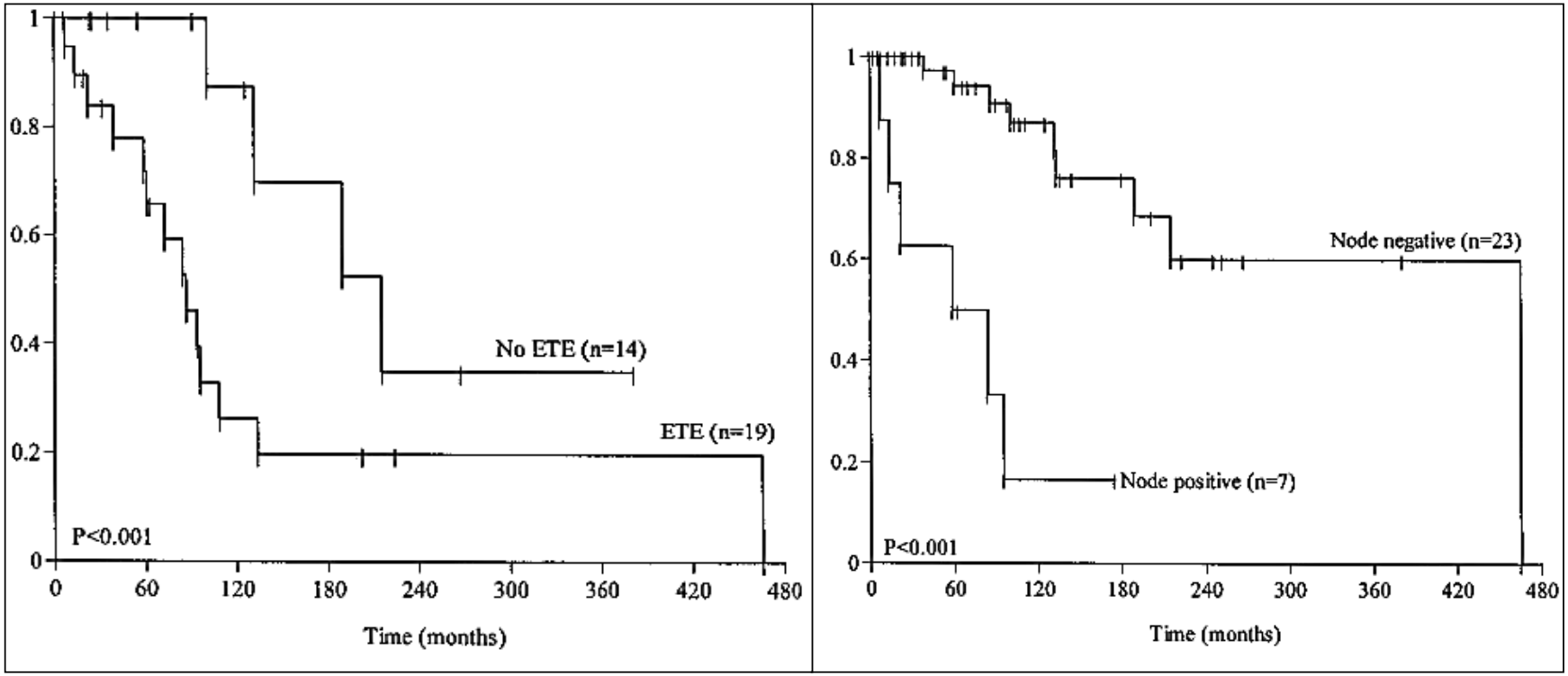
Oncocytic tumors and vascular invasion



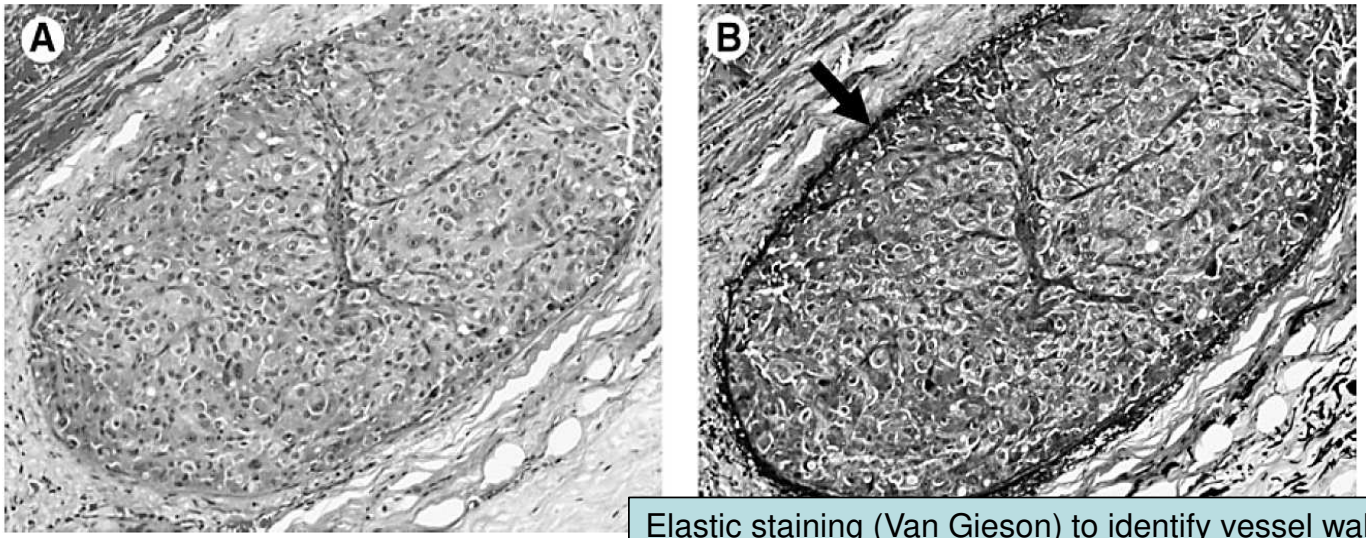
- Age older (>45)
- Male gender
- Large tumor (>4 cm)
- Extra-thyroidal extension*
- Lymph node metastases*

*Independent predictors of disease recurrence and cause specific mortality and after multivaritate analysis

Cfr. Lopez-Penabad et al. Prognostic factors in patients with Hürthle cell neoplasms of the thyroid. Cancer. 2003;97:1186-1194 & Stojadinovic et al. Hürthle cell carcinoma: a critical histopathologic appraisal. JCO. 2001;19:2616-2625

Oncocytic tumors and vascular invasion

But are they true lymph node metastases?



Elastic staining (Van Gieson) to identify vessel wall

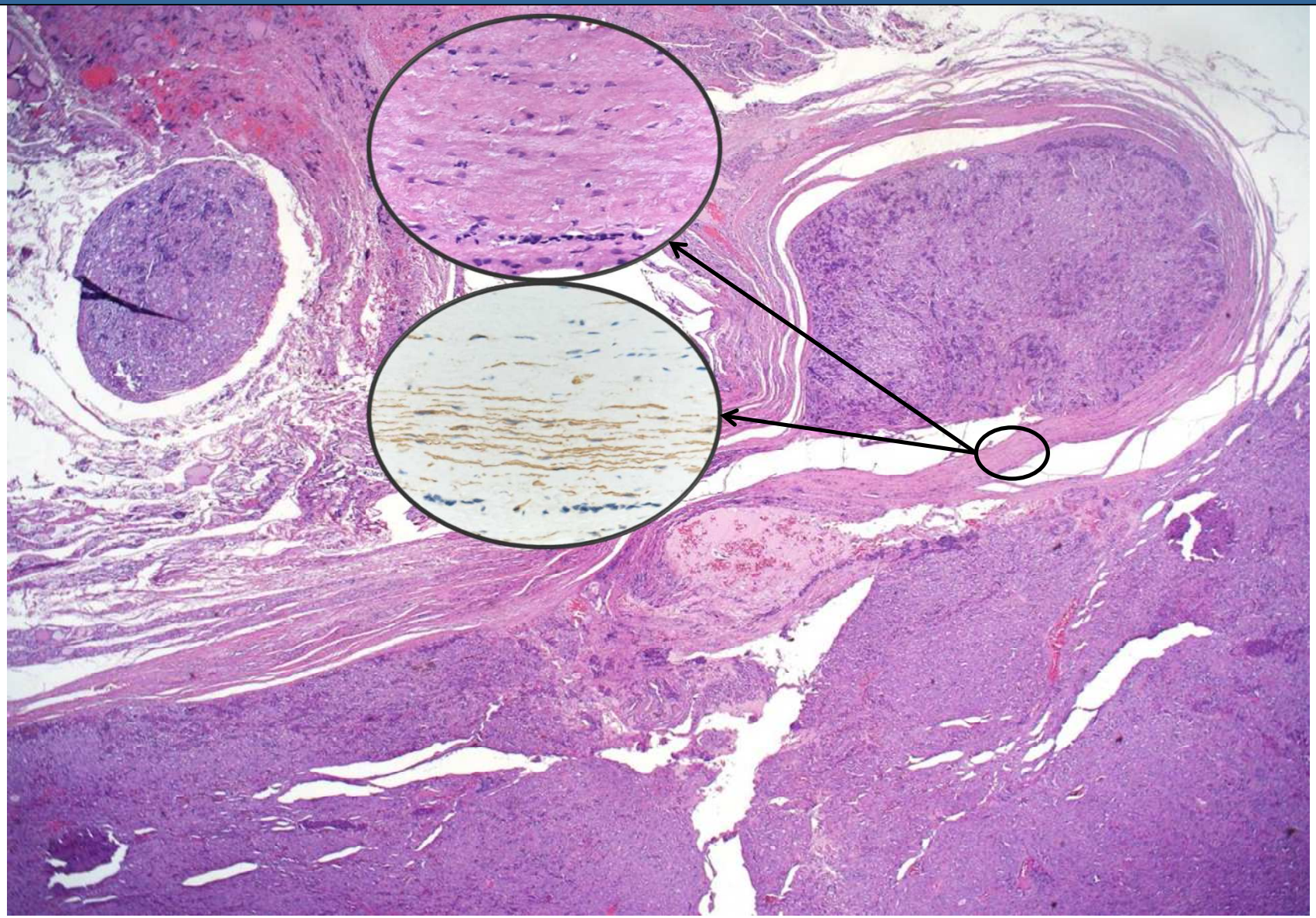
FIG. 2. This nodule of Hürthle cell carcinoma comprises large, polygonal cells with granular, eosinophilic cytoplasm and prominent nucleoli (**A**, hematoxylin and eosin, ×200). This implant is not surrounded by lymphoid tissue; instead, it is surrounded by a compressed layer of elastic fibers (arrow) at the periphery representing residual elastic lamina of a vein (**B**, Verhoeff's Van Gieson, ×200).

24 cases of recurrence in the neck:
in all the dominant mass was a rounded nodule of carcinoma within the soft tissues without LN tissue
→ 13/22 the tumor was in venous vessels
→ True lymph node metastases in 6/24 (25%), in 5/24 the lymph node metastases were <0.5 cm and did not represent the dominant mass, in the 6th case there were 2 metastases (2.9 and 1.0 cm) with larger dominant soft-tissue implants

- "**Relative infrequency of true lymph node metastases** runs counter to the notion that lymph node metastases are common in HCC"
- "**Patients with HCC may not always require formal compartmental lymph node dissections**, and in cases where there is clinically apparent loco-regional spread of disease, wide excision of the nodules alone may provide local control similar to a compartmental lymphadenectomy"

Cfr. Bishop JA, Wu G, Tufano RP, Westra WH. Histological patterns of locoregional recurrence in Hürthle cell carcinoma of the thyroid gland. Thyroid. 2012;22:690-694

Oncocytic tumors and vascular invasion



Oncocytic tumors and vascular invasion

Pitfalls in thyroid tumour pathology

Rosai J, Kuhn E, Carcangiu ML

Histopathology. 2006 Aug;49(2):107-20

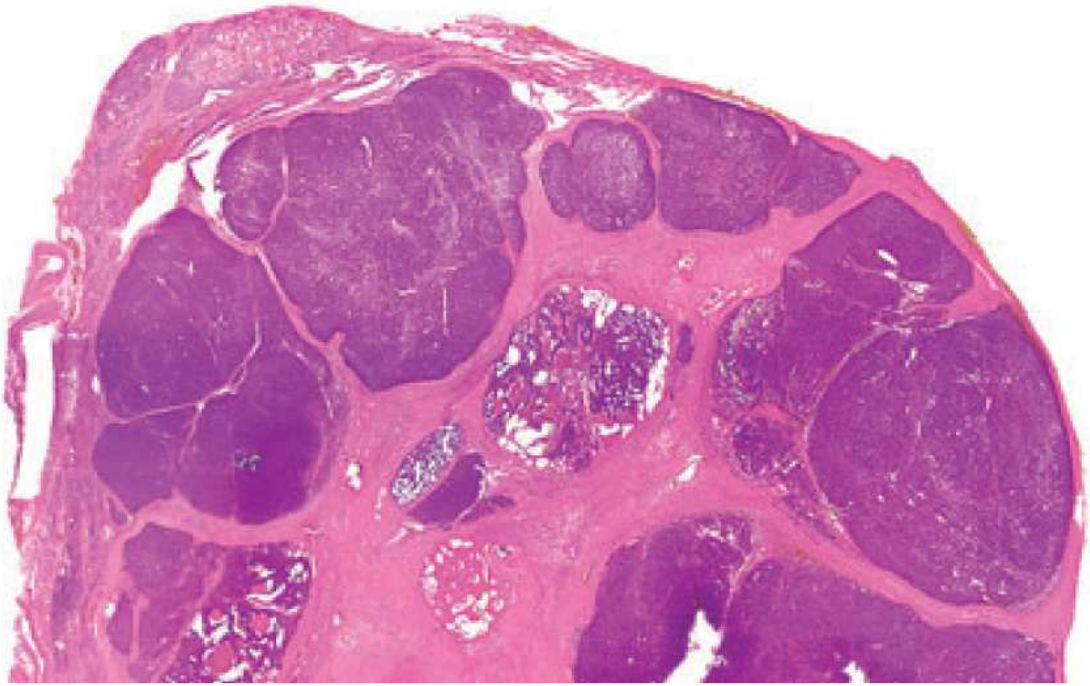


Figure 16. Multinodular pattern of invasion of Hurthle cell carcinoma simulating the pattern of growth of nodular hyperplasia.

Multinodular pattern of invasion in oncocytic carcinoma simulating nodular hyperplasia

- 'Neoplastic look' of the nodules that have solid and/or trabecular rather than follicular growth
- Conspicuous fibrous bands around and between the nodules
- Smaller nodules representing the extension of a main, centrally located tumor mass