Seminar of Young Pathologists
Litomysl, Czech Republic
April 12-13, 2024

Poorly differentiated and anaplastic thyroid carcinomas

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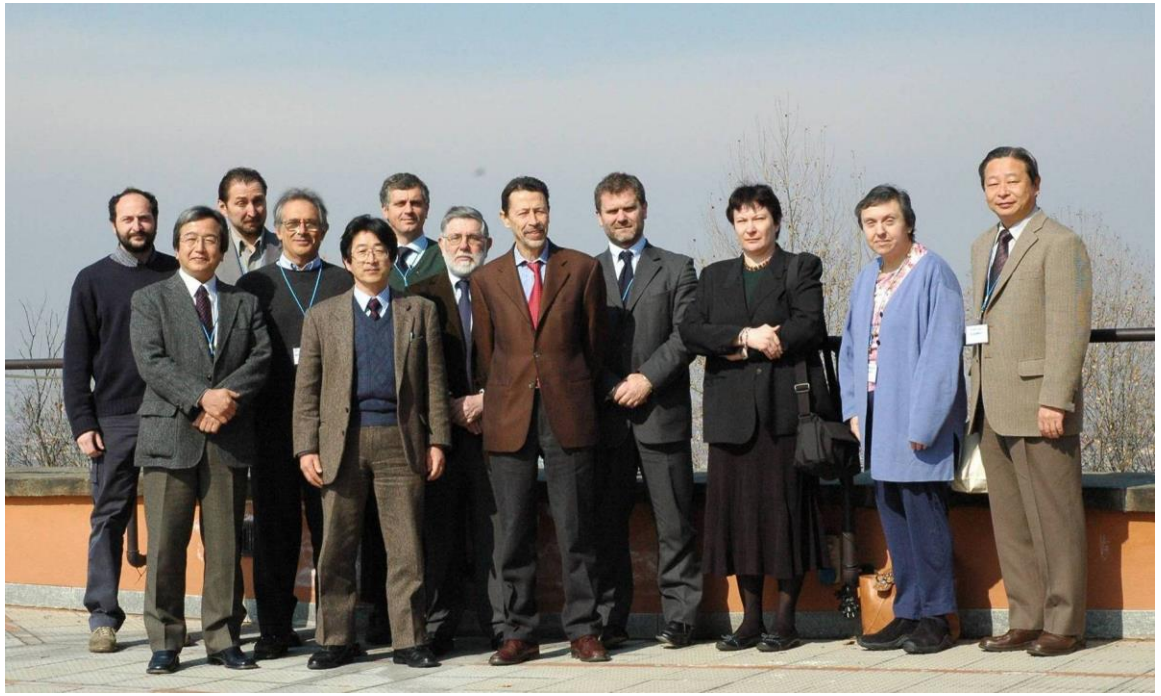
Multi-continental study on poorly differentiated thyroid carcinoma (2006)



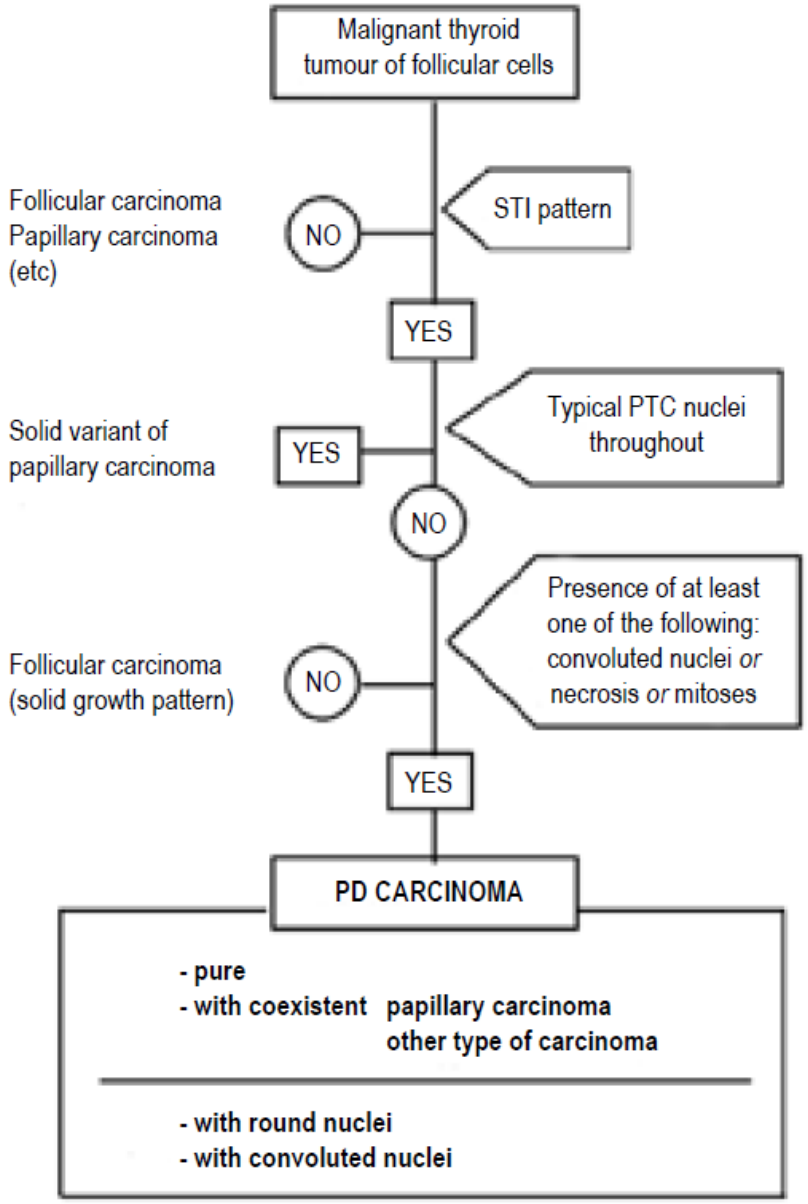
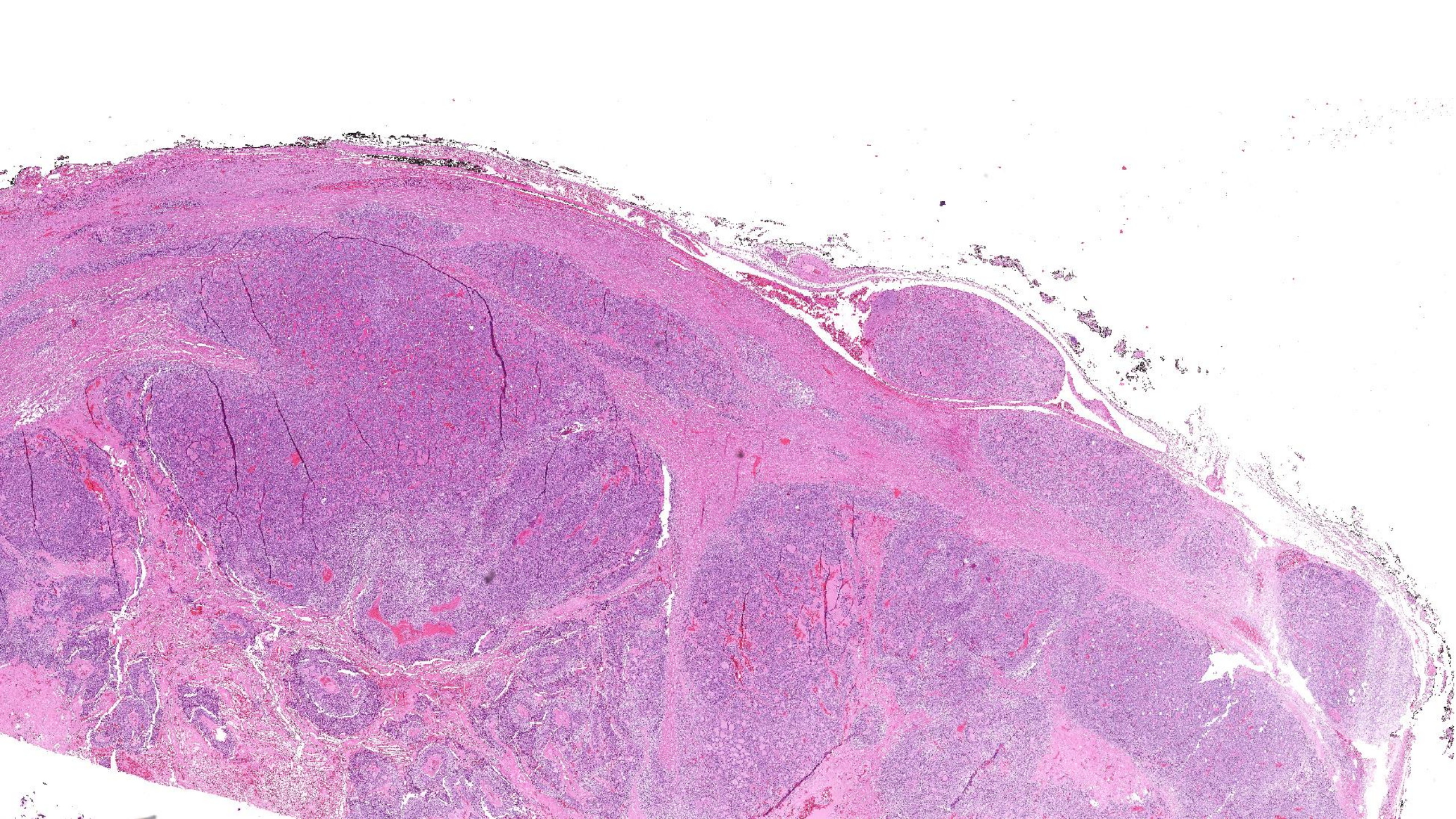
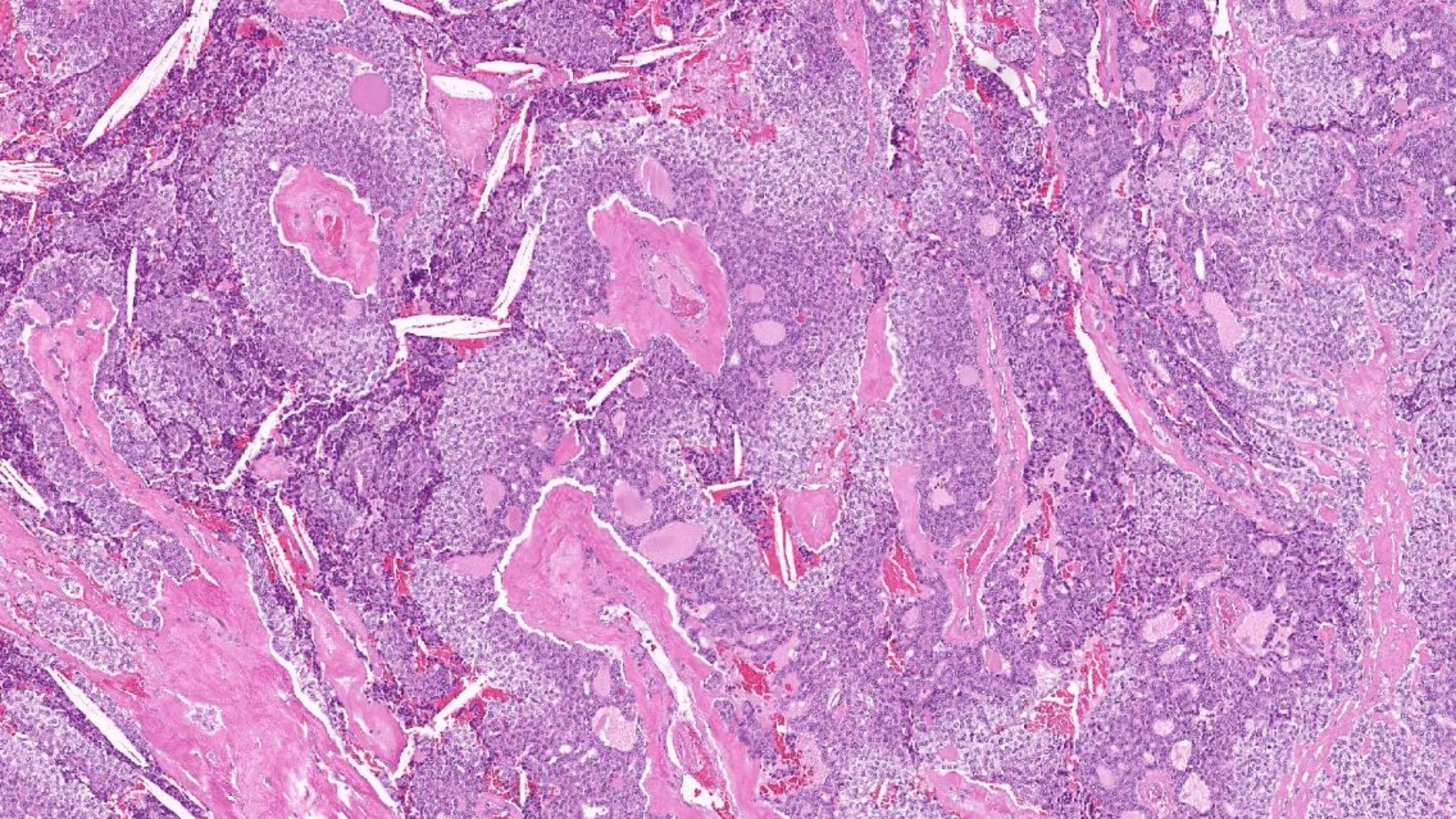
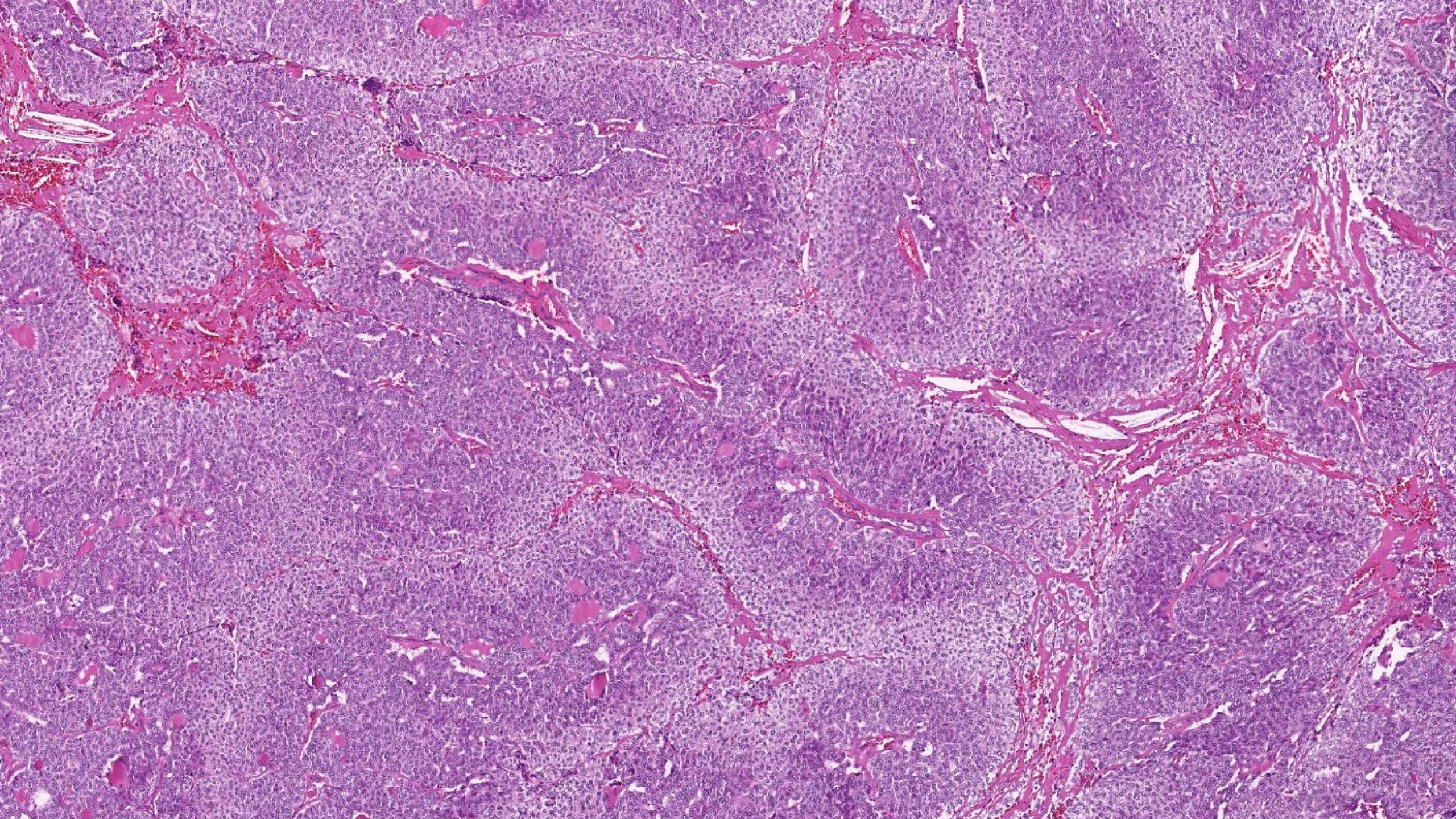


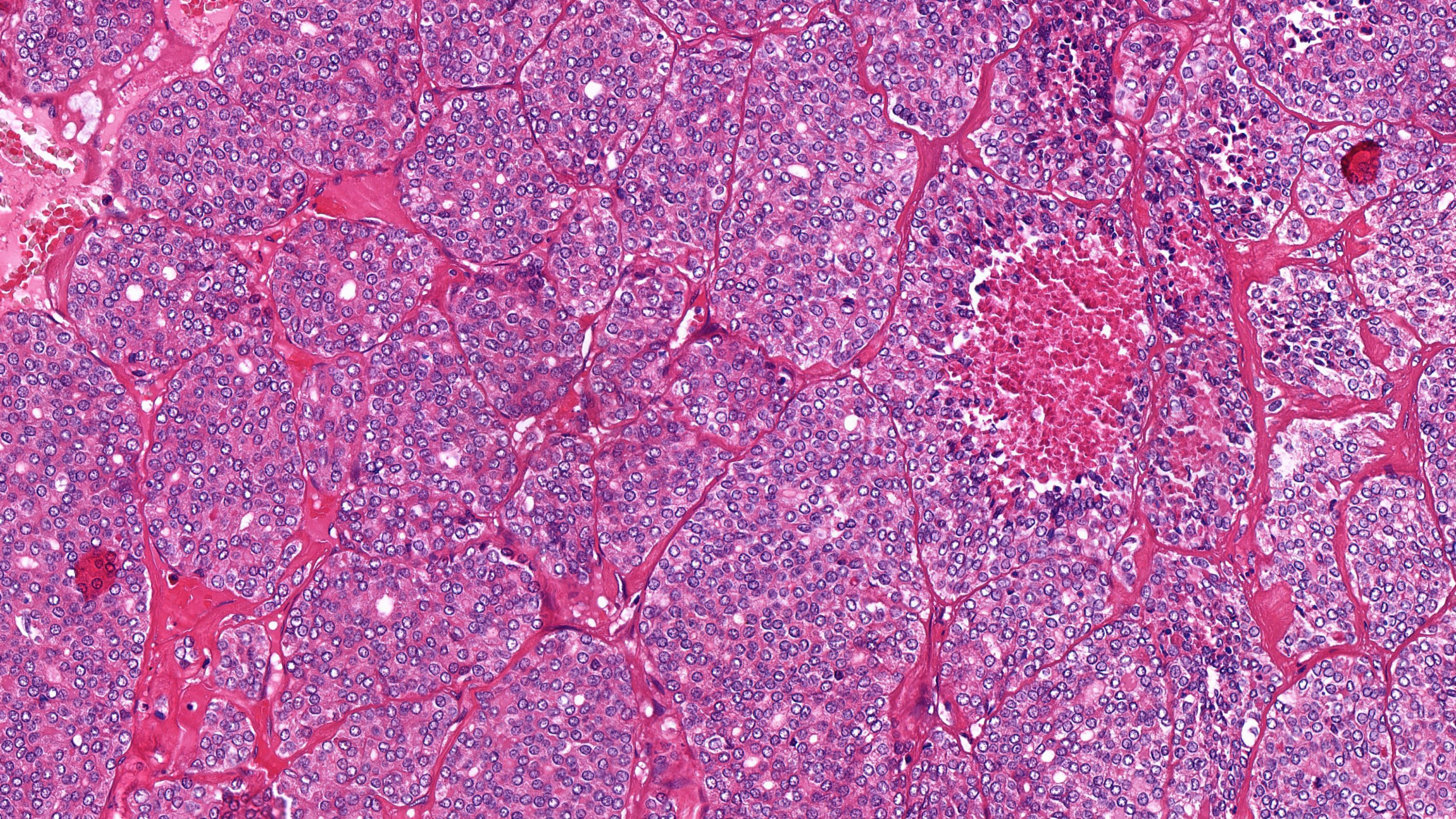
Fig. 4537 Algorithm for the diagnosis of poorly differentiated (PD) thyroid carcinoma using the Turin consensus criteria.

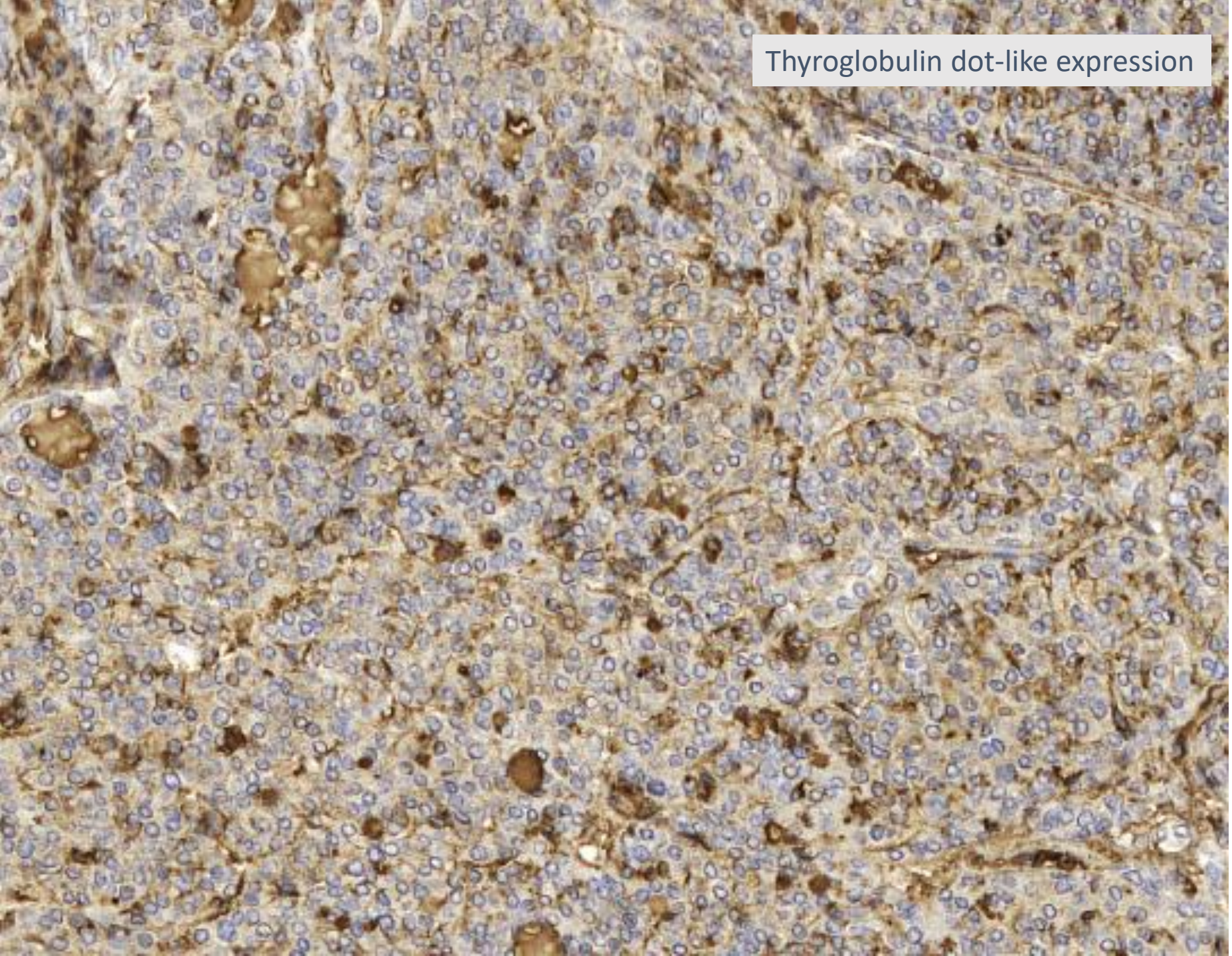
WHO book, 2017



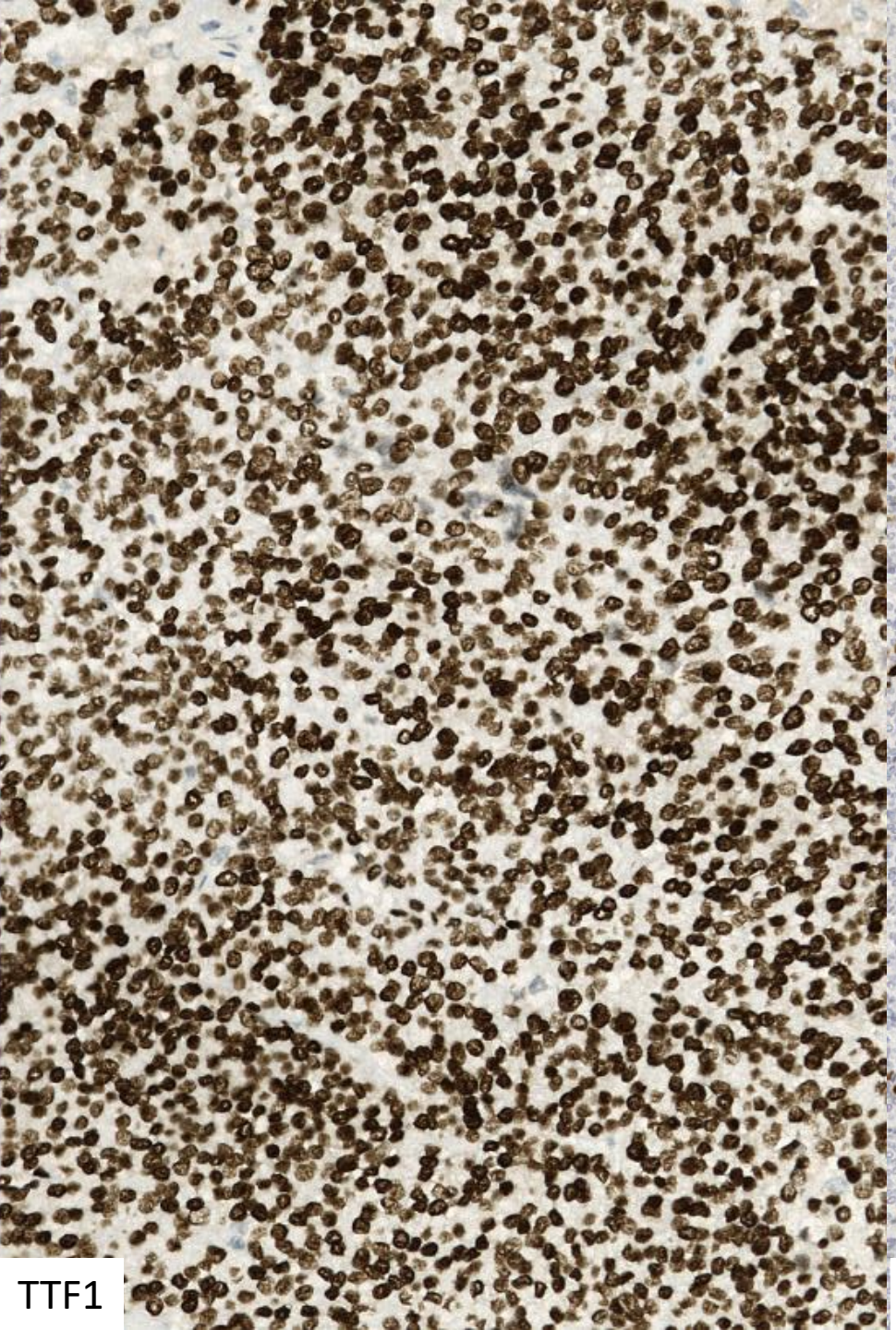




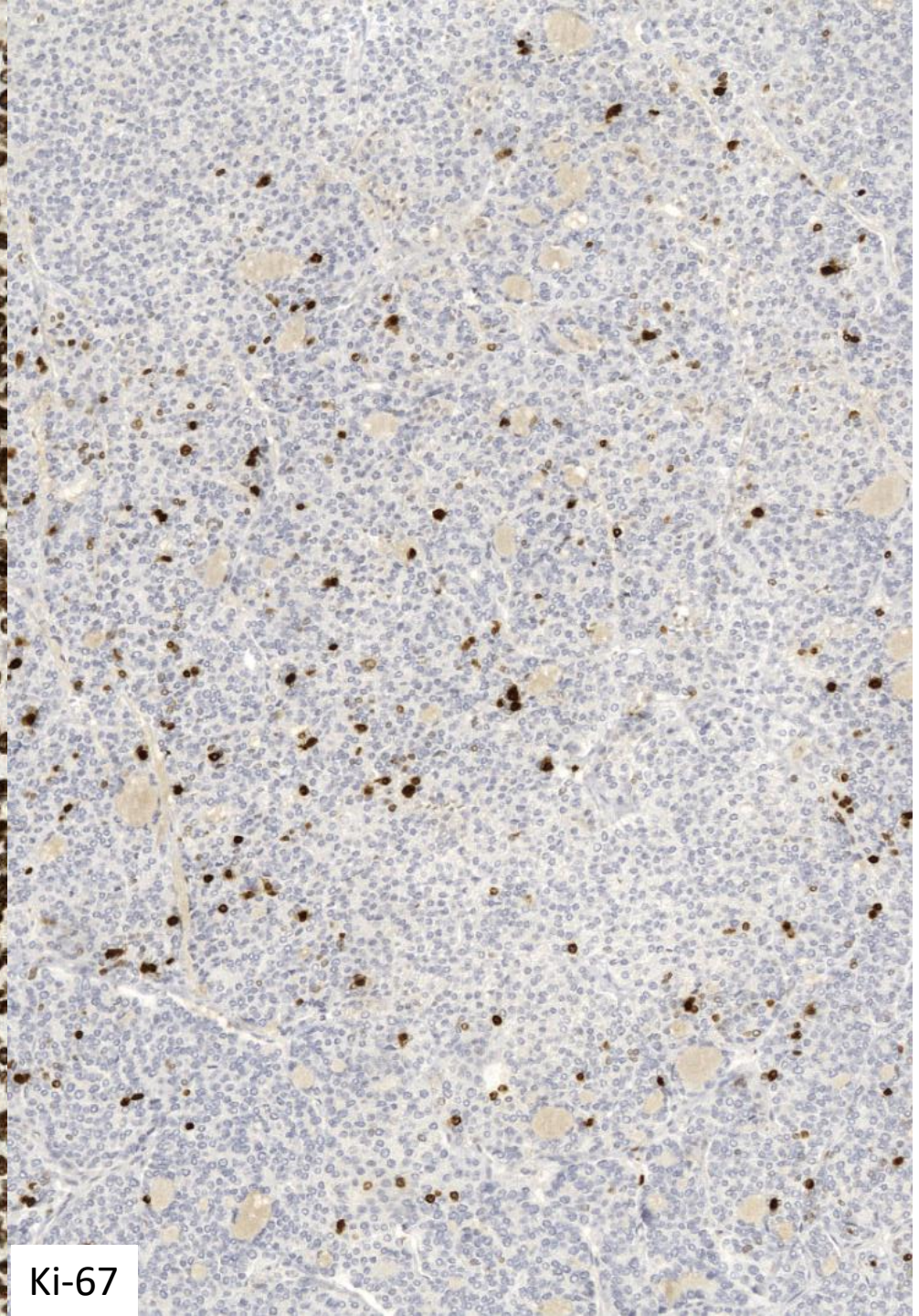




Determinant for the differential diagnosis with anaplastic carcinoma

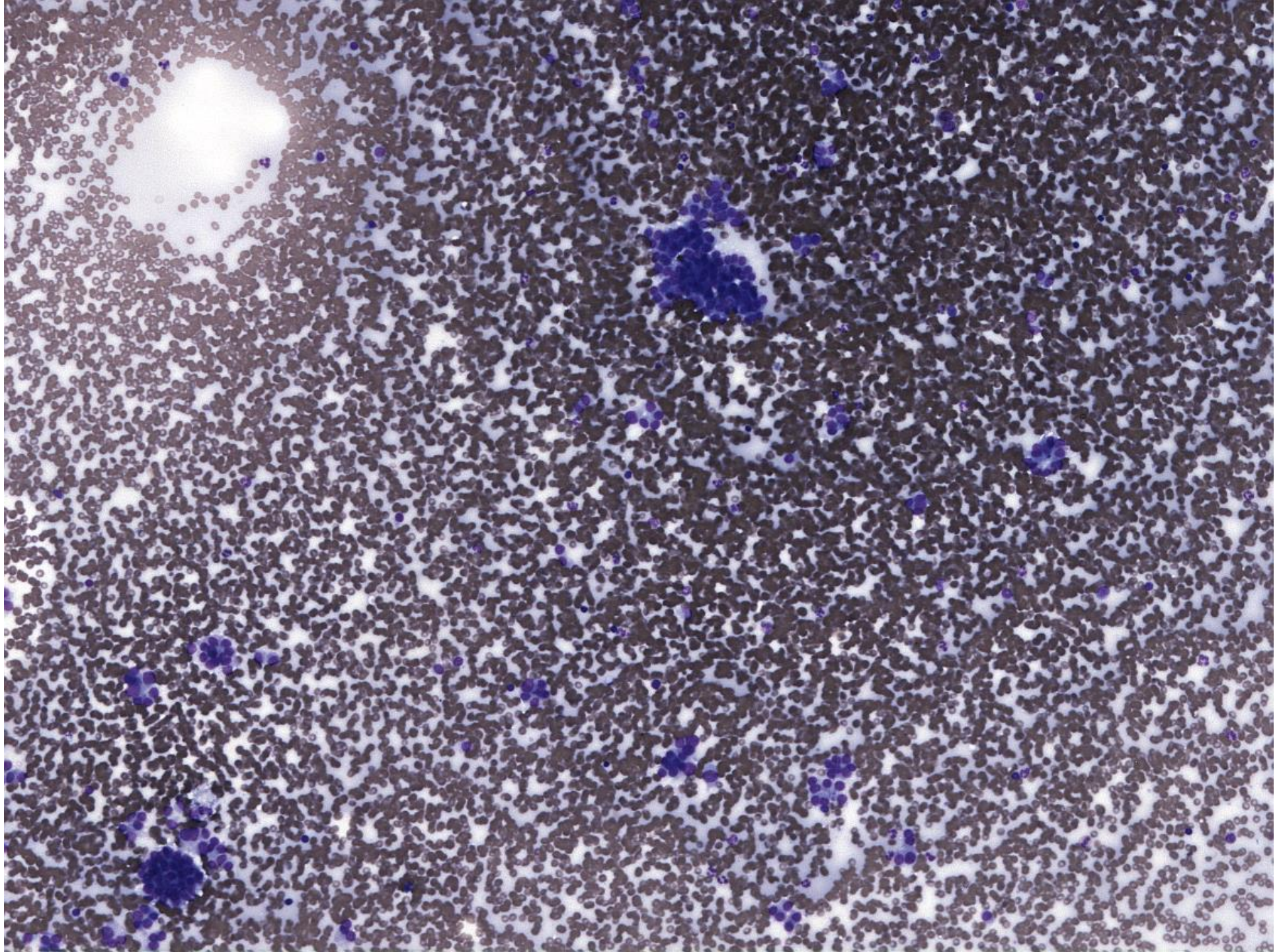


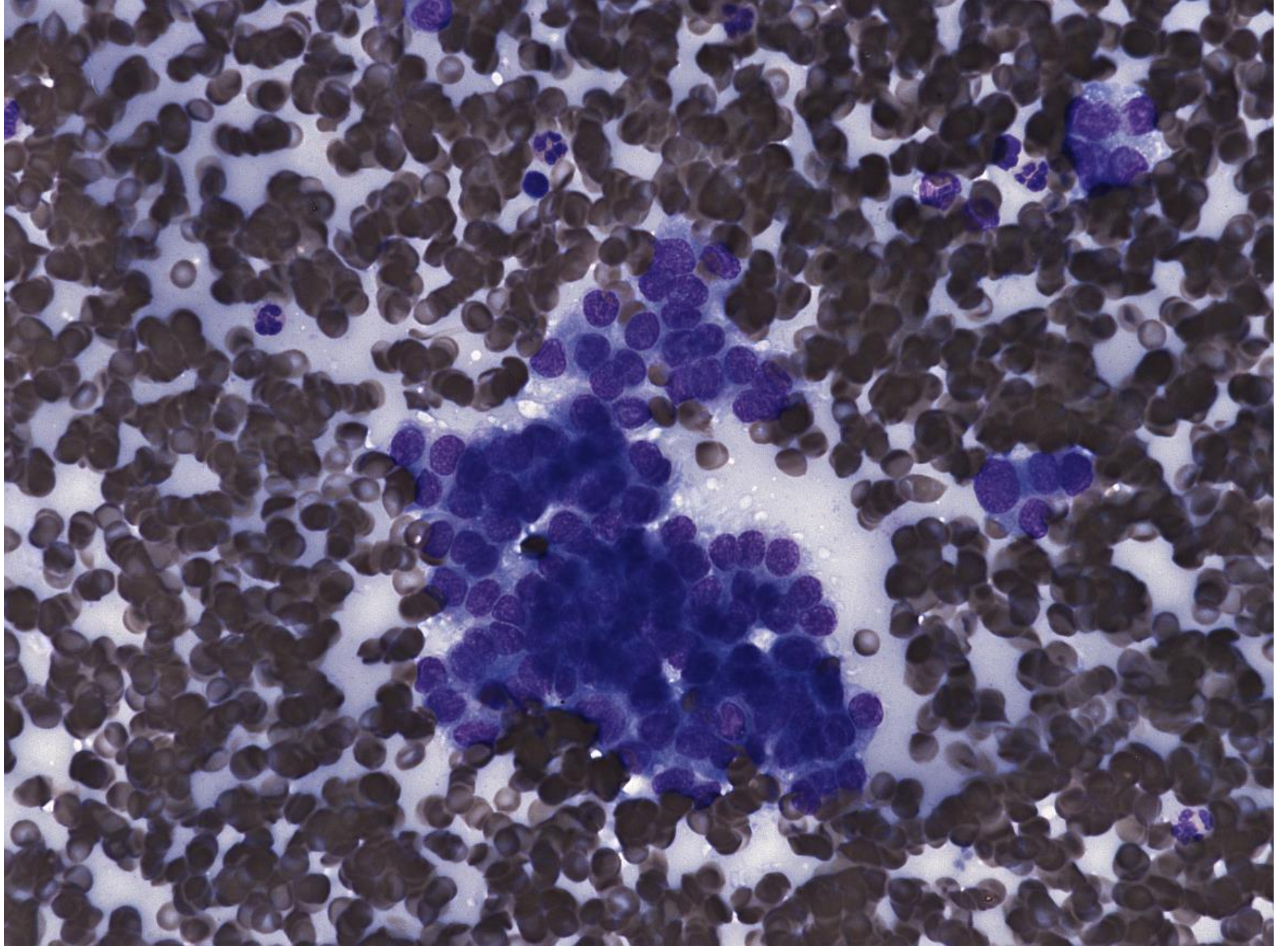
TTF1

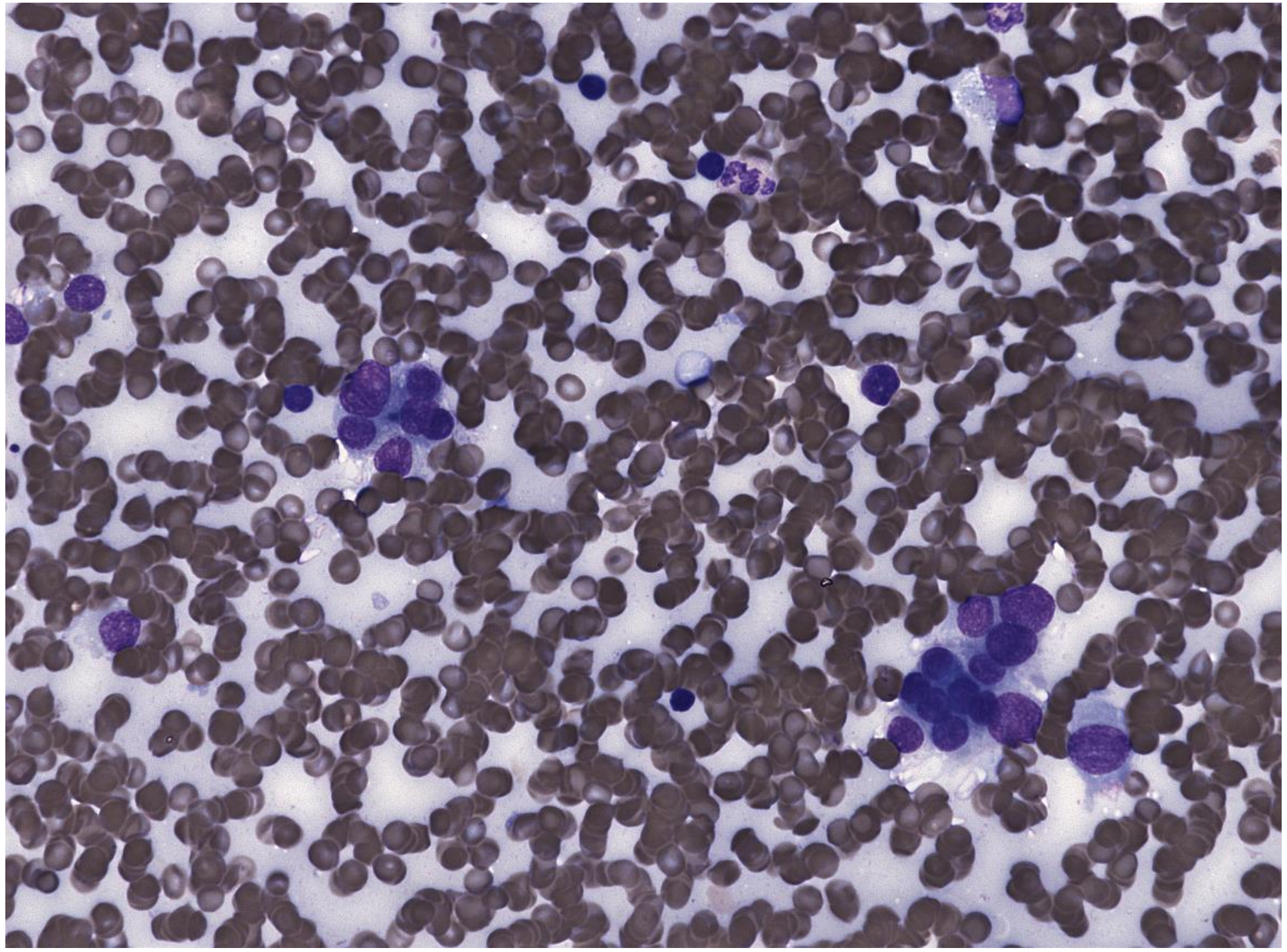


Ki-67

Determinant for the differential diagnosis with anaplastic carcinoma







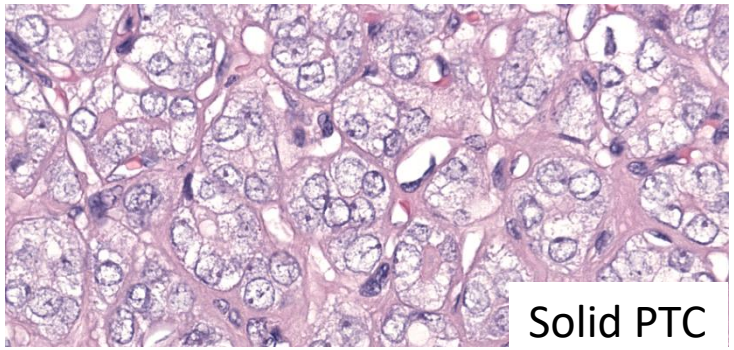
Touching points with other entities

- Solid/ trabecular subtype of papillary carcinoma
- Widely invasive follicular carcinoma
- Widely invasive oncocytic carcinoma
- WDC with focal high-grade features /poorly differentiated component

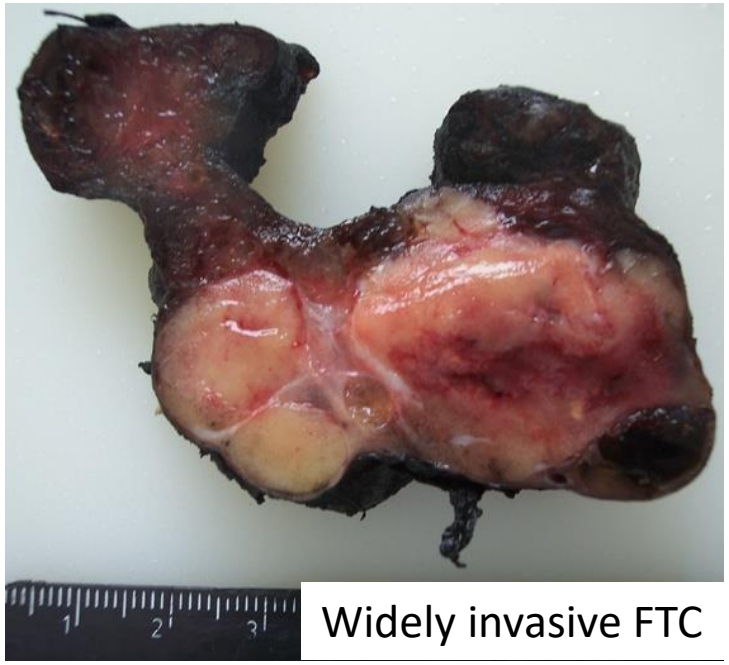
› Cancer. 2006 Mar 15;106(6):1286-95. doi: 10.1002/cncr.21739.

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

David Hiltzik [1], Diane L Carlson, R Michael Tuttle, Shaokun Chuai, Nicole Ishill, Ashok Shaha, Jatin P Shah, Buvanesh Singh, Ronald A Ghossein



Solid PTC



Widely invasive FTC

RAS and BRAF sharply distinguishes between PDTCs defined by the Turin (PDTC-Turin) versus MSKCC (PDTC-MSK) criteria

J Clin Invest. 2016 Mar 1;126(3):1052-66. doi: 10.1172/JCI85271. Epub 2016 Feb 15.

Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers

Iñigo Landa, Tihana Ibrahimpasic, Laura Boucai, Rileen Sinha, Jeffrey A Knauf, Ronak H Shah, Snjezana Dogan, Julio C Ricarte-Filho, Gnana P Krishnamoorthy, Bin Xu, Nikolaus Schultz, Michael F Berger, Chris Sander, Barry S Taylor, Ronald Ghossein, Ian Ganly, James A Fagin

PDTCs that met the Turin standard histological definition were strongly associated with RAS mutations. By contrast, those defined based on the presence of high mitotic rate and necrosis irrespective of other characteristics were markedly enriched for BRAF.

News! 5th Edition of the WHO

Endocrine Pathology (2022) 33:27–63
https://doi.org/10.1007/s12022-022-09707-3

Overview of the 2022 WHO Classification of Thyroid Neoplasms

Zubair W. Baloch[1] · Sylvia L. Asa[2] · Justine A. Barletta[3] · Ronald A. Ghossein[4] · C. Christofer Juhlin[5,6] · Chan Kwon Jung[7] · Virginia A. LiVolsi[1] · Mauro G. Papotti[8] · Manuel Sobrinho-Simões[9] · Giovanni Tallini[10,11] · Ozgur Mete[12]

Table 4 Prognostically relevant classification of follicular cell derived carcinomas of the thyroid

Histotype	Differentiation (growth pattern)	Grade (mitotic activity, tumor necrosis)	Prognosis
PTC	Good (papillae, follicles)	Low	Excellent
FTC			
OCA			
DHGTC (papillary, follicular, oncocytic)		High	Intermediate
PDTC	Poor (solid/trabecular/insular growth)		
ACA	Absent (undifferentiated growth)		Dismal

PTC - papillary thyroid carcinoma; FTC - follicular thyroid carcinoma; OCA - oncocytic carcinoma, DHGTC - differentiated high grade thyroid carcinoma; PDTC - poorly differentiated thyroid carcinoma; ACA - anaplastic carcinoma.

Tumors with mixed histologic features should be typed according to the component with highest grade and least differentiation

<5%

Table 1 WHO classification scheme of thyroid neoplasms, 5th edition

Developmental abnormalities

1. Thyroglossal duct cyst
2. Other congenital thyroid abnormalities

Follicular cell–derived neoplasms

1. Benign tumors
   a. Thyroid follicular nodular disease
   b. Follicular adenoma
   c. Follicular adenoma with papillary architecture
   d. Oncocytic adenoma of the thyroid
2. Low-risk neoplasms
   a. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
   b. Thyroid tumors of uncertain malignant potential
   c. Hyalinizing trabecular tumor
3. Malignant neoplasms
   a. Follicular thyroid carcinoma
   b. Invasive encapsulated follicular variant papillary carcinoma
   c. Papillary thyroid carcinoma
   d. Oncocytic carcinoma of the thyroid
   e. Follicular-derived carcinomas, high-grade
      i. Differentiated high-grade thyroid carcinoma
      ii. Poorly differentiated thyroid carcinoma
   f. Anaplastic follicular cell–derived thyroid carcinoma

(...)

News! 5th Edition of the WHO

Table 5 Diagnostic criteria for high-grade follicular cell–derived thyroid carcinomas

	PDTC (Turin criteria)	DHGTC
Growth pattern	Required: solid/trabecular/insular	Papillary, follicular, solid*
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 $\geq$ 3/2 mm^2 Tumor necrosis Convoluted nuclei	Minimum requirement: one of the following two features: Mitotic count $\geq$ 5/2 mm^2 Tumor necrosis
Anaplastic features	Absent	Absent

PDTC, poorly differentiated thyroid carcinoma; *DHGTC*, differentiated high-grade thyroid carcinoma

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

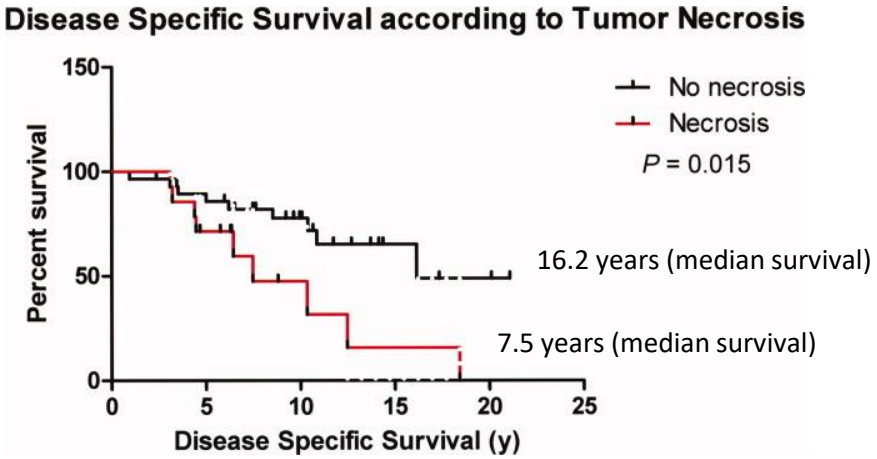
50% of high-grade non-anaplastic thyroid carcinomas will not uptake radioactive iodine

› Cancer. 2008 Jul 1;113(1):48-56. doi: 10.1002/cncr.23515.

Histopathologic characterization of radioactive iodine-refractory fluorodeoxyglucose-positron emission tomography-positive thyroid carcinoma

Michael Rivera [1], Ronald A Ghossein, Heiko Schoder, Daniel Gomez, Steven M Larson, R Michael Tuttle

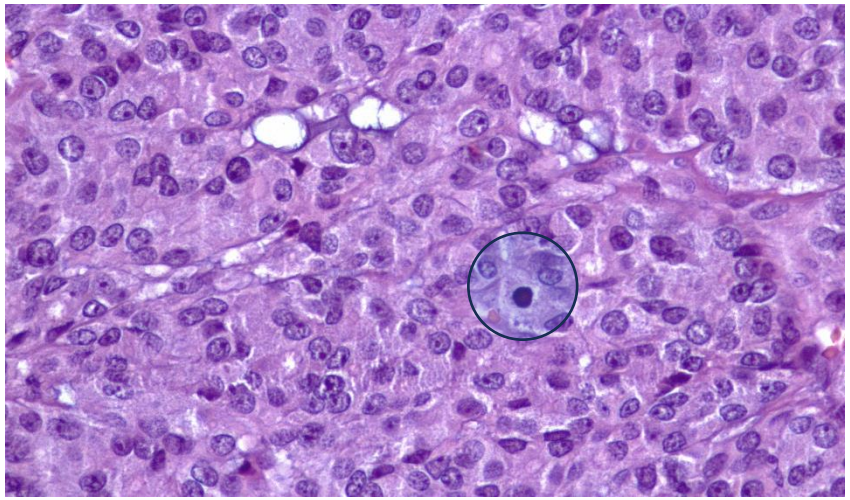
Histopathologic characterization of radioactive iodine-refractory fluorodeoxyglucose-positron emission tomography-positive thyroid carcinoma

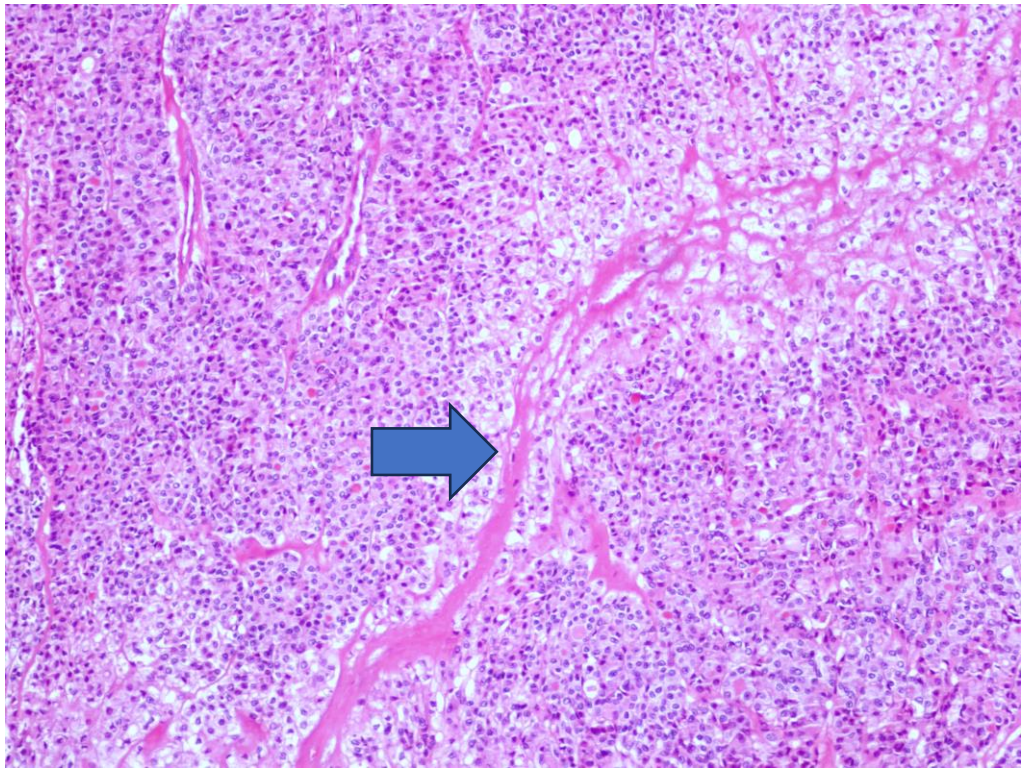


16.2 years (median survival)

7.5 years (median survival)

Cancer, Volume: 113, Issue: 1, Pages: 48-56, First published: 20 June 2008, DOI: (10.1002/cncr.23515)





Endocrine Pathology (2023) 34:234–246
https://doi.org/10.1007/s12022-023-09770-4

RESEARCH

High Grade Differentiated Follicular Cell-Derived Thyroid Carcinoma Versus Poorly Differentiated Thyroid Carcinoma: A Clinicopathologic Analysis of 41 Cases

Lester D. R. Thompson[1]

Accepted: 28 April 2023 / Published online: 17 May 2023

the remaining six patients alive ($n=4$) or dead ($n=2$) with metastatic disease (median 25.8 months). Criteria associated with an increased risk of developing metastatic disease: widely invasive tumors; age $\geq$ 55 years; male; advanced tumor size and stage; extrathyroidal extension; but not increased mitotic rate or higher labeling index. There were 24 PDTC, median age

Histopathology. 2022 Jan;80(2):322-337. doi: 10.1111/his.14550. Epub 2021 Oct 7.

Primary high-grade non-anaplastic thyroid carcinoma: a retrospective study of 364 cases

Bin Xu [1], Julia David [2], Snjezana Dogan [1], Iñigo Landa [3], Nora Katabi [1], Maelle Saliba [1], Anjanie Khimraj [1], Eric J Sherman [4], Robert Michael Tuttle [2], Giovanni Tallini [5], Ian Ganly [6], James A Fagin [2], Ronald A Ghossein [1]

Methods and results: This study included 364 HGTC patients: 200 patients (54.9%) were diagnosed with poorly differentiated thyroid carcinoma (PDTC), based on the Turin consensus (HGTC-PDTC), and 164 were diagnosed with high-grade features that did not meet the Turin criteria (HGTC-nonPDTC). HGTCs are aggressive: the 3-year, 5-year, 10-year and 20-year disease-specific survival (DSS) rates were 89%, 76%, 60%, and 35%, respectively. Although DSS was similar between HGTC-PDTC and HGTC-nonPDTC patients, HGTC-PDTC was associated with higher rate of radioactive iodine avidity, a higher frequency of RAS mutations, a lower frequency of BRAF V600E mutations and a higher propensity for distant metastasis (DM) than HGTC-nonPDTC. Independent clinicopathological markers of worse outcome were: older age, male sex, extensive necrosis and lack of encapsulation for DSS;

European Thyroid JOURNAL | J Tong, M Ruan *et al.* | Poorly differentiated thyroid carcinoma | 11:2 | e220021

REVIEW

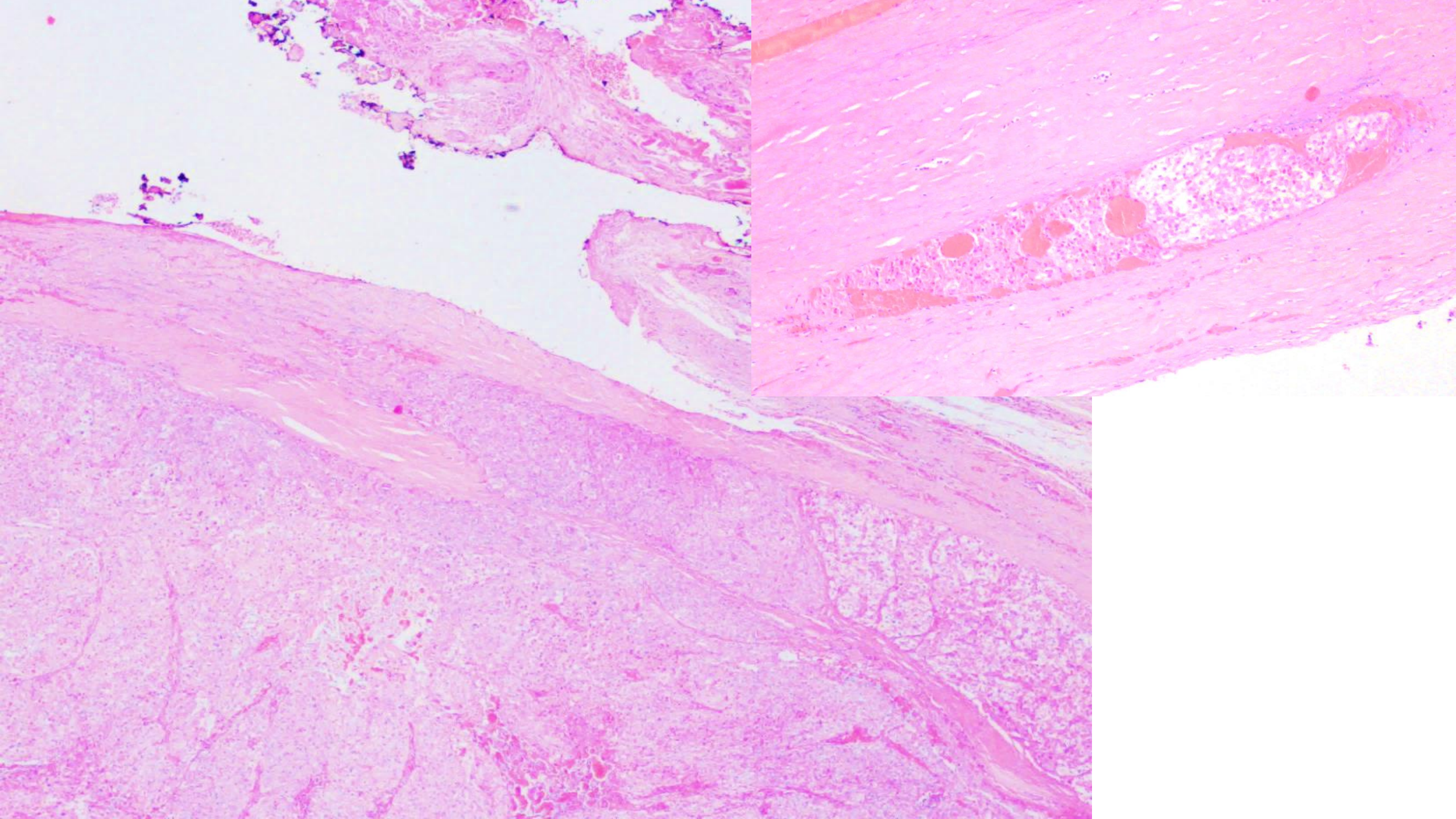
Poorly differentiated thyroid carcinoma: a clinician's perspective

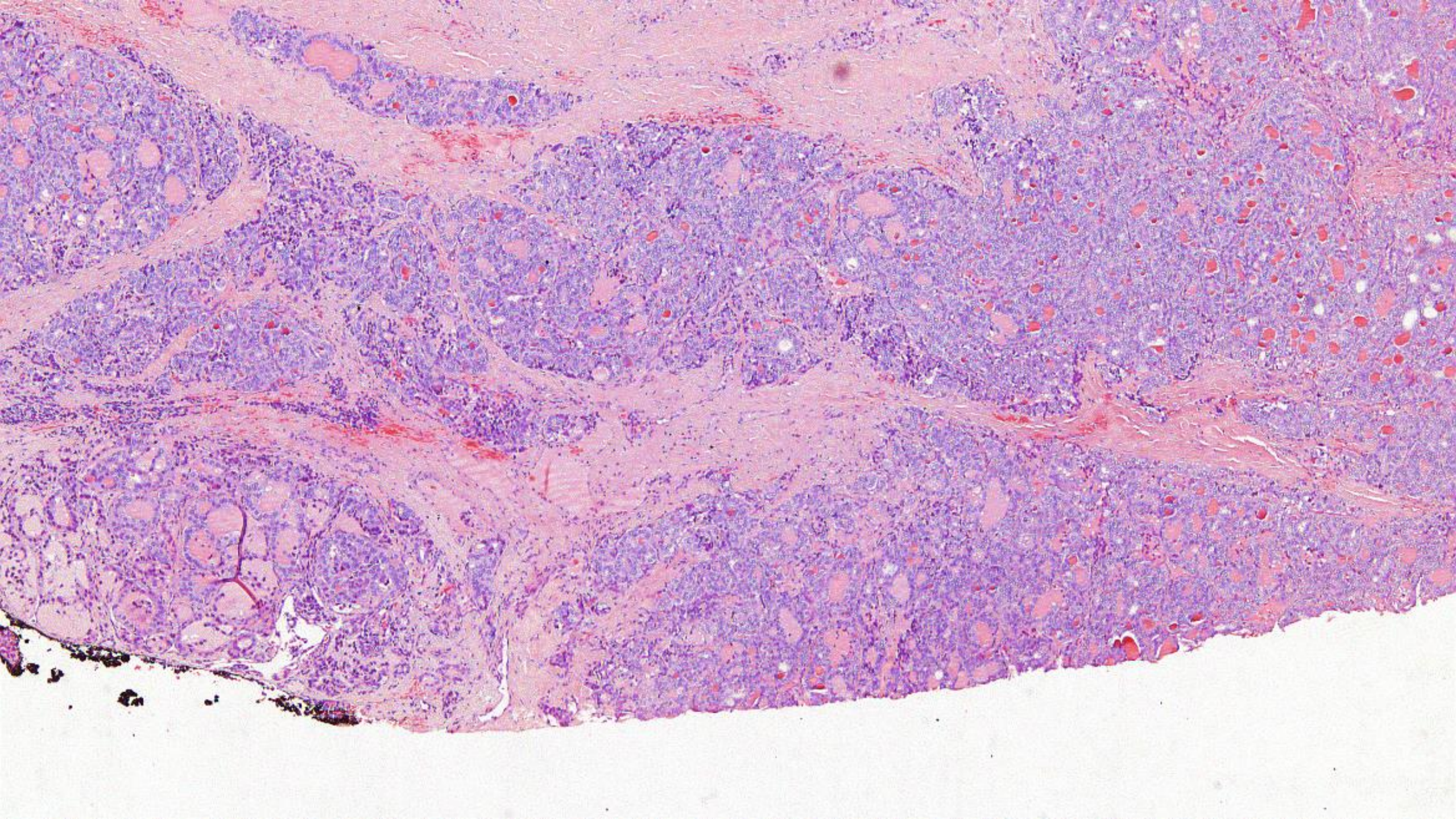
Junyu Tong[1,2,*], Maomei Ruan[2,3,*], Yuchen Jin[2], Hao Fu[2], Lin Cheng[2], Qiong Luo[1], Zhiyan Liu[2,4], Zhongwei Lv[1] and Libo Chen[1]

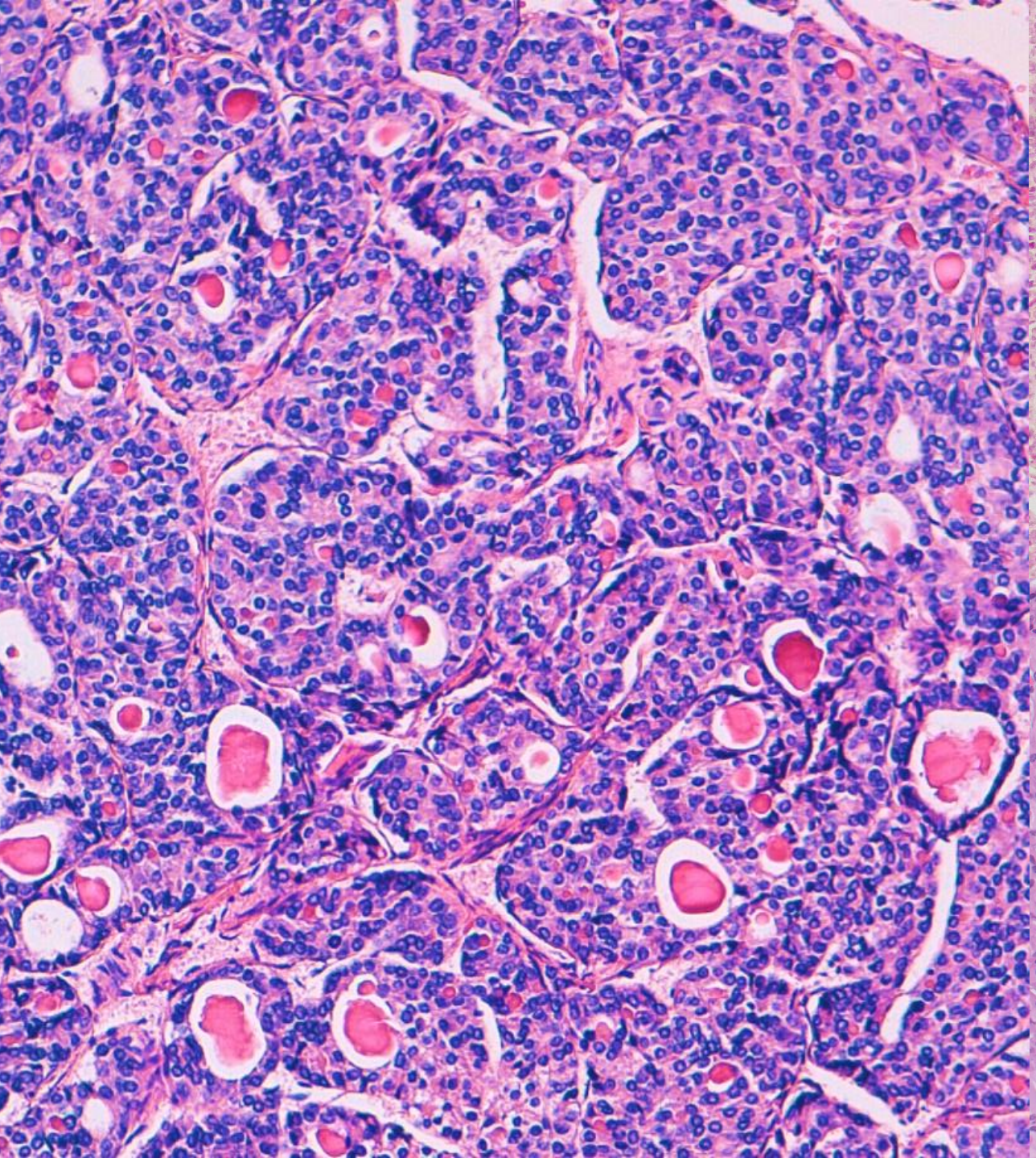
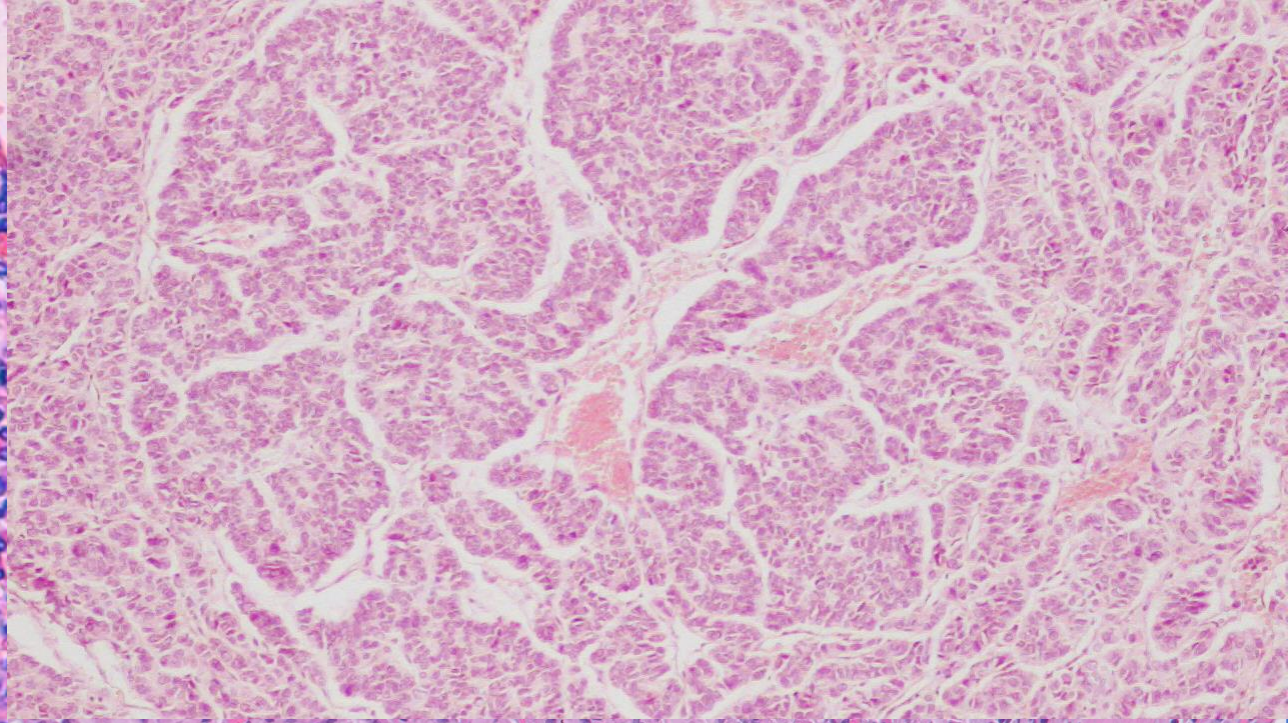
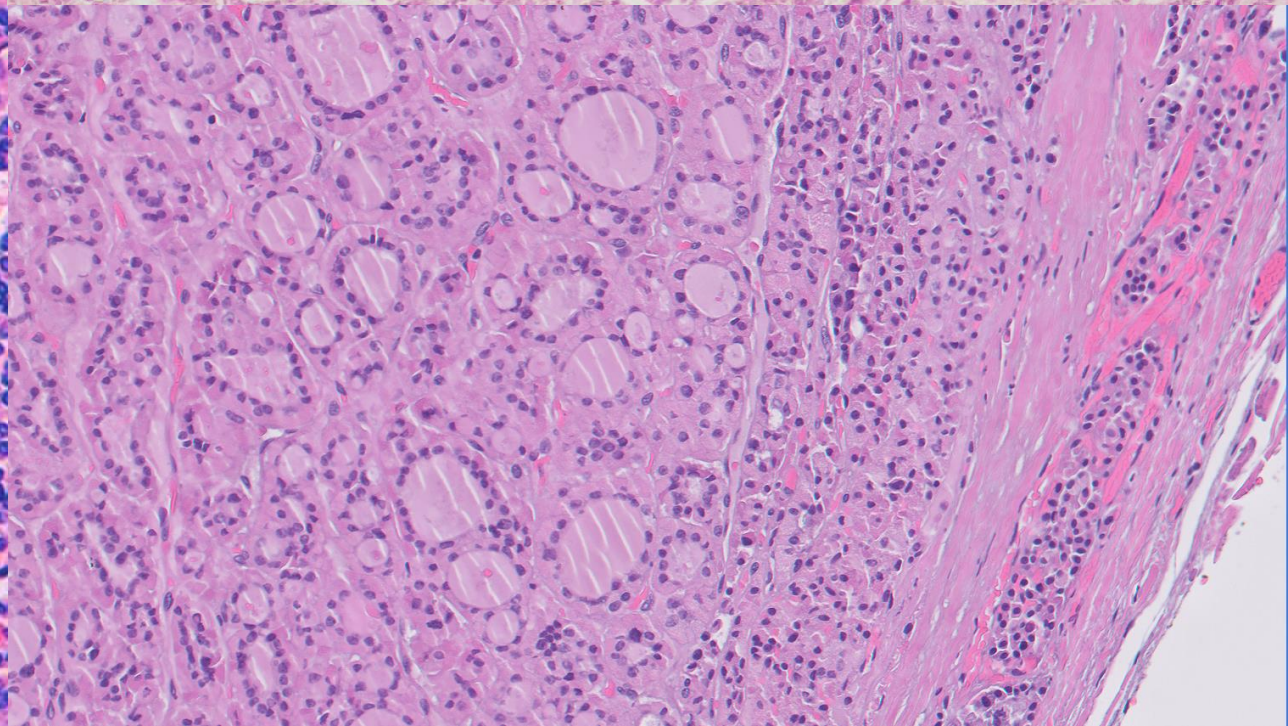
After radioactive iodine

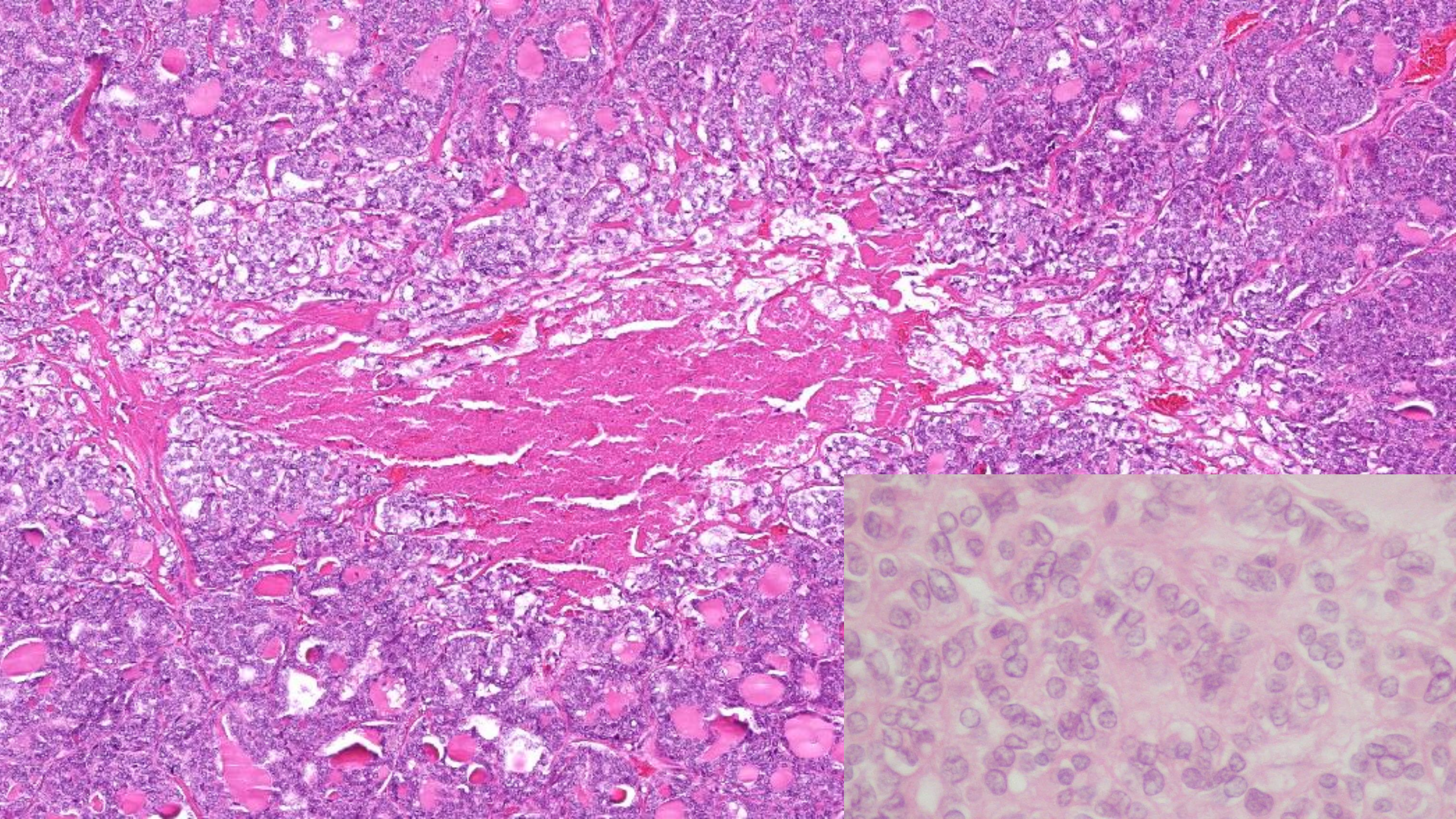
- External beam radiation therapy
- Classic chemotherapy

- Molecular targeted therapy (angiogenesis inhibitors, kinase inhibitor therapy,…)
- Differentiation therapy (retinoic acid, thyrosine kinase inhibitors,…)
- Immunotherapy (monotherapy or combination)

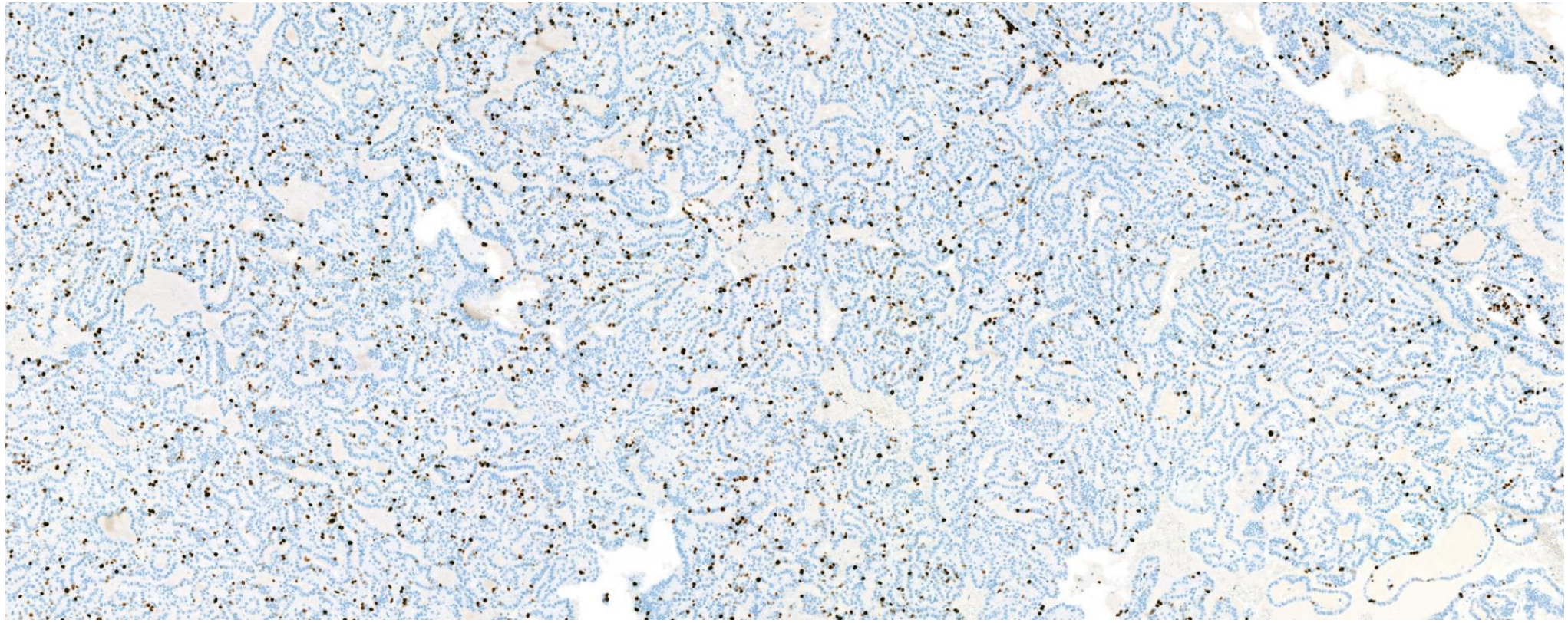


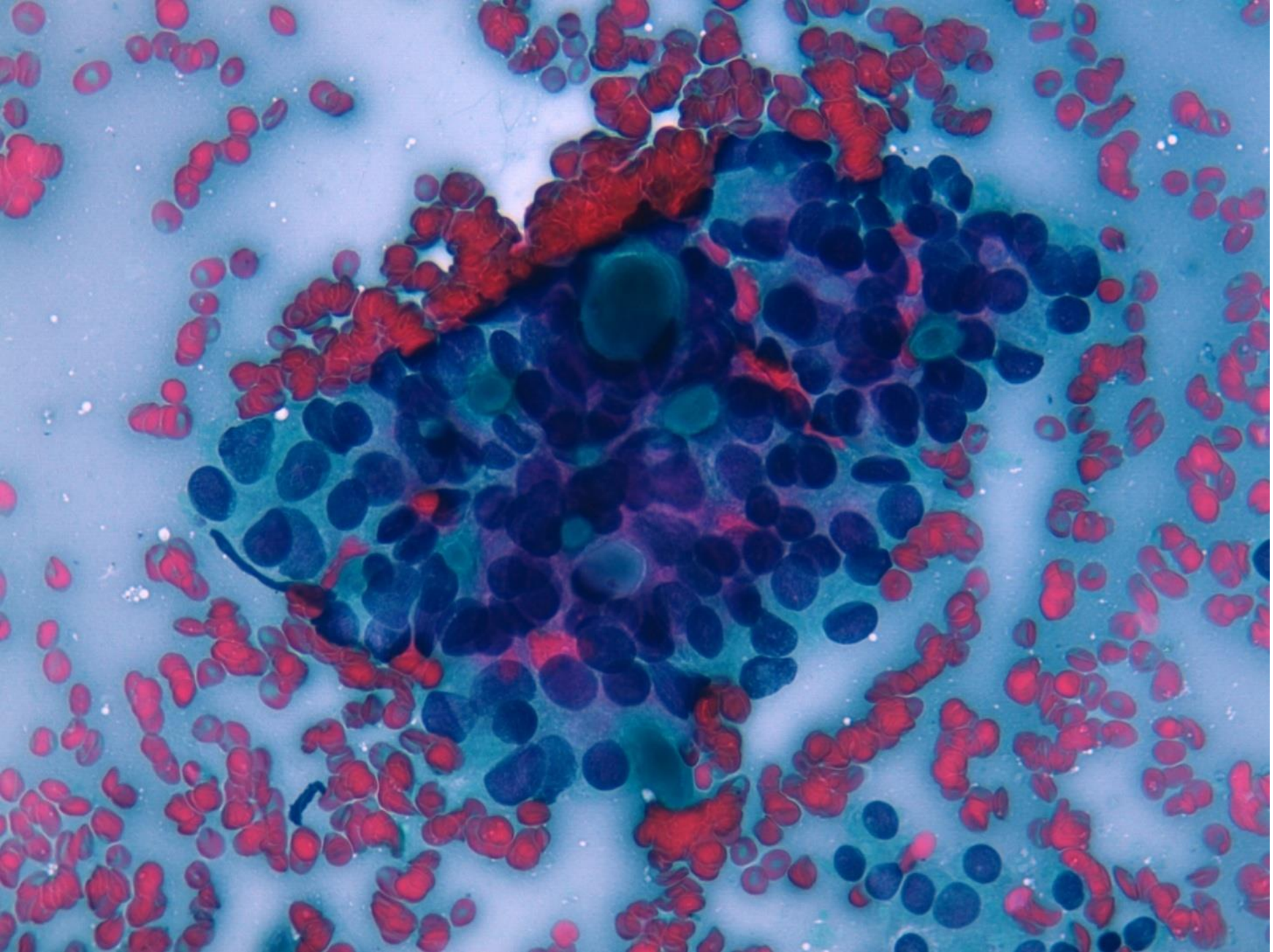




Ki-67 (or PHH3) for detecting hot spots





Cytological features of HGDTC are those of their “low-grade” counterparts

How about encapsulated PDTC and HGDTC?

ELSEVIER

Human Pathology

Volume 41, Issue 2, February 2010, Pages 172-180

Original contribution

Encapsulated thyroid tumors of follicular cell origin with high grade features (high mitotic rate/tumor necrosis): a clinicopathologic and molecular study ☆

Michael Rivera MD [a], Julio Ricarte-Filho PhD [b, d], Snehal Patel MD [c], Michael Tuttle MD [b], Ashok Shaha MD [c], Jatin P. Shah MD [c], James A. Fagin MD [b, d], Ronald A. Ghossein MD [a]

THYROID
Volume 33, Number 5, 2023

DOI: 10.1089/thy.2023.0032

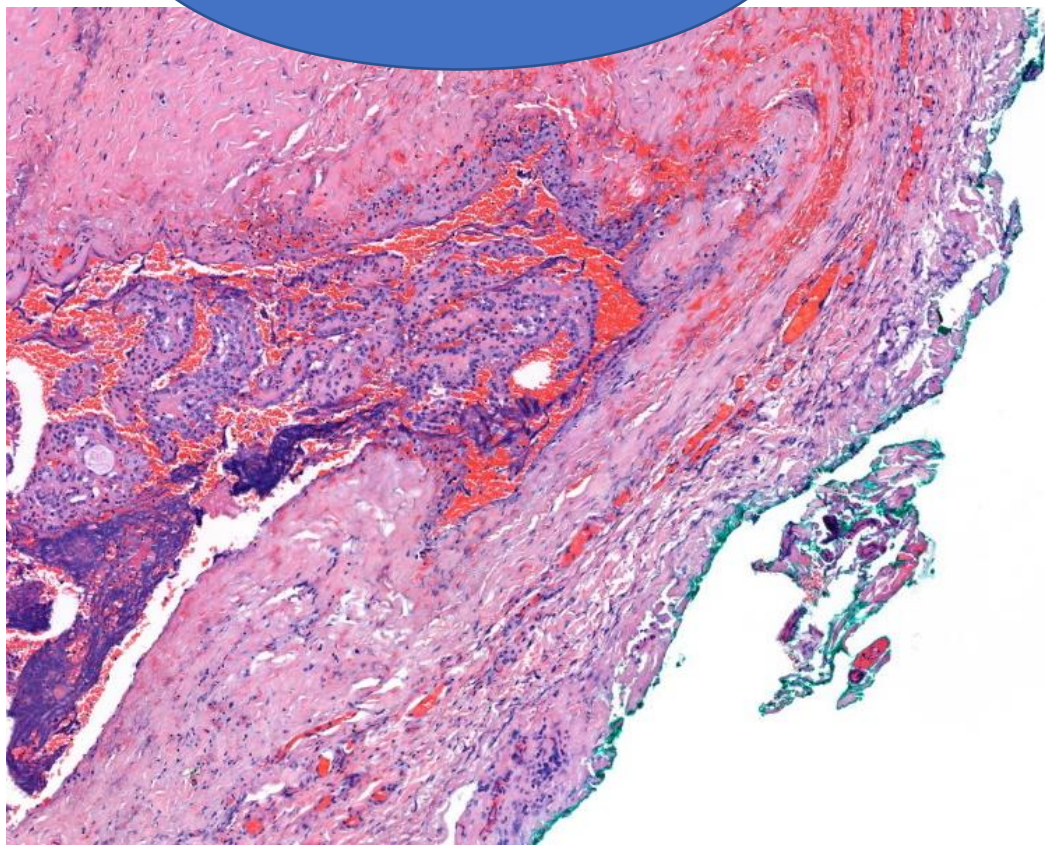
THYROID SURGERY

Open camera or QR reader and scan code to access this article and other resources online.

Large (>4 cm) Intrathyroidal Encapsulated Well-Differentiated Follicular Cell-Derived Carcinoma Without Vascular Invasion May Have Negligible Risk of Recurrence Even When Treated with Lobectomy Alone

Ronald Ghossein,[1] Ian Ganly,[2] R. Michael Tuttle,[3] and Bin Xu[1]

Carefully search for vascular invasion



Published in final edited form as:

Mod Pathol. 2020 July ; 33(7): 1264–1274. doi:10.1038/s41379-020-0458-7.

Poorly differentiated thyroid carcinoma of childhood and adolescence: A distinct entity characterized by *DICER1* mutations

Rebecca D Chernock[1,2,*], **Barbara Rivera**[3,4,*], **Nicla Borrelli**[5], **D. Ashley Hill**[6], **Somayyeh Fahiminiya**[7], **Tasha Shah**[4], **Anne-Sophie Chong**[8], **Barina Aqil**[9], **Mitra Mehrad**[10], **Thomas J Giordano**[11,12], **Rachel Sheridan**[13], **Meilan M Rutter**[14,15], **Louis P. Dehner**[1], **William D. Foulkes**[3,4,7,8], **Yuri E Nikiforov**[5]

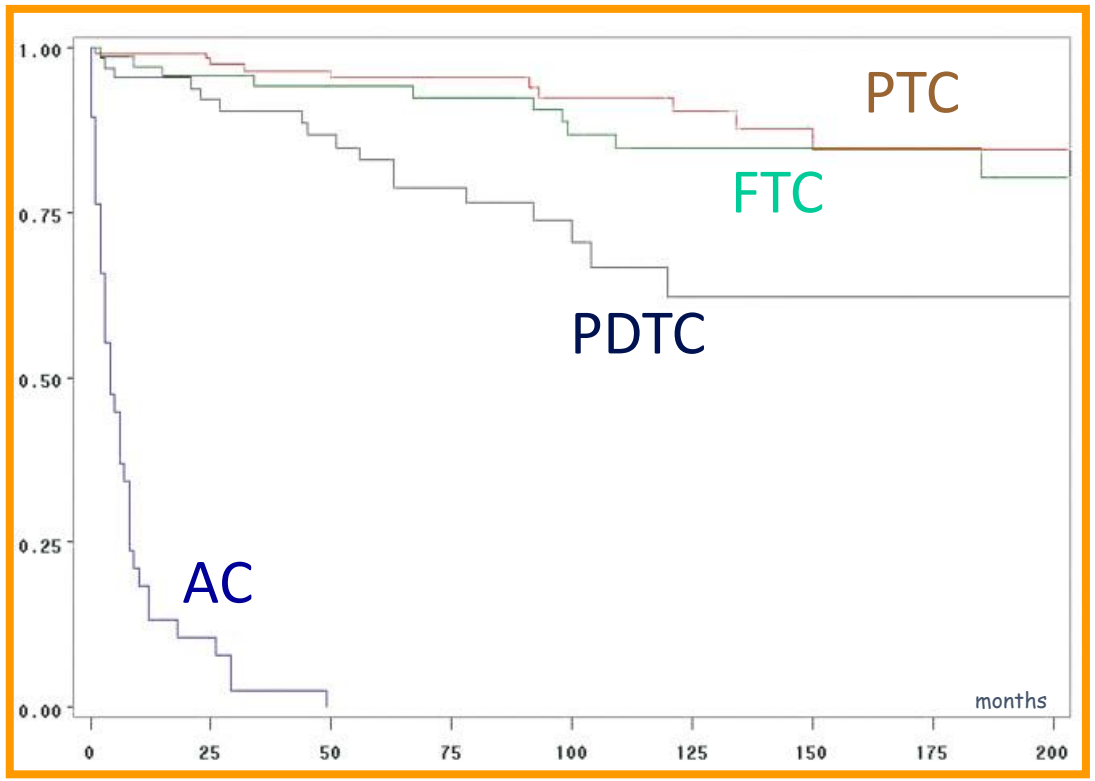
Abstract

Poorly differentiated thyroid carcinomas (PDTC) in young individuals are rare and their clinical and histopathologic features, genetic mechanisms, and outcomes remain largely unknown. Here, we report a detailed characterization of a series of 6 PDTC in patients ≤ 21 years old defined by Turin diagnostic criteria studied for mutations and gene fusions characteristic of thyroid cancer using targeted next-generation sequencing (NGS) and whole exome sequencing (WES). All tumors had solid, insular or trabecular growth pattern and high mitotic rate, and 5 out of 6 tumors showed tumor necrosis. Targeted NGS assay identified somatic mutations in the *DICER1* gene in 5 of 6 (83%) tumors, all of which were "hotspot" mutations encoding the metal-ion binding sites of the RNase IIIb domain of *DICER1*. WES was performed in 5 cases which confirmed all hotspot mutations and detected 2 tumors with additional inactivating *DICER1* alterations. Of these two, one was a germline pathogenic *DICER1* variant and the other had loss of heterozygosity for *DICER1*. No other mutations or gene fusions characteristic of adult well-differentiated thyroid cancer and PDTC (*BRAF*, *RAS*, *TERT*, *RET/PTC* and other) were detected. On follow-up, available for 5 patients, 3 patients died of disease 8-24 months after diagnosis, whereas 2 were alive with no disease. The results of our study demonstrate that childhood- and adolescent-onset PDTC are genetically distinct from adult-onset PDTC in that they are strongly associated with *DICER1* mutations and may herald DICER1 syndrome in a minority. As such, all young persons with PDTC may benefit from genetic counselling. Furthermore, their clinically aggressive behavior contrasts sharply with the indolent nature of the great majority of thyroid tumors with *DICER1* mutations reported to date.

Anaplastic carcinoma

“Elderly patients with longstanding goiters”

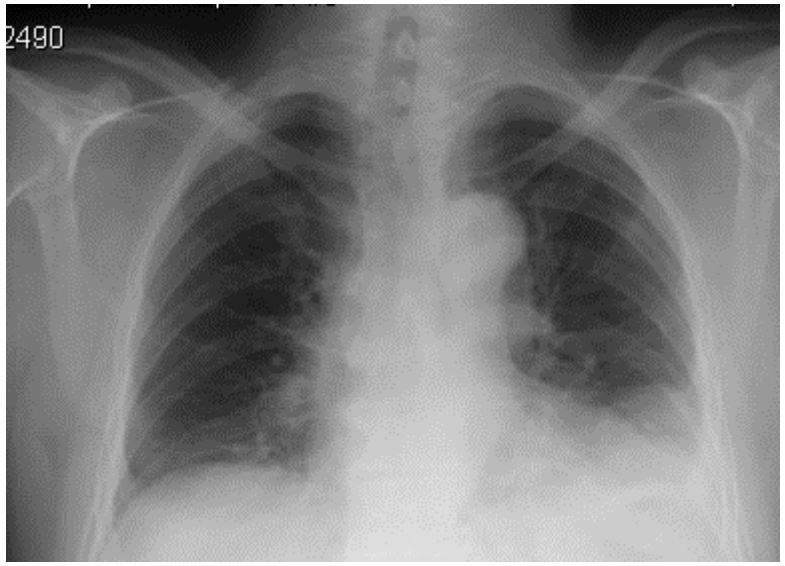
Decreasing frequency of cases (<<<1%)

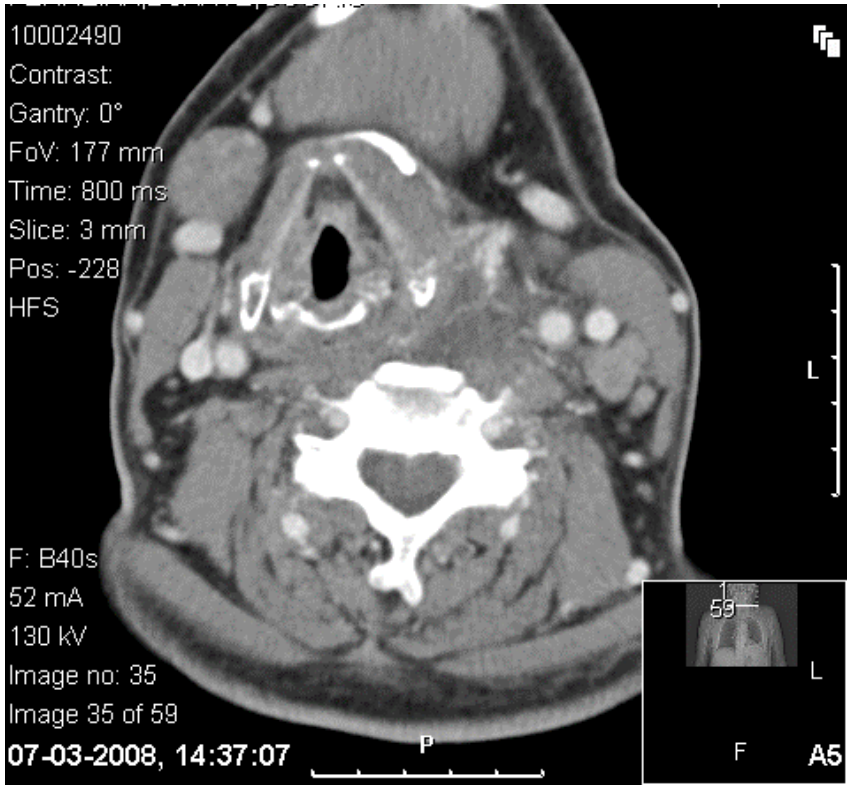


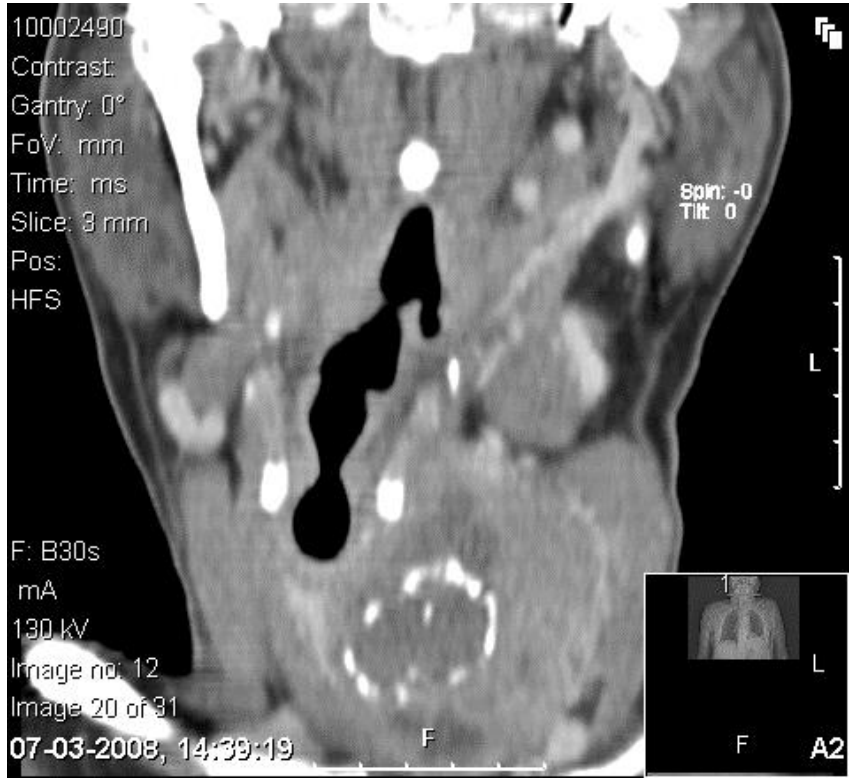
Volante M *et al*, Am J Surg Pathol, 2007

Rapidly evolving clinical course

- 60-year-old male patient with a large mass in the left lobe of the thyroid and enlarged neck lymph nodes

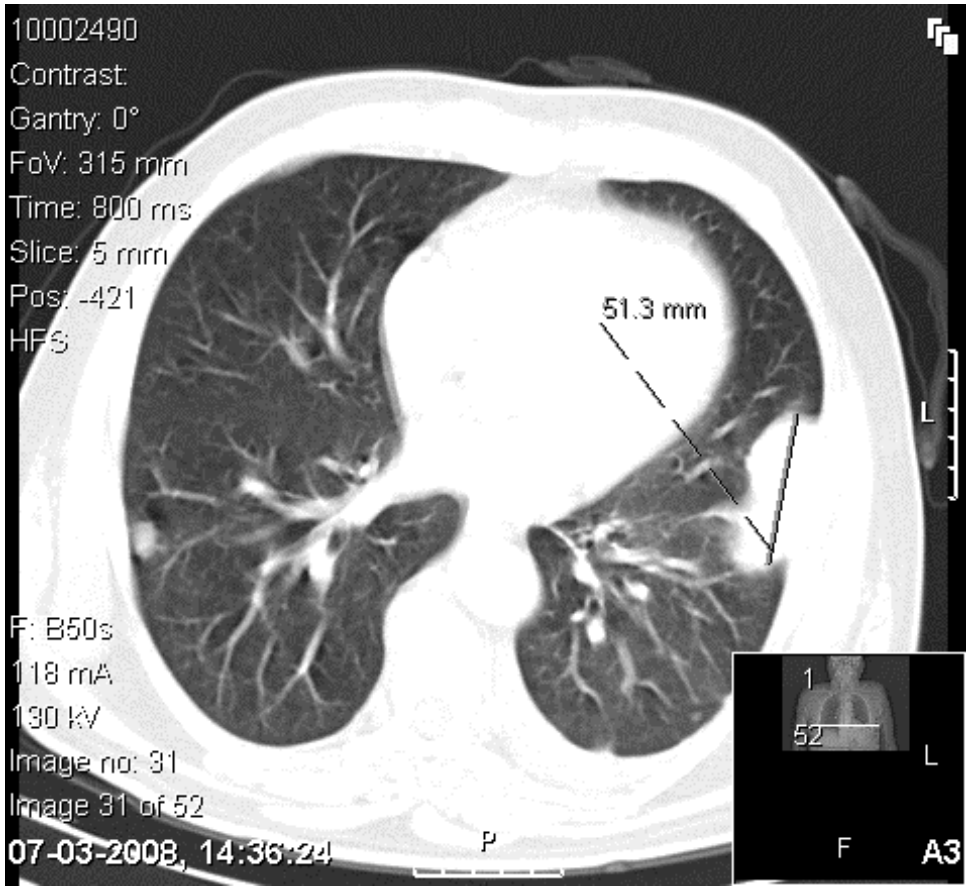


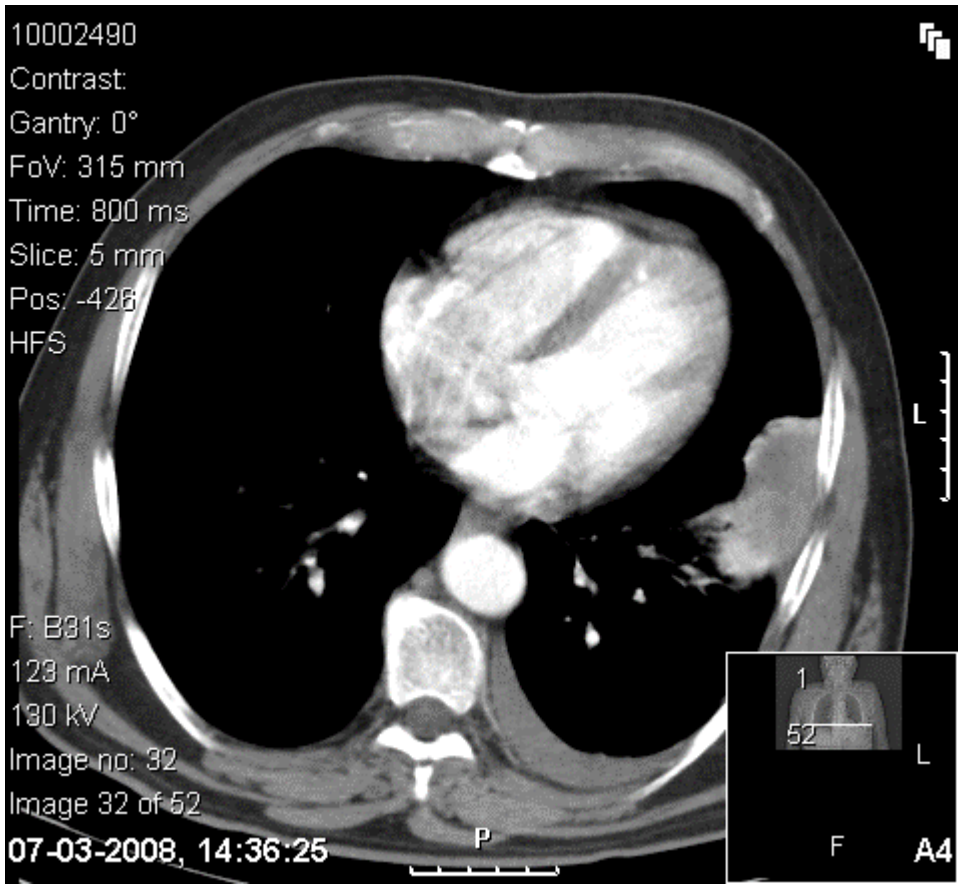




Rapidly evolving clinical course

- The patient developed lung metastases and died 6 months after the diagnosis





Springer Link

Original Article | Published: 11 February 2022

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

Bin Xu ✉, Lingxin Zhang, Reza Setoodeh, Abhinita S. Mohanty, Iñigo Landa, Bonnie Balzer, Vera Tiedje, Ian Ganly, Snjezana Dogan, James A. Fagin & Ronald Ghossein

Endocrine **76**, 612–619 (2022) | Cite this article

280 Accesses | Metrics

Abstract

Purpose

Anaplastic thyroid carcinoma (ATC) is the most lethal form of thyroid cancer with most patients dying of their disease within a few months. Only a very small percentage of long-term survivors (LTS) are alive for 2 years or longer. In this retrospective case-control study, we provided a comprehensive comparison between 46 ATC LTSs and 75 ATC control patients who suffered disease-specific mortality within 2 years, aiming to identify factors that may be associated with prolonged survival in ATC.

Methods

A comprehensive clinicopathologic and molecular comparison was performed between 46 ATC LTSs and 75 ATC control patients. Peripheral neutrophil count and neutrophil-to-lymphocyte ratio (NLR) were recorded. The composition of the tumor microenvironment was compared using immunohistochemistry.

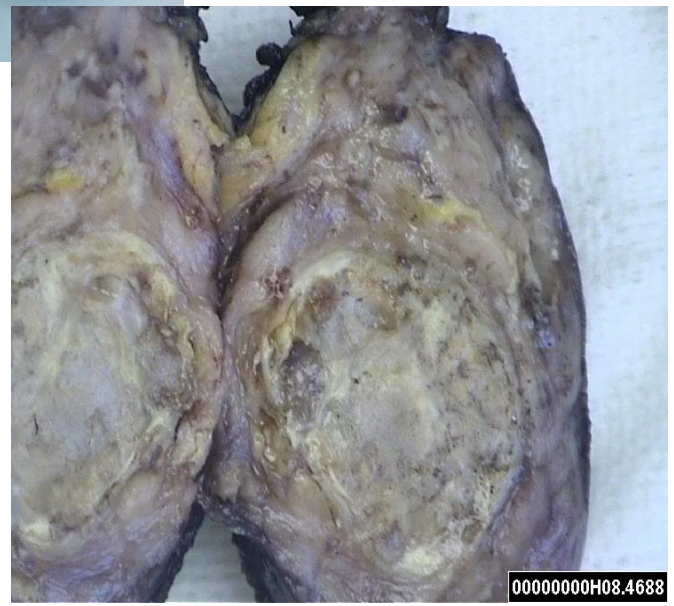
Results

Compared with ATC control patients, ATC LTSs were characterized by 1) higher frequency of (primary) resection as well as clinicopathologic parameters attributed to resectability; 2) lower rate of concurrent *RAS/BRAF* and *TERT* promoter mutations; 3) lower peripheral neutrophil count and NLR; and 4) lower number of tumor-infiltrating neutrophils/myeloid-derived suppressor cells (MDSC). The survival benefits of low peripheral neutrophil counts and low NLR persisted even when controlling for distant metastasis status at presentation.

Conclusions

In addition to traditional beneficial prognostic factors, e.g., surgical resection, factors attributed to resectability, and absence of co-existing *RAS/BRAF* and *TERT* promoter mutations, we herein show that tumor-infiltrating and circulating neutrophils/MDSC are adverse prognostic factors in ATC.

Macroscopy



Large, hard and invasive mass, with necrosis, hemorrhage, and solid fleshy areas

FIG. 2.

Differentiated thyroid cancer

When age at diagnosis is…	*And T is…*	*And N is…*	*And M is…*	*Then the stage group is…*
< 55 yrs	Any T	Any N	M0	I
	Any T	Any N	M1	II
≥ 55 yrs	T1	N0/NX	M0	I
	T1	N1	M0	II
	T2	N0/NX	M0	I
	T2	N1	M0	II
	T3a/T3b	Any N	M0	II
	T4a	Any N	M0	III
	T4b	Any N	M0	IVA
	Any T	Any N	M1	IVB

Anaplastic thyroid cancer

T is…	*And N is…*	*And M is…*	*Then the stage group is…*
T1-T3a	N0/NX	M0	IVA
T1-T3a	N1	M0	IVB
T3b	Any N	M0	IVB
T4	Any N	M0	IVB
Any T	Any N	M1	IVC

Eighth edition American Joint Committee on Cancer prognostic stage groups for differentiated thyroid cancer (top panel) and anaplastic thyroid cancer (bottom panel).

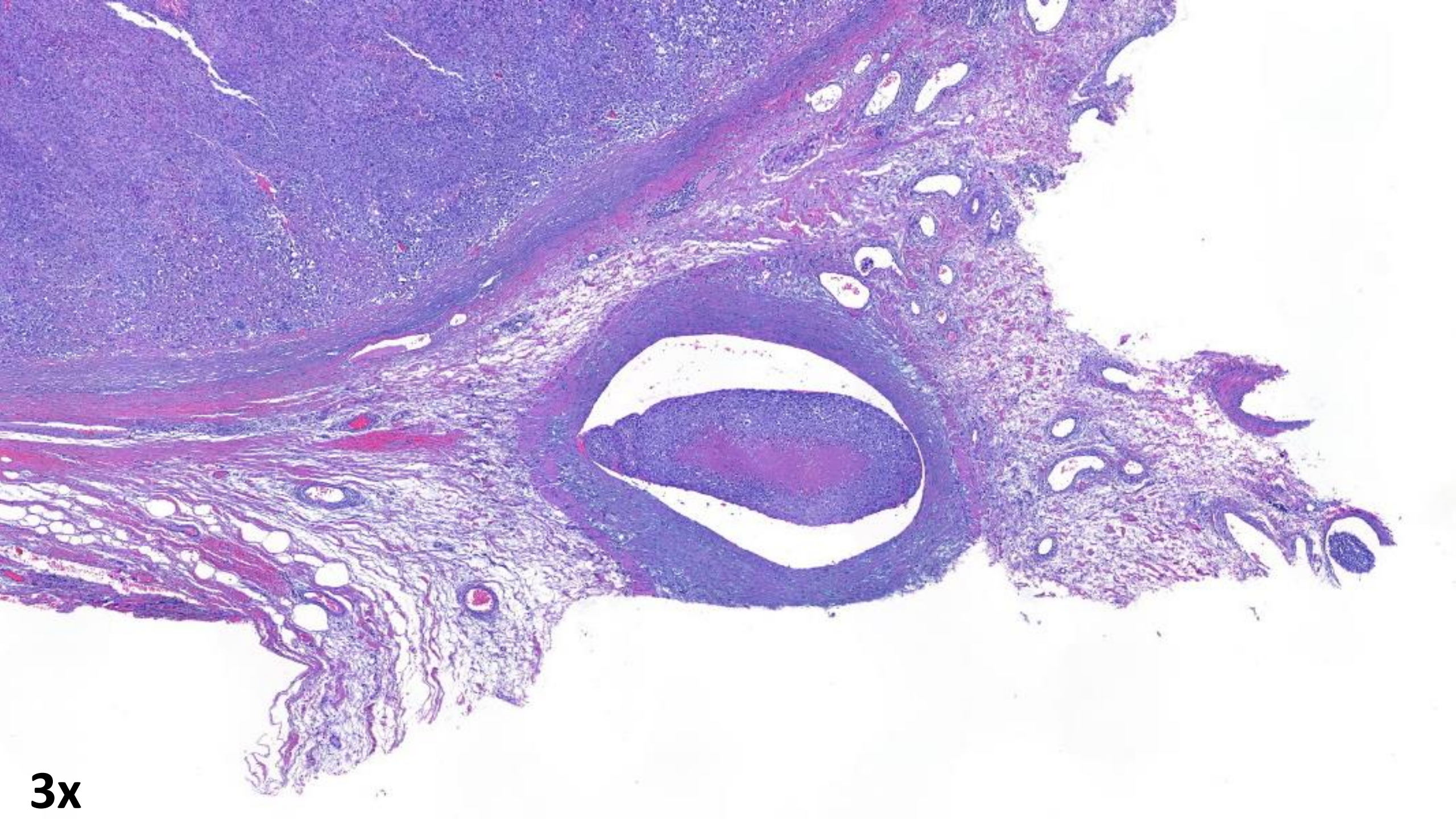
- Evaluate tumour size
- Evaluate extent of invasion
- Dissect lymph nodes
- Characterize the completeness of surgery
- Extensivelly collect fragments from well preserved areas

This is the case of a 50 year-old male patient submitted to left lobectomy *plus* isthmectomy. The specimen weighted 200g and was almost total occupied by a fleshy neoplasm

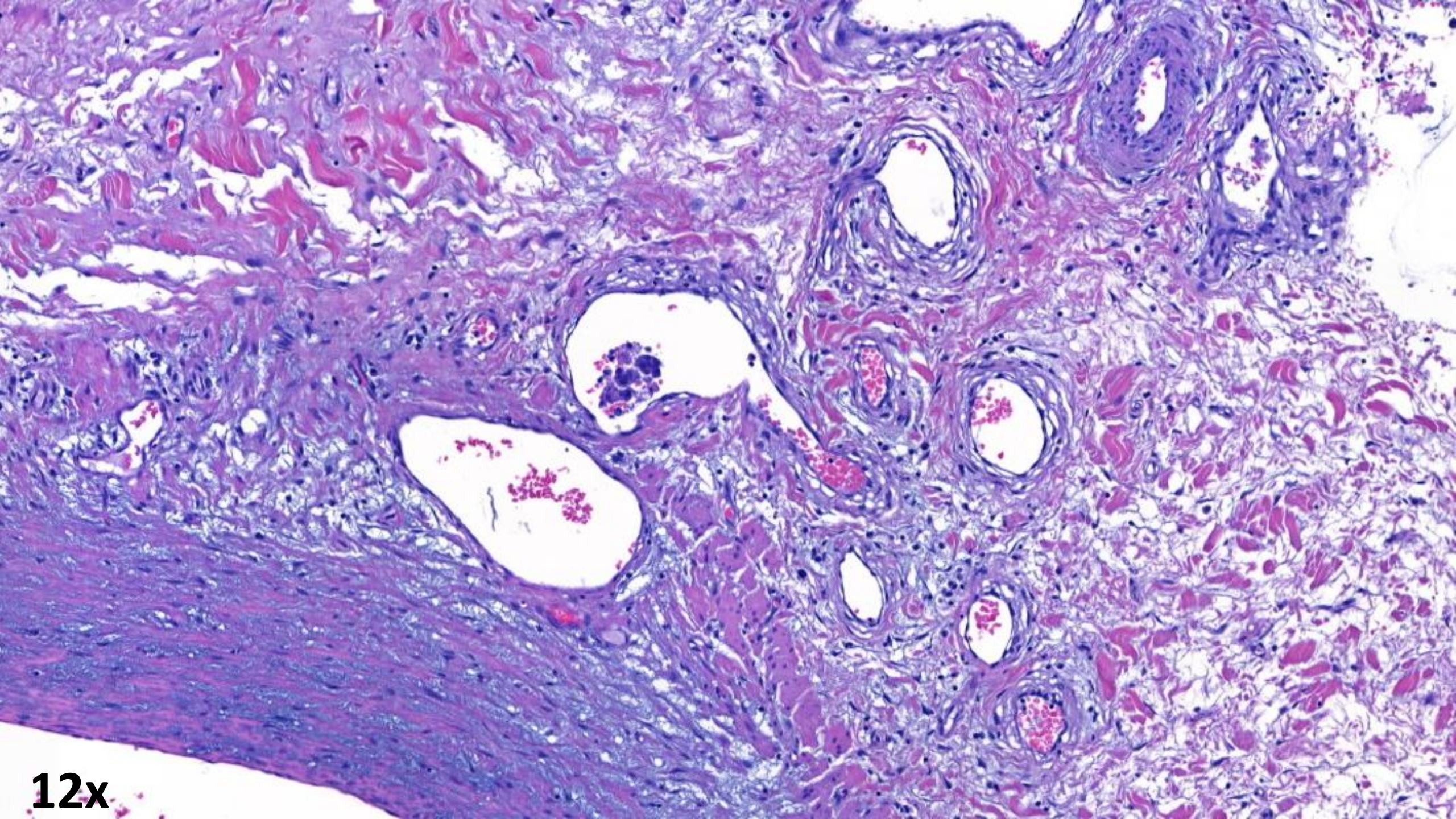
Microscopy of an anaplastic carcinoma case

50-year-old male. The lobectomy specimen weighted 200g

2x



3x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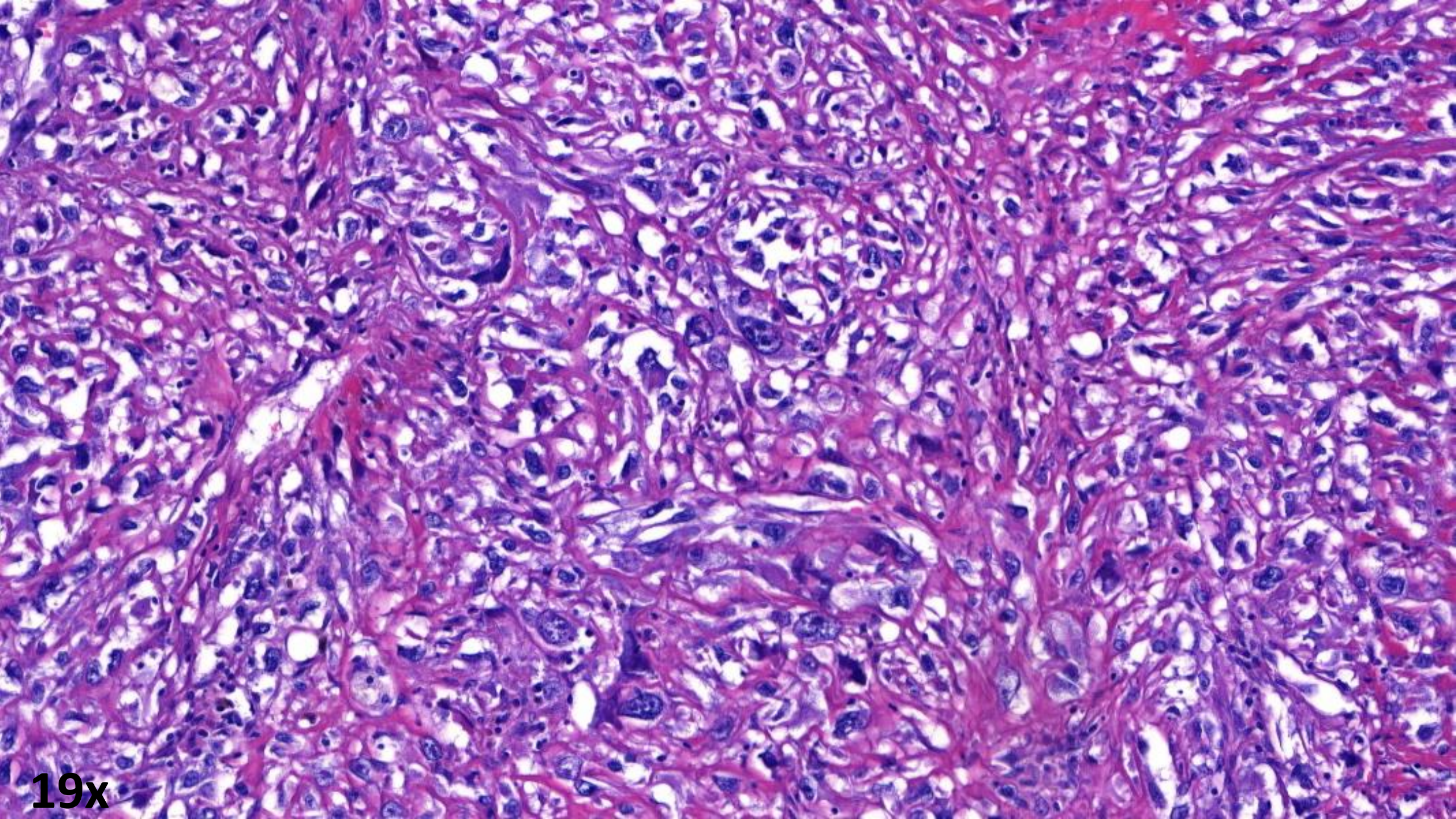
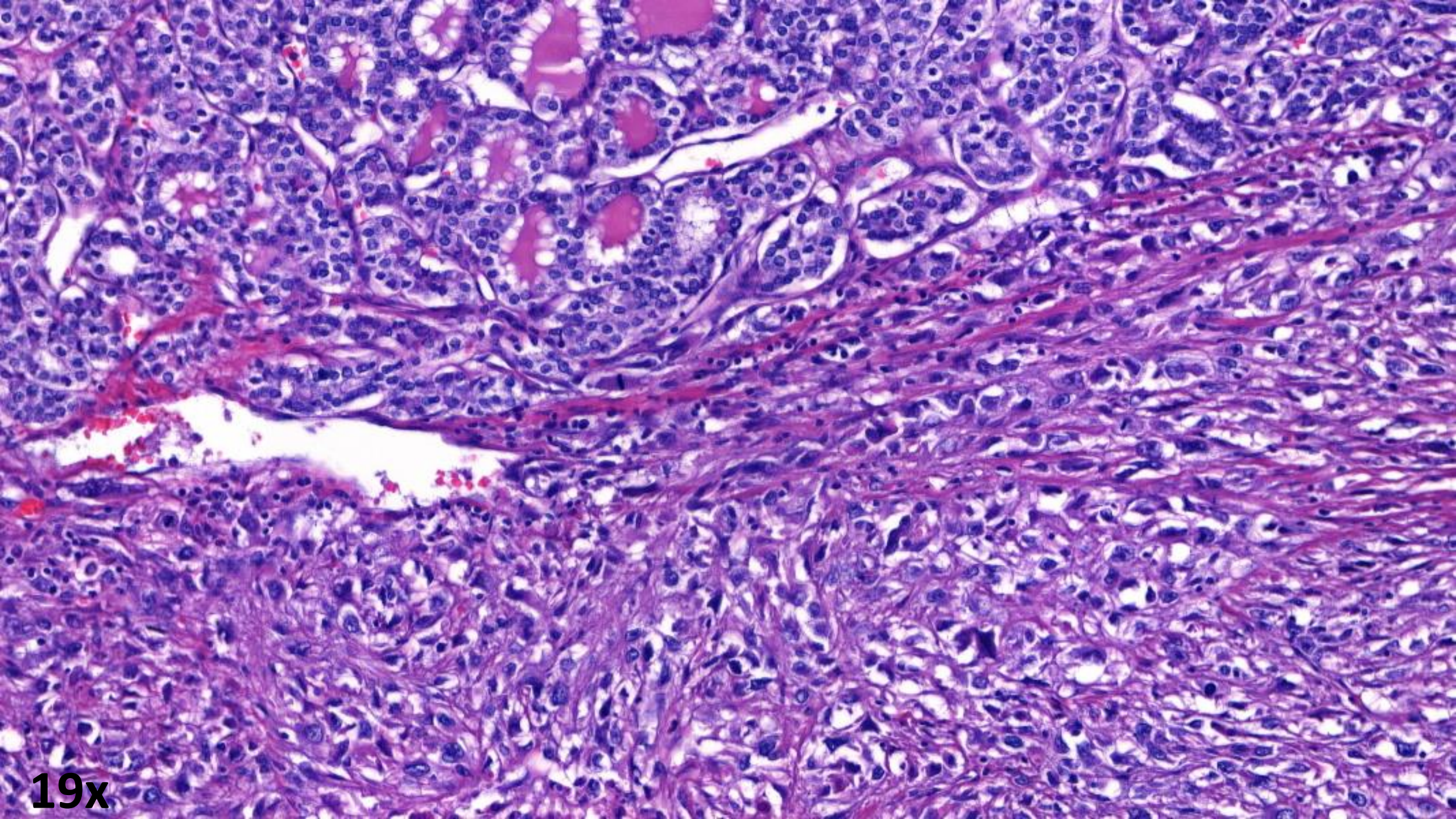
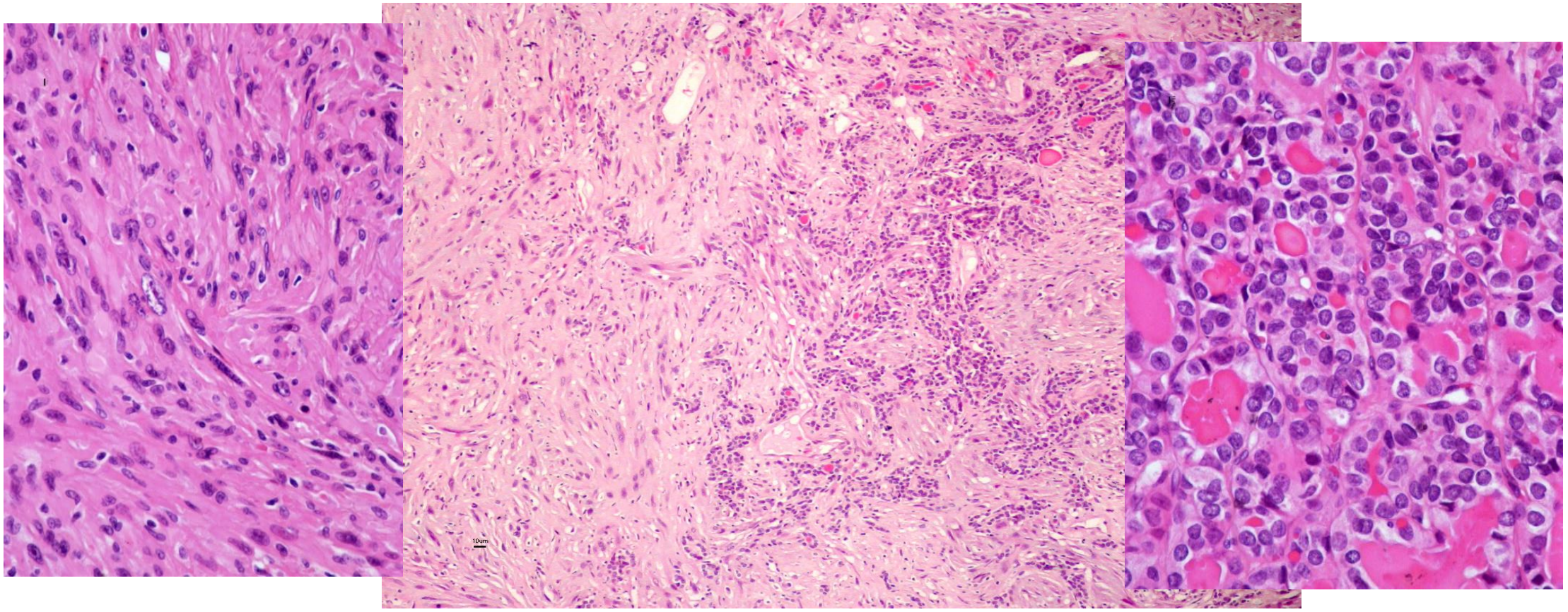

19x


19x

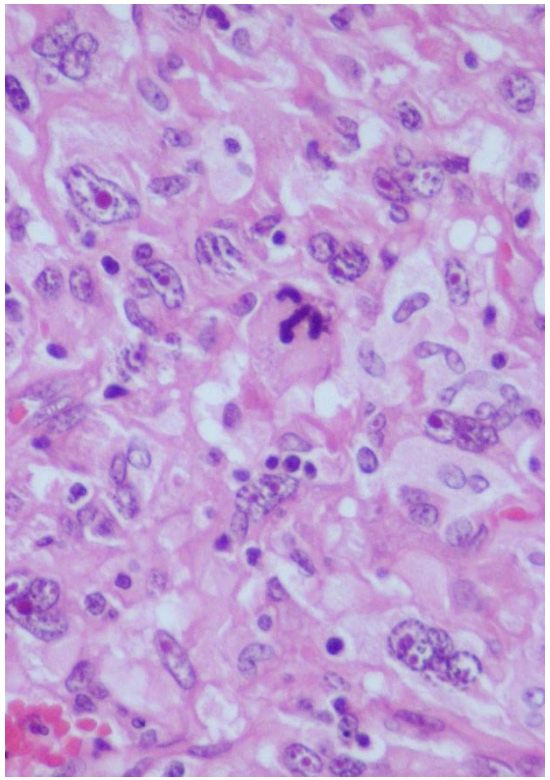
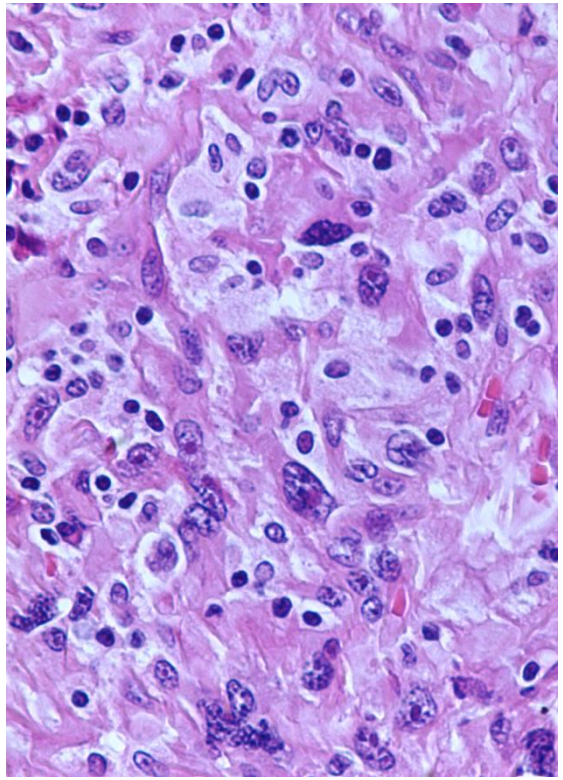
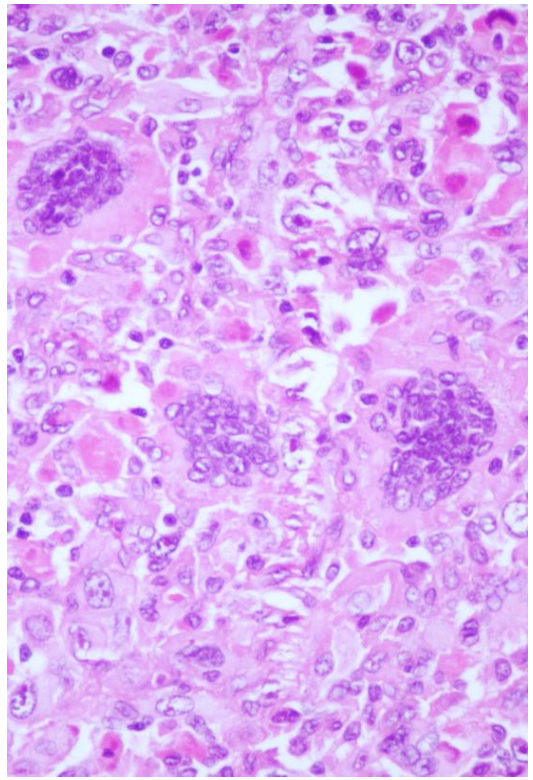
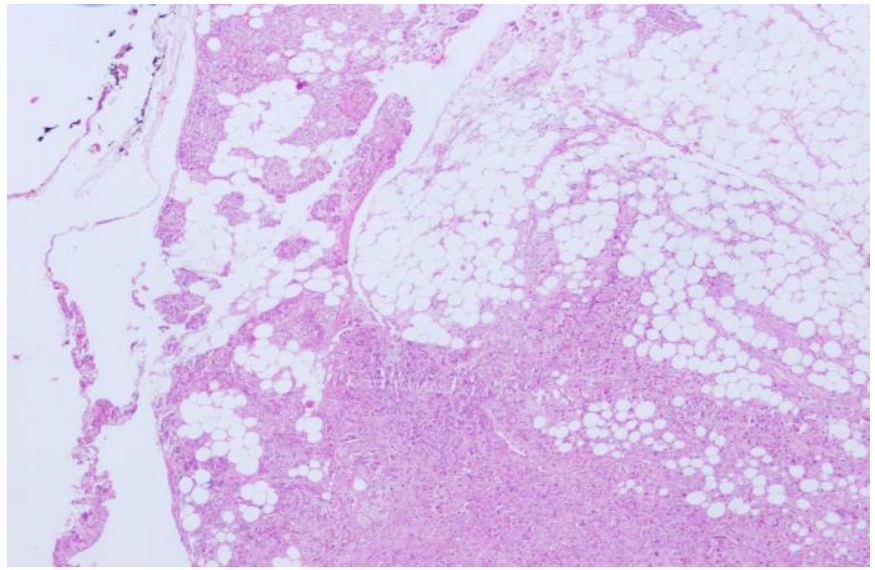
Anaplastic carcinoma

Anaplastic carcinoma with paucicelular components



Anaplastic carcinoma

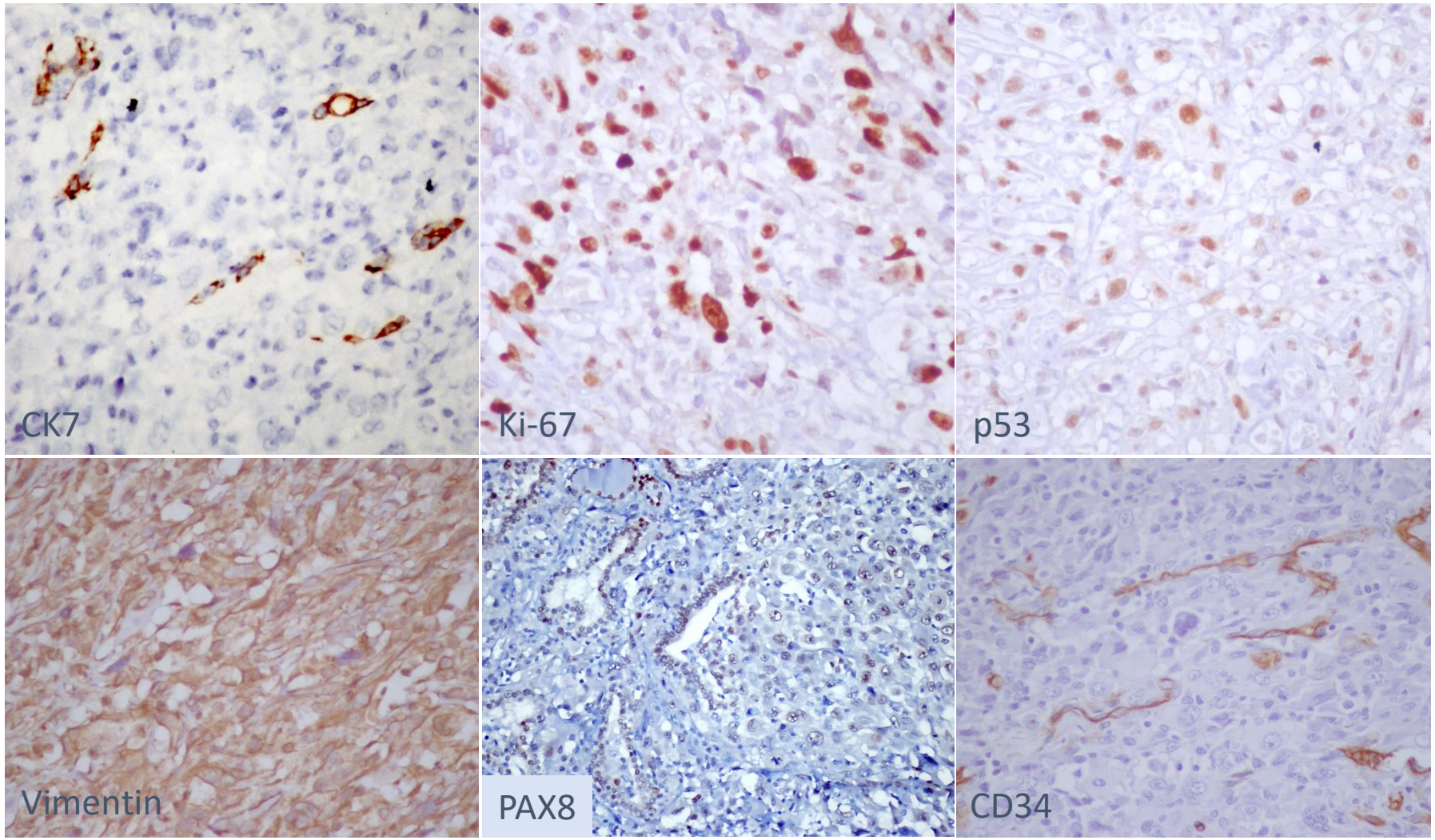
- The spindle cell areas can display a fascicular or storiform pattern of growth as well as foci of bone formation, skeletal muscle differentiation and angiossarcoma-like areas.
- Cells range from epithelioid to giant and spindle cells, are poorly cohesive and invade the adjacent tissues. Overall, the nuclei are atypical, pleomorphic and bizarre and have a very high mitotic index.

Anaplastic carcinoma

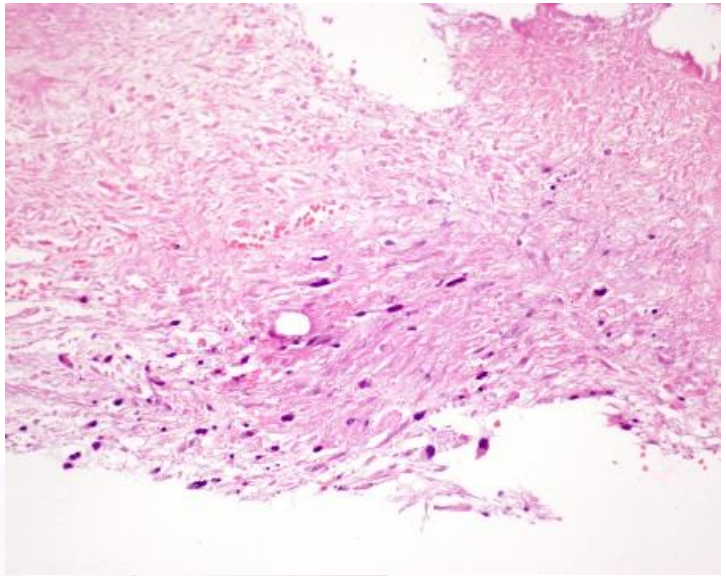
TG &TTF1 negative
CD45 negative
S100 negative

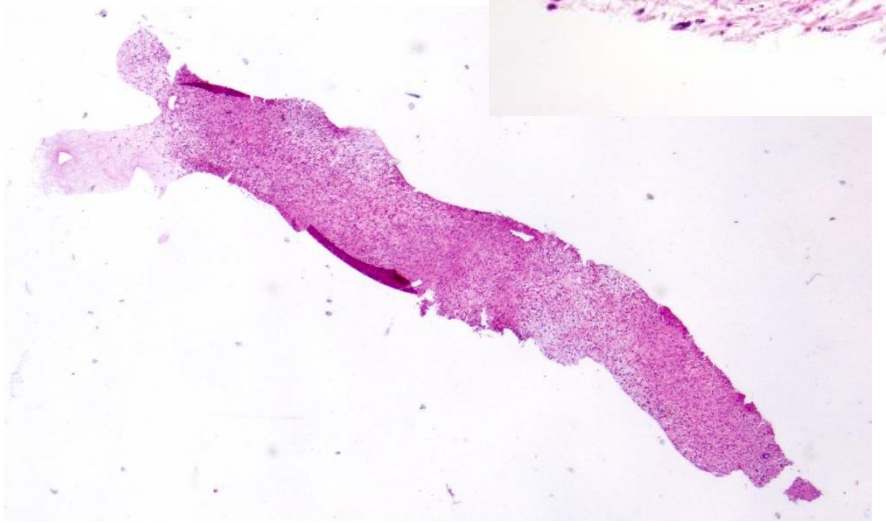
Differential diagnosis



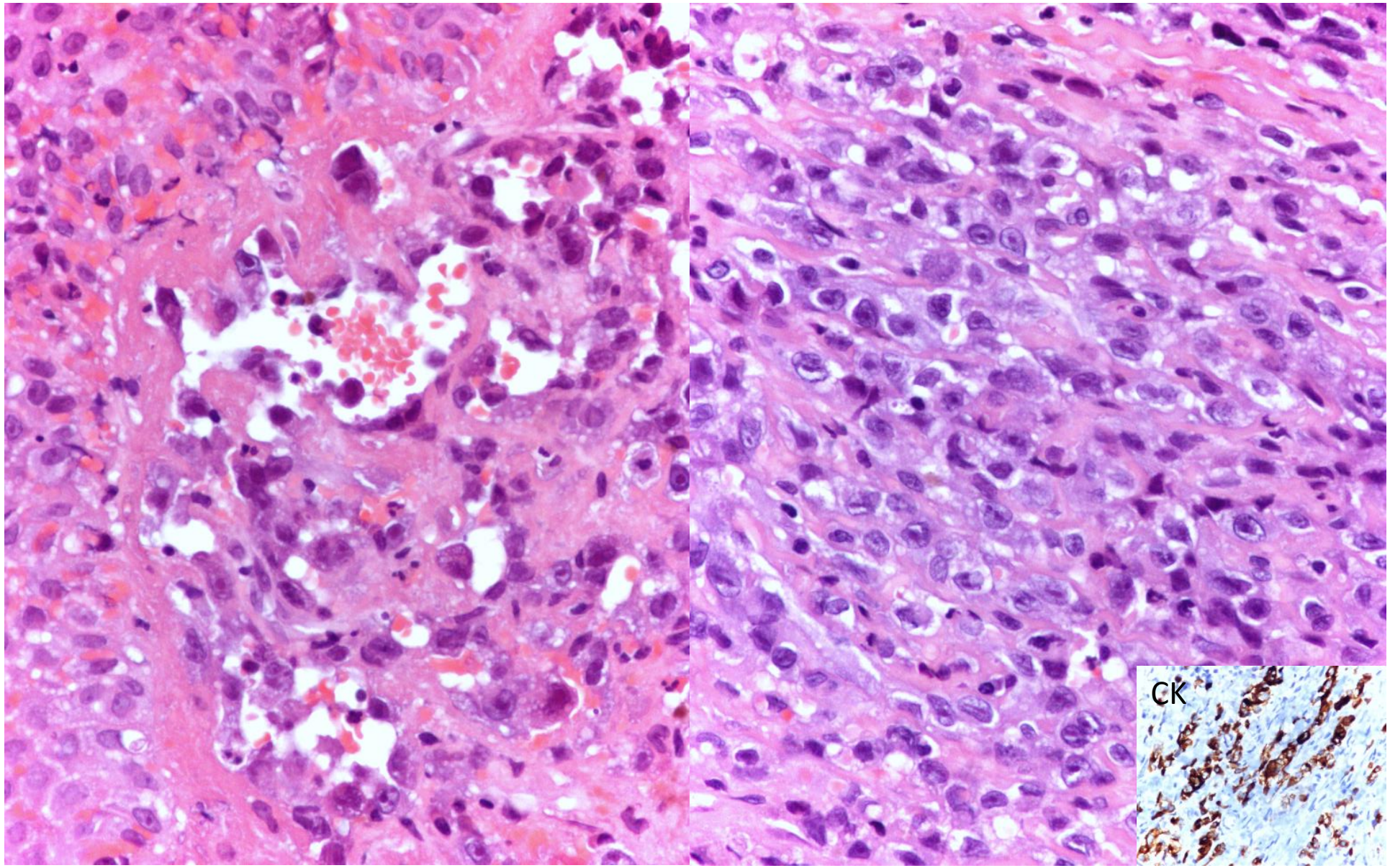
Differential diagnosis

- Paucicelular lesions
- Highly mitotic lesions
- Spindle cell lesions
- Inflammatory-cell rich lesions

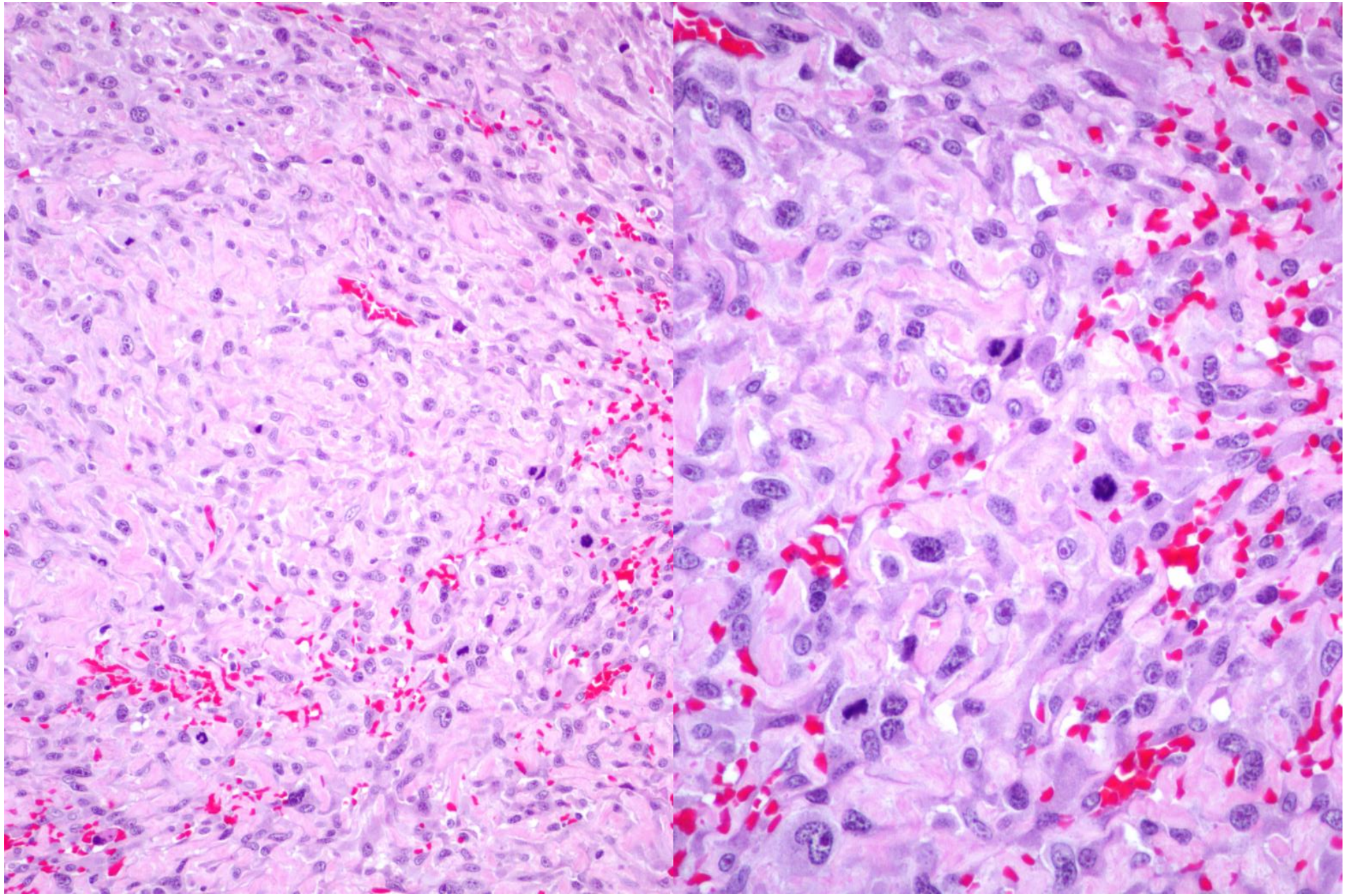




Elderly female patient with a long standing nodular goiter that reported a sudden increase in the size of the neck with compressive symptoms and dyspnea. The imagiologic study reported a mass in the thyroid that involved the respiratory tree. A bronchus biopsy was taken.



Angiosarcoma



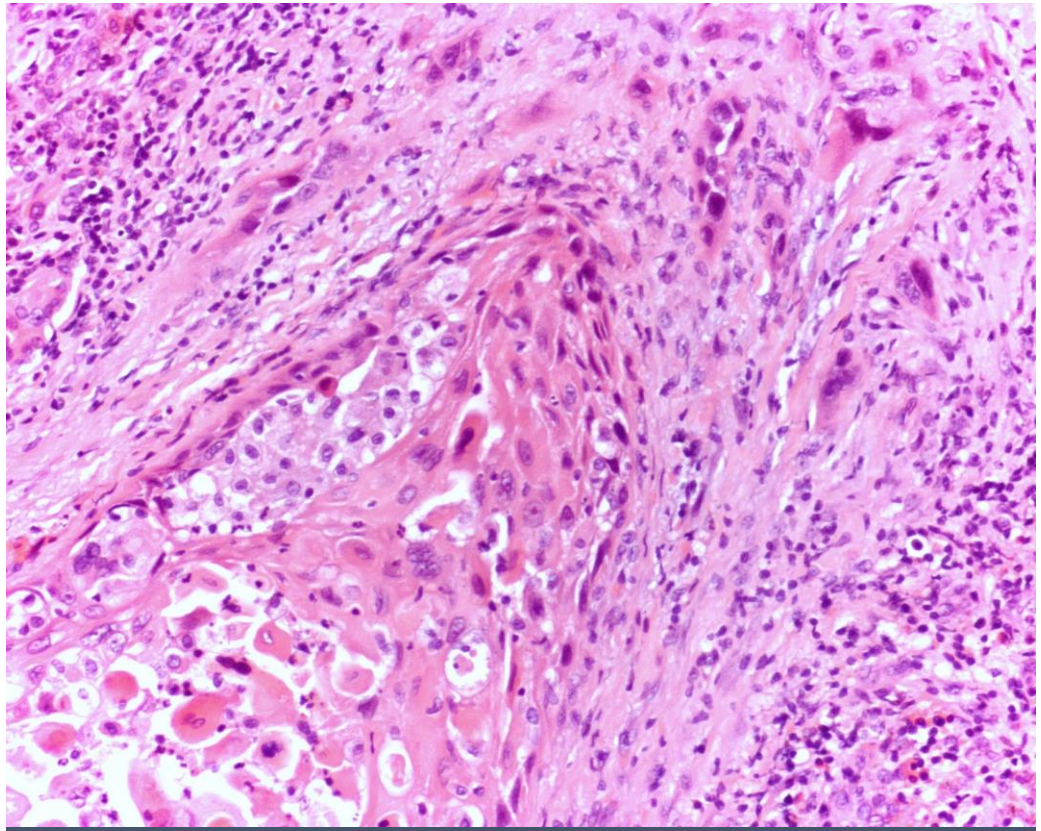
Hemangioendothelioma epithelioid

Squamous cell carcinoma of the thyroid is now considered as a subtype of anaplastic carcinoma

Rationale:

Primary squamous cell carcinoma of the thyroid

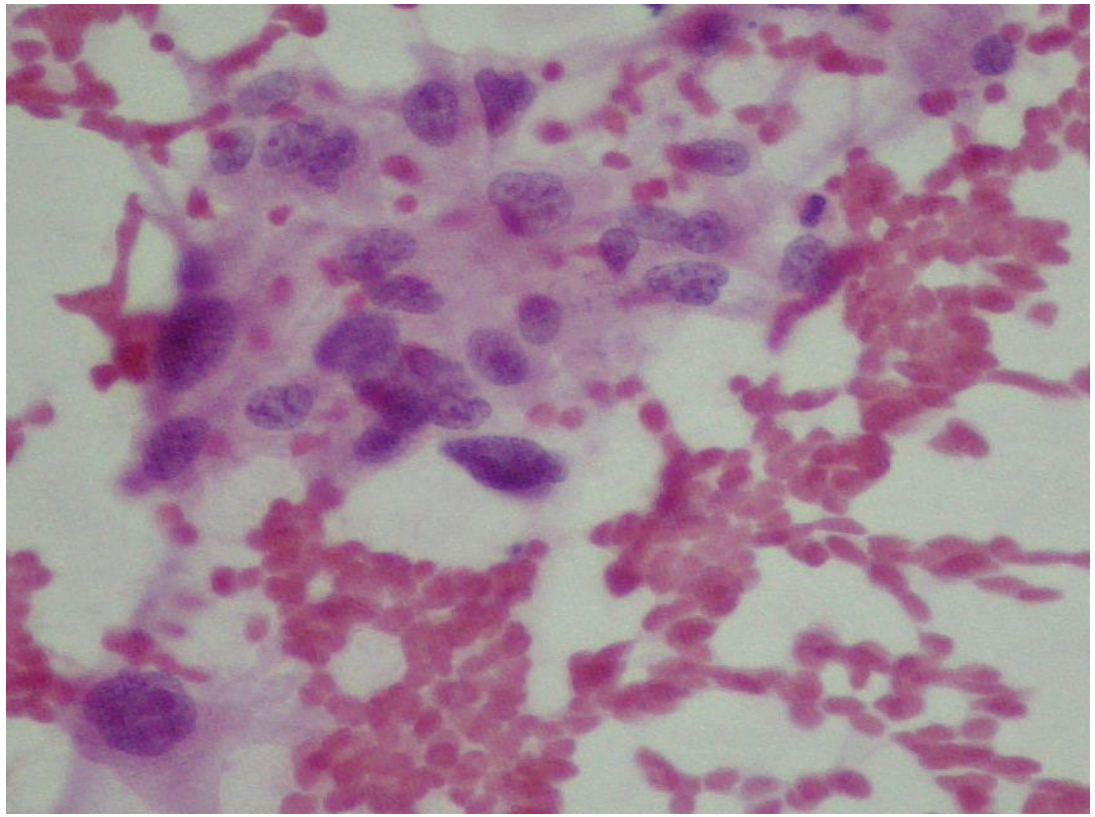
- has often a differentiated thyroid carcinoma component
- has an outcome similar to anaplastic carcinoma
- expresses PAX8 and TTF1 in 91% and 38% of cases, respectively
- carries *BRAF* V600E mutations in 60% of cases

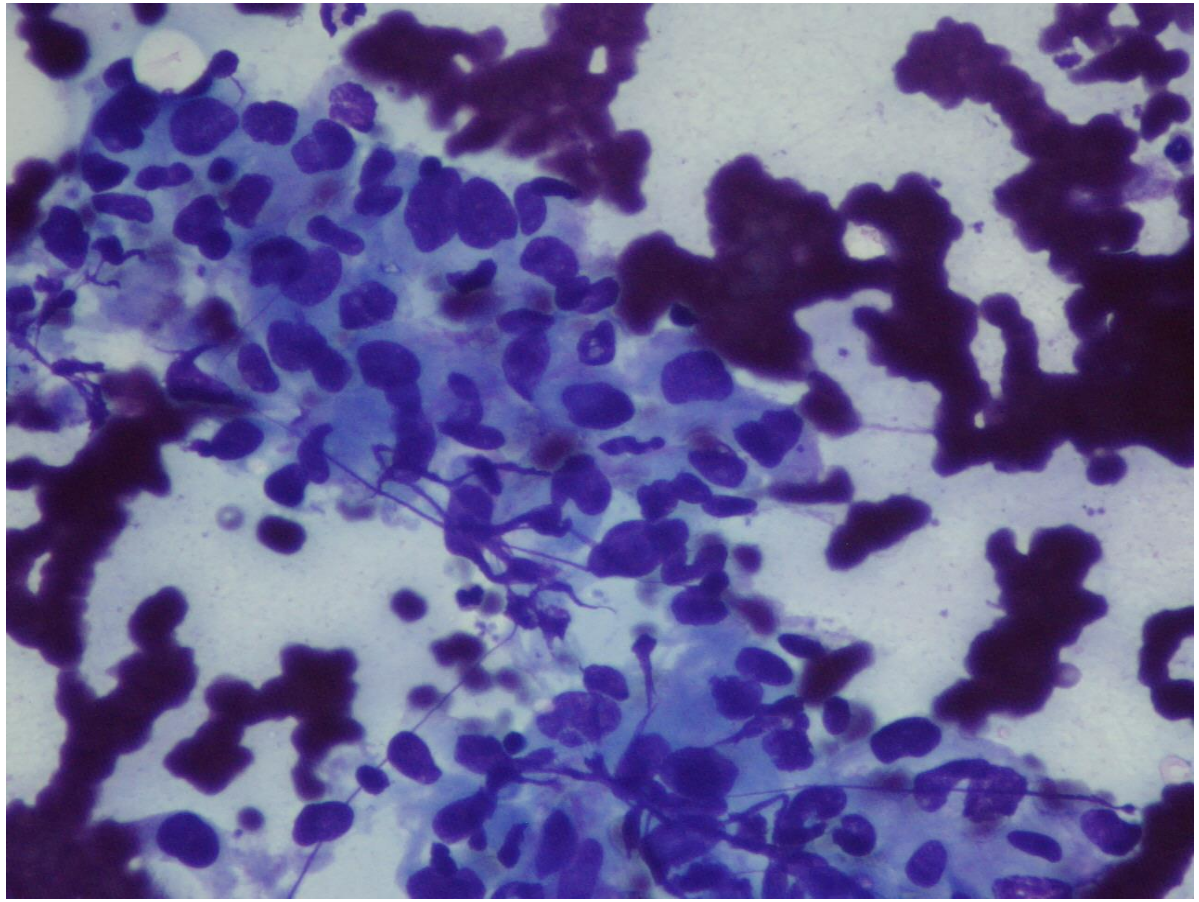


Squamous cell subtype of anaplastic carcinoma

Many patients are not presenting at a surgical stage

- Cytological aspirates may constitute the only available material for disease characterization



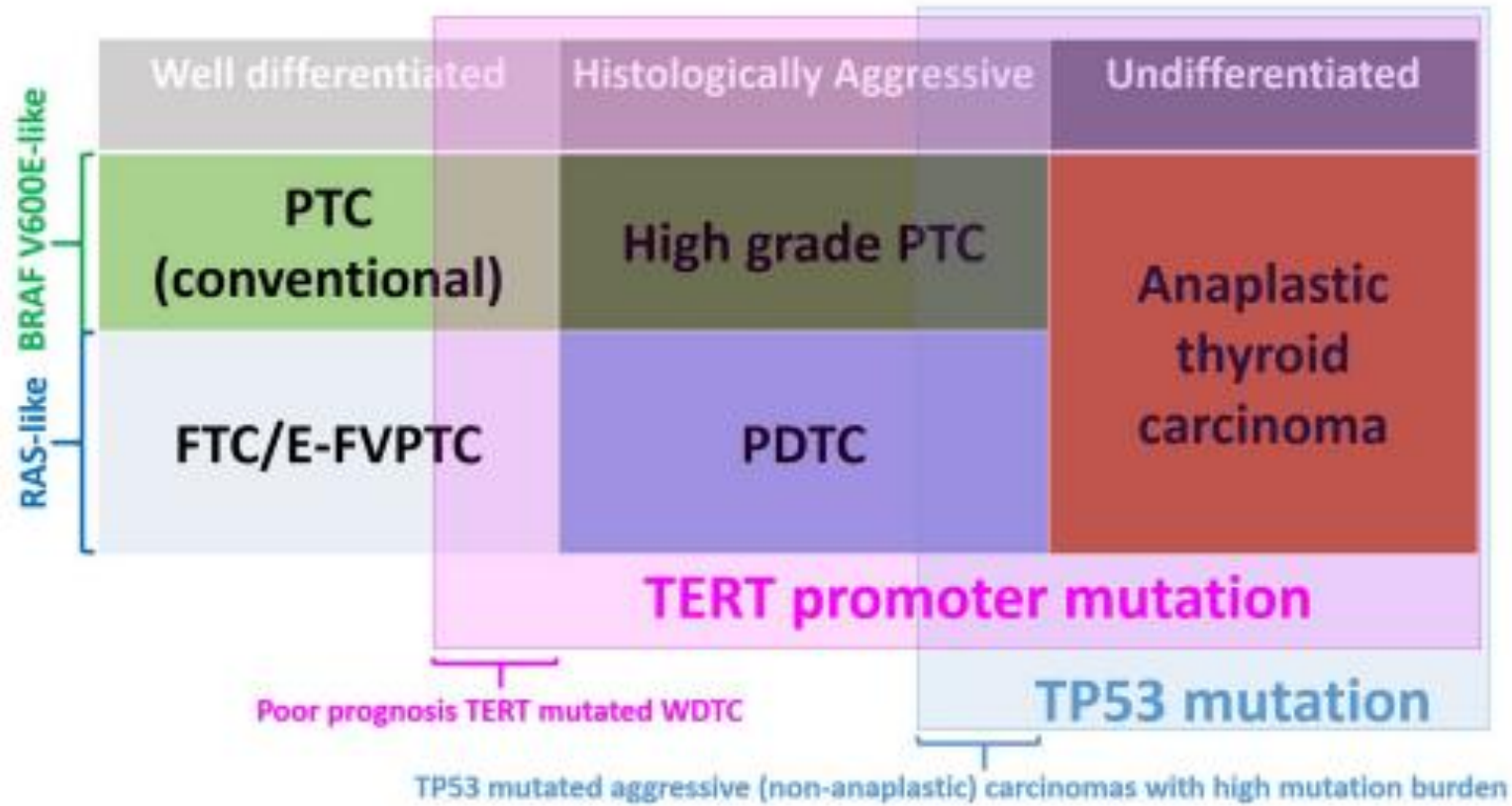


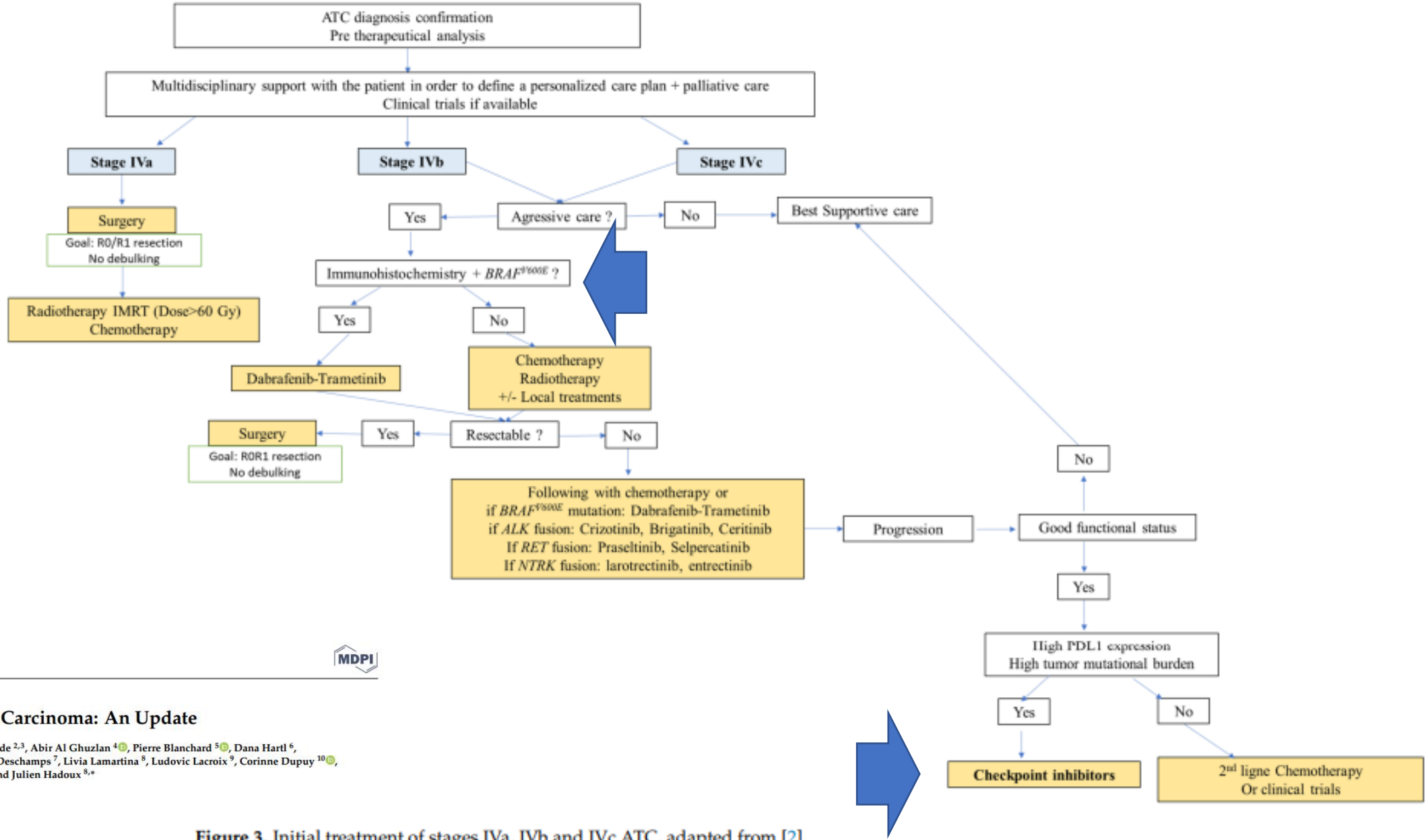
Endocrine Pathology (2021) 32:63–76
https://doi.org/10.1007/s12022-021-09665-2

Molecular Pathology of Poorly Differentiated and Anaplastic Thyroid Cancer: What Do Pathologists Need to Know?

Marco Volante[1] · Alfred K. Lam[2] · Mauro Papotti[1] · Giovanni Tallini[3]

Accepted: 4 January 2021 / Published online: 4 February 2021





cancers

MDPI

Review

Anaplastic Thyroid Carcinoma: An Update

Arnaud Jannin [1,2], Alexandre Escande [2,3], Abir Al Ghuzlan [4], Pierre Blanchard [5], Dana Hartl [6], Benjamin Chevalier [1,2], Frédéric Deschamps [7], Livia Lamartina [8], Ludovic Lacroix [9], Corinne Dupuy [10], Eric Baudin [8], Christine Do Cao [1] and Julien Hadoux [8,*]

Figure 3. Initial treatment of stages IVa, IVb and IVc ATC, adapted from [2].

original reports abstract

PD-1 Blockade in Anaplastic Thyroid Carcinoma

Jaume Capdevila, MD, PhD[1]; Lori J. Wirth, MD[2]; Thomas Ernst, MD[3]; Santiago Ponce Aix, MD[4]; Chia-Chi Lin, MD, PhD[5]; Rodryg Ramlau, MD, PhD[6]; Marcus O. Butler, MD[7]; Jean-Pierre Delord, MD, PhD[8]; Hans Gelderblom, MD, PhD[9]; Paolo A. Ascierto, MD[10]; Angelica Fasolo, MD[11]; Dagmar Führer, MD, PhD[12]; Marie Luise Hütter-Krönke, MD[13]; Patrick M. Forde, MBBCh[14]; Anna Wrona, MD, PhD[15]; Armando Santoro, MD[16]; Peter M. Sadow, MD, PhD[2]; Sebastian Szpakowski, PhD[17]; Hongqian Wu, PhD[18]; Geraldine Bostel, PhD[19]; Jason Faris, MD[17]; Scott Cameron, MD, PhD[17]; Andreea Varga, MD[20]; and Matthew Taylor, MD[21]

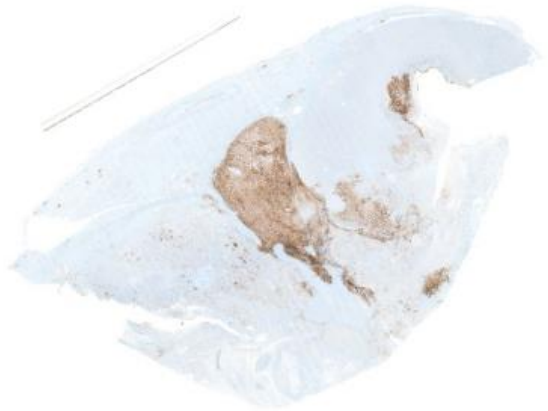
PURPOSE Anaplastic thyroid carcinoma is an aggressive malignancy that is almost always fatal and lacks effective systemic treatment options for patients with *BRAF*-wild type disease. As part of a phase I/II study in patients with advanced/metastatic solid tumors, patients with anaplastic thyroid carcinoma were treated with spartalizumab, a humanized monoclonal antibody against the programmed death-1 (PD-1) receptor.

METHODS We enrolled patients with locally advanced and/or metastatic anaplastic thyroid carcinoma in a phase II cohort of the study. Patients received 400 mg spartalizumab intravenously, once every 4 weeks. The overall response rate was determined according to RECIST v1.1.

RESULTS Forty-two patients were enrolled. Adverse events were consistent with those previously observed with PD-1 blockade. Most common treatment-related adverse events were diarrhea (12%), pruritus (12%), fatigue (7%), and pyrexia (7%). The overall response rate was 19%, including three patients with a complete response and five with a partial response. Most patients had baseline tumor biopsies positive for PD-L1 expression (n = 28/40 evaluable), and response rates were higher in PD-L1–positive (8/28; 29%) versus PD-L1–negative (0/12; 0%) patients. The highest rate of response was observed in the subset of patients with PD-L1 ≥ 50% (6/17; 35%). Responses were seen in both *BRAF*-nonmutant and *BRAF*-mutant patients and were durable, with a 1-year survival of 52.1% in the PD-L1–positive population.

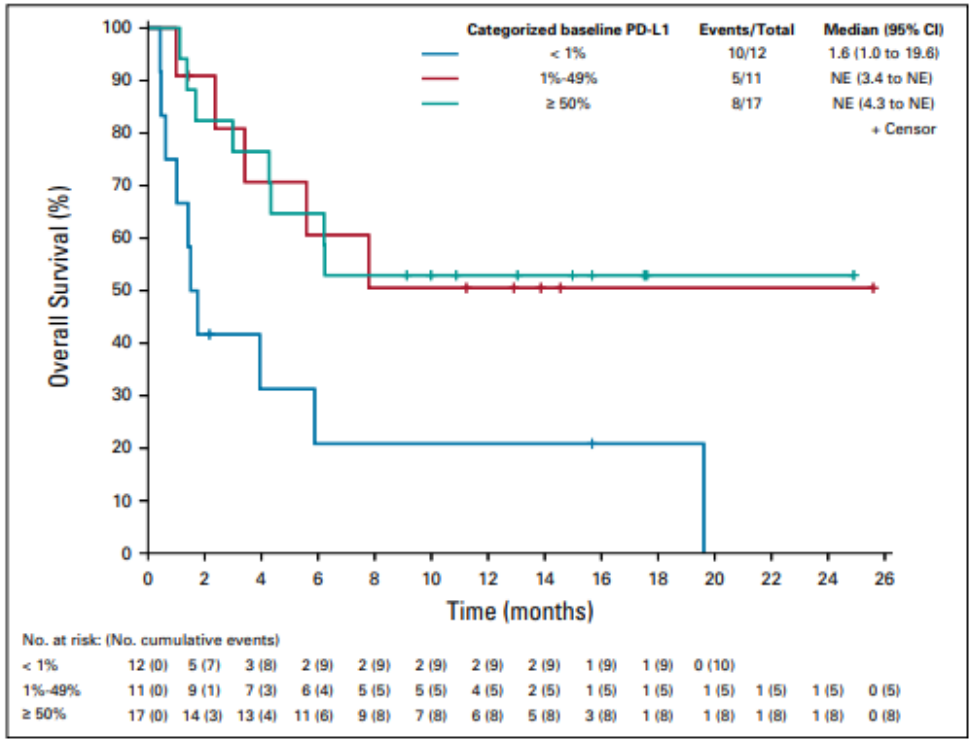
CONCLUSION To our knowledge, this is the first clinical trial to show responsiveness of anaplastic thyroid carcinoma to PD-1 blockade.

J Clin Oncol 38:2620-2627. © 2020 by American Society of Clinical Oncology



PD-L1, 22C3,0x

PD-1 Blockade in Anaplastic Thyroid Carcinoma



Seminar of Young Pathologists
Litomysl, Czech Republic
April 12-13, 2024

Poorly differentiated and anaplastic thyroid carcinomas

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