NEUROENDOCRINE NEOPLASMS OF THE FEMALE GENITAL TRACT- WHO 2020

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TO DISCUSS

- WHO 2020 Classification of neuroendocrine neoplasms in female genital tract and changes from prior classification
- Advantages of new classification
- Pathological features in various sites with emphasis on recent studies
- Molecular study on endometrial neuroendocrine carcinomas with reflections on endometrial neuroendocrine carcinomas

WHO 2020- NEUROENDOCRINE NEOPLASMS (NEN)

- Separate stand-alone chapter (chapter 11) for neuroendocrine neoplasms (NEN) at various sites (except for ovarian carcinoids)
- Categories:-
  - NEUROENDOCRINE TUMOUR (NET)
  - NEUROENDOCRINE CARCINOMA (NEC) (small cell and large cell NEC)
  - MIXED NEUROENDOCRINE- NON NEUROENDOCRINE NEOPLASMS (carcinoma admixed with neuroendocrine carcinoma)

INTRODUCTION CHAPTER- WHO 2020 NEUROENDOCRINE NEOPLASMS

- Uncommon or rare at all sites in female genital tract
- Part of decision to employ same terminology for neuroendocrine neoplasms at all body sites (all 5th edition WHO volumes)
- Assists pathologists and clinicians in managing patients with NEN at all sites
- Key feature is distinction between well-differentiated NETs (still called carcinoid tumours in some systems) and poorly differentiated NECs
- Dichotomous distinction between NET and NEC supported by genetic, clinical, epidemiological, morphological and prognostic data at many sites; not a spectrum of differentiation
- In endometrium and cervix, NEC much more common than NET
- In ovary, NET (carcinoids) much more common than NEC
- Carcinoid terminology remains in ovary because of good prognosis and because no evidence for grading

Modern Pathology
https://doi.org/10.1038/s41379-018-0110-y

ARTICLE

A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal

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Received: 22 May 2018 / Revised: 14 June 2018 / Accepted: 14 June 2018
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PMID 28735441

Curr Oncol Rep (2017) 19:59
DOI 10.1007/s11912-017-0617-2

GYNECOLOGIC CANCERS (NS REED, SECTION EDITOR)

Pathology of Neuroendocrine Tumours of the Female Genital Tract

Brooke E. Howitt[1] · Paul Kelly[2,3] · W. Glenn McCluggage[2,3]

NEW NEUROENDOCRINE MARKER- AJSP 2021;45;147-159; PMID 33264139

ORIGINAL ARTICLE

INSM1 Is Less Sensitive But More Specific Than Synaptophysin in Gynecologic High-grade Neuroendocrine Carcinomas

An Immunohistochemical Study of 75 Cases With Specificity Test and Literature Review

Qiong Zou, MD, Lily Zhang, MD,† Zhiqiang Cheng, MD,‡ Xiaojing Guo, MD,‡ and Dengfeng Cao, MD, PhD†*

NEW NEUROENDOCRINE MARKER- PMID 33323849

International Journal of Gynecological Pathology
00:1–8, Lippincott Williams & Wilkins, Baltimore
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Original Article

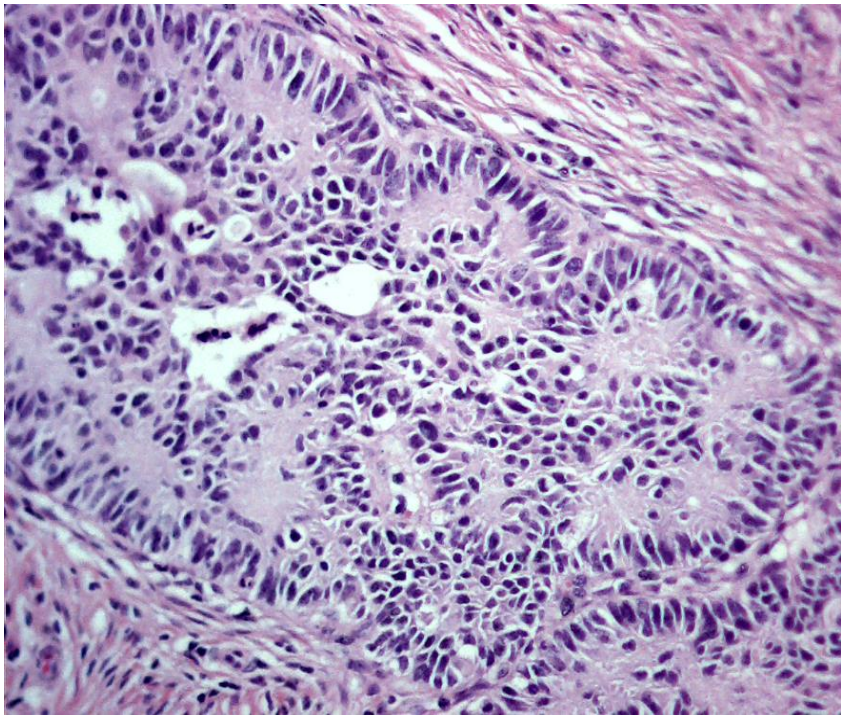
Insulinoma-associated Protein 1 Expression and Its Diagnostic Significance in Female Genital Tract Neuroendocrine Carcinomas

Ching-Heng Ting, M.D., M.S., Tao-Yeuan Wang, M.D., and Pao-Shu Wu, M.D., Ph.D.

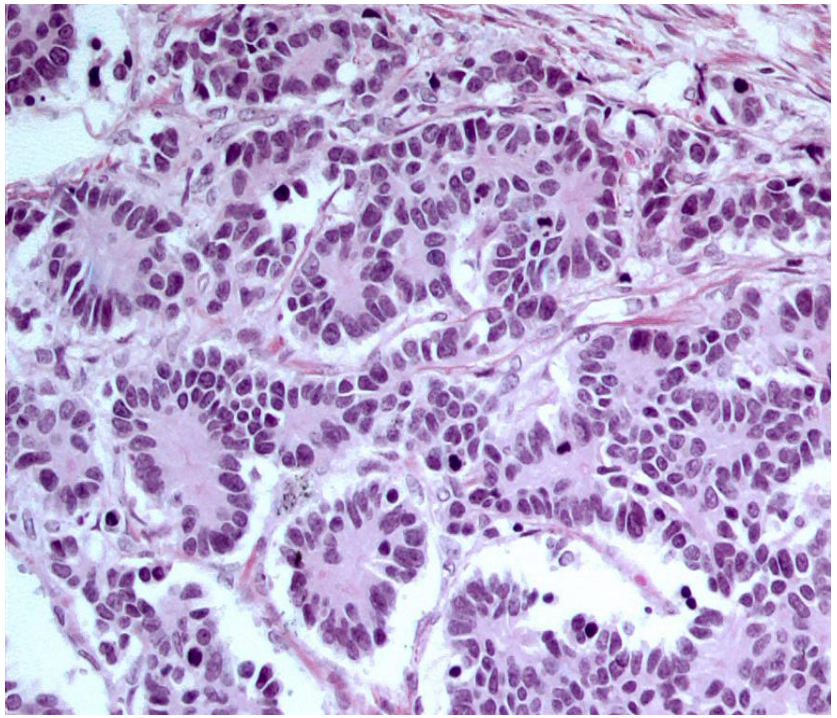
NEUROENDOCRINE TUMOUR (NET)

- Definition- low or intermediate-grade epithelial neoplasm with morphological and immunohistochemical features of neuroendocrine differentiation
- Acceptable terms- carcinoid tumour, typical carcinoid tumour, atypical carcinoid tumour
- Occur at all sites in female genital tract but extremely rare except in ovary
- Trabecular, nested/ insular, glandular/ acinar growth patterns
- Grade 1 or grade 2 (nuclear features, mitotic activity)
- Mainly isolated case reports with no large studies with follow-up (apart from ovarian carcinoids)

NET- BLUE BOOK PICTURES



Grade 1

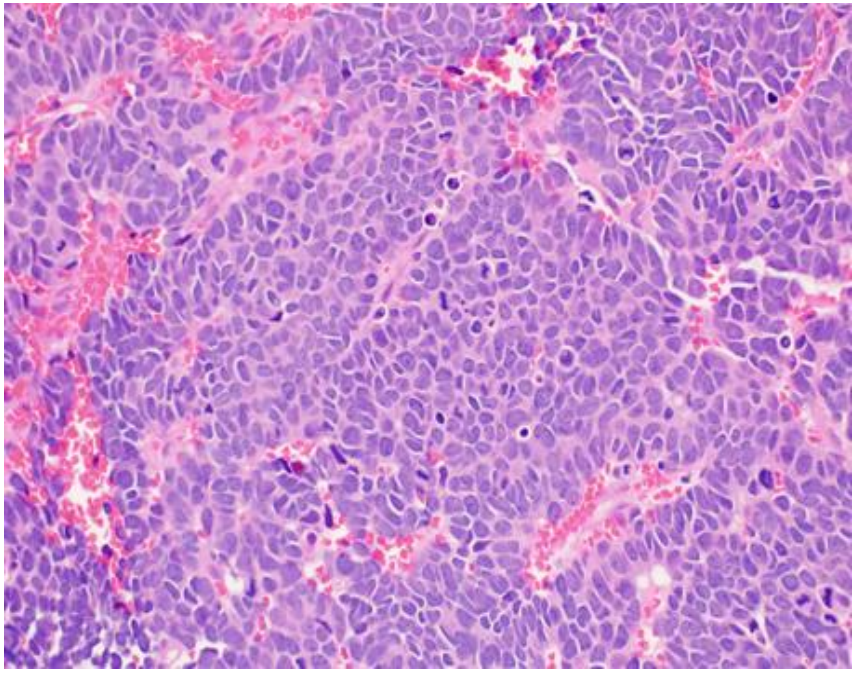


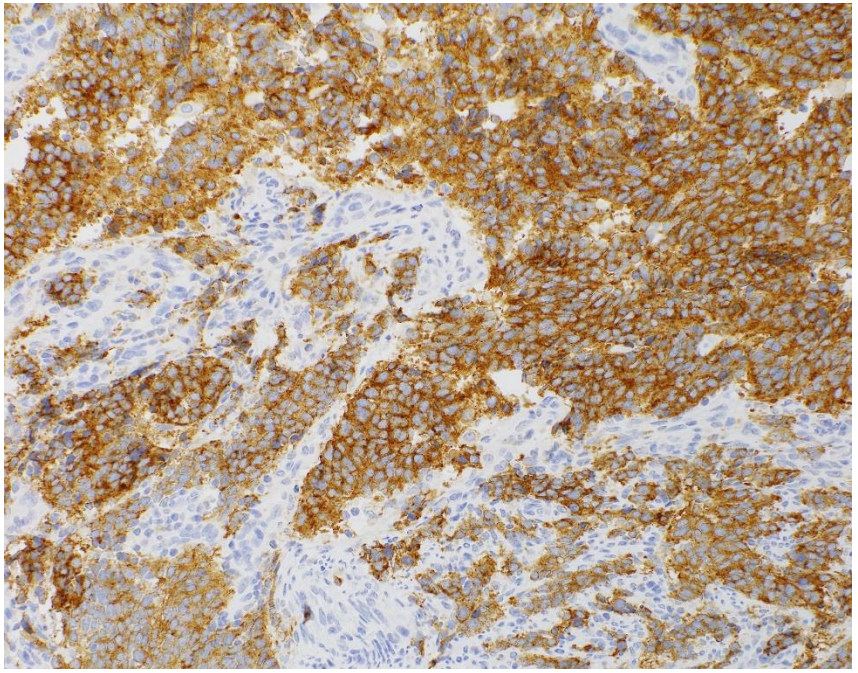
Grade 2

NEUROENDOCRINE CARCINOMA (NEC)

- SCNEC- high-grade carcinoma composed of small to medium sized cells with scant cytoplasm and exhibiting neuroendocrine differentiation
- LCNEC- high-grade carcinoma composed of large cells with neuroendocrine differentiation
- Carcinoma admixed with neuroendocrine carcinoma- a carcinoma of non-neuroendocrine type admixed with a NEC component (state individual tumour types and their approximate proportions)

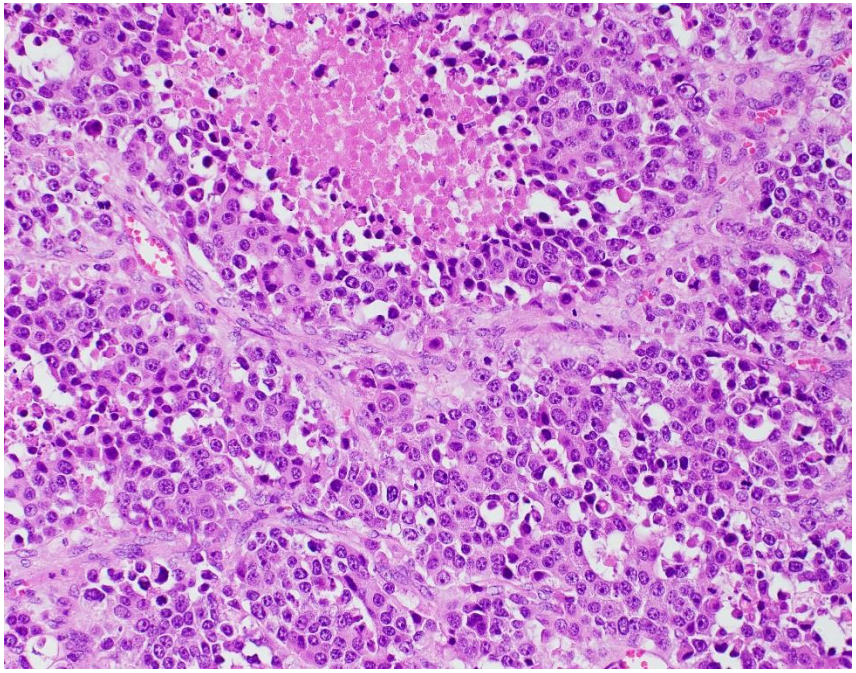
NEC (SCNEC) - BLUE BOOK PICTURES

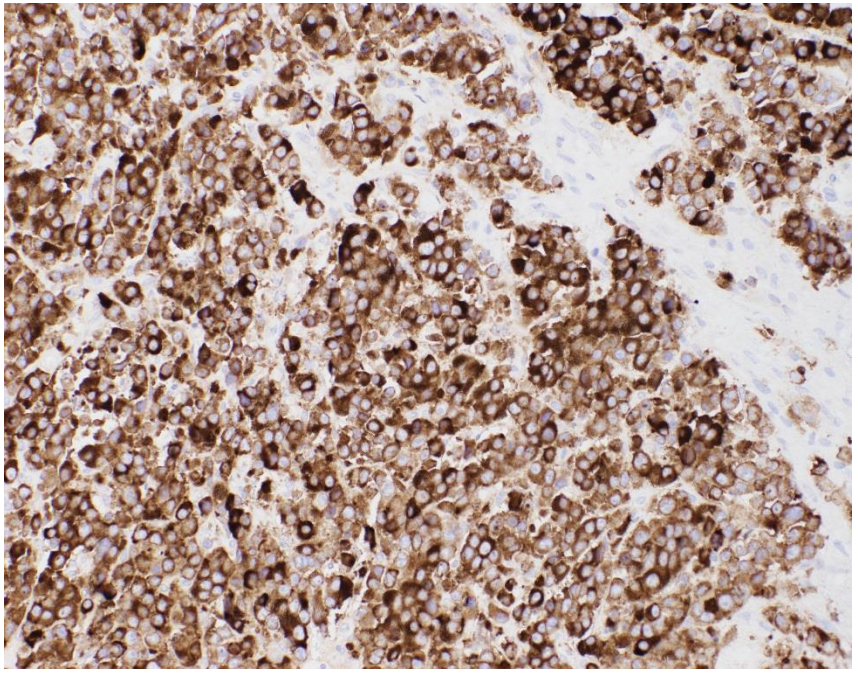




synaptophysin

NEC (LCNEC)- BLUE BOOK PICTURES





synaptophysin

OVARY

- Carcinoid term still used (included in germ cell tumour chapter in category of “monodermal teratomas and somatic-type tumours arising from a dermoid cyst”)
- Separate terminology retained because of excellent prognosis of ovarian carcinoids
- Category of NEC introduced (SCNEC and LCNEC); replaces old WHO “small cell carcinoma of pulmonary type” (this was a very poor term); remember small cell carcinoma of hypercalcaemic type is not a neuroendocrine carcinoma
- Category of carcinoma admixed with NEC also included (various types of adenocarcinomas)
- Paraganglioma included in section on MISCELLANEOUS TUMOURS

PARAGANGLIOMA OVARY; PMID 16699314

ORIGINAL ARTICLE

Paraganglioma of the Ovary

Report of Three Cases of a Rare Ovarian Neoplasm, Including Two Exhibiting Inhibin Positivity

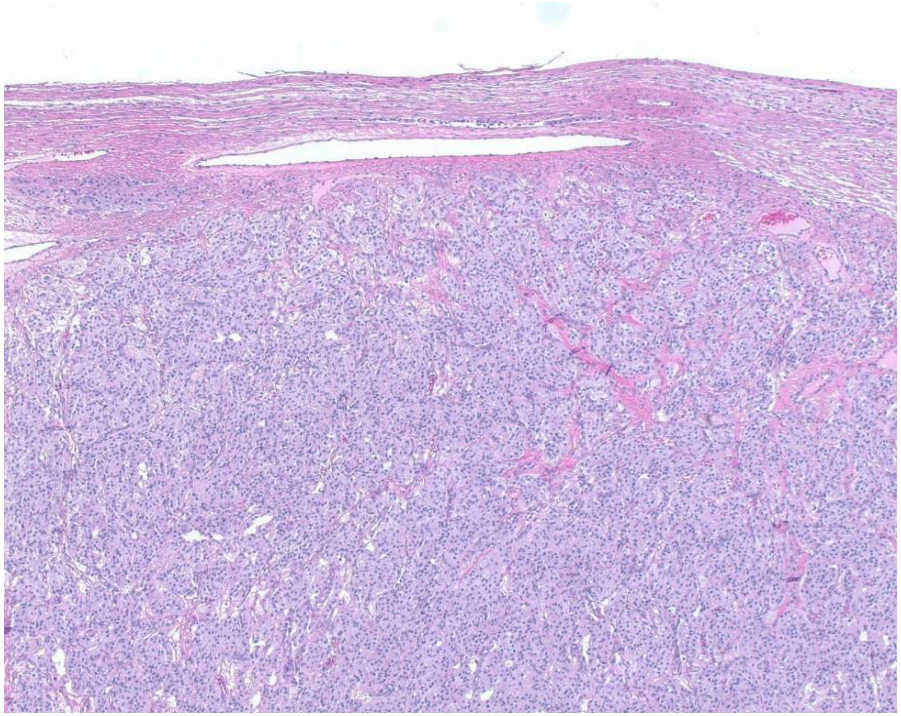
W. Glenn McCluggage, FRCPath and Robert H. Young, MD, FRCPath†*

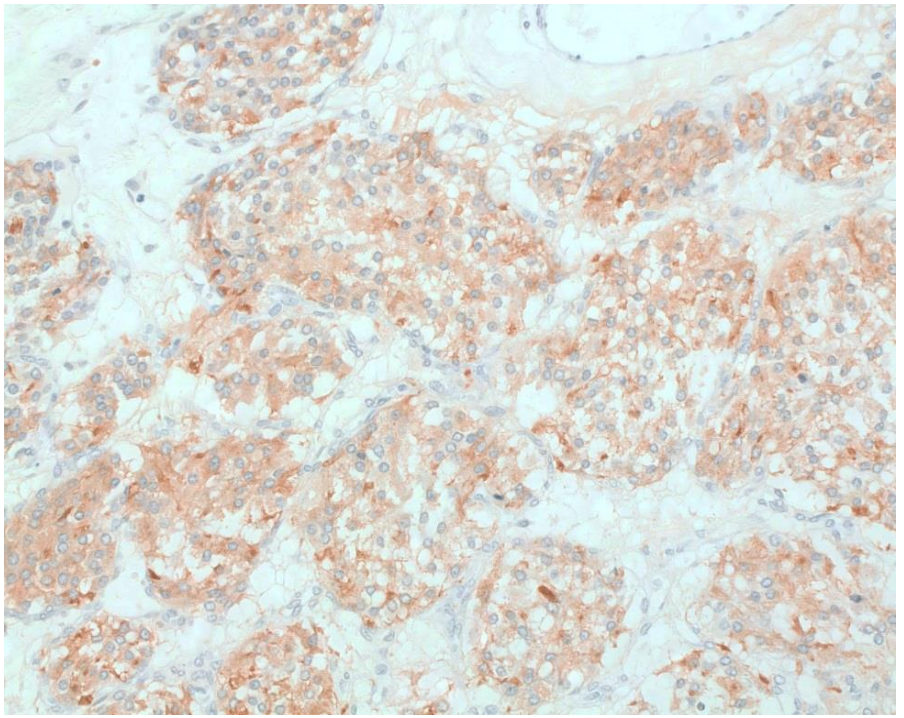
Abstract: Paraganglioma is one of the rarest neoplasms to involve the ovary, whether primary or metastatic, with only two previous reports. We describe three examples that occurred in patients 22, 58, and 68 years of age. Two patients had

Key Words: ovary, paraganglioma, immunohistochemistry, differential diagnosis

(*Am J Surg Pathol* 2006;30:600–605)

PARAGANGLIOMA OVARY; PMID 16699314





chromogranin

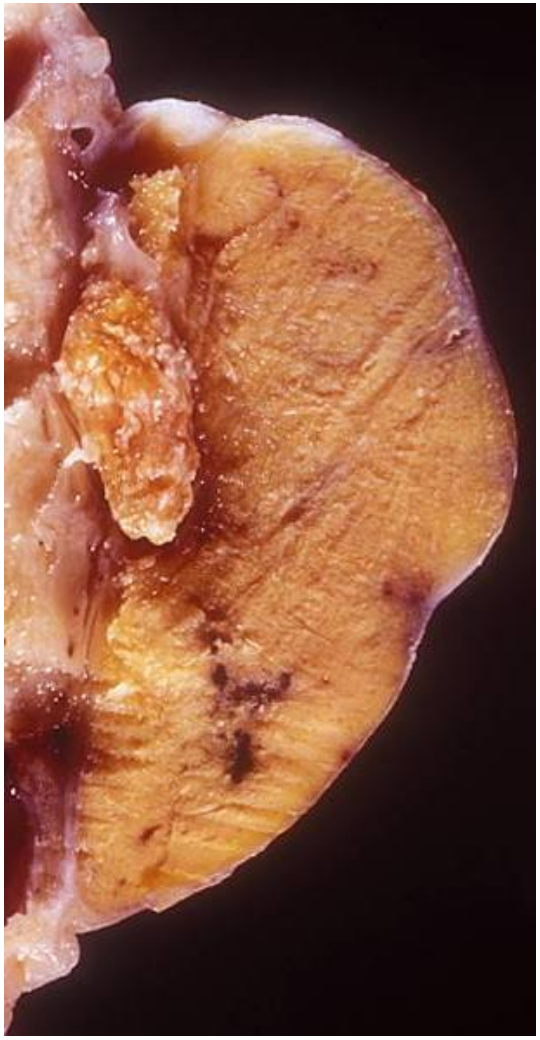
OVARIAN CARCINOIDS

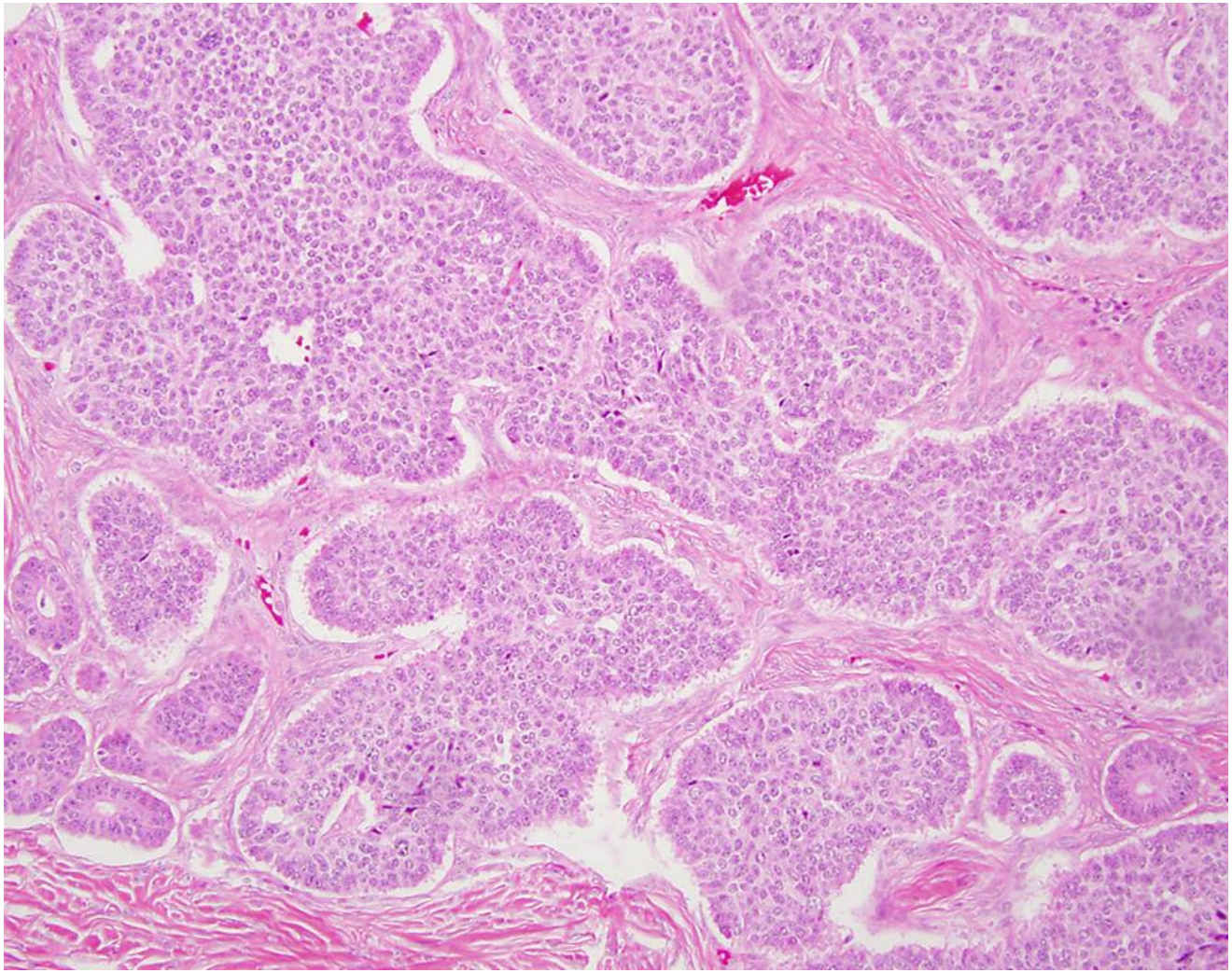
- Usually arise in dermoid cyst (yellow nodule)
- Rarely arise in other tumours- Brenner, YST, Sertoli Leydig cell tumour, mucinous tumours
- Usually small but occasionally large and overgrow pre-existing dermoid
- Insular (most common- identical to mid-gut carcinoid), trabecular (identical to hind-gut carcinoid) (need to exclude metastasis unless associated dermoid cyst or other neoplasm)
- Strumal- admixed with thyroid tissue
- Mucinous/ goblet cell- very uncommon and aggressive (need to exclude metastasis unless dermoid cyst)- similar to those tumours arising in appendix where terminology is controversial
- Extremely good prognosis but occasionally spread outside the ovary
- Immunohistochemistry of limited value in distinguishing between primary and secondary ovarian carcinoid

DISTINCTION BETWEEN PRIMARY AND SECONDARY OVARIAN CARCINOID- IHC OF LIMITED VALUE; PROBLEMS IF UNILATERAL, NO OTHER TUMOUR COMPONENT AND NO OTHER FEATURES OF METASTASIS

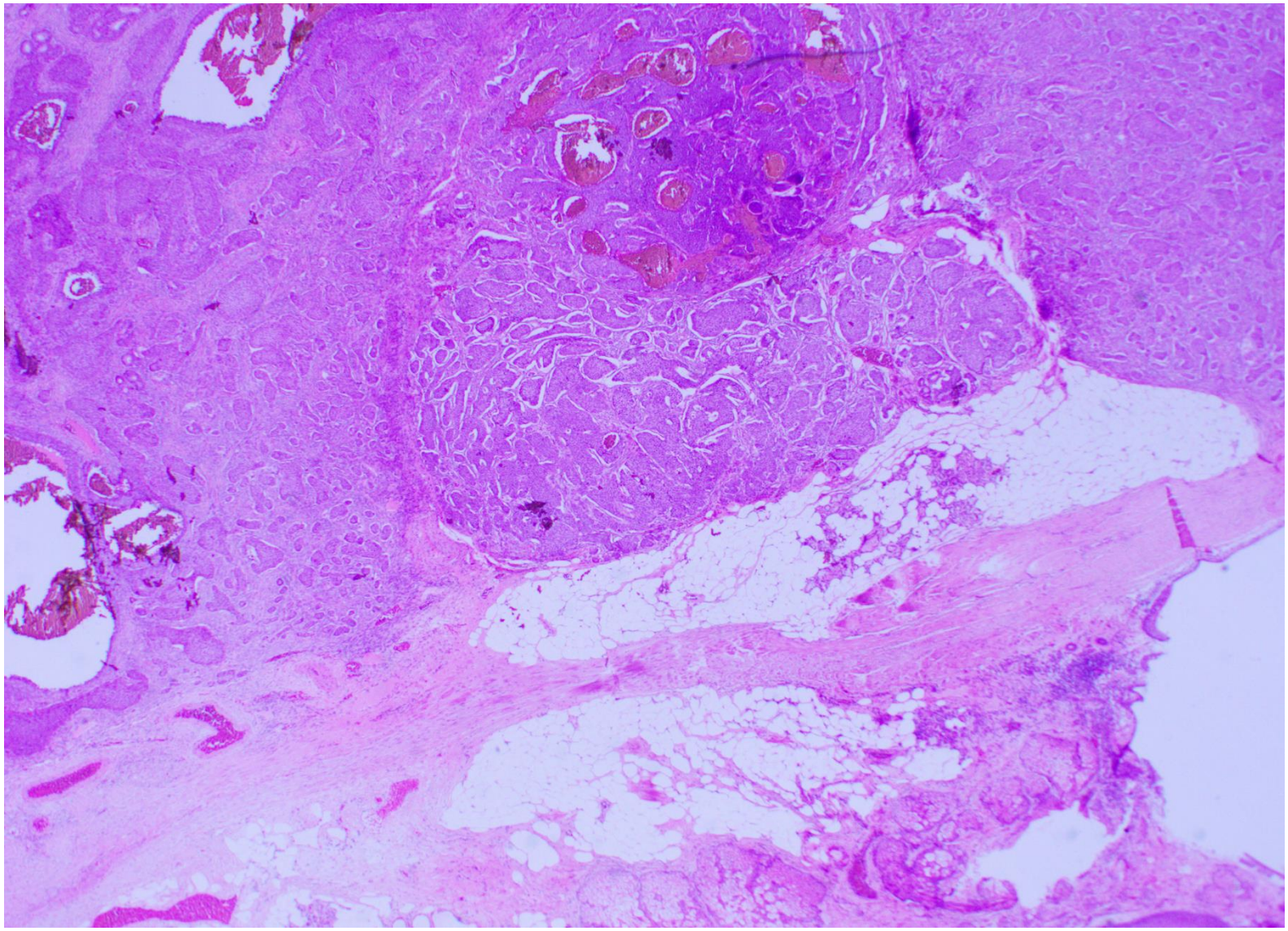
	PRIMARY CARCINOID	SECONDARY CARCINOID
Presence of dermoid cyst (or rarely other ovarian neoplasm)	Usually yes	No
Histology of extraovarian neuroendocrine neoplasm	No	Sometimes
Laterality	Almost always unilateral	Often bilateral
Nodular pattern of ovarian involvement	Usually no	Often
Surface involvement	Usually no	Often
Lymphovascular invasion	Usually no	Often
Extraovarian involvement	Usually no	Often

INSULAR CARCINOID

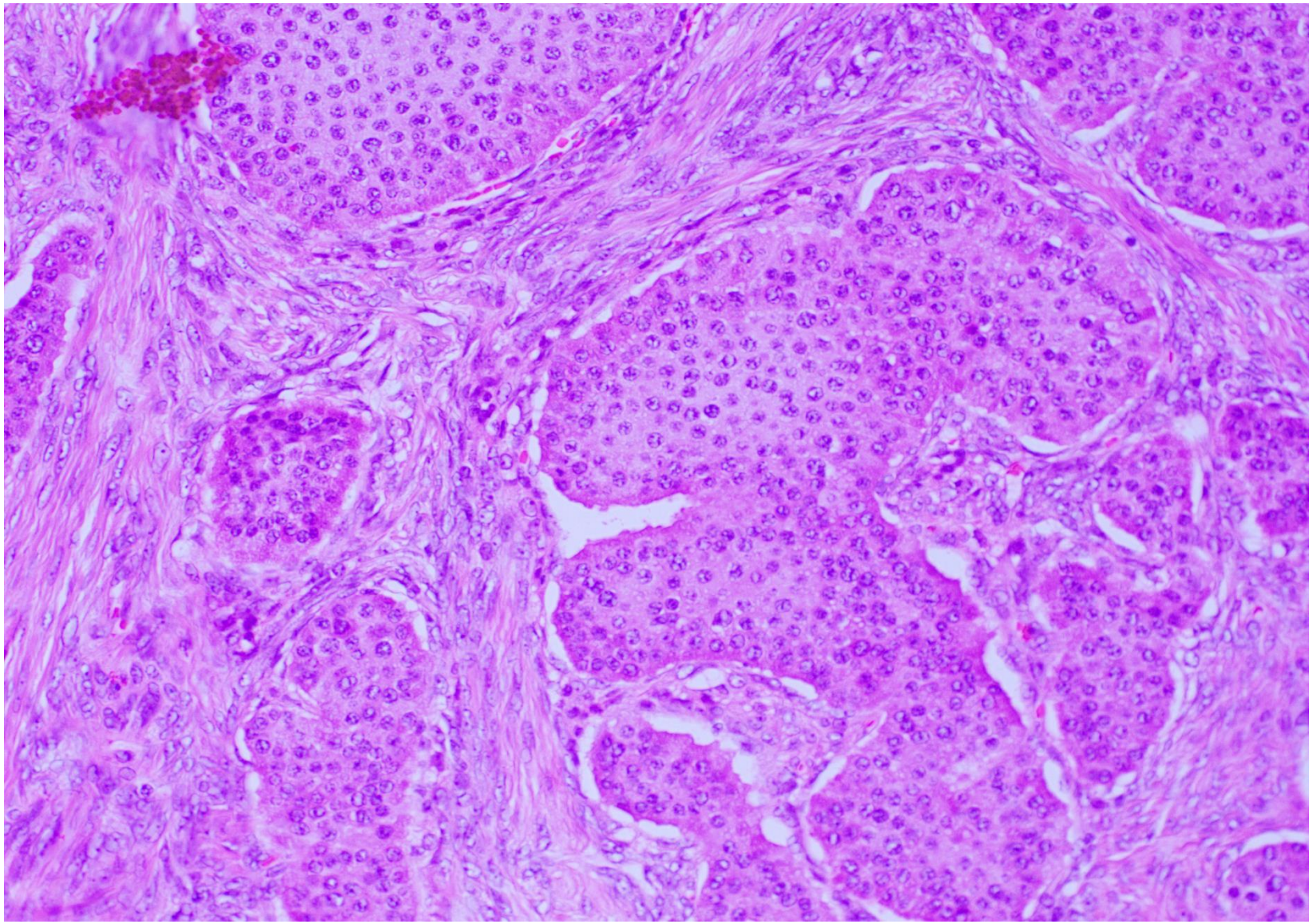




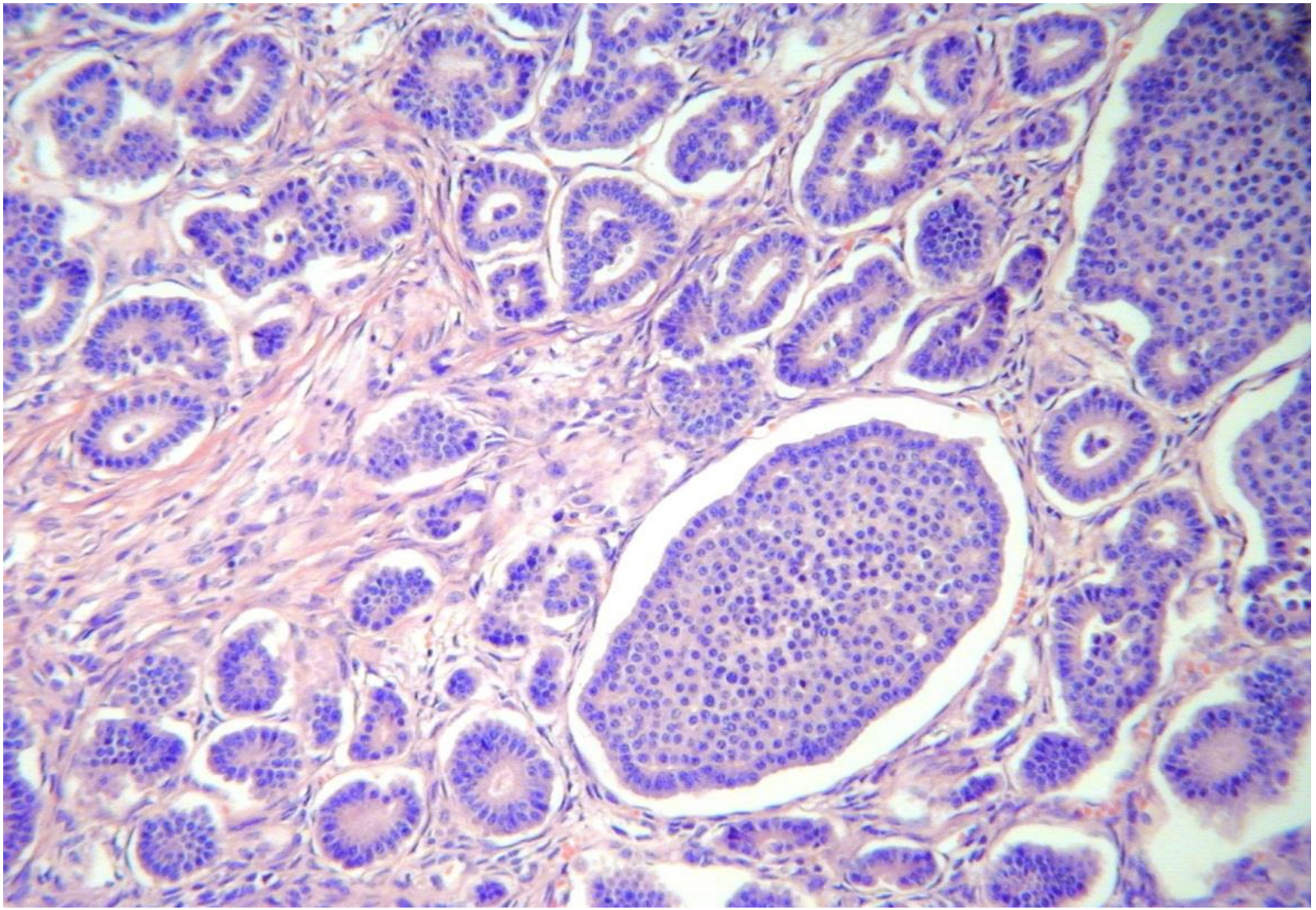
INSULAR CARCINOID



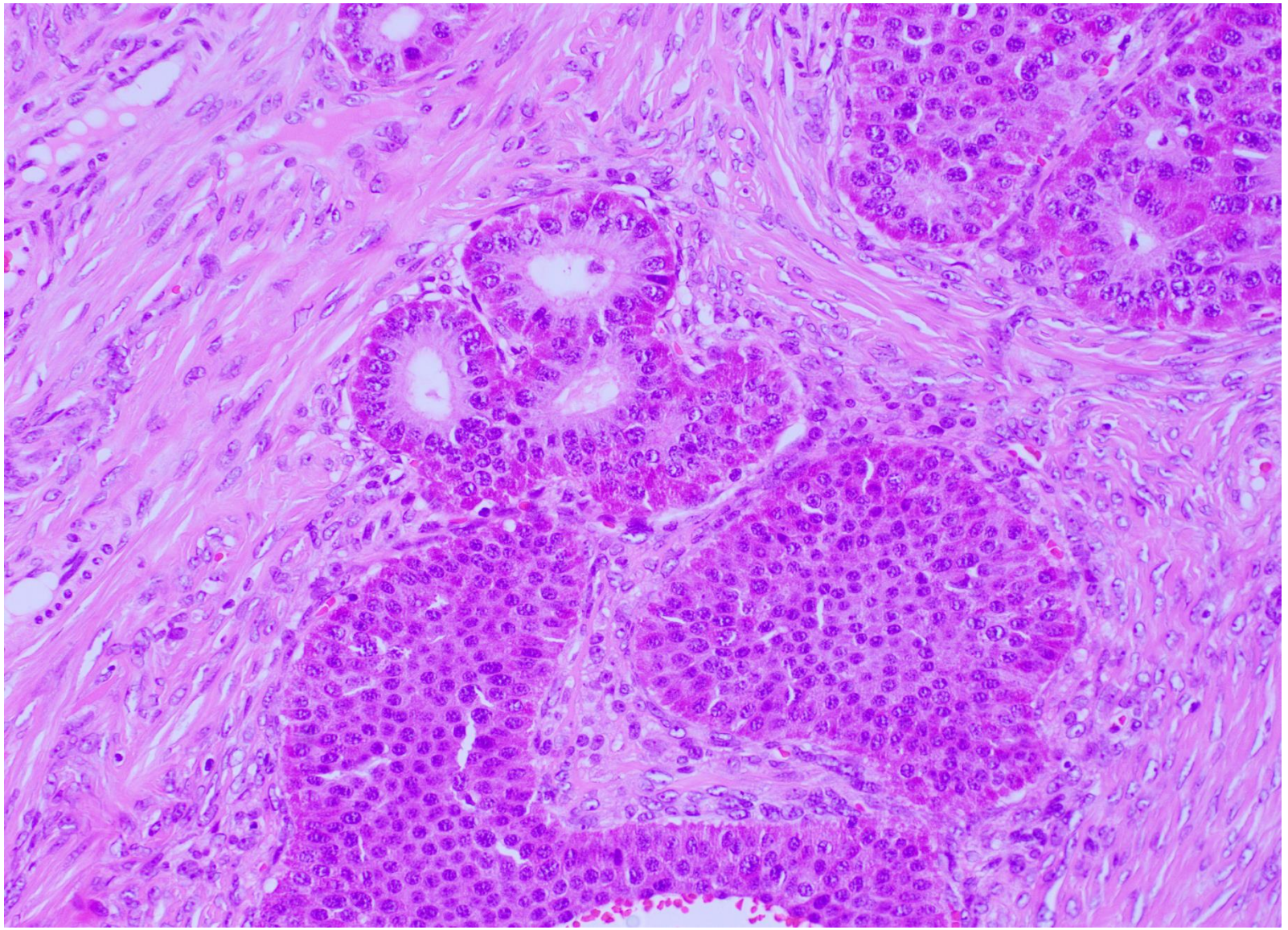
INSULAR CARCINOID



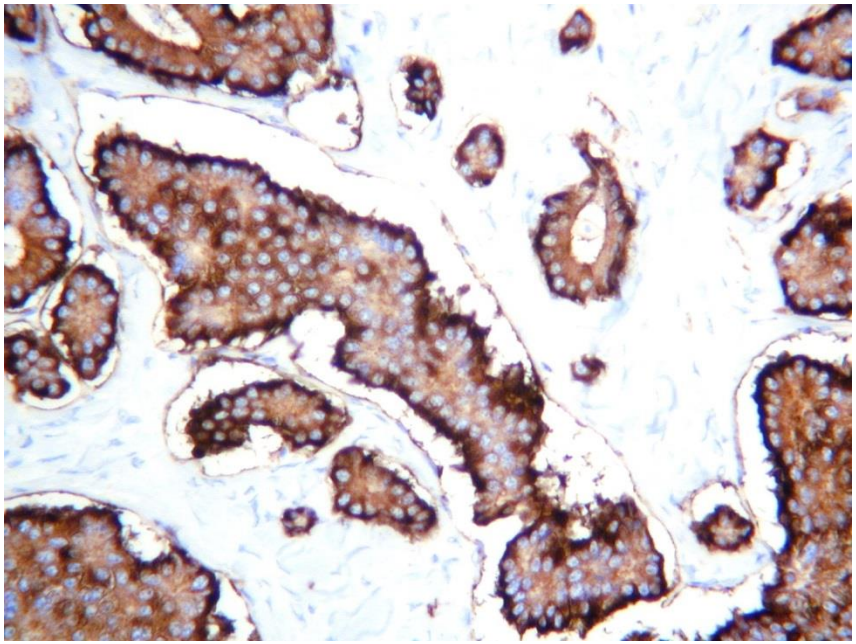
INSULAR CARCINOID



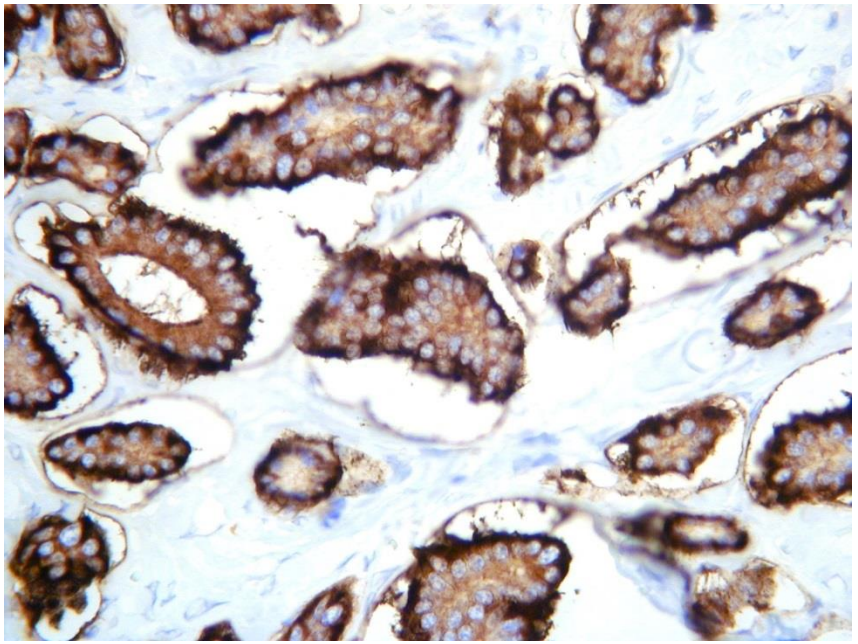
INSULAR CARCINOID



INSULAR CARCINOID

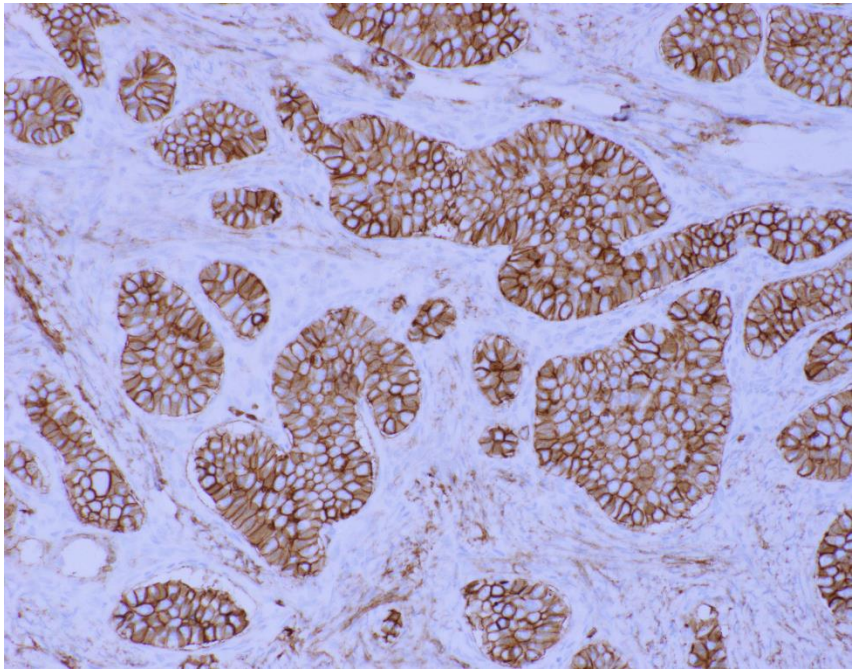


chromogranin

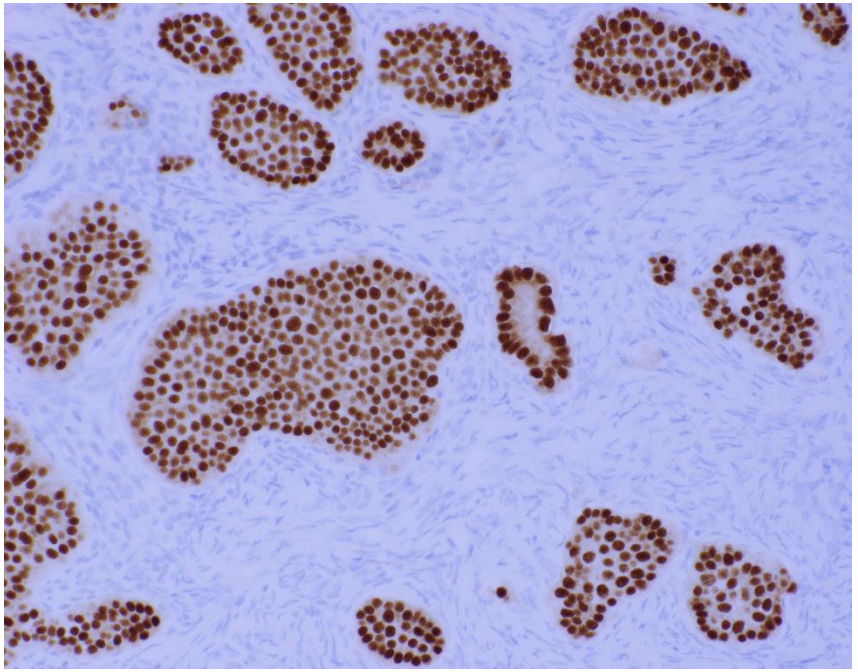


synaptophysin

INSULAR CARCINOID

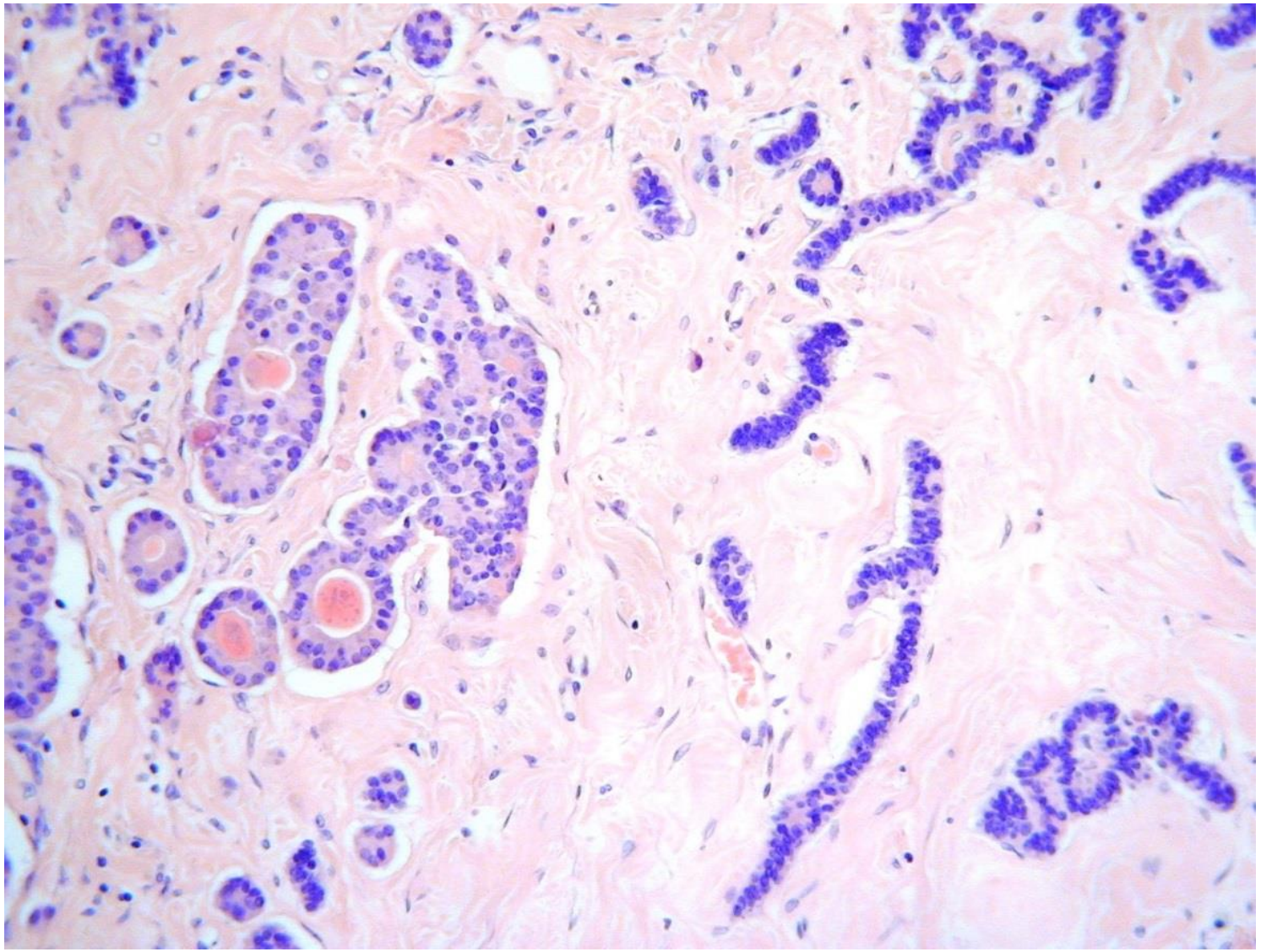


CD56

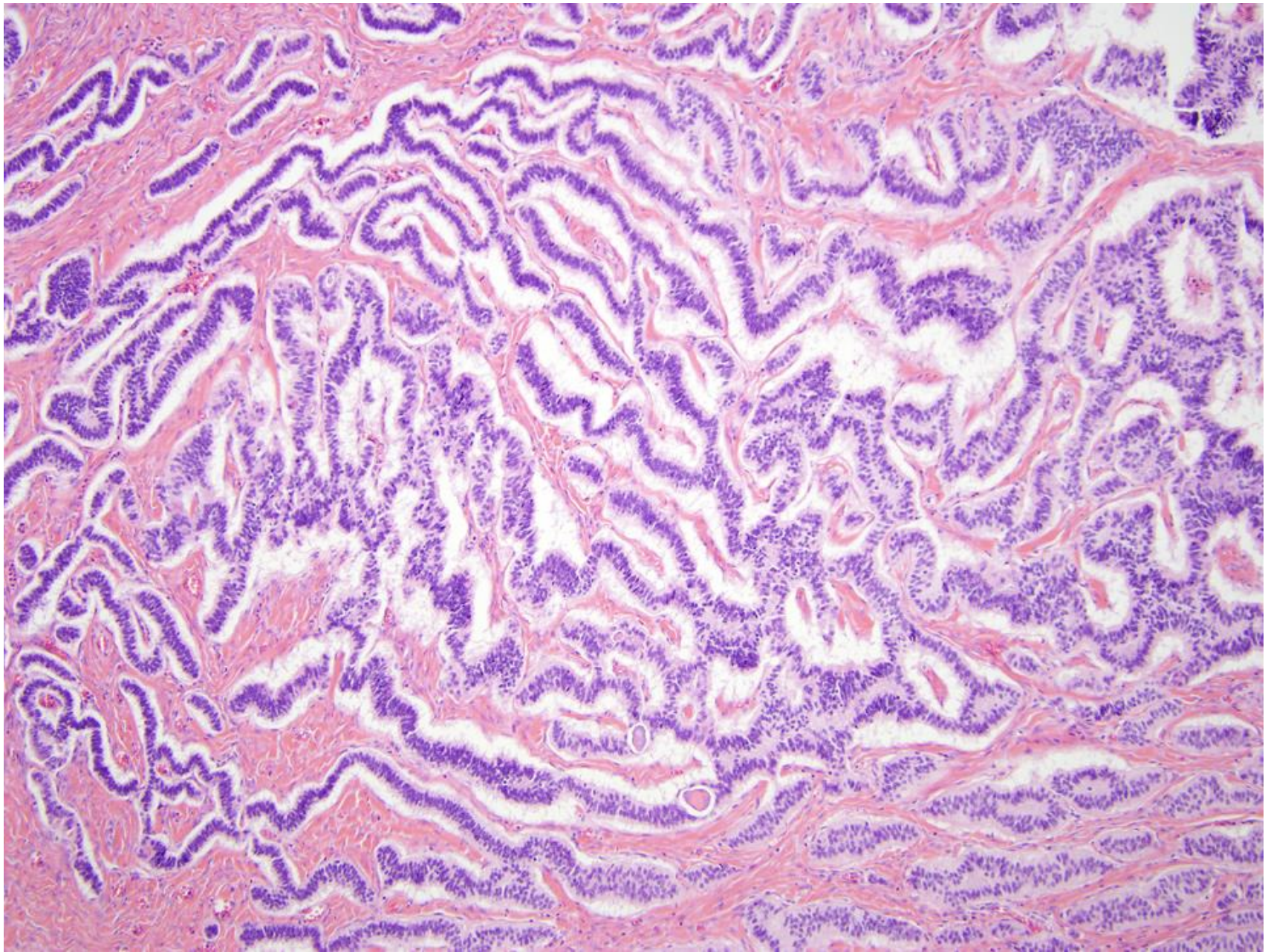


CDX2

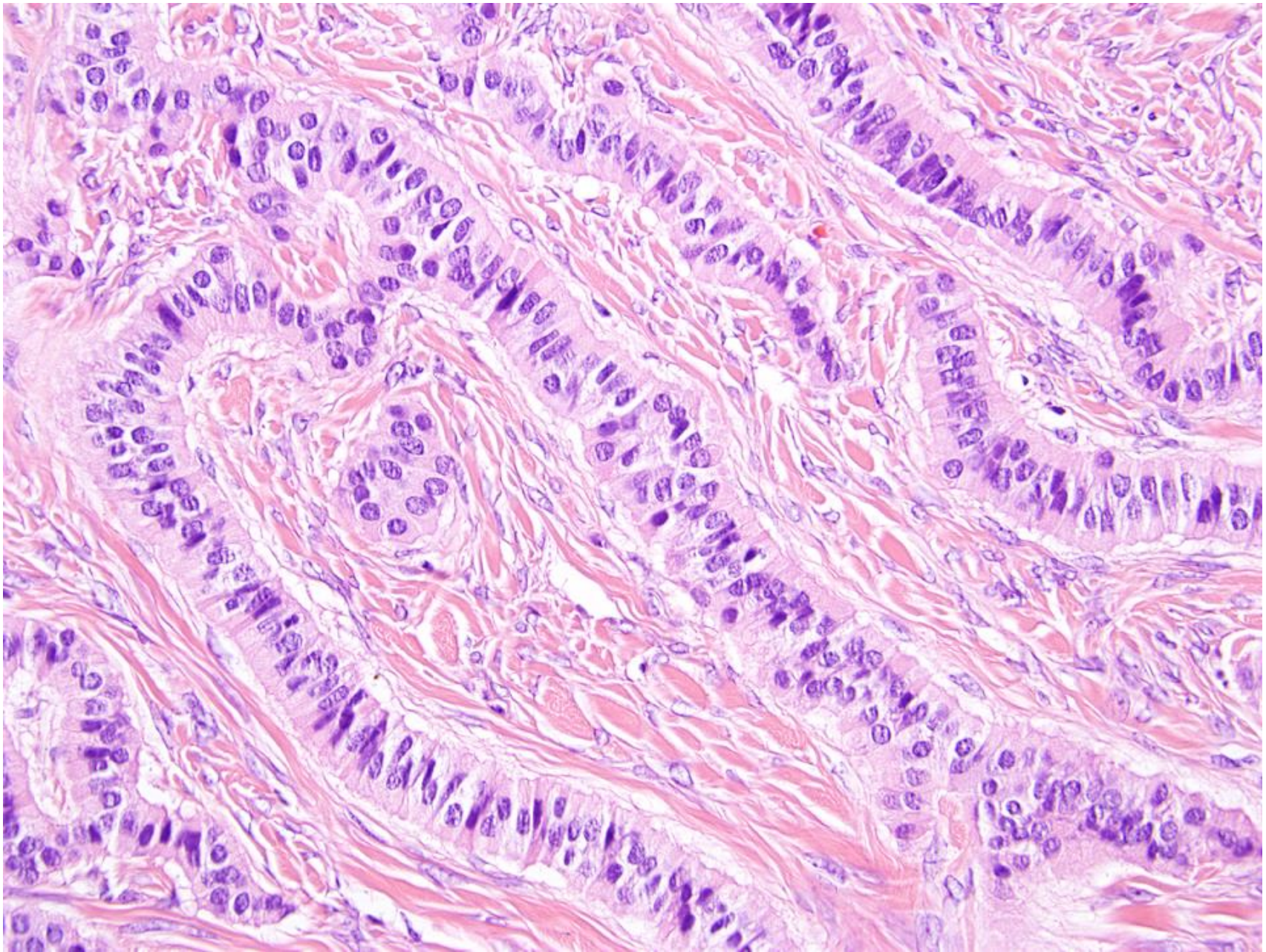
TRABECULAR CARCINOID



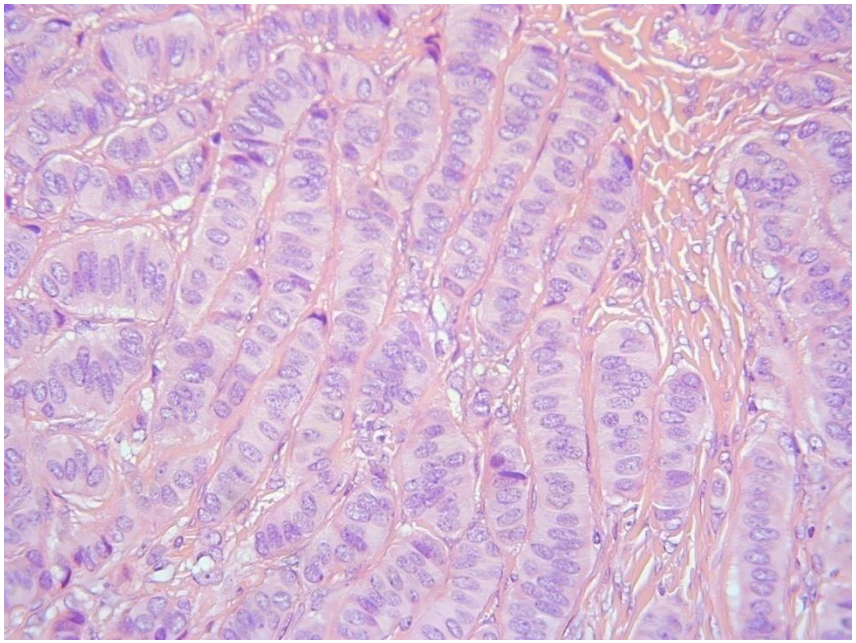
TRABECULAR CARCINOID

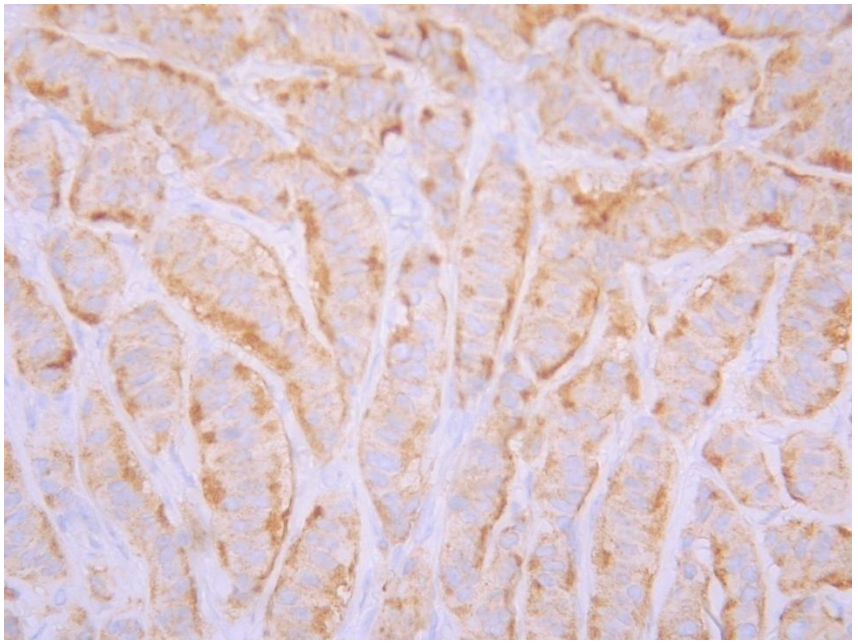


TRABECULAR CARCINOID



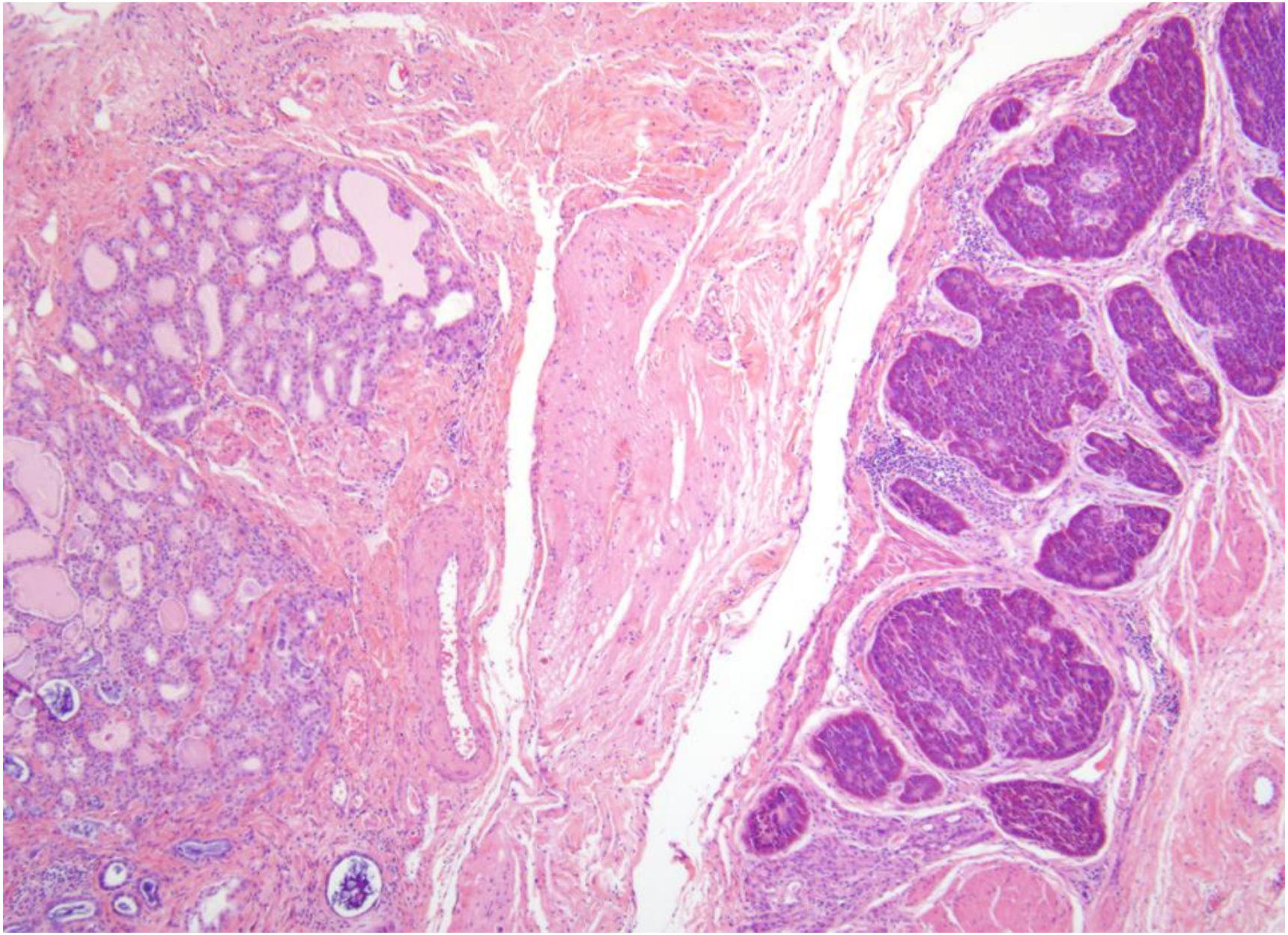
TRABECULAR CARCINOID (often chromogranin negative)



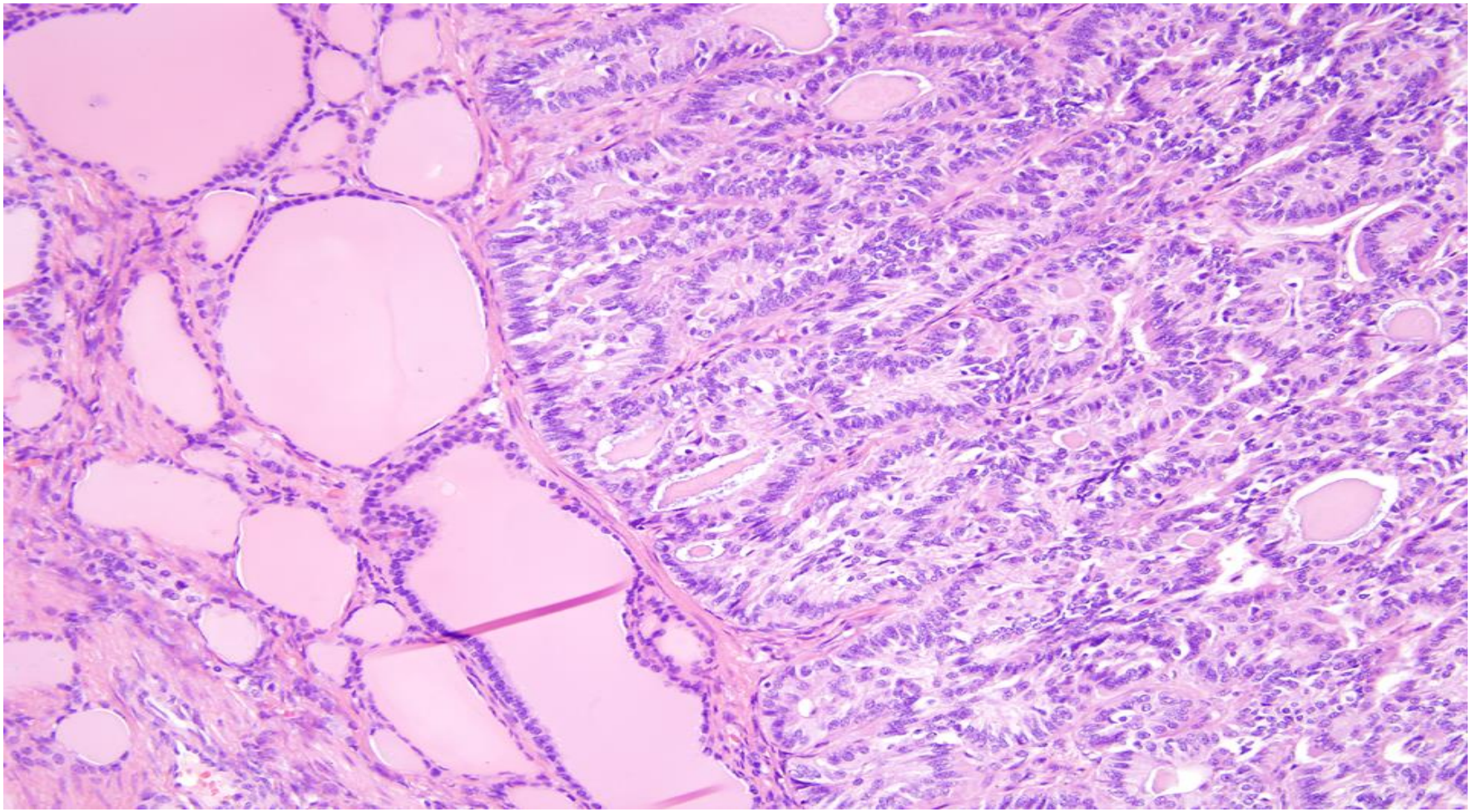


synaptophysin

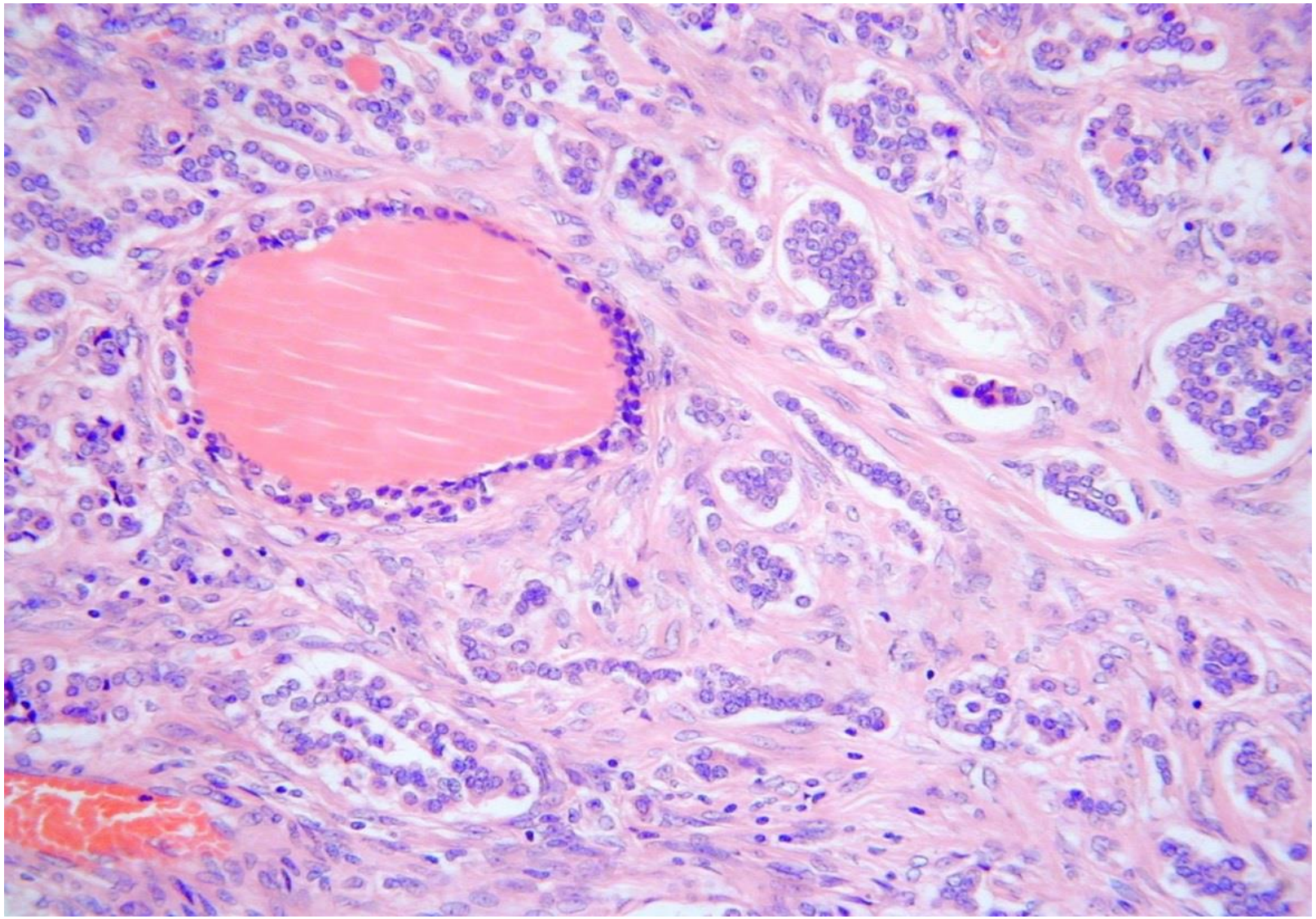
STRUMAL CARCINOID



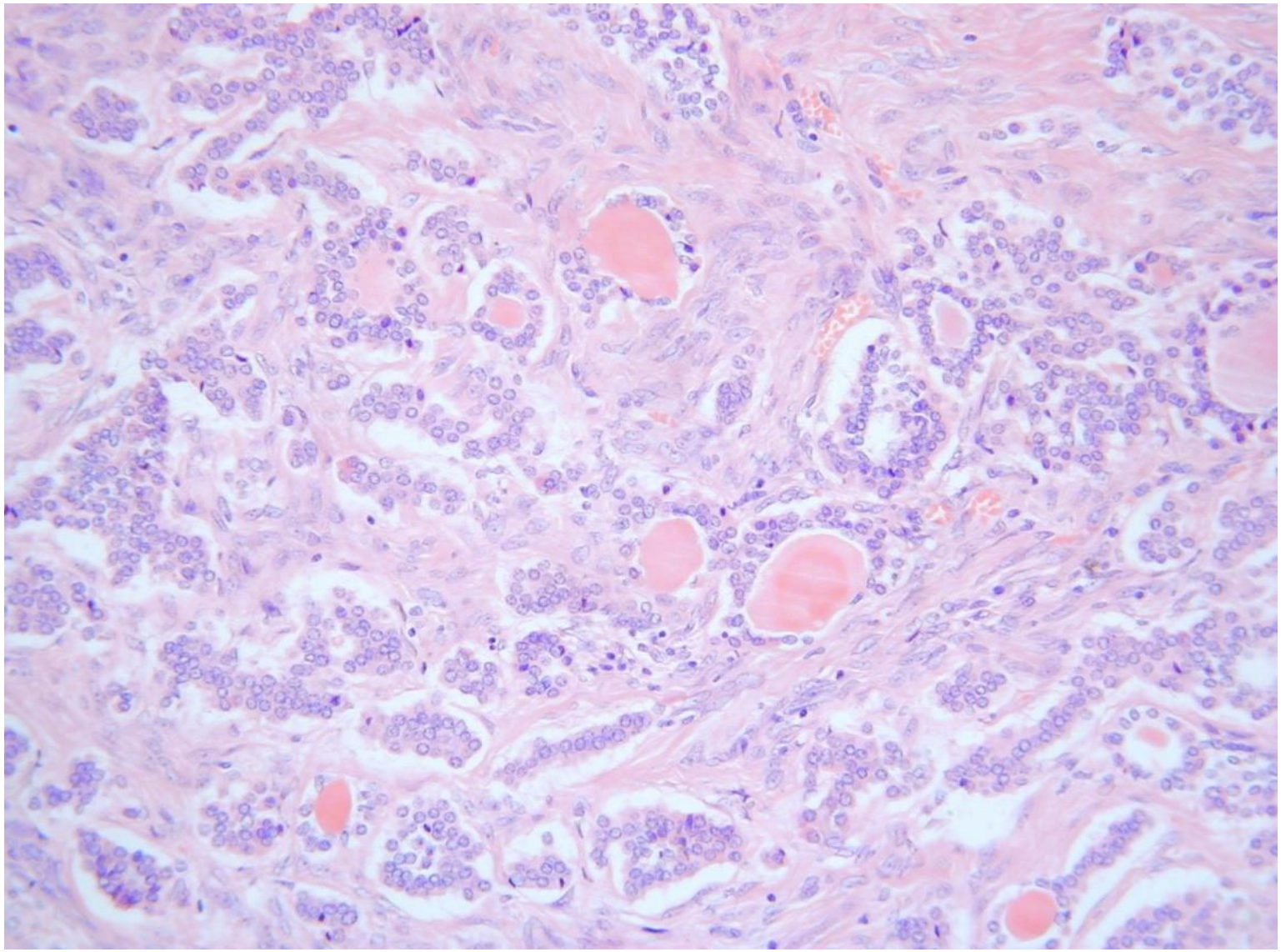
STRUMAL CARCINOID



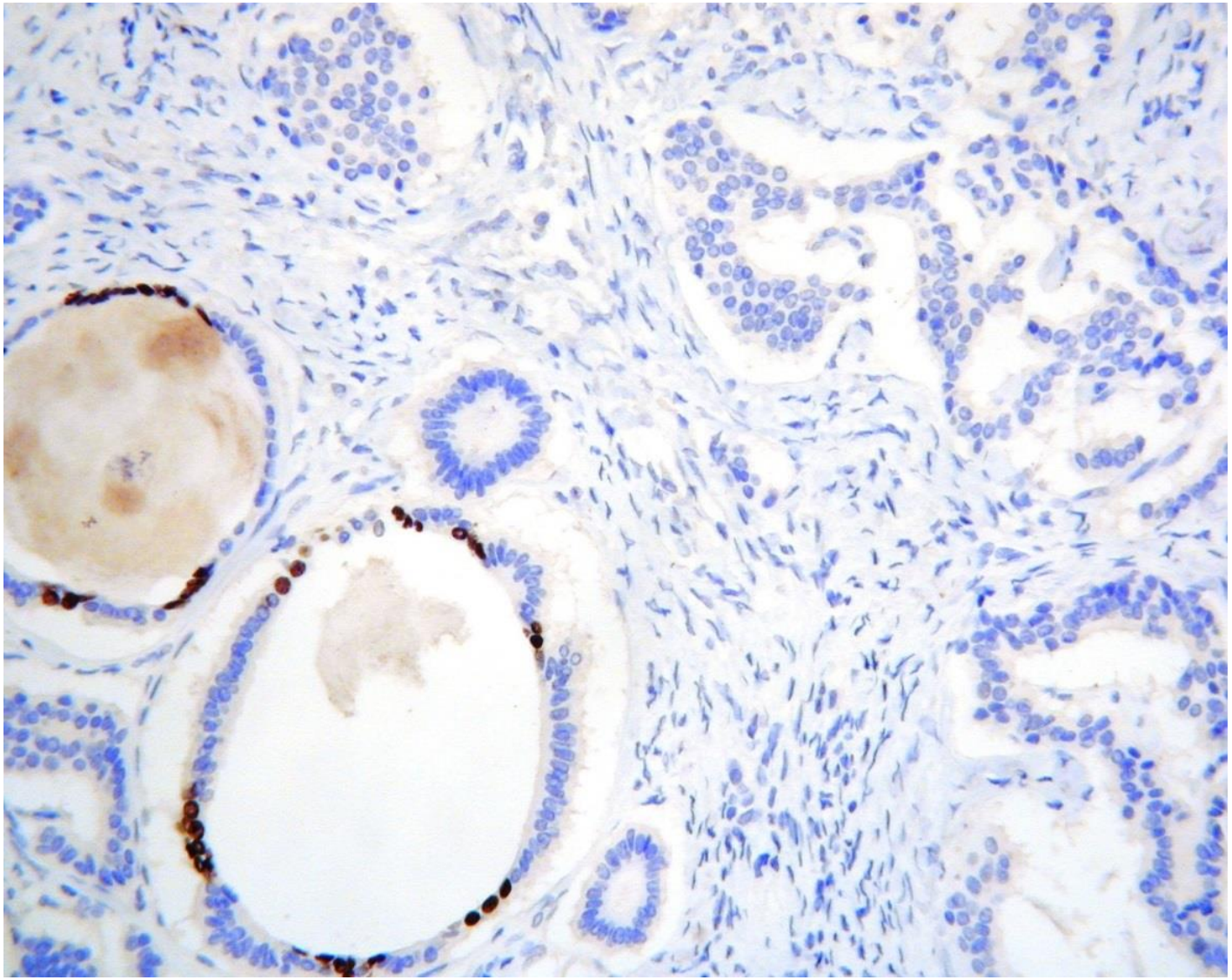
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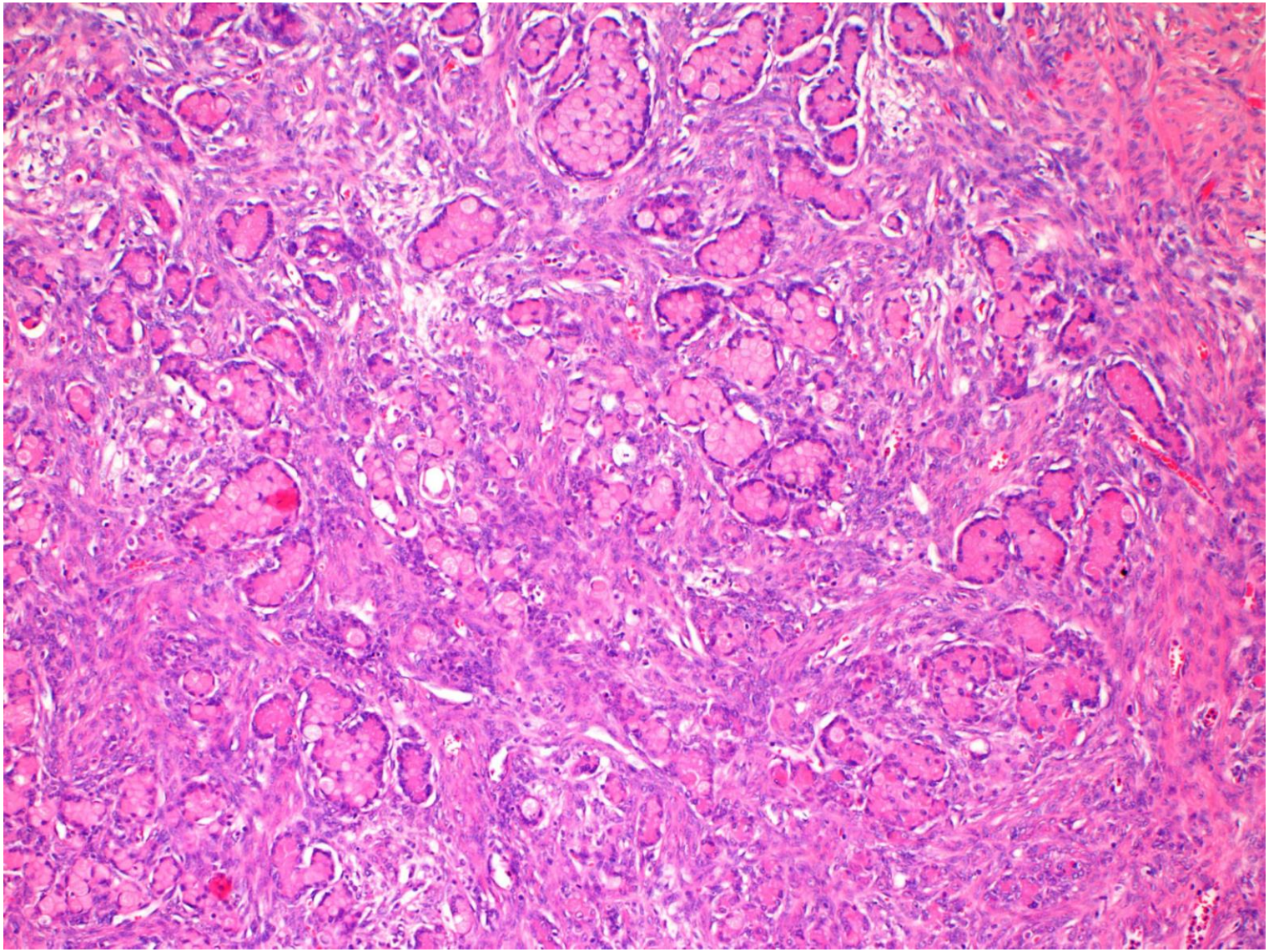
STRUMAL CARCINOID



STRUMAL CARCINOID- TTF1



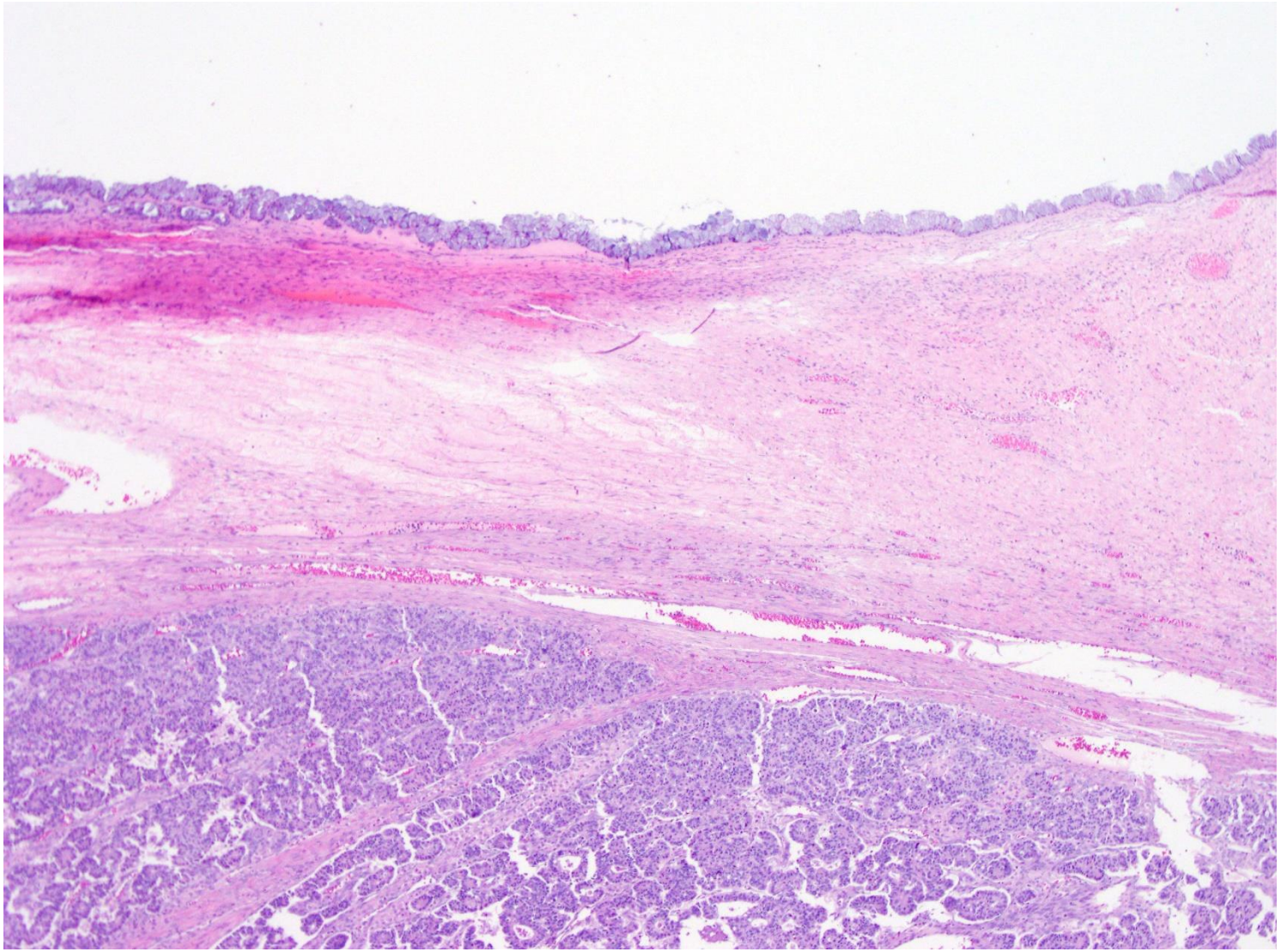
MUCINOUS/ GOBLET CELL CARCINOID



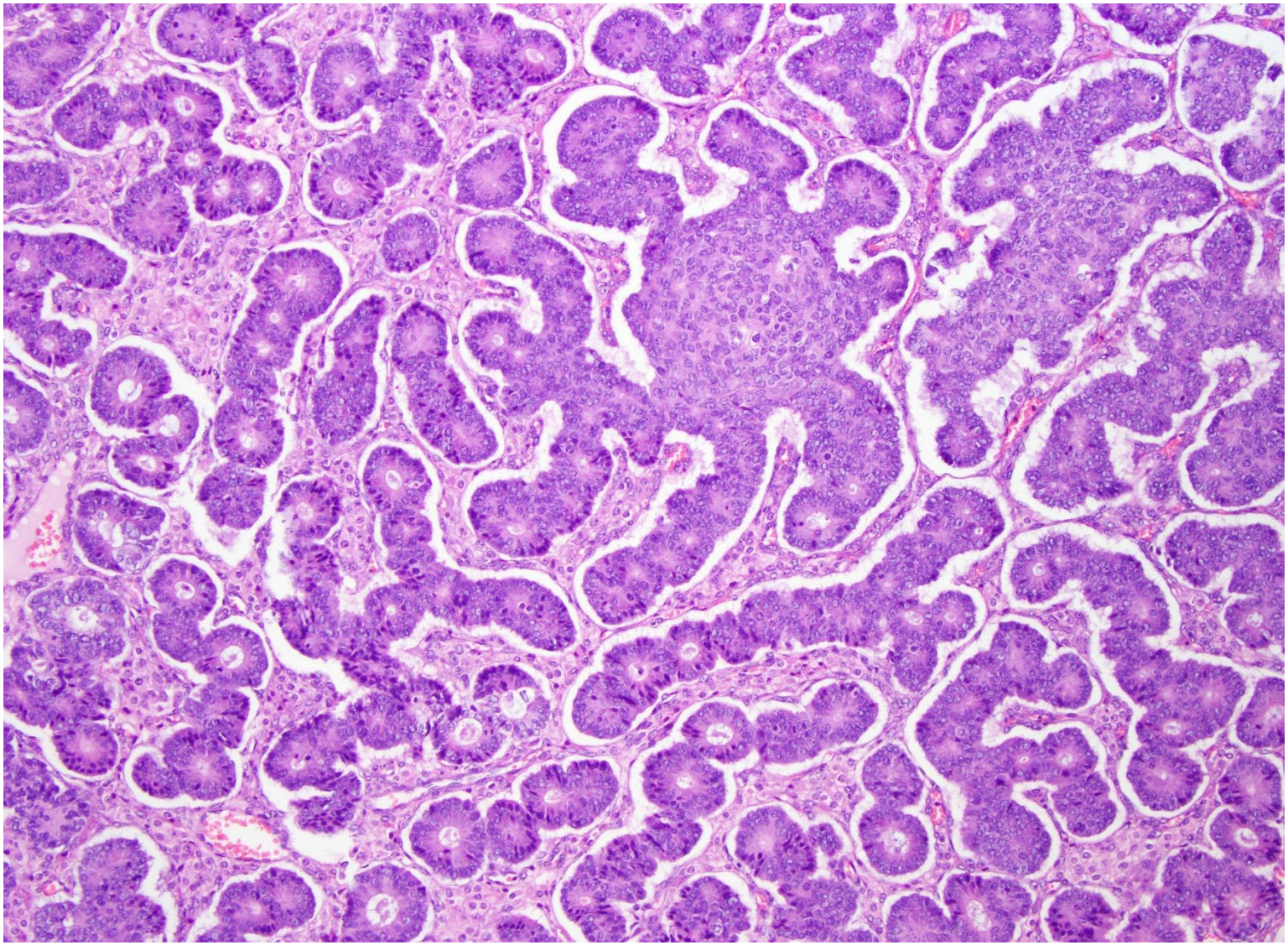
NEUROENDOCRINE CARCINOMAS OF OVARY

- Rare and aggressive neoplasms
- SCNEC and LCNEC occur but sometimes overlap and difficult to distinguish
- Often occur in association with another tumour type- especially endometrioid carcinoma
- Rarely arise in teratomas
- Need to exclude secondary if no other tumour type

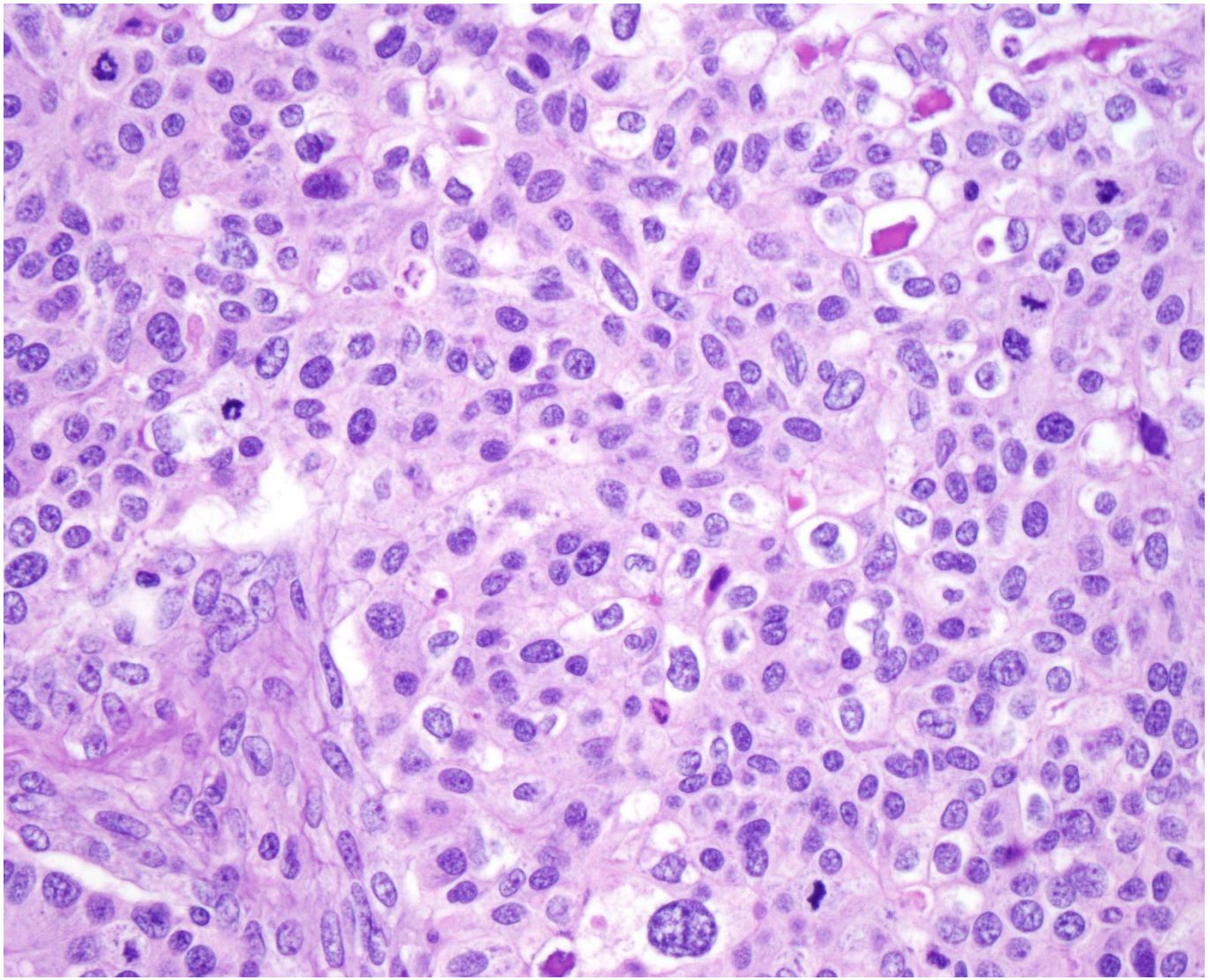
OVARY- NEC (LCNEC)



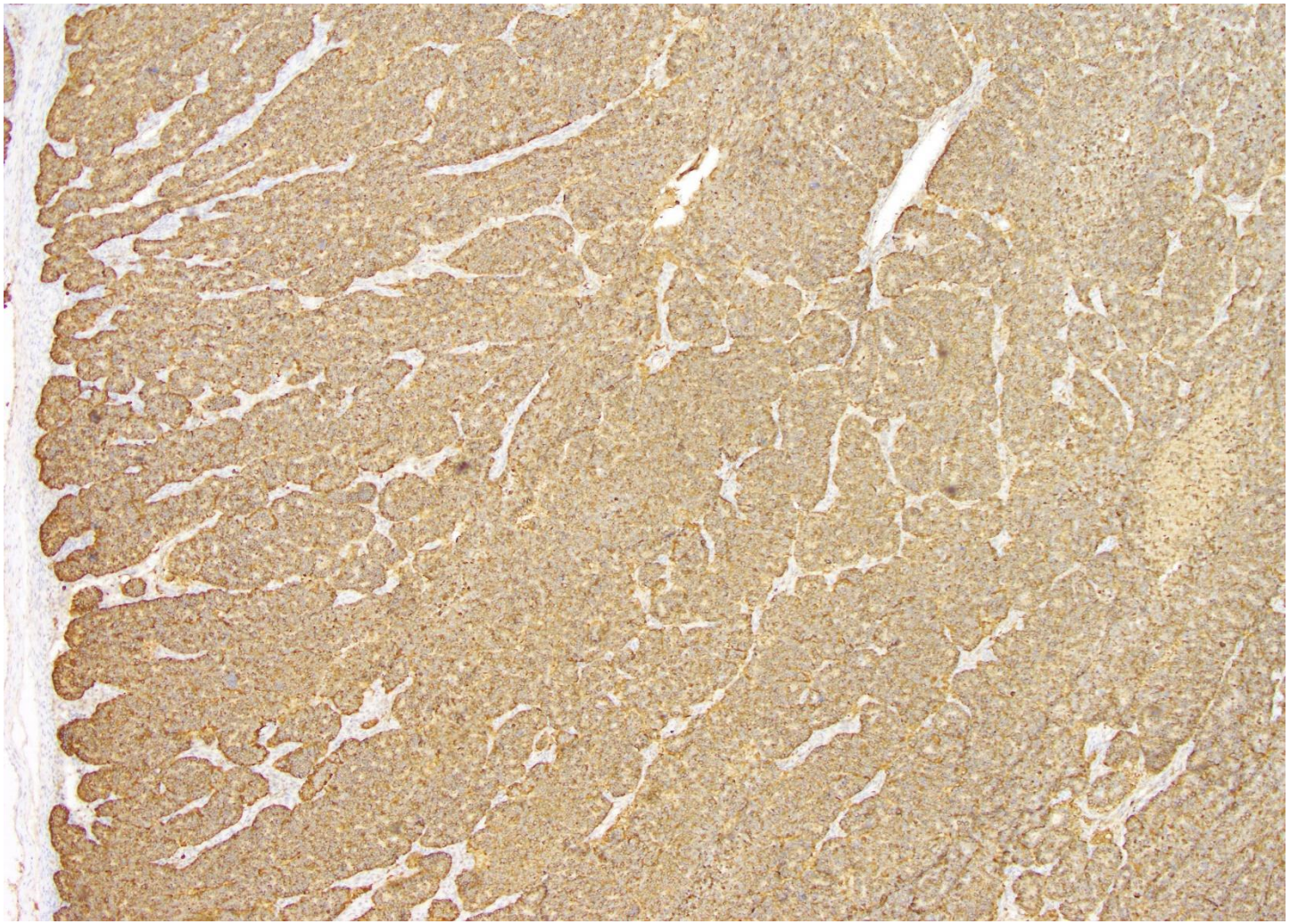
OVARY- NEC (LCNEC)



OVARY- NEC (LCNEC)

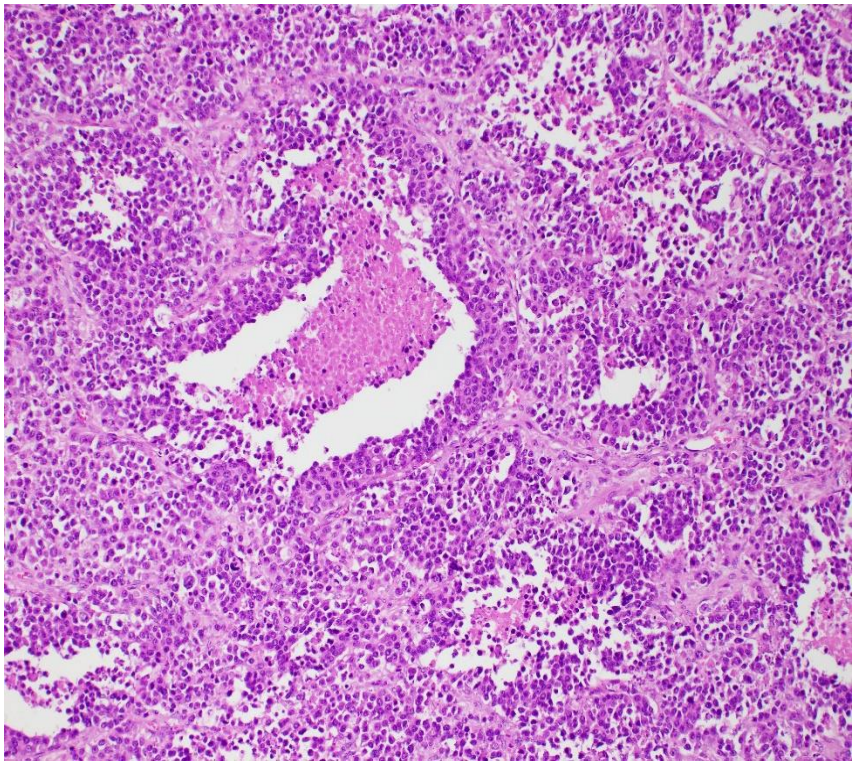


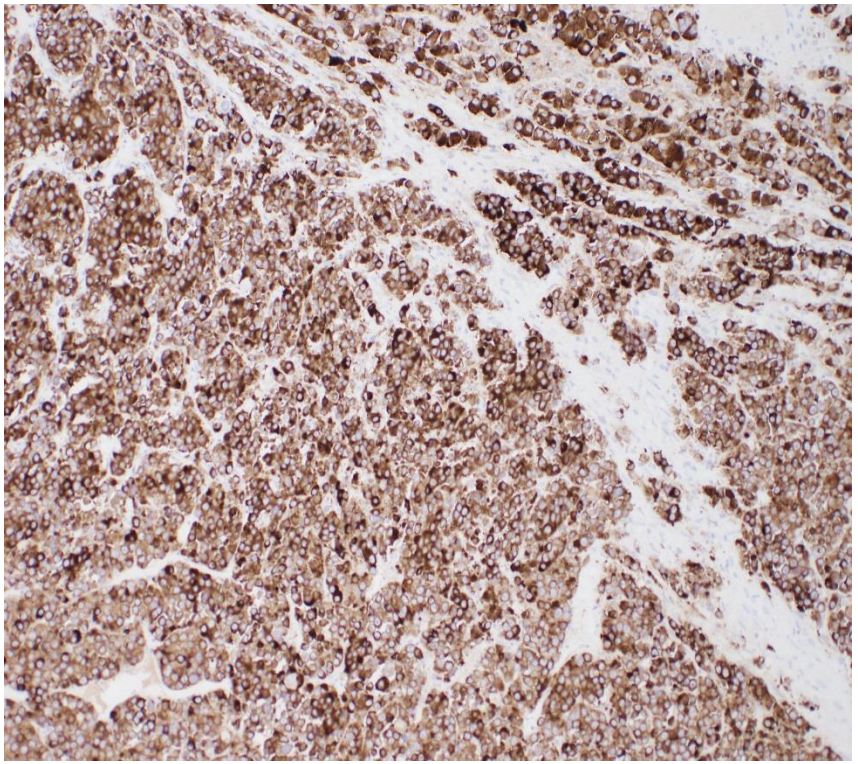
OVARY- NEC (LCNEC)



chromogranin

NEUROENDOCRINE CARCINOMA (LCNEC) OVARY





synaptophysin

FALLOPIAN TUBE

International Journal of Gynecological Pathology
38:78–84, Lippincott Williams & Wilkins, Baltimore
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Original Article

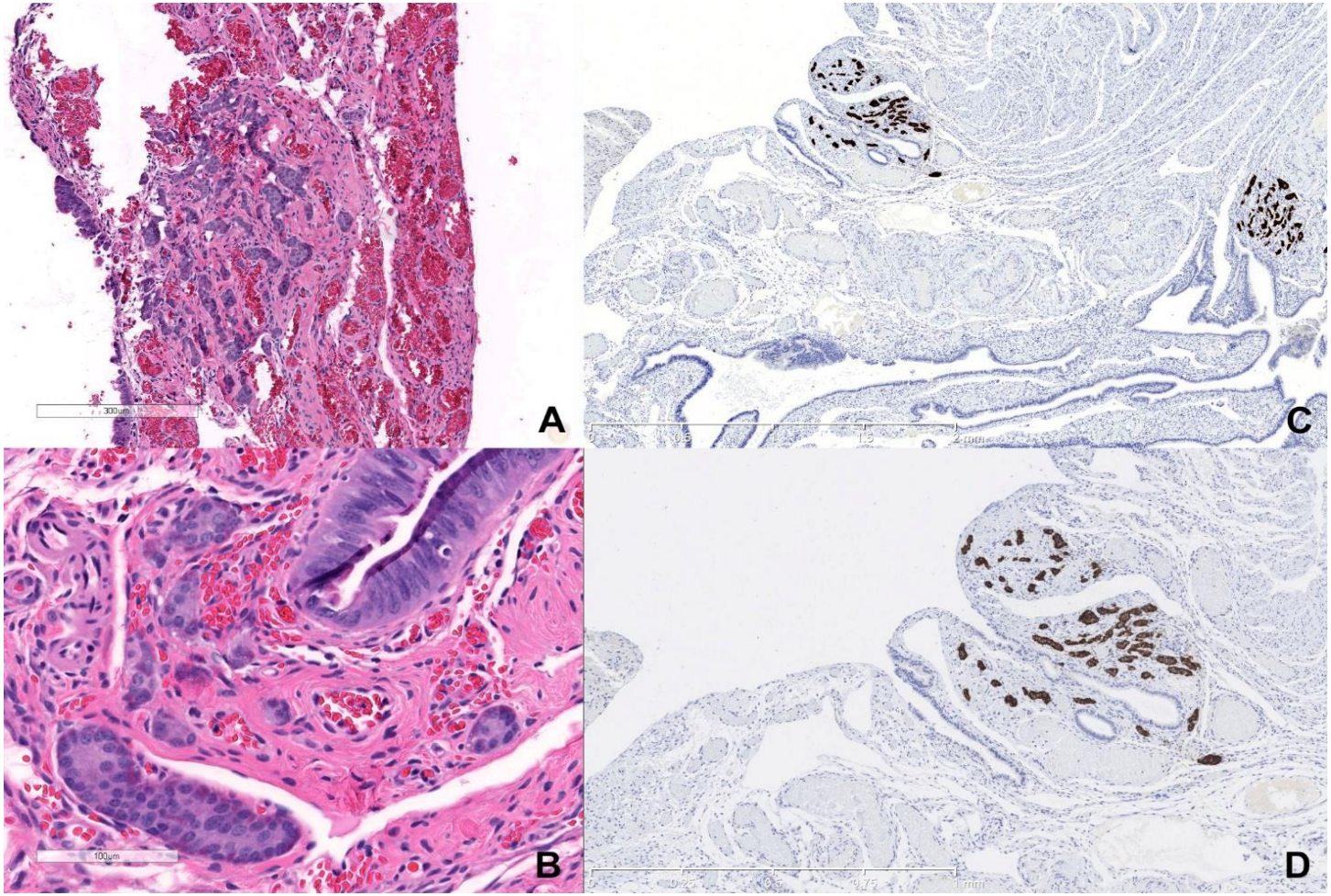
Neuroendocrine Tumors of the Fallopian Tube: Report of a Case Series and Review of the Literature

Katherine Grondin, MD, Marianne Lidang, M.D., Marie Boenelycke, M.D., Isabel Alvarado-Cabrero, M.D., C. Simon Herrington, F.R.C.Path., and W. Glenn McCluggage, F.R.C.Path.

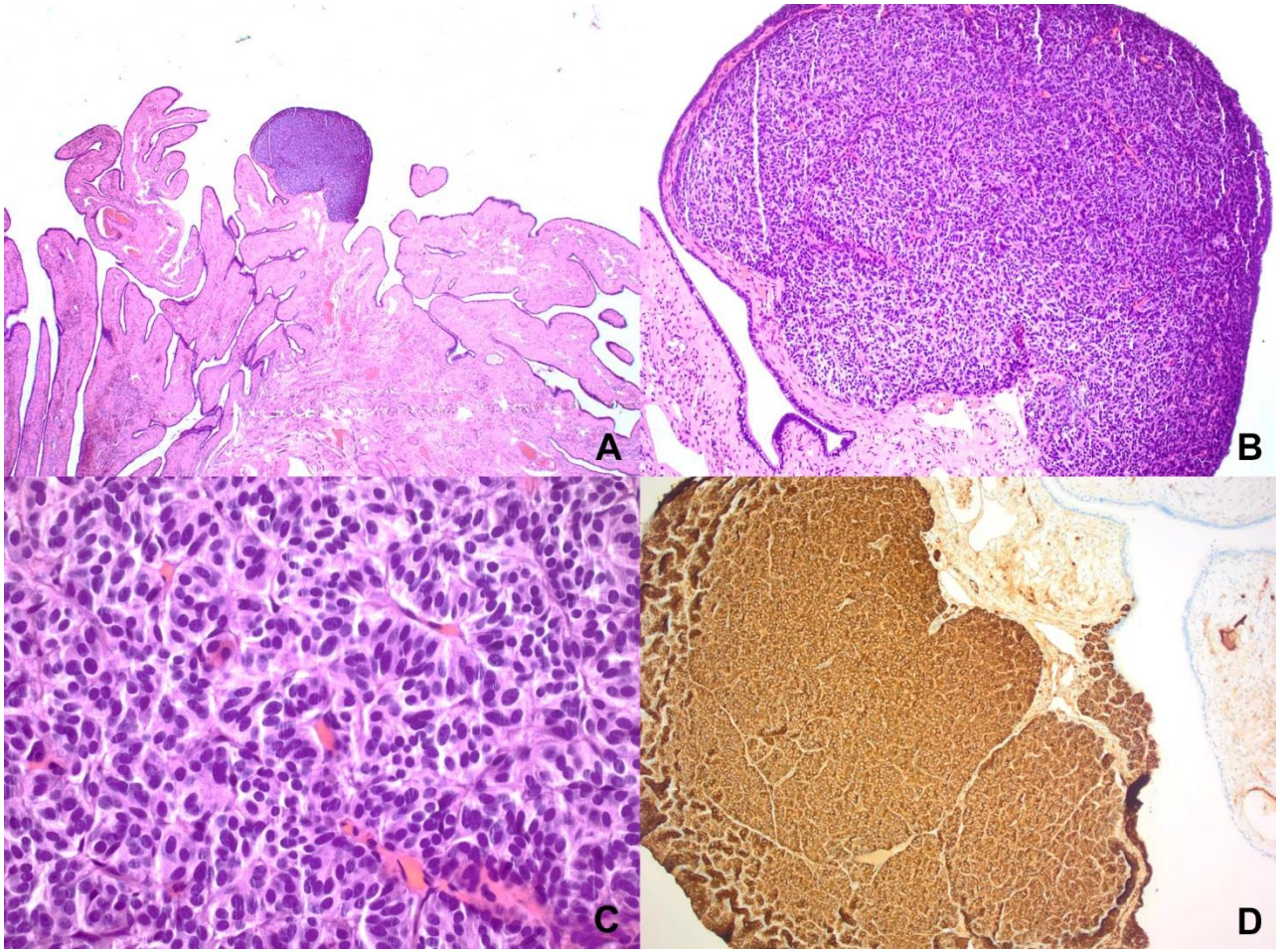
FALLOPIAN TUBE

- PMID 29019870
- Only 1 prior case report of tubal carcinoid in teratoma
- Report of 4 cases- 2 carcinoid/ low-grade NET and 2 high-grade neuroendocrine carcinomas
- Demonstrated chromogranin positive cells in normal fallopian tubes (9/16)
- Need to exclude metastasis before making diagnosis

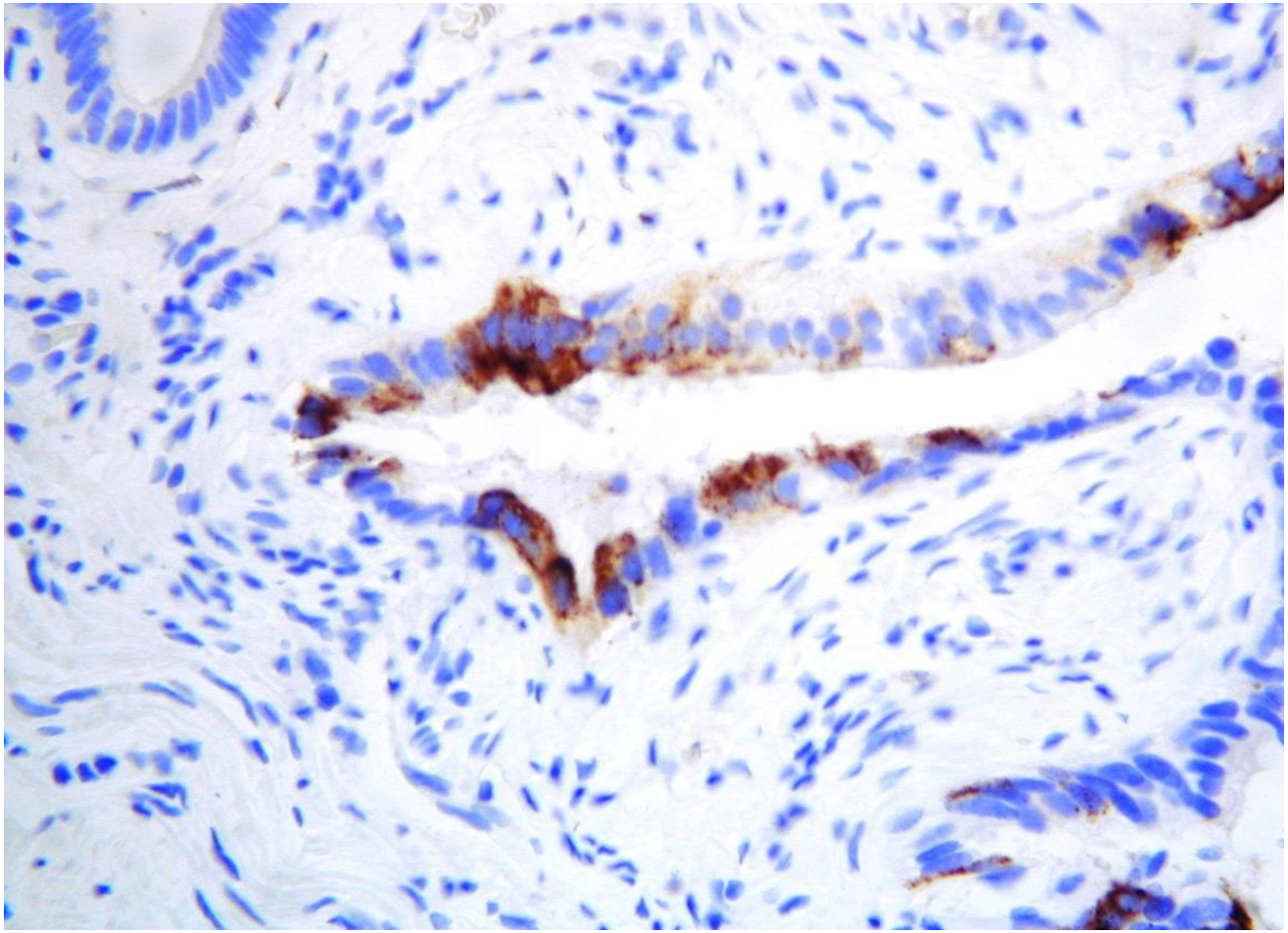
FALLOPIAN TUBE



FALLOPIAN TUBE



FALLOPIAN TUBE



chromogranin

CERVICAL NEUROENDOCRINE NEOPLASMS (WHO 2003)

- typical carcinoid
- atypical carcinoid
- small cell **neuroendocrine** carcinoma (most common)
- large cell neuroendocrine carcinoma

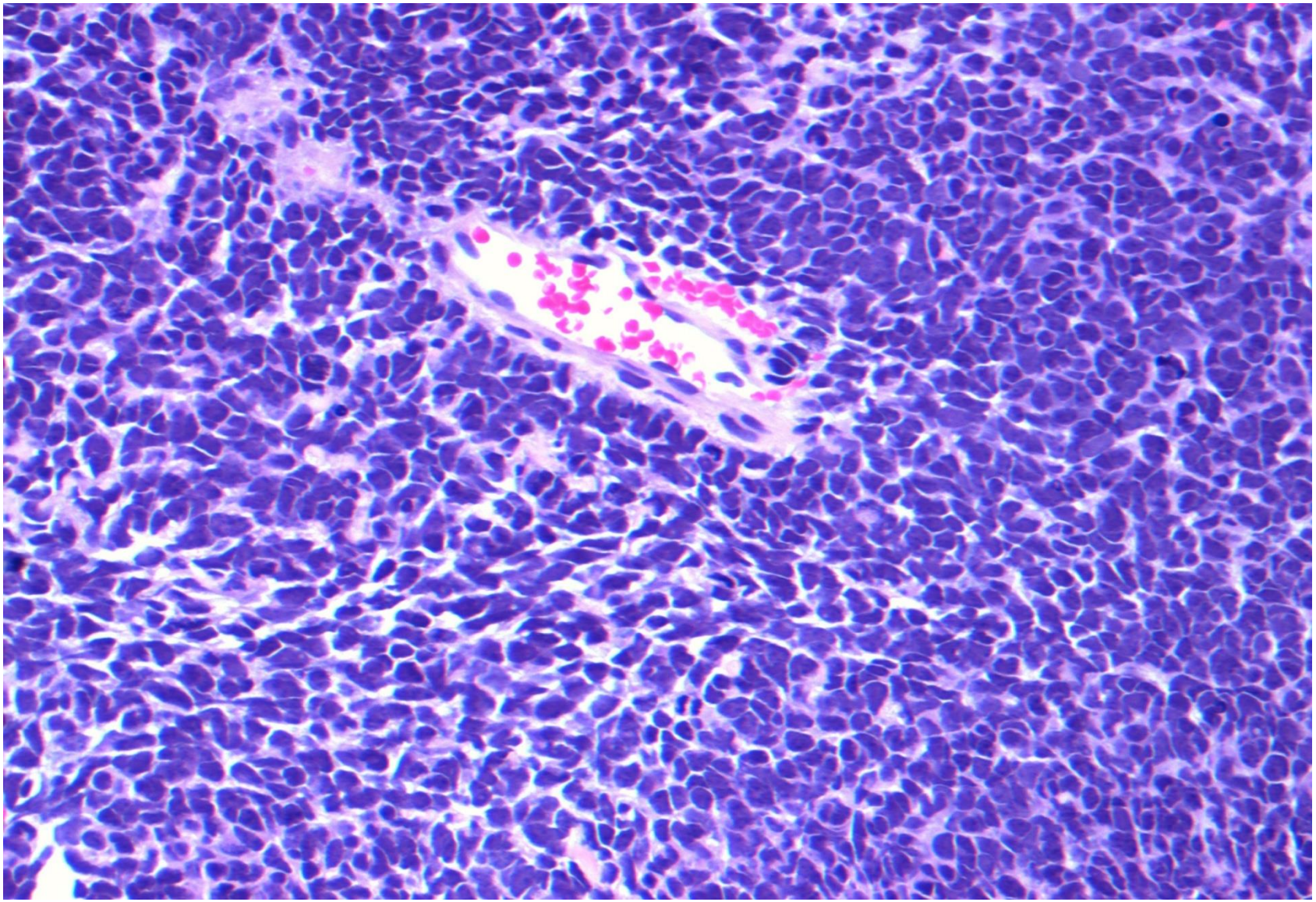
CERVICAL NEUROENDOCRINE NEOPLASMS (WHO 2014 and 2020)

- low grade neuroendocrine **tumour** (NET) (carcinoid and atypical carcinoid)
- high grade neuroendocrine **carcinoma** (NEC) (small cell and large cell neuroendocrine carcinoma)
- also category of carcinoma admixed with neuroendocrine carcinoma

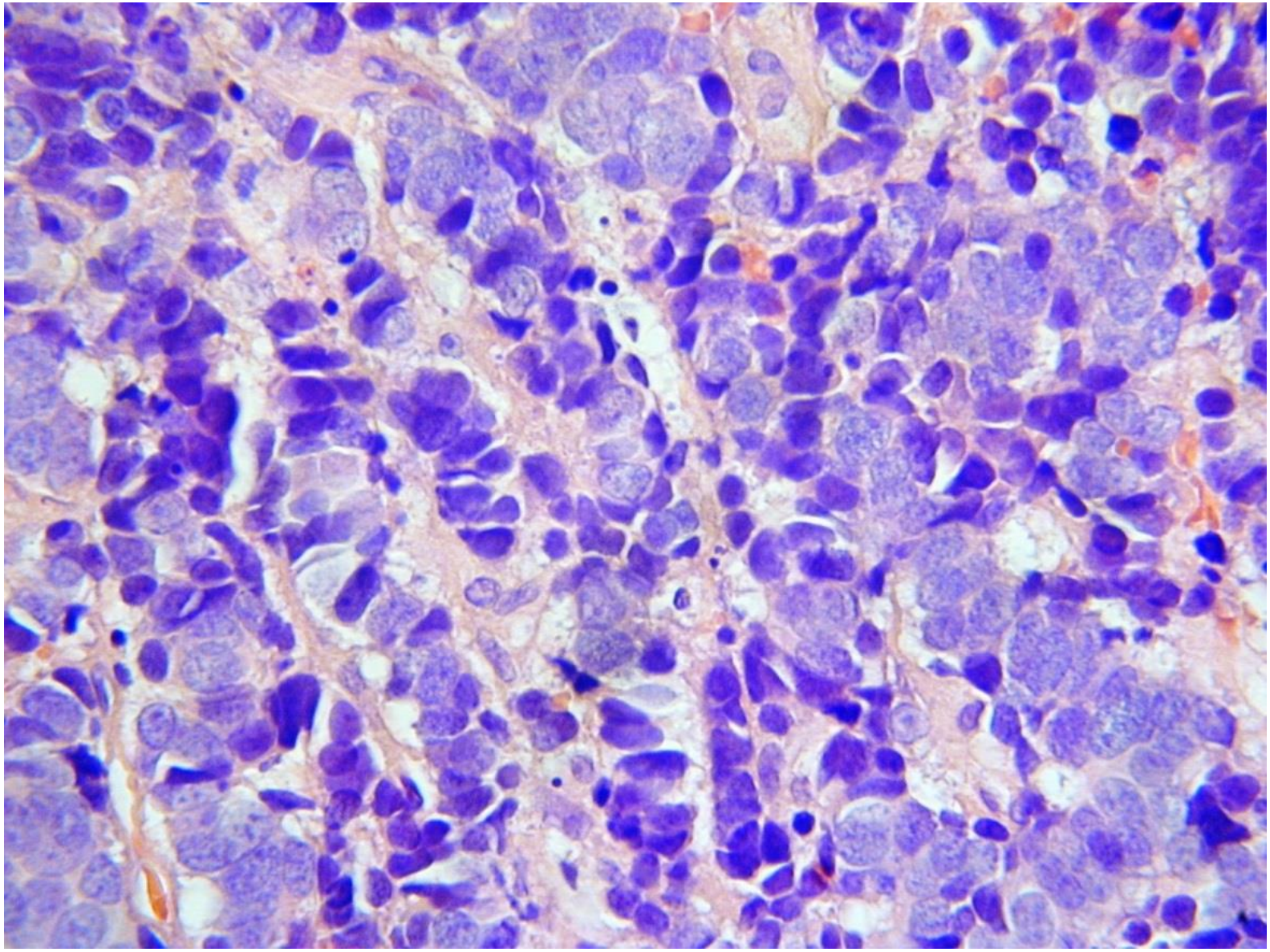
CERVICAL NEUROENDOCRINE CARCINOMAS

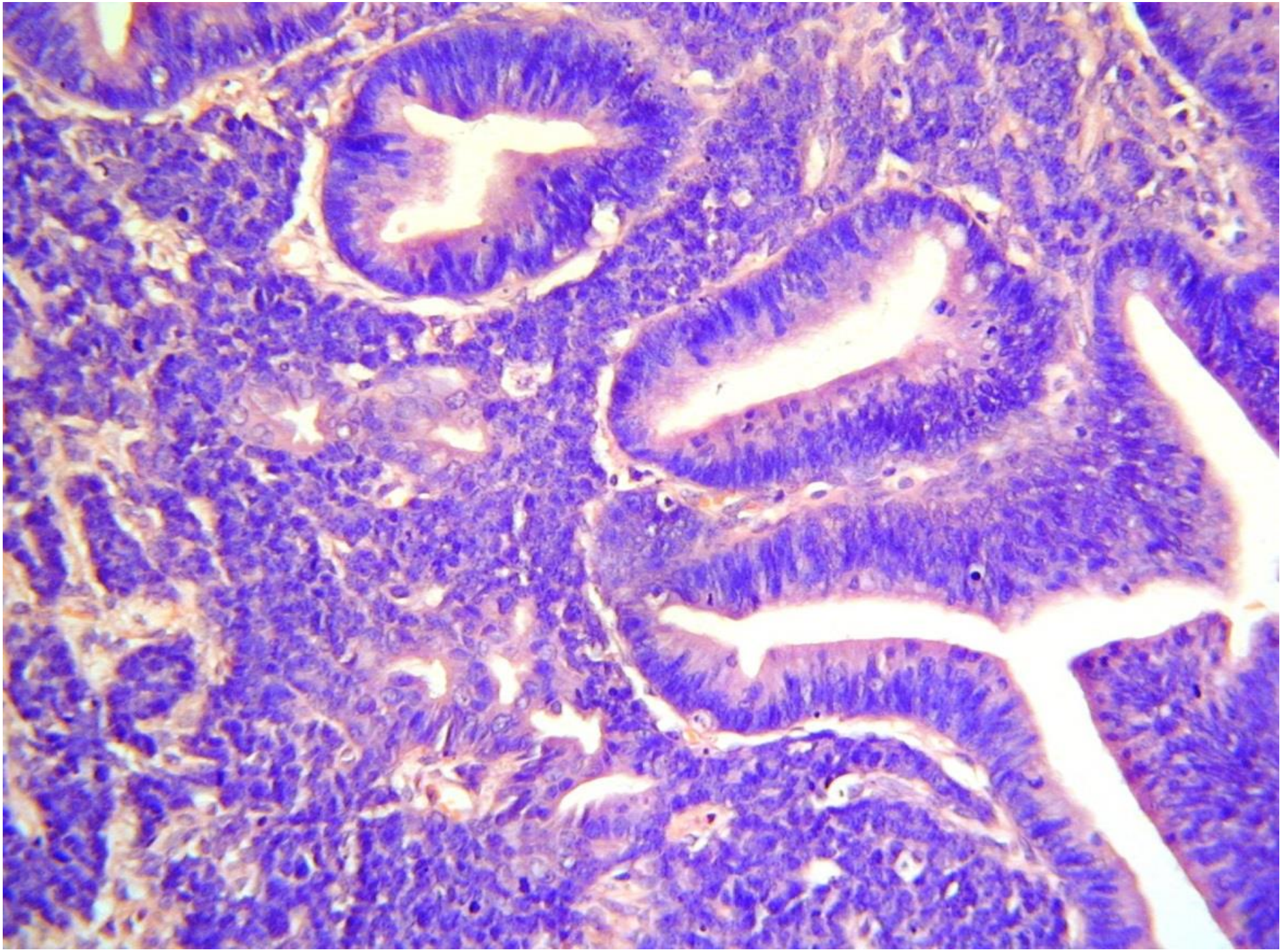
- often young females
- SCNEC/LCNEC (can be morphological overlap and occasionally admixtures)
- usually HPV-associated neoplasms (HPV 18 > 16) (may be useful in ascertaining site of origin)
- significant association with premalignant/malignant glandular lesions (more uncommonly squamous lesions); may be underestimated since often only punch biopsy performed
- SCNEC- not small cell carcinoma (get small cell variant of squamous carcinoma and causes confusion)
- SCNEC- can make diagnosis in absence of neuroendocrine marker positivity, although usually at least one positive
- LCNEC- need neuroendocrine marker positivity

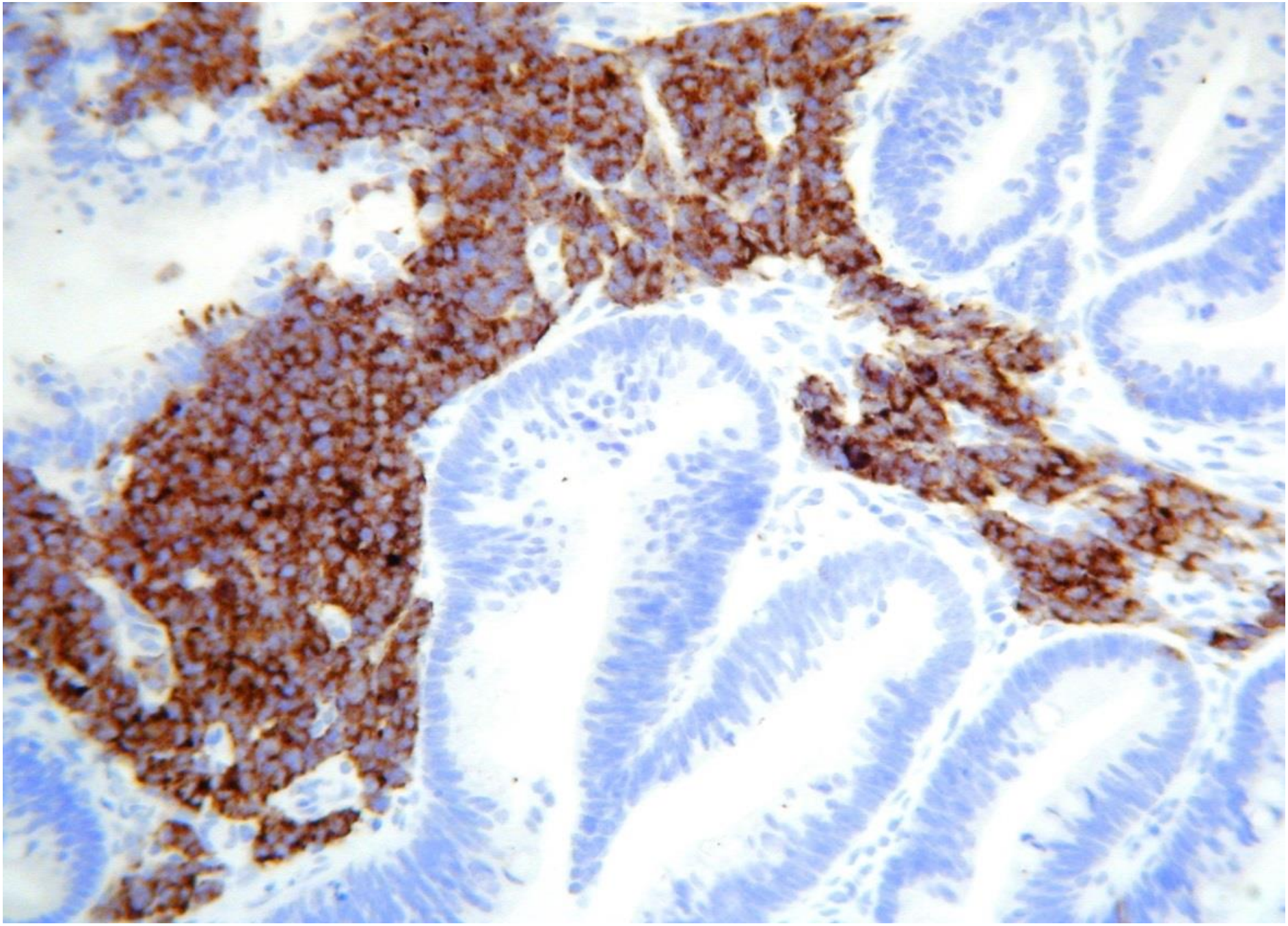
SCNEC



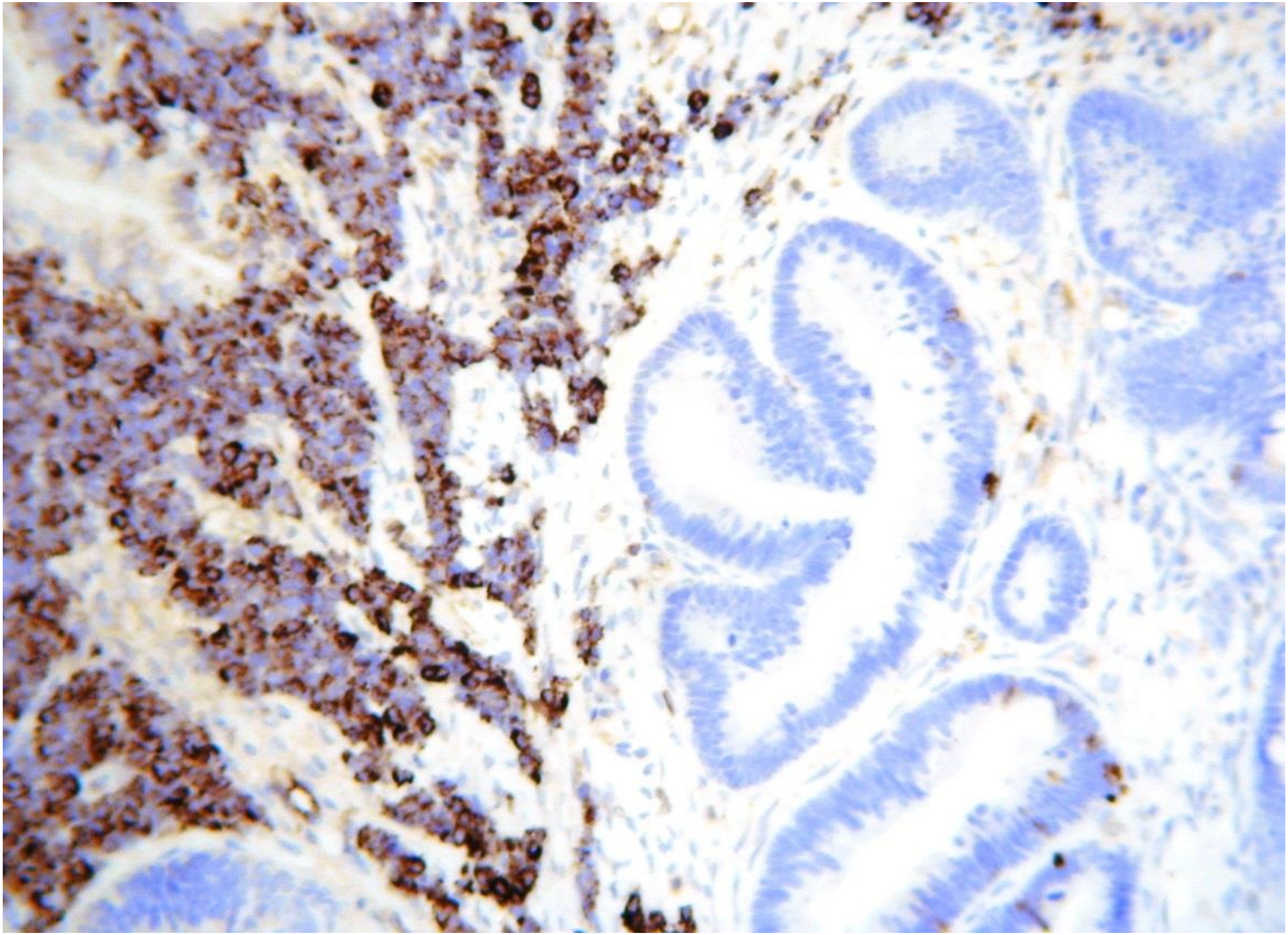
SCNEC- LARGER CELLS







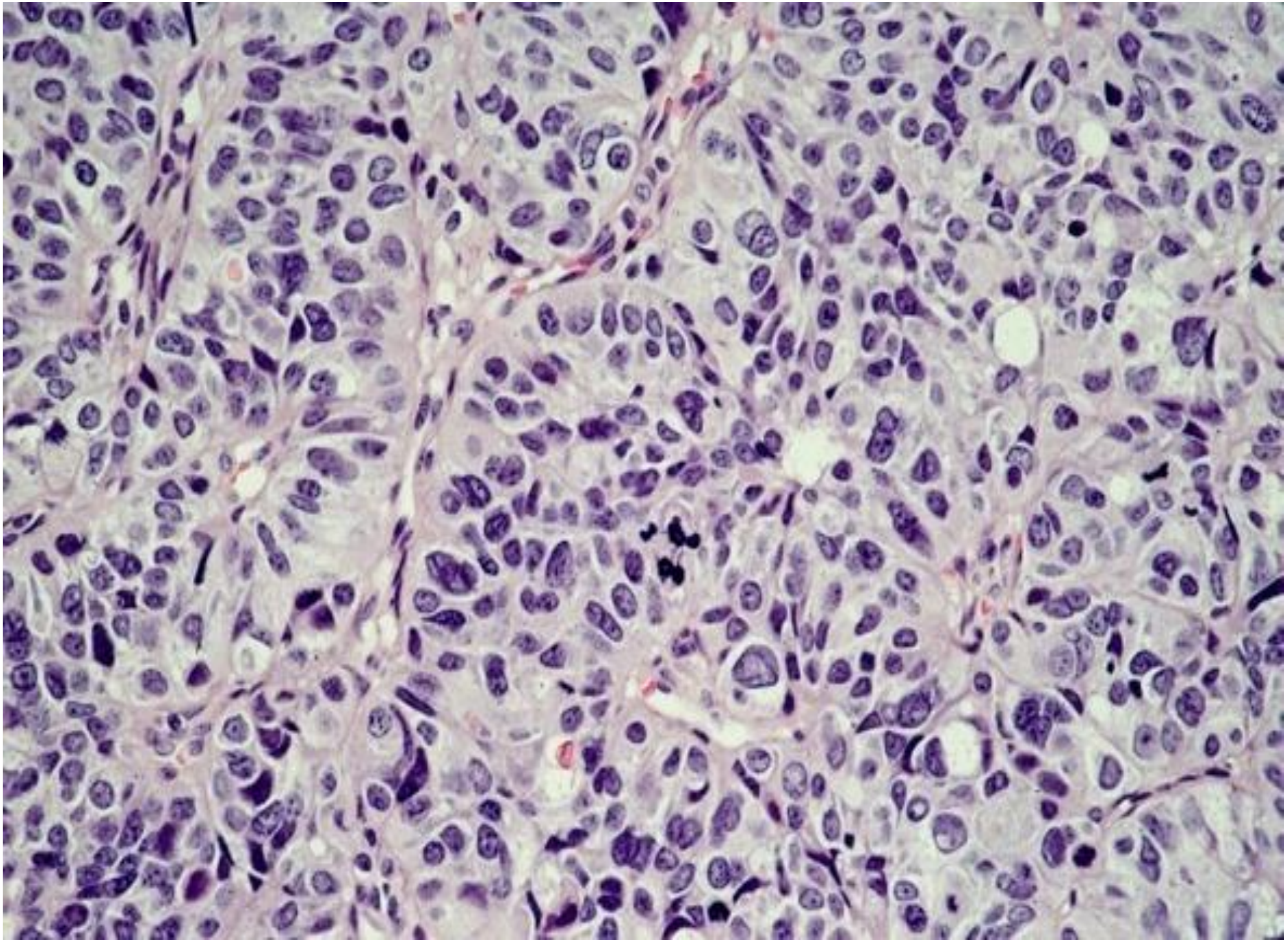
synaptophysin

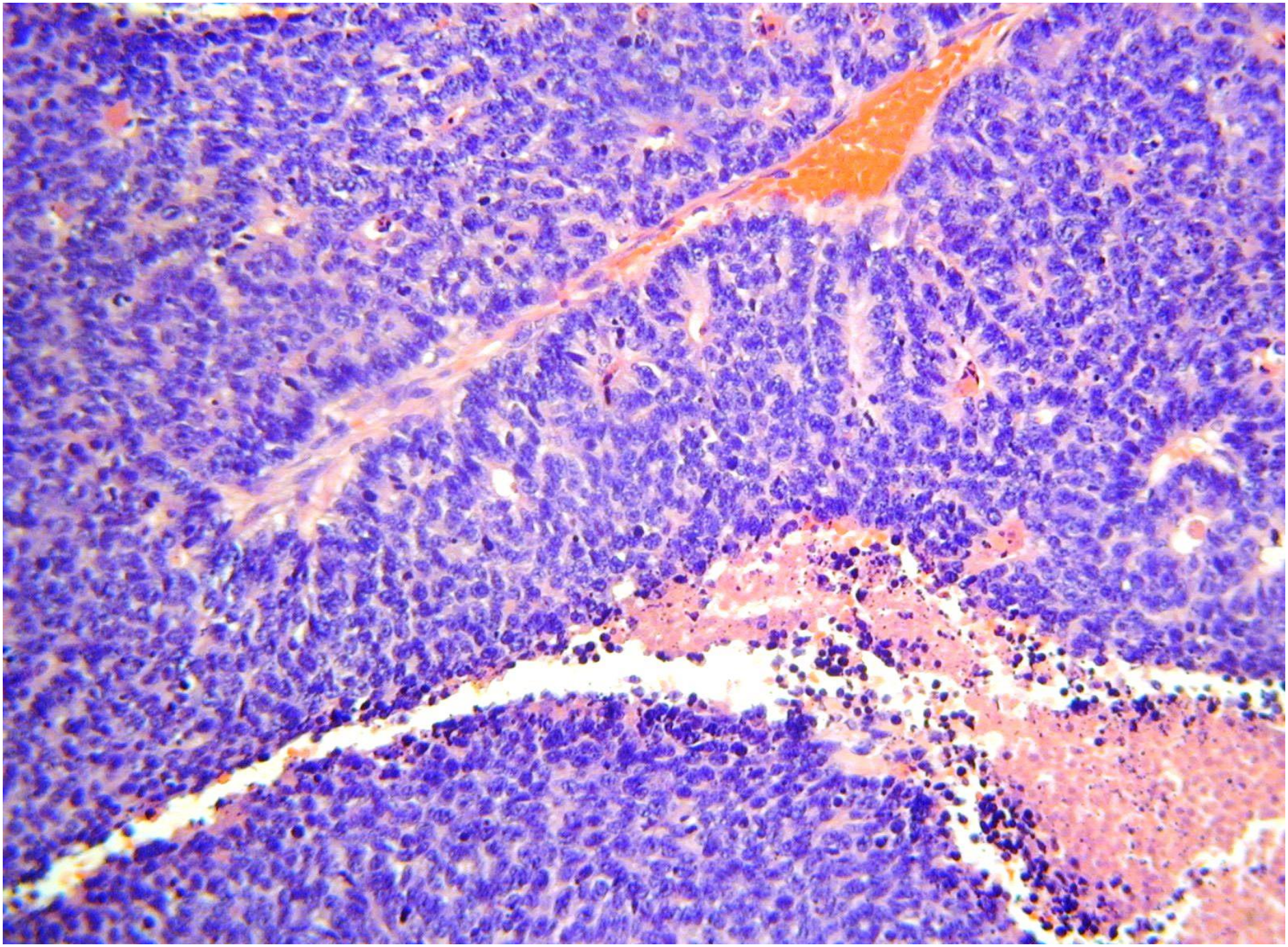


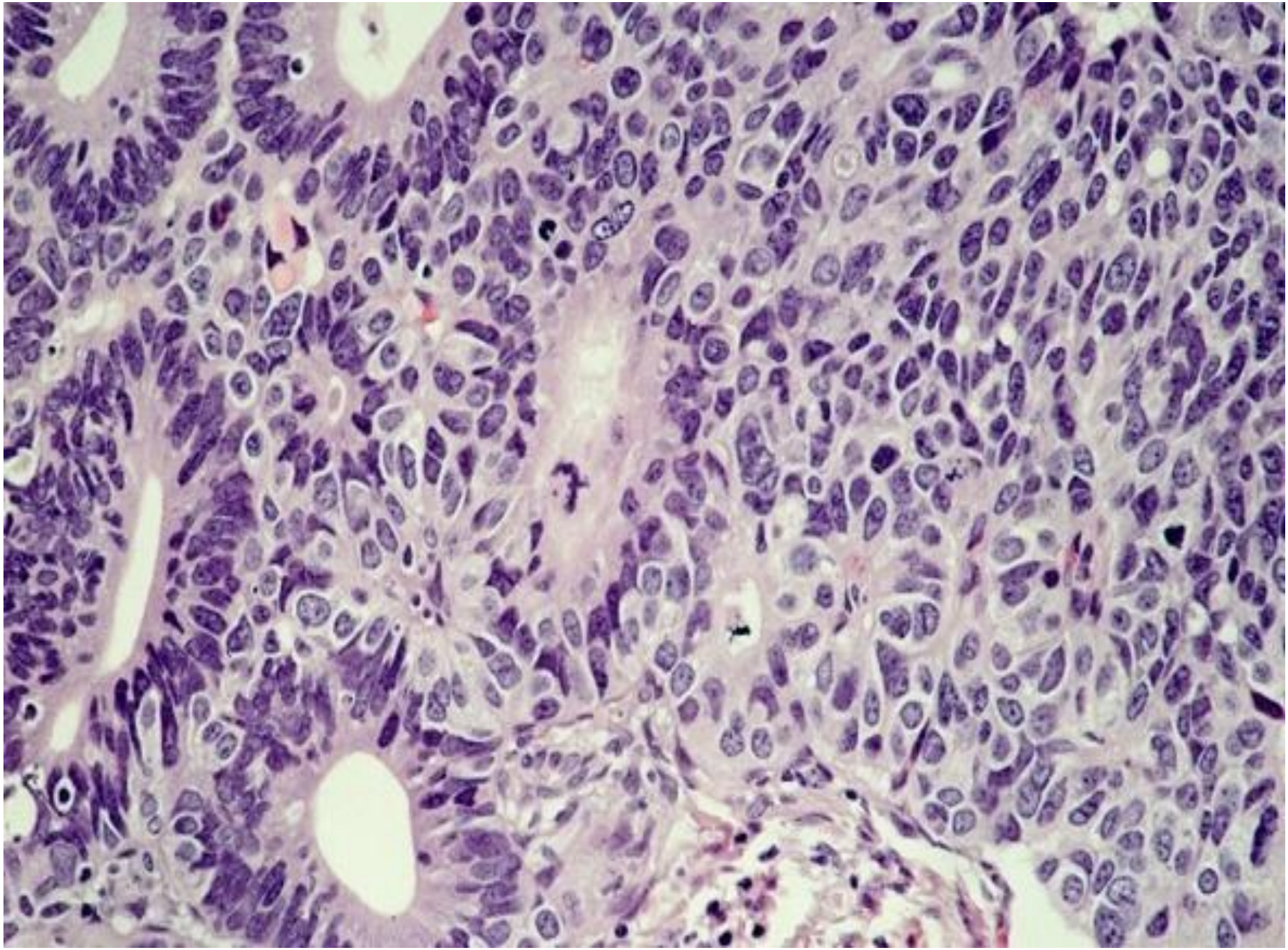
chromogranin

LARGE CELL NEUROENDOCRINE CARCINOMA (LCNEC)

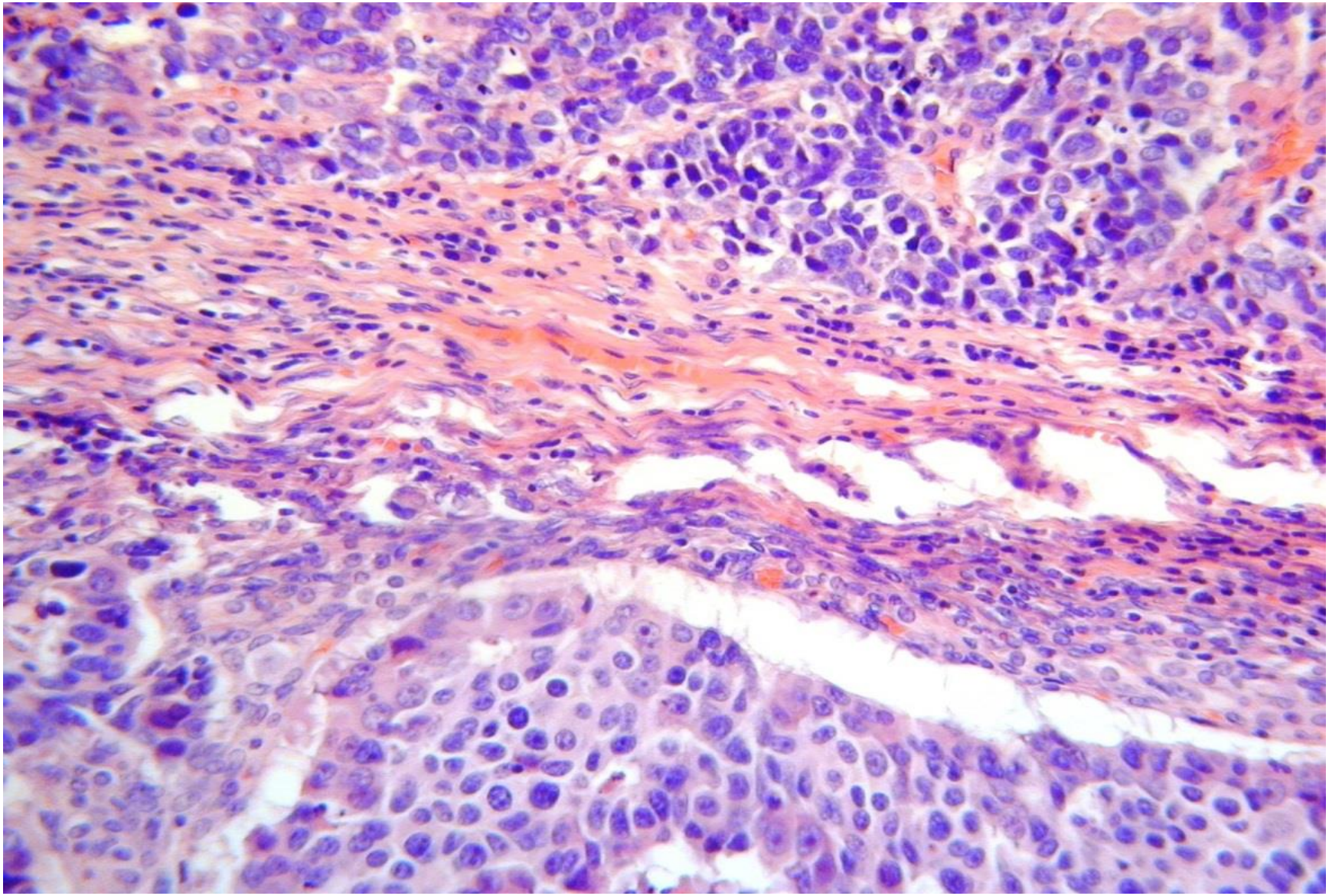
- insular, trabecular, glandular/ acinar, rosettes, solid growth patterns
- more than scant cytoplasm
- often extensive necrosis
- may see eosinophilic cytoplasmic granules
- may get nuclear palisading
- **need immunohistochemical evidence of neuroendocrine differentiation**







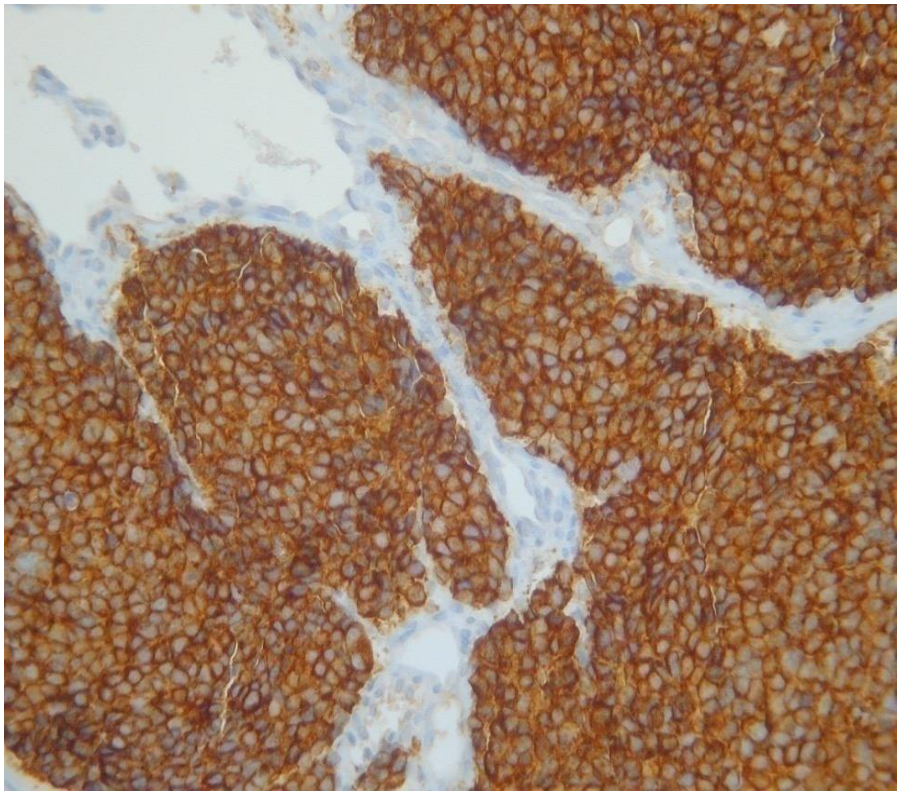
ADMIXTURE OF SCNEC AND LCNEC

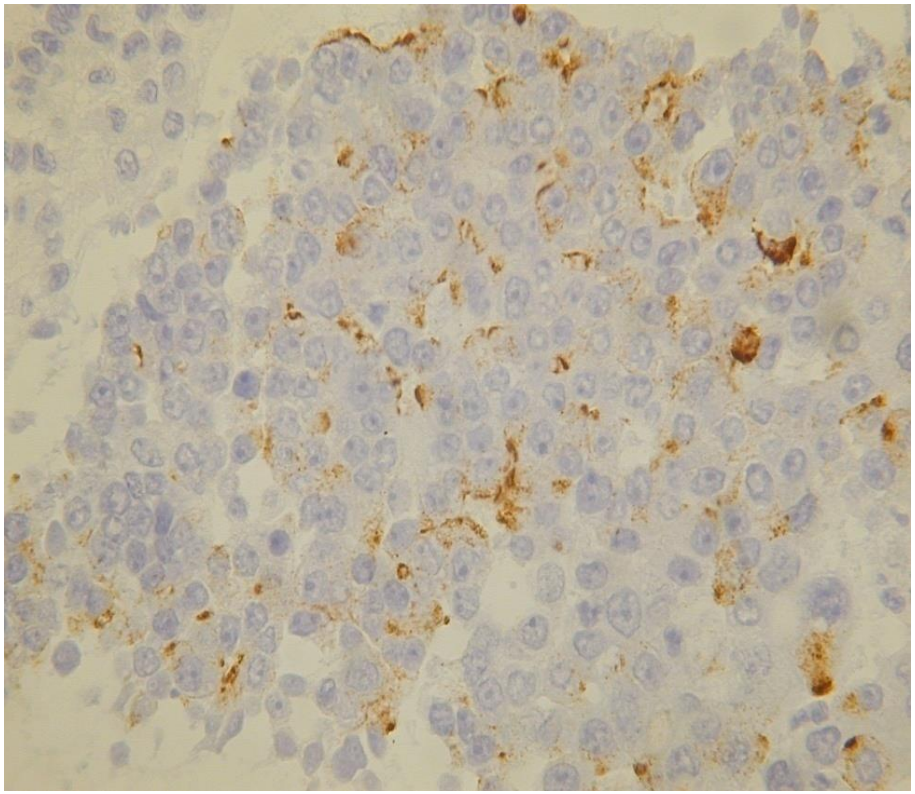


NEUROENDOCRINE MARKERS IN CERVICAL NEUROENDOCRINE CARCINOMAS (AJSP 2010;34;525-532)

- 52% chromogranin positive (most specific)
- 90% CD56 positive (sensitive but non-specific)
- 90% synaptophysin positive (sensitive)
- 43% PGP9.5 positive

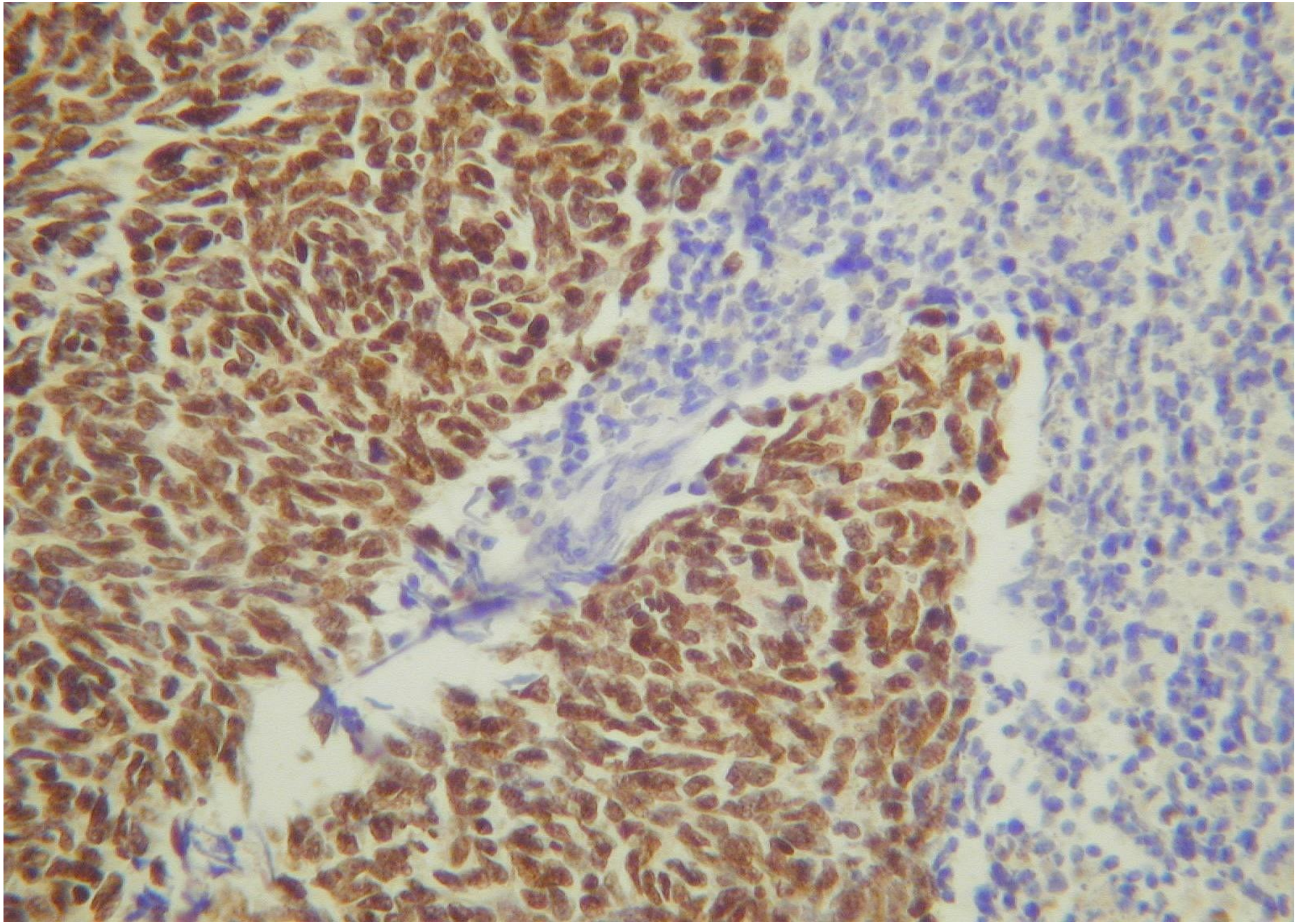
CHROMOGRANIN





TTF1

- 71% of cervical neuroendocrine carcinomas positive (85% SCNEC; 50% LCNEC)
- immunoreactivity often diffuse
- of no value in distinction from a pulmonary metastasis

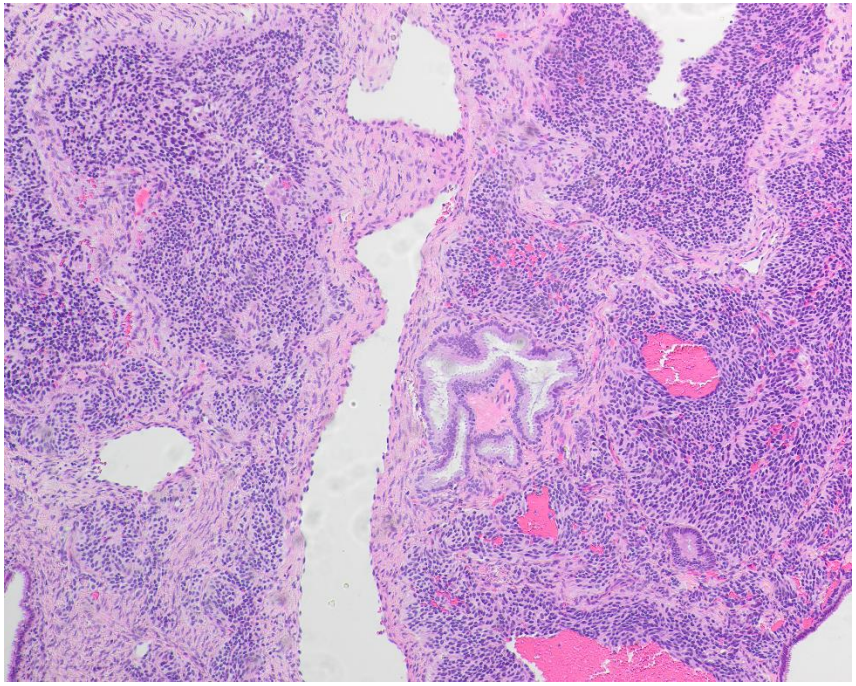


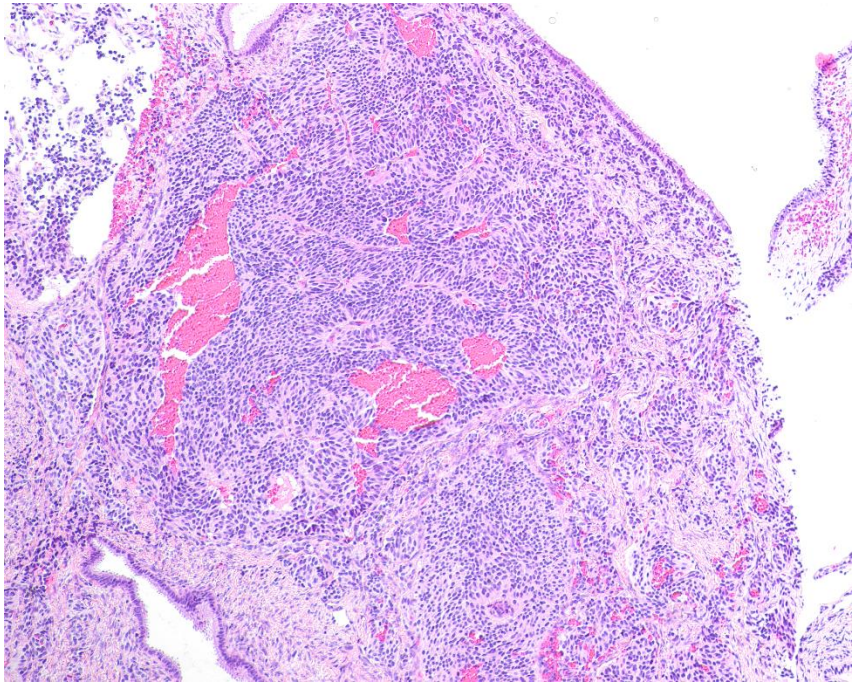
TTF1

CERVIX-NET

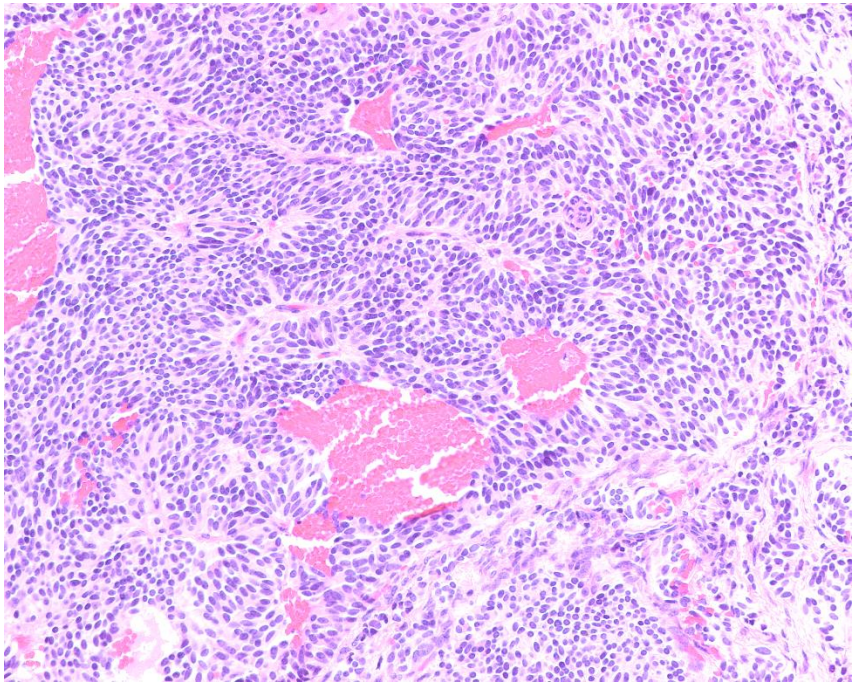
- Previously called typical and atypical carcinoid
- very rare
- occasional reports in literature but some not convincing from reviewing pictures
- ? HPV-independent

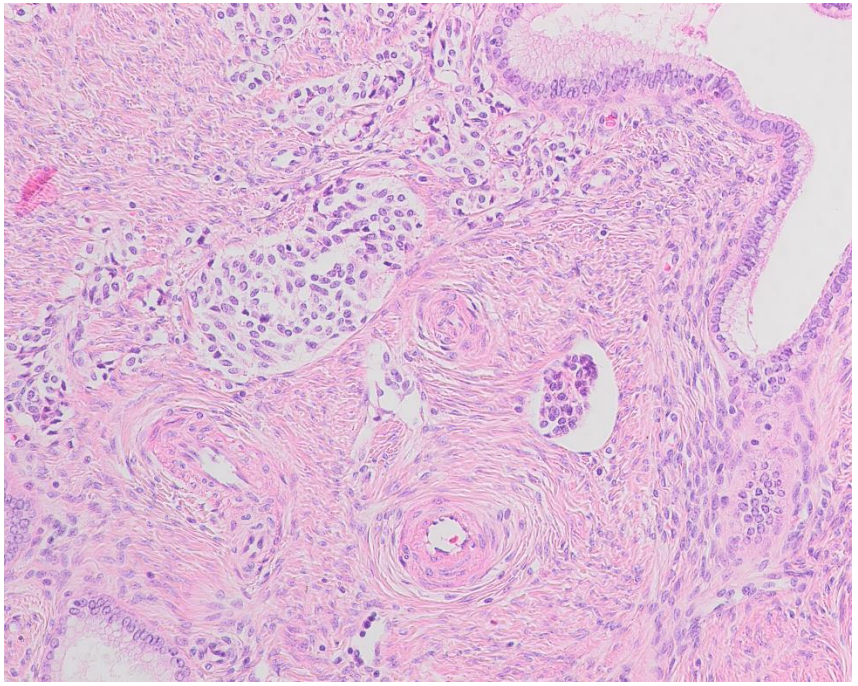
CERVICAL WELL-DIFFERENTIATED NET



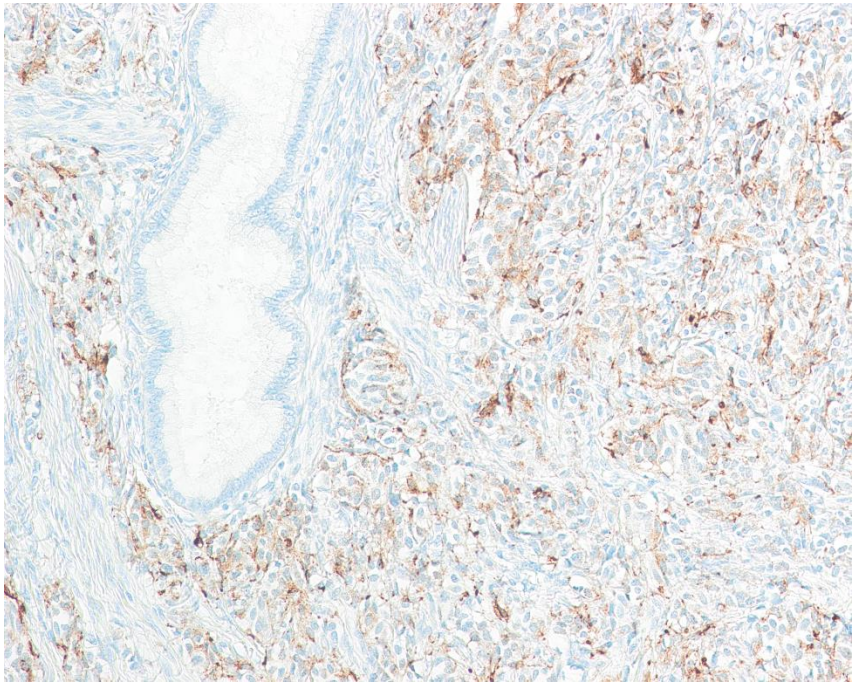


CERVICAL WELL-DIFFERENTIATED NET

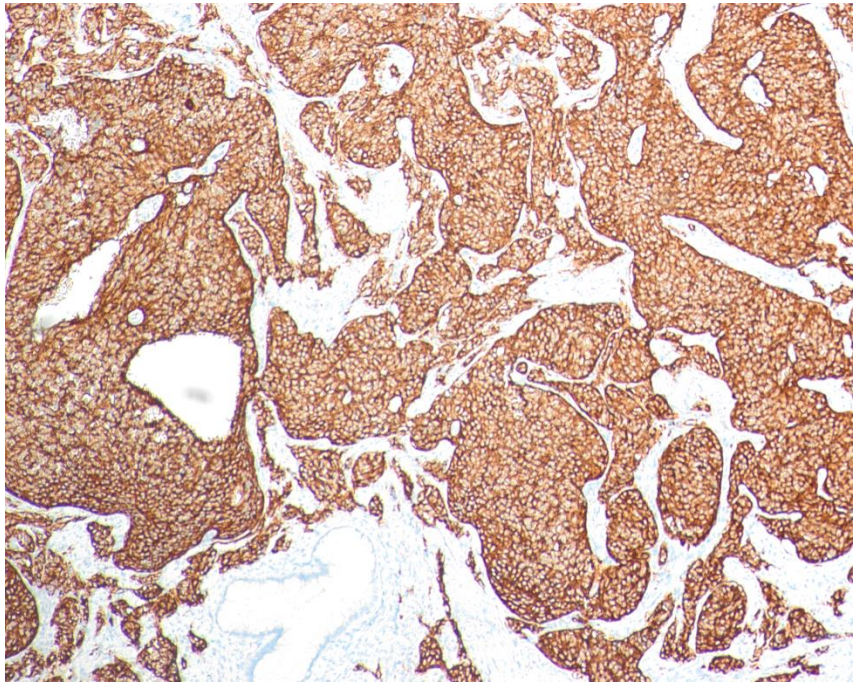




CERVICAL WELL-DIFFERENTIATED NET



chromogranin



synaptophysin

VULVA AND VAGINA

- Neuroendocrine neoplasms (NET and NEC) very rare
- Always need to exclude metastasis
- Also get Merkel cell carcinomas in vulva

PMID 32826525

ORIGINAL ARTICLE

High-grade Neuroendocrine Carcinomas of the Vulva

A Clinicopathologic Study of 16 Cases

Peter P. Chen, MD, PhD, Preetha Ramalingam, MD,* Isabel Alvarado-Cabrero, MD, PhD,† Elizabeth D. Euscher, MD,* Priyadharsini Nagarajan, MD, PhD, MBBS,* Barrett C. Lawson, MD,* and Anais Malpica, MD**

PMID 32826525

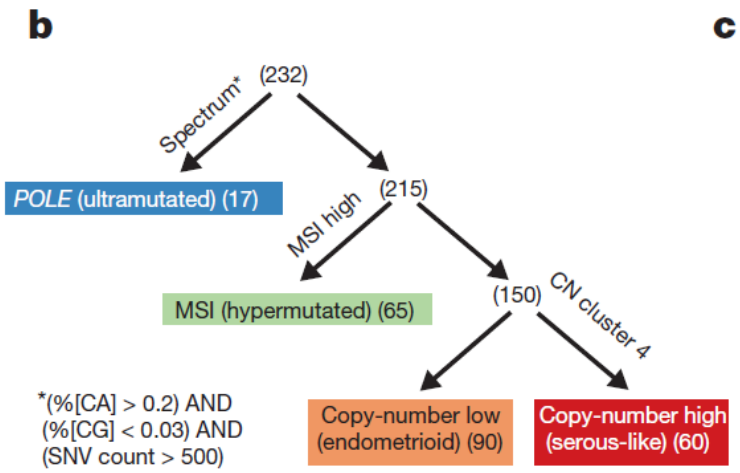
- AJSP 2020; in press
- 16 vulval high-grade neuroendocrine carcinomas; 14 small cell, 2 large cell
- 6 of small cell were CK20, NFT positive Merkel cell carcinomas (most positive for Merkel cell polyomavirus)
- High-risk HPV positive in most of other small cell neoplasms
- Aggressive neoplasms

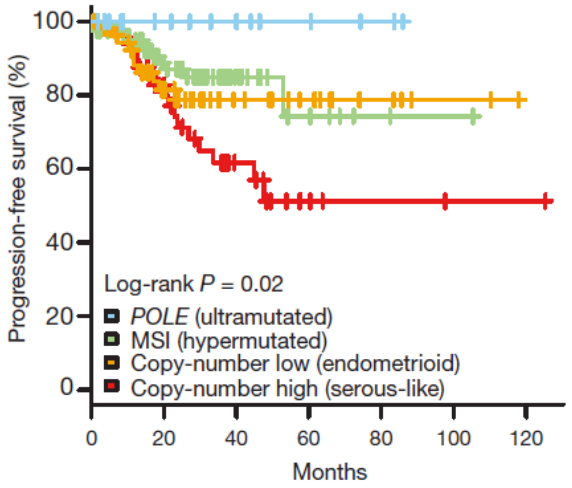
ENDOMETRIUM NEUROENDOCRINE NEOPLASMS

- Similar comments to cervix and ovary
- NET (typical and atypical carcinoid) very rare
- SCNECs and LCNECs occur but sometimes morphological overlap and acceptable to classify as HIGH-GRADE NEUROENDOCRINE CARCINOMA
- Often associated with another tumour type (most commonly endometrioid)

MOLECULAR CLASSIFICATION OF ENDOMETRIAL CARCINOMAS

- Included only endometrioid and serous histotypes

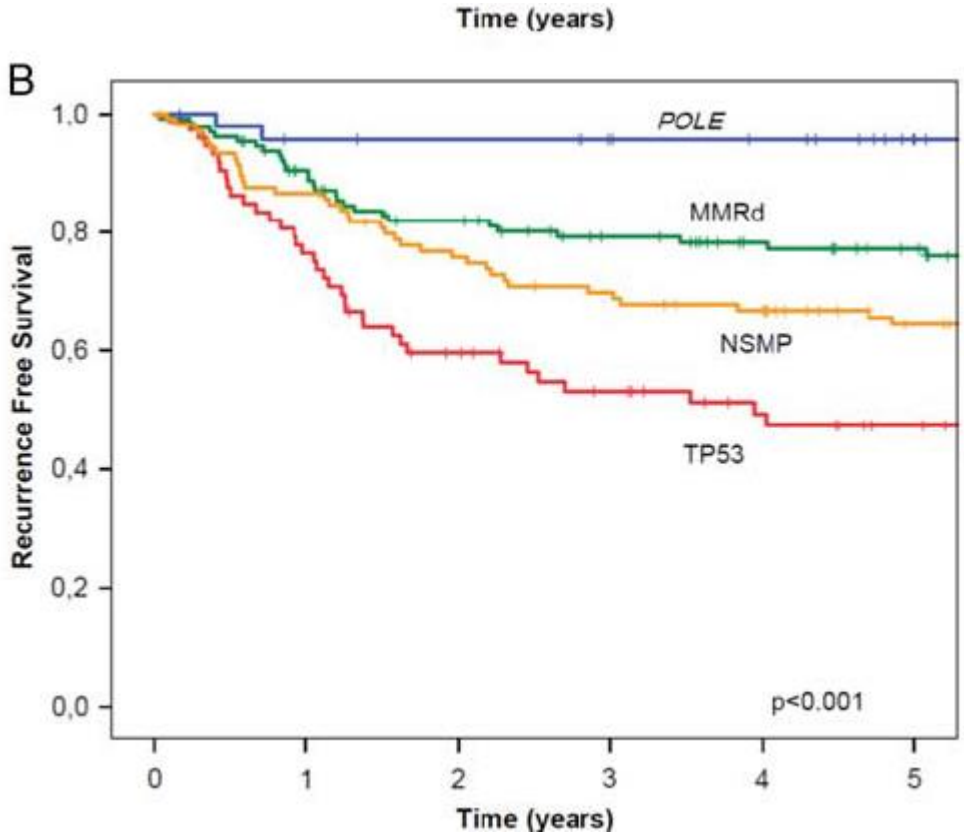




Nature. 2013 May 2;497(7447):67-73.

Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups

Tjalling Bosse, MD, Remi A. Nout, MD,* Jessica N. McAlpine, MD,† Melissa K. McConechy, MD,‡ Heidi Britton, MD,‡ Yaser R. Hussein, MD,§ Carlene Gonzalez, BA,§ Raji Ganesan, MD,‖ Jane C. Steele, MD,‖ Beth T. Harrison, MD,¶ Esther Oliva, MD,¶ August Vidal, MD,# Xavier Matias-Guiu, MD,# Nadeem R. Abu-Rustum, MD,** Douglas A. Levine, MD,** C. Blake Gilks, MD,‡ and Robert A. Soslow, MD§*



MOLECULAR CLASSIFICATION OF ENDOMETRIAL CARCINOMAS

- Since the TCGA publication, other studies have looked at:

  Uterine undifferentiated/dedifferentiated carcinoma (11% *POLE*-mutated, 45% MSI, 11% *TP53*-mutated/CN-H, 28% CN-L/NSMP)

  Uterine clear cell carcinoma (6% *POLE*-mutated, 13% MSI, 34% *TP53*-mutated/CN-H, 47% CN-L/NSMP)

  Uterine carcinosarcoma (5.3% *POLE*-mutated, 7.3% MSI, 73.9% *TP53*-mutated/CN-H, 13.5% CN-L/NSMP)

- No studies to date have looked at neuroendocrine carcinomas of the endometrium in the context of TCGA classification

PMID 32773531. AJSP 2020;44;1541-1548

ORIGINAL ARTICLE

Molecular Characterization of Neuroendocrine Carcinomas of the Endometrium

Representation in All 4 TCGA Groups

Brooke E. Howitt, MD,† Fei Dong, MD,‡ Marina Vivero, MD,‡ Varsha Shah, FRCPath,§ Neal Lindeman, MD,‡ J. Kenneth Schoolmeester, MD,‖ Michele Baltay, MS,‡ Laura MacConaill, PhD,‡ Lynette M. Sholl, MD,‡ Marisa R. Nucci, MD,* and W. Glenn McCluggage, FRCPath¶*

AIMS OF THE STUDY

1) Characterize the molecular alterations found in endometrial NEC

2) Classify cases into endometrial TCGA molecular subgroups

3) Compare molecular alterations of NEC component and carcinoma in cases with mixed histology

METHODS

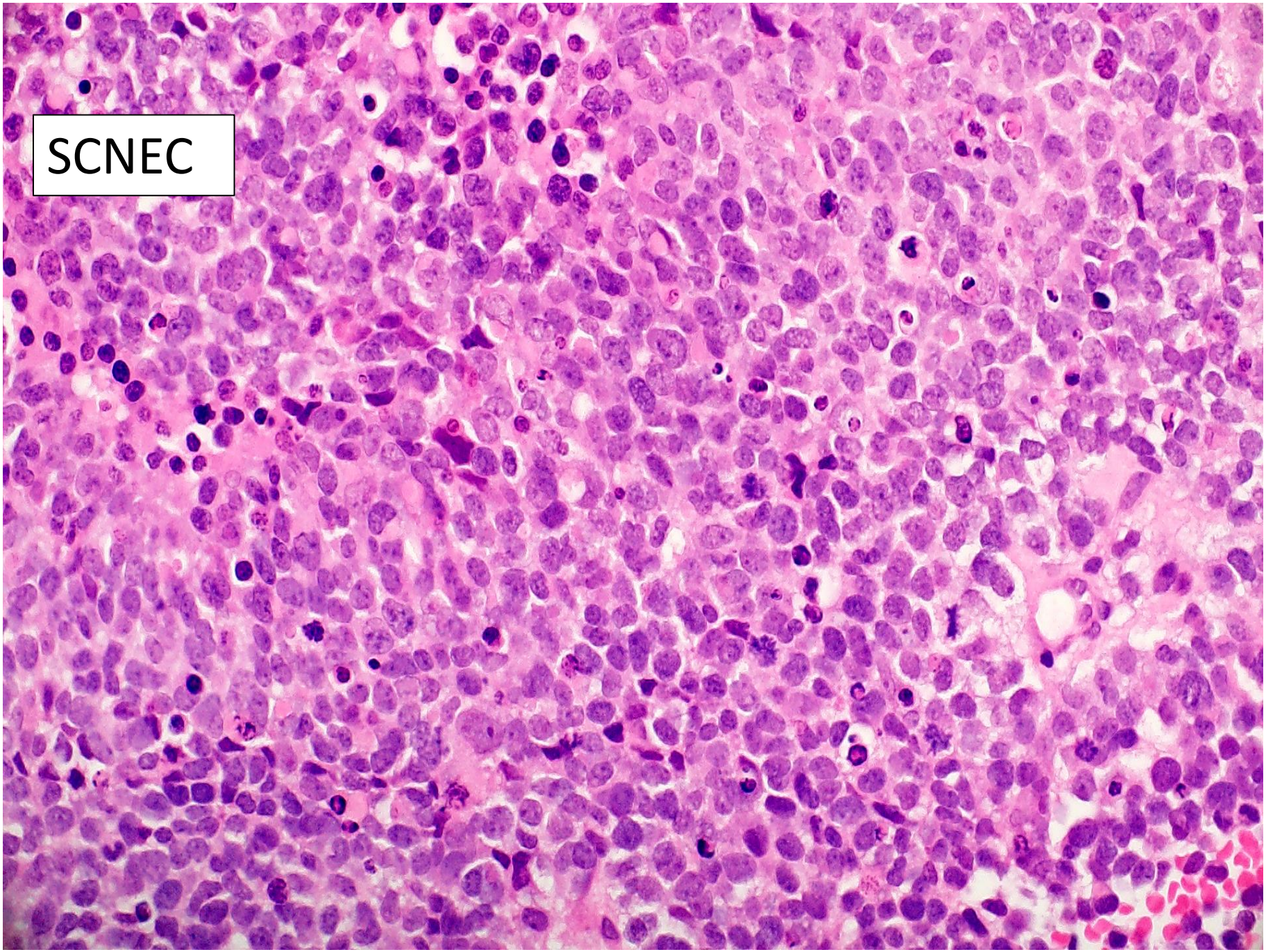
- 14 cases of endometrial NEC from 4 institutions (diagnosed with WHO 2014 criteria):
  - Pure (n=4)
  - Mixed with endometrioid carcinoma or carcinosarcoma (n=10)

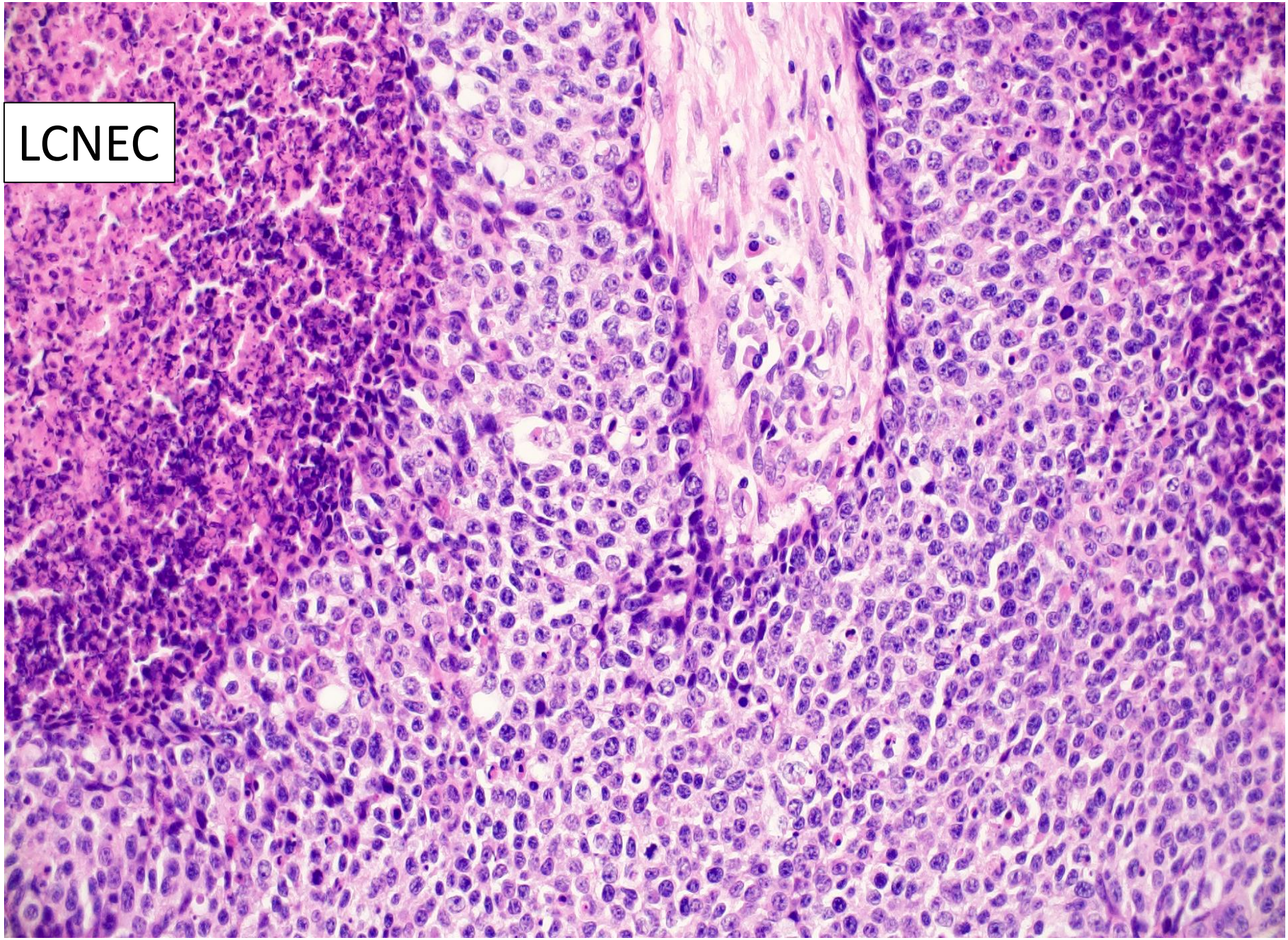
- Massively parallel sequencing (Oncopanel, BWH)
  - Complete exonic regions of 447 genes
  - Single nucleotide variations (mutations and small insertions/deletions)
  - Copy number variations

- Clinical follow-up, histologic, and immunophenotypic features were also evaluated when possible
  - Synaptophysin, chromogranin, CD56, TTF1, MMR, PAX8, Rb1

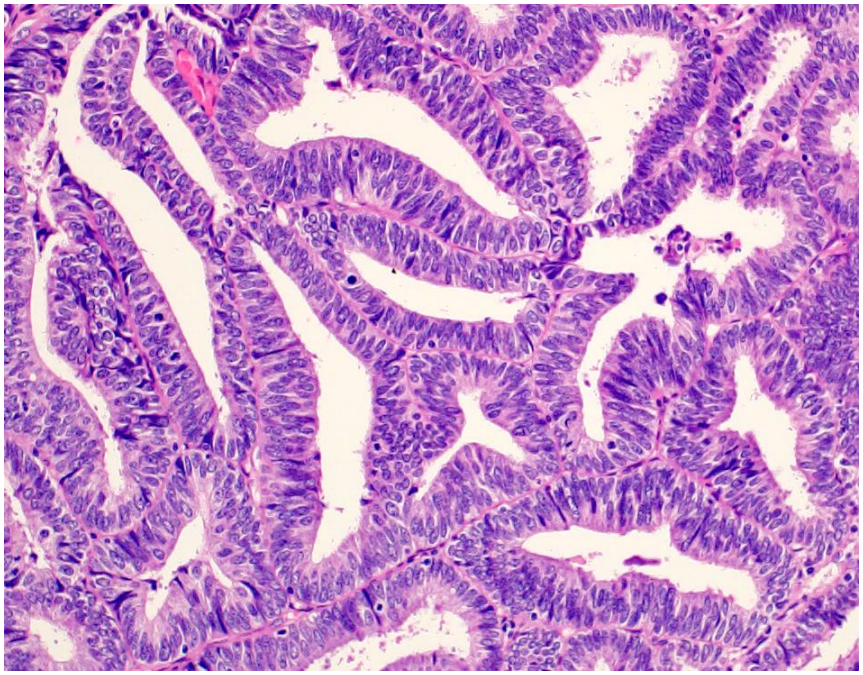
METHODS

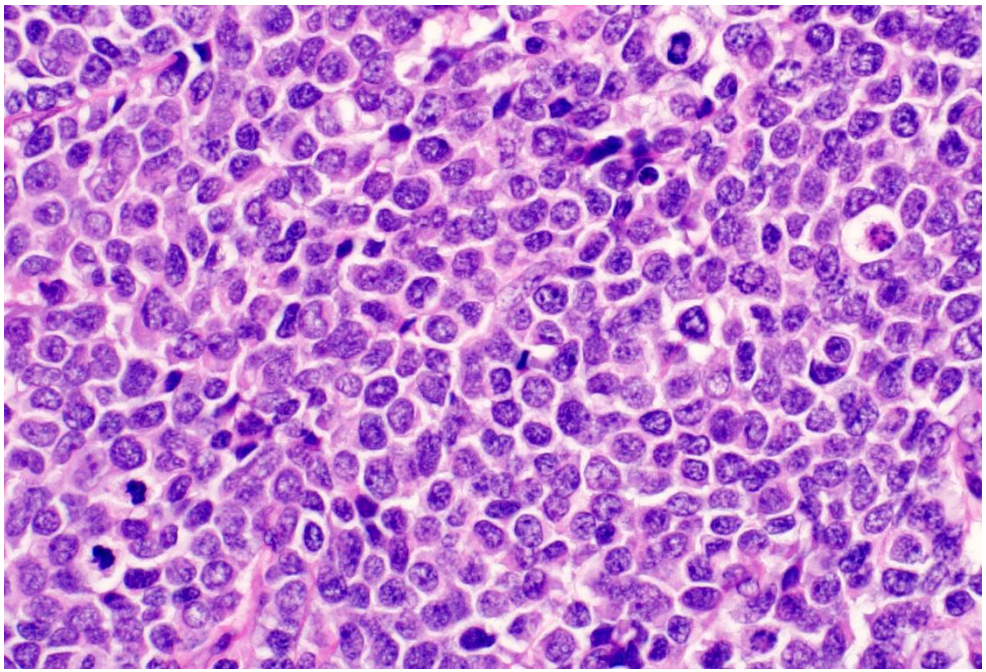
- **<u>Cases were categorized using TCGA classification as:</u>**
  - ***POLE*-ultramutated**
    - (defined by presence of *POLE* mutation)
  - **Microsatellite instability (MSI)**
    - (defined by molecular signature/pattern of mutations/ immunohistochemistry)
  - **Copy number high (CN-H)**
    - (defined by presence of *TP53* mutation)
  - **Copy number low (CN-L) or "no specific molecular profile"**
    - (defined by absence of *POLE* mutation, MSI signature and *TP53* alterations)


SCNEC


LCNEC

Endometrioid Carcinoma and NEC in Mixed Case



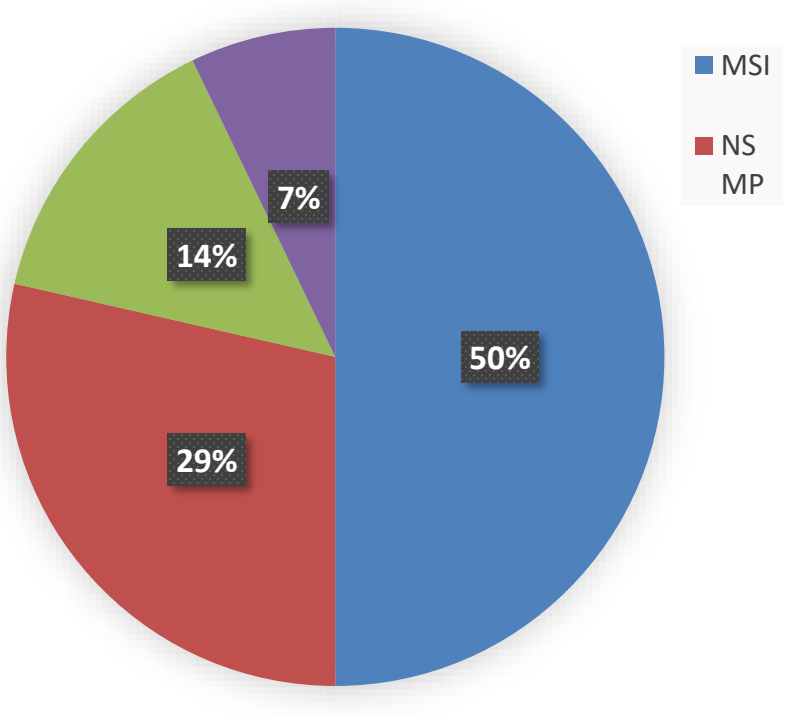


RESULTS

- 14 cases of endometrial NEC:
  - 4 pure NEC (2 SCNEC, 2 LCNEC)
  - 10 mixed:
    - 9 with endometrioid carcinoma
    - 1 with carcinosarcoma
- 8/10 mixed cases were able to have the individual components macro-dissected and sequenced
- Morphology review:
  - 8/14 LCNEC
  - 6/14 SCNEC

SUMMARY OF MOLECULAR RESULTS

- **<u>7/14 (50%) cases classified as MSI</u>**
  - 3 LCNEC; 4 SCNEC (all mixed carcinomas)
- **<u>1/14 cases (7%) *POLE*-mutated</u>**
  - LCNEC (mixed endometrioid carcinoma/LCNEC)
- **<u>2/14 cases CN-H (14%) (*TP53* mutated)</u>**
  - 2 SCNEC (both pure)
- **<u>4/14 cases CN-L (29%) (no specific molecular profile)</u>**
  - 4 LCNEC (including both mixed and pure)



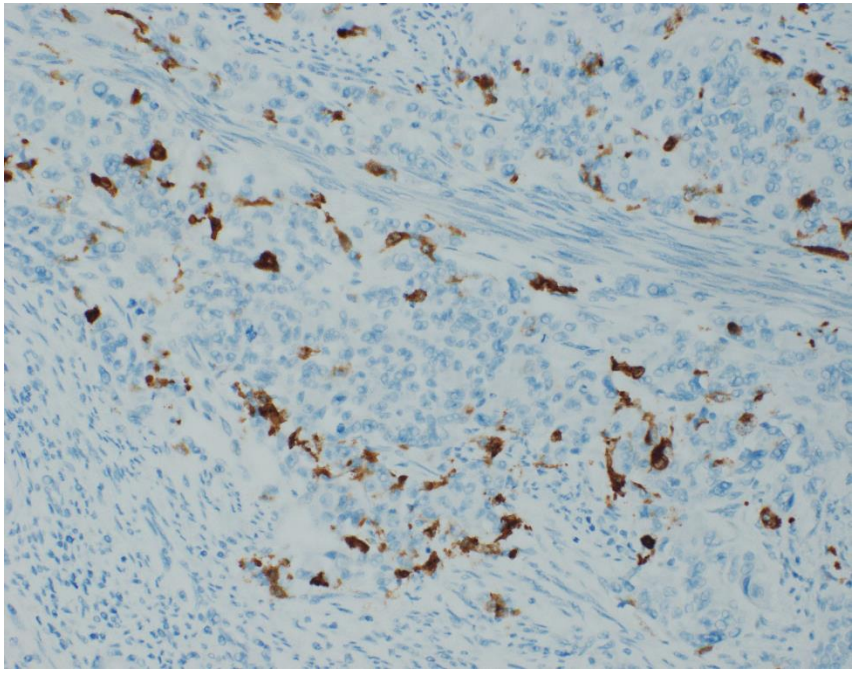
COMPARISON OF NEC AND ADENOCARCINOMA IN MIXED CASES

- THE MOLECULAR SUBTYPE CLASSIFICATION WAS IDENTICAL ACROSS THE TWO COMPONENTS IN ALL MIXED CASES
- IN GENERAL, THERE WAS A VERY HIGH CONCORDANCE OF MUTATIONS IDENTIFIED BETWEEN THE TWO COMPONENTS (PROOF THAT NOT COLLISION TUMOURS)

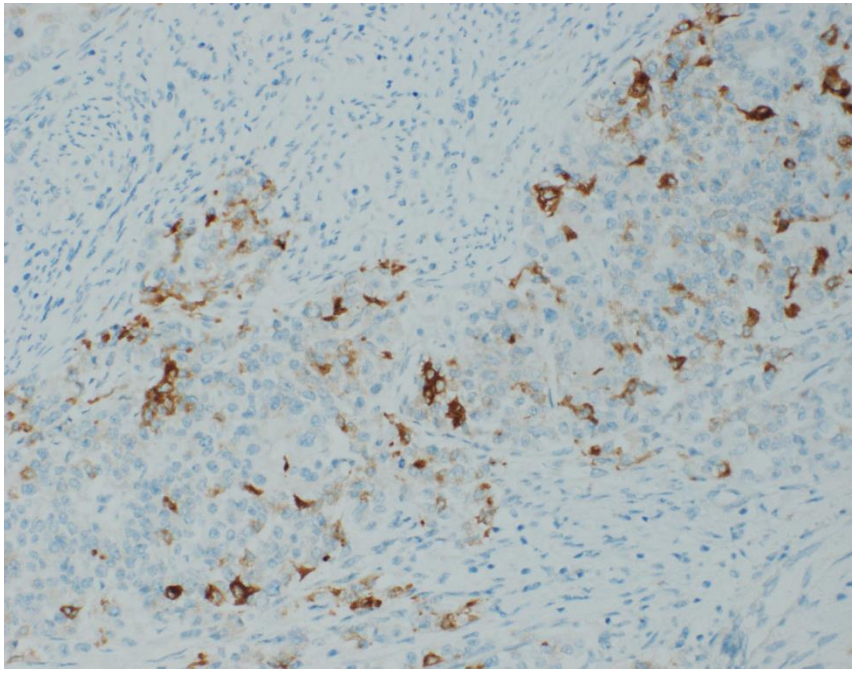
SUMMARY

- NEC of the endometrium comprise a molecularly heterogeneous group of tumors distributed amongst all 4 molecular groups
- Mixed NEC and other carcinoma types share common mutations, suggesting these are clonally related rather than “collision” tumours
- At the molecular level, NEC of the endometrium more closely resemble other histologic subtypes of endometrial carcinoma rather than small cell lung carcinoma
- Many NEC of the endometrium may be more closely related to other tumour types rather than true NEC
- Don’t base diagnosis of NEC on basis of immunohistochemistry but need appropriate morphology
- Some LCNEC may represent poorly differentiated endometrioid, solid serous or undifferentiated carcinoma exhibiting “neuroendocrine differentiation”
- Diagnostic thresholds for endometrial NEC, particularly LCNEC, should be revisited
- Should test for MSI/ MMR proteins in all endometrial NEC (additional treatment options in recurrent or metastatic setting)

NEUROENDOCRINE MARKERS IN UTERINE GRADE 3 ENDOMETRIOID CARCINOMA

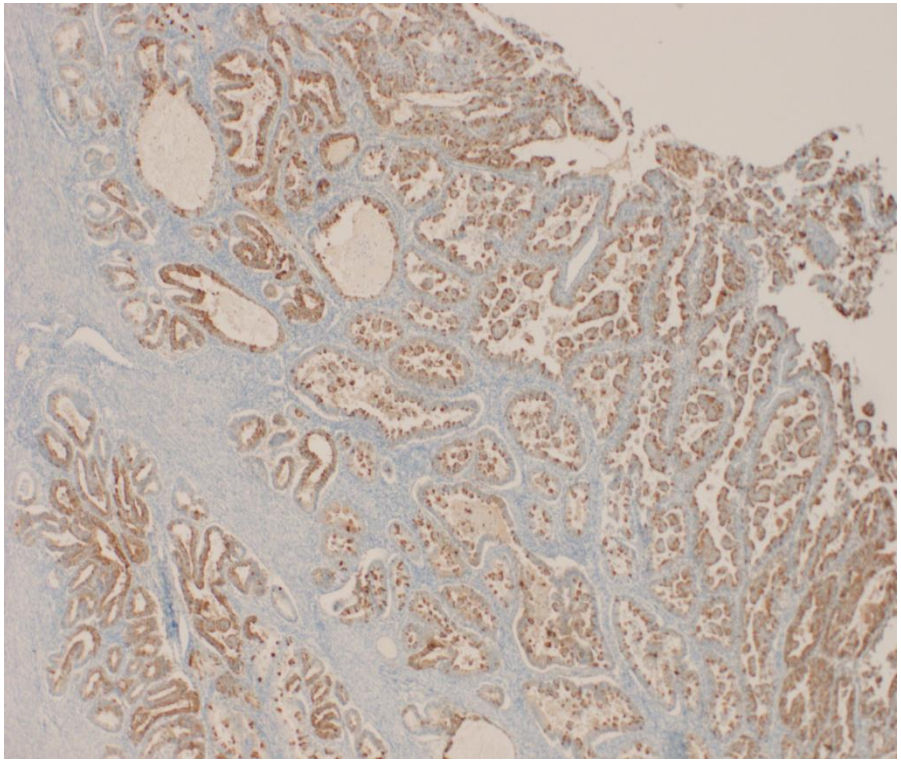


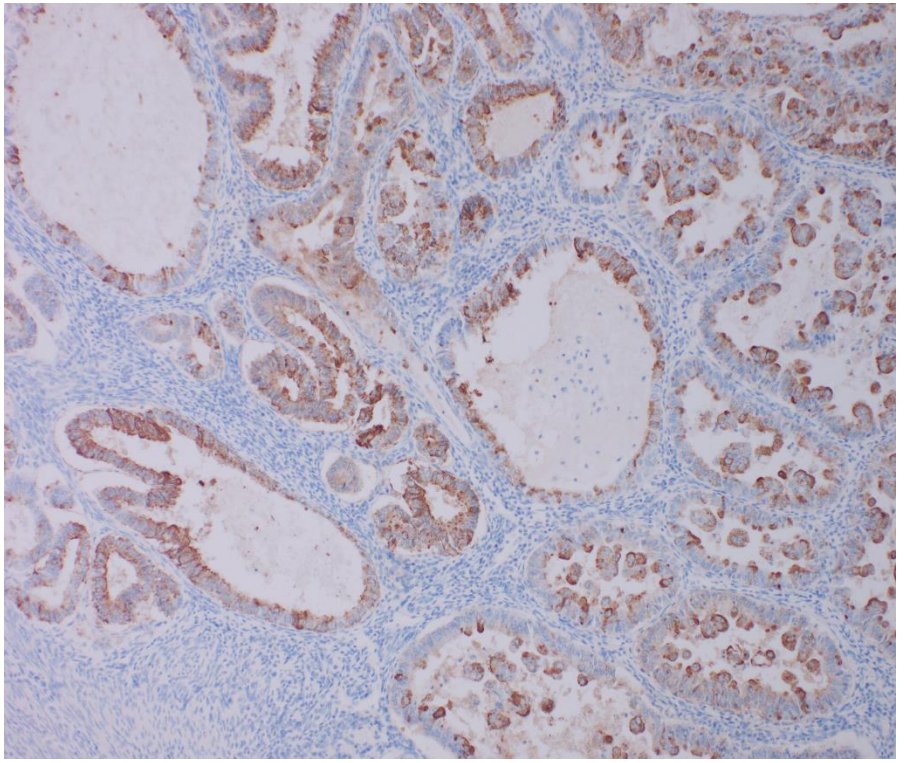
chromogranin



synaptophysin

CHROMOGRANIN IN UTERINE GRADE 1 ENDOMETRIOID CARCINOMA





PMID 31040050. Pathology 2019;51;369-374

Pathology (June 2019) **51(4)**, pp. 369–374

ANATOMICAL PATHOLOGY

Expression of neuroendocrine markers in non-neuroendocrine endometrial carcinomas

August W. Moritz[1], Matthew P. Schlumbrecht[2], Mehrdad Nadji[1], Andre Pinto[1]

[1]Department of Pathology, University of Miami Miller School of Medicine, Miami, FL, United States; [2]Department of Obstetrics and Gynecology, Division of Gynecological Oncology, University of Miami Miller School of Medicine, Miami, FL, United States

PMID 31040050. Pathology 2019;51;369-374

- Endometrial tumours- endometrioid, serous, clear cell, undifferentiated/ dedifferentiated, carcinosarcoma
- Stained with chromogranin, synaptophysin, CD56, TTF1
- 66% expressed more than 1 neuroendocrine marker; most, but not all, focal staining with single marker
- Serous and carcinosarcoma most likely to be positive

PMID 26945341

HHS Public Access

Author manuscript

Am J Surg Pathol. Author manuscript; available in PMC 2018 June 13.

Published in final edited form as:

Am J Surg Pathol. 2016 May ; 40(5): 577–586. doi:10.1097/PAS.0000000000000633.

Neuroendocrine Carcinoma of the Endometrium: A Clinicopathologic Study of 25 Cases

Cady E. Pocrnich, MD, FRCPC, **Preetha Ramalingam, MD**, **Elizabeth D. Euscher, MD**, and **Anais Malpica, MD**

Department of Pathology, The University of Texas, MD Anderson Cancer Center, Houston, Texas

PMID 26945341

- 25 cases (age 37-87)
- 10 pure; 15 admixed with other tumour types (most commonly endometrioid)
- 4 SCNEC, 15 LCNEC, 6 admixture
- Required expression of at least 1 neuroendocrine marker in at least 10% of cells (arbitrary)
- All were positive for more than 1 neuroendocrine marker
- **Abnormal MMR expression in 8 of 18 cases**
- 28% survived at least 5 years

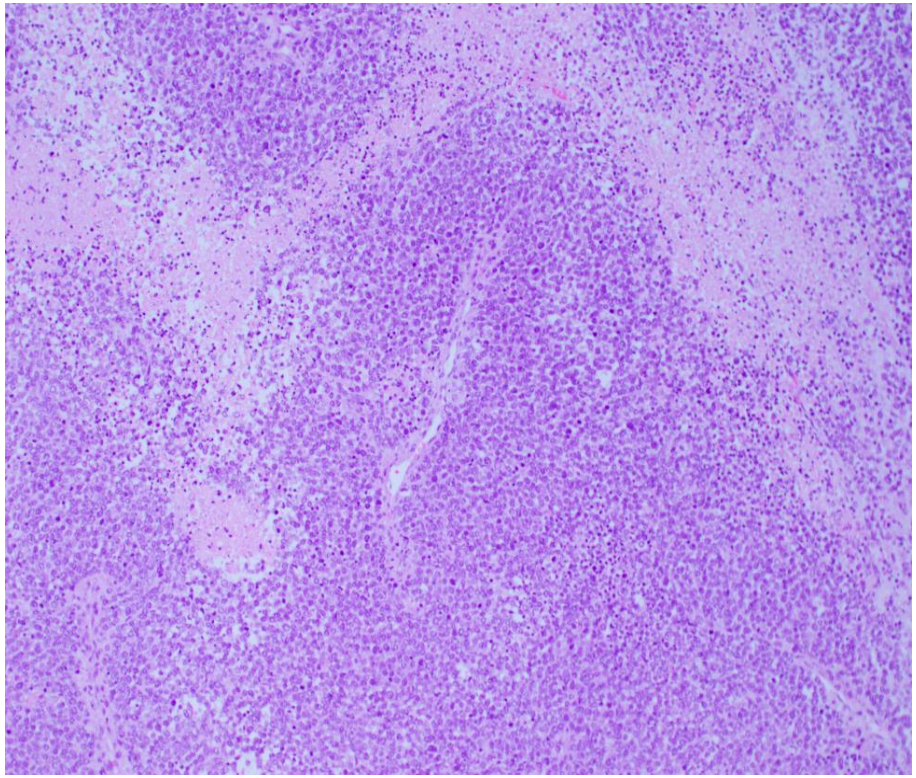
UNDIFFERENTIATED ENDOMETRIAL CARCINOMA

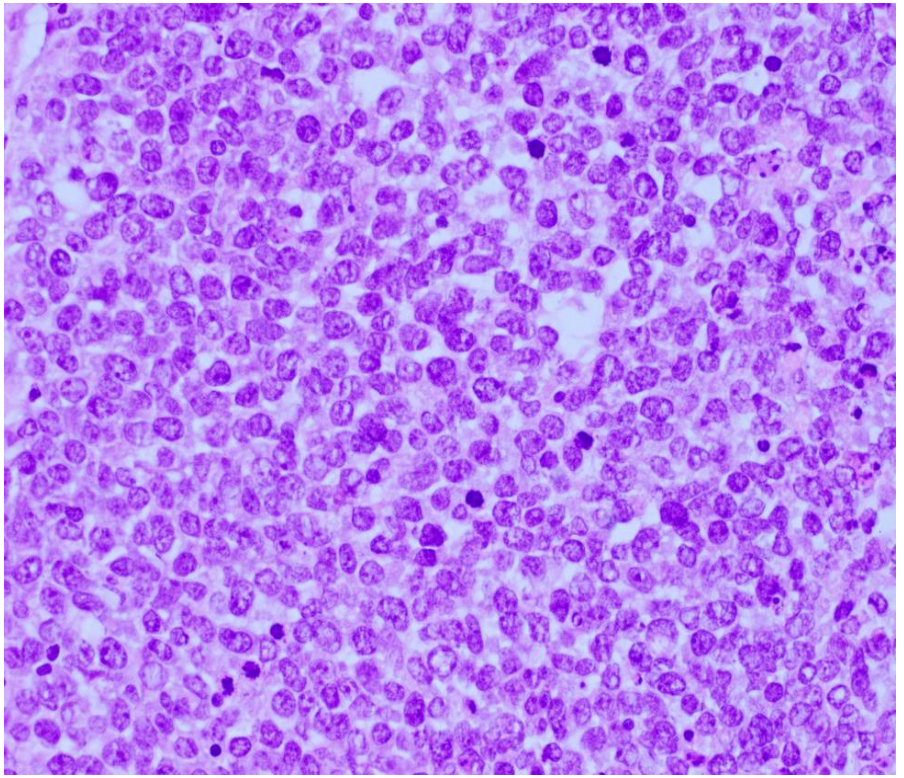
- category included in WHO 2014 classification
- specific histological diagnosis; pathologists often reluctant to make diagnosis
- may be associated with low-grade endometrioid adenocarcinoma (dedifferentiated carcinoma or mixed endometrioid and undifferentiated carcinoma)
- similar tumours in ovary (less common)
- undifferentiated/dedifferentiated element may be seen only in recurrence or metastasis
- extremely poor prognosis
- **WHO 2020- chromogranin or synaptophysin may be expressed in a minority of tumour cells, usually < 10%**

WIDE DIFFERENTIAL DIAGNOSIS OF UNDIFFERENTIATED CARCINOMA

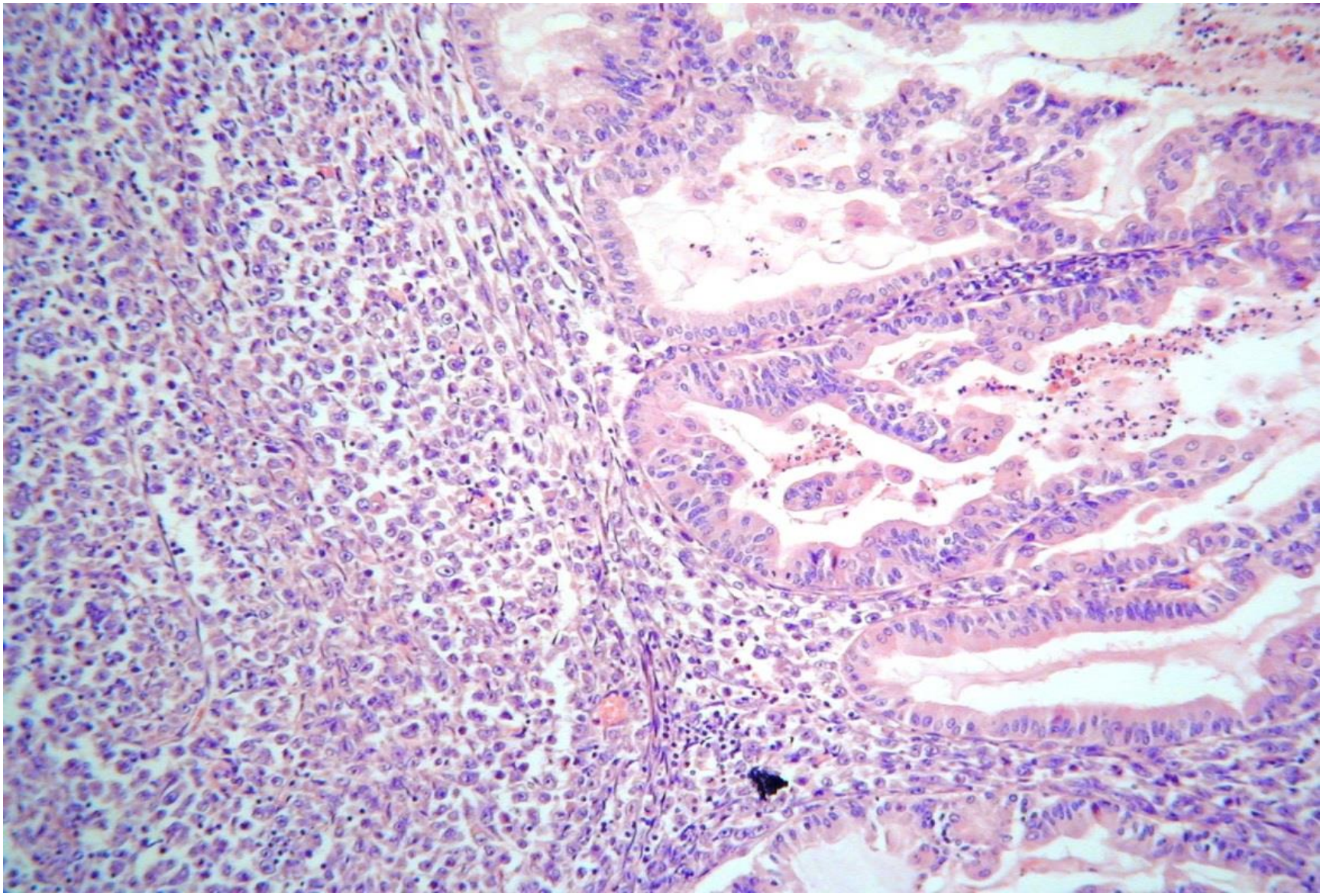
- grade 3 endometrioid adenocarcinoma
- solid variant of serous carcinoma
- carcinosarcoma
- **high-grade neuroendocrine carcinoma**
- malignant lymphoma/ plasmacytoma
- undifferentiated sarcoma
- other sarcomas (PNET, epithelioid sarcoma)

UNDIFFERENTIATED CARCINOMA





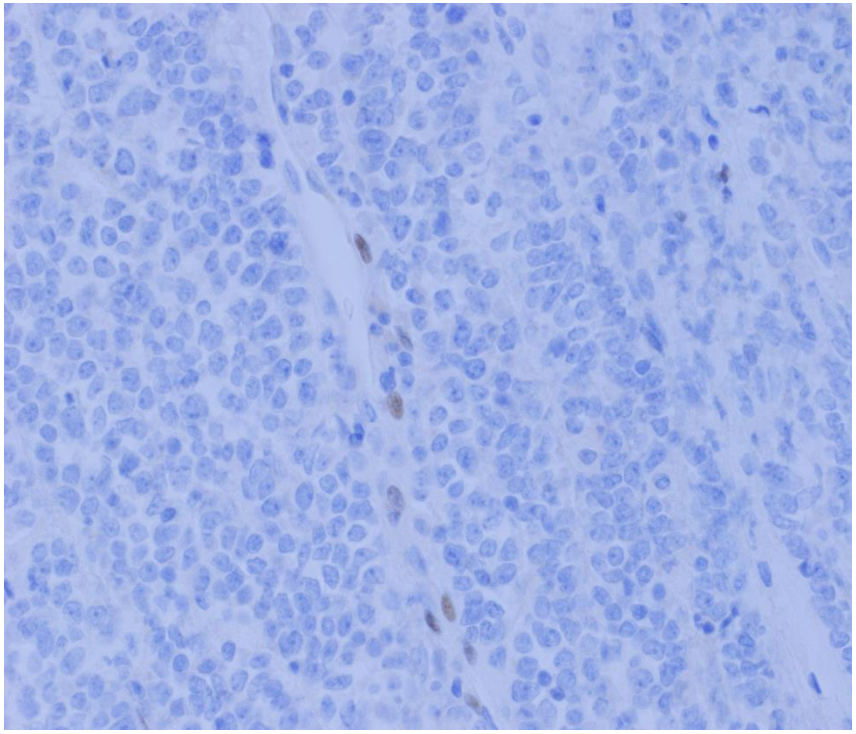
DEDIFFERENTIATED CARCINOMA



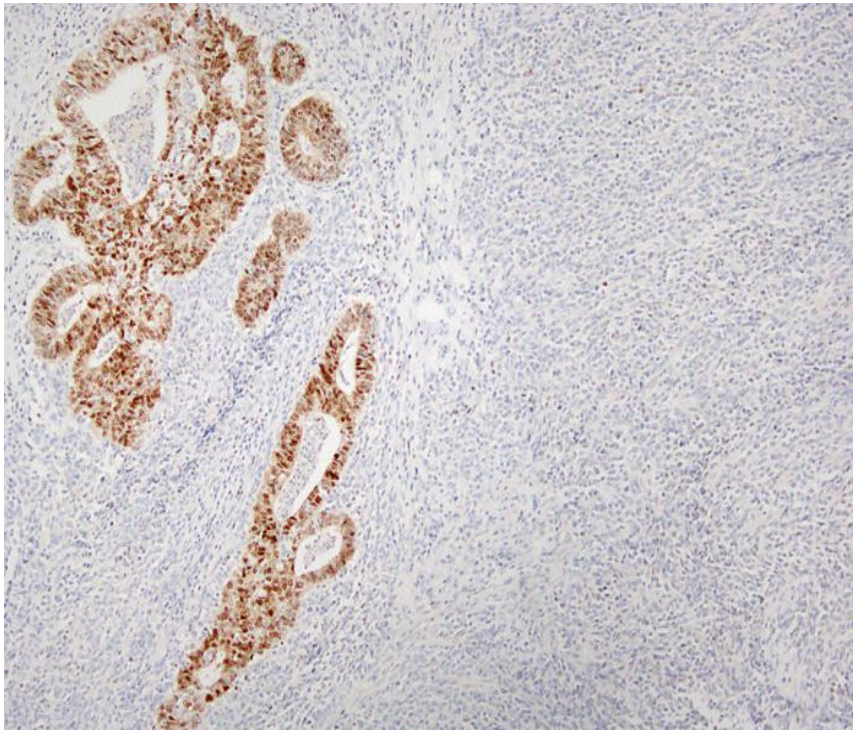
IMMUNOHISTOCHEMISTRY- UNDIFFERENTIATED (AND DEDIFFERENTIATED) CARCINOMA

- cytokeratin and EMA staining may be very focal, although strong; EMA staining more consistent than cytokeratins
- **neuroendocrine marker positivity (arbitrarily up to 10% but may be more) not uncommon; problems with differentiation between undifferentiated carcinoma and neuroendocrine carcinoma**
- usually focal p16 and wild-type p53
- ER, PR, PAX8, E-cadherin- often negative
- often loss of SWI-SNF complex proteins (SMARCA4/ BRG1 or SMARCB1/ INI1 or ARID1A); usually retained in low-grade endometrioid component
- **often loss of MMR proteins; sometimes retained in low-grade endometrioid component; most often get loss of MLH1/PMS2- usually secondary to MLH1 methylation**

UNDIFFERENTIATED ENDOMETRIAL CARCINOMA

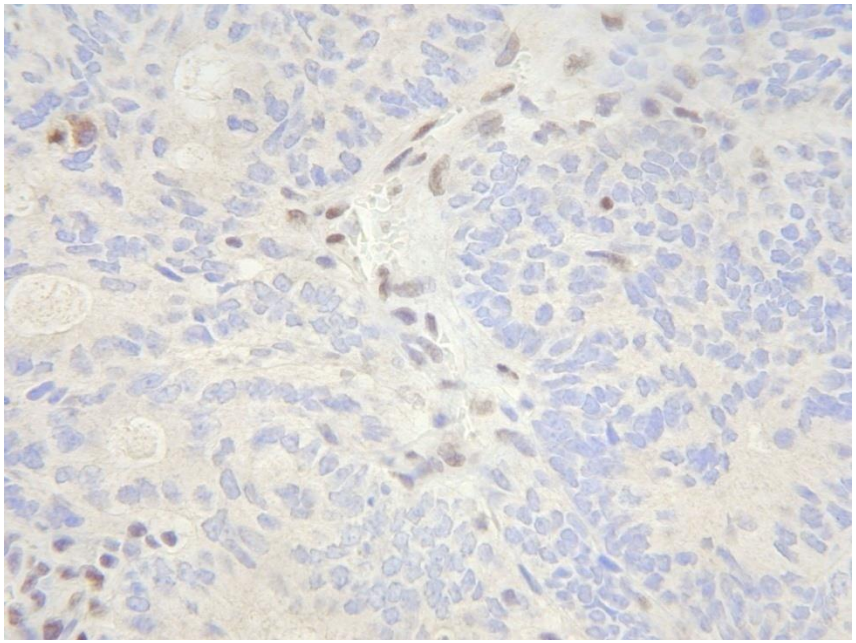


ER

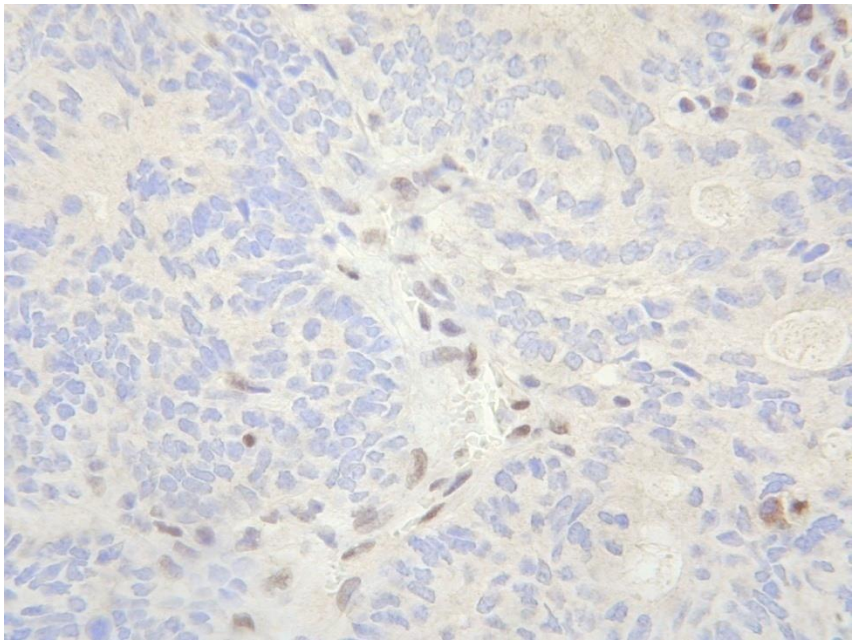


PAX8

MMR IMMUNOHISTOCHEMISTRY IN UNDIFFERENTIATED CARCINOMA

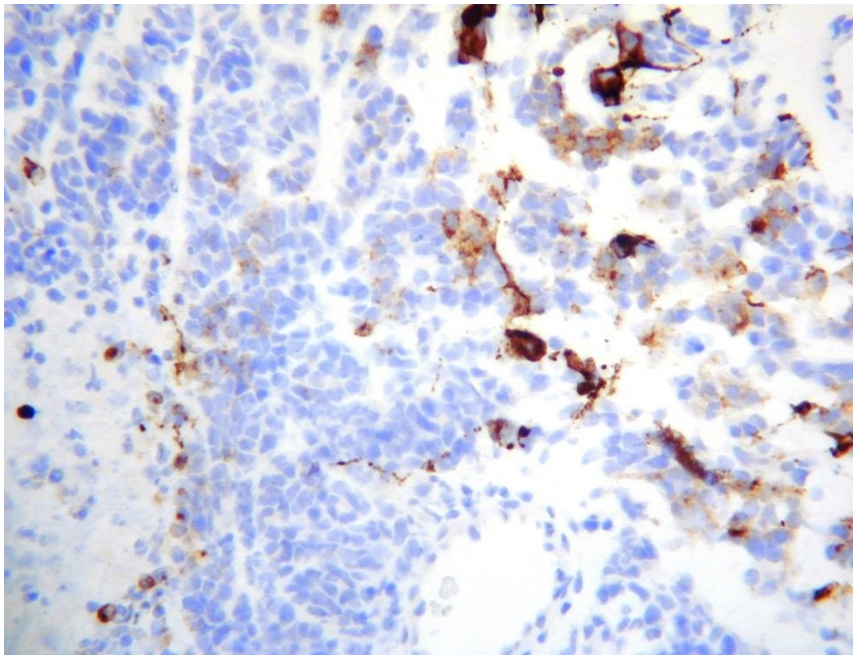


MLH1

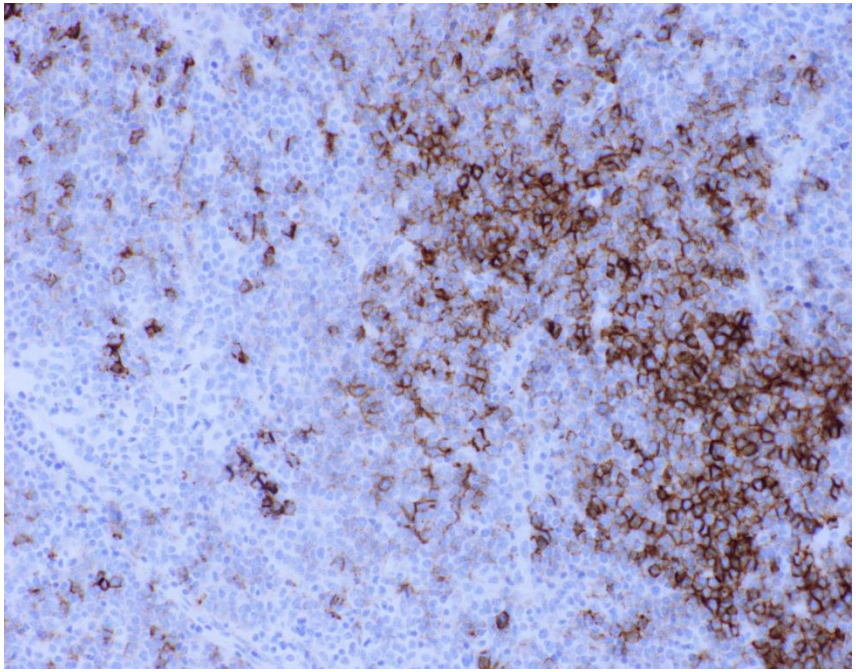


PMS2

UNDIFFERENTIATED ENDOMETRIAL CARCINOMA

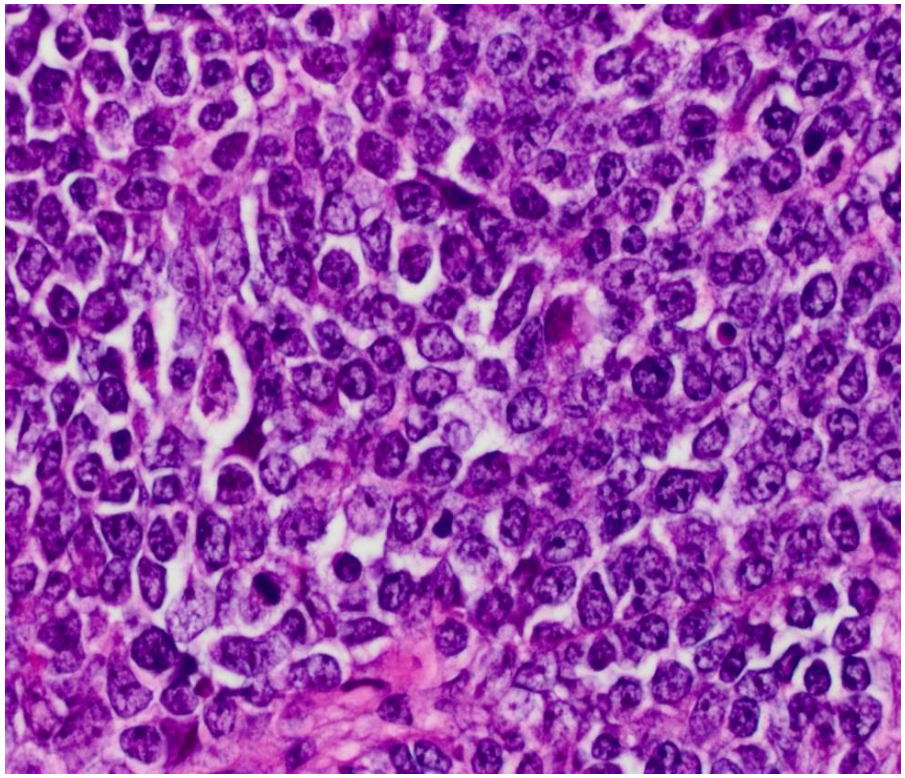


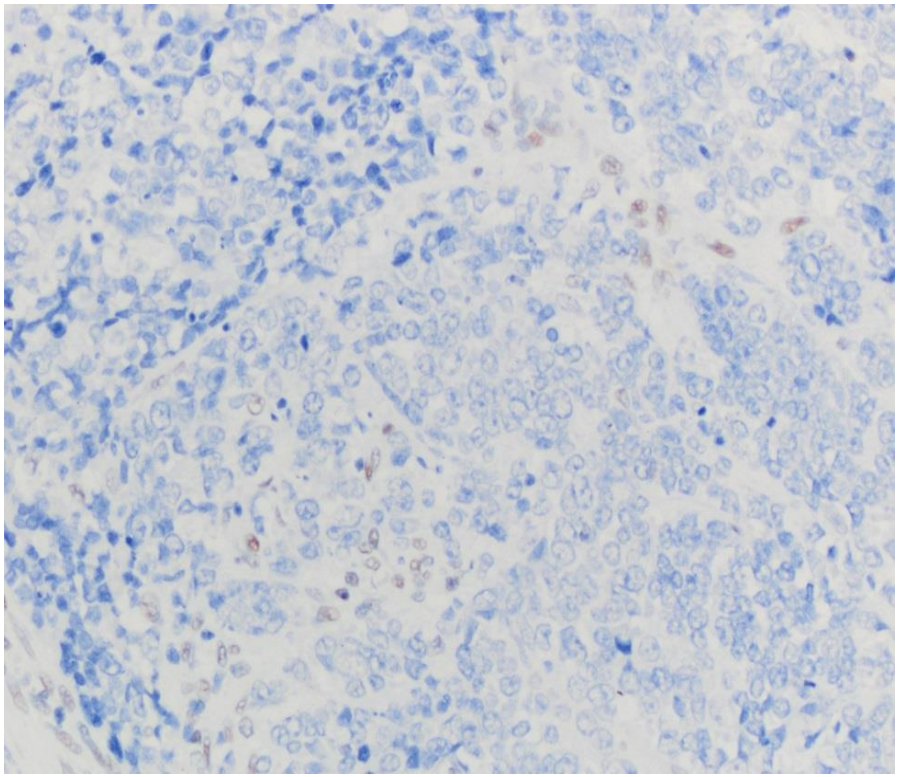
synaptophysin



CD56

LOSS OF SMARCA4 (BRG1)





OVERLAP BETWEEN NEC AND UNDIFFERENTIATED CARCINOMA IN ENDOMETRIUM

- Both may be associated with another tumour type
- Similar, predominantly solid, morphology
- Typically negative with PAX8, ER
- Both may express neuroendocrine markers variably
- Both may be associated with MMR deficiency
- ? SWI-SNF marker deficiency specific for undifferentiated carcinomas but not lost in all

ENDOMETRIUM NEC

- Classification of endometrial high-grade carcinomas problematic
- Ovary –carcinoma classification more straightforward
- In endometrial high-grade carcinomas, more likely to do neuroendocrine markers because of poor interobserver agreement on classification