Clownfish and Anemone

A unique symbiotic relationship of two molecular pathways

Alireza Khani

Douglass Hanly Moir Pathology

THE 47TH ANNUAL SCIENTIFIC MEETING of the Australasian Division of the International Academy of Pathology

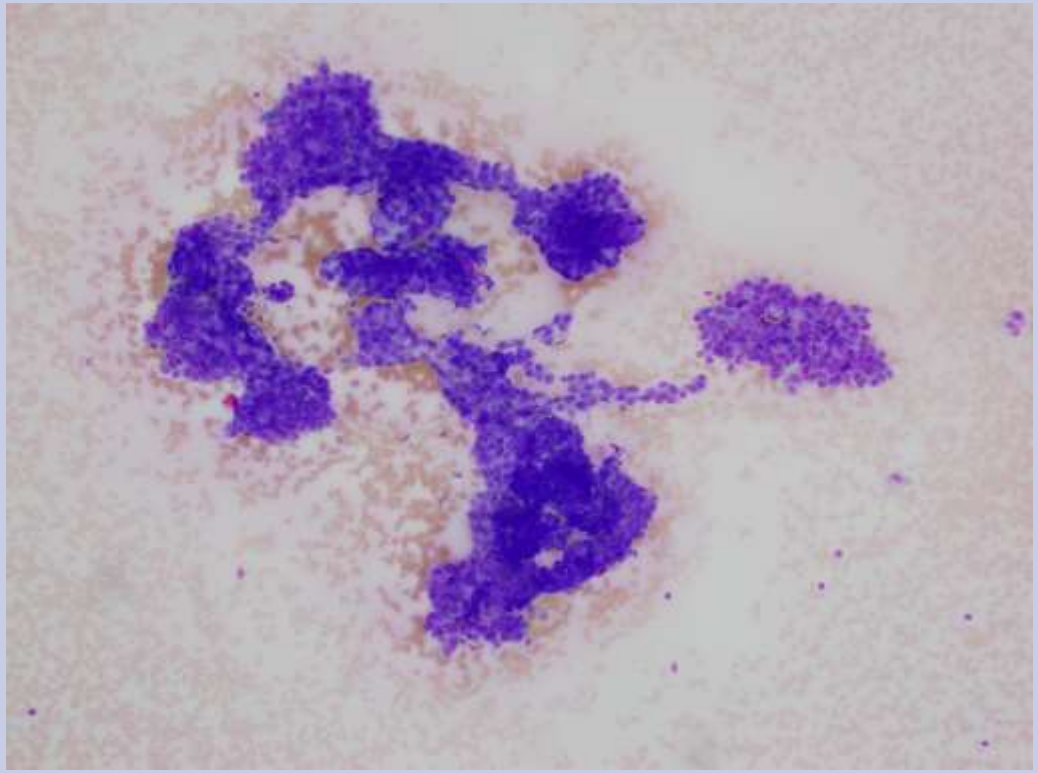
Disclosure of Relevant Financial Relationships

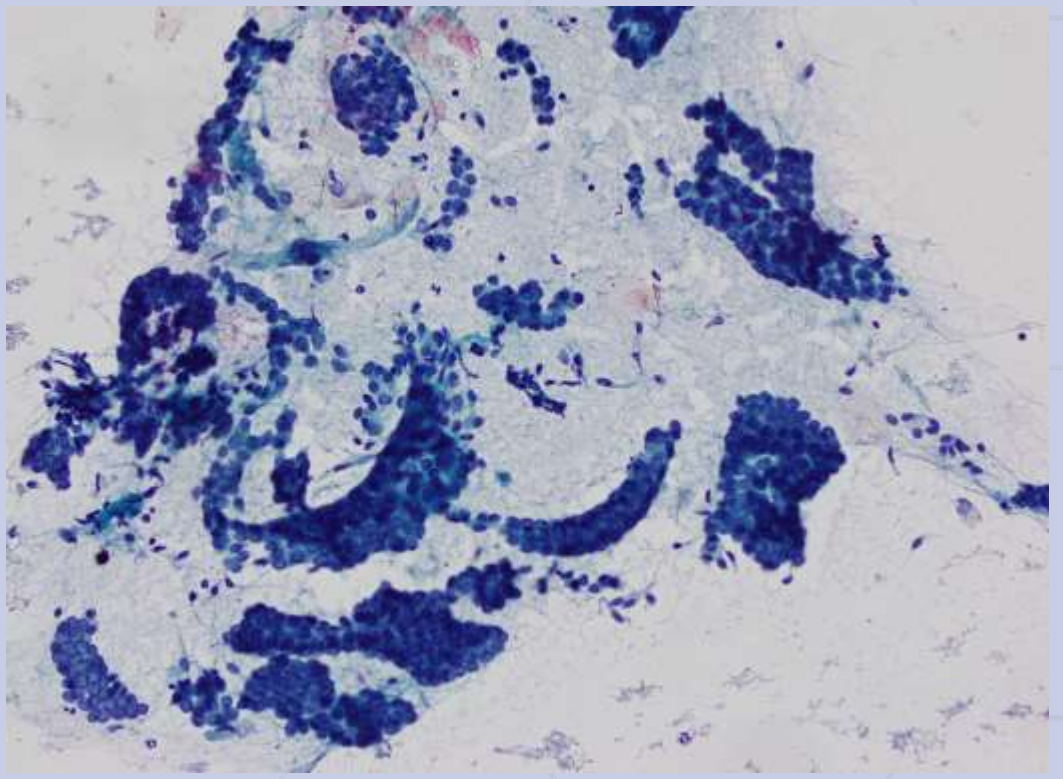
No relevant financial relationships

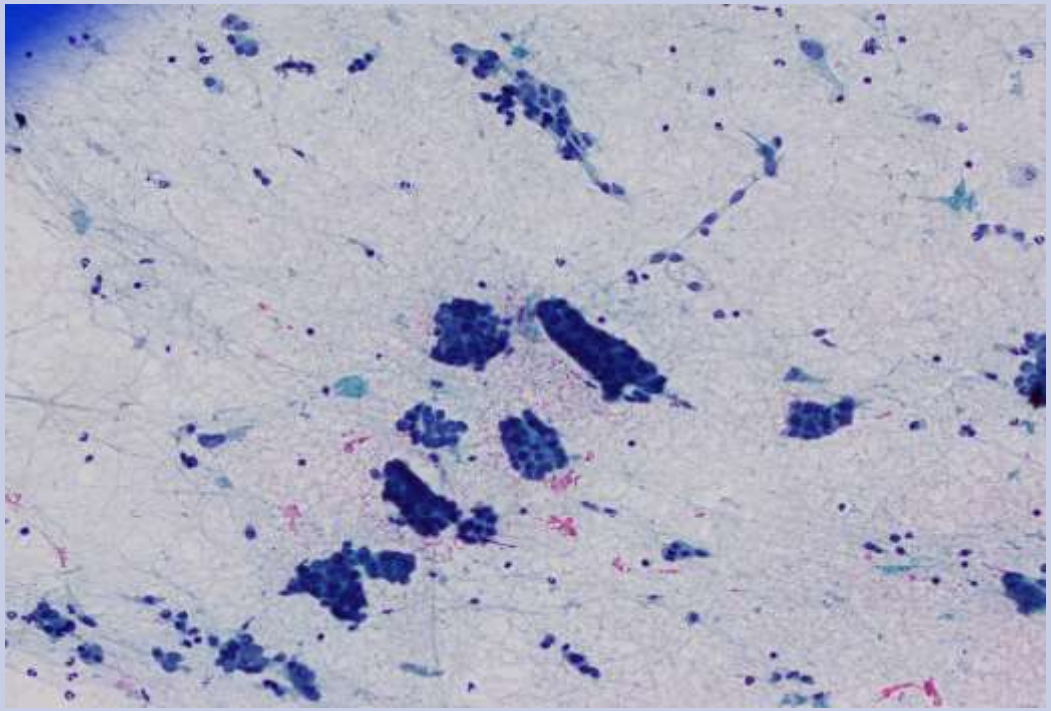
Case

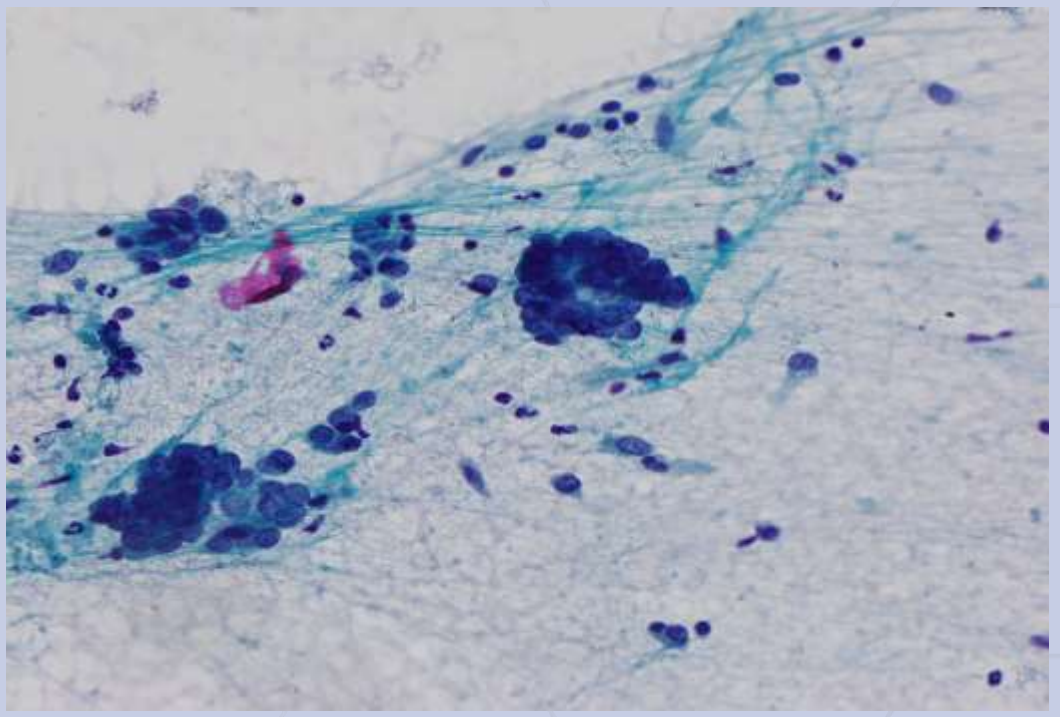
17-year-old female presented with a 4cm left-sided neck lump without cervical lymphadenopathy

An US confirmed a 40 mm solid, heterogenous non-calcified, TIRADS 4 thyroid nodule



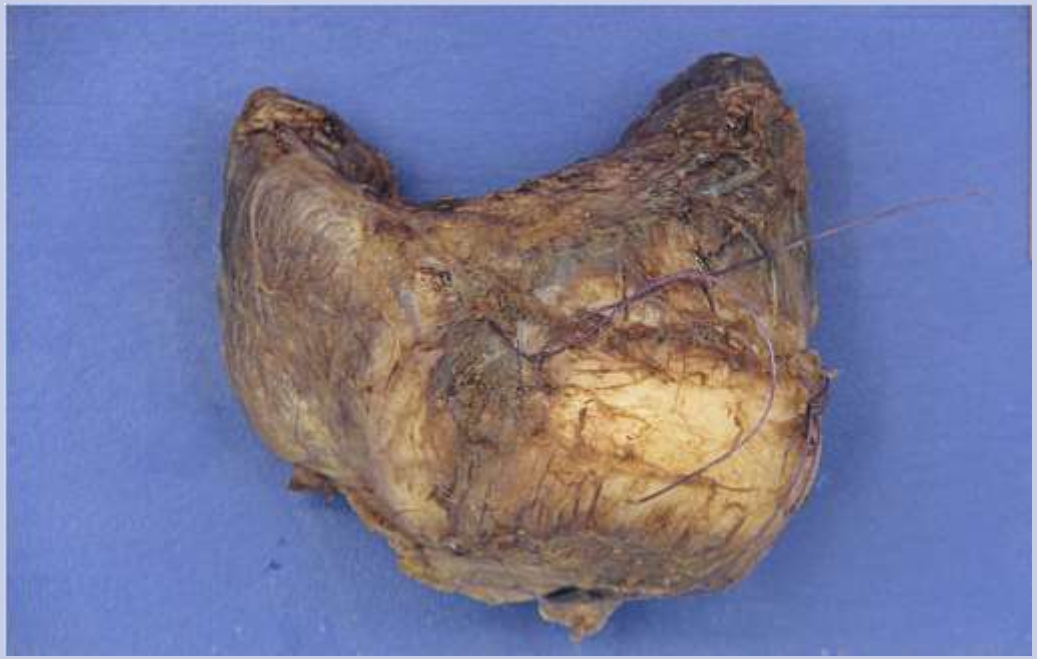


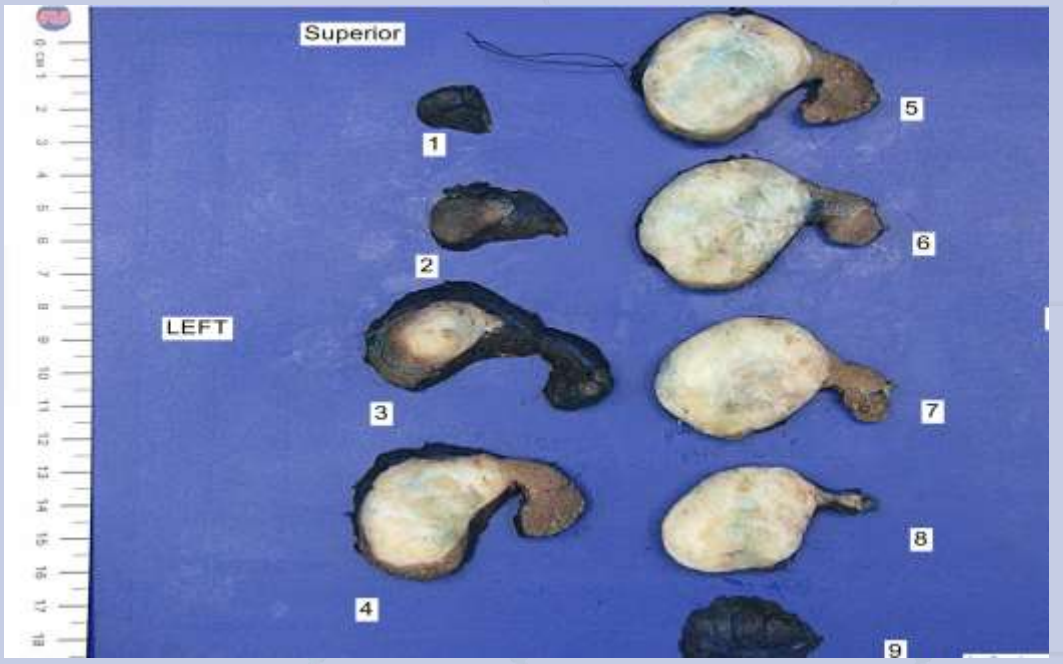




OPERATIVE MANAGEMENT

- The patient had a total thyroidectomy with bilateral central neck dissection.
- The cancer appeared to occupy the whole of the left lobe of the thyroid and extended across the midline
- There was no evidence of nerve involvement intraoperatively.




Superior
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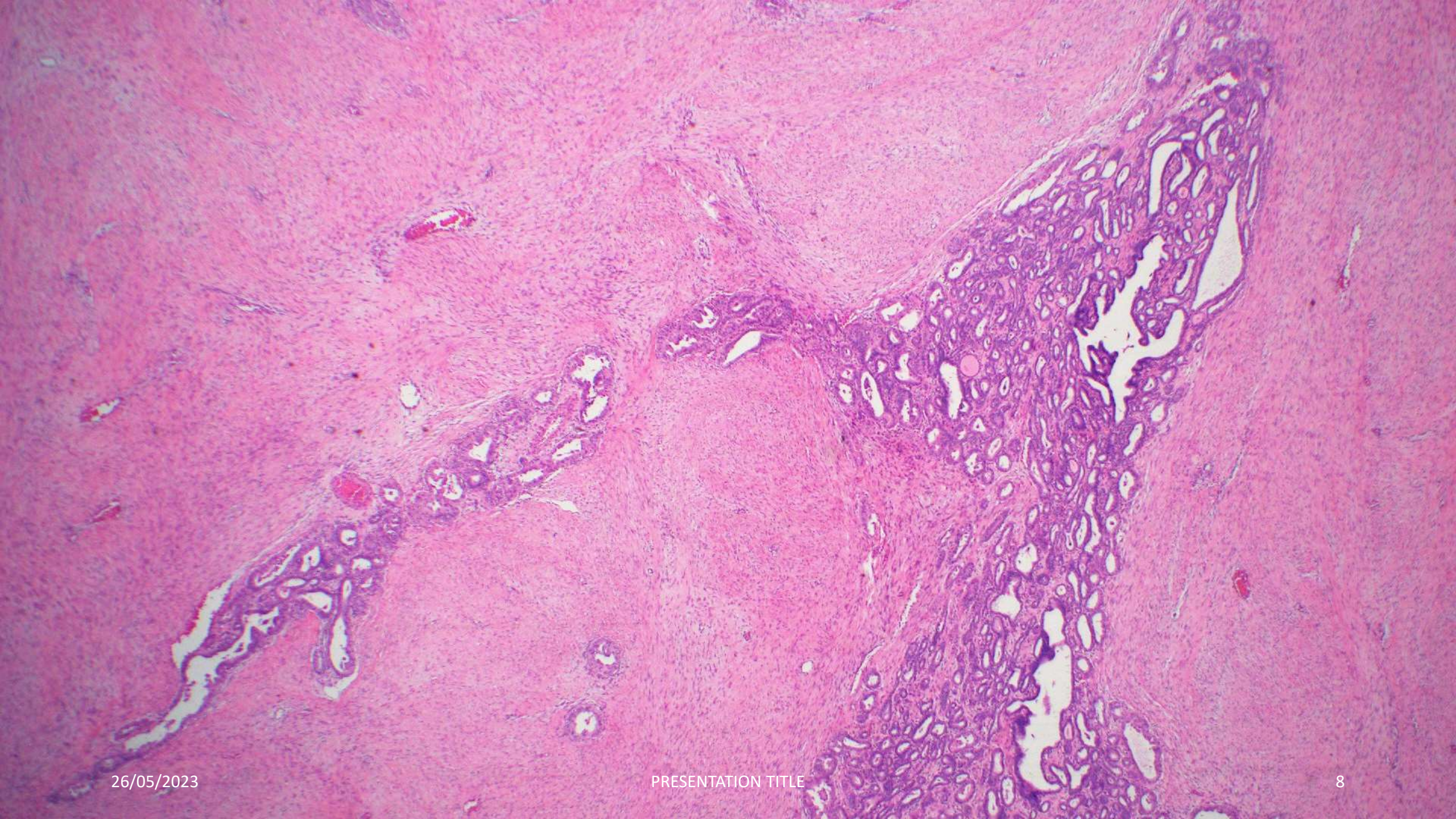
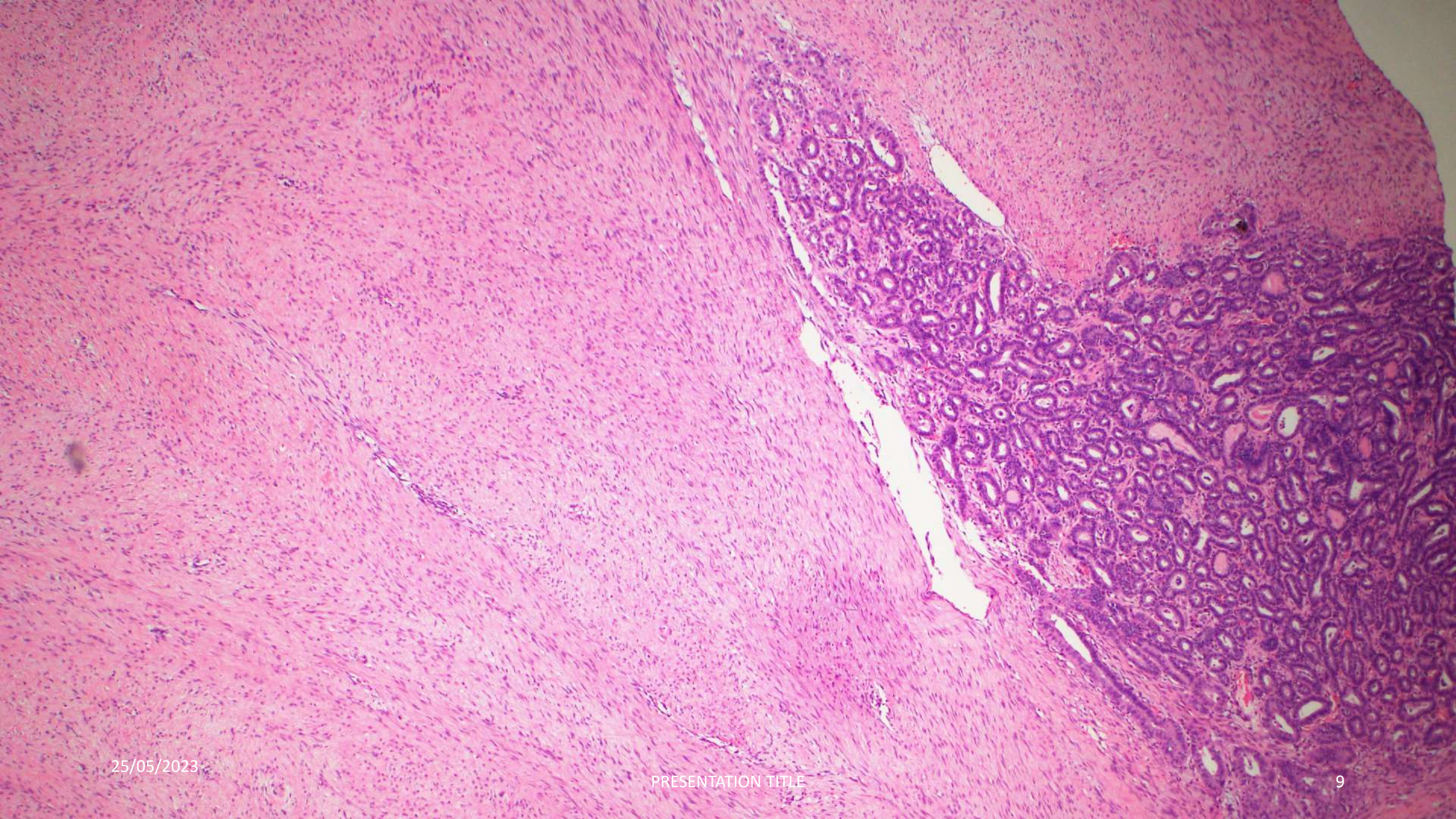
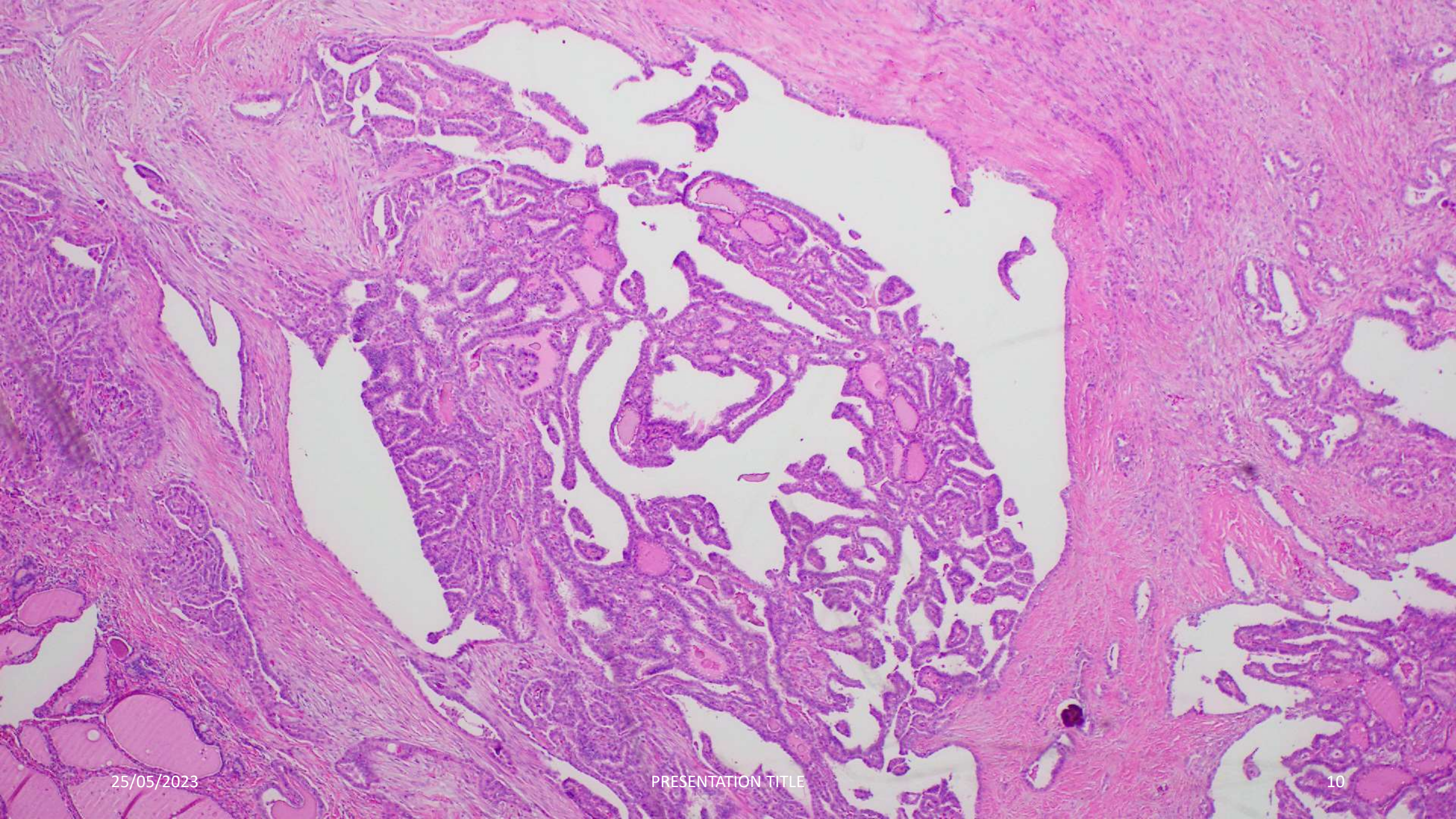
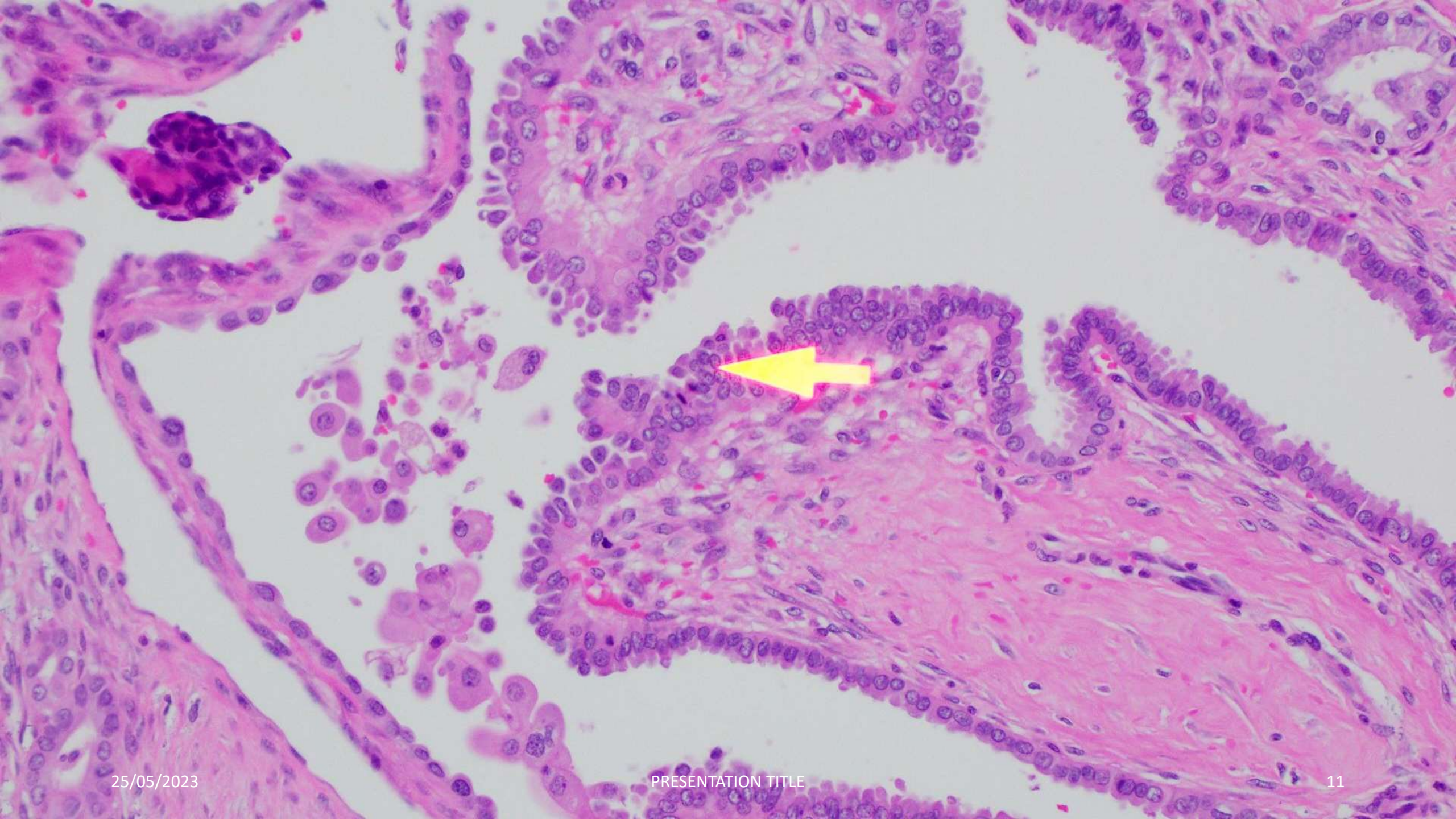
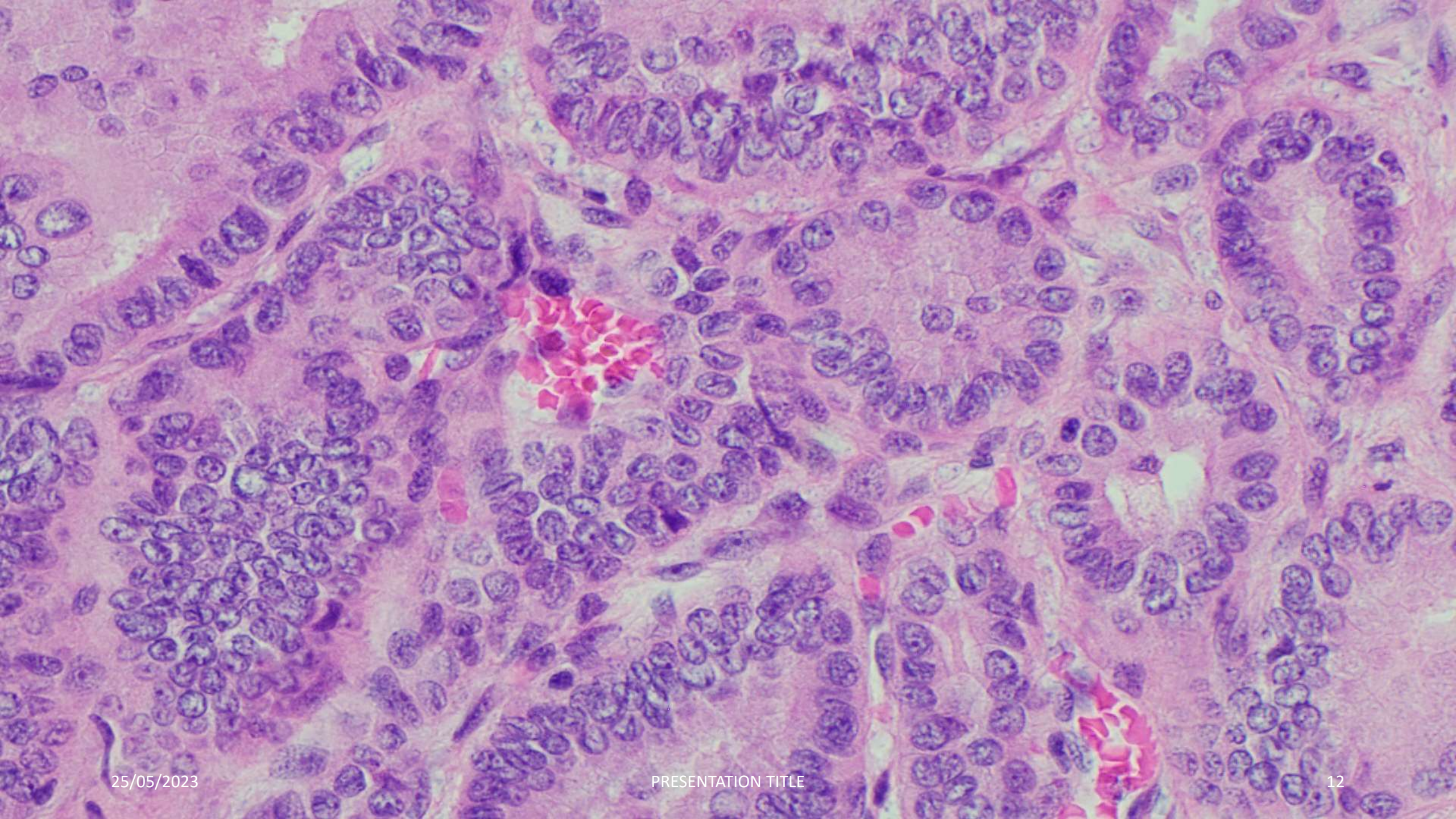
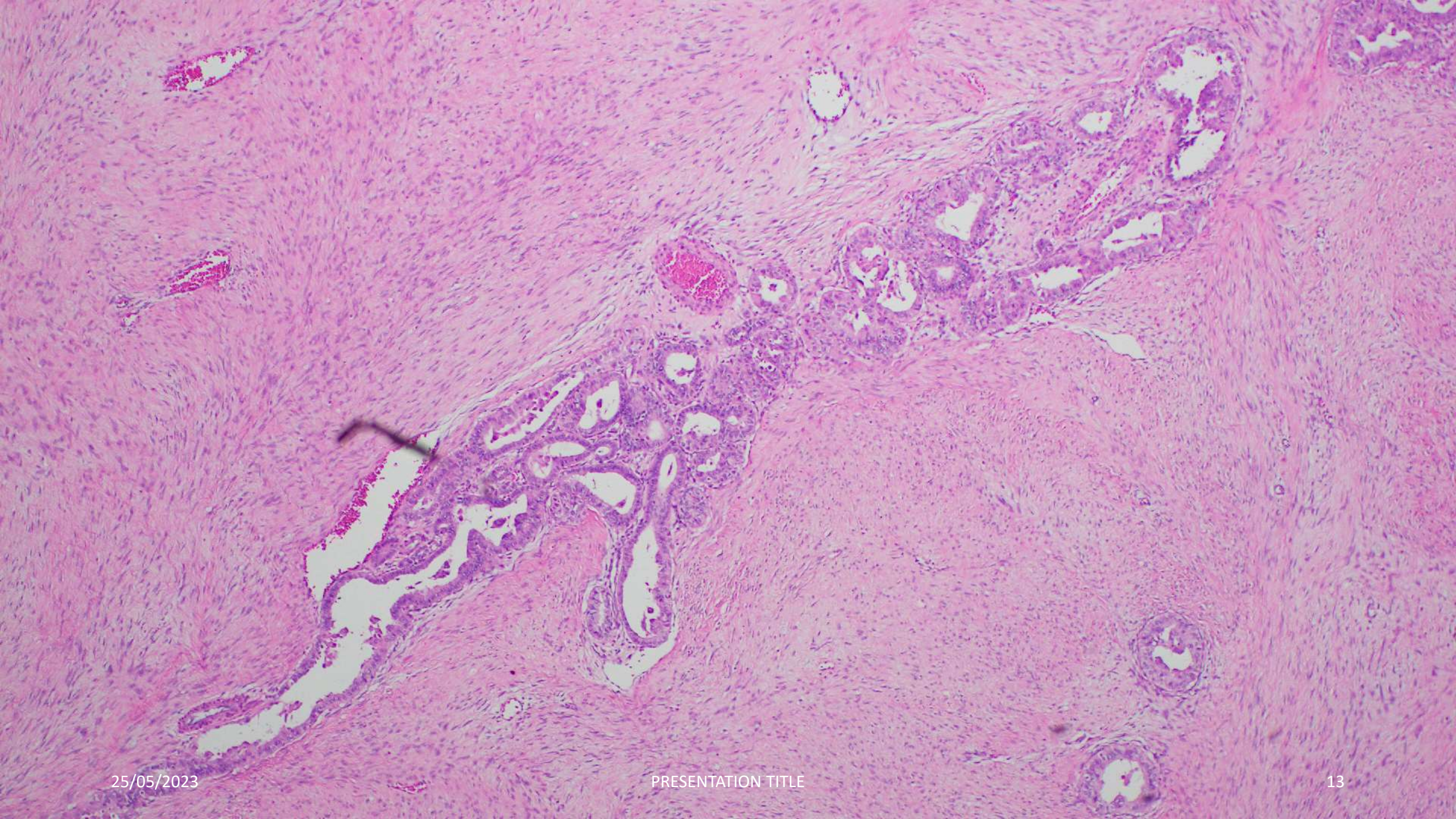


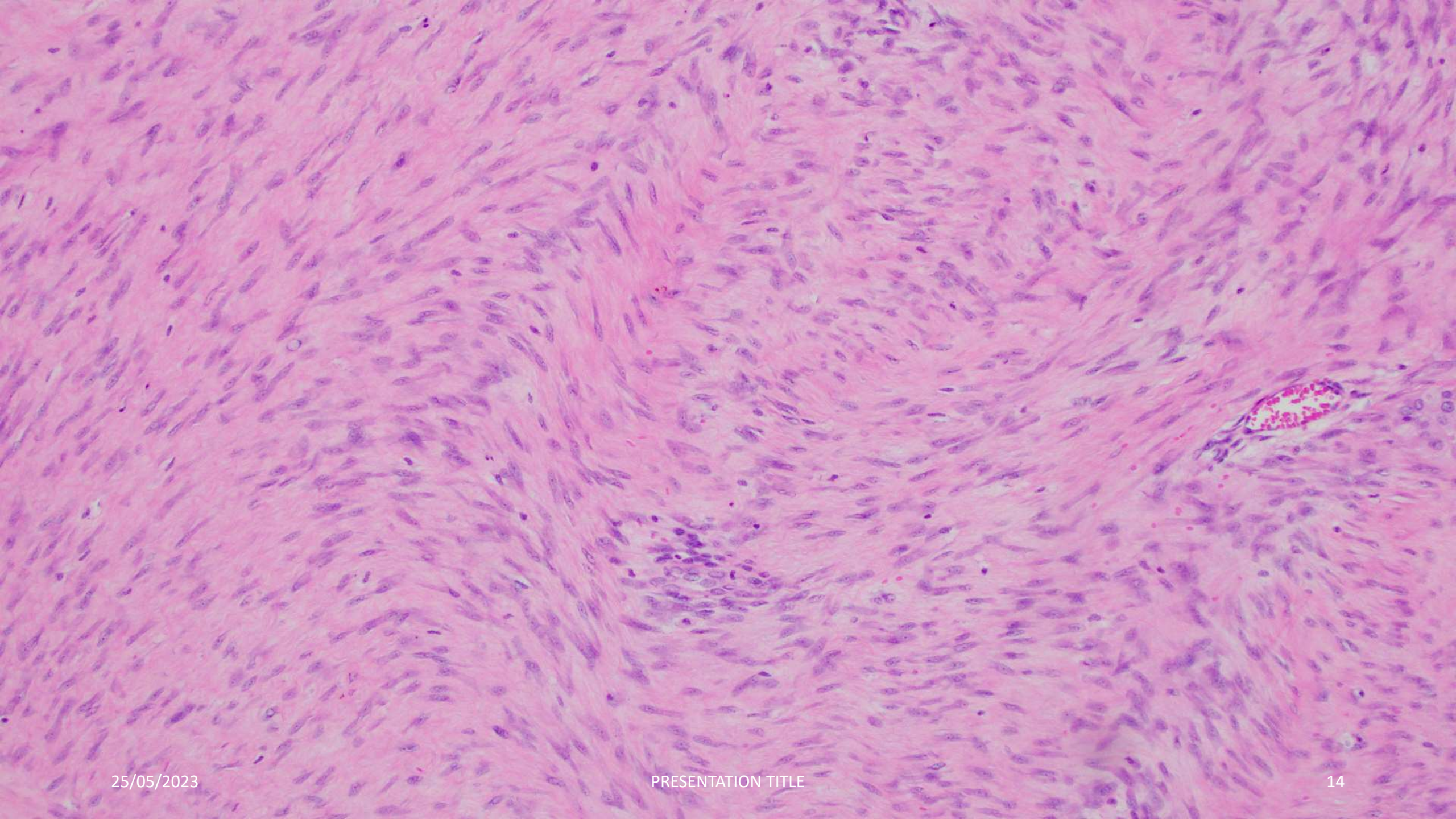


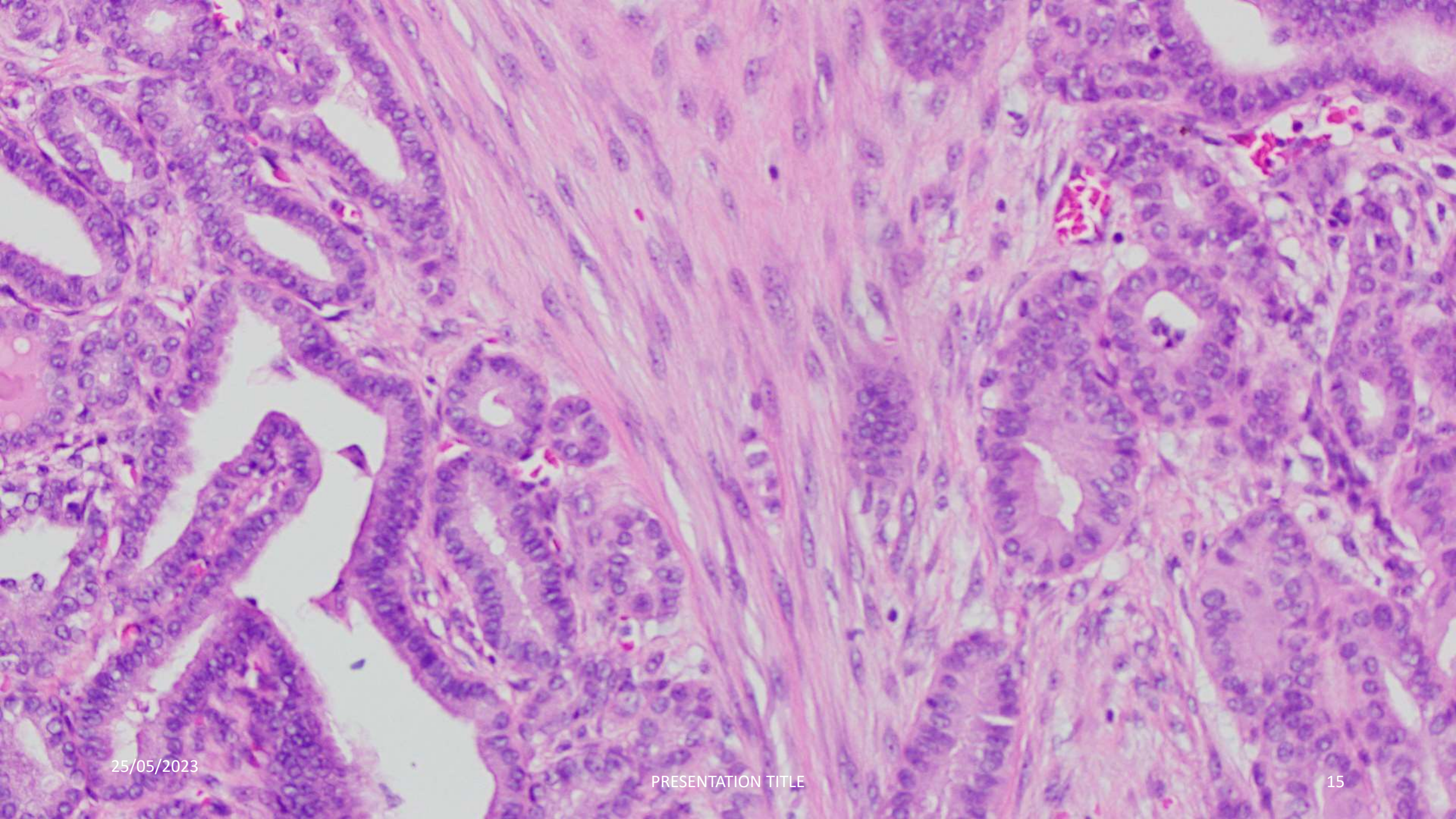


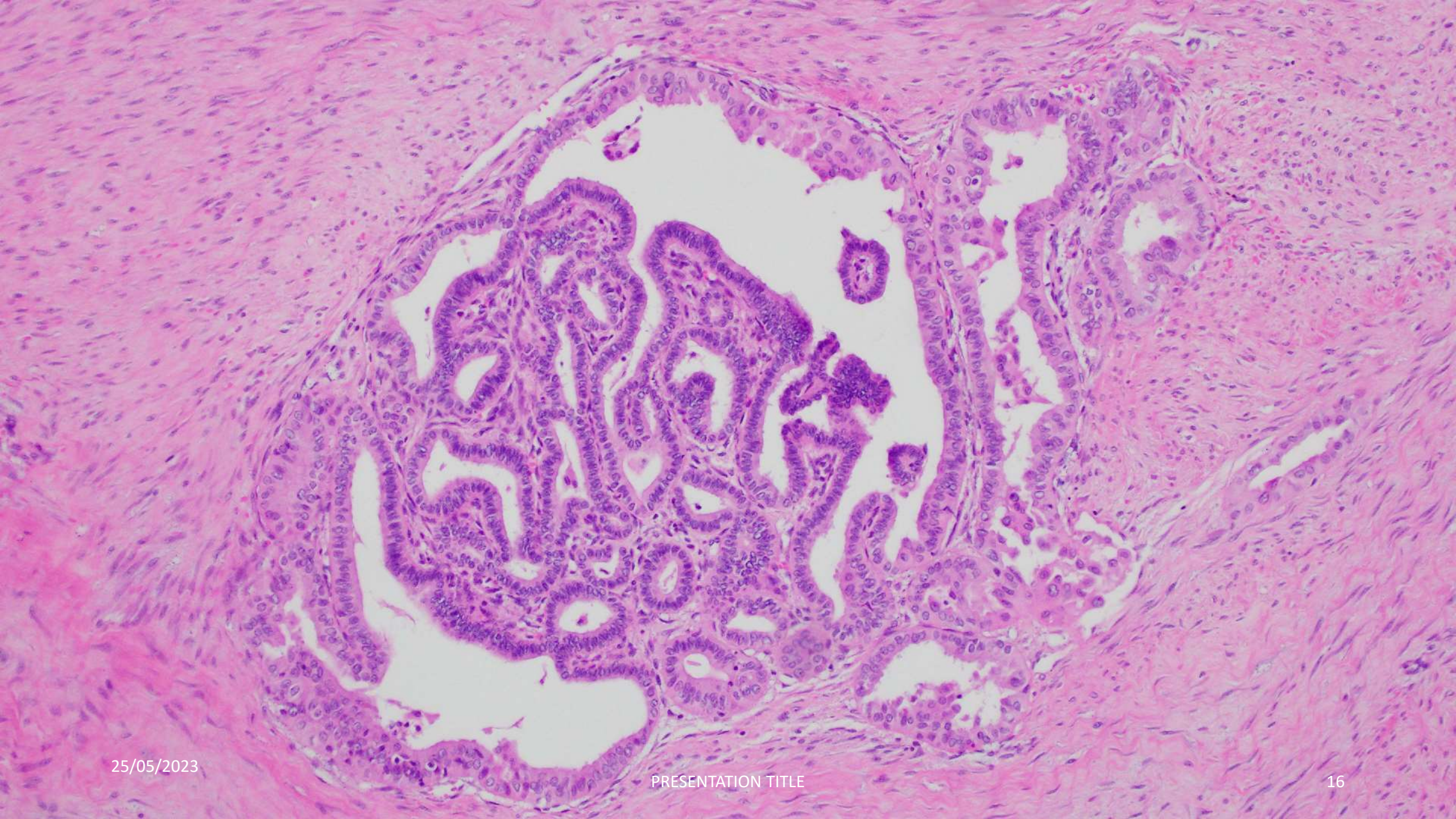


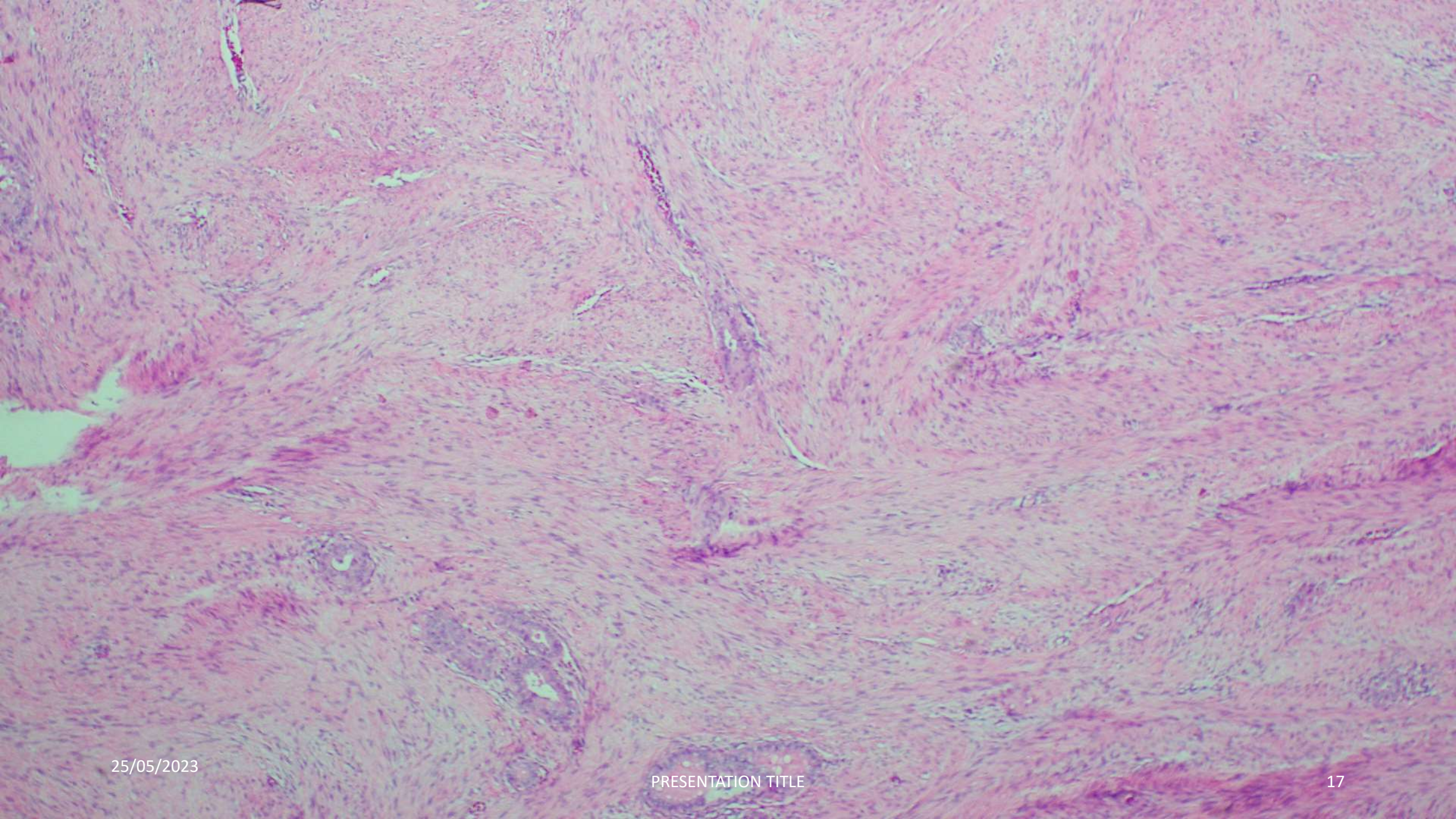


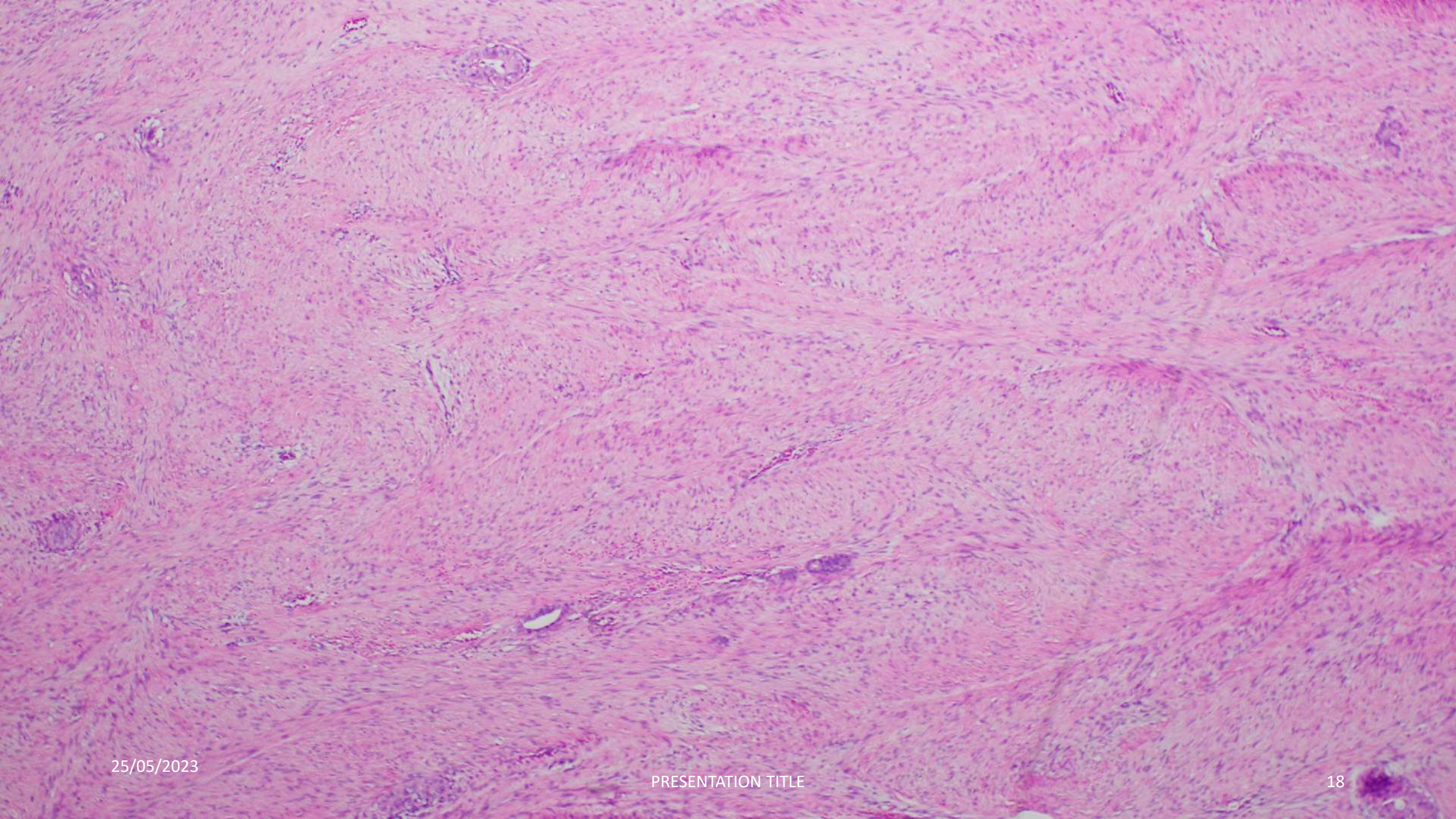


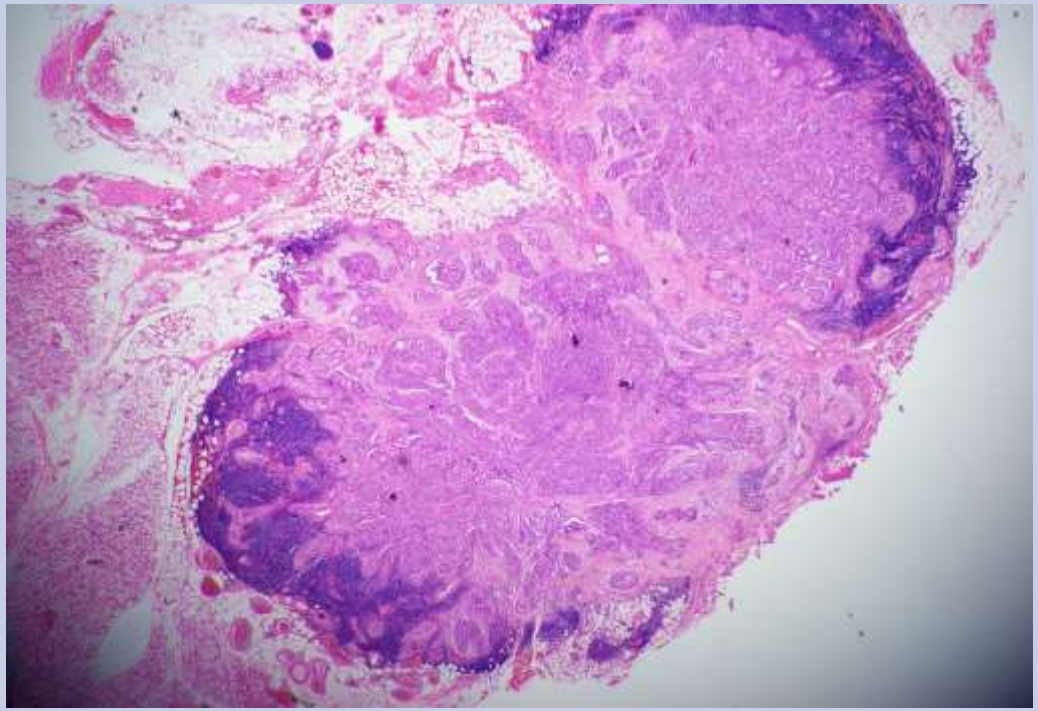


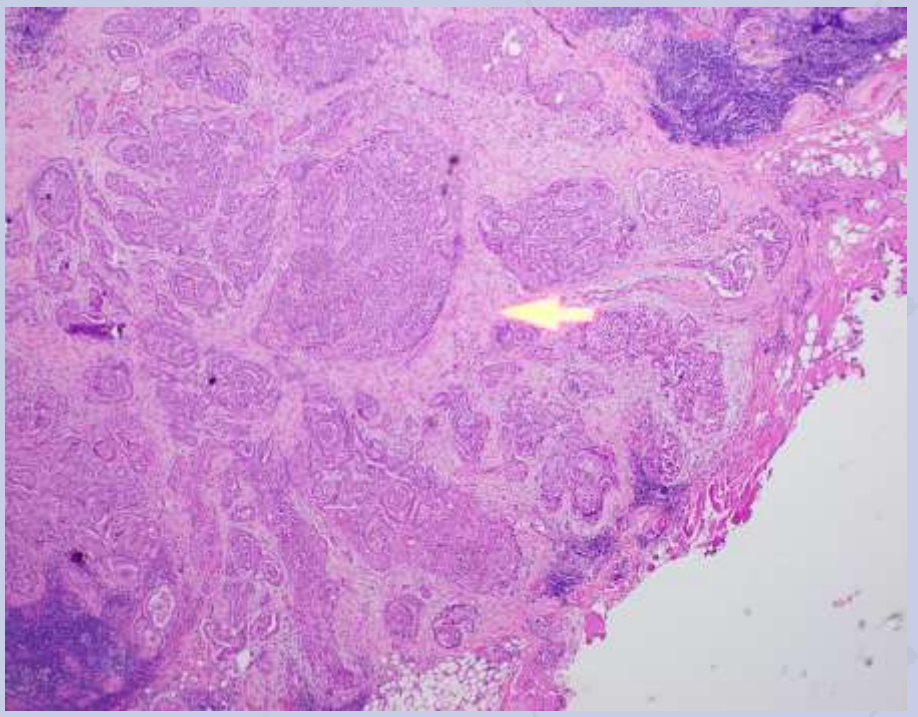


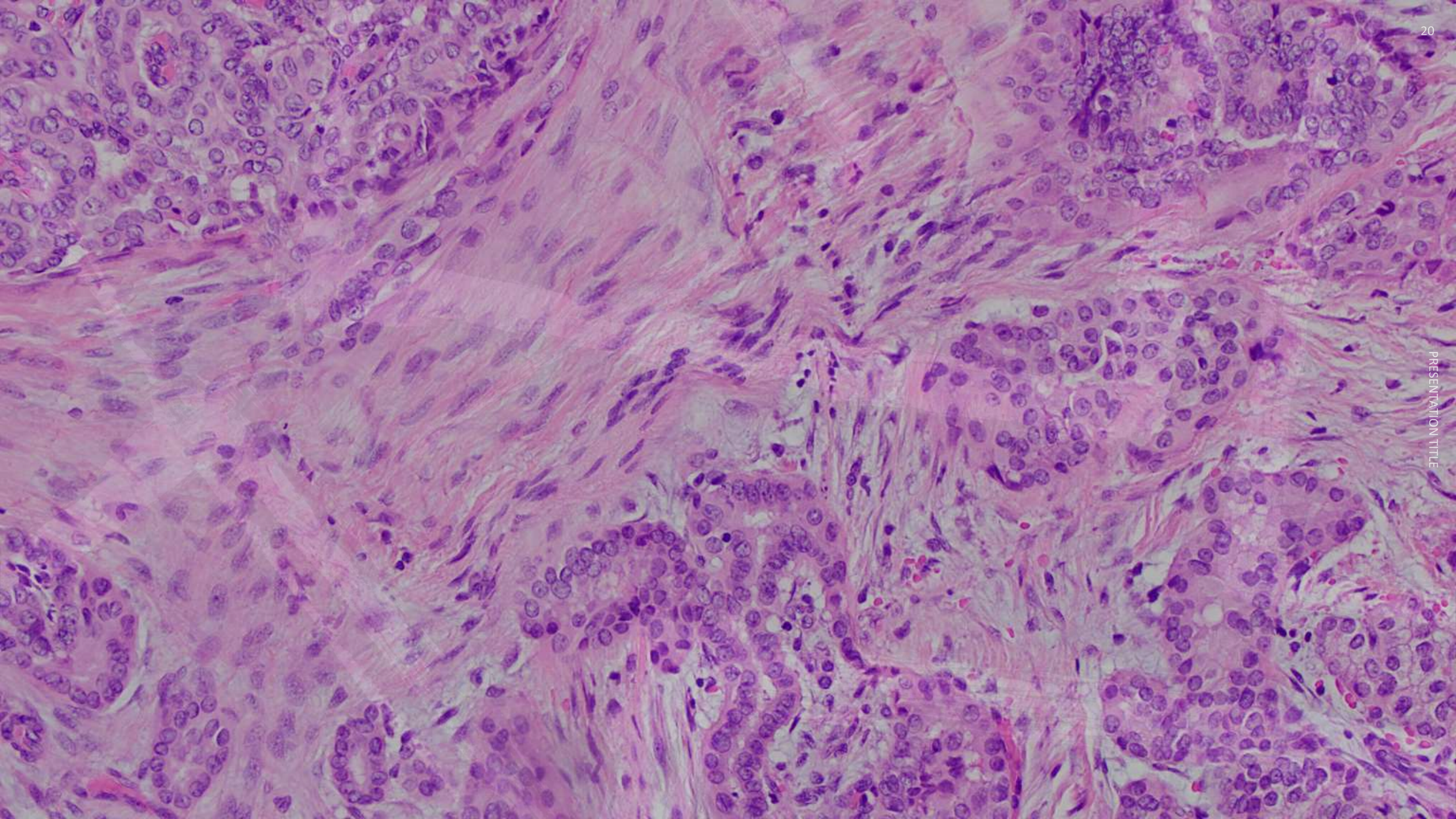


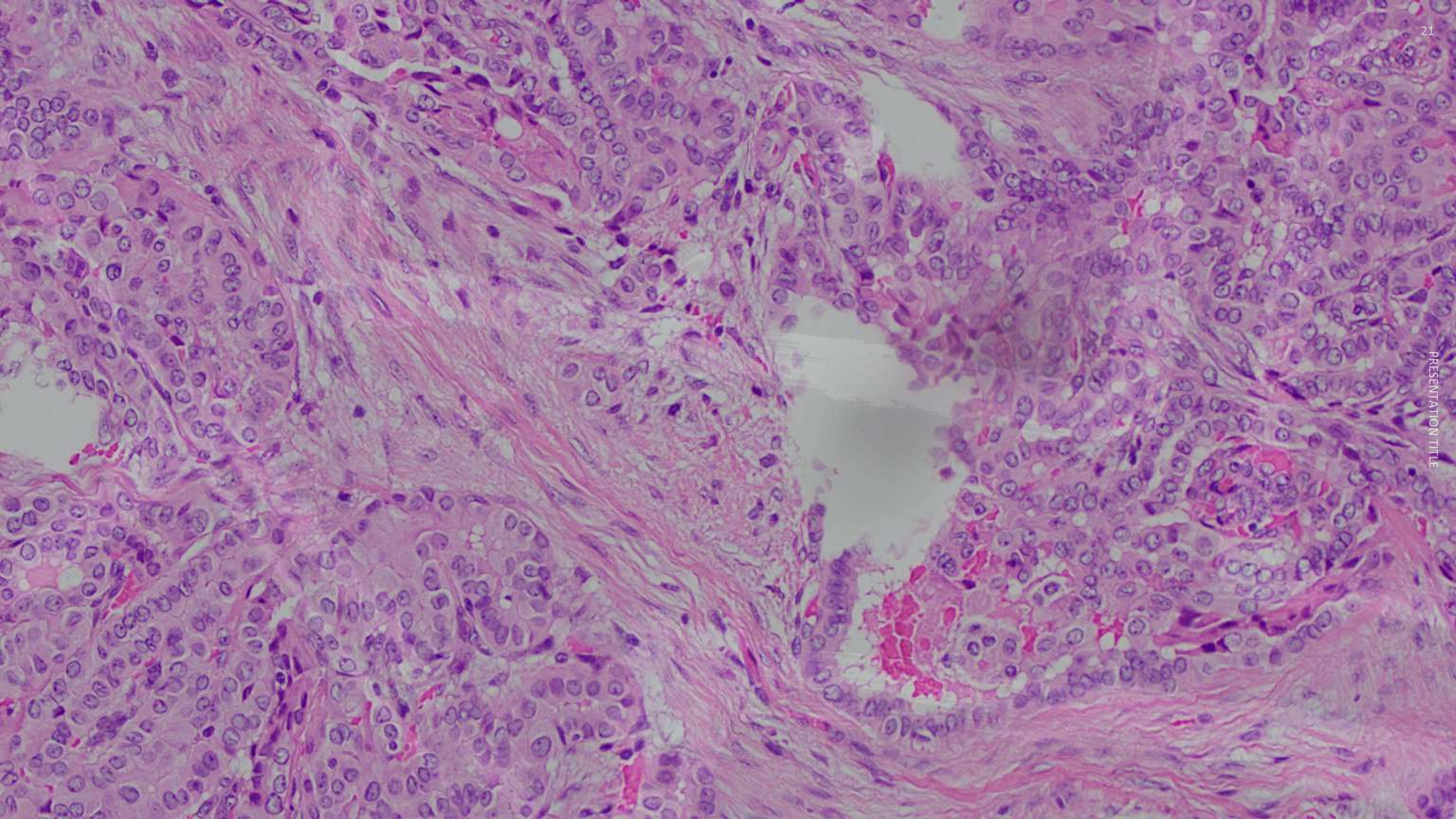










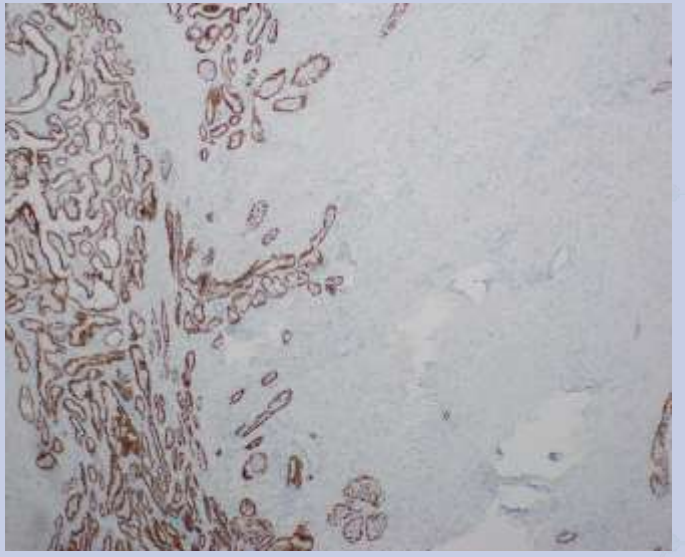


- Epithelial component:

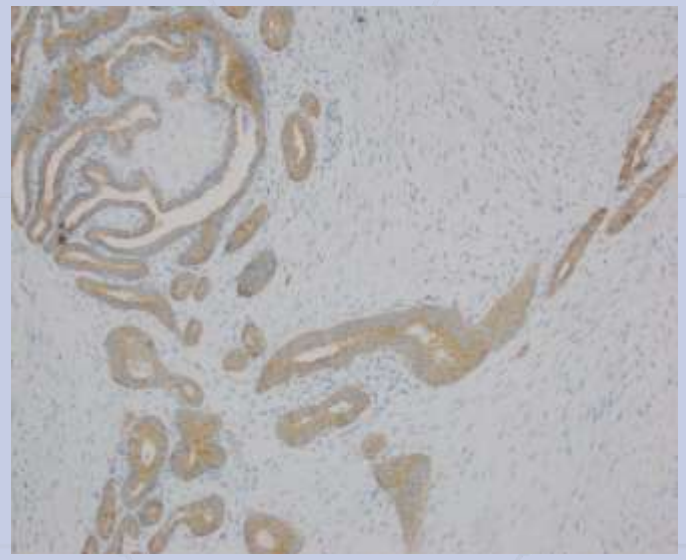
Positive: AE1/AE3, Pax8, TTF1, Thyroglobulin, BRAF

Negative: Calcitonin, NE markers, S100, SMA, Sox10, Desmin, ALK

TTF1



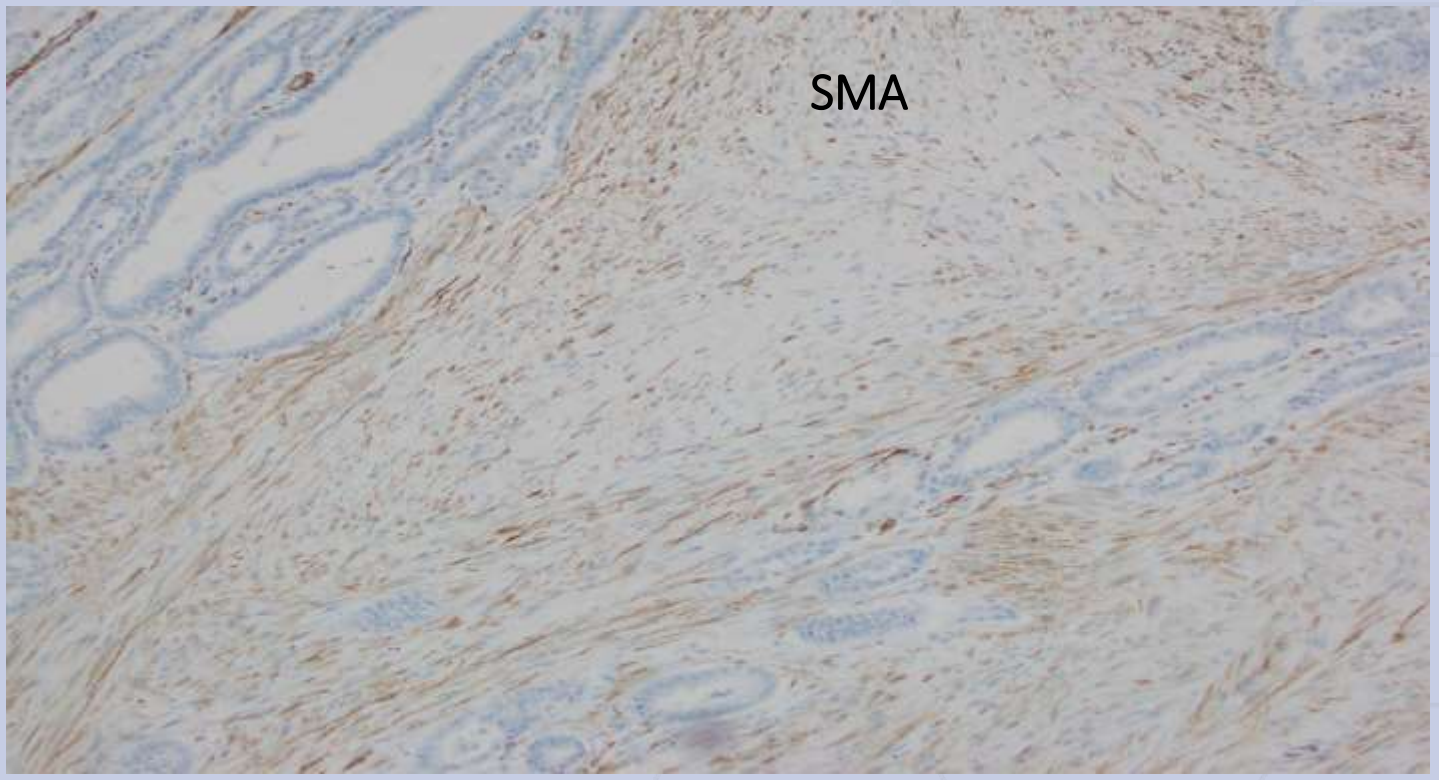
BRAF V600E

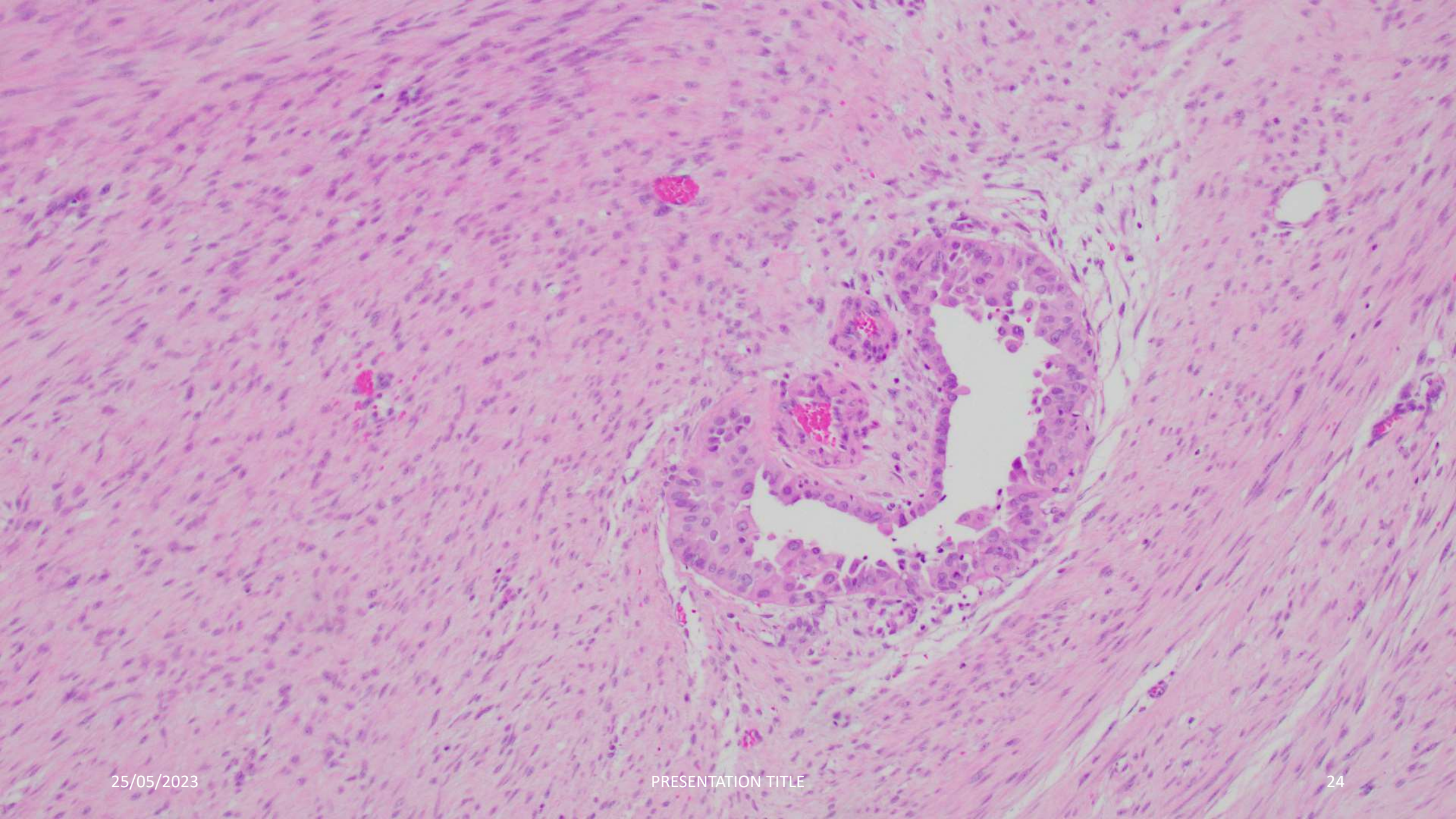


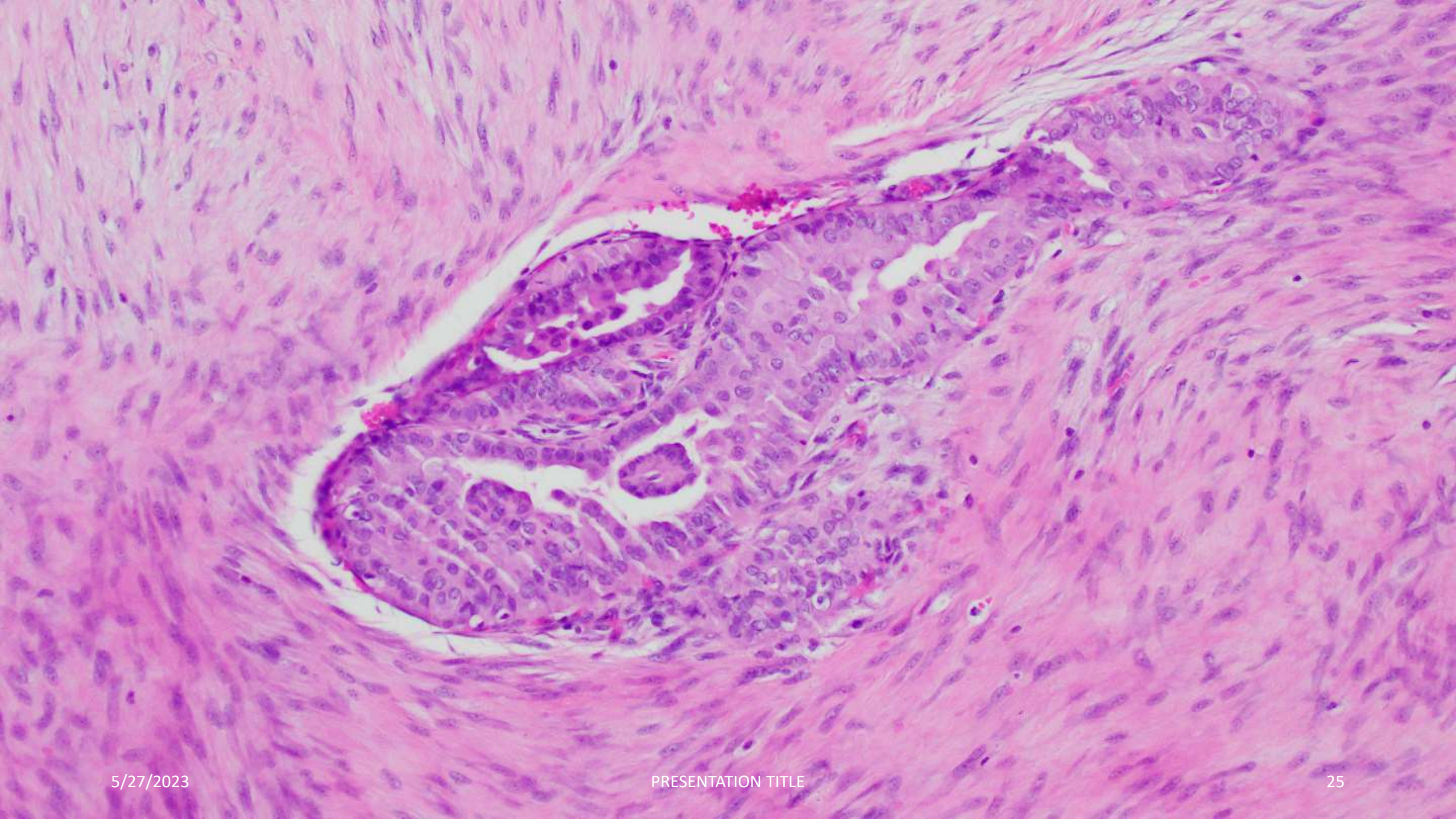
Mesenchymal component

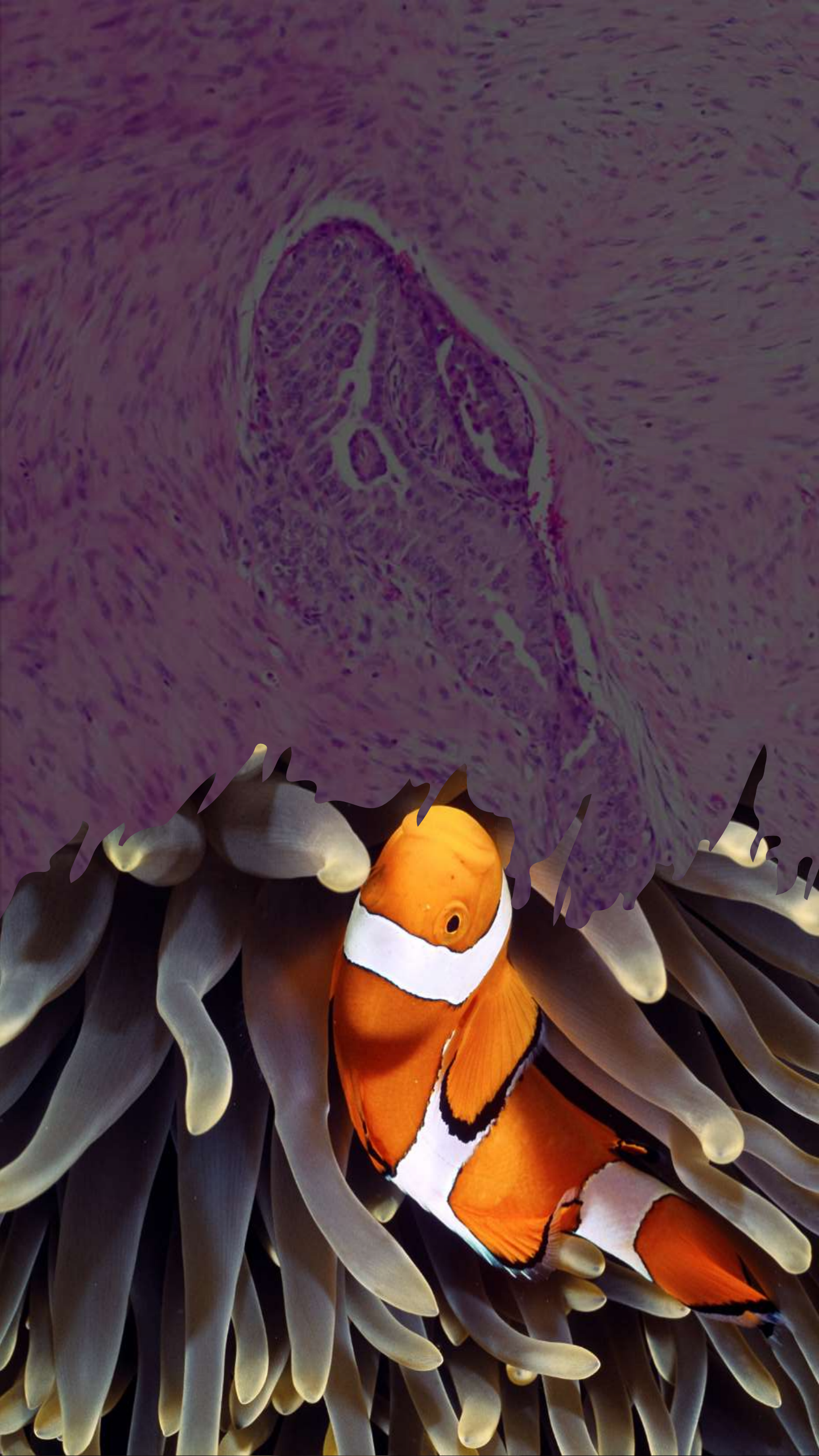
Positive: SMA

Negative: CK, Pax8, TTF1,Desmin,CD34, CK, ERG, CD31, S100, Sox10, Pan-Trk etc









Spindle cells DDX in thyroid

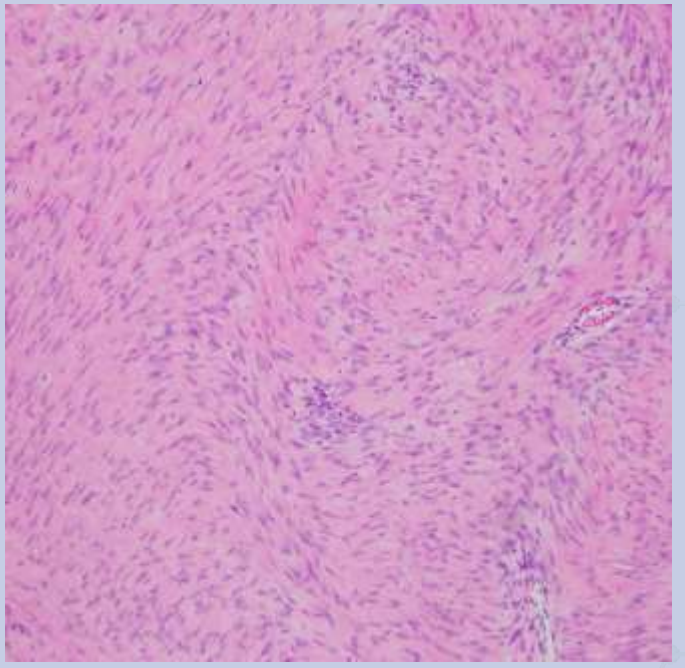
Fibrous variant of Hashimoto's thyroiditis

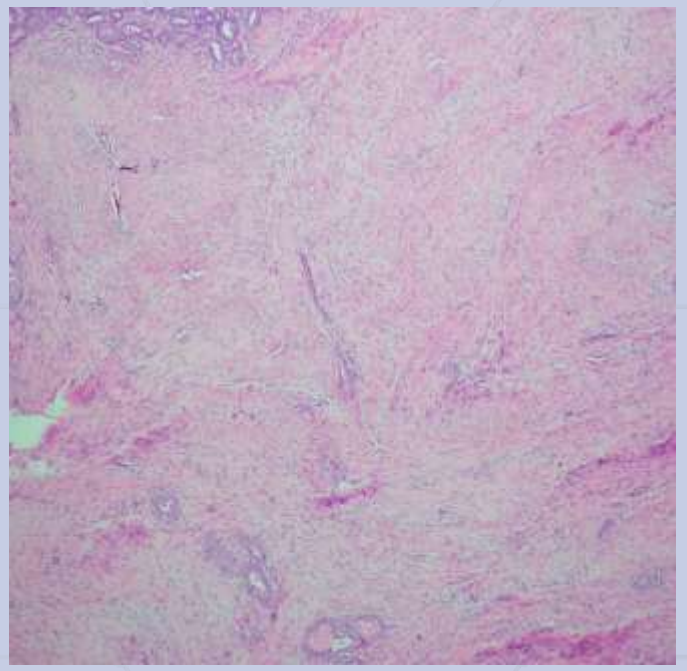
Riedel's thyroiditis

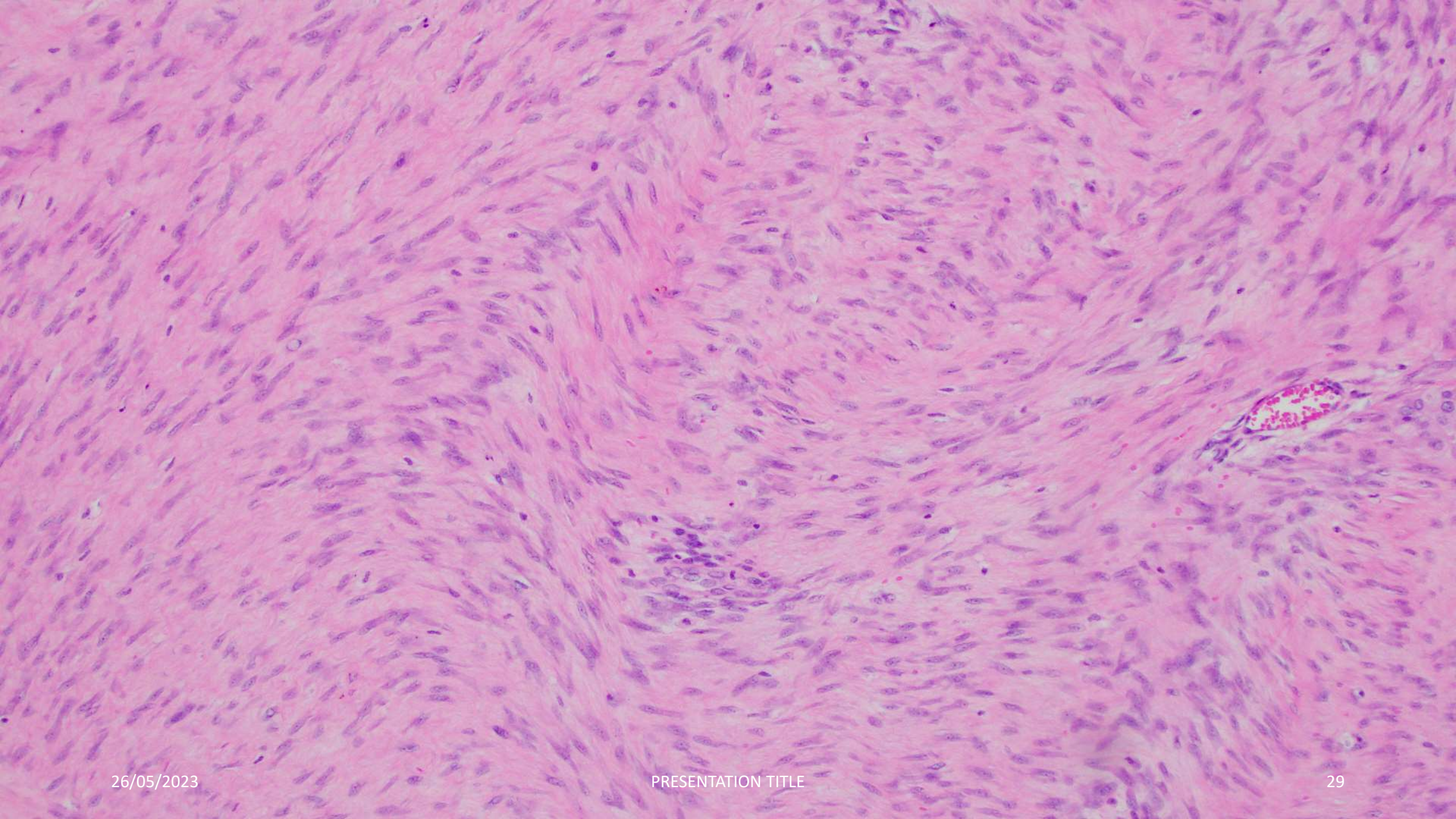
Post-operative spindle cell nodules, and scarring following fine-needle aspiration

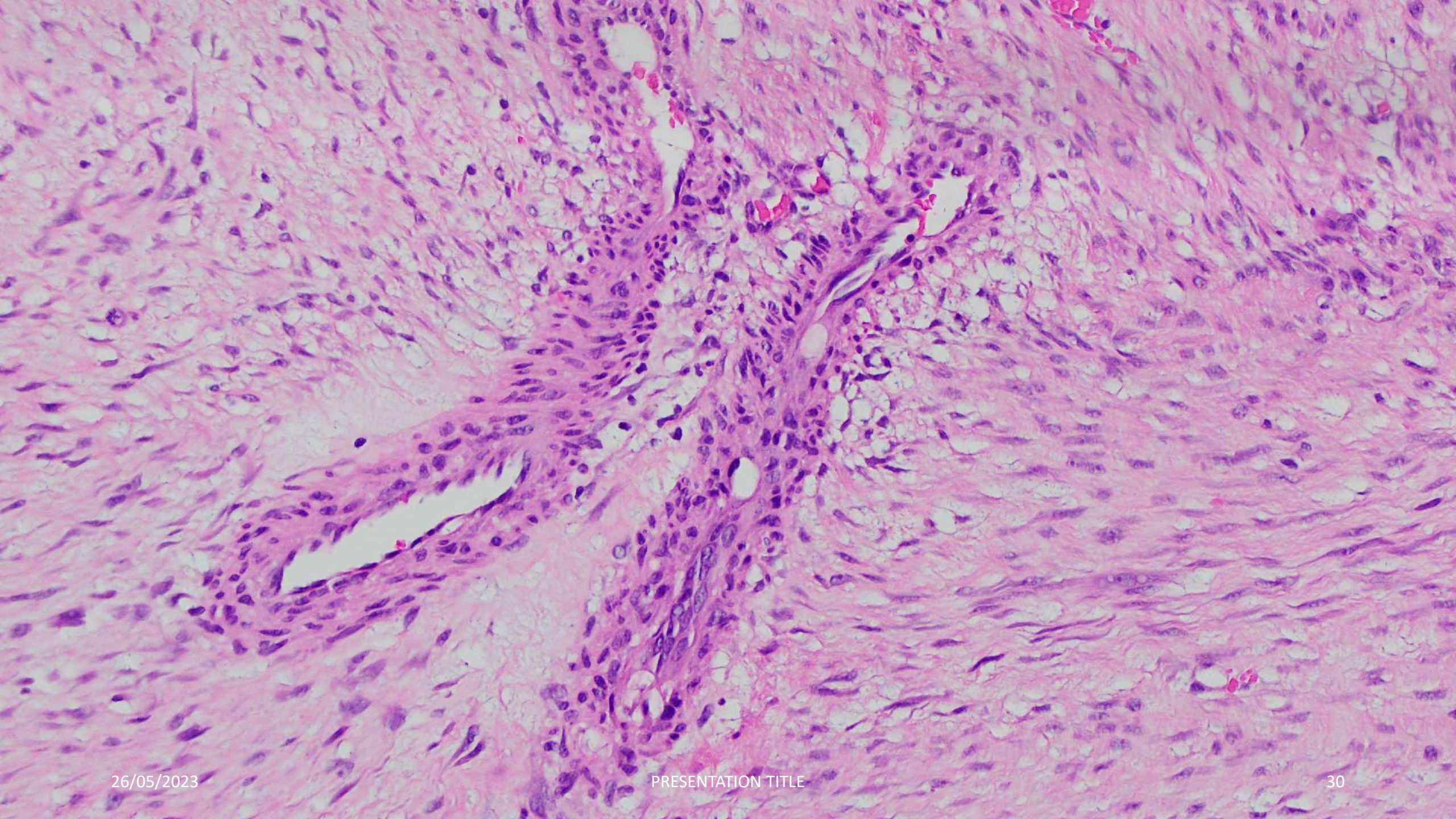
Spindle cells DDX in thyroid

- Anaplastic thyroid carcinoma
- Spindle cell PTC
- Medullary thyroid carcinoma
- Mesenchymal spindle cell neoplasms









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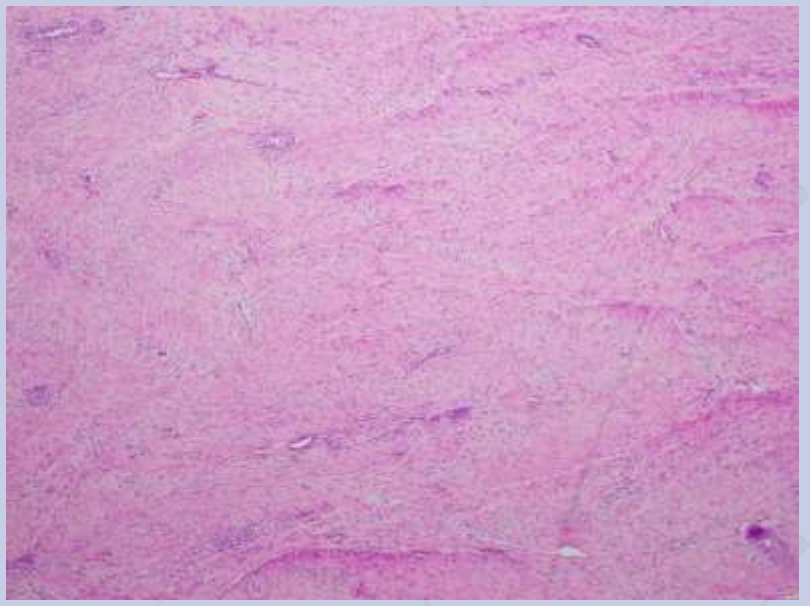
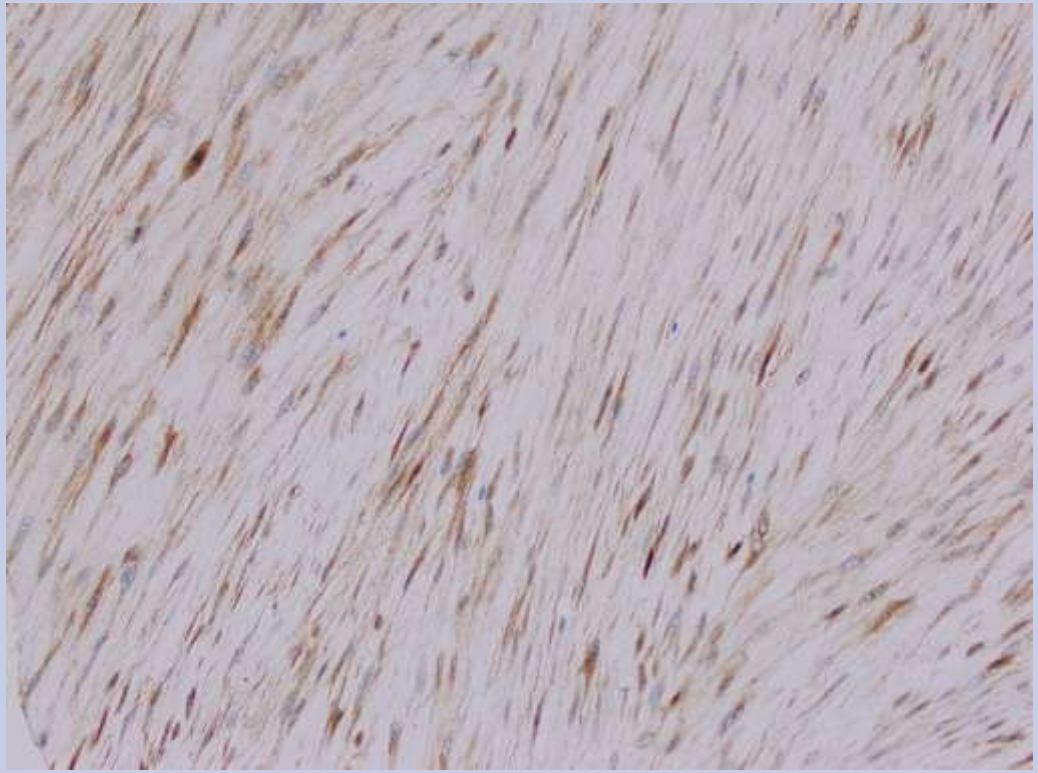
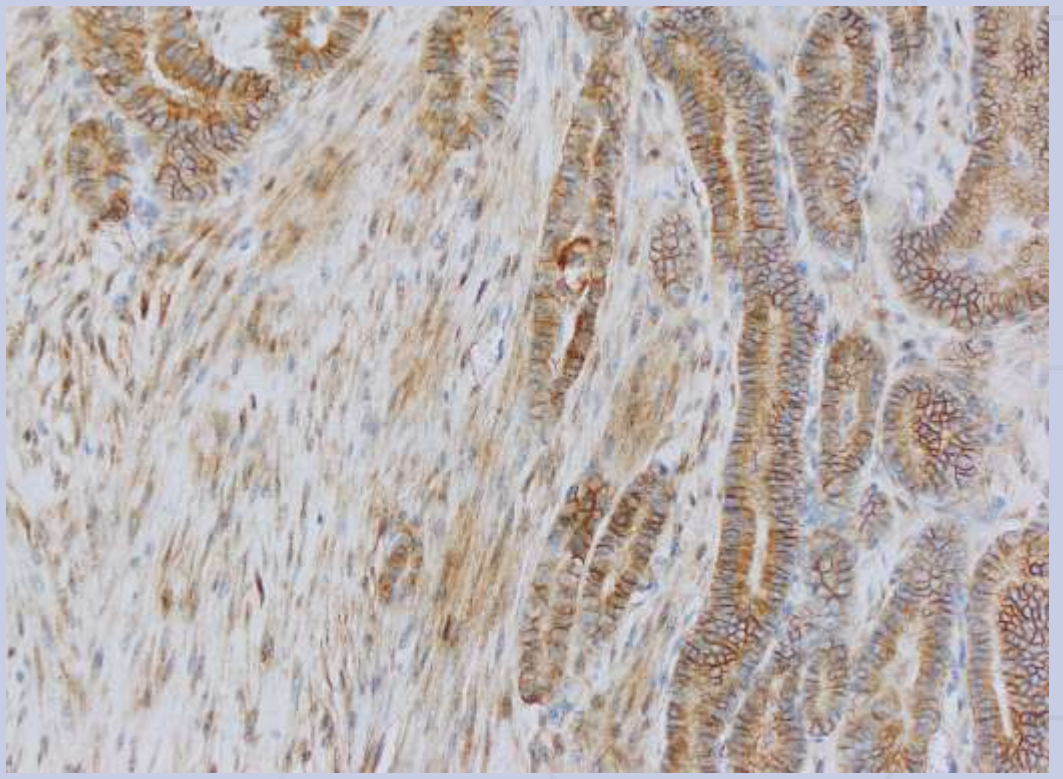
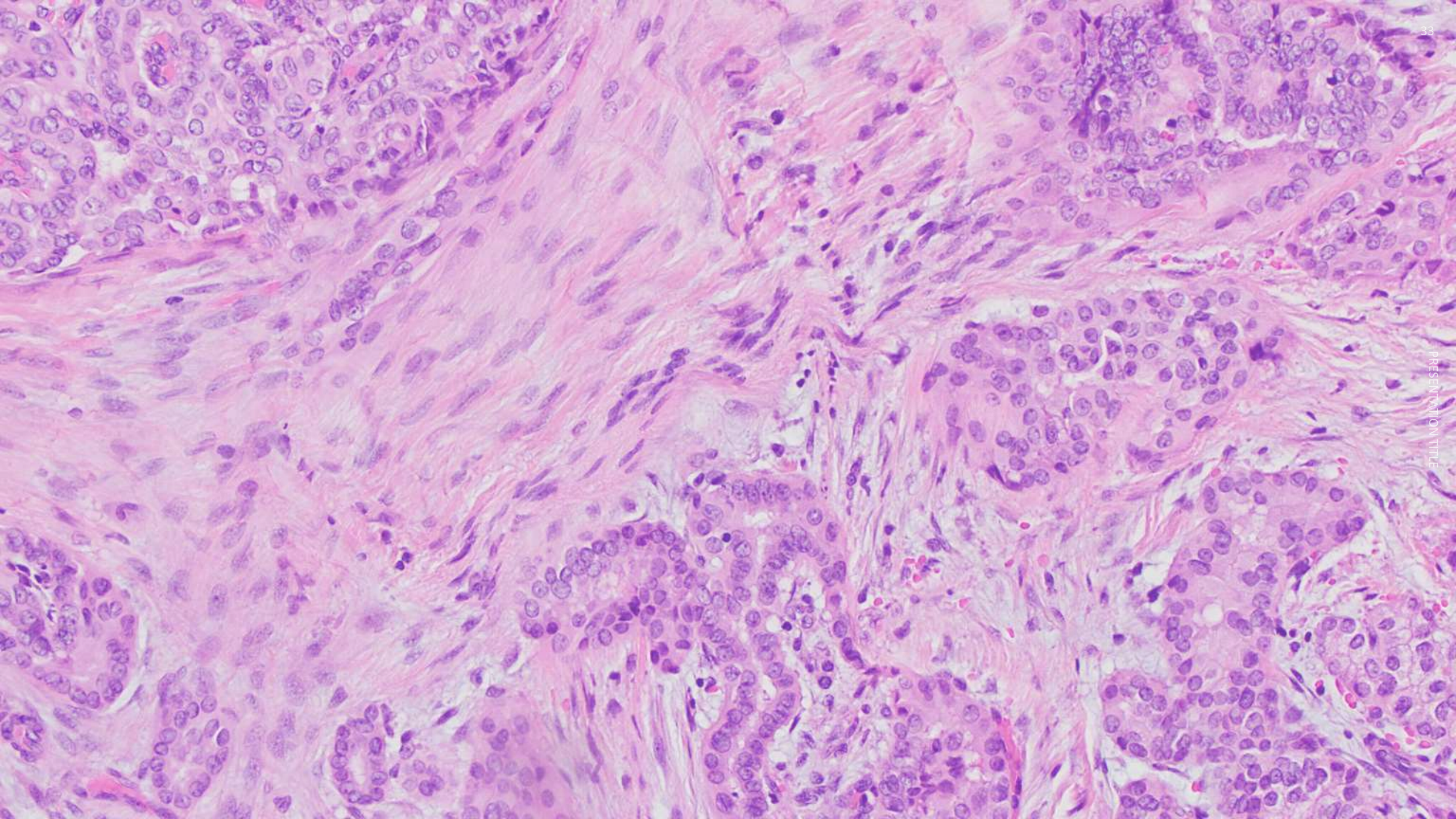
Desmoid fibromatosis

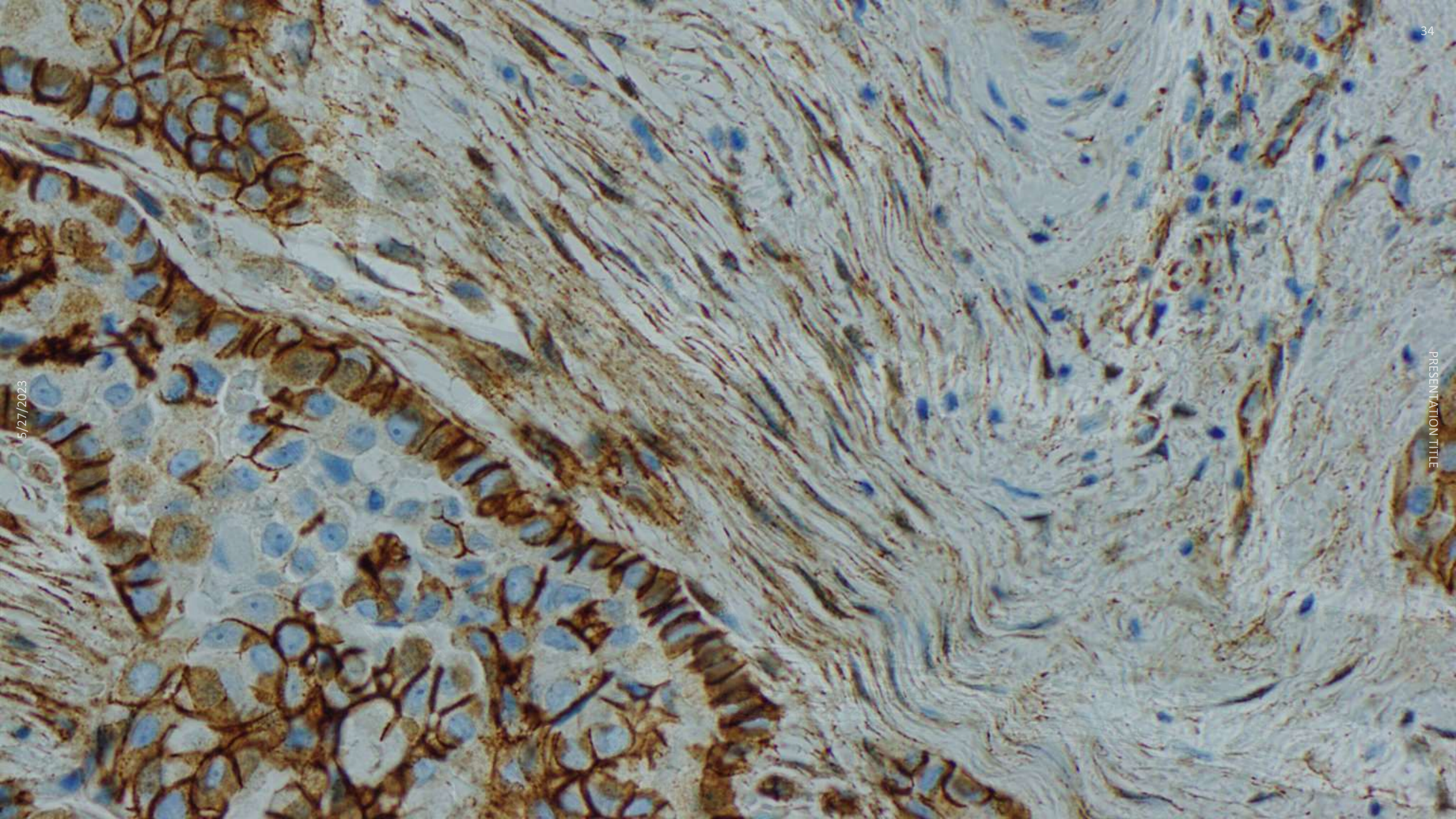


β-catenin









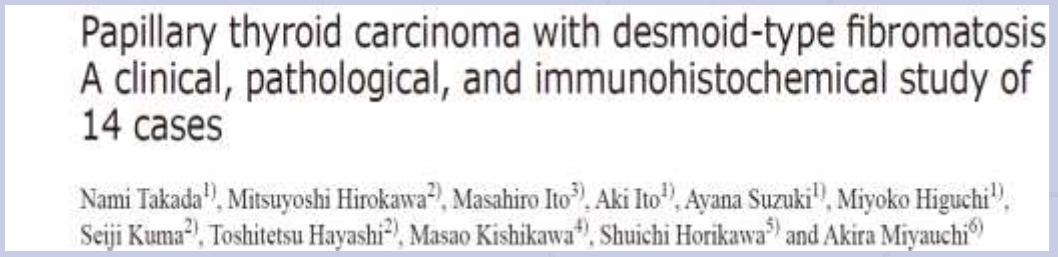

so what?!

- Ostrowski et al. Myxomatous change in papillary carcinoma of thyroid.Surg. Pathol. 1989

- Chan, J.K. et al. Papillary carcinoma of thyroid with exuberant nodular fasciitis-like stroma. Report of three cases. Am. J. Clin. Pathol. 1991

- fibromatosis-like stroma, nodular fasciitis-like stroma and myofibroblastic stroma

- Metastatic lymph nodes were detected in 12 of the 13 cases
- Lymph node metastases harbored a DTF component
- CTNNB1 mutations in one of eight cases tested, despite positive beta-catenin staining by IHC in the majority of their cases (low sensitivity of direct sequencing using capillary electrophoresis)



Papillary thyroid carcinoma with desmoid-type fibromatosis
A clinical, pathological, and immunohistochemical study of 14 cases

Nami Takada[1)], Mitsuyoshi Hirokawa[2)], Masahiro Ito[3)], Aki Ito[1)], Ayana Suzuki[1)], Miyoko Higuchi[1)], Seiji Kuma[2)], Toshitetsu Hayashi[2)], Masao Kishikawa[4)], Shuichi Horikawa[5)] and Akira Miyauchi[6)]

- Mesenchymal component showed typical aberrant nuclear and cytoplasmic immunoreactivity for β-catenin and harbored a heterozygous somatic activating mutation in the corresponding CTNNB1 gene

- This mutation has never been reported in thyroid stroma

- The term 'papillary thyroid carcinoma with desmoid-type fibromatosis' should be used

Papillary thyroid carcinoma with nodular fasciitis-like stroma and *β*-catenin mutations should be renamed papillary thyroid carcinoma with desmoid-type fibromatosis

Caterina Rebecchini[1,5], Antoine Nobile[1,5], Simonetta Piana[2], Rossella Sarro[1], Bettina Bisig[1], Sykiotis P Gerasimos[3], Chiara Saglietti[1], Maurice Matter[4], Laura Marino[3] and Massimo Bongiovanni[1]

β-catenin

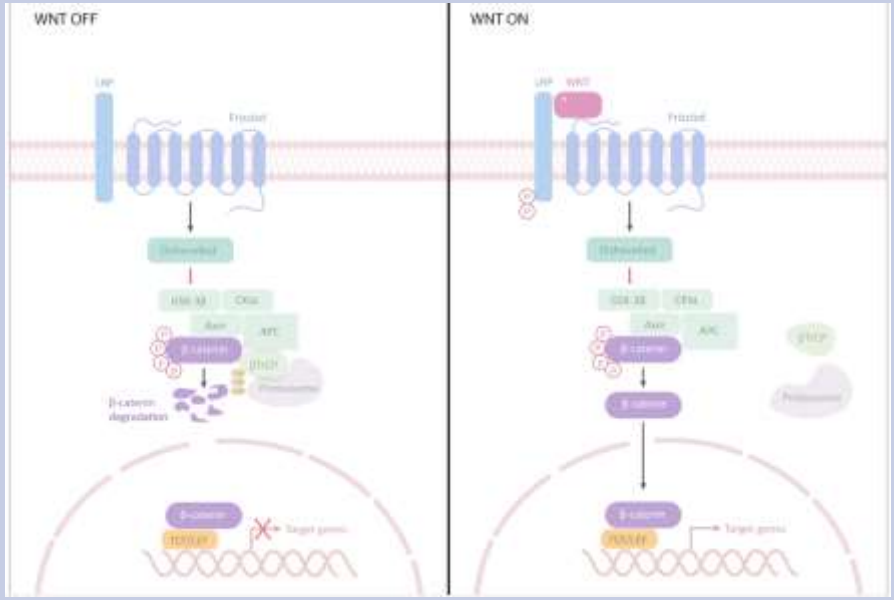
CTNNB1 gene mutations were identified in six/seven cases

CTNNB1 activating mutations are the driver events behind PTC-DTF

Papillary thyroid carcinoma with prominent myofibroblastic stromal component: clinicopathologic, immunohistochemical and next-generation sequencing study of seven cases

David Suster[1] · Michael Michal[2,3,4] · Michiya Nishino[1] · Simonetta Piana[5] · Massimo Bongiovanni[6] · Olga Blatnik[7] · Veronika Hájková[4] · Nikola Ptáková[4] · Michal Michal[2,4] · Saul Suster[8]

Mutations in Exon 3 of CTNNB1

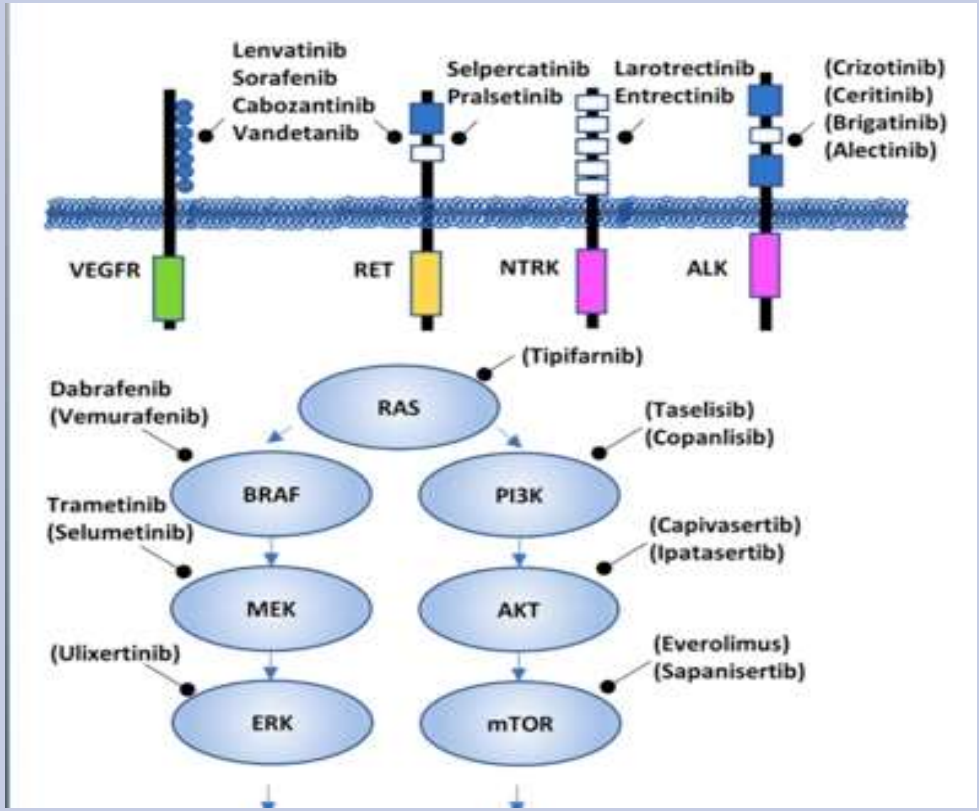


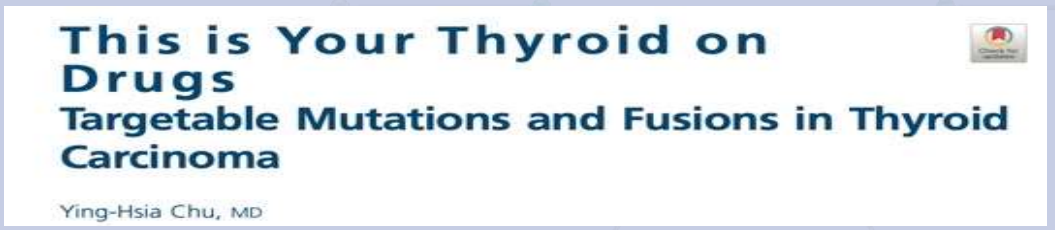
Beta-catenin is encoded by the *CTNNB1* gene, plays a crucial role as a key transcription factor of the Wnt-signaling pathway

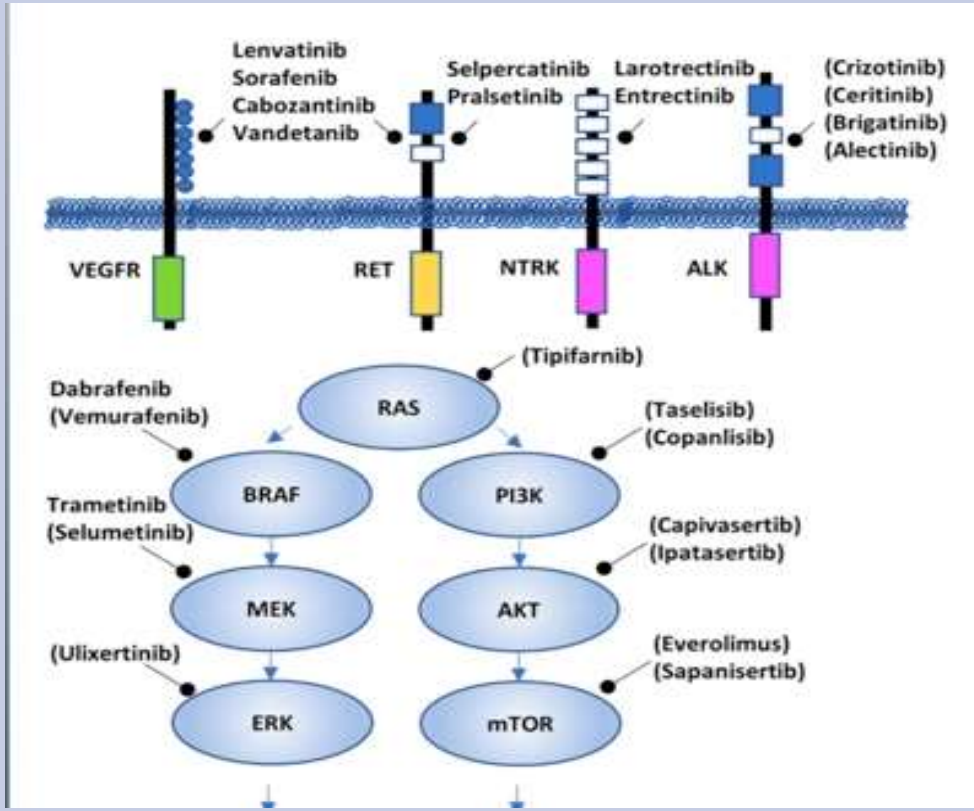
Mutations in *CTNNB1* can impair the degradation of beta-catenin, causing it to accumulate in the cytoplasm and enter the nucleus to form complexes with TCF/LEF

Resulting in abnormal cell proliferation, which can be oncogenic in various tumour types, including desmoid-type fibromatosis

MAPK pathway are the main drivers for well-differentiated thyroid carcinomas






Lenvatinib
Sorafenib
Cabozantinib
Vandetanib
Selpercatinib
Pralsetinib
Larotrectinib
Entrectinib
(Crizotinib)
(Ceritinib)
(Brigatinib)
(Alectinib)
VEGFR
RET
NTRK
ALK
(Tipifarnib)
RAS
Dabrafenib
(Vemurafenib)
(Taselisib)
(Copanlisib)
BRAF
PI3K
Trametinib
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(Sapanisertib)
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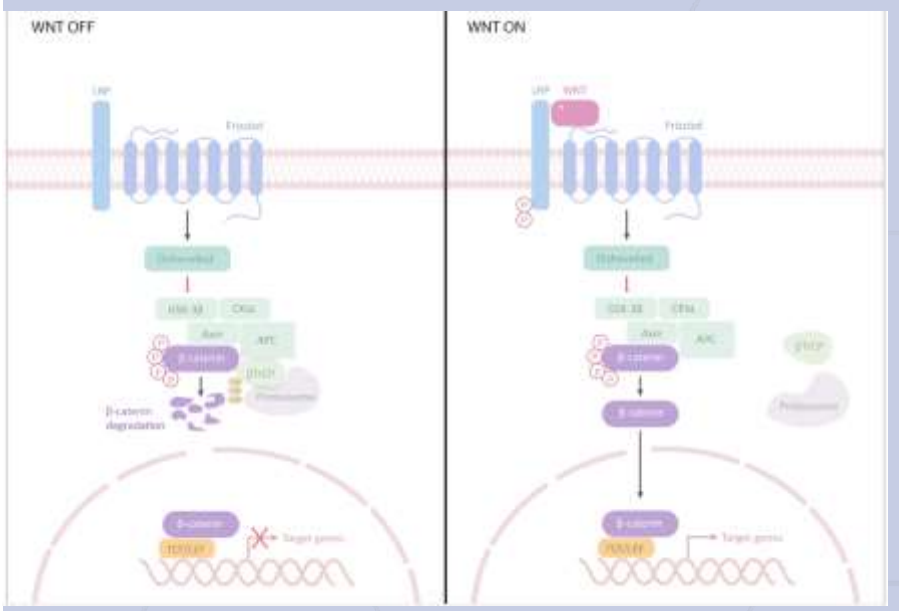
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NGS

Genomic Findings

IA		IB	IIC	IID
BRAF	p.V600E c.1799T>A	No variants reported.	No variants reported.	No variants reported.
CTNNB1	p.T41A c.121A>G			

The tissue block tested has predominantly metastatic deposit of papillary thyroid carcinoma with very little stroma (less than 5%).

This report should be read in conjunction with the report vide accession # 224842257, where NGS testing has been performed a block from the thyroidectomy specimen.

Genomic Findings

IA		IB	IIC	IID
BRAF	p.V600E c.1799T>A	No variants reported.	No variants reported.	No variants reported.

Papillary thyroid carcinoma with fibromatosis/fasciitis like/ desmoid-type stroma

The exact proportions of the PTC and DTF components are not established for this entity, and the extent of the desmoid-type stroma may vary in individual cases

- 45 mm PTC-DTF
- Vascular invasion
- Extrathyroid extension
- 4/4 lymph nodes involved by carcinoma
- One lymph node shows both component
- R0

Follow-up

- The patient was discussed at MDM, had adjuvant RAI, serial ultrasound and blood test for ongoing surveillance
- Whole-body iodine scan 48 hours post RAI did not demonstrate metastatic disease elsewhere
- At 4 months post-operatively the patient was well and bloods showed a Thyroglobulin of 1.30ng/mL (1.50 - 38.5) and Anti-thyroglobulin antibodies <1.3IU/mL (<20)
- Patient will have ongoing surveillance

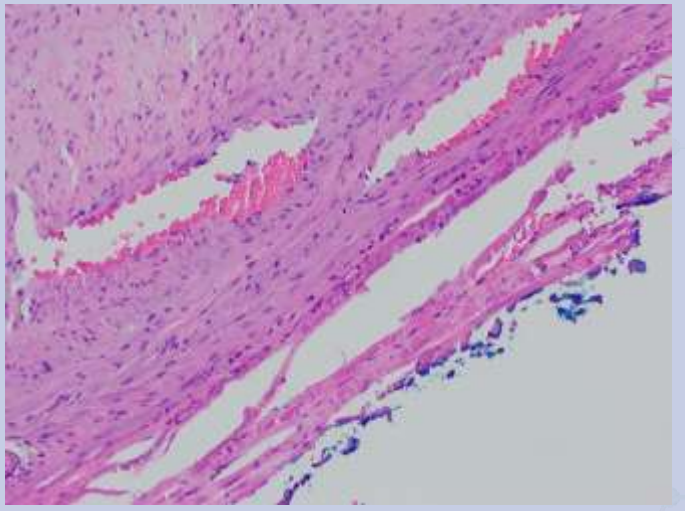
Challenges

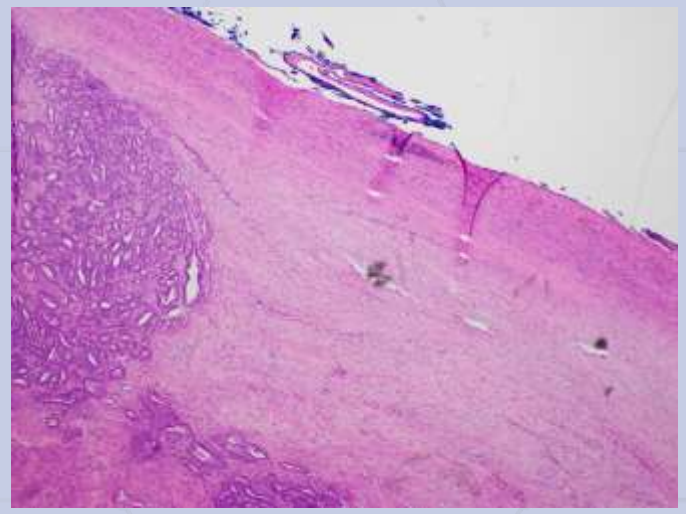
- Misinterpreting the fibrotic component as benign reactive fibrosis
- Spindle cells may be mistaken for transformation into anaplastic thyroid carcinoma
- Use of thyroglobulin as a tumour marker is only partly informative
- Mesenchymal cells are not expected to concentrate iodine

Challenges

Appropriate resection margin status of the mesenchymal component

Surgical clearance is of utmost importance in the management of PTC-DTF, as the DTF component is not sensitive to RAI





Take-home message

PTC with desmoid-type fibromatosis (PTC-DTF) is an exceedingly rare subtype consisting of two distinct components, a mainly *BRAF* p.V600E- mutated PTC intermingled with a *CTNNB1* driven soft tissue neoplasm

Awareness of this particular entity may allow for more accurate diagnosis and more efficient management of patients with these tumours

MDM is an essential part of management as there are no established management guidelines

Ongoing surveillance is prudent as most reported cases are limited by a short follow-up duration

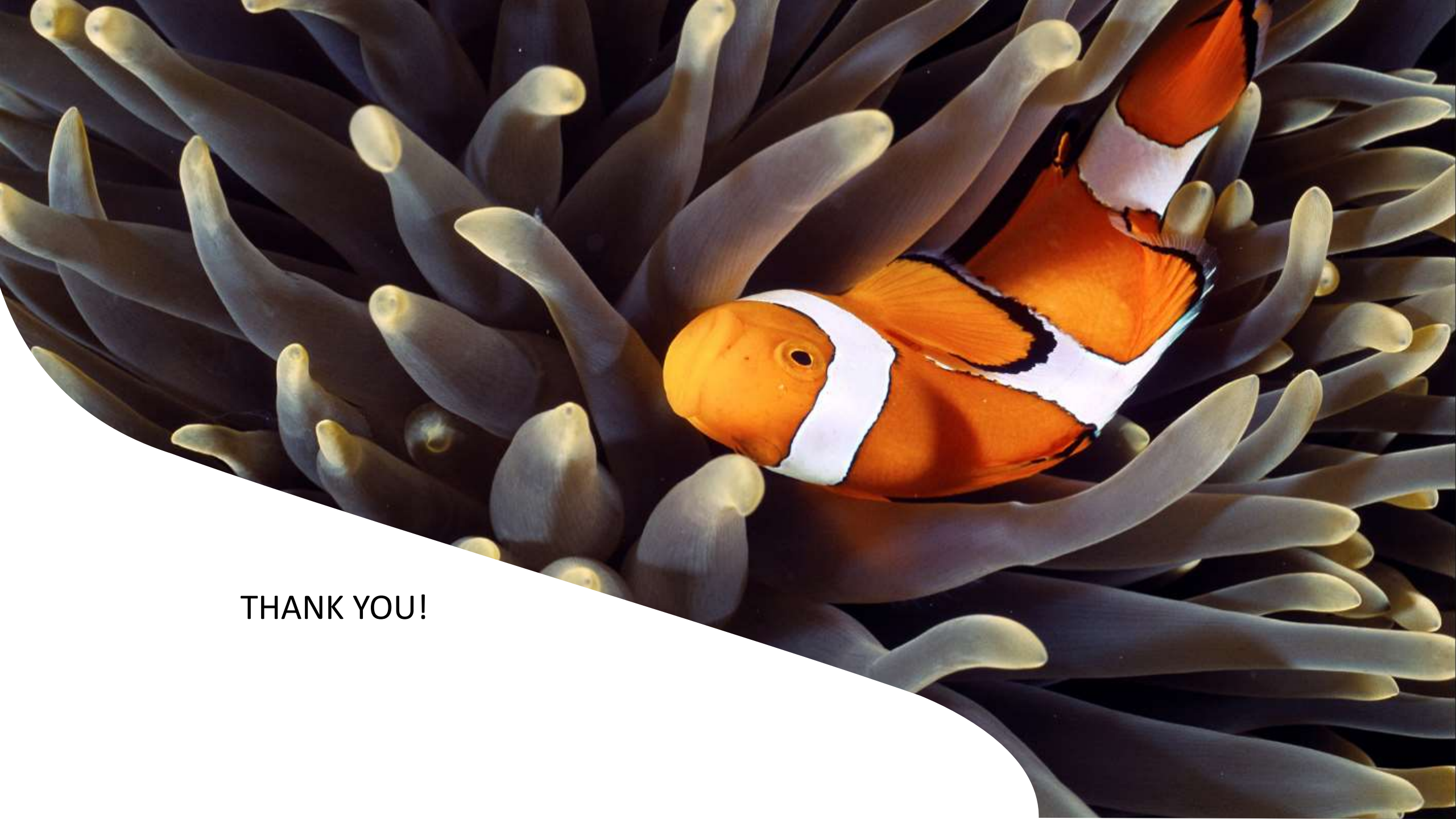
Thank You

Endocrine team Douglass Hanly Moir

Soft tissue team Douglass Hanly Moir

Molecular department Monash health

A/Prof Stan Sidhu (Endocrine Surgeon)



THANK YOU!