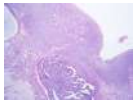
Endometriosis-associated neoplasia

THE BRITISH ASSOCIATION OF GYNAECOLOGICAL PATHOLOGISTS

16th Annual Meeting, June 13-14, London

Prof. Ben Davidson, MD PhD
Department of Pathology, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway



Oslo universitetssykehus

Disclosures

- None

Oslo universitetssykehus

Endometriosis

- Common (15-25% of women in reproductive age)
- Peritoneum and pelvis organs most frequently involved
- Clinically divided into ovarian endometriosis (endometriomas), superficial peritoneal endometriosis, and deep infiltrating endometriosis
- Dysmenorrhea, dyspareunia and infertility
- Risk of neoplasia

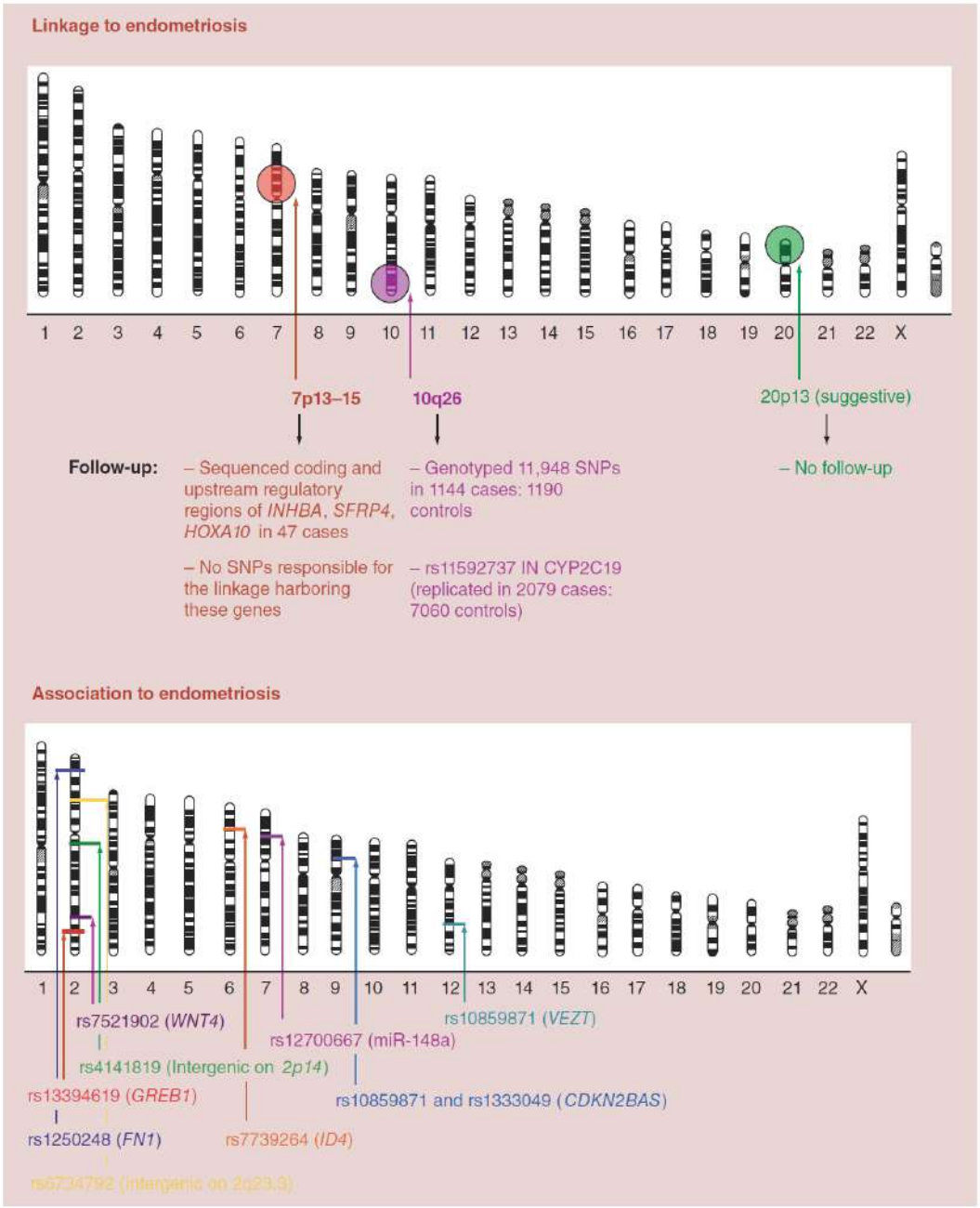
Table 1. Candidate gene association studies of endometriosis published from April 2012 to December 2013, and summarized evidence for the genes from all candidate gene association studies to date.

Candidate gene	Chr	Number of studies with association 2008–2013[†]		Significant/total up to 2013 (n/n)[‡]
		Significant (n cases; n controls)	Nonsignificant (n cases; n controls)	
ACP1	2p25	Italian (132; 359) [12]	–	1/1
CETP	16q21	Iranian (97; 107) [13]	–	1/1
CYP17A1	10q24	Polish (115; 197) [14]	–	2/10
CYP19A1	15q21	Polish (115; 197) [14]	–	5/7
DRD2	11q23	Brazilian (58; 49) [15]	–	1/1
FOXP3	Xp11.23	Han Chinese (314; 358) [16]	–	1/1
GSTM1	1p13	Brazilian (50; 46) [17]	–	8/14
GSTT1	22q11	Brazilian (50; 46) [17]	–	3/10
IL-10	1q31–32	–	Chinese (1080; 1134), Danish (100; 358)[§] [18]	5/7
TP53	17p13	Italian (132; 359) [12] Brazilian (50; 46) [17]	–	6/11
PTPN22	1q13	Italian (132; 359) [12]	–	4/5
TNFA	6p21	Iranian (135; 173) [19]	–	2/3
VEGF	6p21–12	Asian, Caucasian (3313; 3393)[¶] [20] Indian (302, 324) [21]	Iranian (135; 173) [19]	12/15
VEGFR-2	4q11–q12	Northern Chinese (571; 580) [22]	–	1/1

[†]When more than one polymorphism was investigated in a study, the result is indicated as significant if one or more of the variants were reported as significant by the authors.
[‡]Total number of candidate studies is combined with data from our review in 2012 [10].
[§]Literature-based meta-analysis of three polymorphisms in *IL-10* gene from eight case–control studies from seven Chinese and one Danish population [55].
[¶]Literature-based meta-analysis of five polymorphisms in *VEGF* gene from 14 Asian case–control studies [57].

Rahmioglu et al., Womens Health 2015;11:577-86

Oslo universitetssykehus



Rahmioglu et al., Womens Health 2015;11:577-86

Oslo universitetssykehus

Table 3. Eight genome-wide significant genetic variants robustly associated with endometriosis.

SNP	Chr	Position (HG19)	P_{meta} [†]	OR_{all} [‡] (95% CI)	$OR_{stage\ III/IV}$ [§] (95% CI)	Nearest gene (distance)
rs7521902	1	22490474	1.8×10^{-15}	1.18 (1.13–1.23)	1.25 (1.16–1.33)	*WNT4* (21 Kb)
rs13394619	2	11727257	2.9×10^{-8}	1.13 (1.07–1.20)	1.18 (1.11–1.24)	*GREB 1* (0)
rs4141819	2	67864425	8.8×10^{-6} (9.2×10^{-8})	1.08 (1.04–1.12)	1.16 (1.09–1.24)	Intergenic (*ETAA1*: 227 Kb)
rs1250248	2	216286843	1.1×10^{-4} (8.0×10^{-8})	1.11 (1.04–1.18)	1.26 (1.16–1.38)	*FN1* (0)
rs7739264	6	19785338	6.2×10^{-10}	1.11 (1.08–1.15)	1.20 (1.13–1.28)	*ID4* (52 Kb)
rs12700667	7	25901389	1.6×10^{-9}	1.13 (1.08–1.17)	1.22 (1.14–1.31)	Intergenic (*miR-148a*: 88 Kb, *NFE2L3*: 290 Kb)
rs1537377	9	22169450	1.0×10^{-8}	1.12 (1.08–1.17)	1.18 (1.11–1.26)	*CDKN2B-AS1* (48 Kb)
rs10859871	12	95711626	4.8×10^{-15}	1.18 (1.13–1.22)	1.19 (1.11–1.27)	*VEZT* (17 Kb)

[†]Meta-analysis p-value is from Rahmioglu *et al.* 2014 [40]. For rs4141819 and rs1250248 the meta-analysis p-values including only stage III/IV cases is given in parenthesis, which reach borderline significance.
[‡]Odds ratio including all endometriosis cases.
[§]Odds ratio including only stage III/IV cases.
SNP: Single nucleotide polymorphism.
Adapted from Rahmioglu *et al.* (2014) [40].

Rahmioglu et al., Womens Health 2015;11:577-86

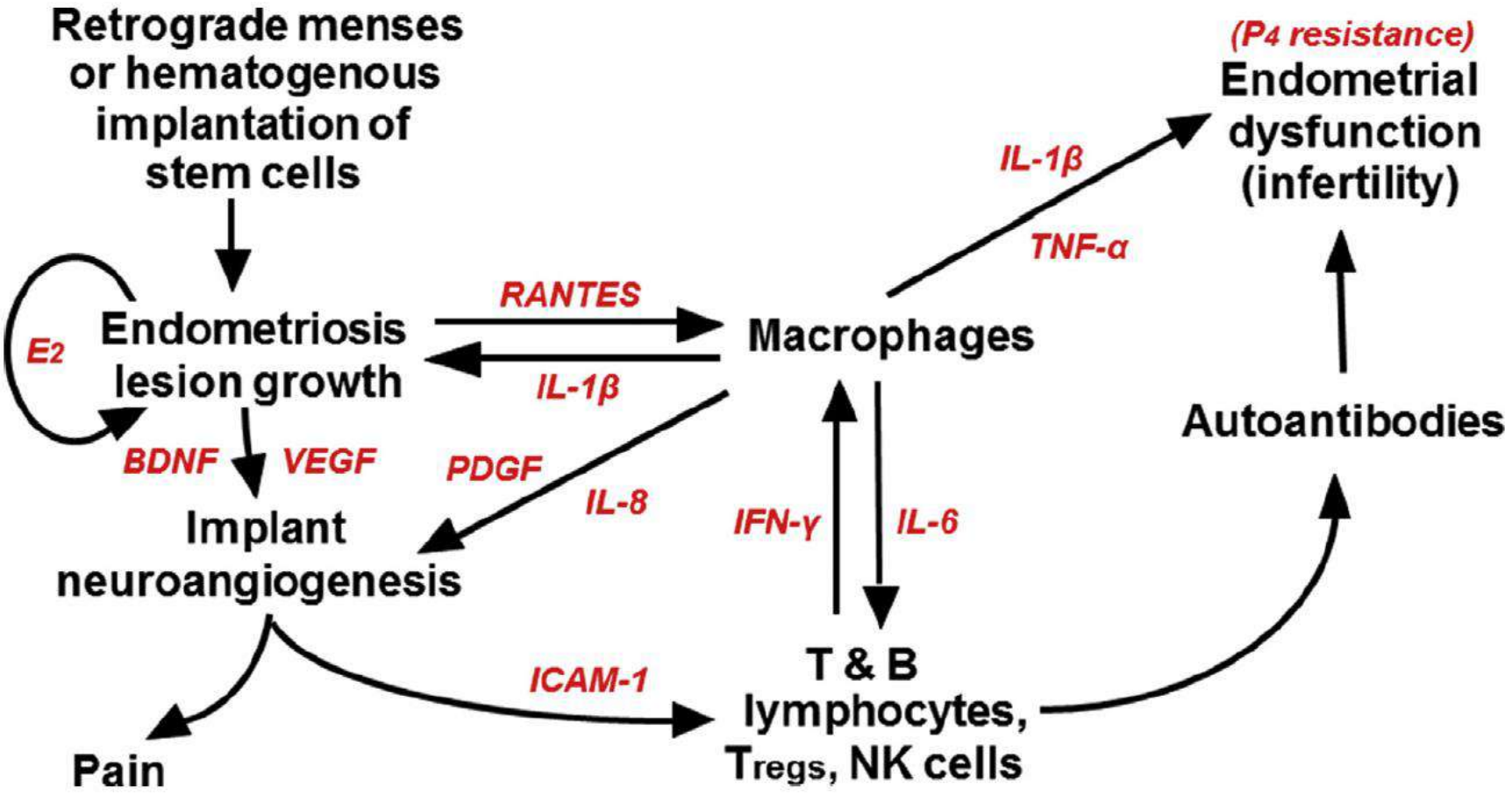
Oslo universitetssykehus

Table 4. Biological functions of potential genes identified for association with endometriosis.

Gene name	Known functions
WNT4	A protein-coding gene that is vital for development of the female reproductive organs. In knockout mice, the loss of WNT4 leads to complete absence of the Müllerian duct and its derivatives [41]. It has been also shown that WNT genes are expressed in the peritoneum and endometrium [42]
GREB1	An early response gene in the estrogen regulation pathway that is involved in hormone-dependent breast cancer cell growth. Its expression was increased in peritoneal eutopic endometrotic lesions when compared with eutopic endometrium, possibly with a role in oestrogen-dependent growth of endometriosis [43]
ETAA1	Encodes for a tumor-specific cell surface antigen in Ewing family of tumors, which is a group of cancers that form in bone or soft tissue that share common features as they develop from the same type of stem cell in the body [44]
FN1	Involved in cell adhesion and migration processes including embryogenesis, wound healing, blood coagulation, host defense and metastasis [45]. It has been shown that *SOX2*, a gene encoding a transcription factor that targets FN1, is a key gene regulating cell migration in ovarian cancer [46]
ID4	An ovarian oncogene, which is also implicated in methylation-related regulatory pathways in breast cancinogenesis [47]. It is also overexpressed in ovarian, endometrial and breast cancer cell lines [48]
NFE2L3	A transcription factor suggested to be involved in cell differentiation, inflammation and carcinogenesis [49]. Its expression was increased in human breast cancer cells [50] and testicular carcinoma tissue samples [51]
miRNA_148a	A microRNA with a role in the Wnt/β-catenin signaling pathway that may have a role in endometriosis development through sex hormone homeostasis regulation [52] and fibrogenesis [53]
HOXA10	Belongs to homeobox A family of transcription factors, which plays essential roles in specifying regional differentiation of the Müllerian duct into oviduct, uterus, cervix and vagina [54]
CDKN2B-AS1	Involved in regulation of CDKN2B, CDKN2A and ARF tumor suppressor genes. CDKN2A inactivation has been reported in endometriosis and endometrial cancer [55]
VEZT	Encodes an adherens junction transmembrane protein. Also, it is a putative tumor suppressor gene, targeting cell migration and invasion genes, growth genes, cellular adhesion genes and a functionally validated cell cycle progression gene called *TCF19*. TCF19 is involved in maintaining immunological balance [56]

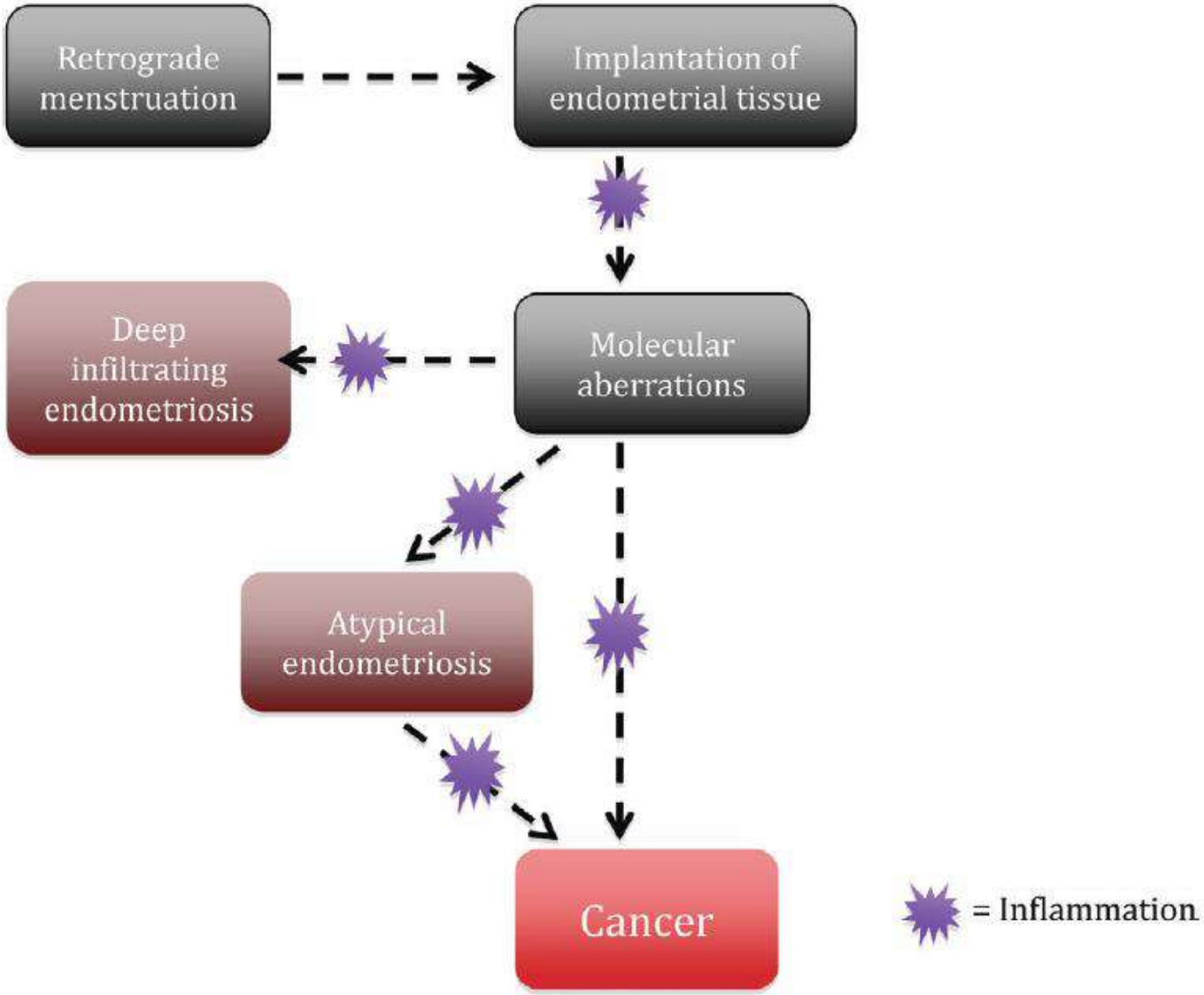
Rahmioglu et al., Womens Health 2015;11:577-86

Oslo universitetssykehus



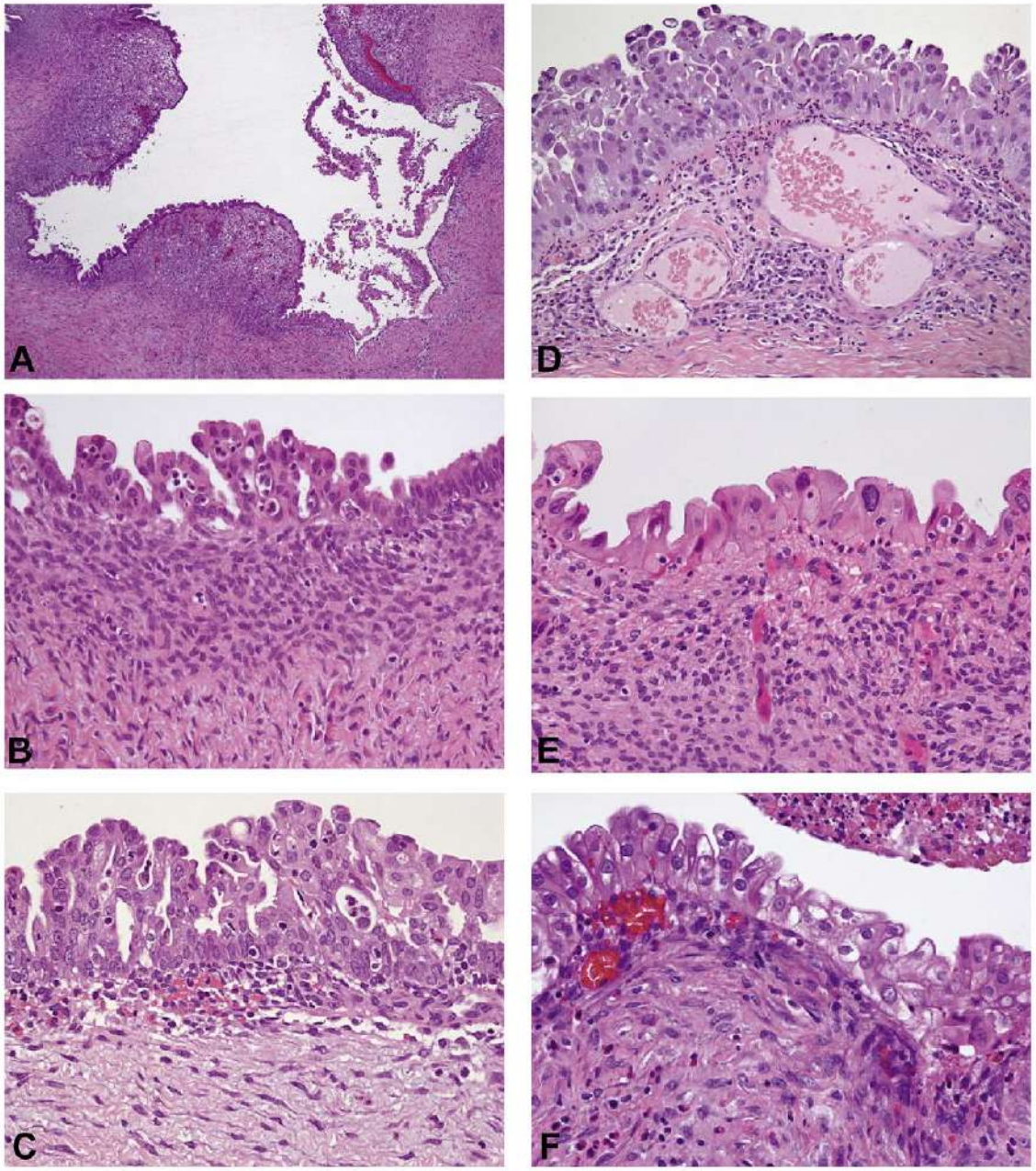
Patel et al., Best Pract Res Clin Obstet Gynaecol 2018;50:50-60

Oslo universitetssykehus



Dawson et al., ecancer 2018;12:803

Oslo universitetssykehus



Matias-Guiu and Stewart, Pathology 2018;50:190-204

Oslo universitetssykehus

Table 1 Upregulated genes selected by complementary DNA microarray analysis

Probe No.	Gene Symbol	Gene Name	Log2 ratio			KEGG pathway category
			B/A > 1	C/B > 1	C/A > 1	
1.	*RBL1*	Retinoblastoma-like 1	1.61	1.05	2.67	Cell cycle TGF-β signaling
2.	*RUVBL1*	RuvB-like 1	1.33	1.96	3.29	Wnt signaling pathway
3.	*BIRC5*	Survivin	1.06	1.19	2.25	Pathway in cancer
4.	*FGFR2*	Fibroblast growth factor receptor 2	3.00	1.37	4.37	MAPK signaling pathway
5.	*FGFR2*	Fibroblast growth factor receptor 2	2.50	1.50	4.00	MAPK signaling pathway
6.	*FGFR2*	Fibroblast growth factor receptor 2	2.17	1.69	3.86	MAPK signaling pathway
7.	*CDC6*	Cell division cycle 6 homolog	1.30	1.80	3.10	Cell cycle
8.	*CDC6*	Cell division cycle 6 homolog	1.17	1.95	3.12	Cell cycle
9.	*LEFTY1*	Left–right determination factor 1	6.10	1.83	8.20	TGF-β signaling pathway
10.	*BMP6*	Bone morphogenetic protein 6	3.35	1.49	4.85	Cytokine interaction
11.	*CCNE1*	Cyclin E1	1.75	2.44	4.19	Cell cycle
12.	*MCM4*	Minichromosome maintenance complex	2.55	1.53	4.07	DNA replication and cell cycle

A, endometrioma; B, endometrioma with clear cell carcinoma; C, clear cell carcinoma; MAPK, mitogen-activated protein kinase; TGF, transforming growth factor.

Taniguchi, J Obstet Gynaecol Res 2017;43:1093-100

Oslo universitetssykehus

Table 1
Common molecular patterns in endometriosis-associated carcinomas.

Endometriosis-associated ovarian clear cell carcinoma	Endometriosis-associated ovarian endometrioid carcinoma
Mutations in • ARID1A • PIK3CA • CTNNB1 • PTEN	Mutations in • PTEN • CTNNB1 • KRAS • ARID1A • PIK3CA • PPP2R1A
Expression of • HNF-1beta ++ • BAF250a – • Napsin A ++ • Nuclear ERα – • Cytoplasmatic ERβ2 – • Cytoplasmatic ERβ5 –	Expression of • BAF250a –

Vercellini et al., Best Pract Res Clin Obstet Gynaecol 2018;51:151-68

Oslo universitetssykehus

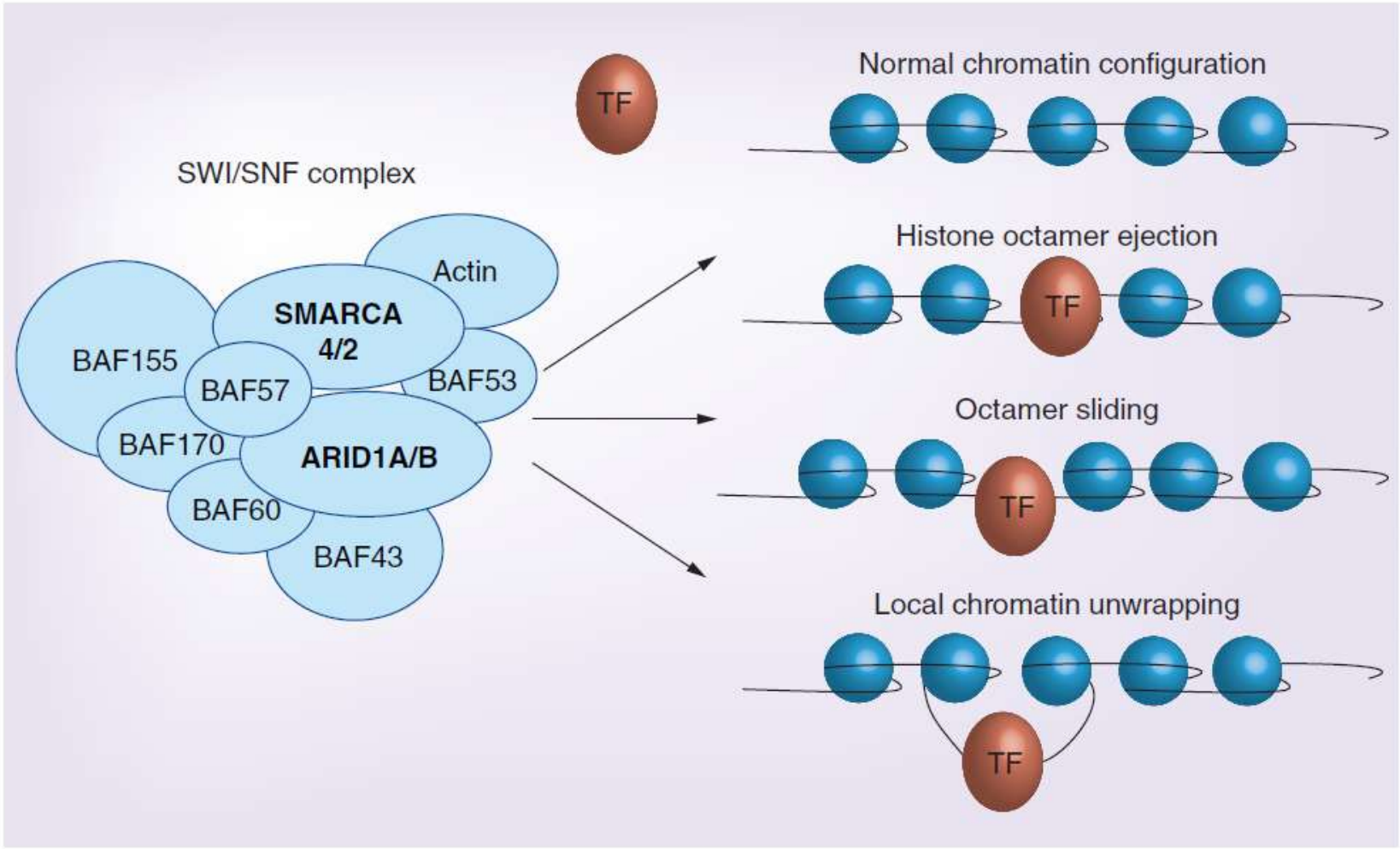
Table 1 Summary of most common molecular alterations and immunohistochemical findings in endometriosis-associated ovarian neoplasms

	Molecular alterations	Immunohistochemistry
EOC	*CTNNB1* (38–50%), *PIK3CA* (30–40%), *ARID1A* (30%), *KRAS* 20%, *PTEN* (20%), MI/MMR protein (12–20%), *PPP2R1A* (12%)	ER/PR positive, nucleo-cytoplasmic β-catenin staining, loss of ARID1A/BAF250a and MMR protein expression
CCC	*ARID1A* (50%), *PIK3CA* (30–40%), *TERT* promoter (16%), MI/MMR protein (5–10%), *Met* amplification (37%), *AKT2* amplification (14%)	Napsin A, AMACR, HNF1β positive, usually ER/PR negative, loss of ARID1A/BAF250a expression
MM/ME tumour	*KRAS* (70%), *ARID1A* (30%), *PIK3CA* (37%),[a] *PTEN* (19%)[a]	ER/PR positive, loss of ARIDIA/BAF250a expression

CCC, clear cell carcinoma; EOC, endometrioid ovarian carcinoma; ER, oestrogen receptor; MI, microsatellite instability; MM/ME, mixed Müllerian/mixed epithelial; MMR, mismatch repair; PR, progesterone receptor.
[a] Seromucinous carcinomas.

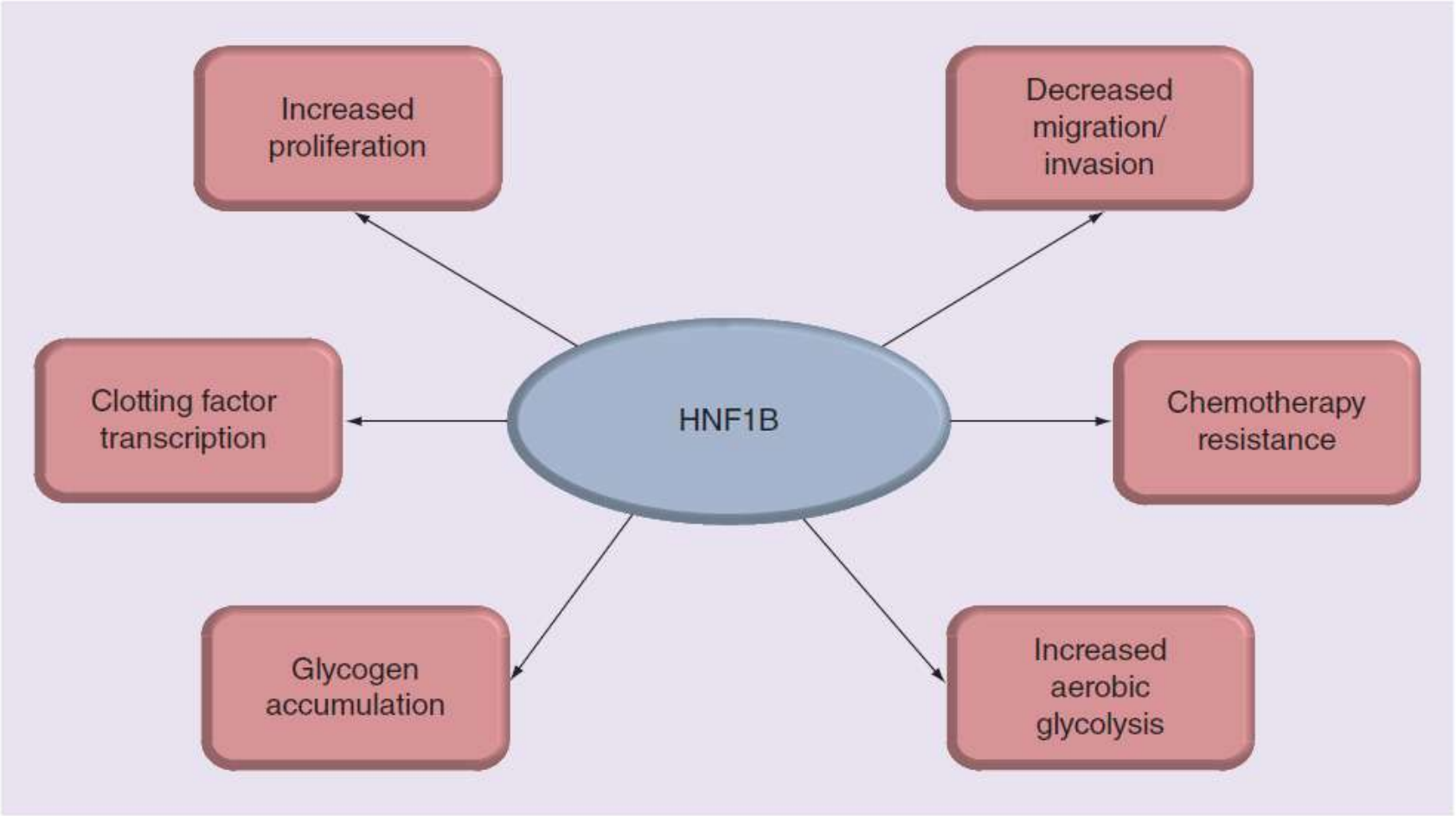
Oslo universitetssykehus

Matias-Guiu and Stewart, Pathology 2018;50:190-204



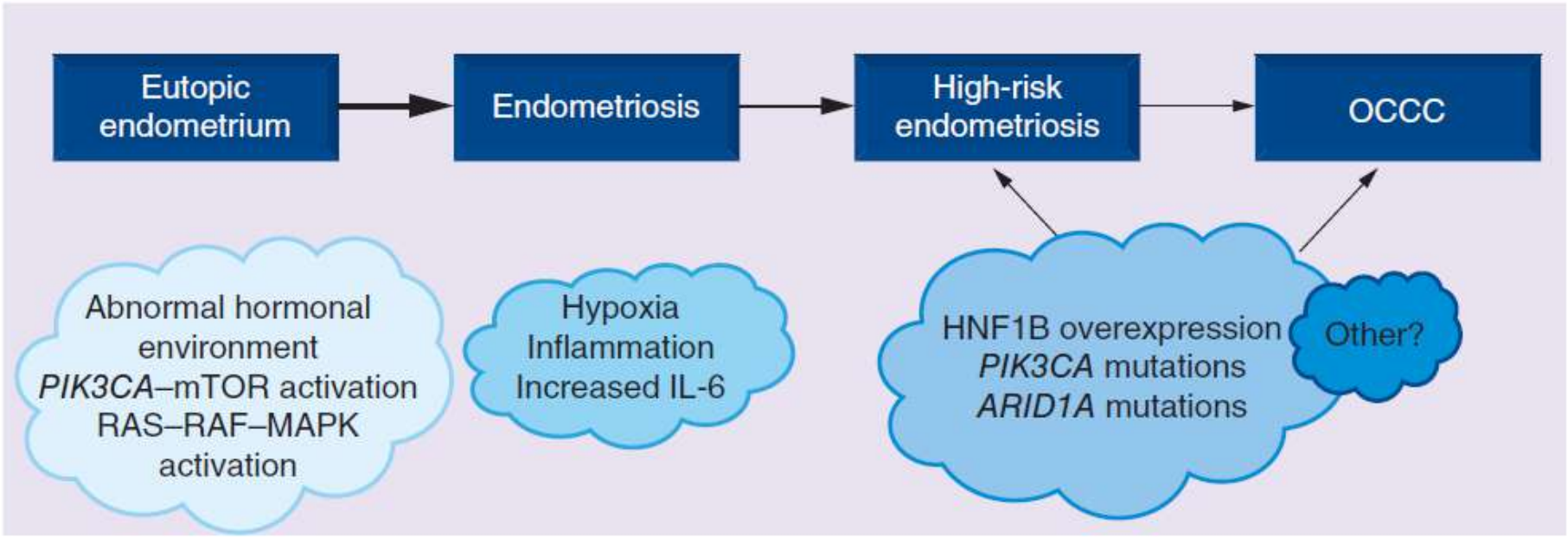
Gounaris and Brenton, Future Oncol 2015;11:1389-1405

Oslo universitetssykehus



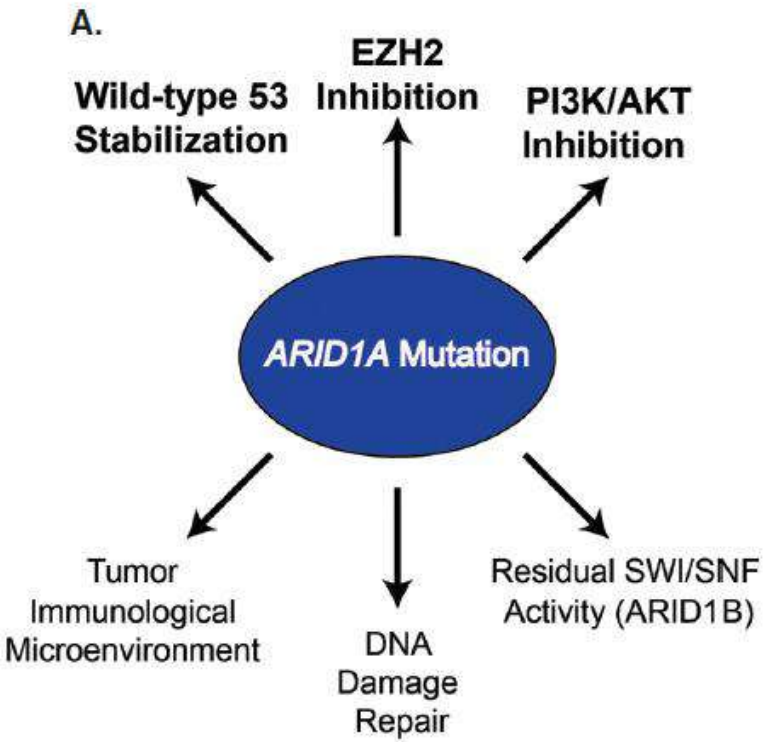
Gounaris and Brenton, Future Oncol 2015;11:1389-1405

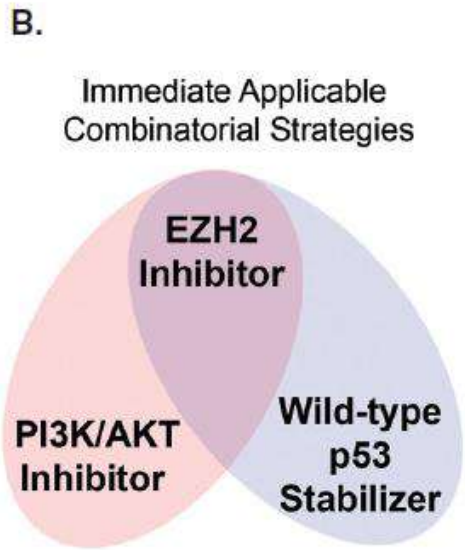
Oslo universitetssykehus



Gounaris and Brenton, Future Oncol 2015;11:1389-1405

Oslo universitetssykehus





Bitler et al., Expert Opin Ther Targets 2015;19:1419-22

Oslo universitetssykehus

Endometriosis-associated tumors

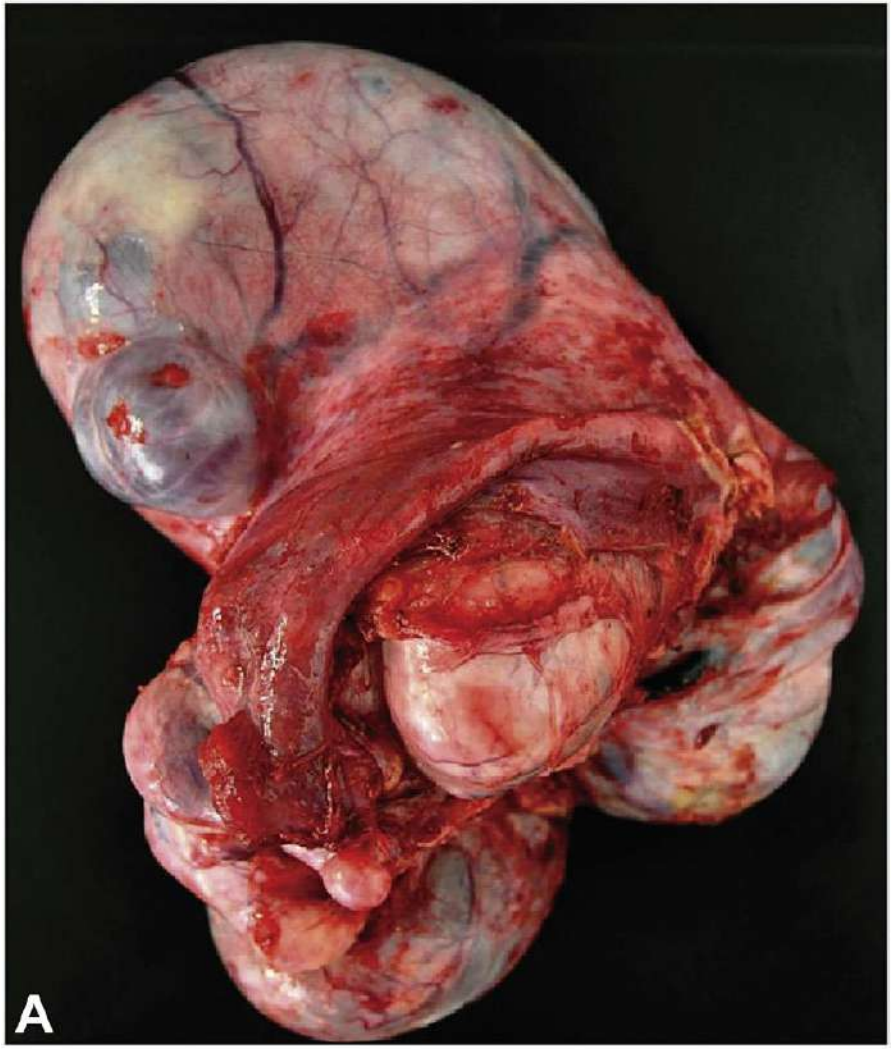
- Endometrioid carcinoma (EC)
- Clear cell carcinoma (CCC)
- Seromucinous tumors
- Low-grade serous carcinoma (LGSC)
- Carcinosarcoma
- Adenosarcoma
- Endometrial stromal sarcoma (ESS)

Endometriosis-associated tumors

- Endometrioid carcinoma (EC)
- Clear cell carcinoma (CCC)
- Seromucinous tumors
- Low-grade serous carcinoma (LGSC)
- Carcinosarcoma
- Adenosarcoma
- Endometrial stromal sarcoma (ESS)

Endometrioid carcinoma

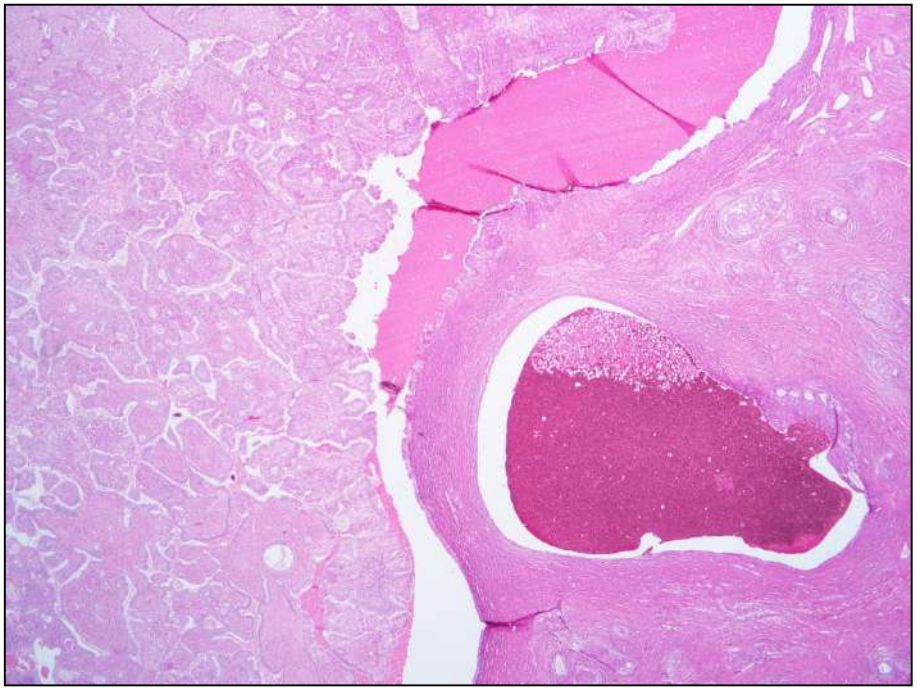
- 10% of ovarian carcinomas in Western countries
- 5th-6th decade (mean = 56 years)
- Endometriosis found in about 40%, generally younger patients
- Tumor in the uterus found in 15-20%
- Majority unilateral, 20% bilateral
- CA 125 elevated in 75%
- Endocrine symptoms may be present
- Majority diagnosed at FIGO stage I
- Generally good prognosis

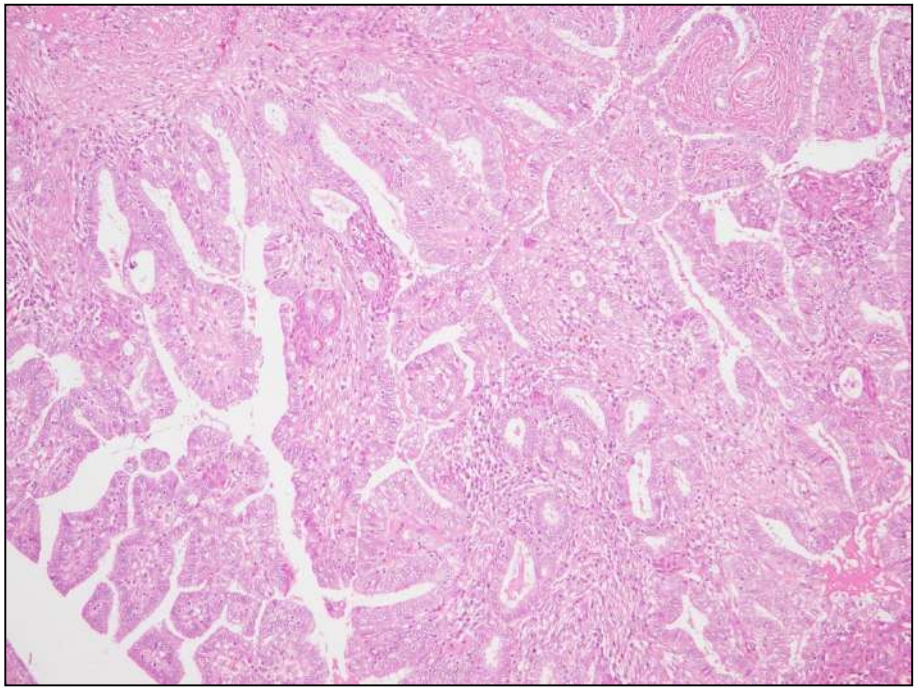


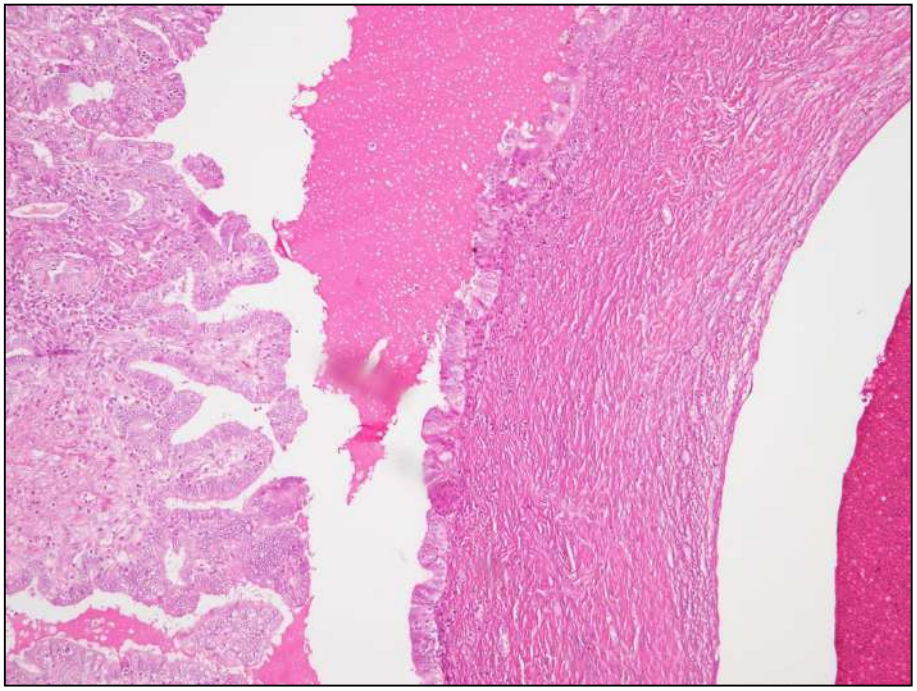


Matias-Guiu and Stewart, Pathology 2018;50:190-204

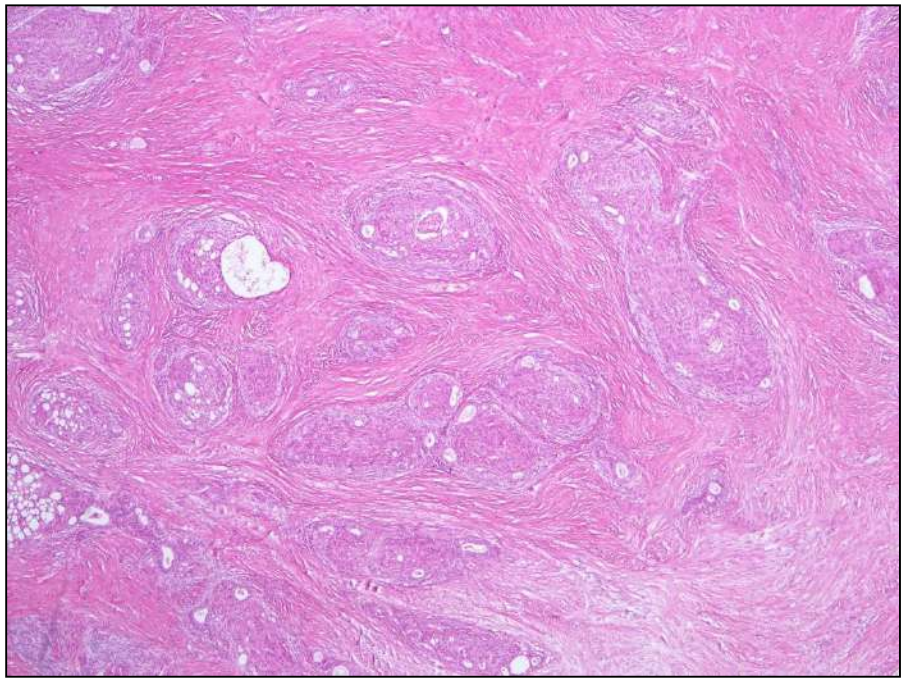
Oslo universitetssykehus

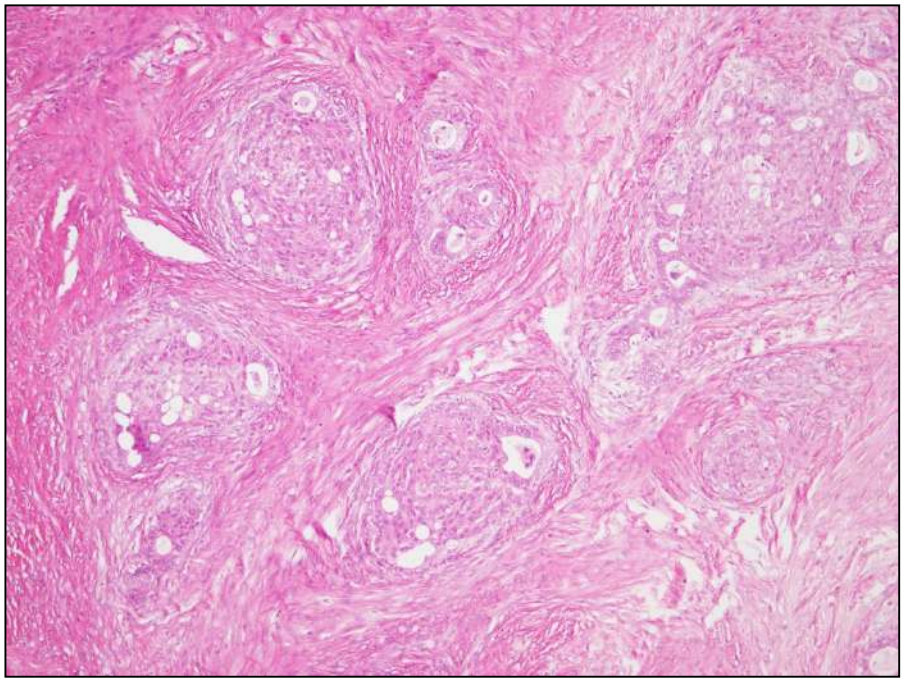


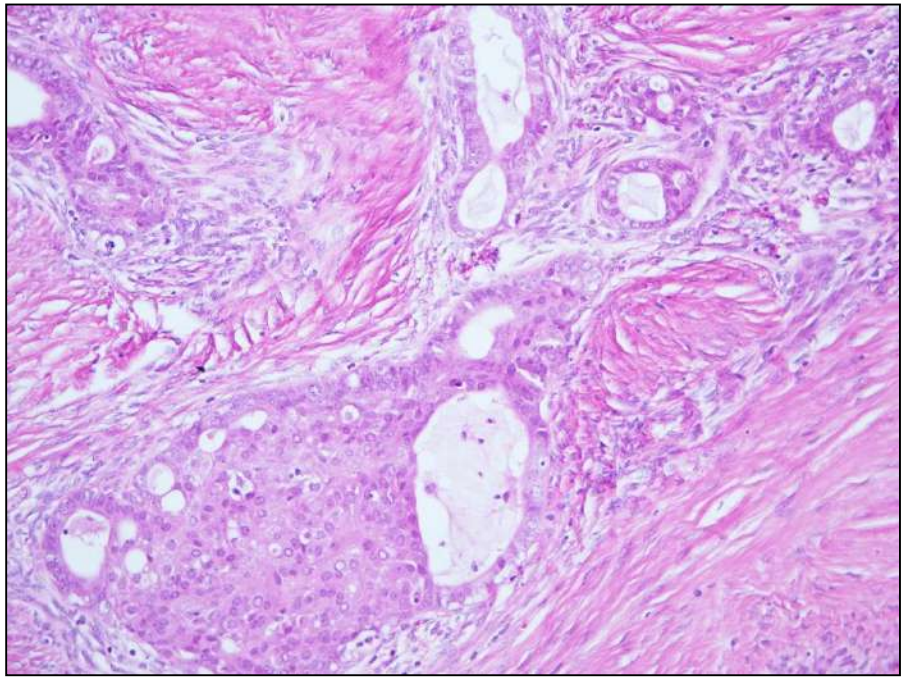




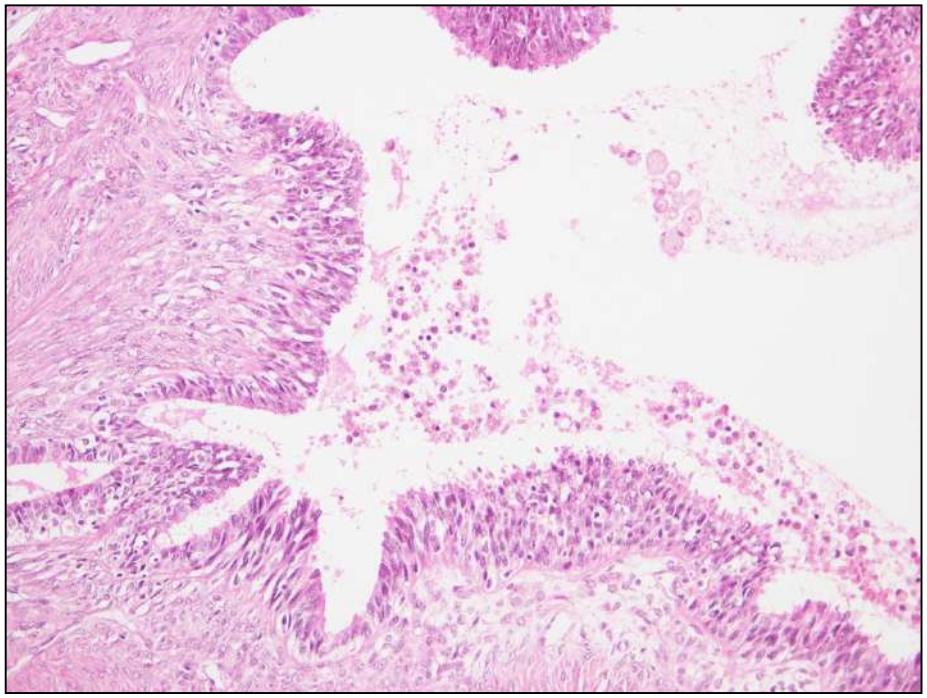
Oslo universitetssykehus

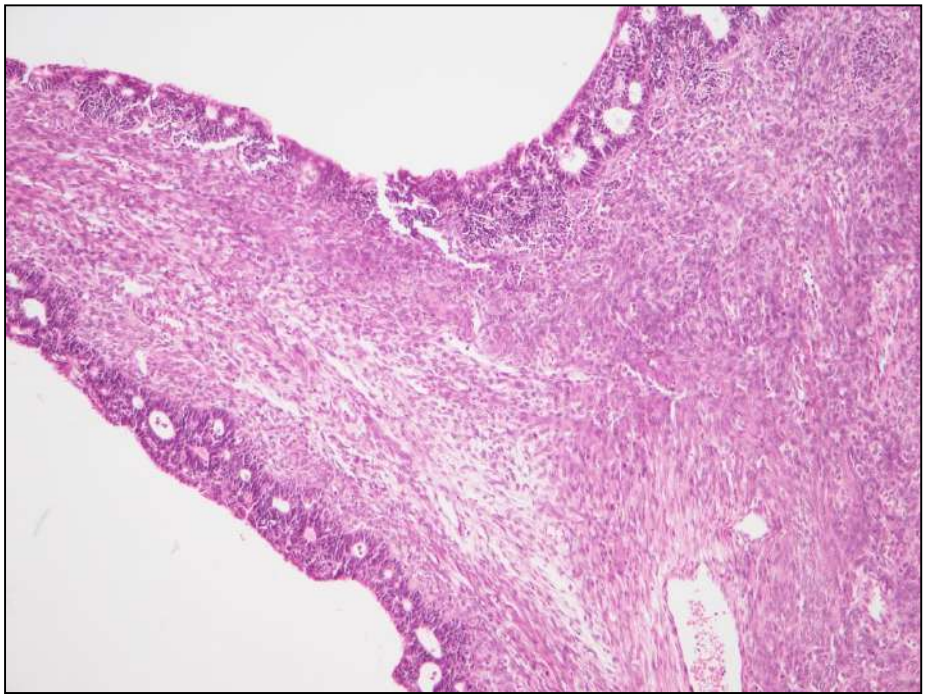


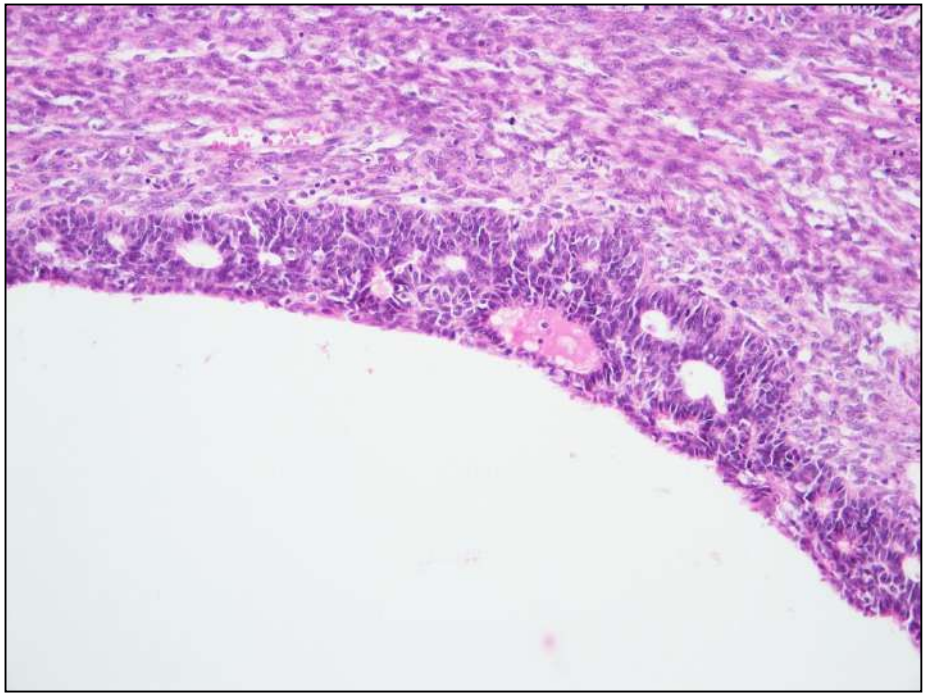




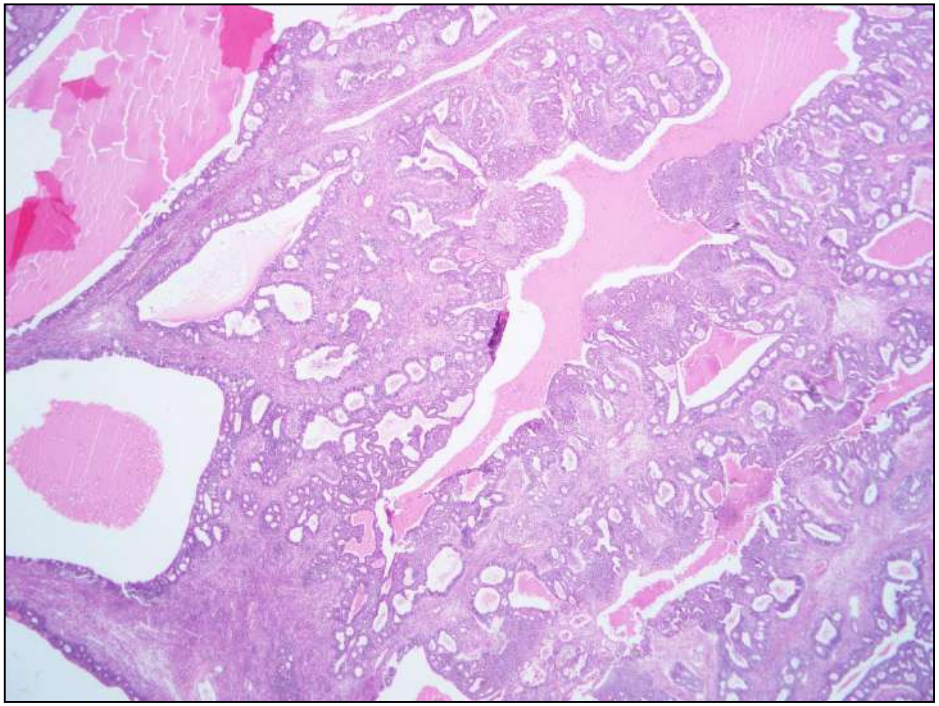
Oslo universitetssykehus

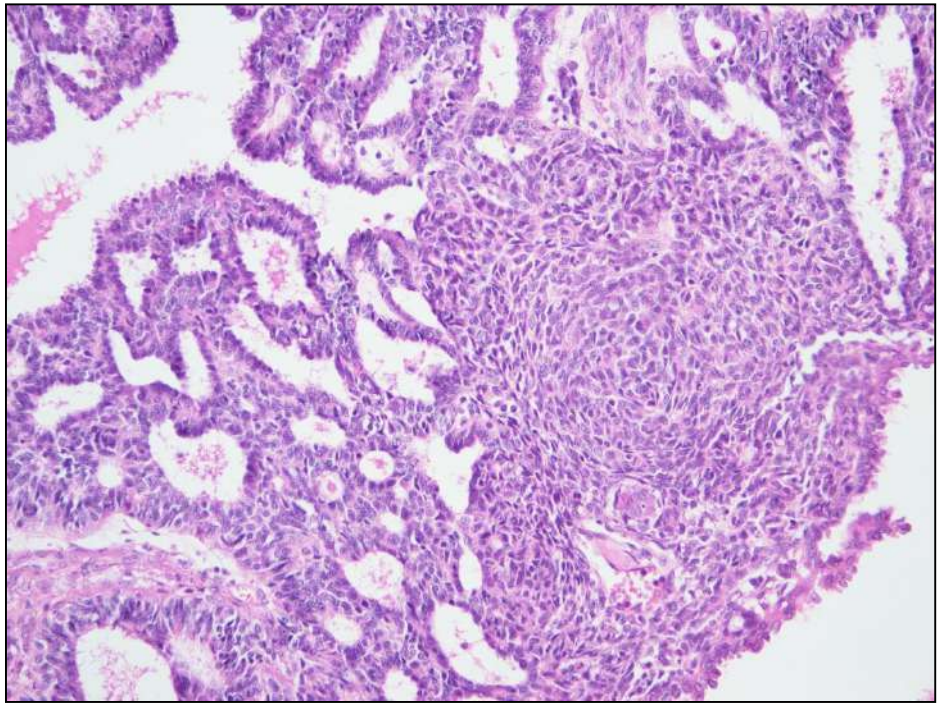


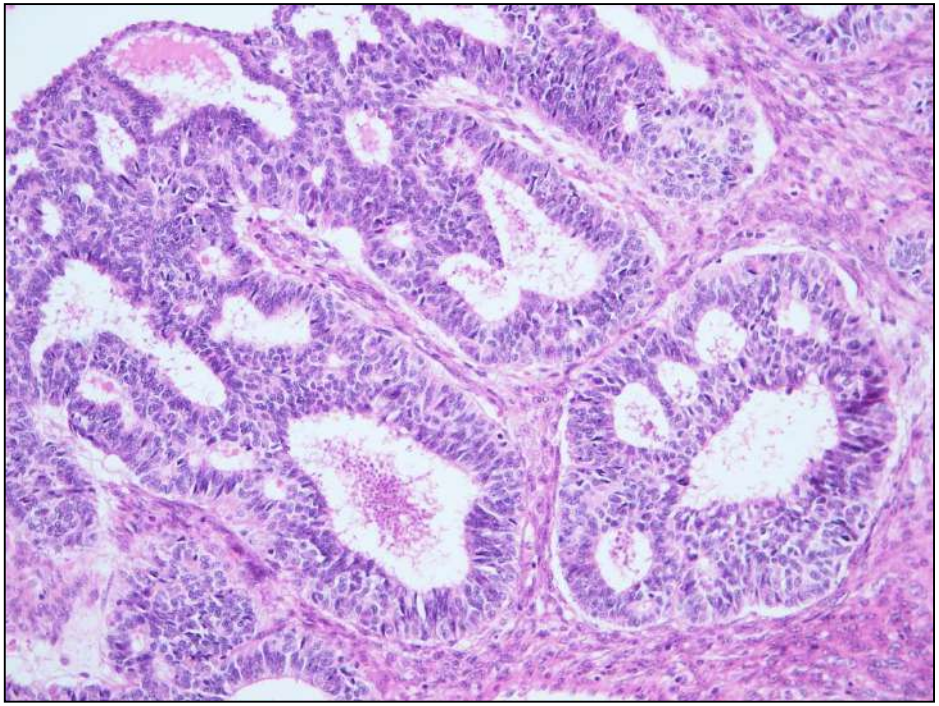




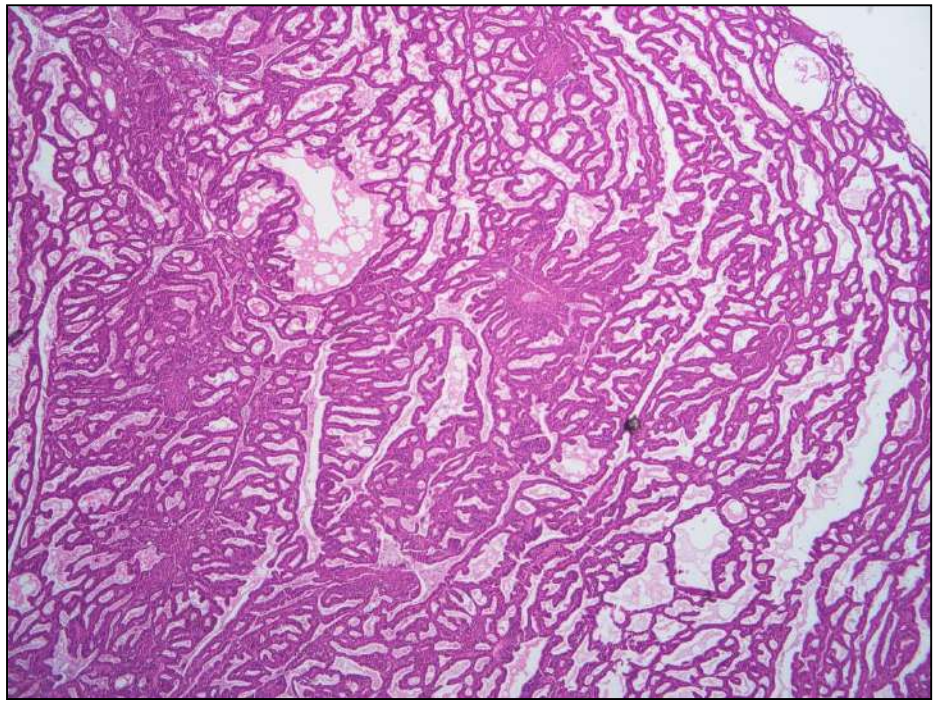
Oslo universitetssykehus

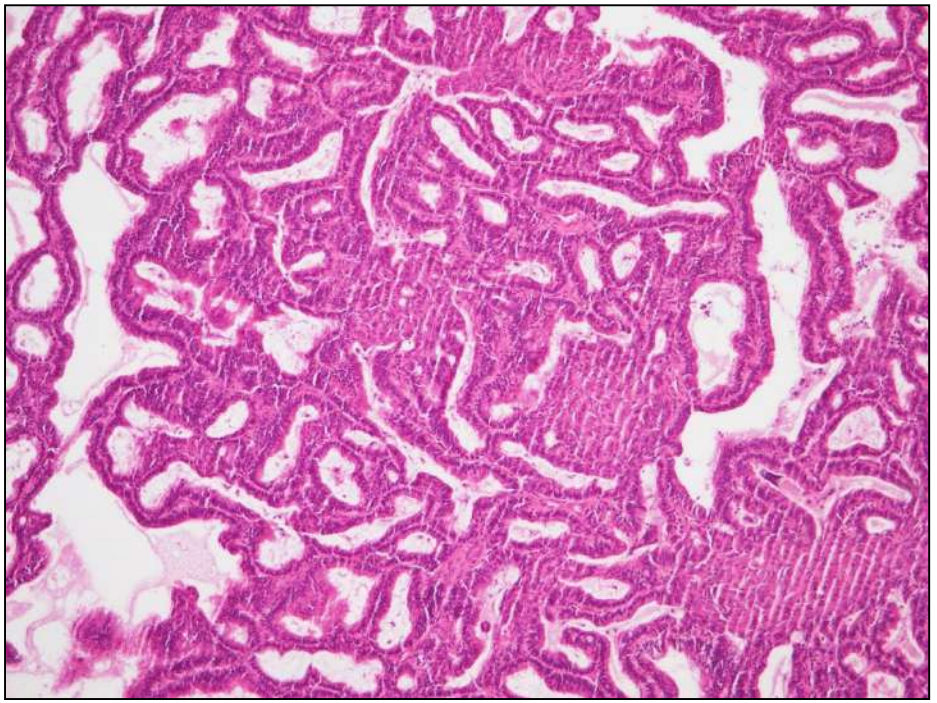


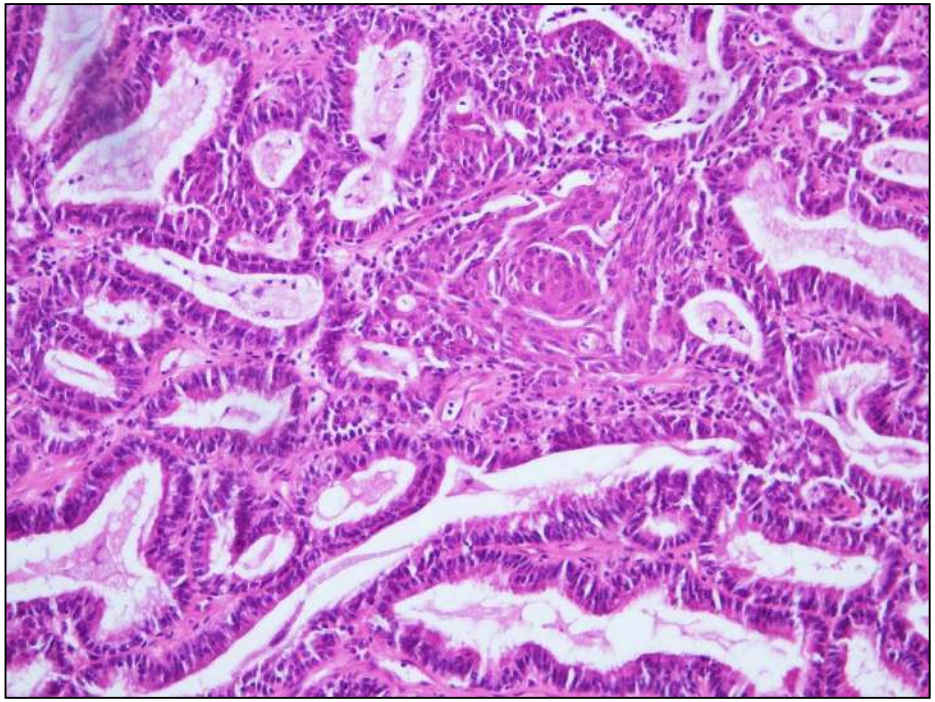


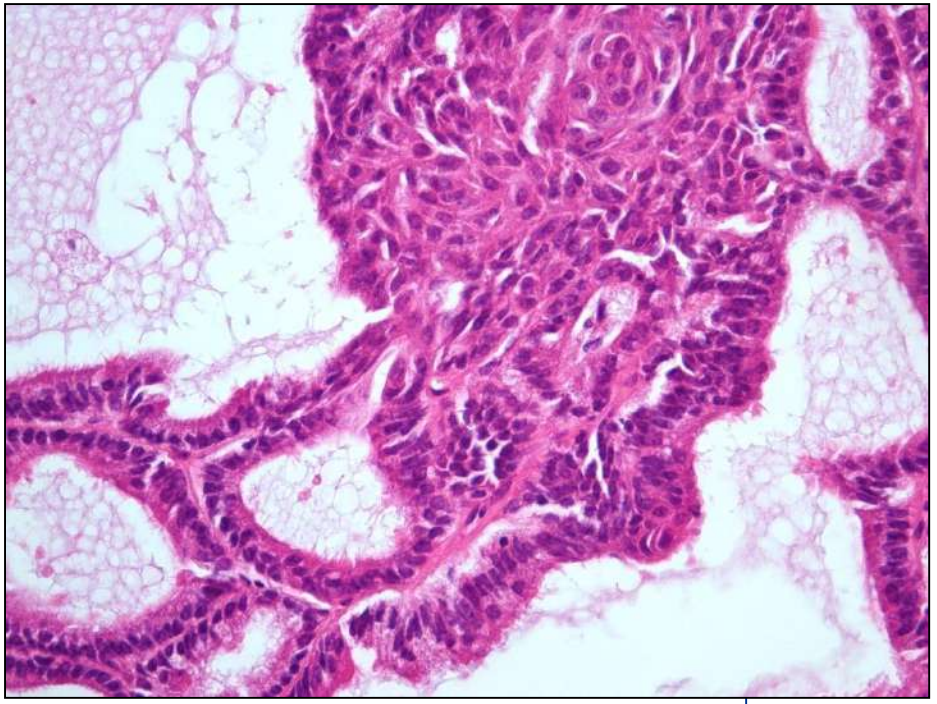


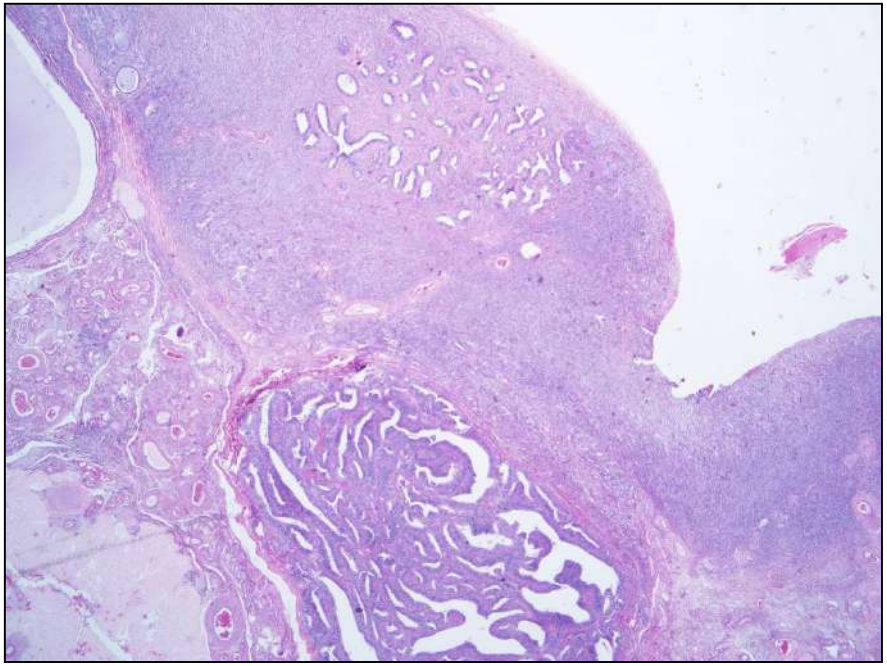
Oslo universitetssykehus

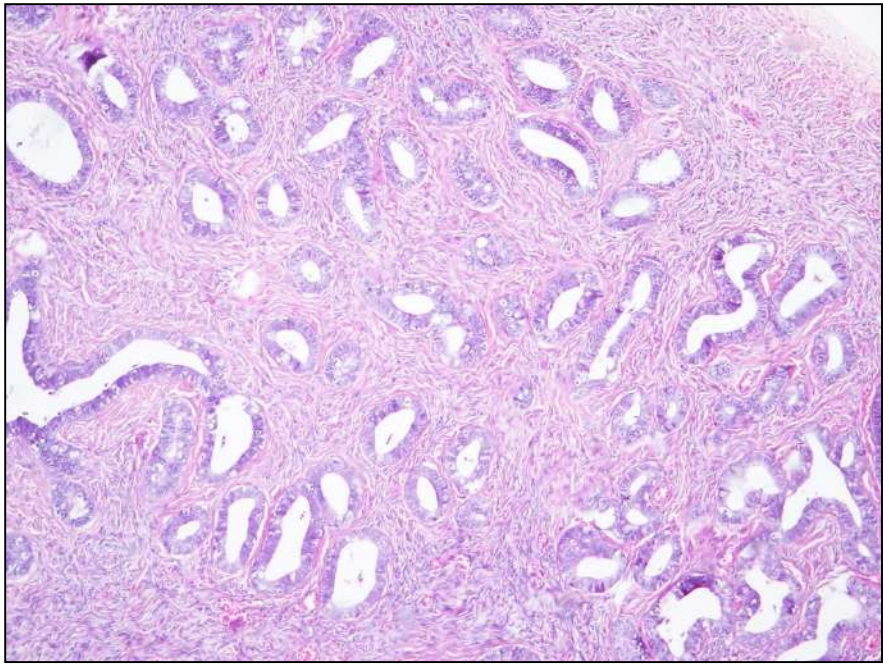


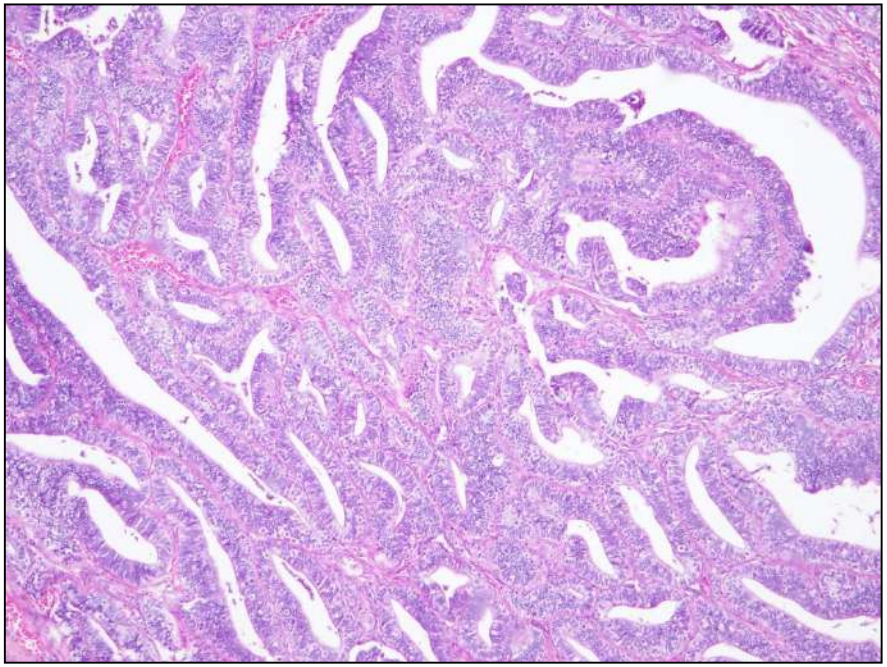


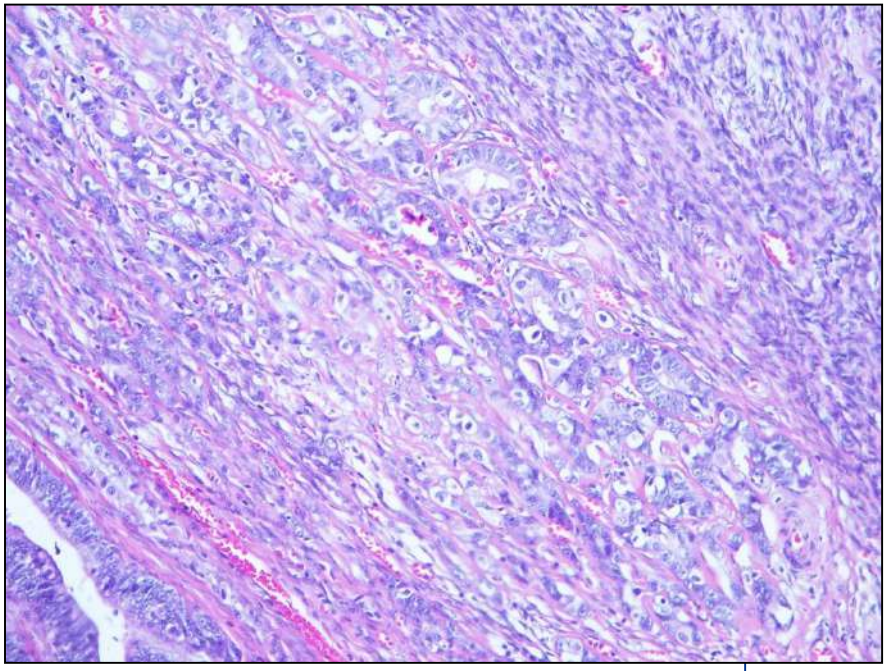


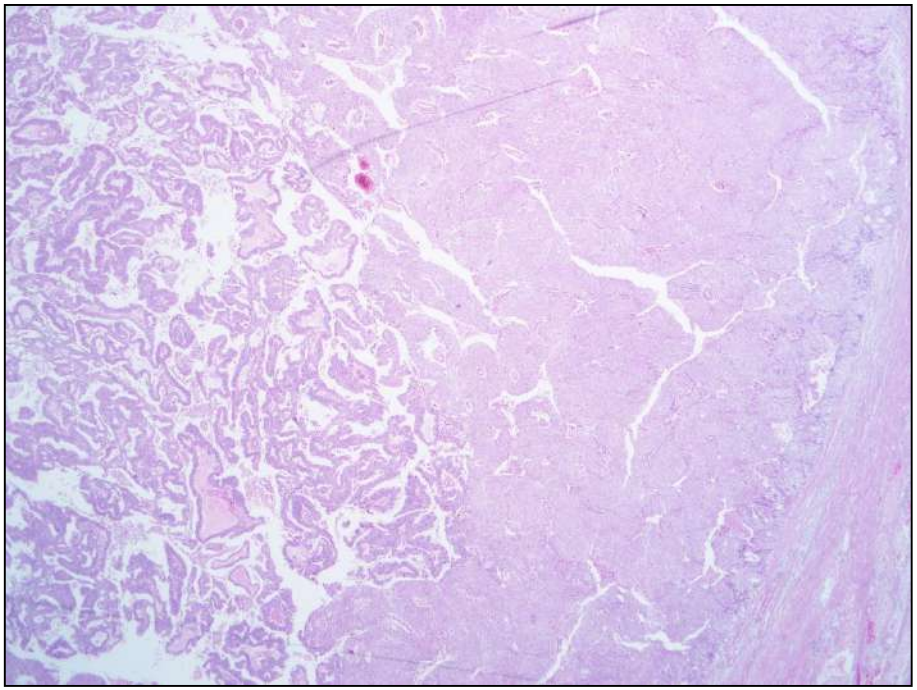


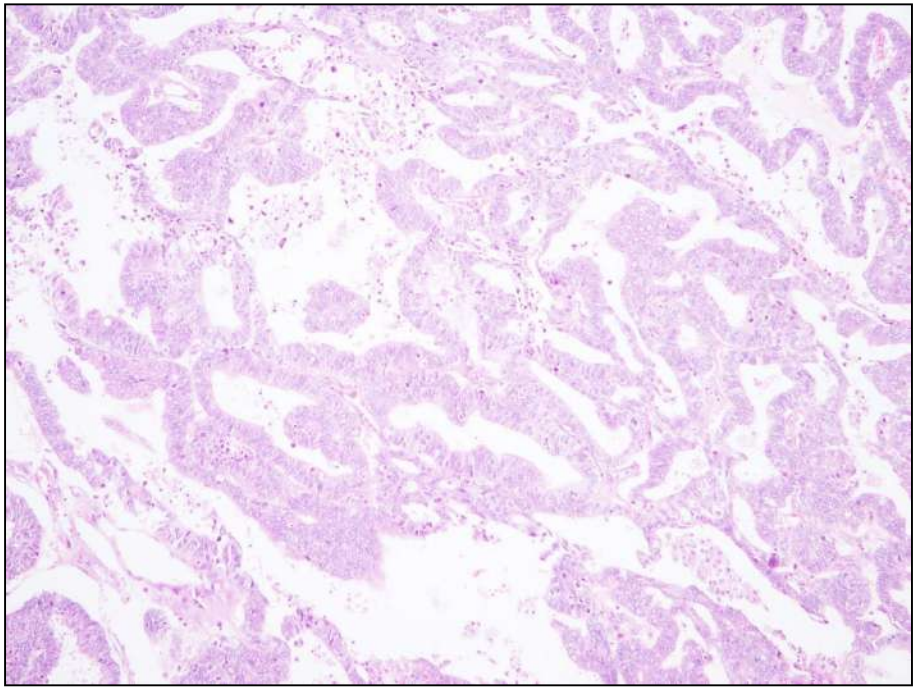


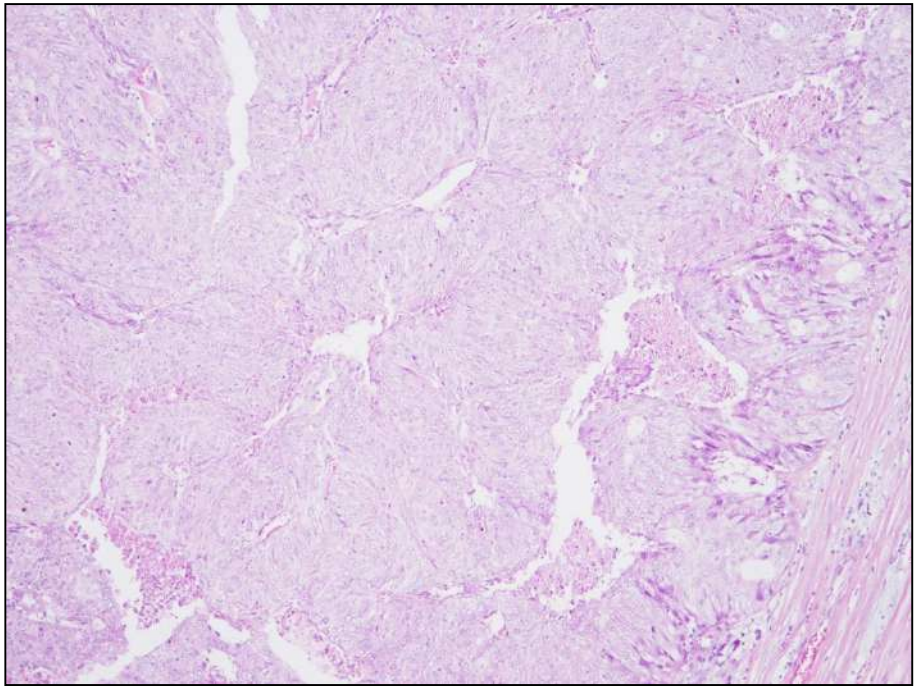


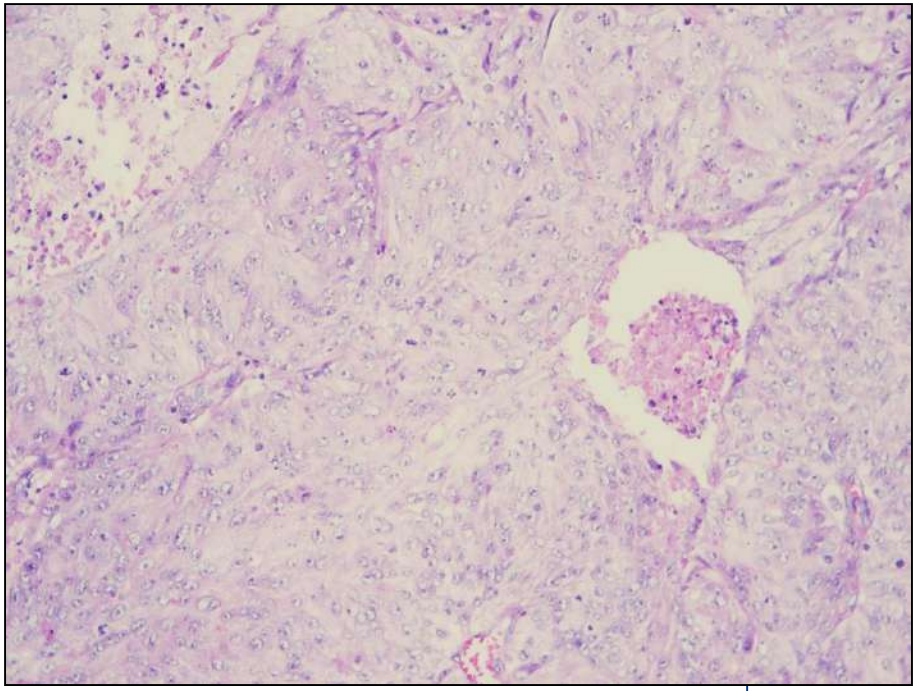


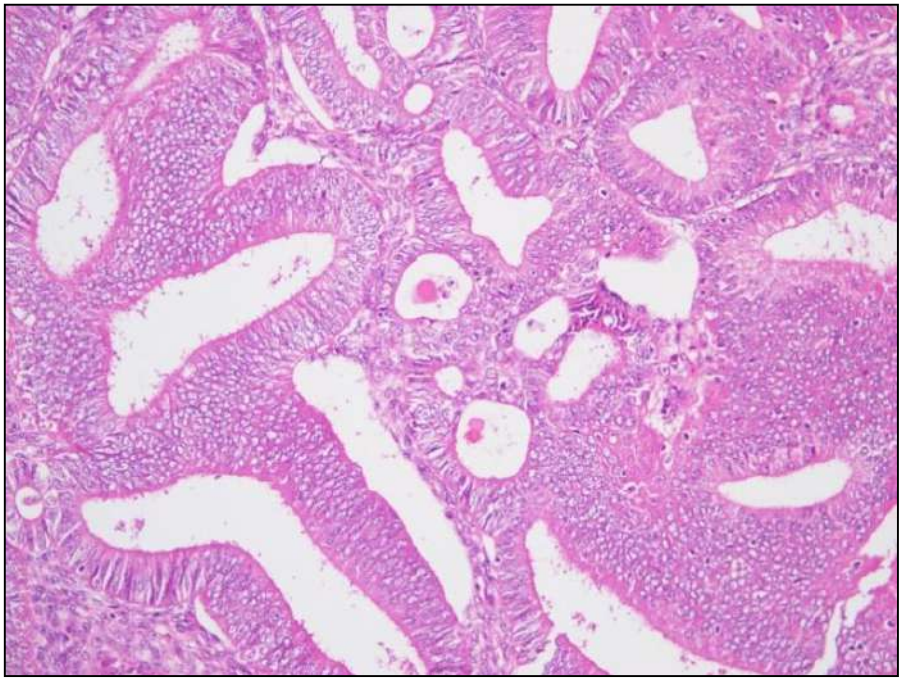


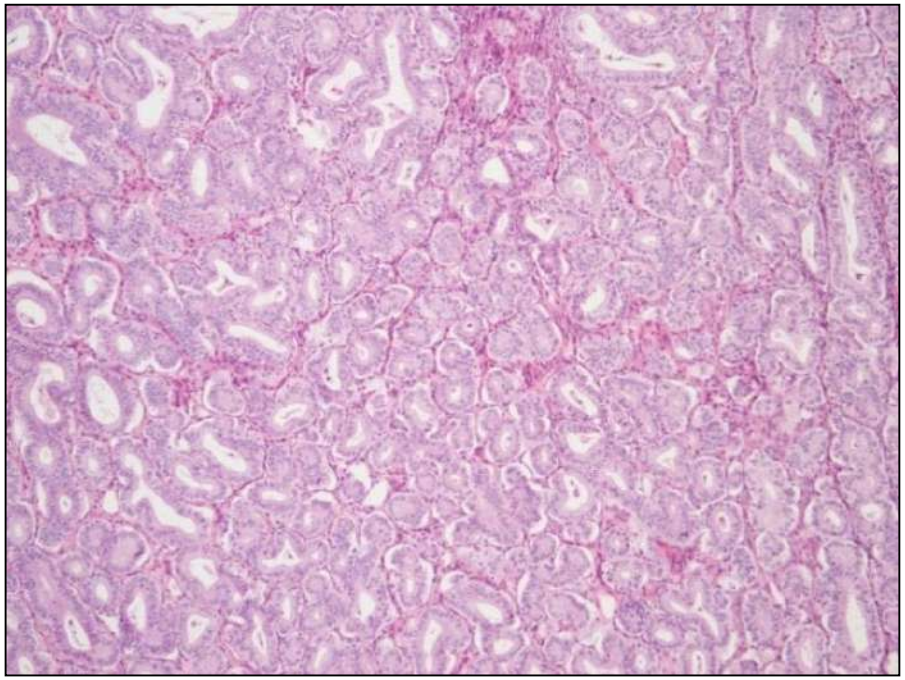


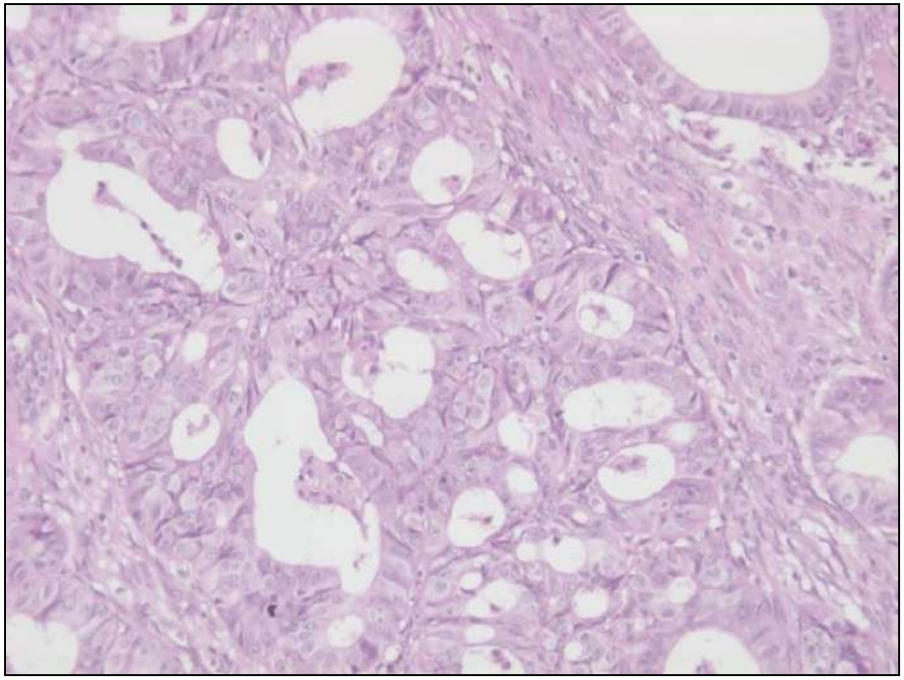




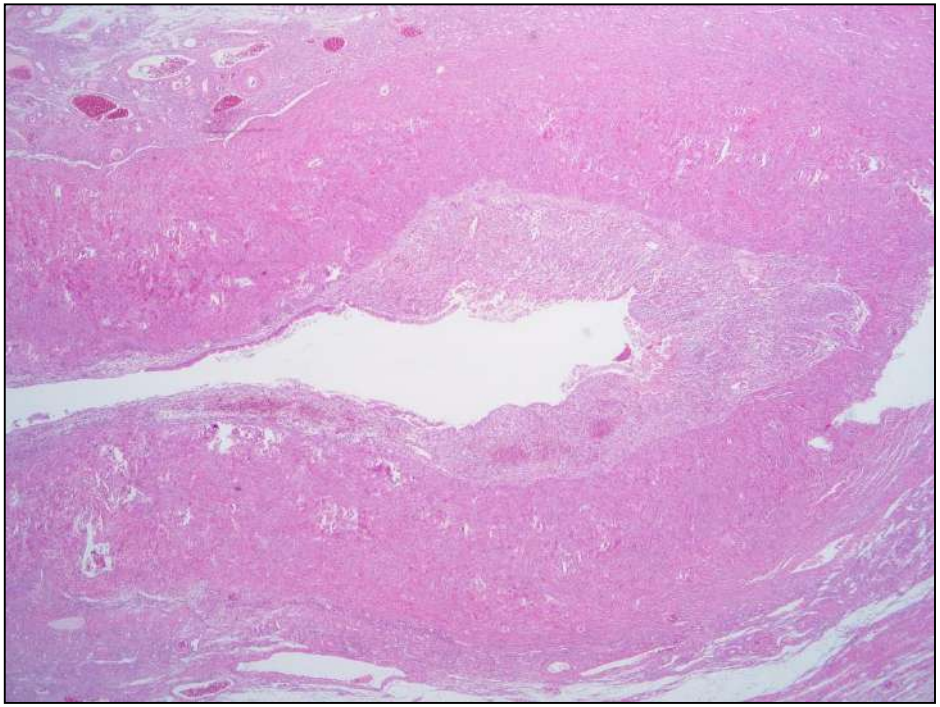


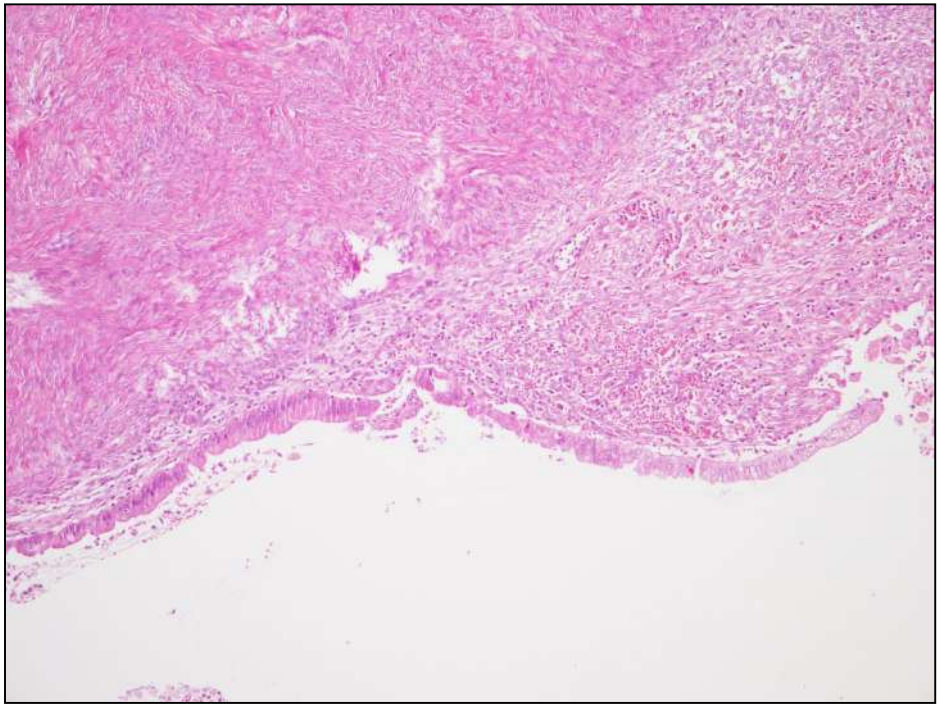


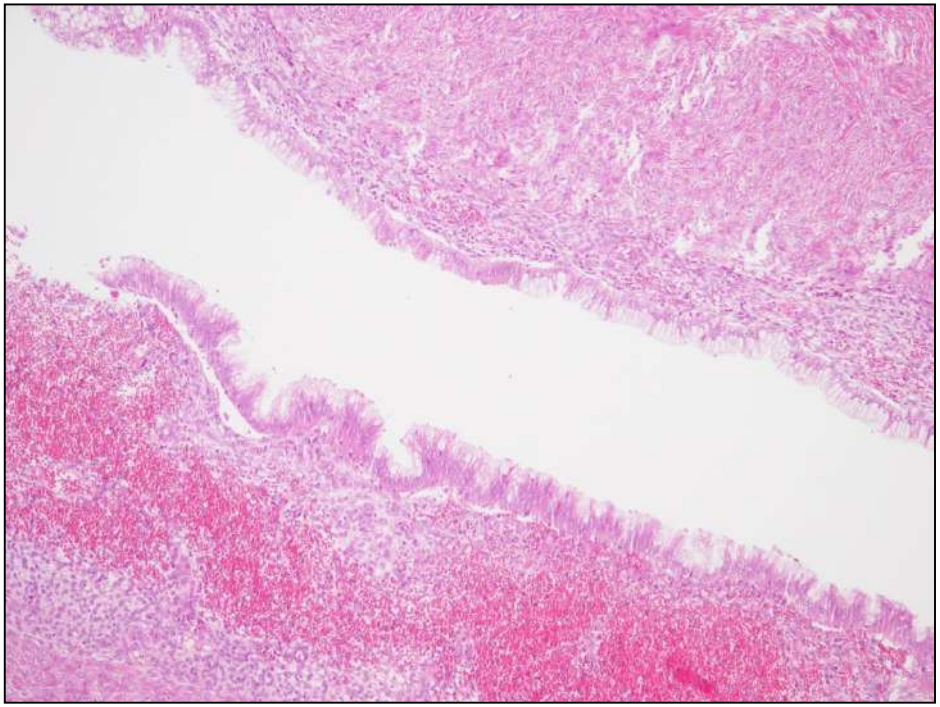


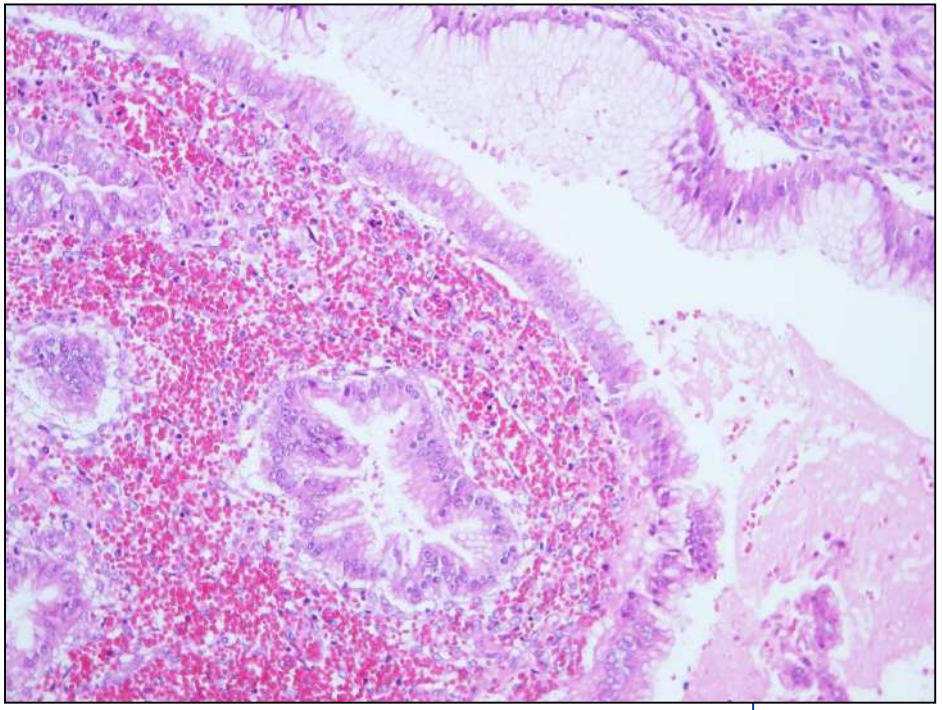


Oslo universitetssykehus



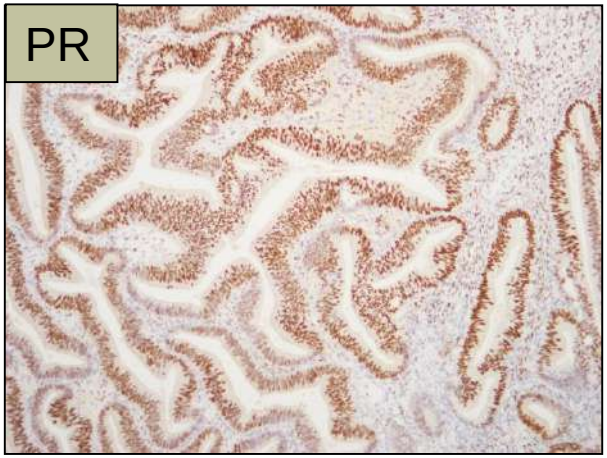


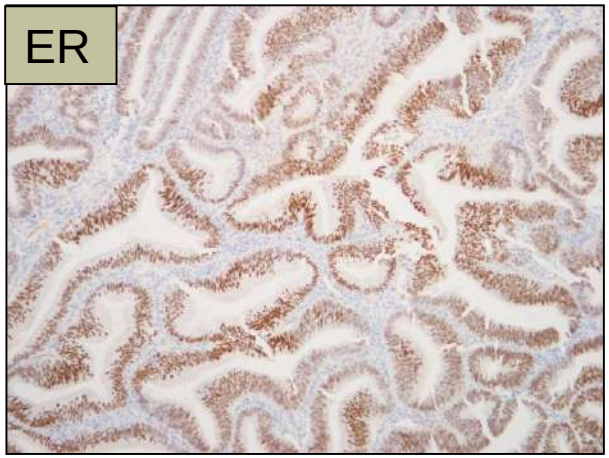


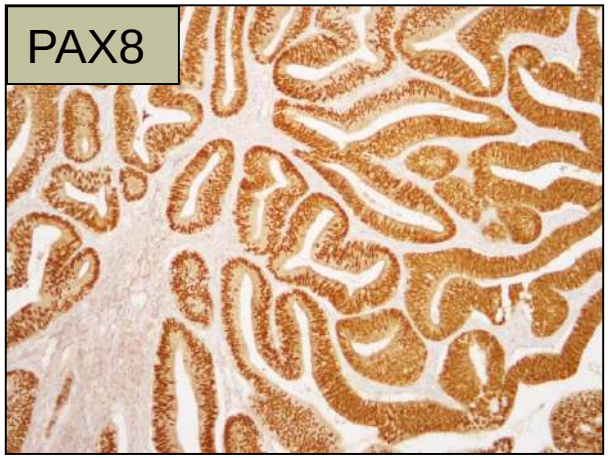


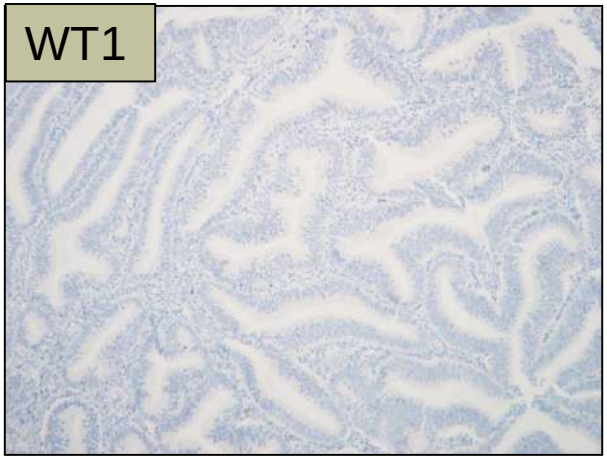
Differential diagnosis

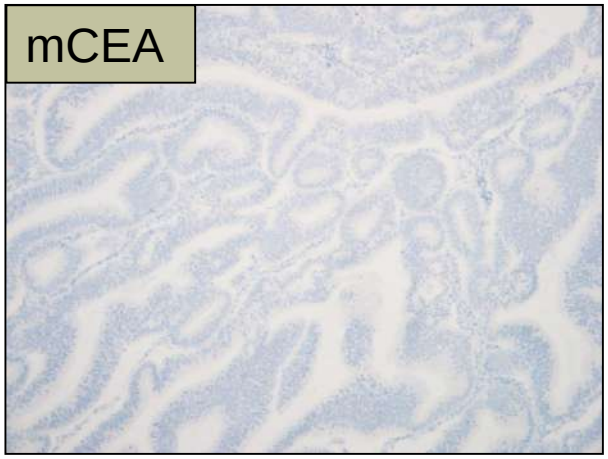
- Mucinous carcinoma (CEA, ER, PR, PAX8, PTEN, MMR proteins; CDX2)
- Adenocarcinoma metastasis (PAX8, SATB2; CK7, CK20, CEA, CDX2)
- Sertoli cell tumor (PAX8, EMA, Inhibin, SF1, FOXL2, calretinin, Melan A)
- Yolk sac tumor (EMA, CK7, PAX8, AFP, SALL4, OCT3/4;
- Glypican 3)

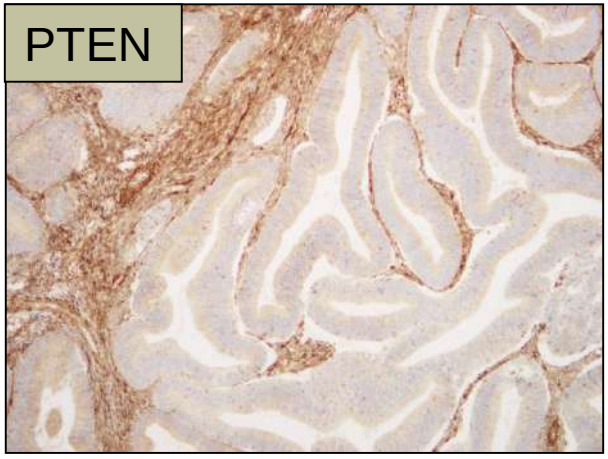




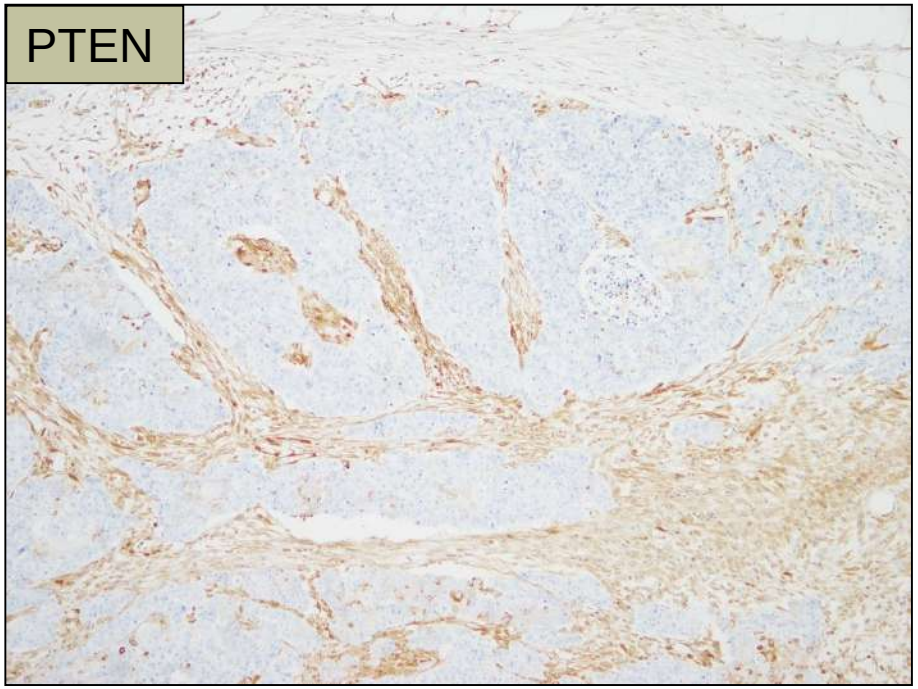


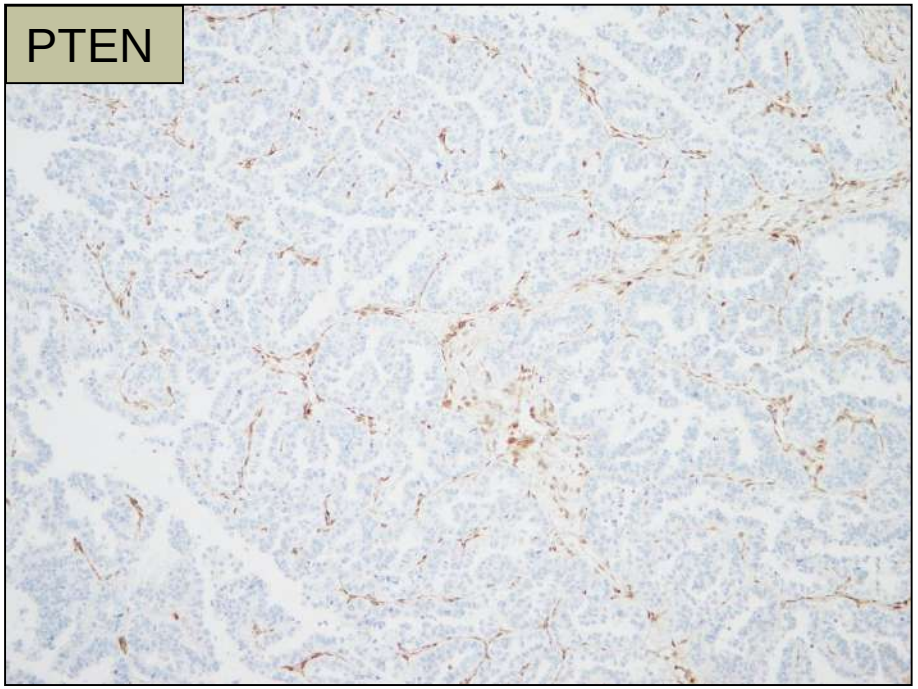


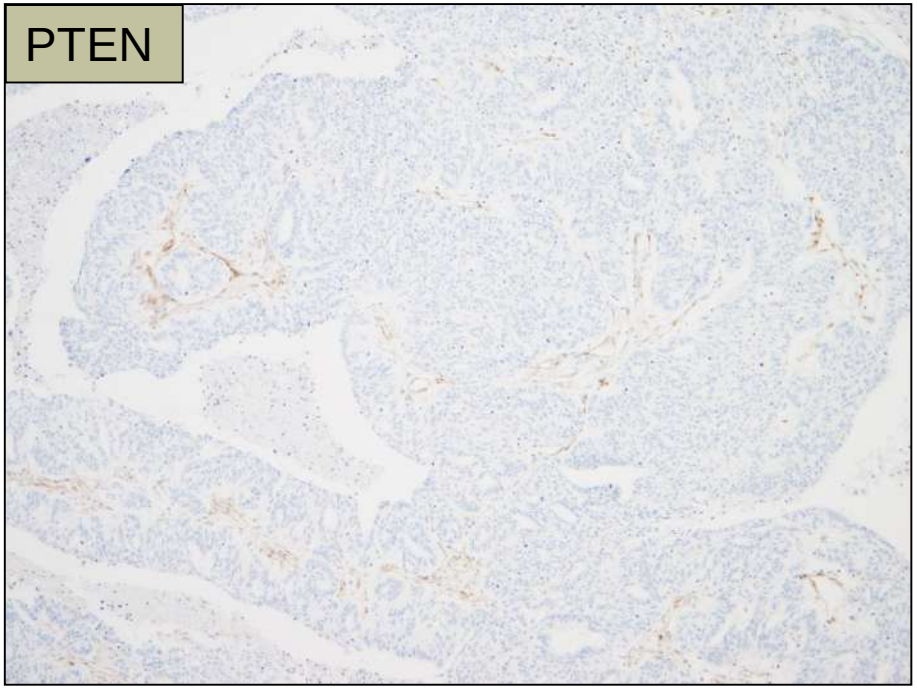


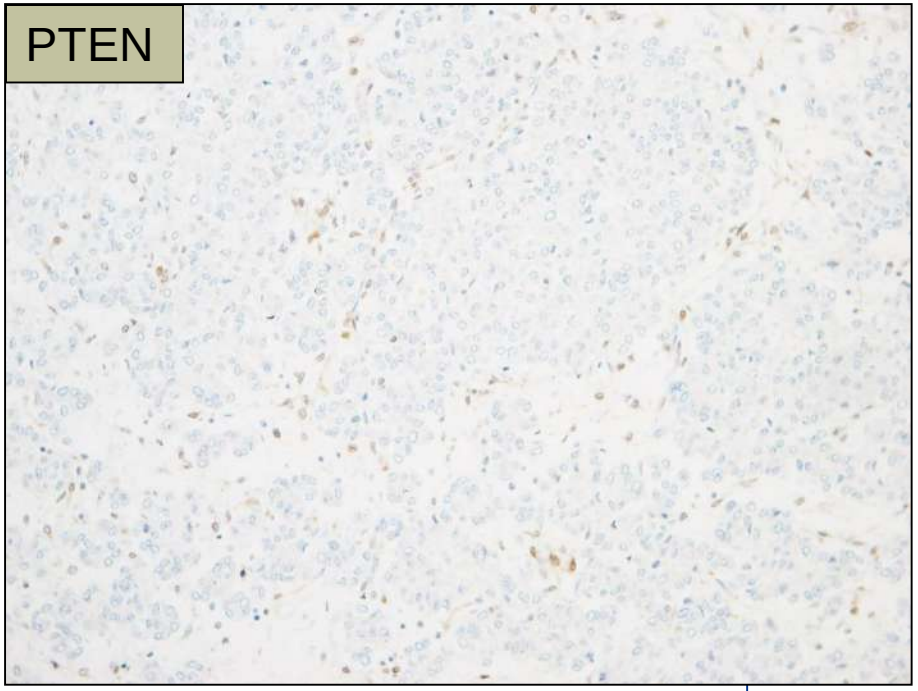


Oslo universitetssykehus

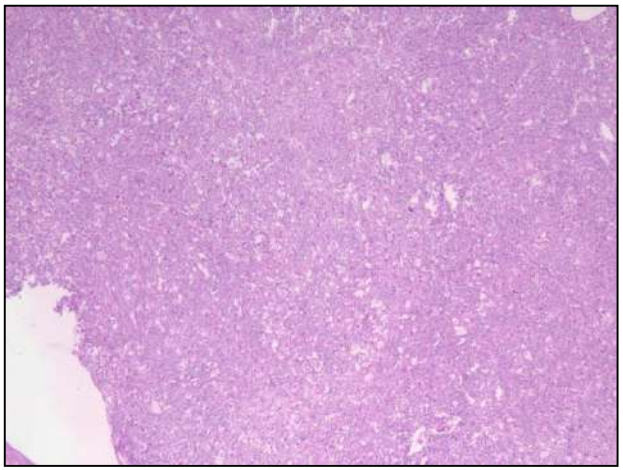

PTEN

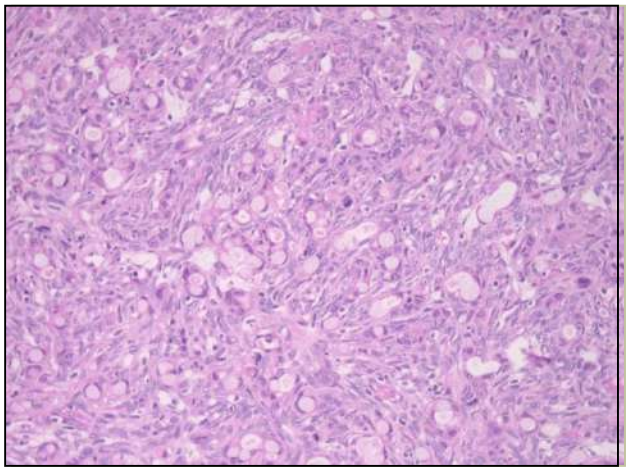

PTEN

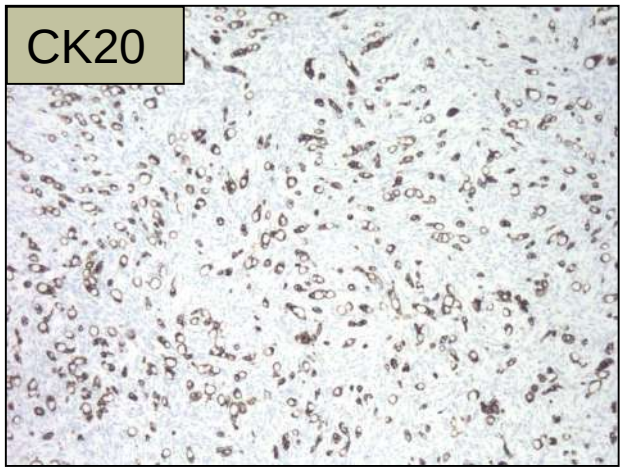

PTEN

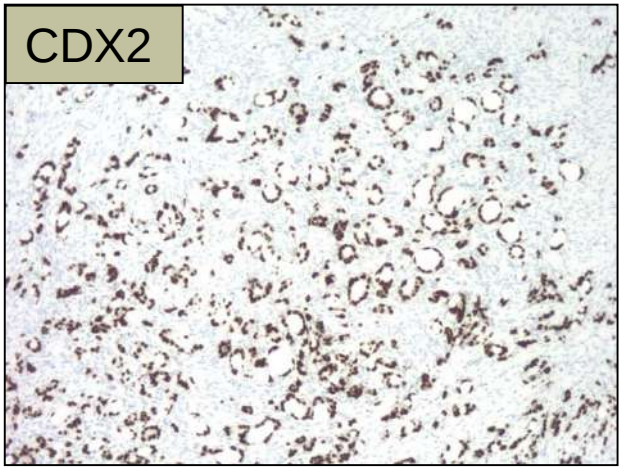

PTEN

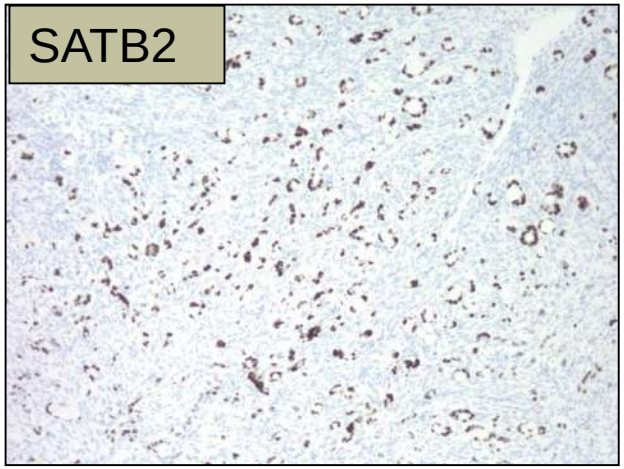
Colon carcinoma metastasis

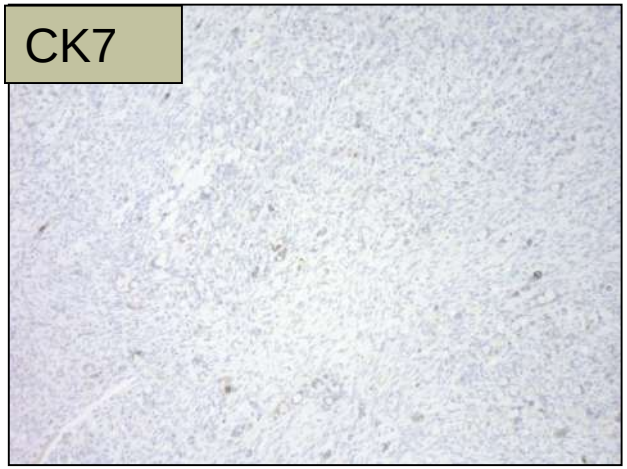






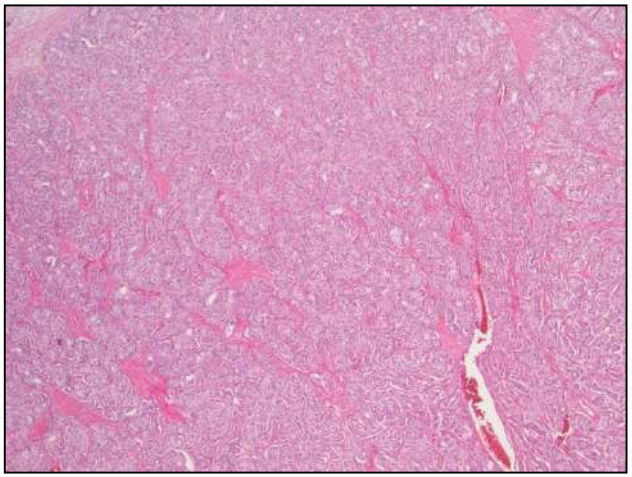
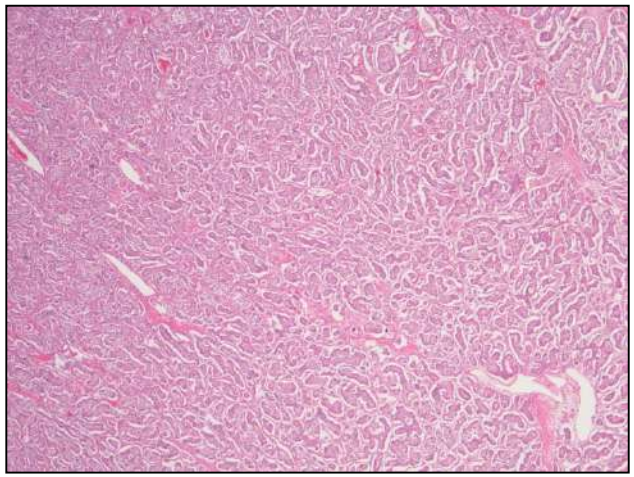
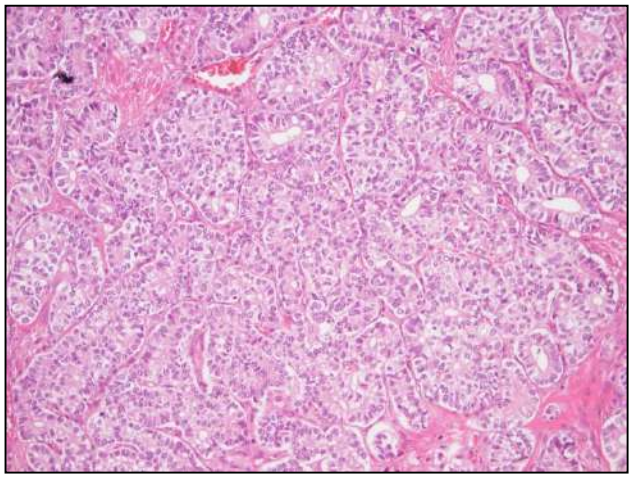
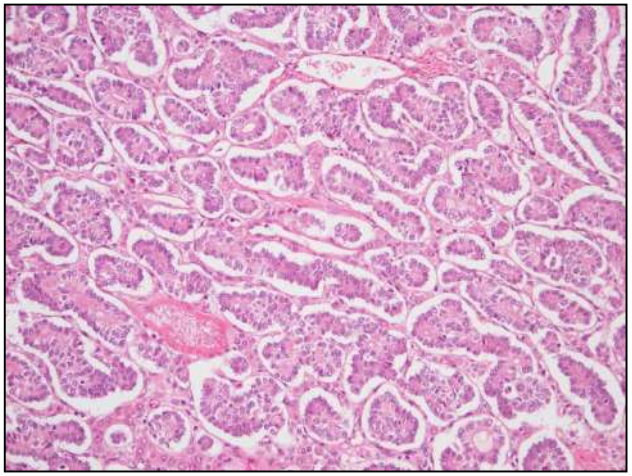
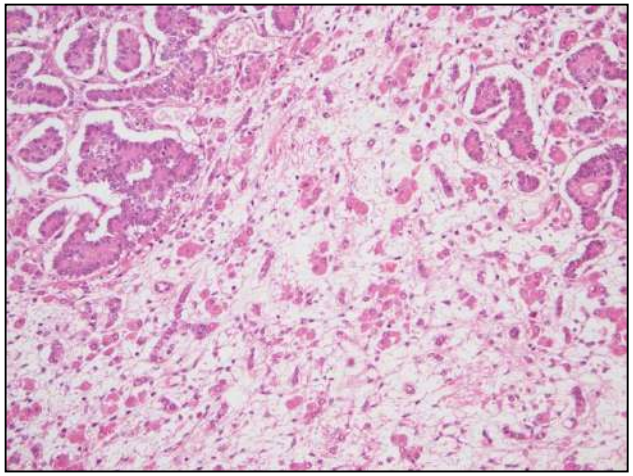




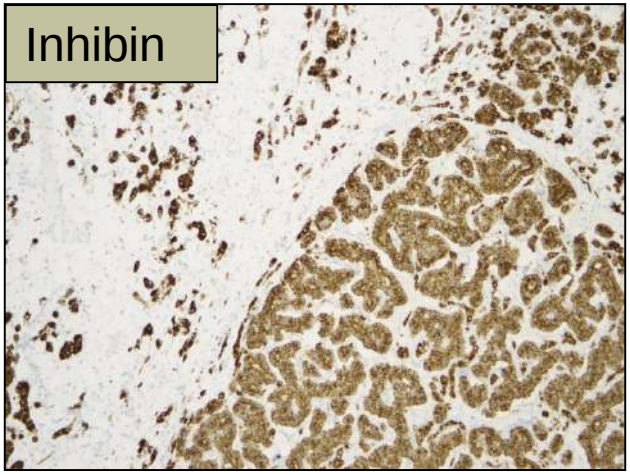


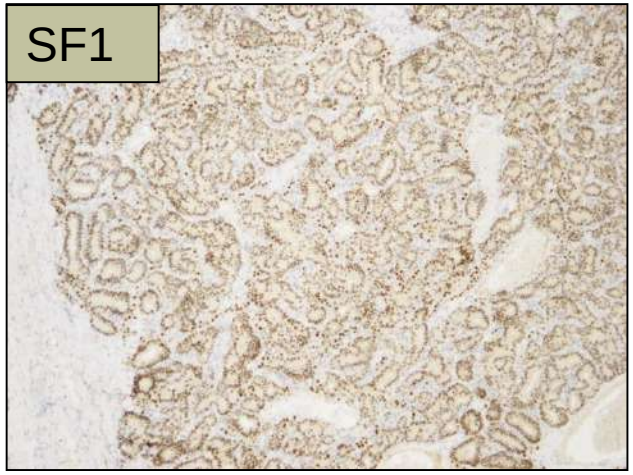
Oslo universitetssykehus

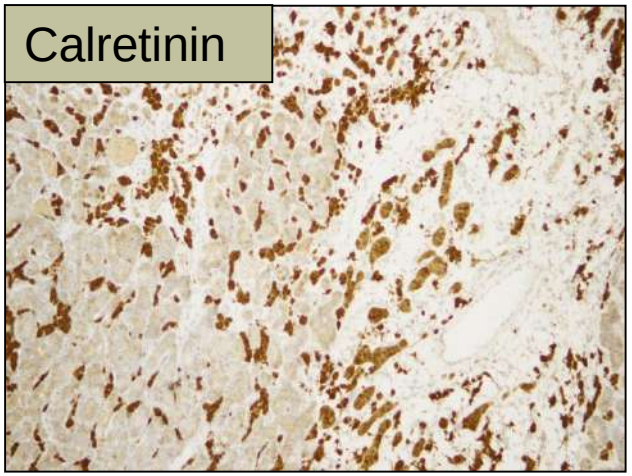
Sertoli-Leydig cell tumor

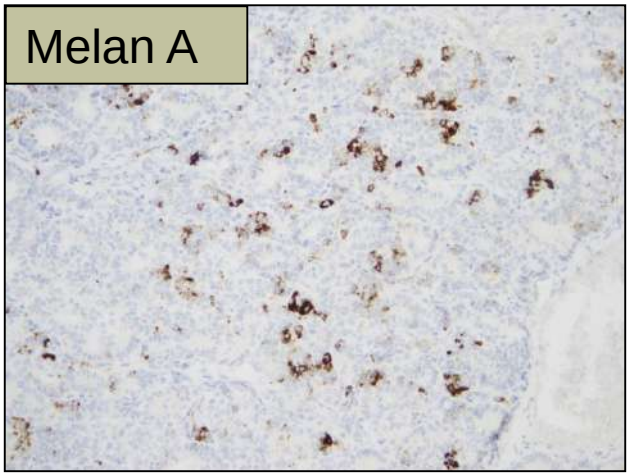






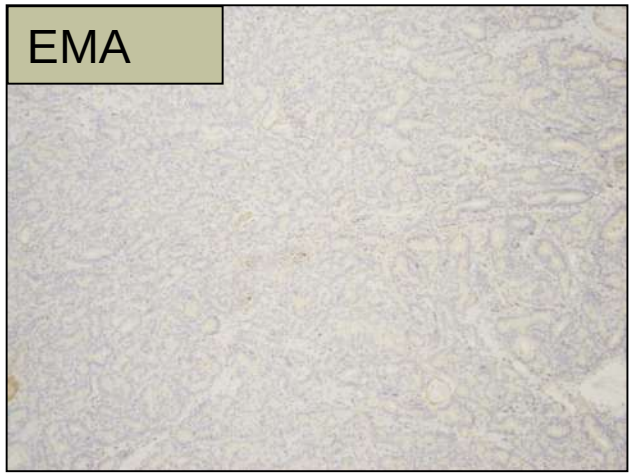
Oslo universitetssykehus


Inhibin


SF1


Calretinin


Melan A

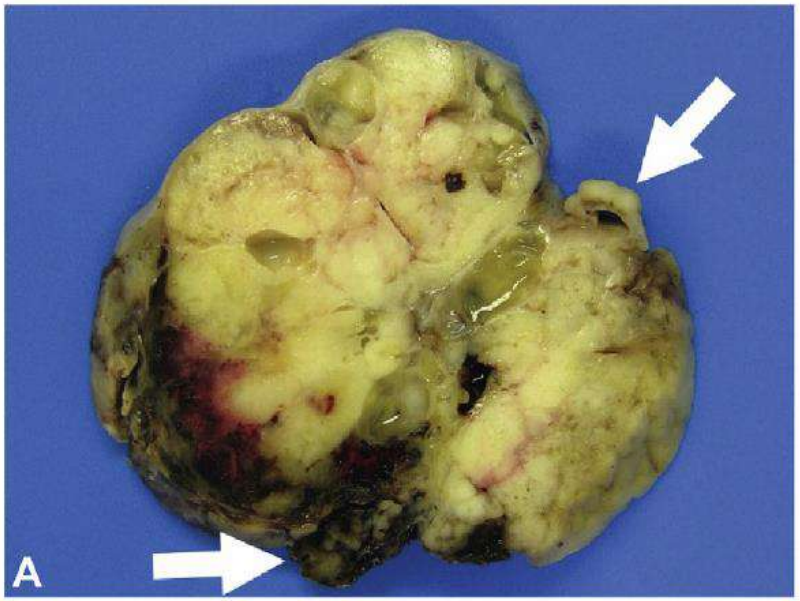

EMA

Endometriosis-associated tumors

- Endometrioid carcinoma (EC)
- Clear cell carcinoma (CCC)
- Seromucinous tumors
- Low-grade serous carcinoma (LGSC)
- Carcinosarcoma
- Adenosarcoma
- Endometrial stromal sarcoma (ESS)

Clear cell carcinoma

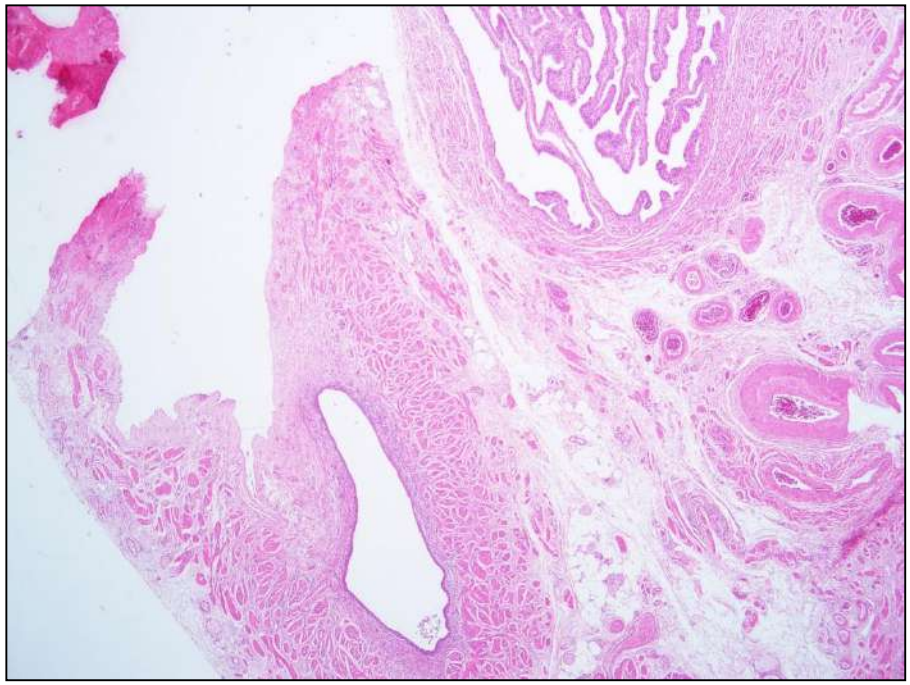
- 10% of ovarian carcinomas in Western countries (25% in Japan)
- 20-40% with endometriosis
- Hypercalcemia or thromboembolism may be present
- Majority unilateral
- Majority diagnosed at FIGO stage I
- Generally good prognosis when confined to the ovary, poor with extra-ovarian disease

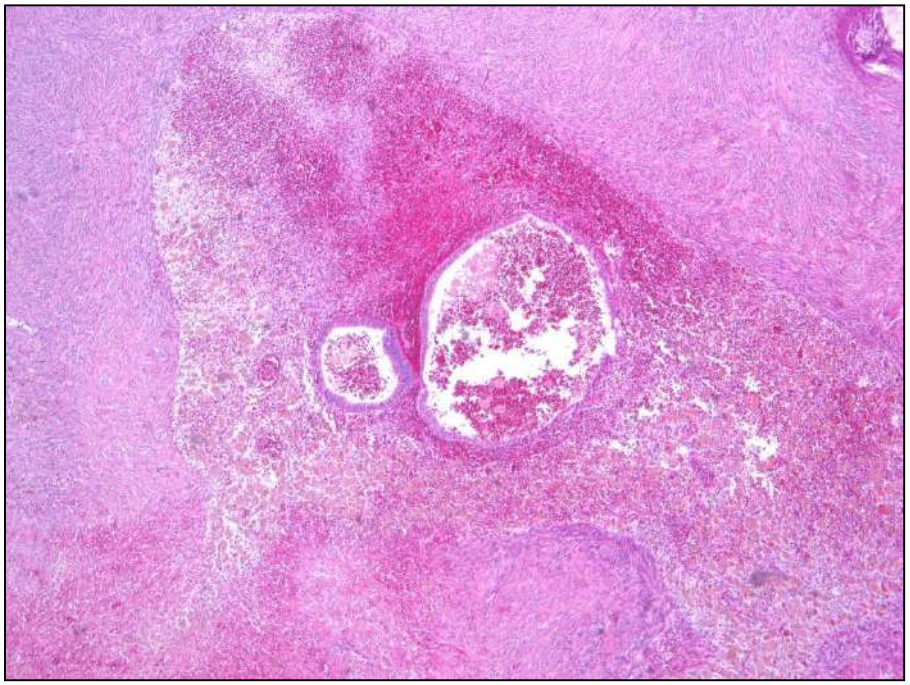


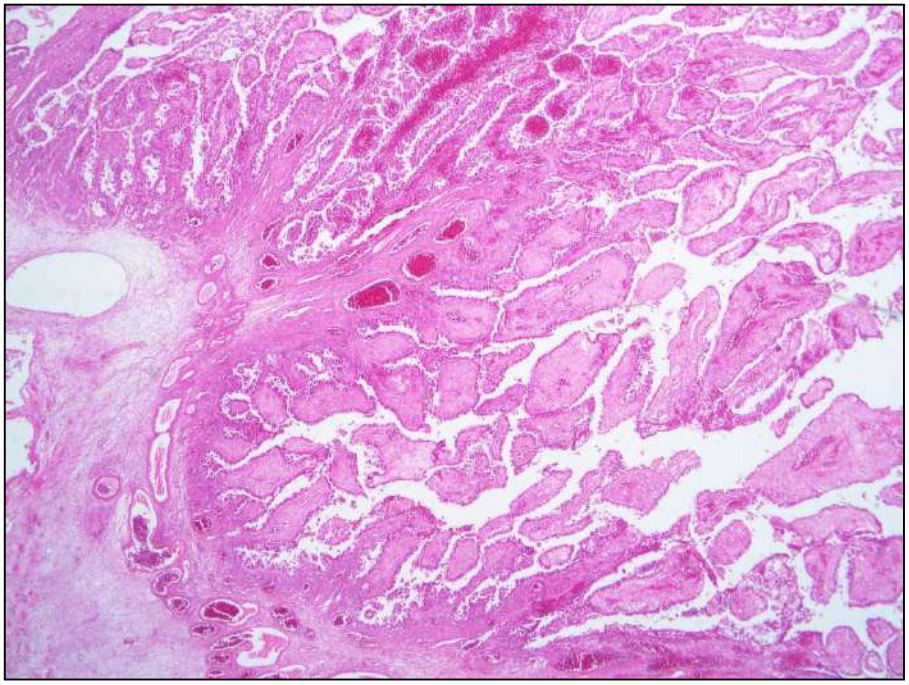


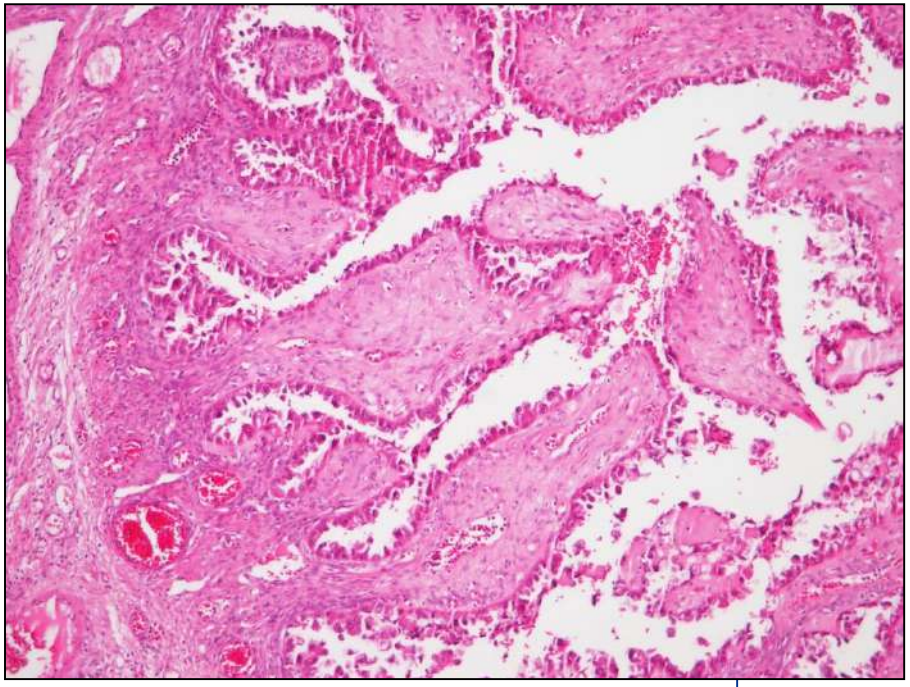
Matias-Guiu and Stewart, Pathology 2018;50:190-204

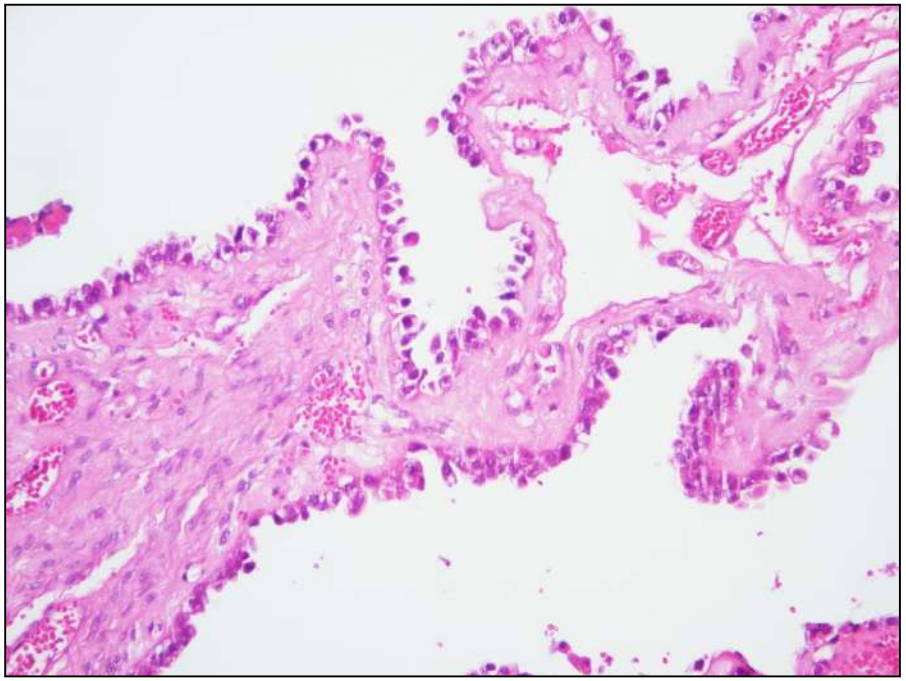
Oslo universitetssykehus

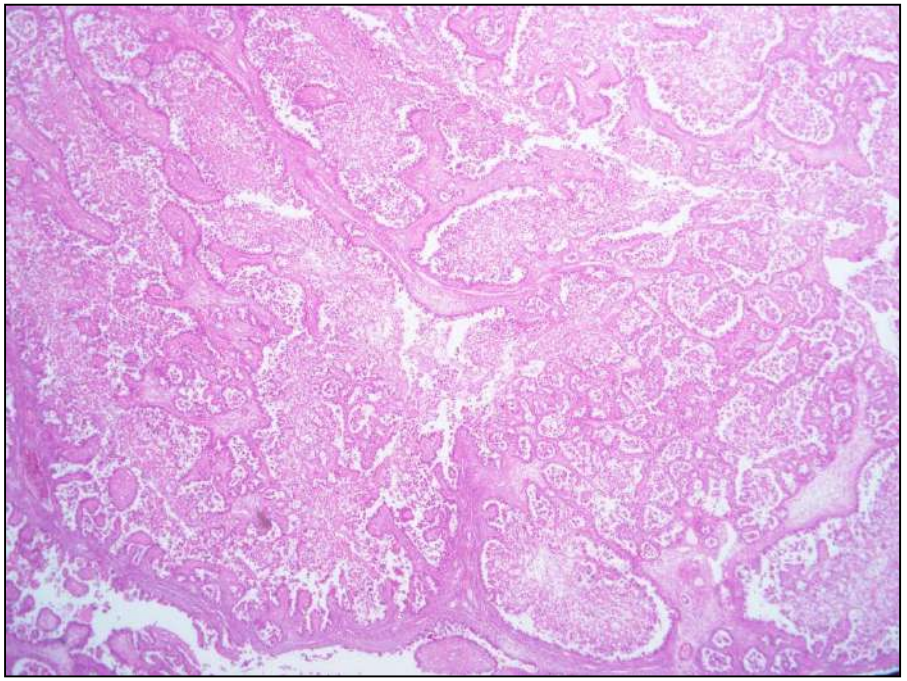


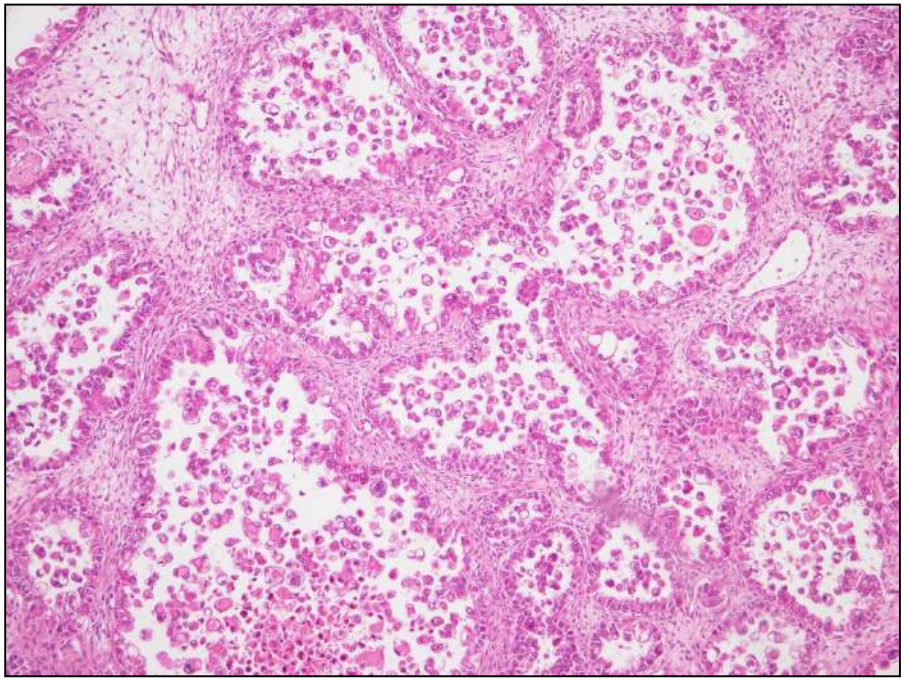


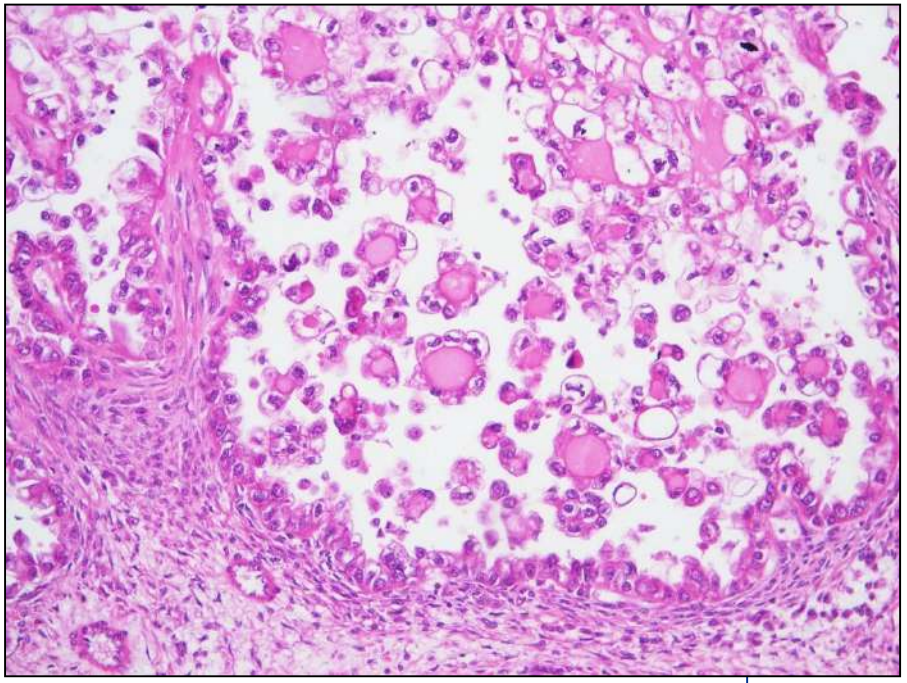


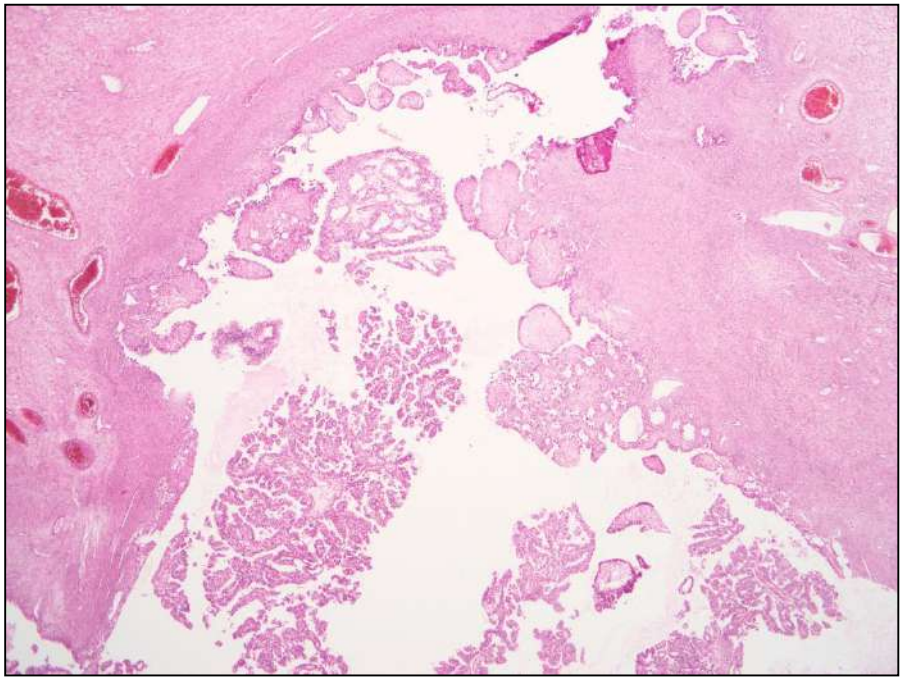


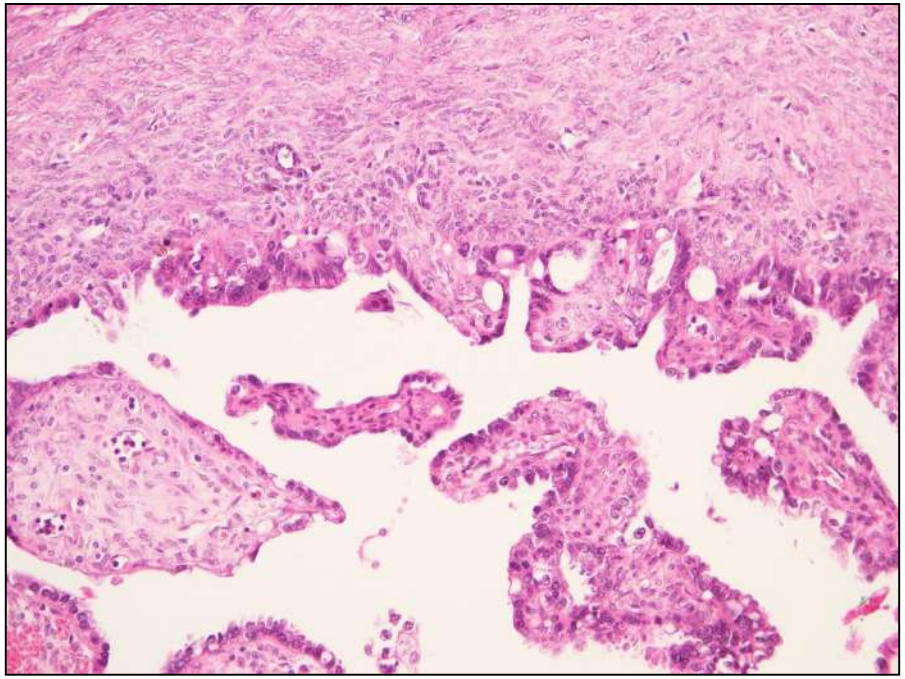


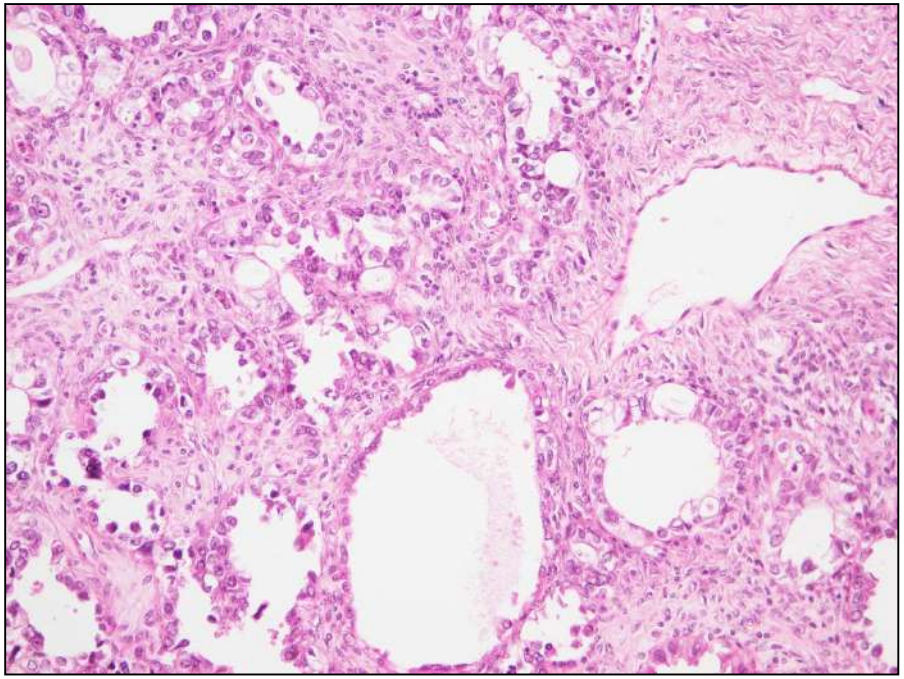


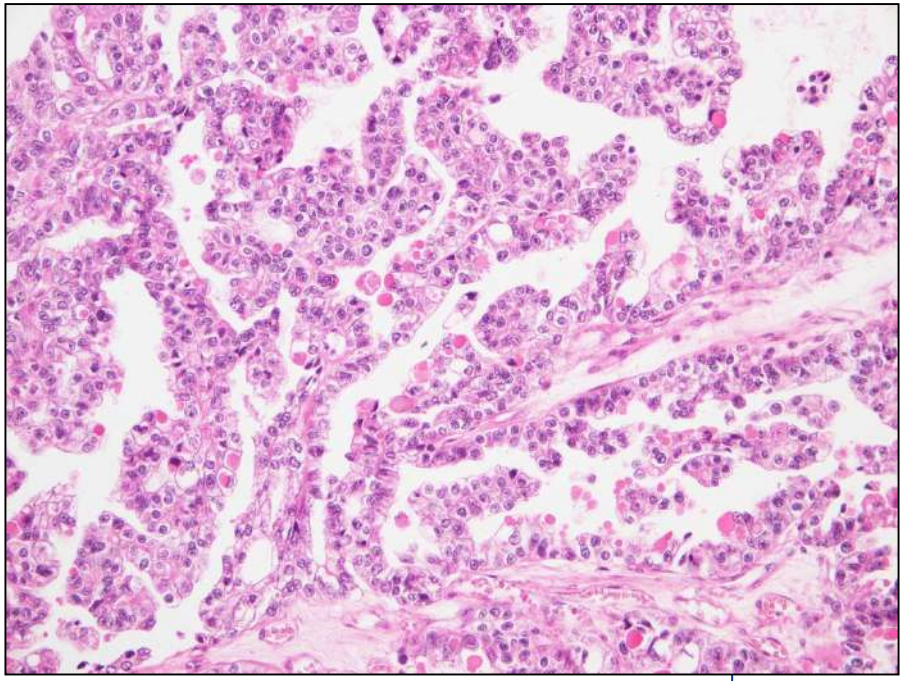


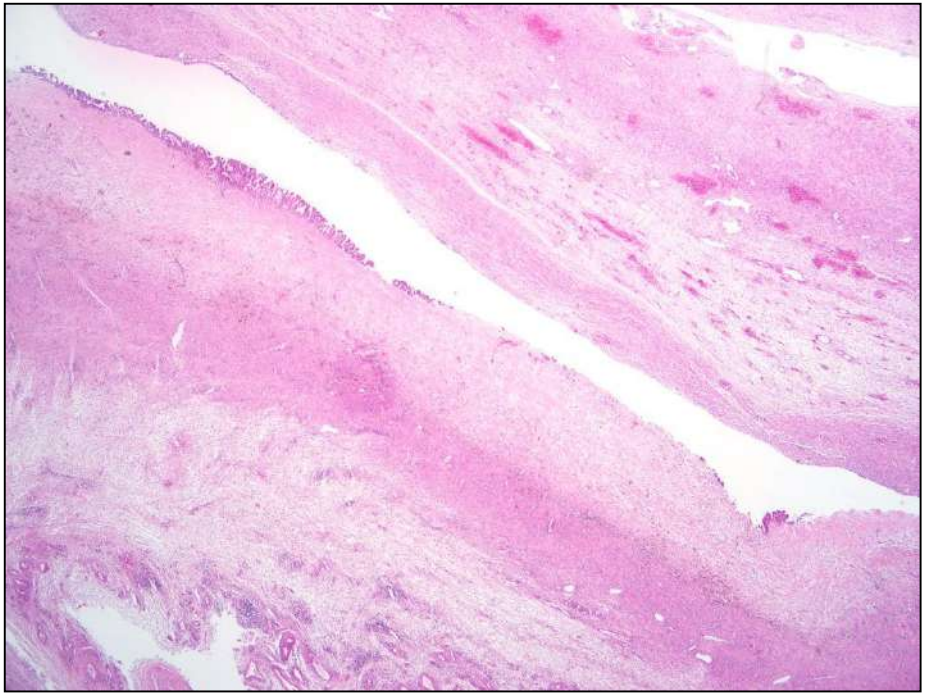


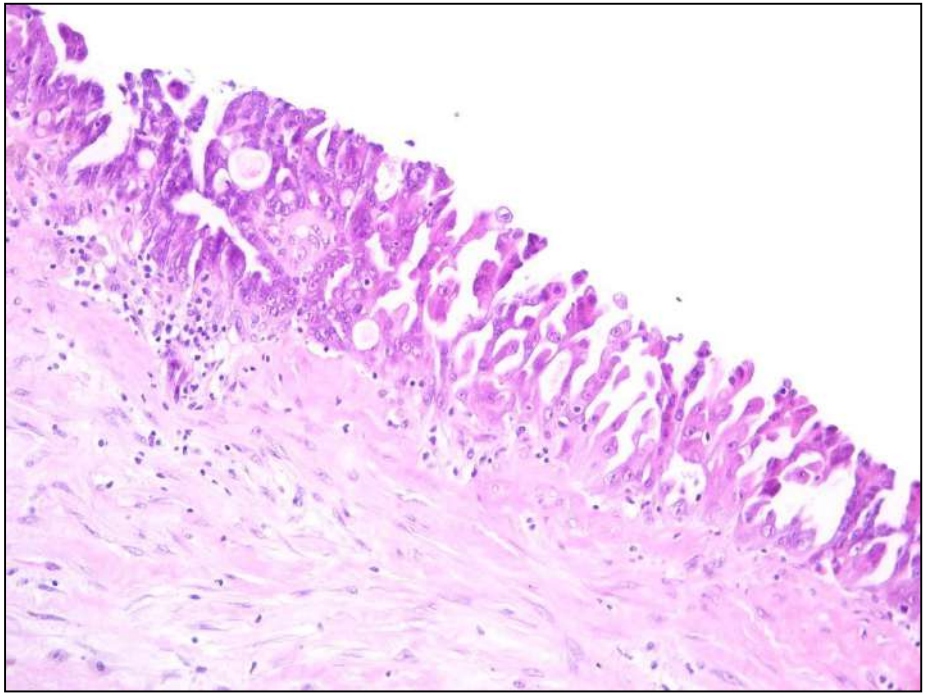




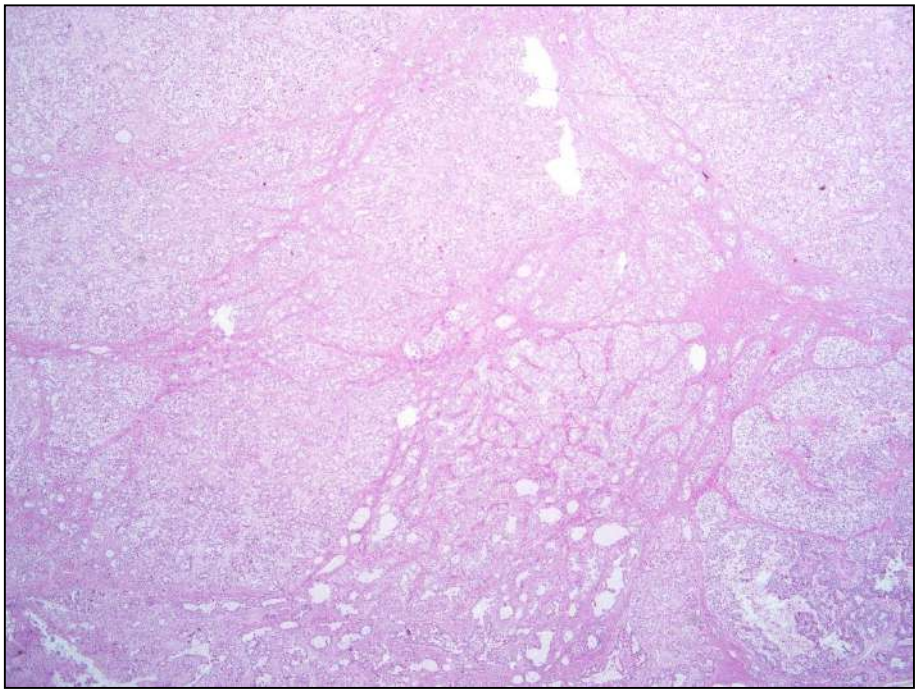


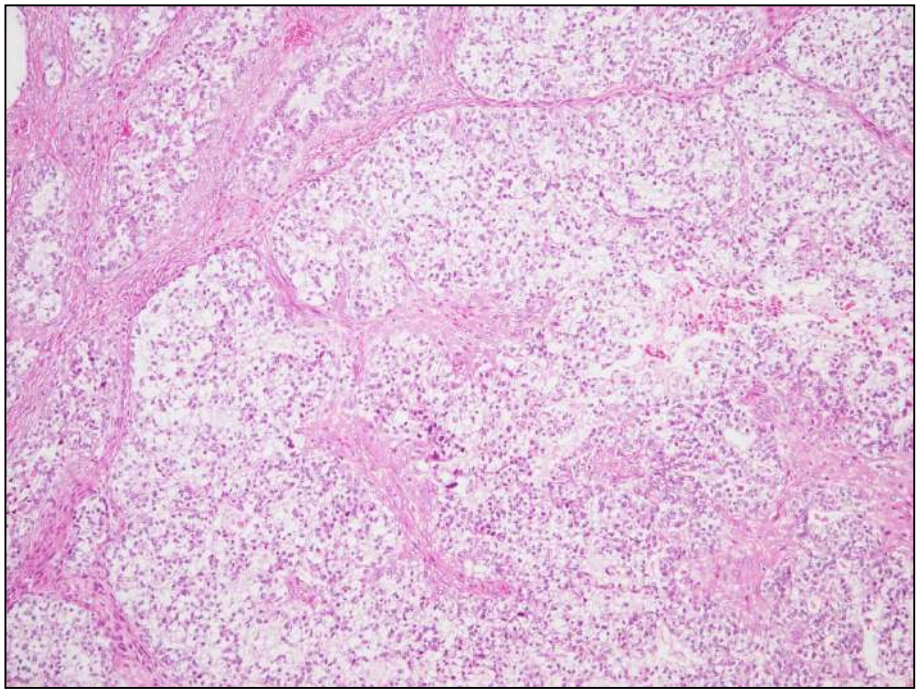


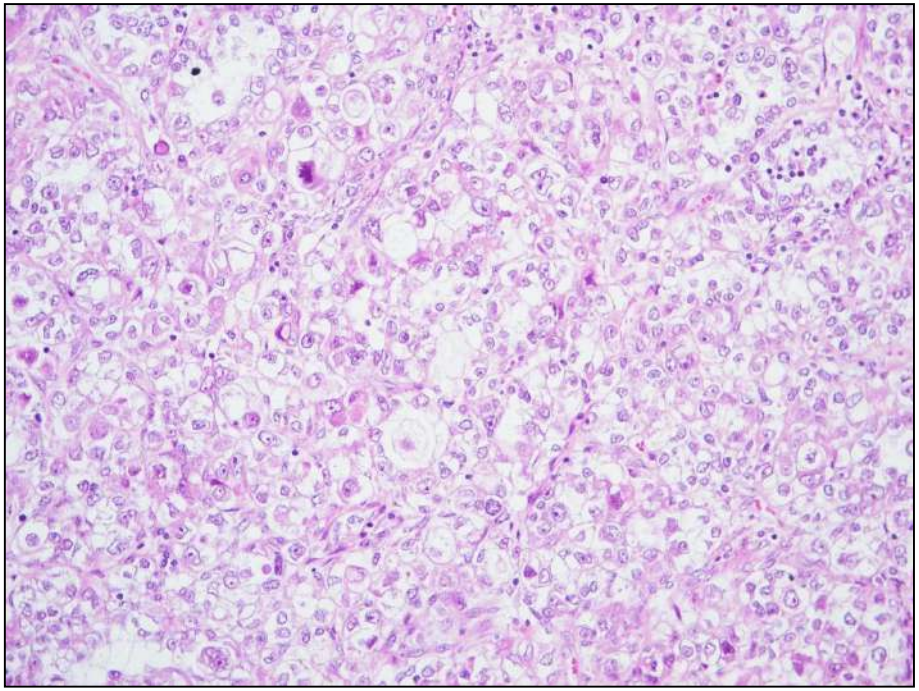


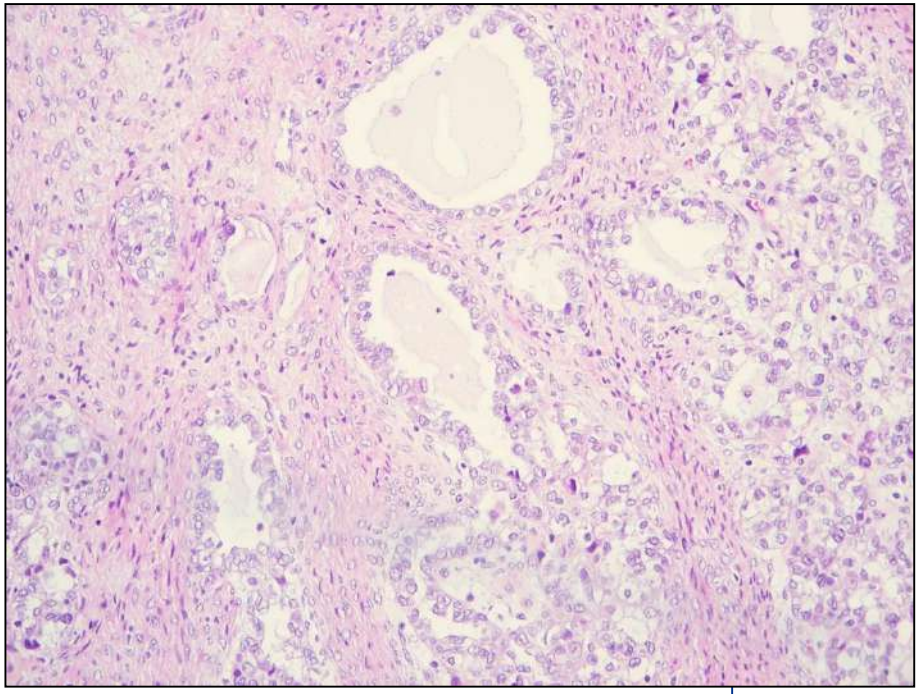


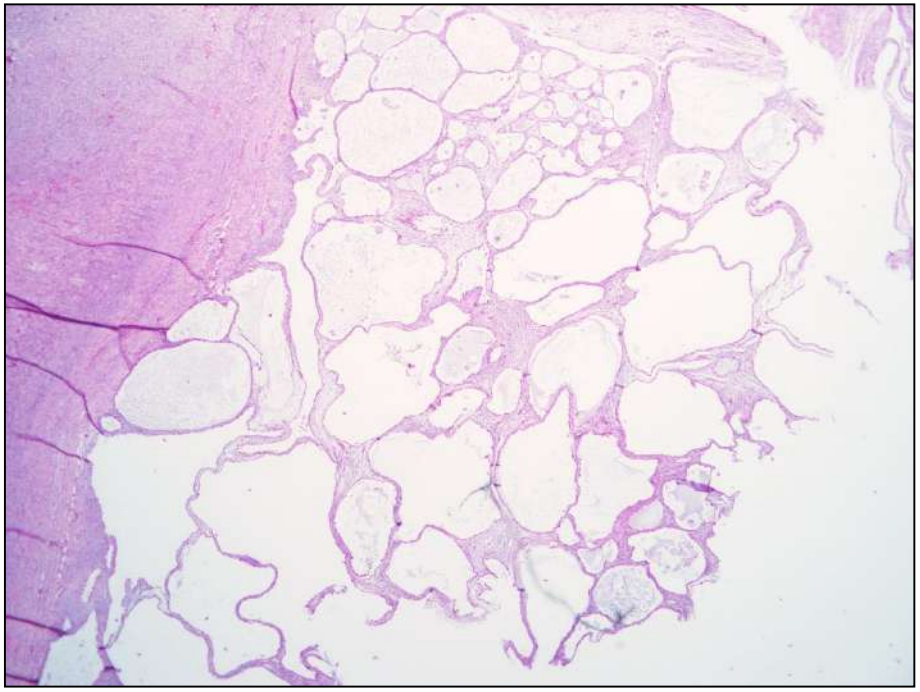
Oslo universitetssykehus

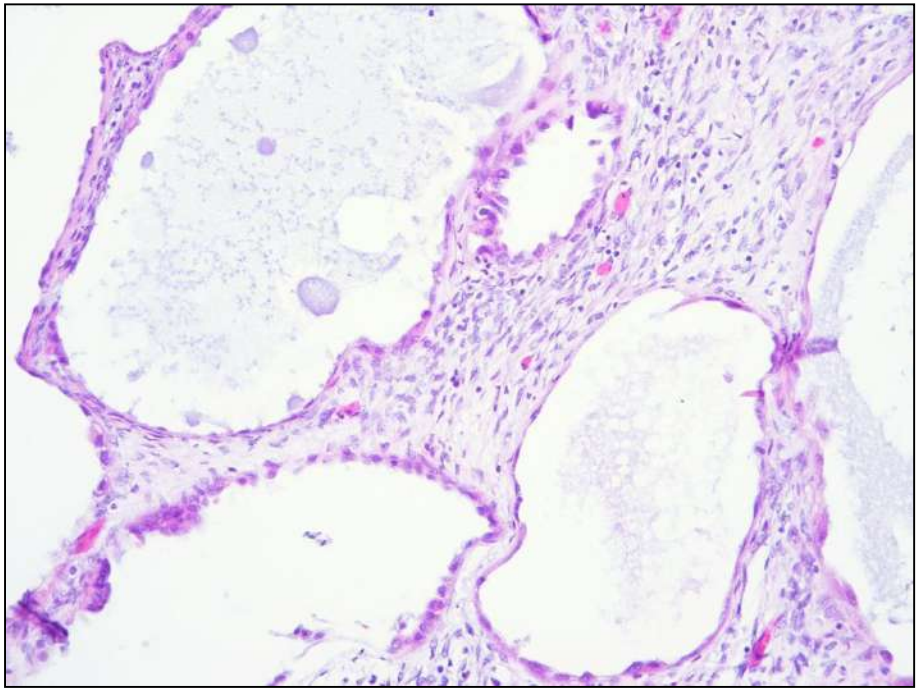


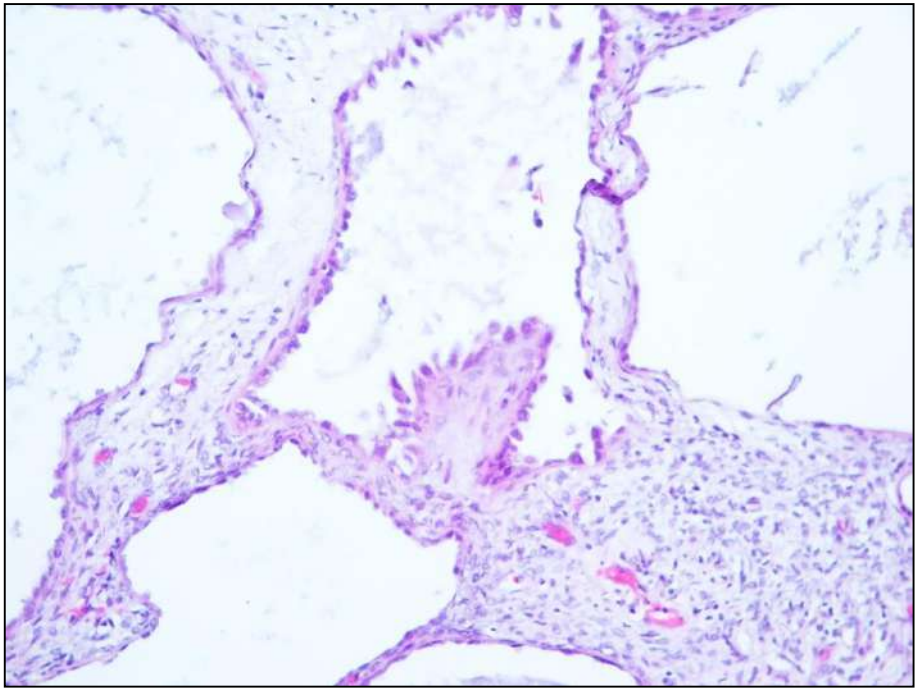


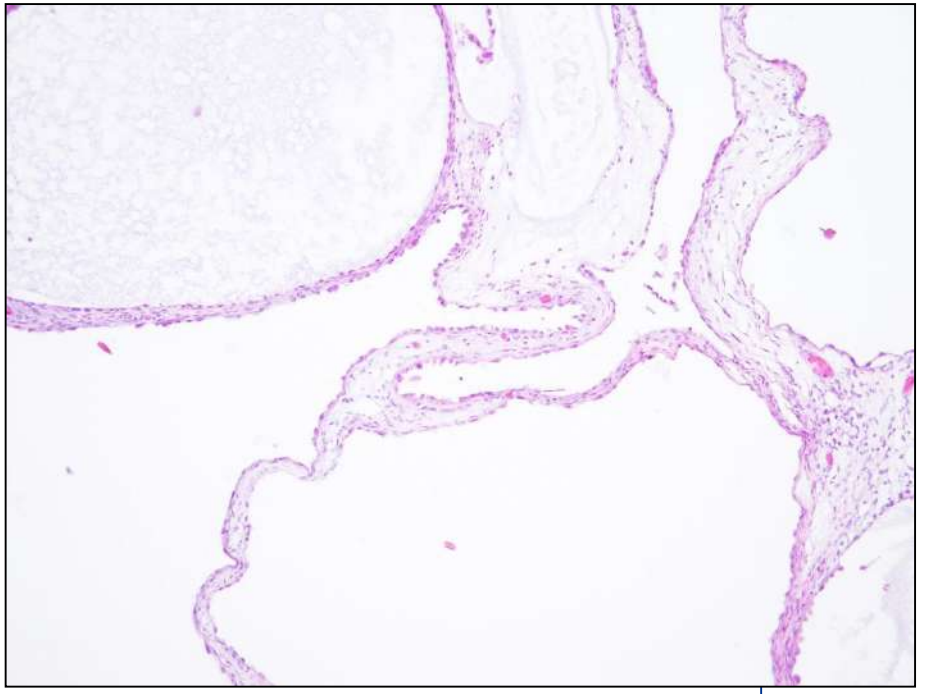


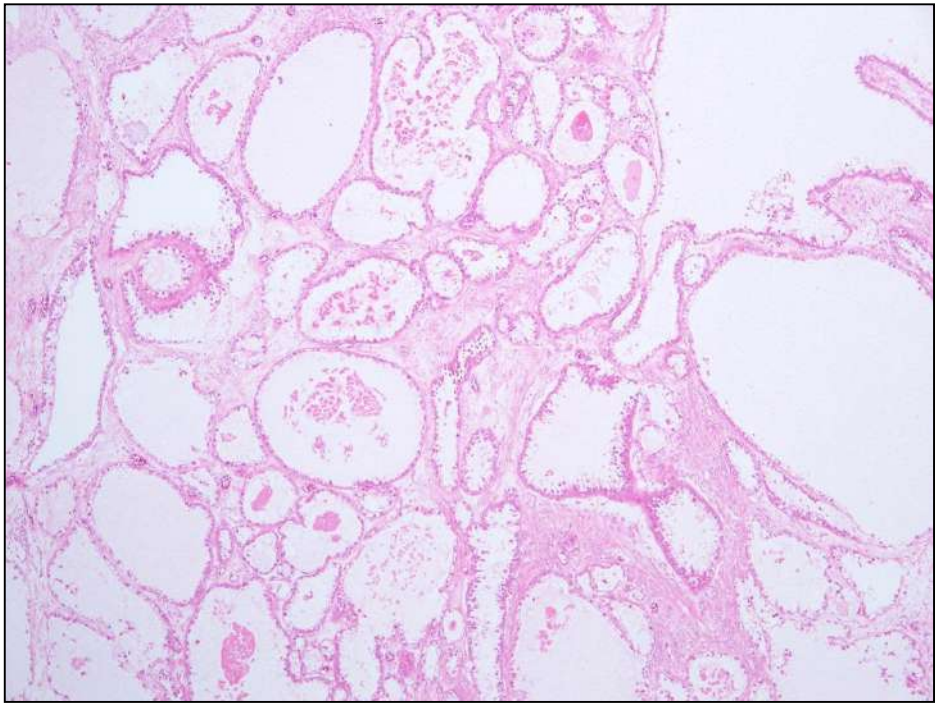


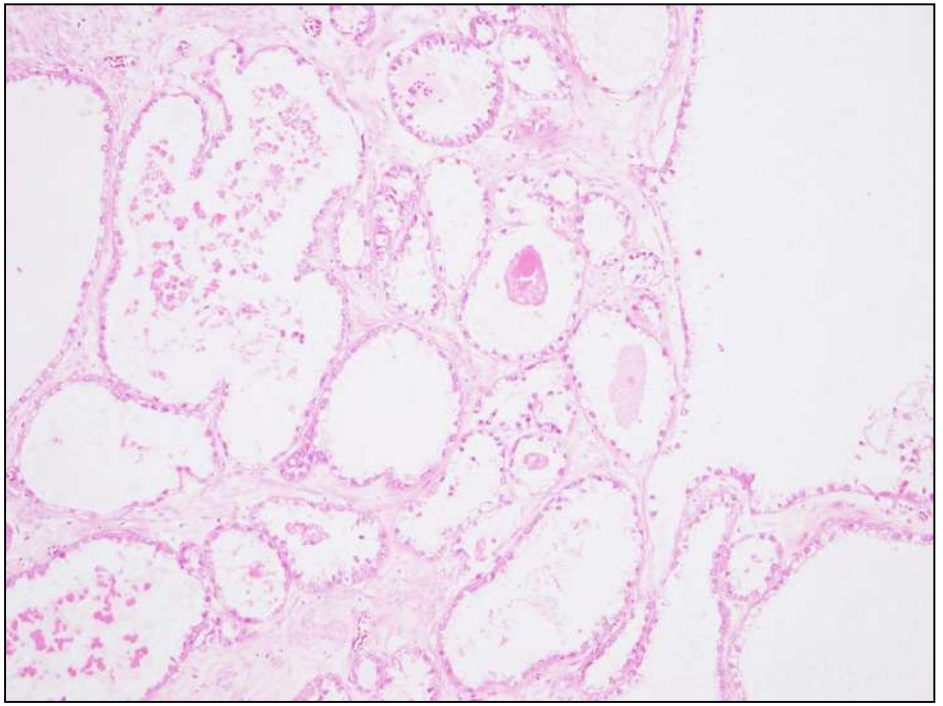


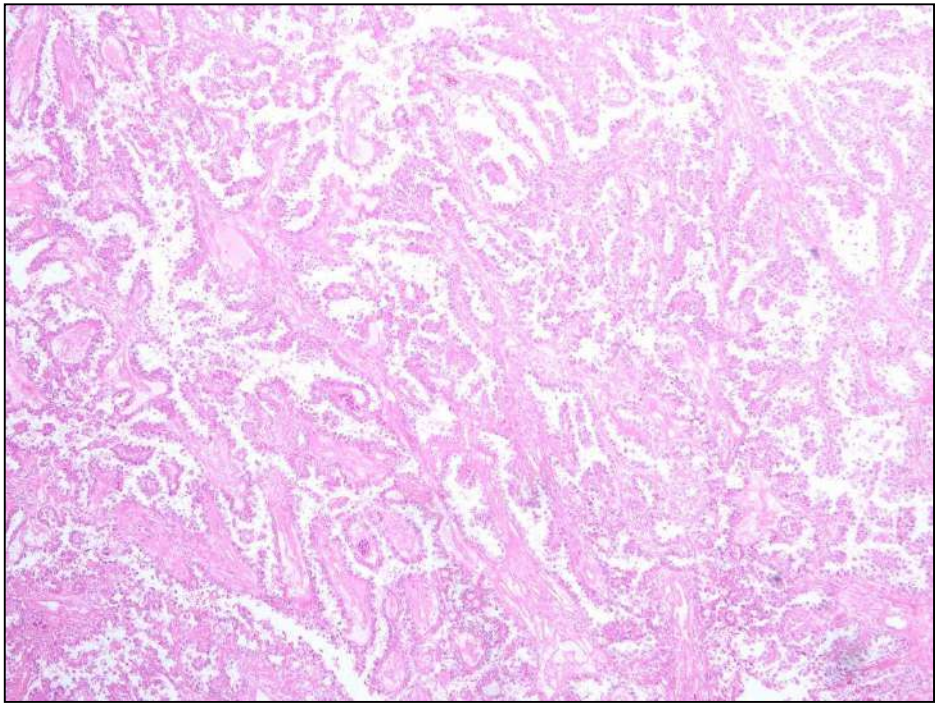


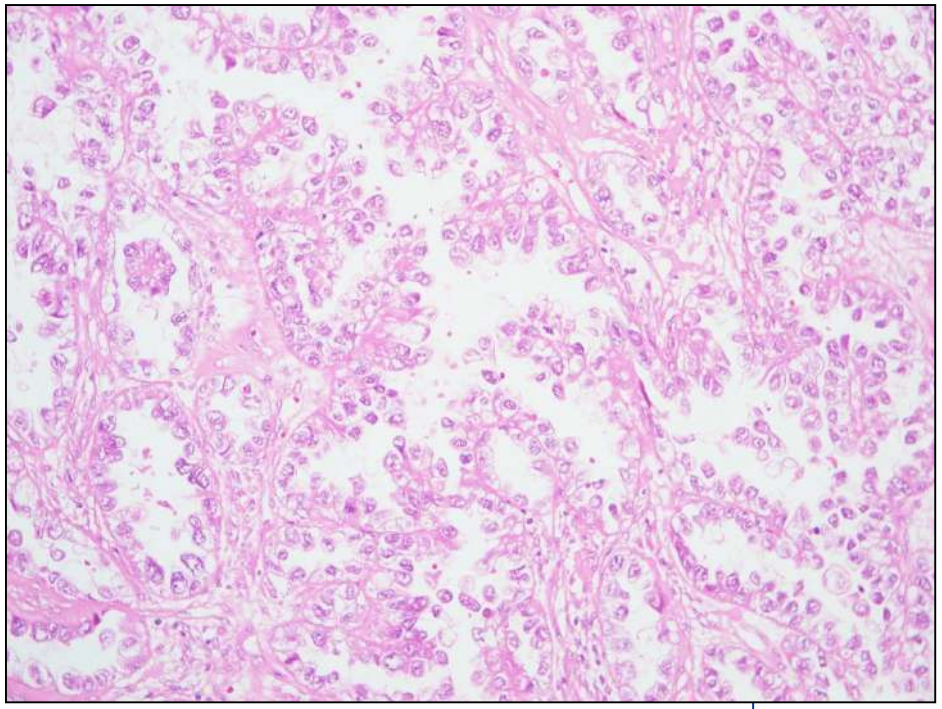


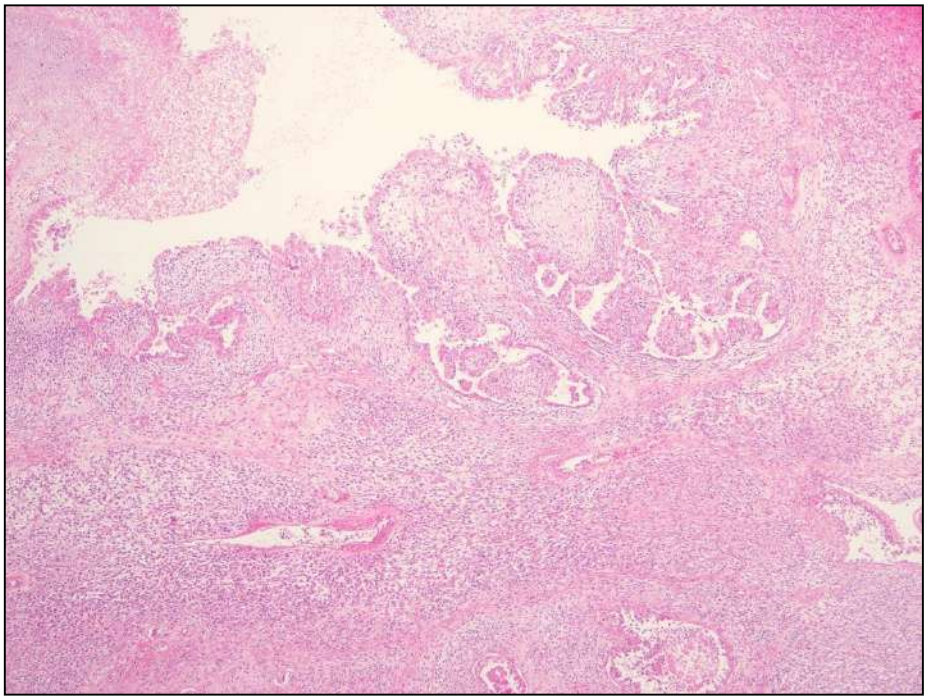


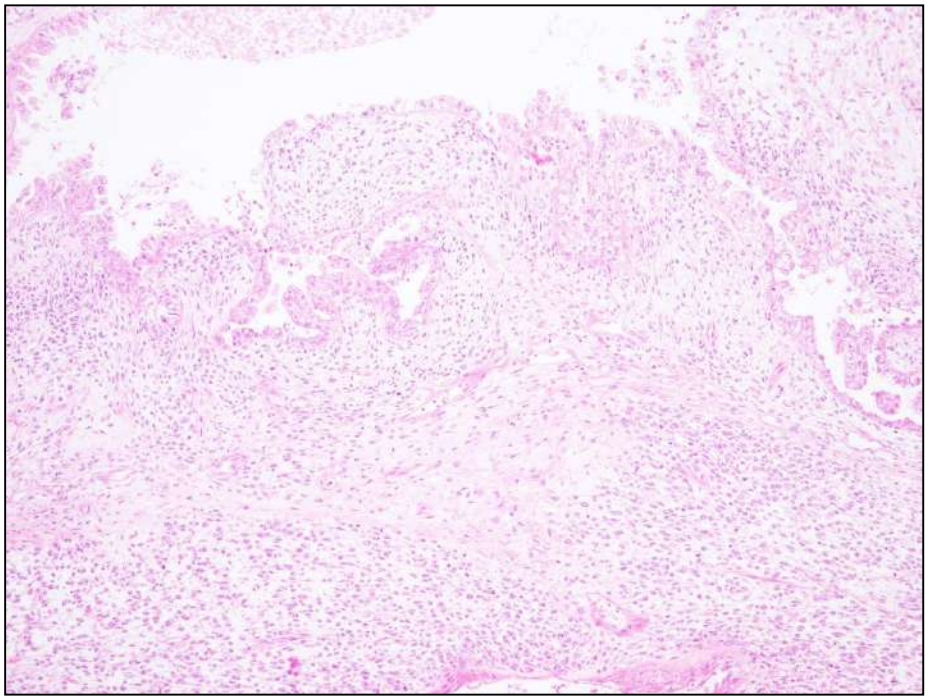


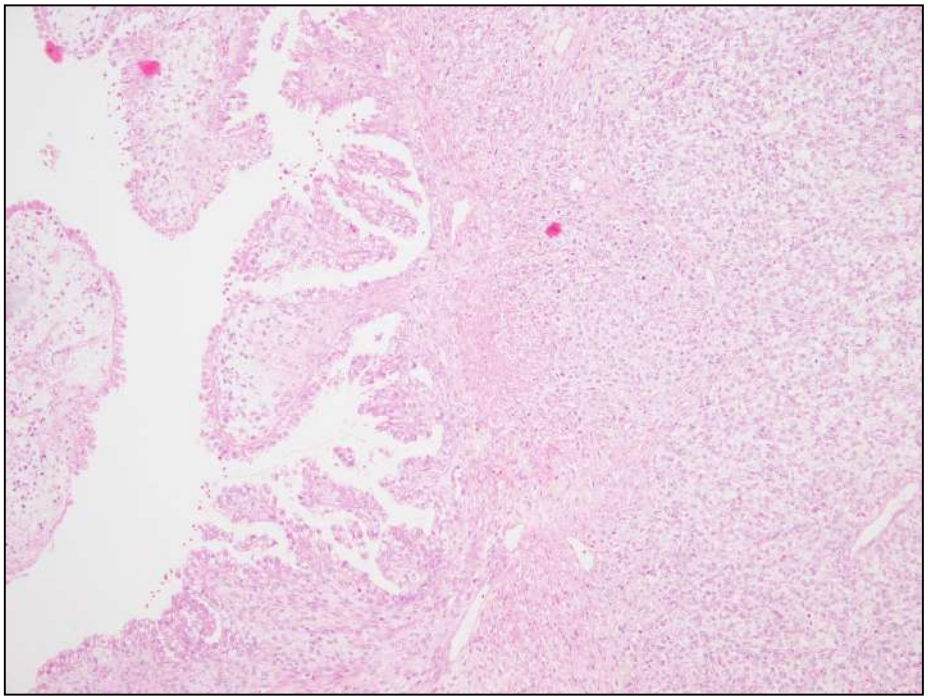


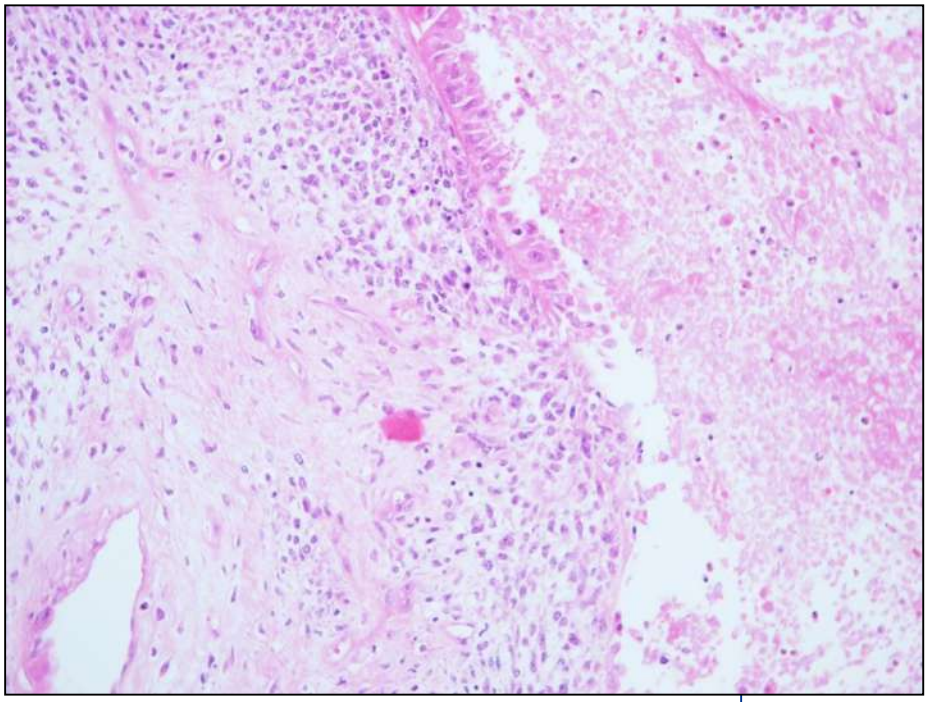






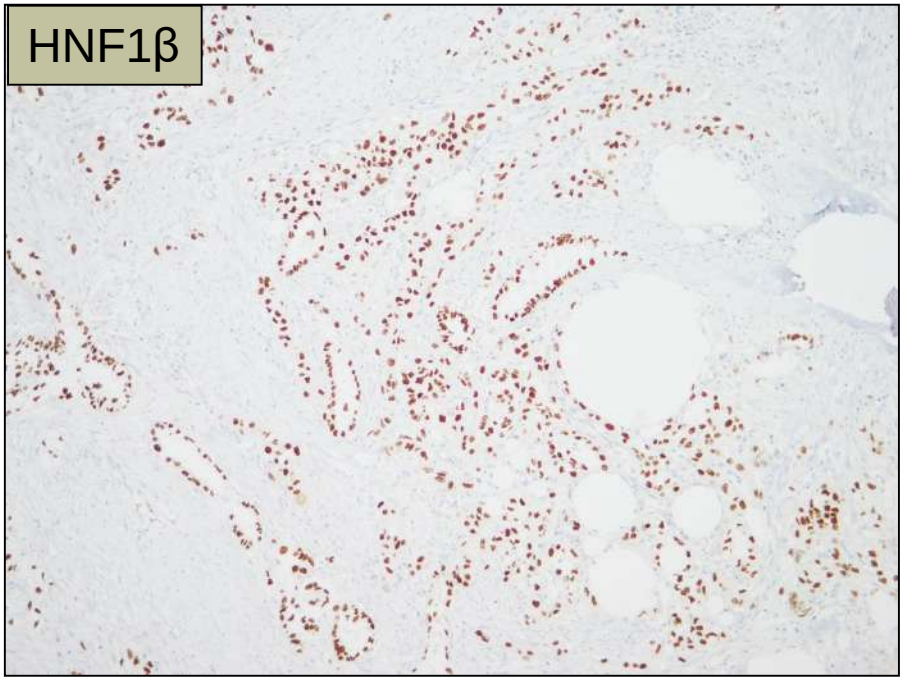


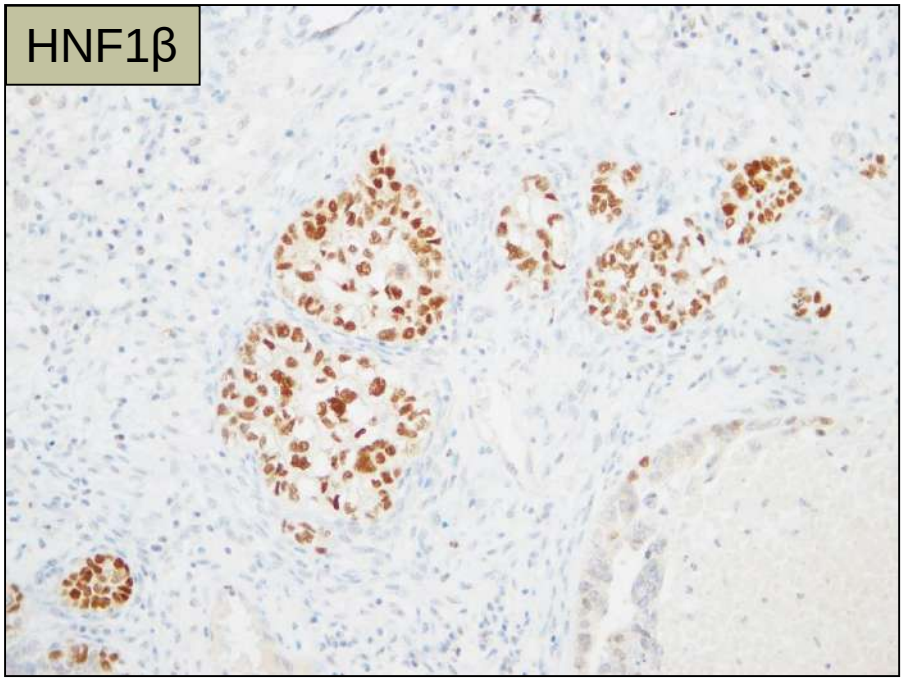


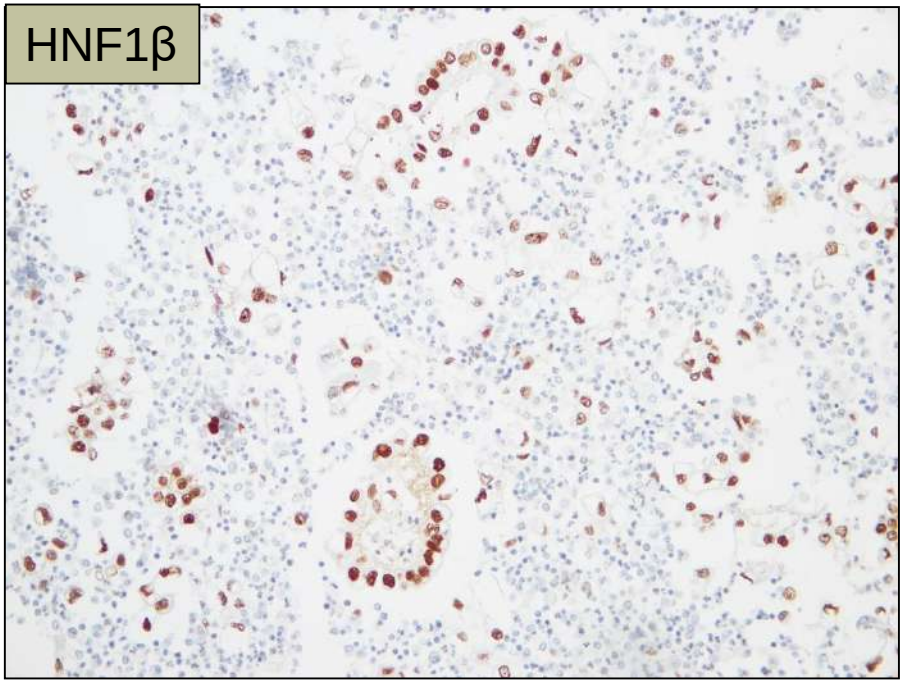


Differential diagnosis

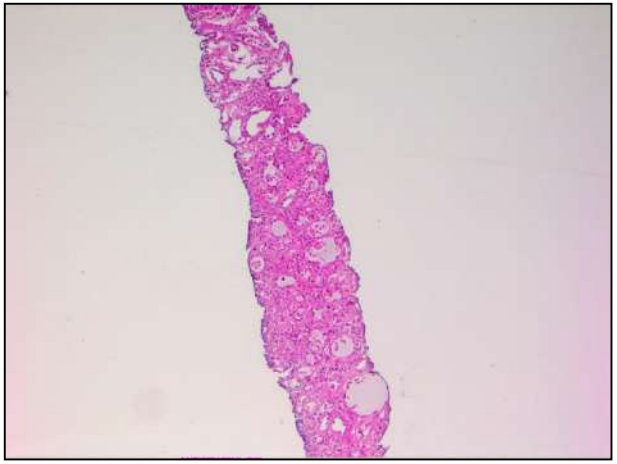
- Endometrioid carcinoma w/secretory change or other carcinomas with clear cells (ER, PR, PTEN, β-catenin, Napsin A, WT1, CEA + AMACR)
- RCC metastasis (RCC, CD10)
- Yolk sac tumor (EMA, CK7, AFP, SALL4, OCT3/4, HNF1b + AMACR)
- PECOMA (PAX8, Melan A, HMB-45, TFE3)
- Sex cord-stromal tumor (PAX8, EMA, Inhibin, SF1, FOXL2, calretinin, Melan A)

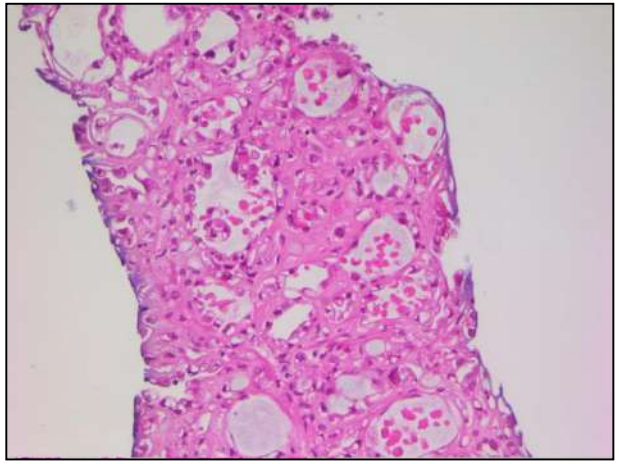


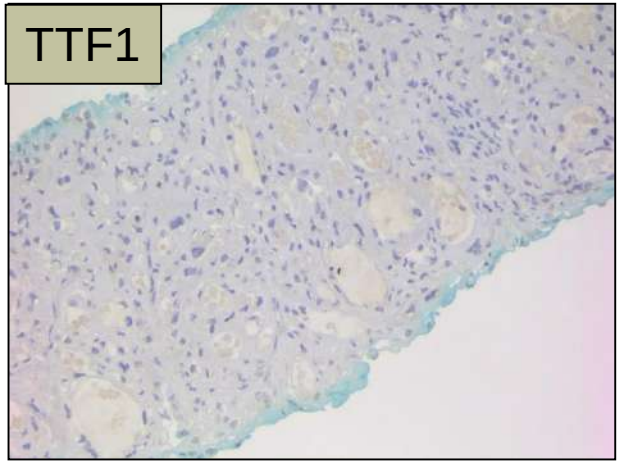


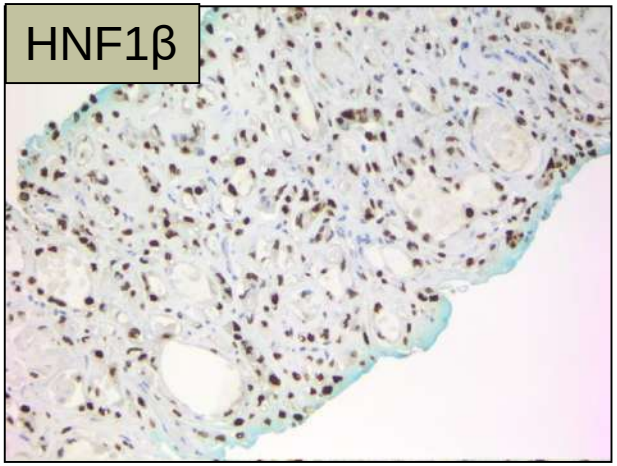


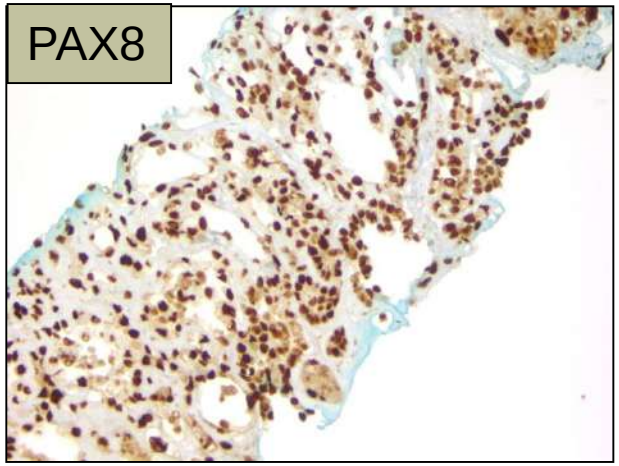
Oslo universitetssykehus

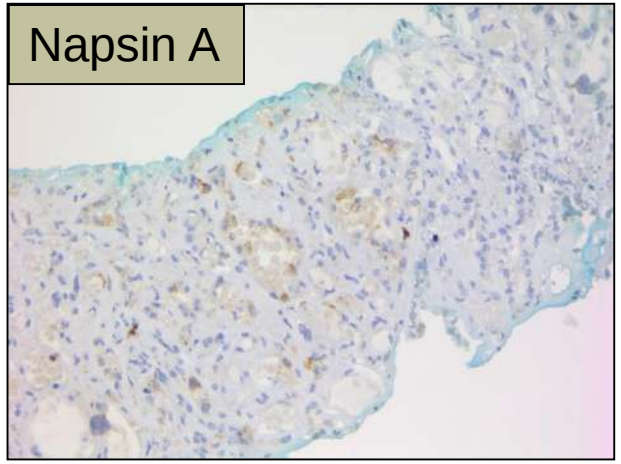




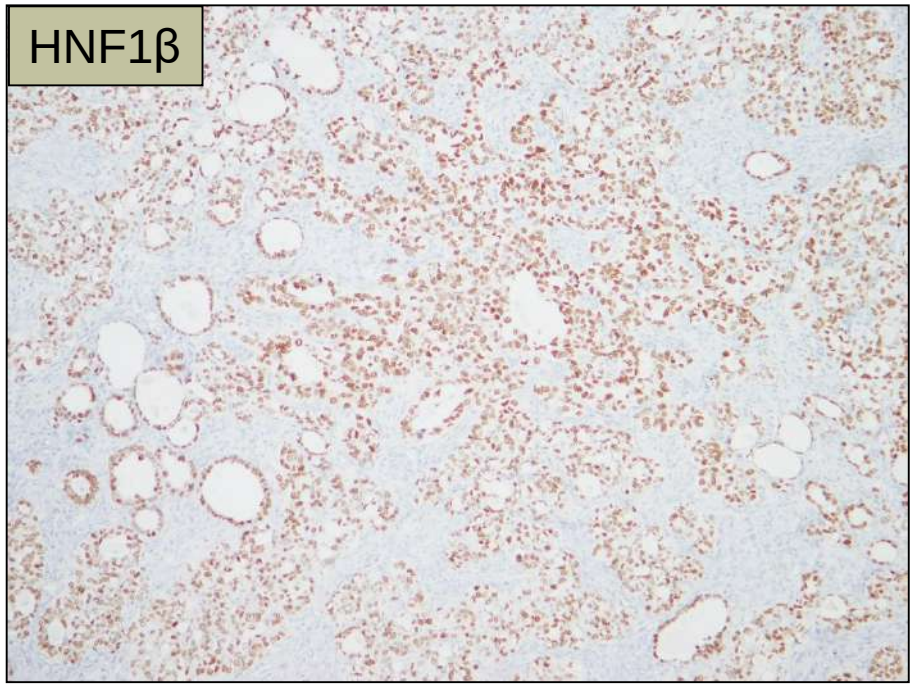


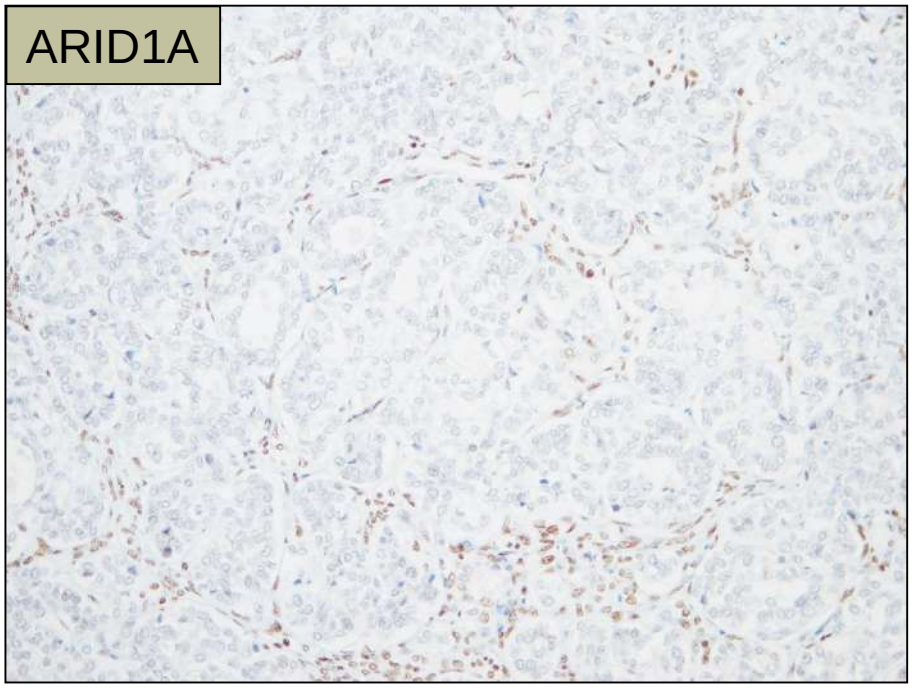


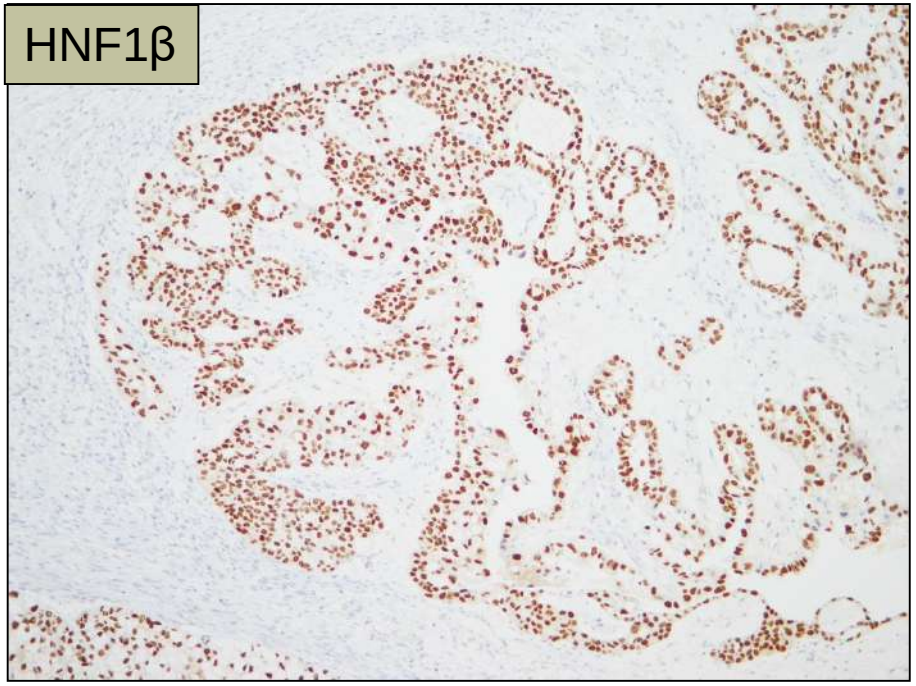


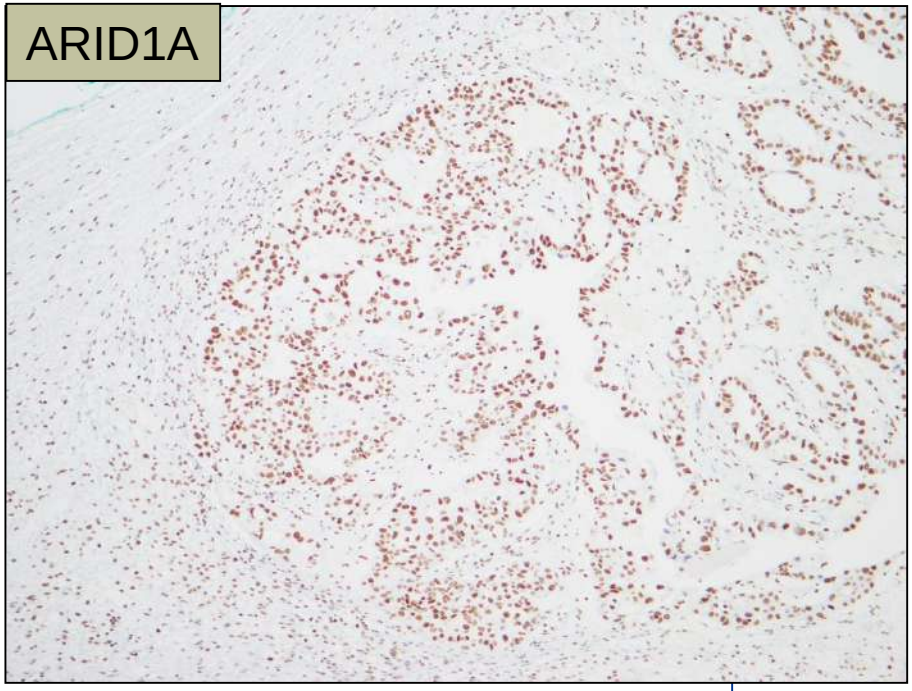


Oslo universitetssykehus


HNF1β

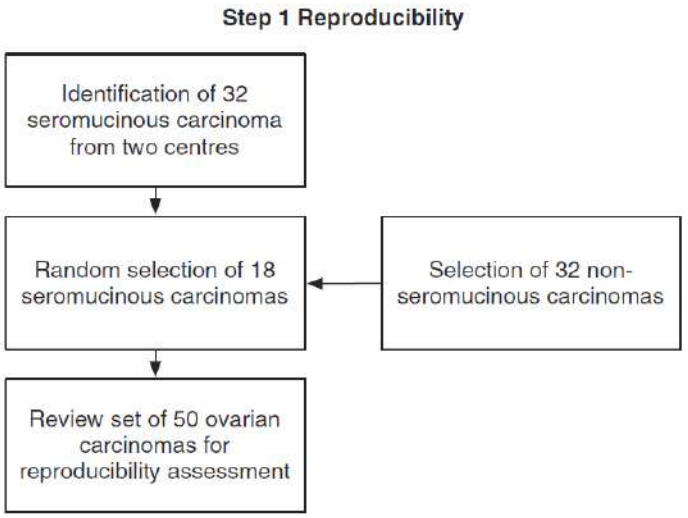

ARID1A


HNF1β


ARID1A

Endometriosis-associated tumors

- Endometrioid carcinoma (EC)
- Clear cell carcinoma (CCC)
- Seromucinous tumors
- Low-grade serous carcinoma (LGSC)
- Carcinosarcoma
- Adenosarcoma
- Endometrial stromal sarcoma (ESS)



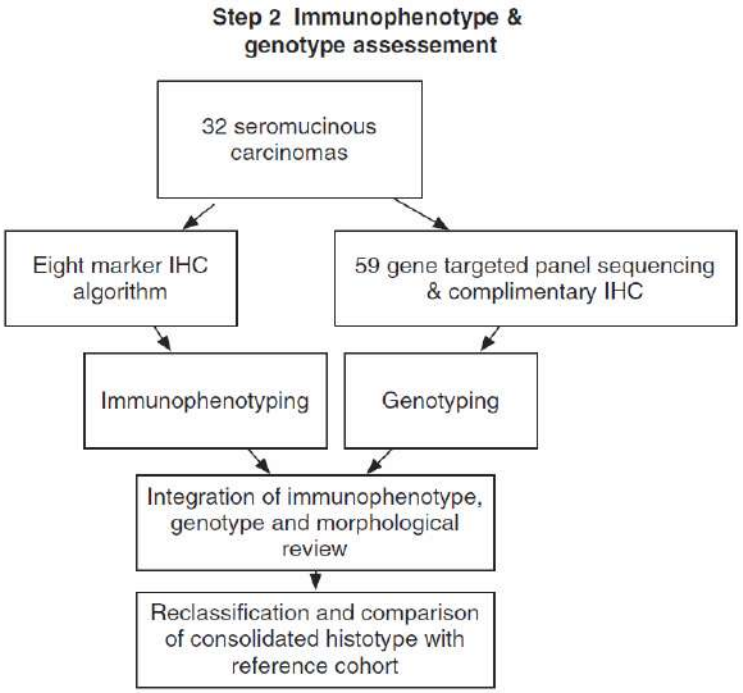


TABLE 2. Seromucinous Carcinoma Study Sample (N = 32)

Parameters	Description	n (%)
Age	Mean (range)	49 (16-79)
Stage	IA	12 (38)
	IC	9 (28)
	II	2 (6)
	III	6 (19)
	Unknown	3 (9)
Endometriosis	Absent	14 (44)
	Present	17 (53)
	Unknown	1 (3)

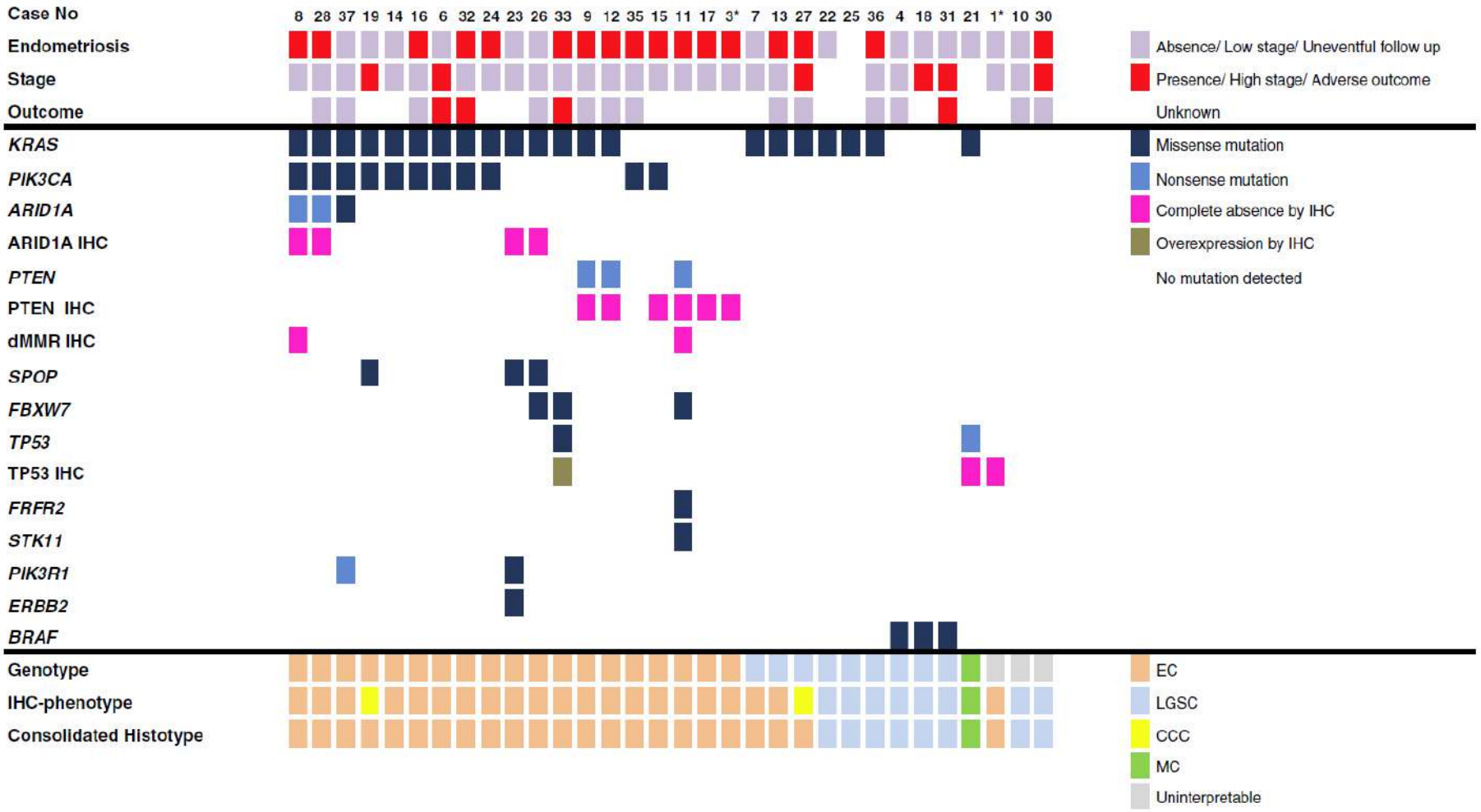
TABLE 1. Histotype-specific IHC Phenotype and Genotype Definitions

Histotype	Immunophenotype[11]	Genotype
Low-grade serous	WT1 present, p53 normal	*KRAS*, *BRAF*, *NRAS*, *ERBB2*, or *FGFR2*[18,19]
Endometrioid	WT1 absent, Napsin A absent, PR present	*CTNNB1*, *PTEN*, *PPP2R1A*, *PIK3R1*, *POLE*, *SPOP*, *FBXW7*, *RPL22*, or deficient mismatch repair[16,20,21] Co-occurrence of *KRAS* and *PIK3CA* mutation
Endometrioid/ clear cell	WT1 absent, Napsin present	*PIK3CA* and *ARID1A*[22,23]
Mucinous	WT1 absent, Napsin A absent, PR absent	Co-occurrence of *KRAS* and *TP53* or *ERBB2* amplification[24]

IHC indicates immunohistochemistry.

Rambau et al., Am J Surg Pathol 2017;41:685-95

Oslo universitetssykehus



Rambau et al., Am J Surg Pathol 2017;41:685-95

Oslo universitetssykehus

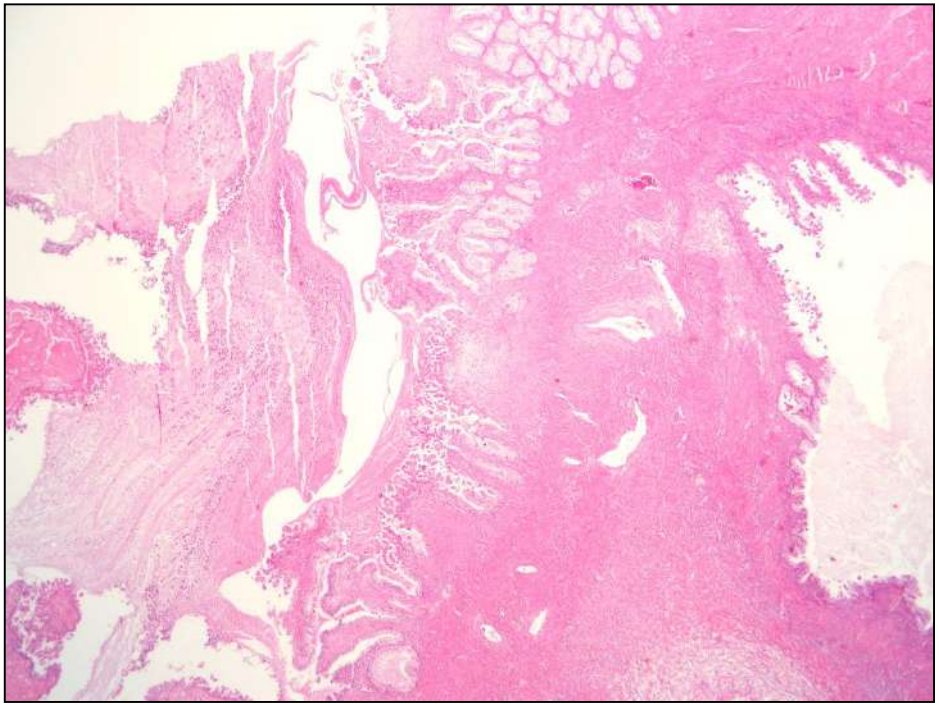
TABLE 3. Immunohistochemical and Mutational Profile Comparing Original Seromucinous With Reclassified Endometrioid Carcinomas

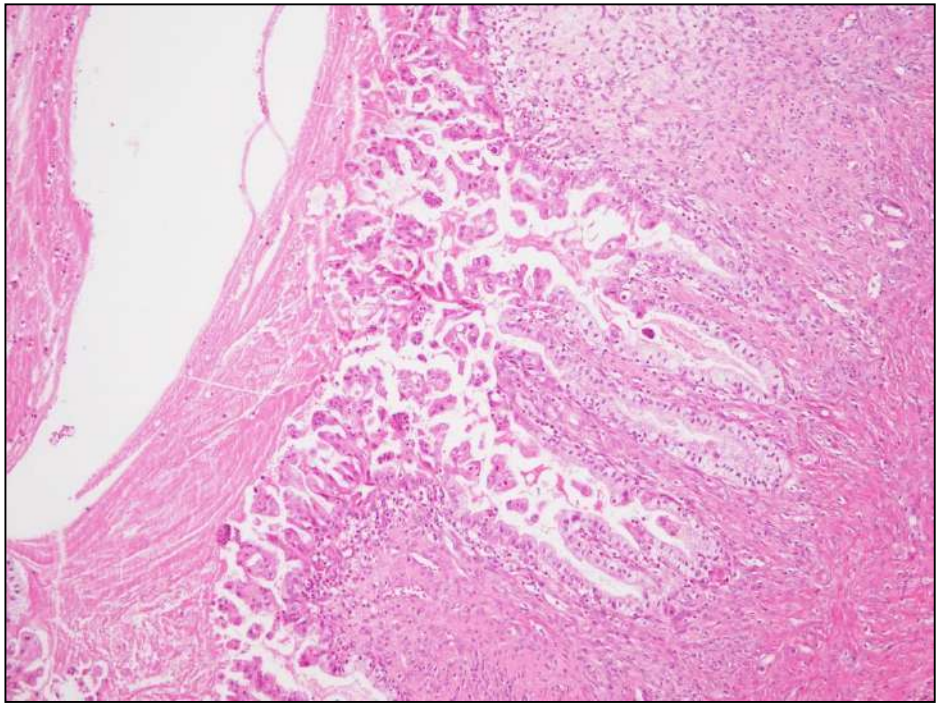
	n/N (%)			
	Original Seromucinous Carcinoma	**Reclassified as EC**	**Reference EC From Köbel and Colleagues[11,16,20]**	***P*-Value Between Reclassified EC and Reference EC**
WT1 present	8/32 (25)	0	14/181 (8)	0.38
TP53 abnormal	3/32 (9)	2/23 (9)	21/181 (12)	1.00
CDKN2A block	5/32 (16)	5/23 (22)	12/181 (7)	0.029
Napsin A present	3/32 (9)	3/23 (13)	21/181 (11.6)	0.74
PR present	30/32(94)	22/23 (96)	157/181 (87)	0.32
TFF3 diffuse	6/32 (19)	6/23 (26)	69/181 (38)	0.36
Vimentin diffuse	18/32 (56)	12/23 (52)	109/181 (60)	0.50
ARID1A absent	4/32 (5)	4/23 (17)	53/181 (29)	0.32
KRAS mut	21/30 (70)	17/21 (81)	10/30 (33)	**0.0014**
PIK3CA mut	11/30 (37)	11/21 (52)	12/30 (40)	0.41
KRAS&PIK3CA mut	9/30 (30)	9/21 (43)	3/30 (10)	0.016
*PTEN mut**	6/32 (19)	6/23 (26)	5/30 (17)	1.00
*ARID1A mut**	5/32 (16)	5/23 (22)	9/30 (30)	0.54
*TP53 mut**	3/32(9)	2/23 (9)	2/30 (7)	1.00
*CTNNB1 mut**	0	0	16/30 (53)	< **0.0001**
PPP2R1A mut	0	0	5/30 (17)	0.061
dMMR	2/32 (6)	2/23 (9)	25/181 (14)	0.74

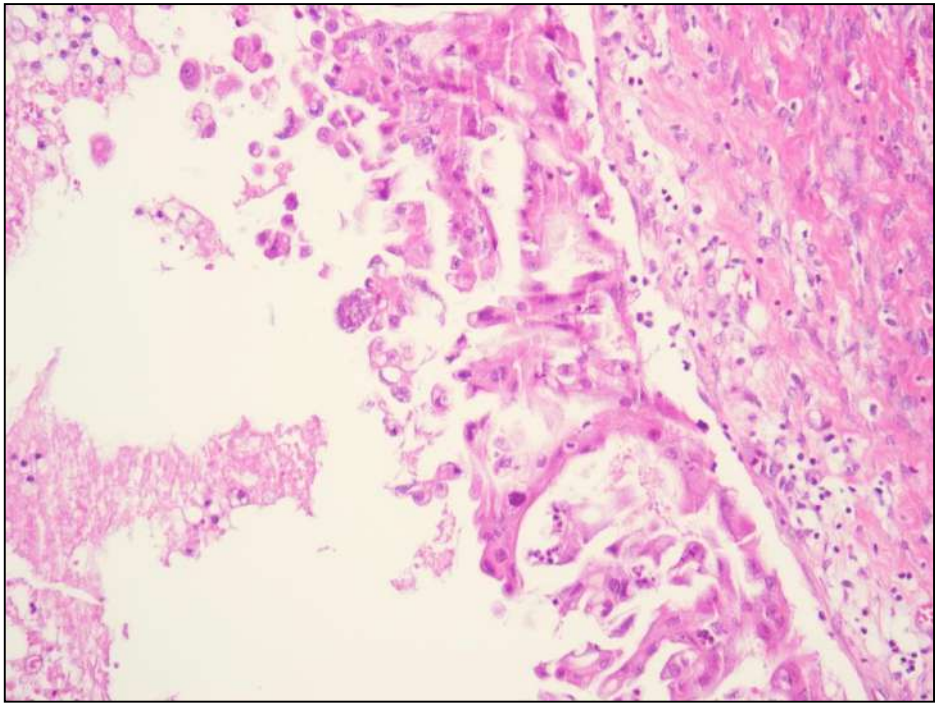
Bold indicates significant after adjusting for multiple testing.
*Combined numbers from sequencing and immunohistochemistry.
EC indicates endometrioid carcinoma; mut, mutated.

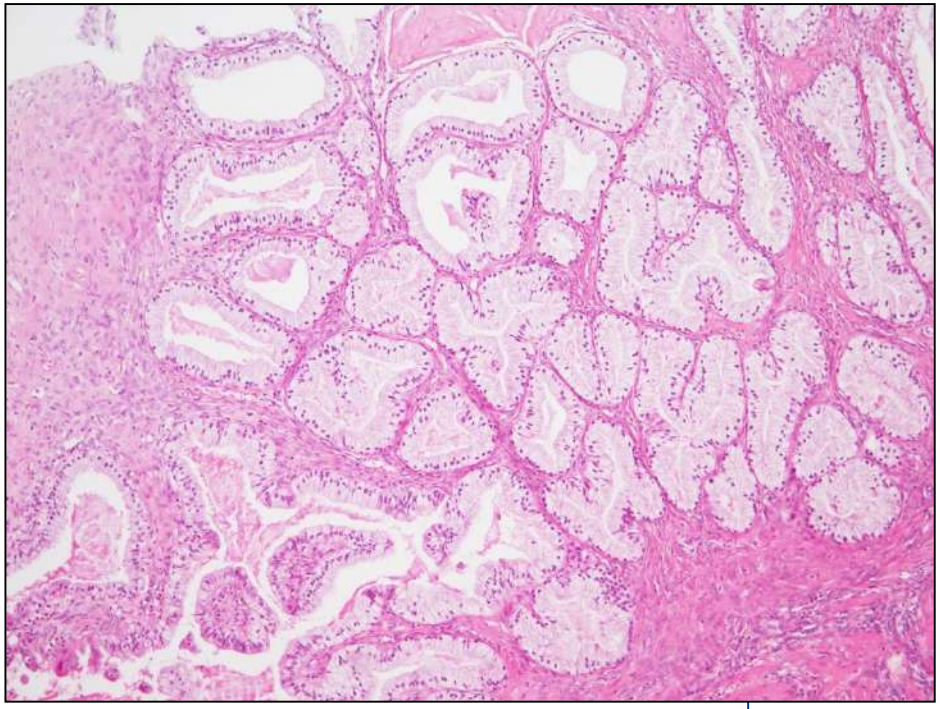
Rambau et al., Am J Surg Pathol 2017;41:685-95

Oslo universitetssykehus



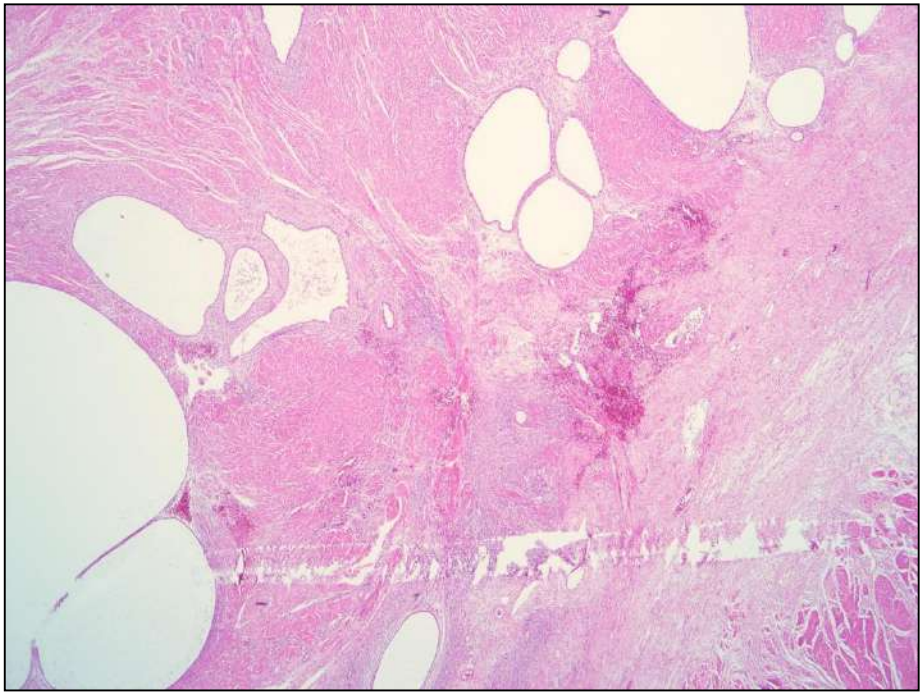


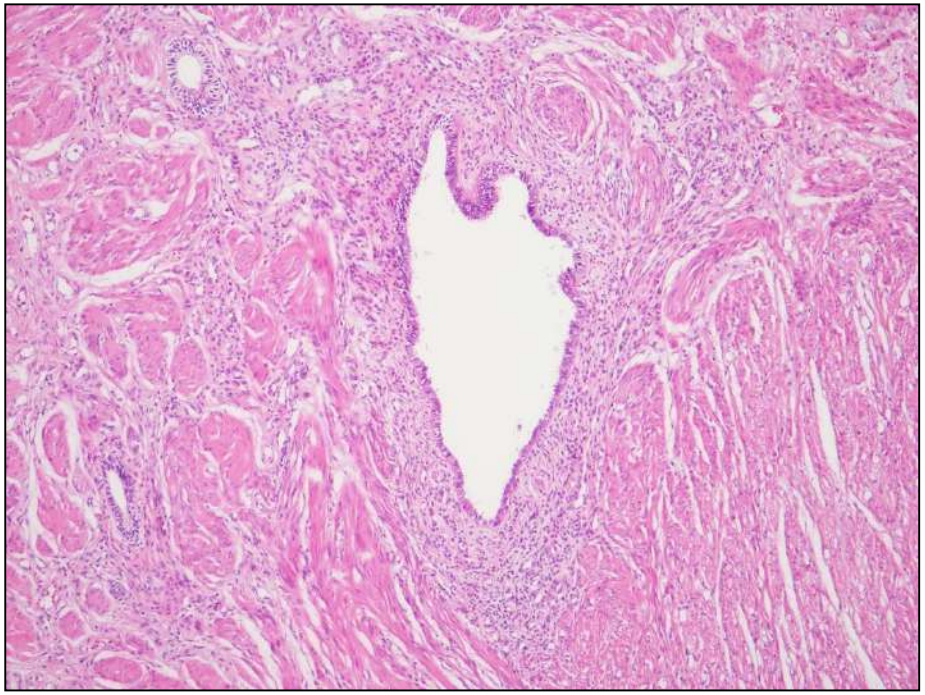




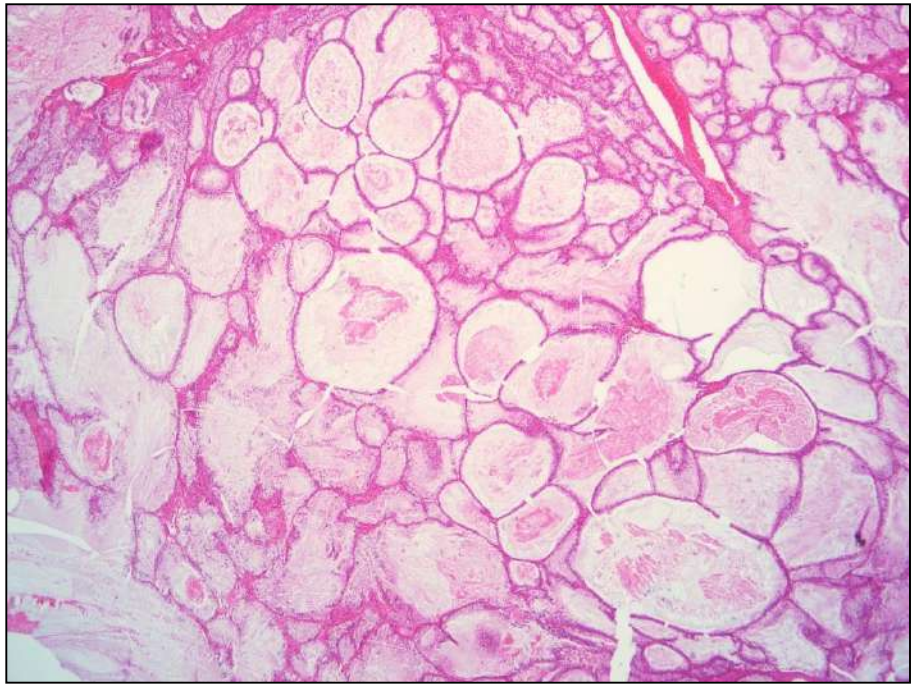


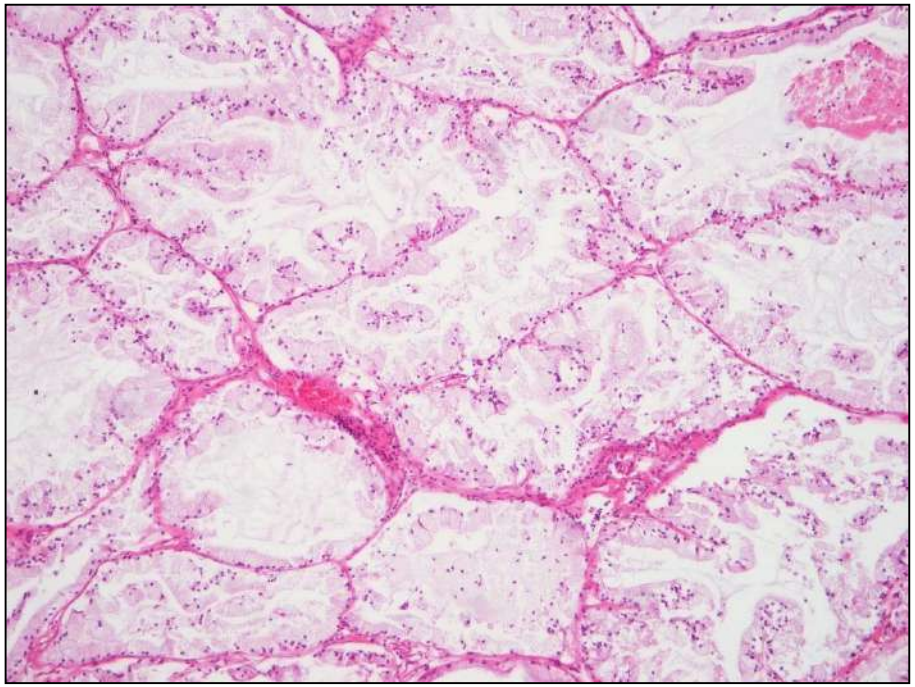
Oslo universitetssykehus

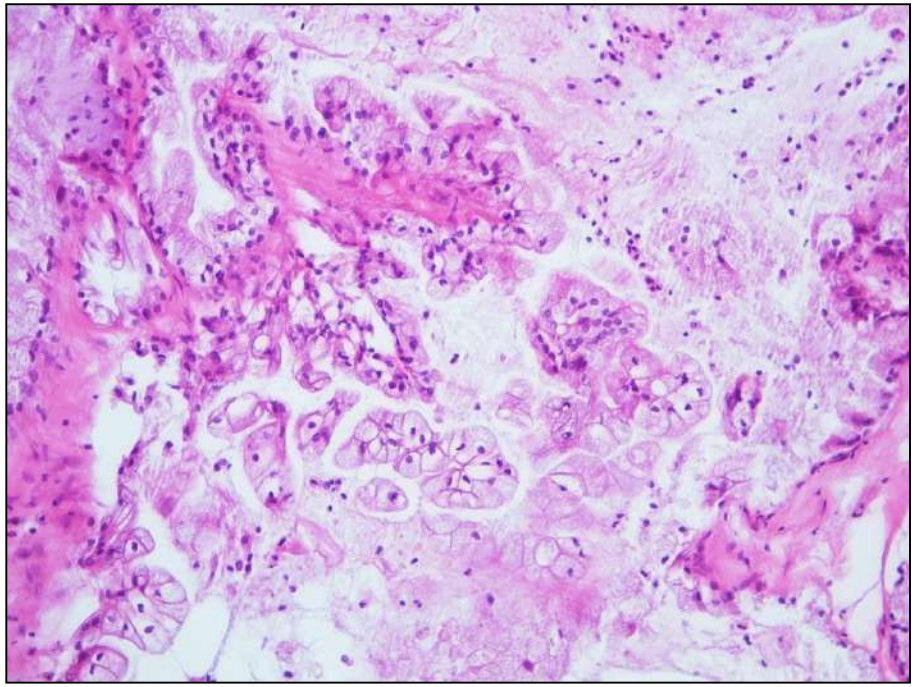


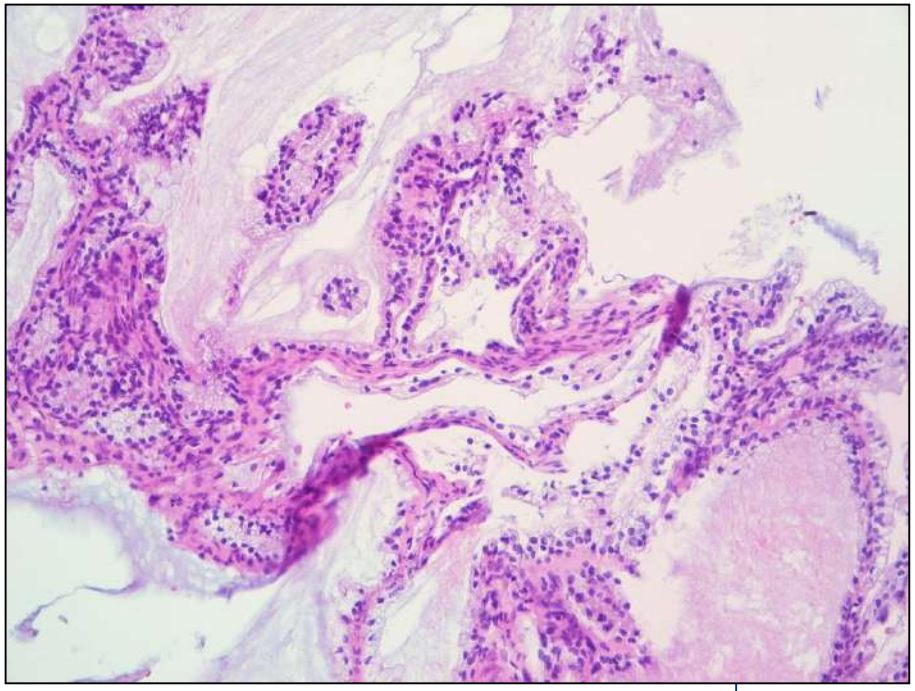


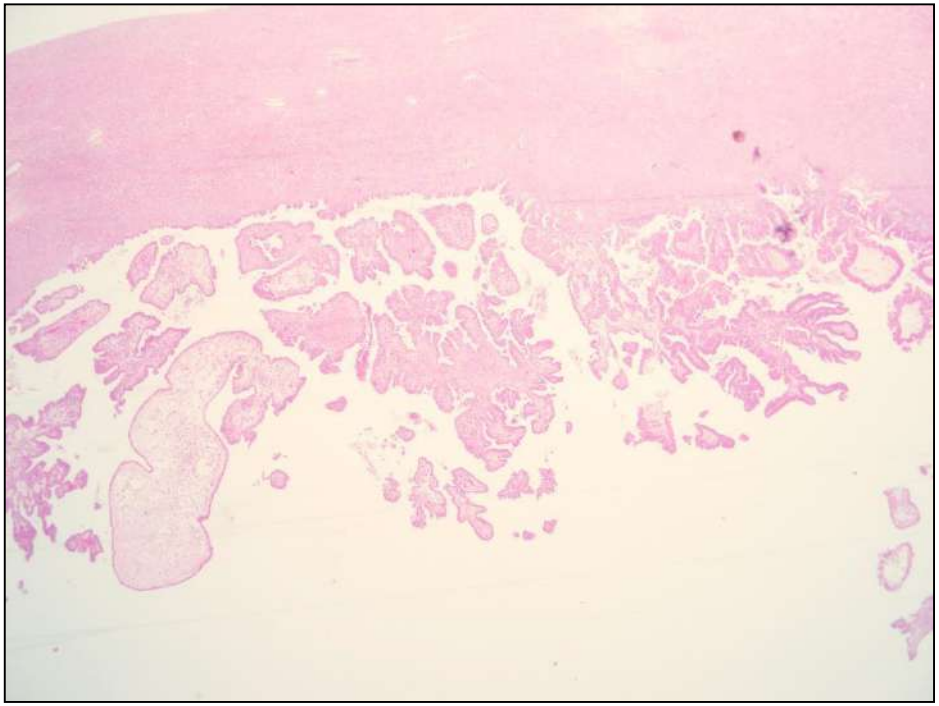
Oslo universitetssykehus

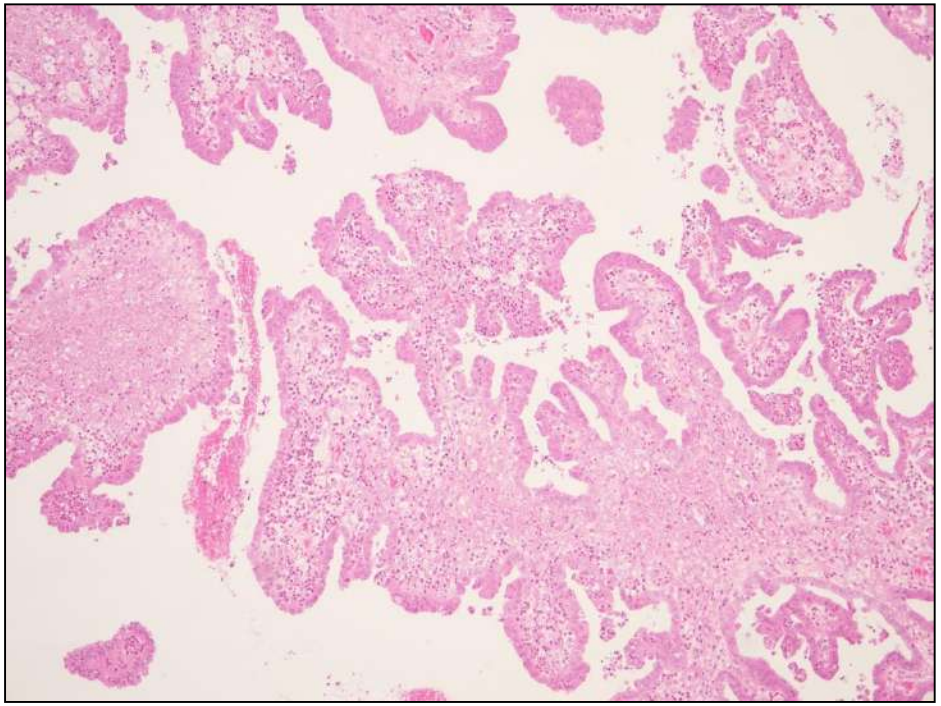


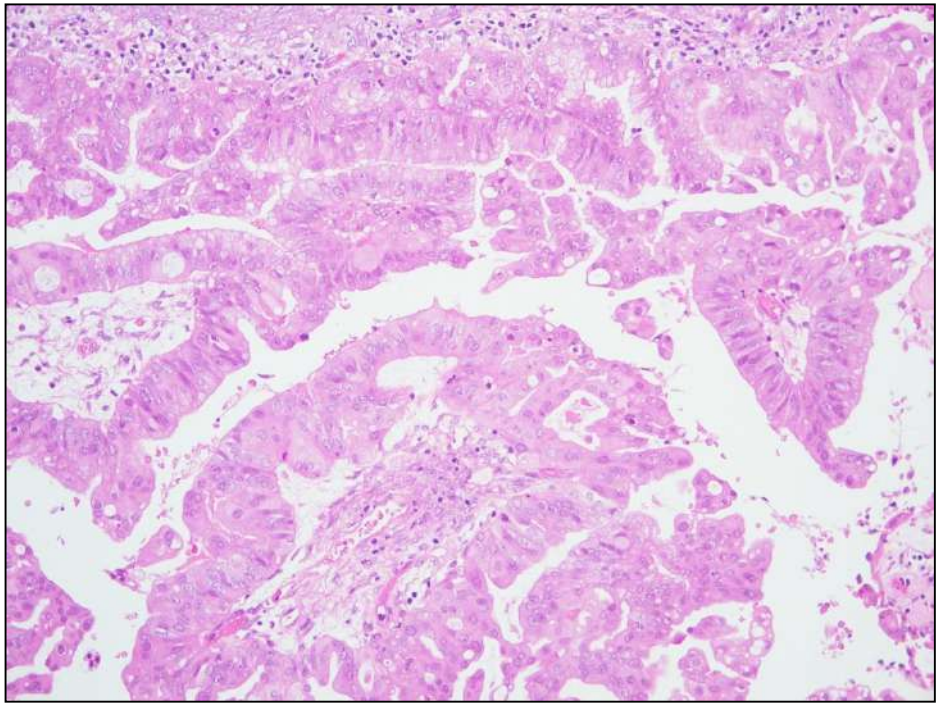


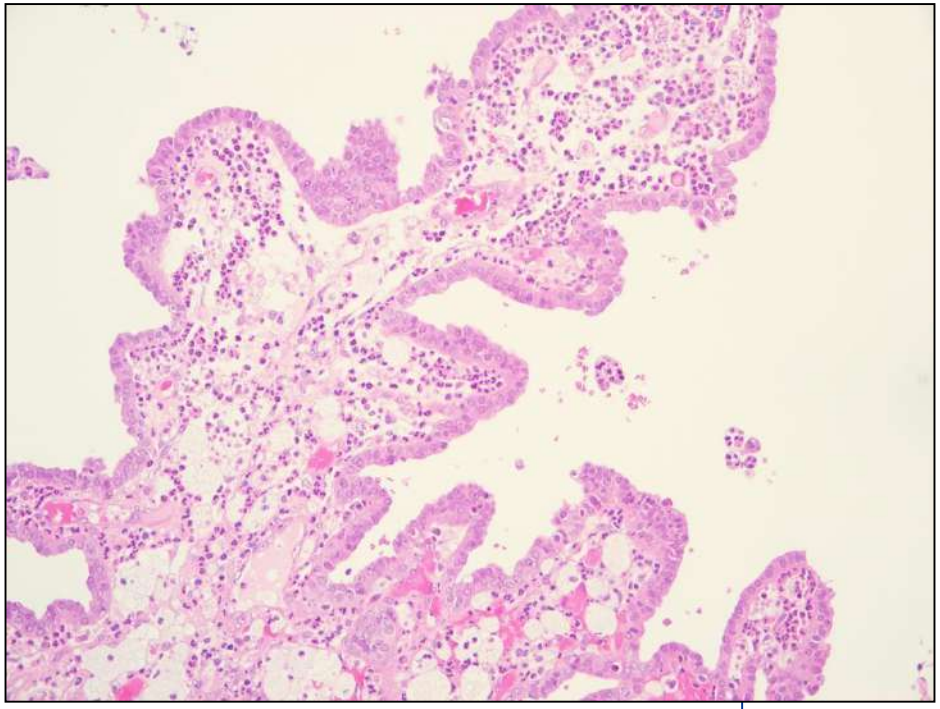


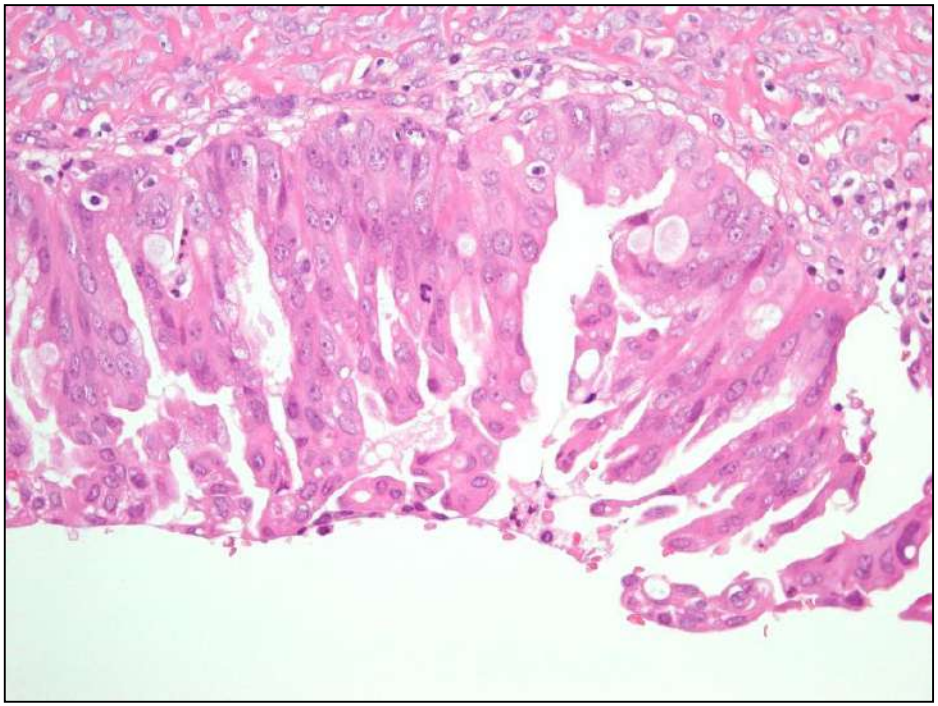


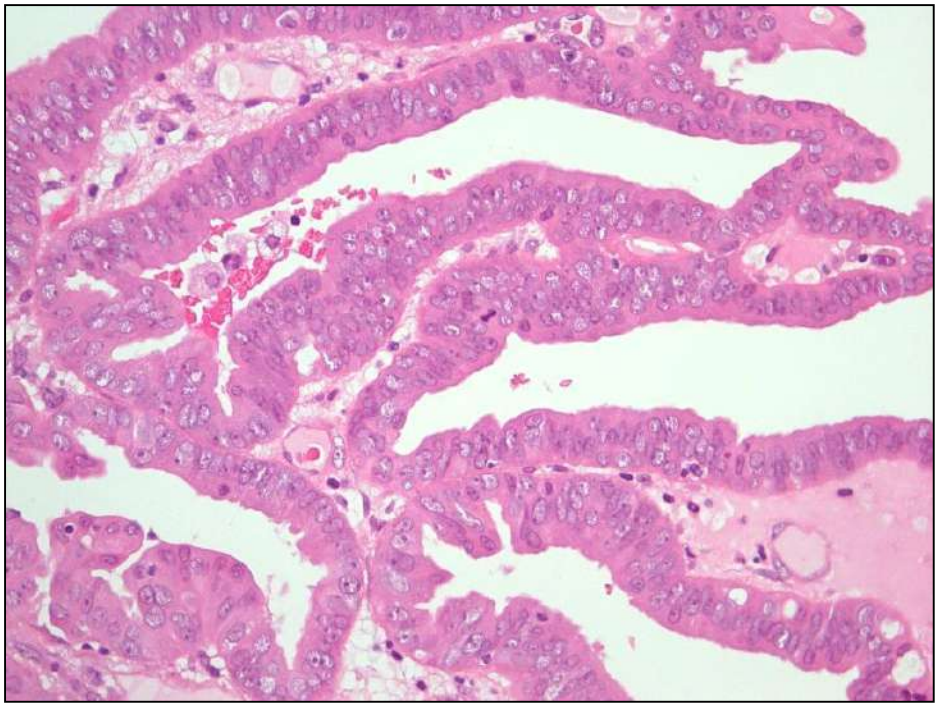




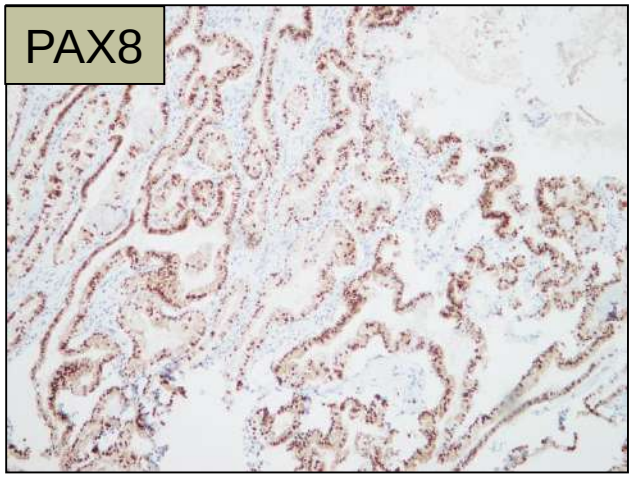


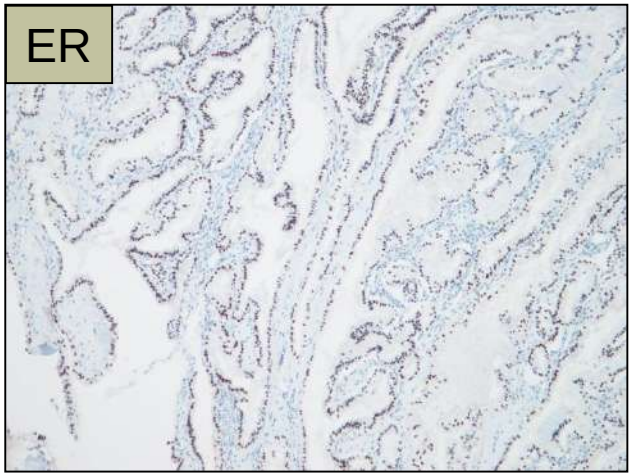


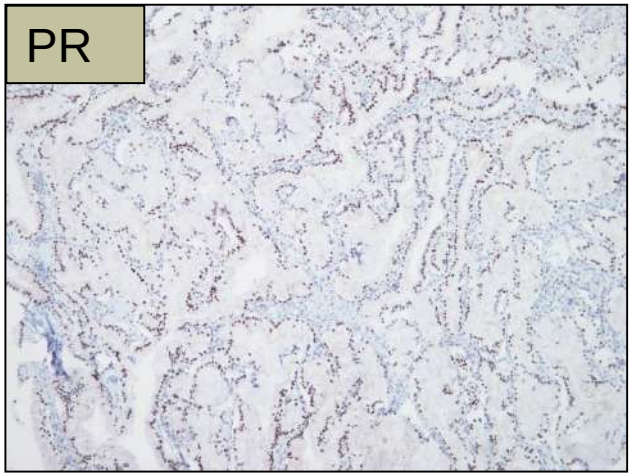


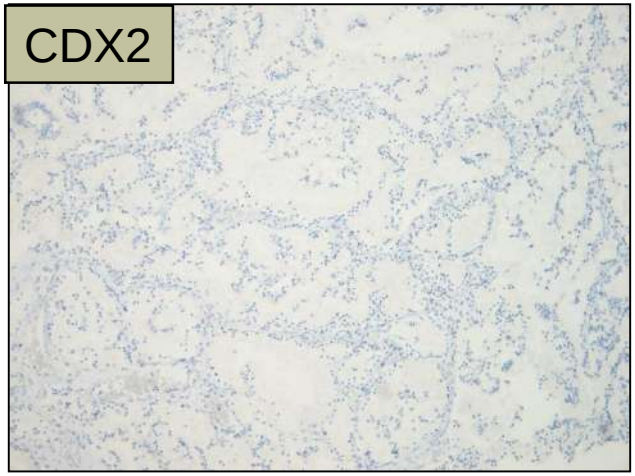


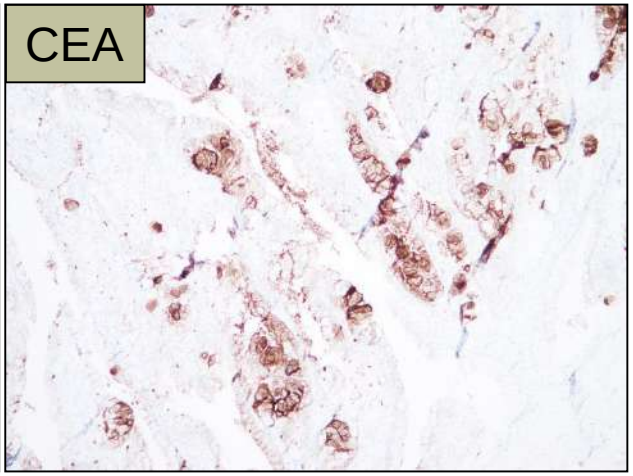
Oslo universitetssykehus

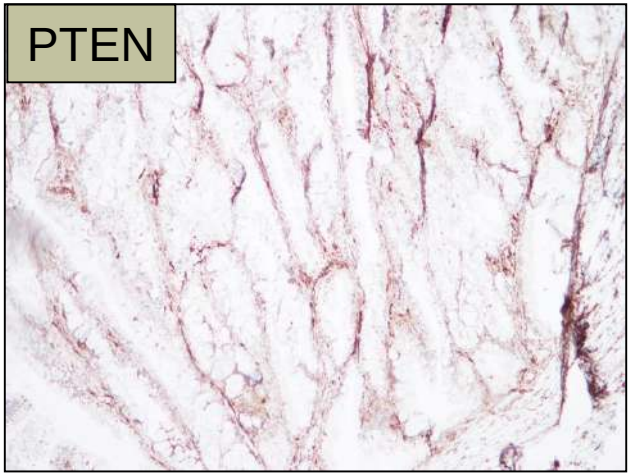








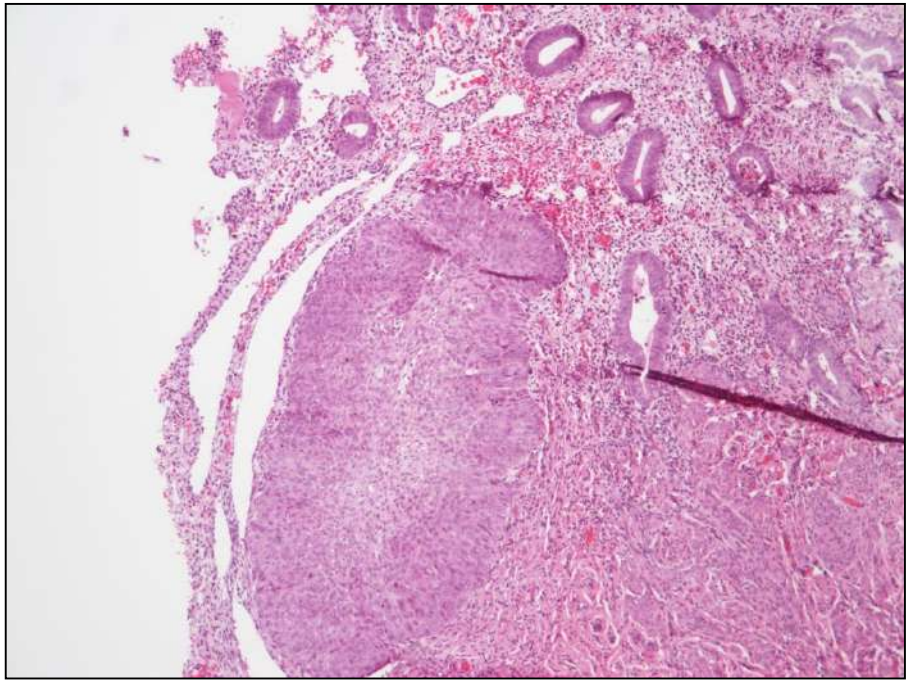


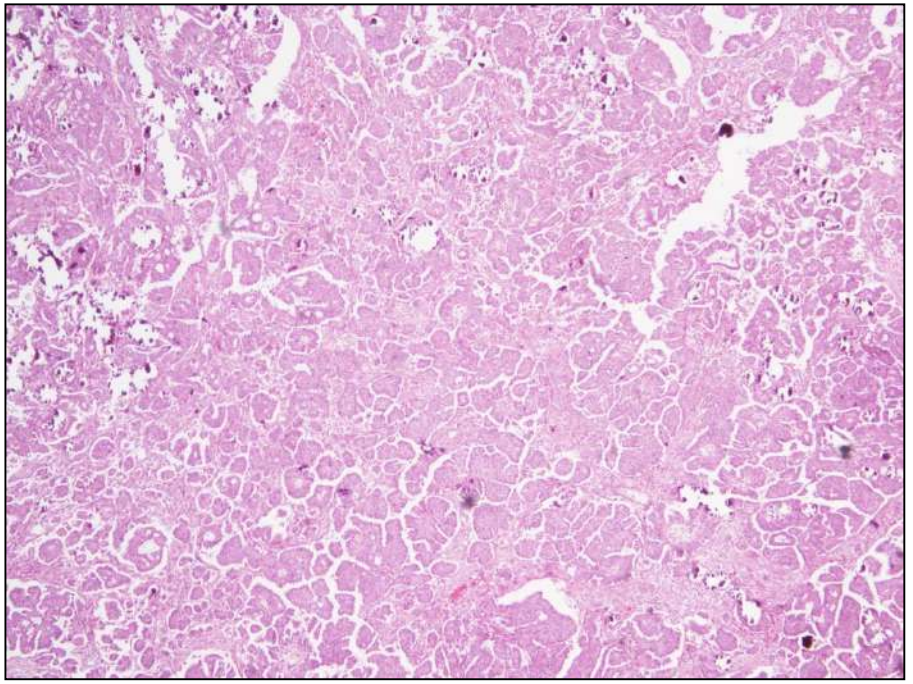


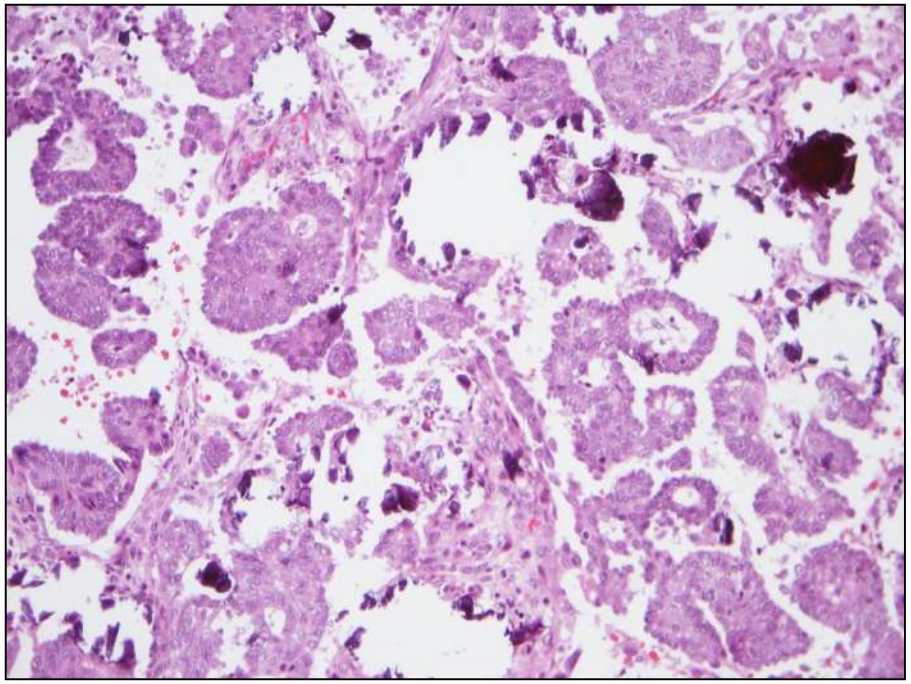
Oslo universitetssykehus

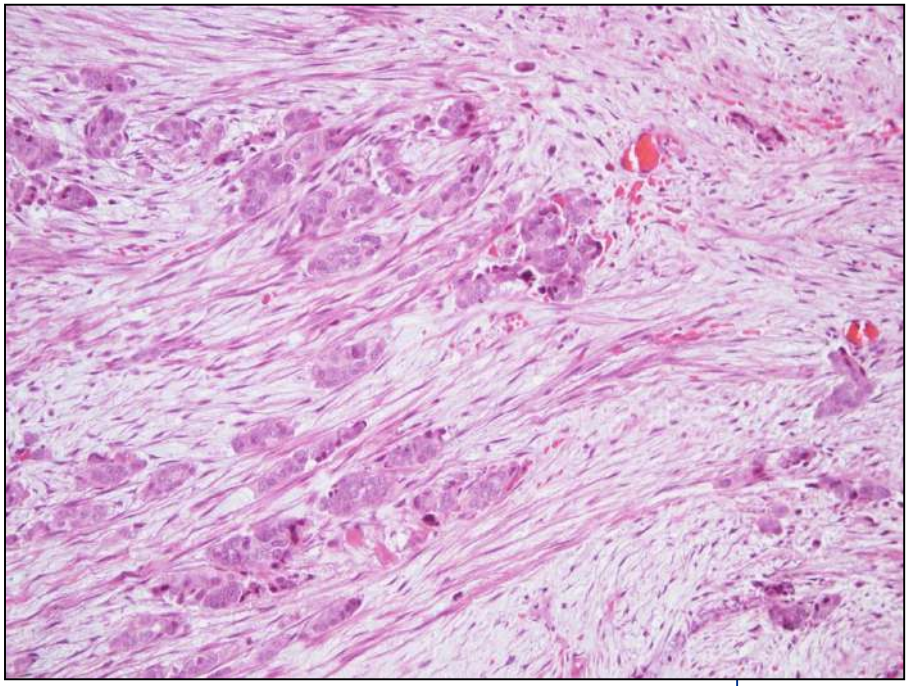
Endometriosis-associated tumors

- Endometrioid carcinoma (EC)
- Clear cell carcinoma (CCC)
- Seromucinous tumors
- Low-grade serous carcinoma (LGSC)
- Carcinosarcoma
- Adenosarcoma
- Endometrial stromal sarcoma (ESS)



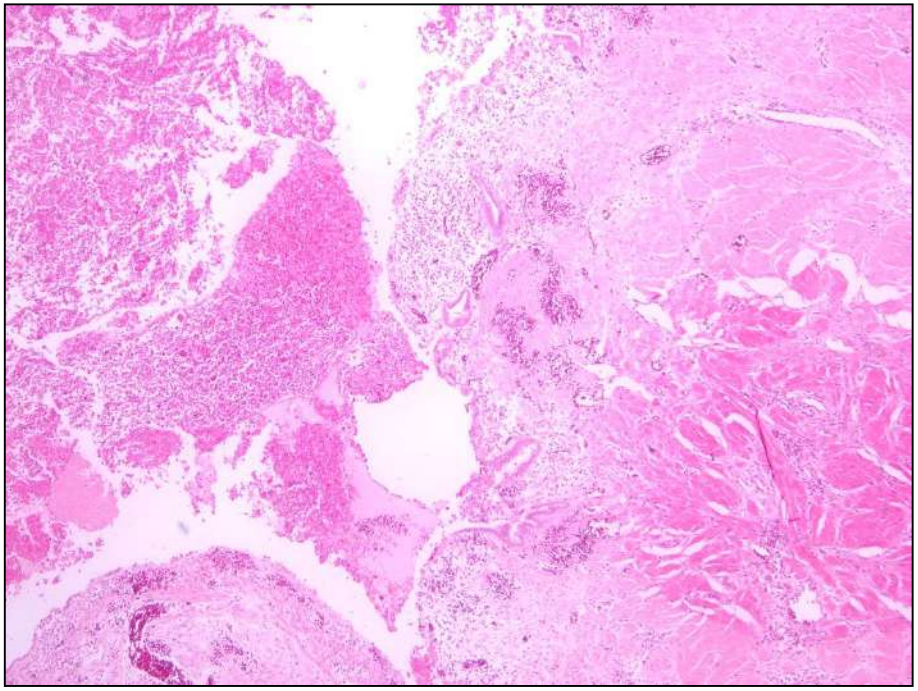


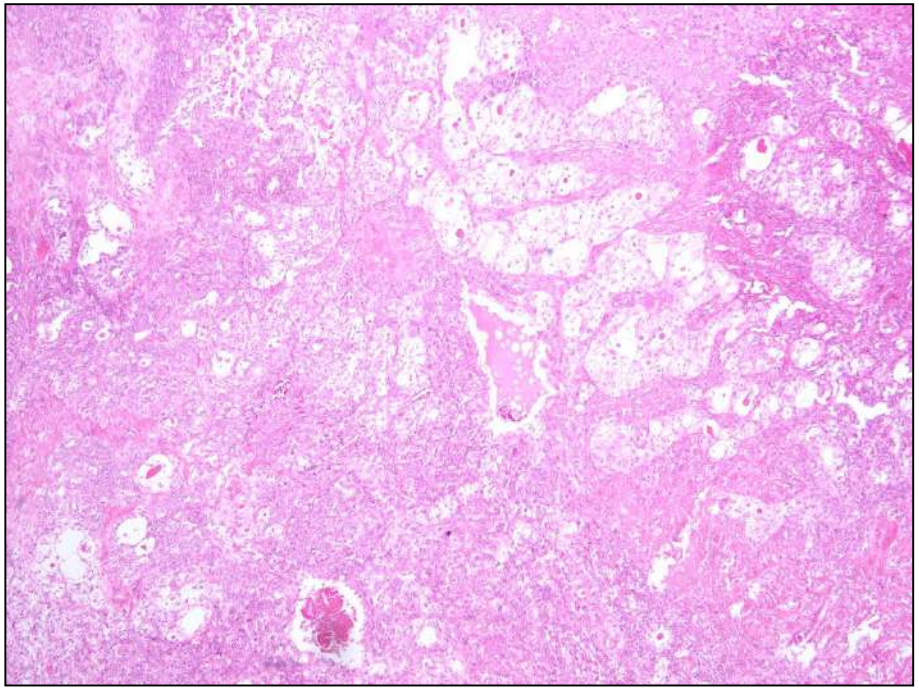


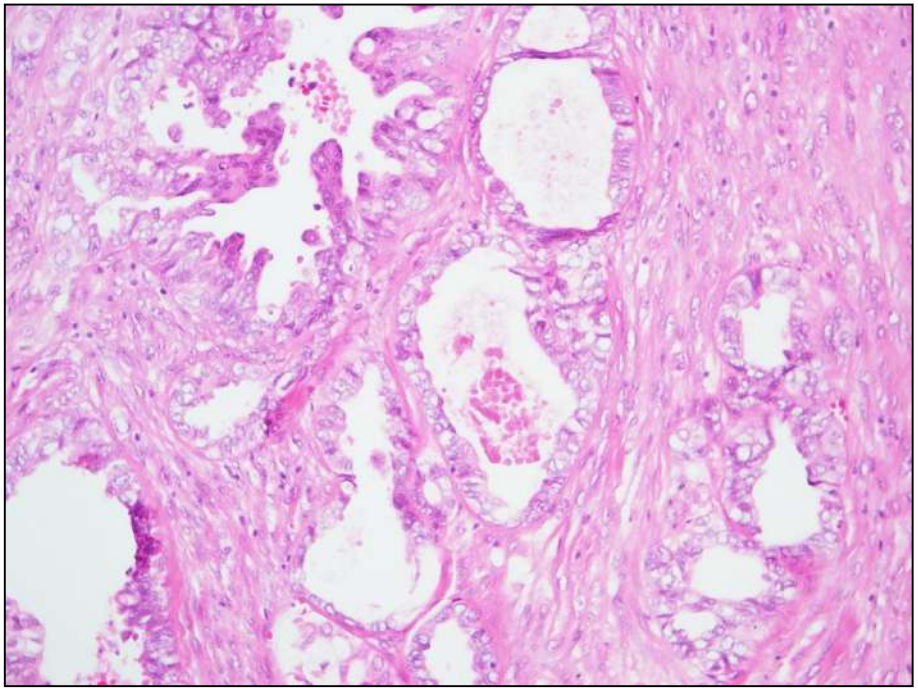


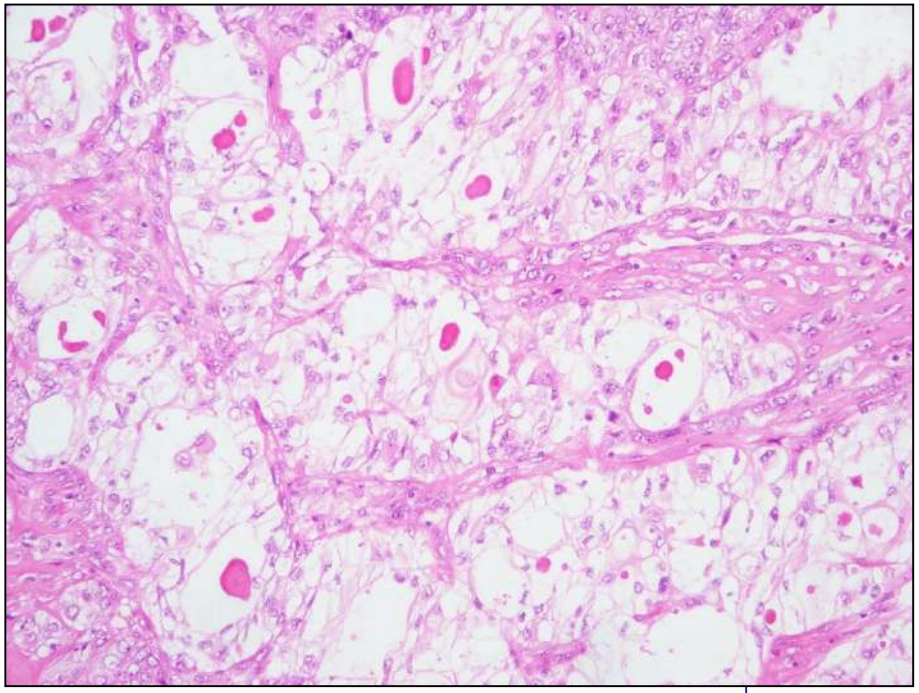
Endometriosis-associated tumors

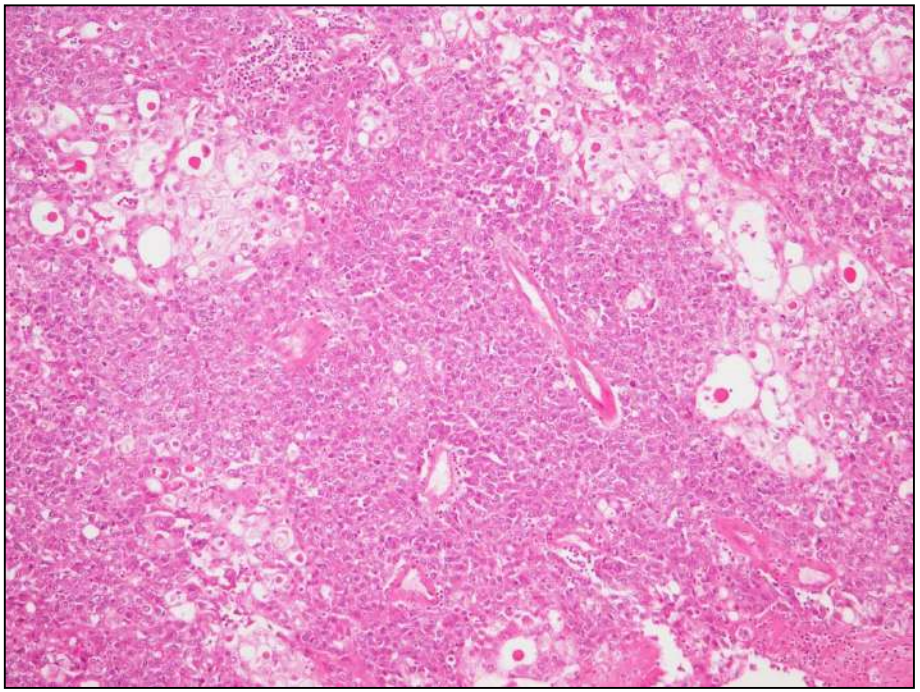
- Endometrioid carcinoma (EC)
- Clear cell carcinoma (CCC)
- Seromucinous tumors
- Low-grade serous carcinoma (LGSC)
- Carcinosarcoma
- Adenosarcoma
- Endometrial stromal sarcoma (ESS)

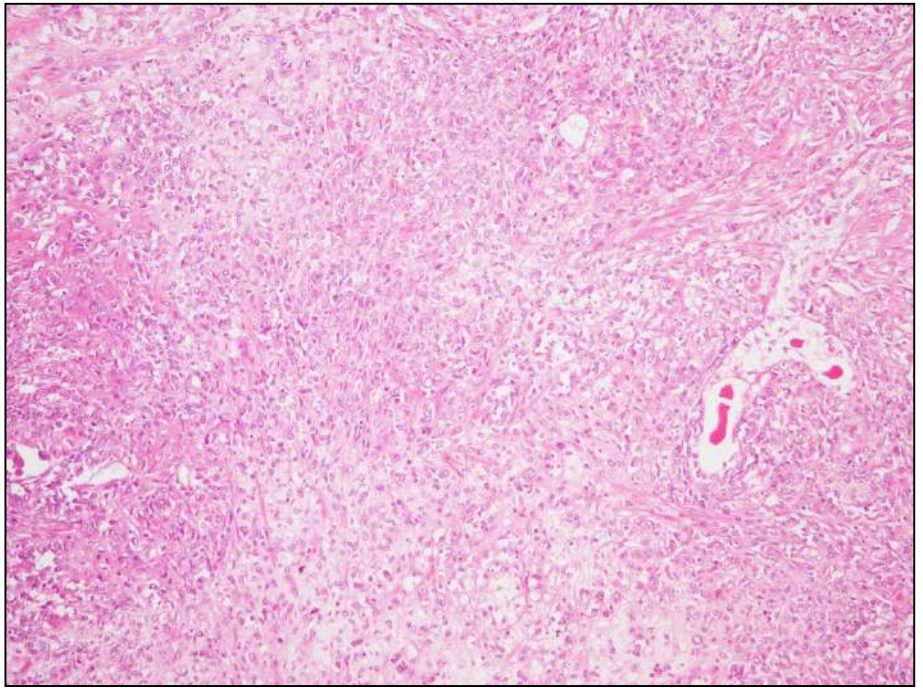


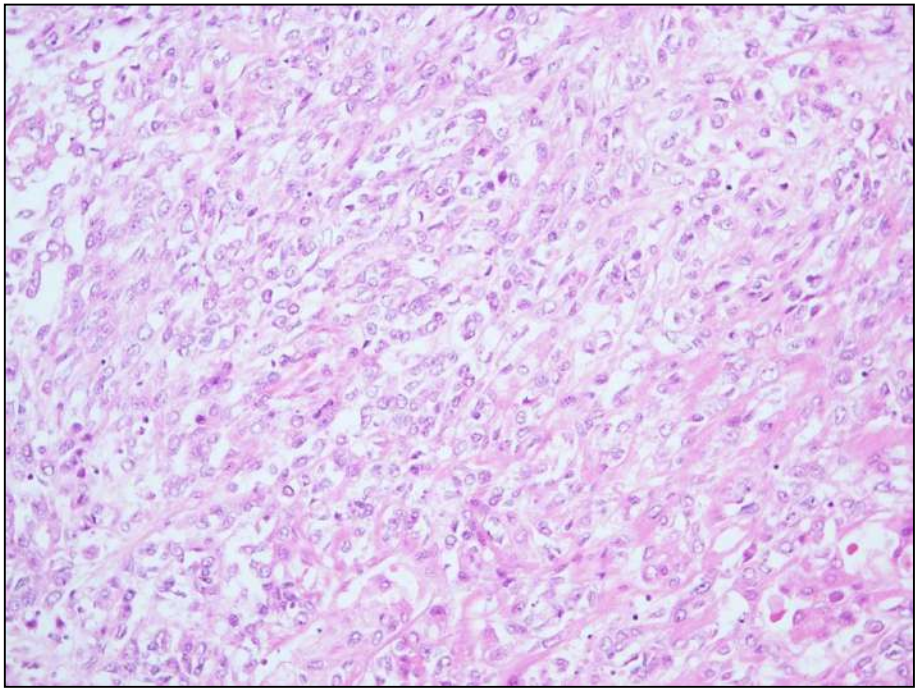


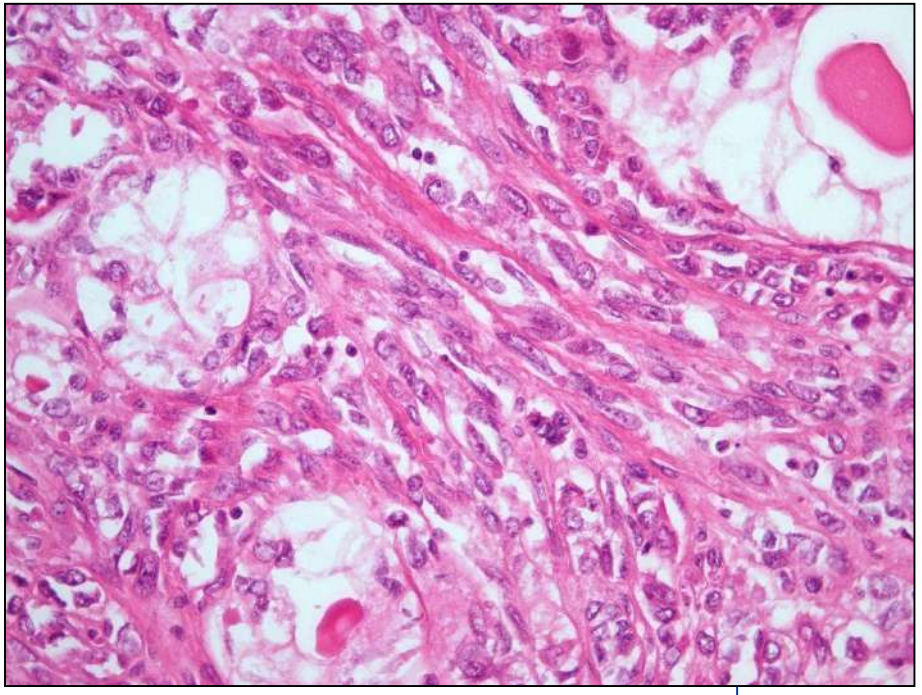


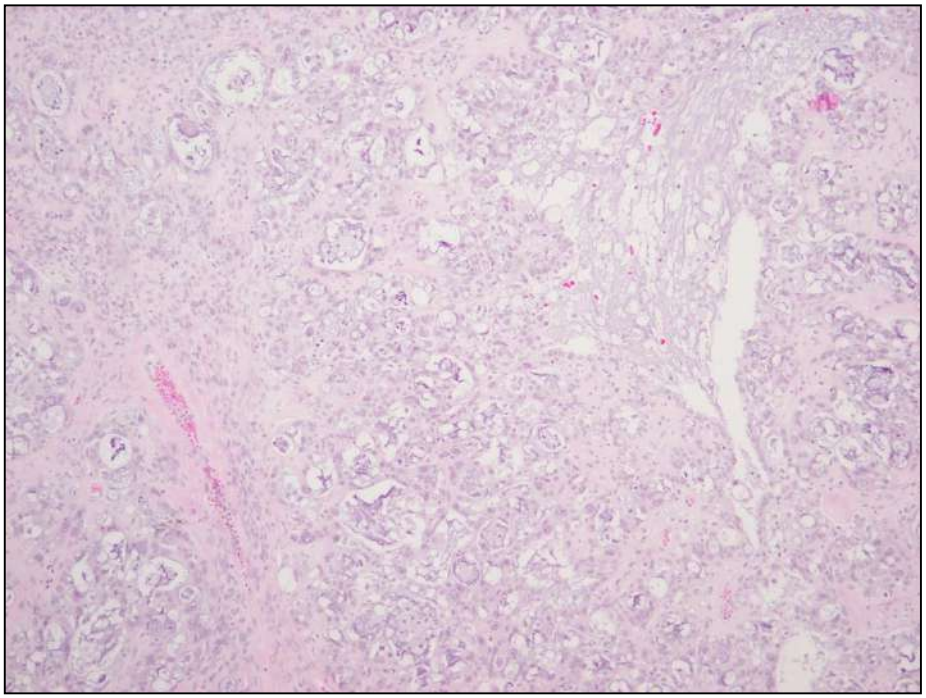


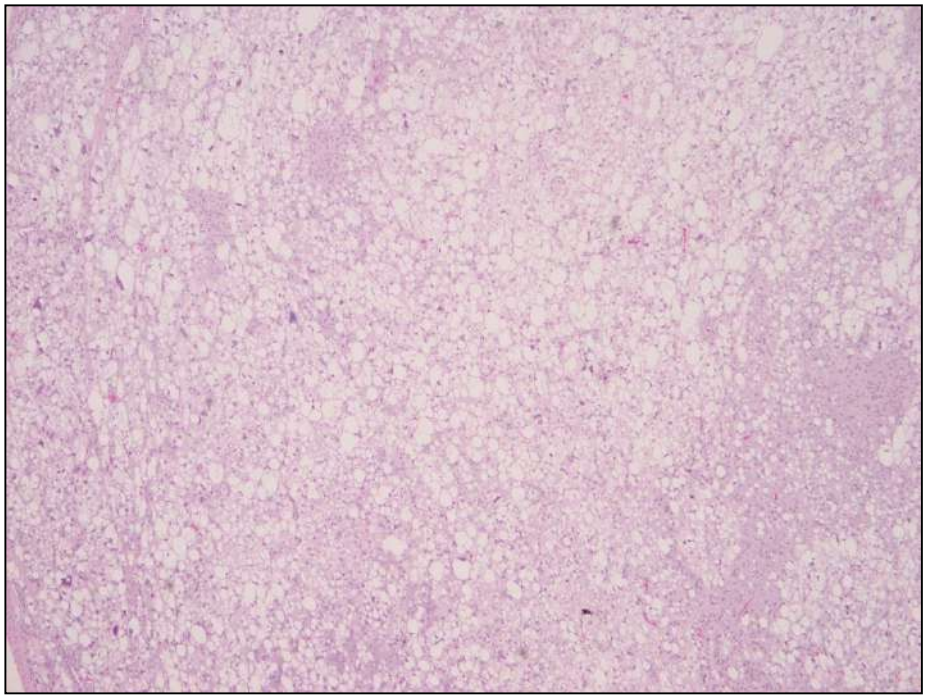


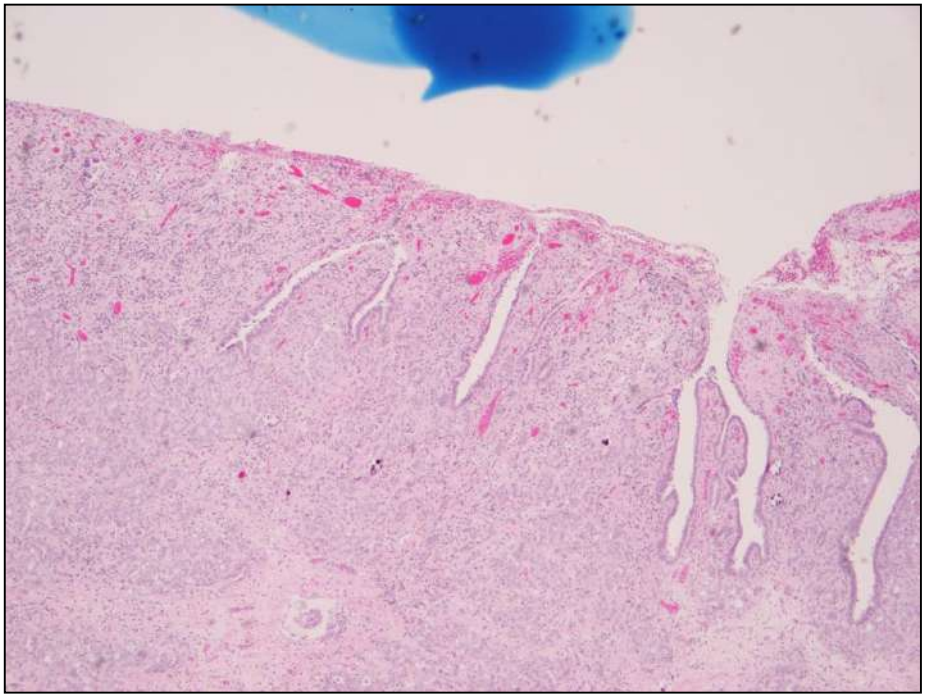




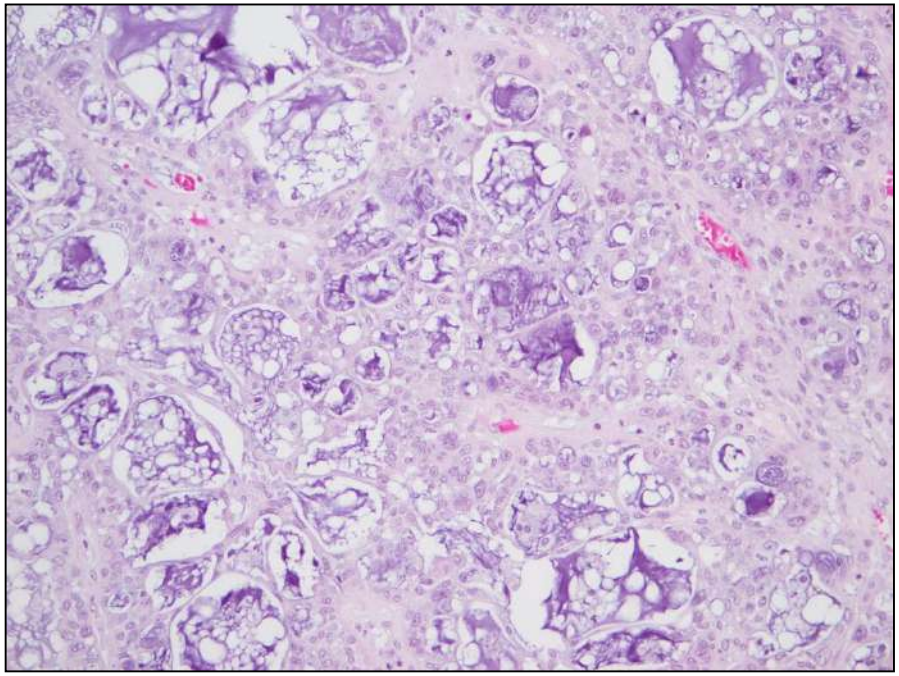


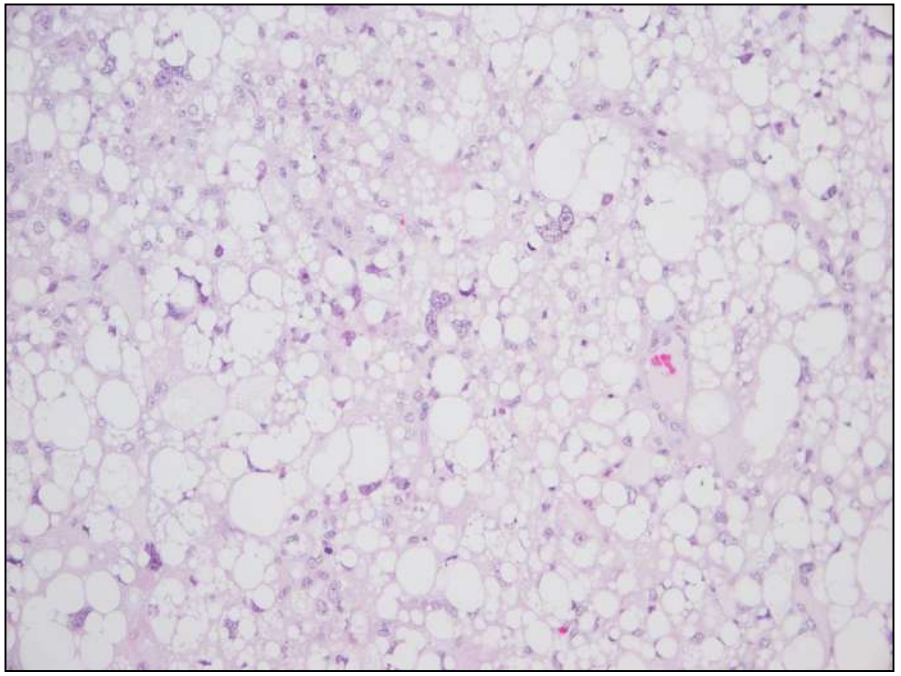


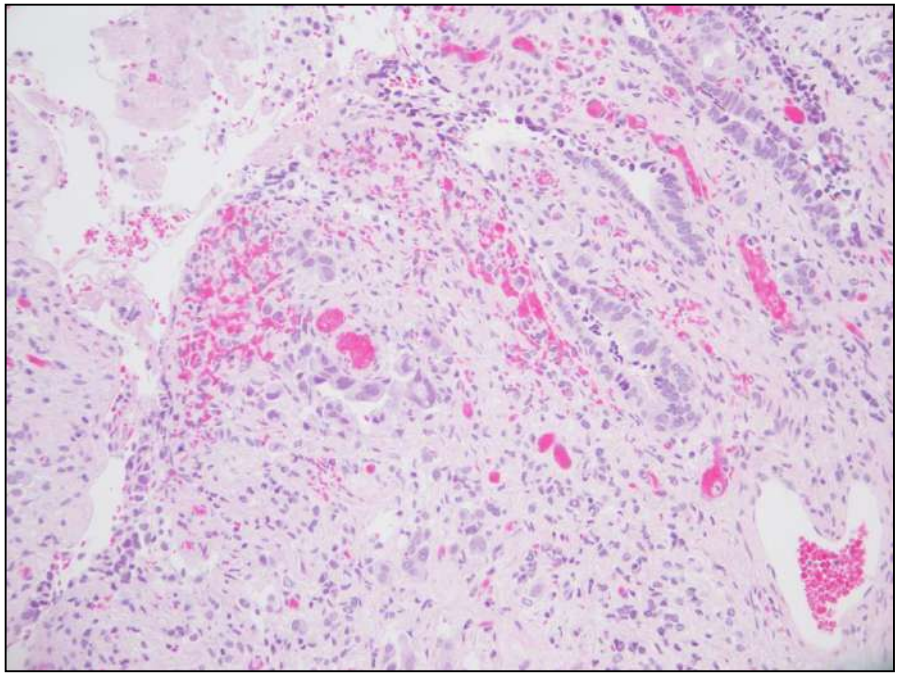


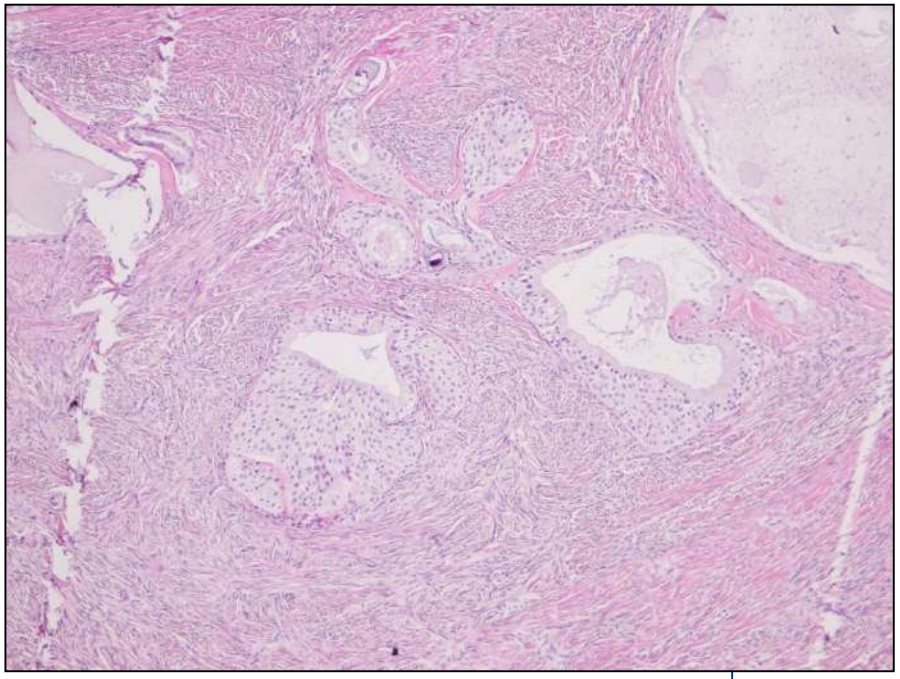


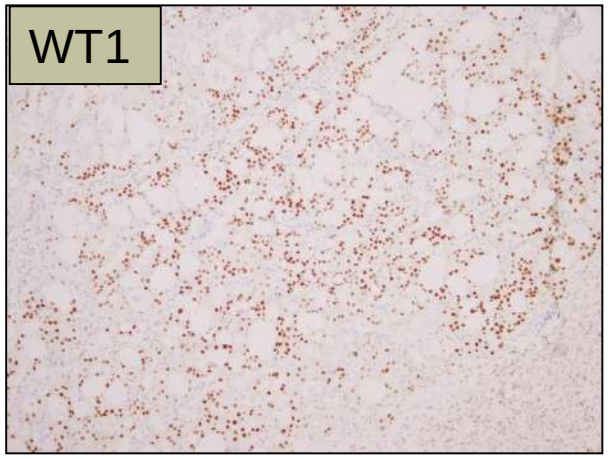
Oslo universitetssykehus

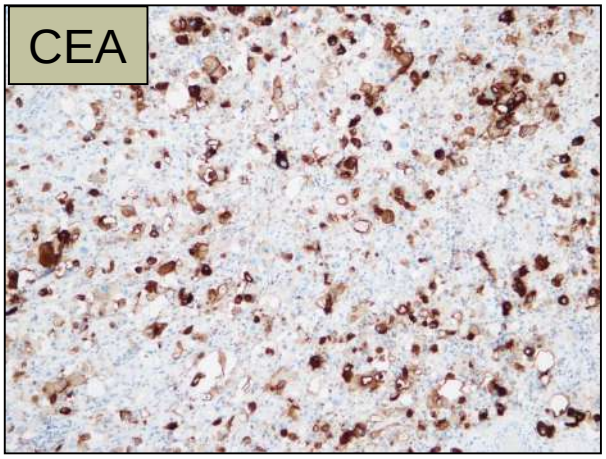


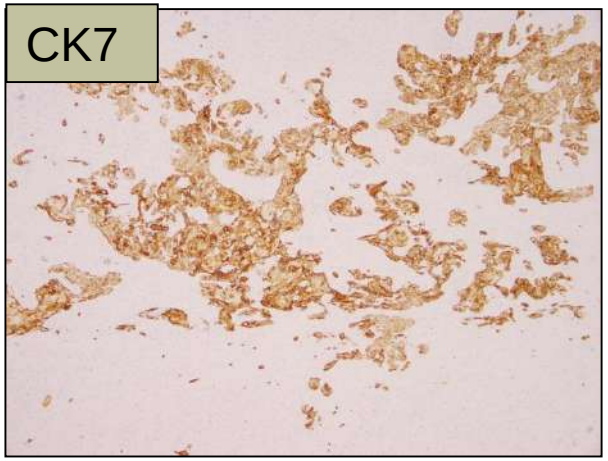


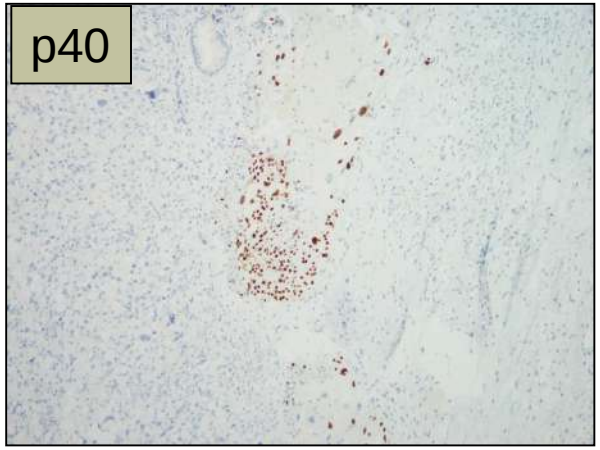


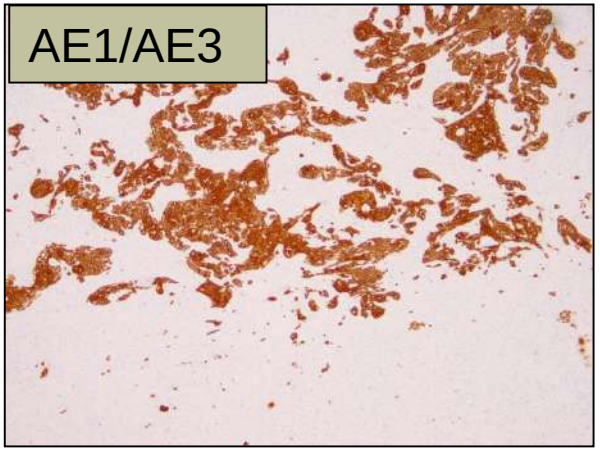


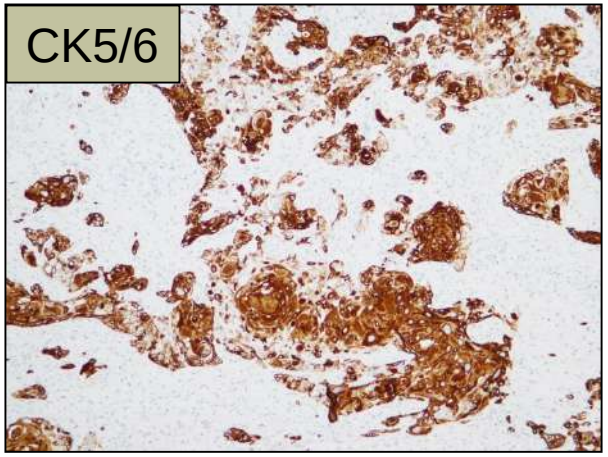


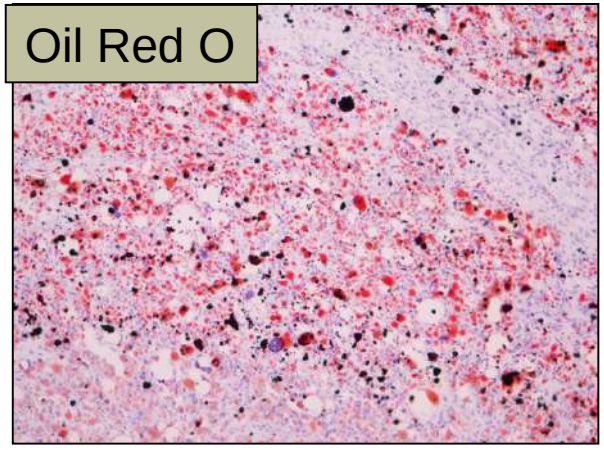


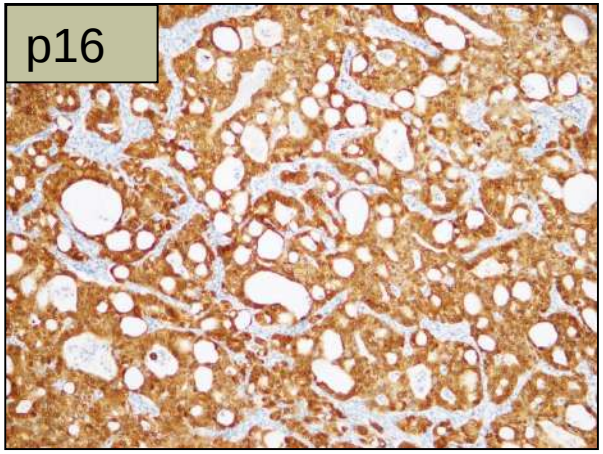








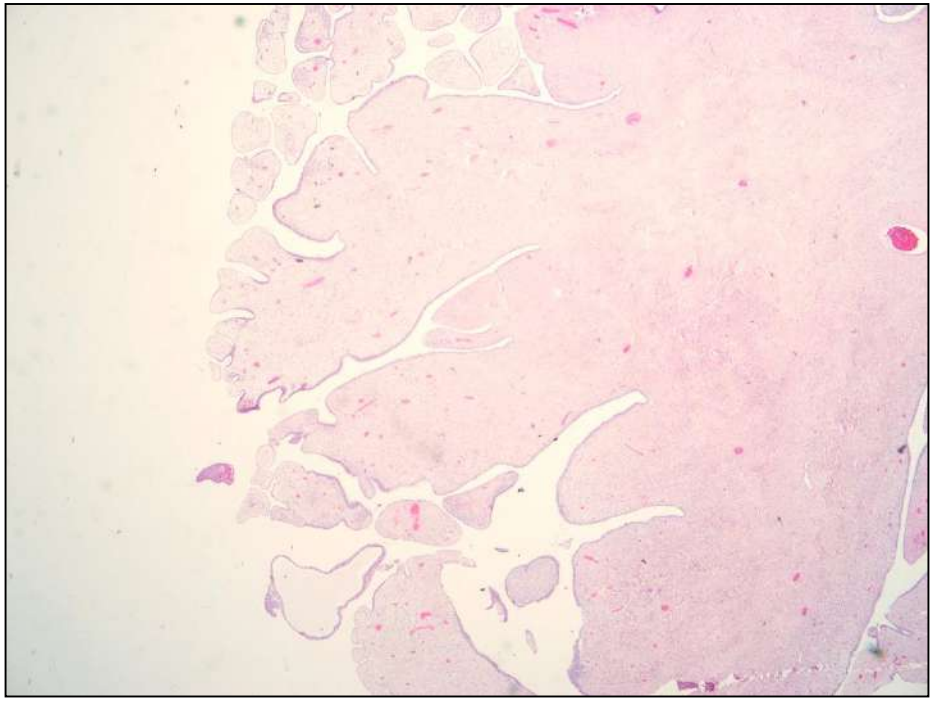
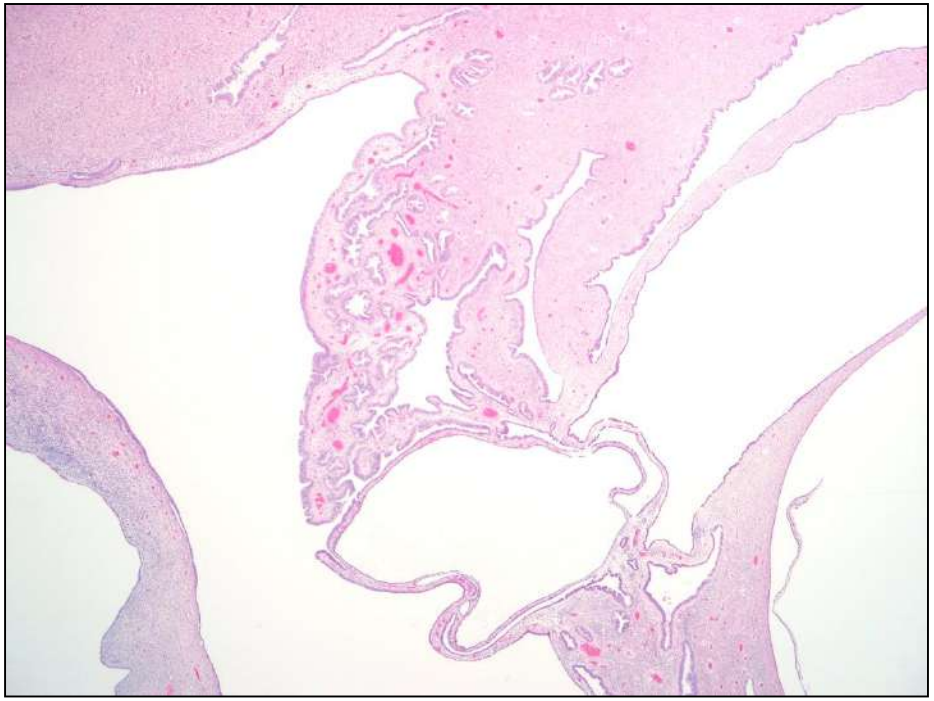
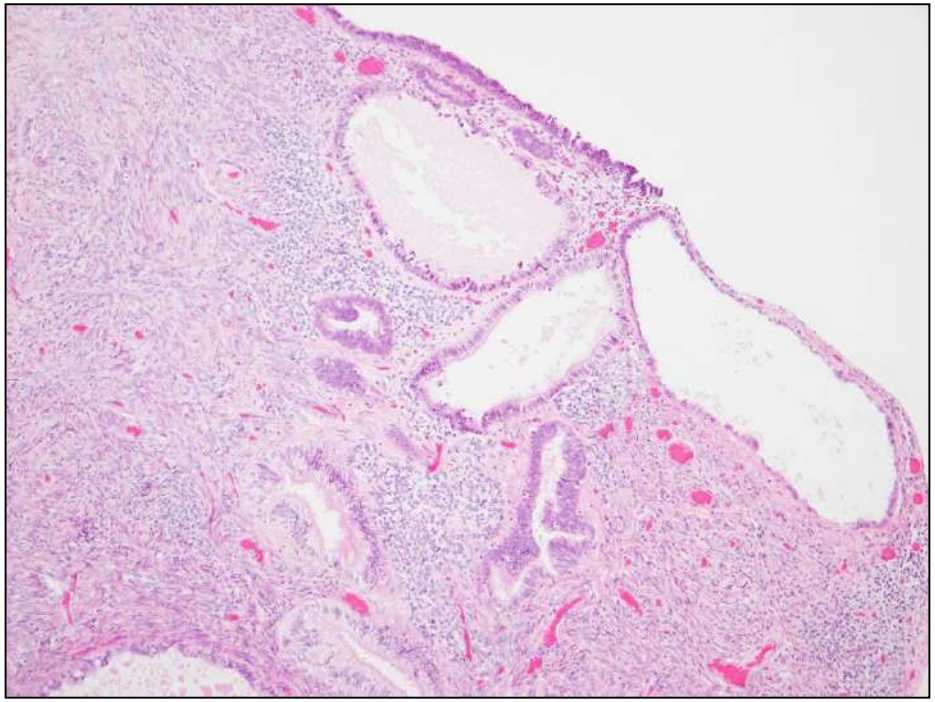
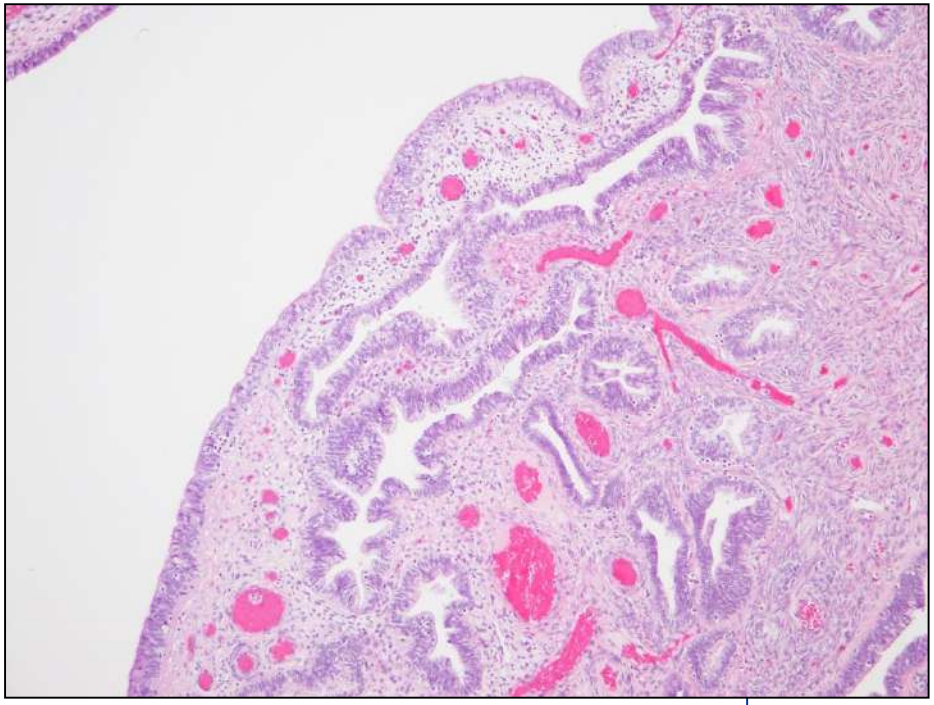


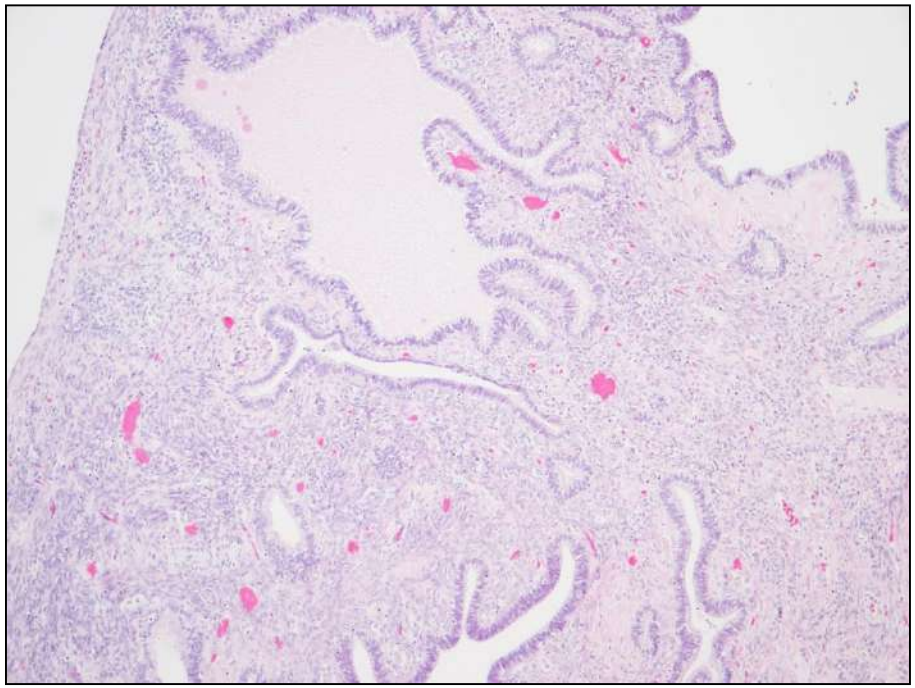


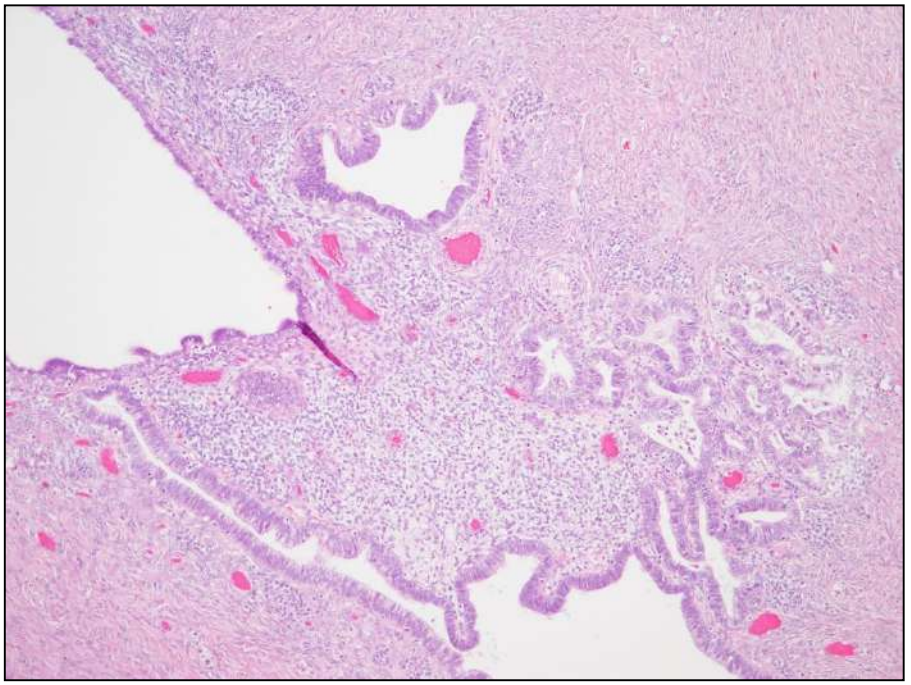
Oslo universitetssykehus

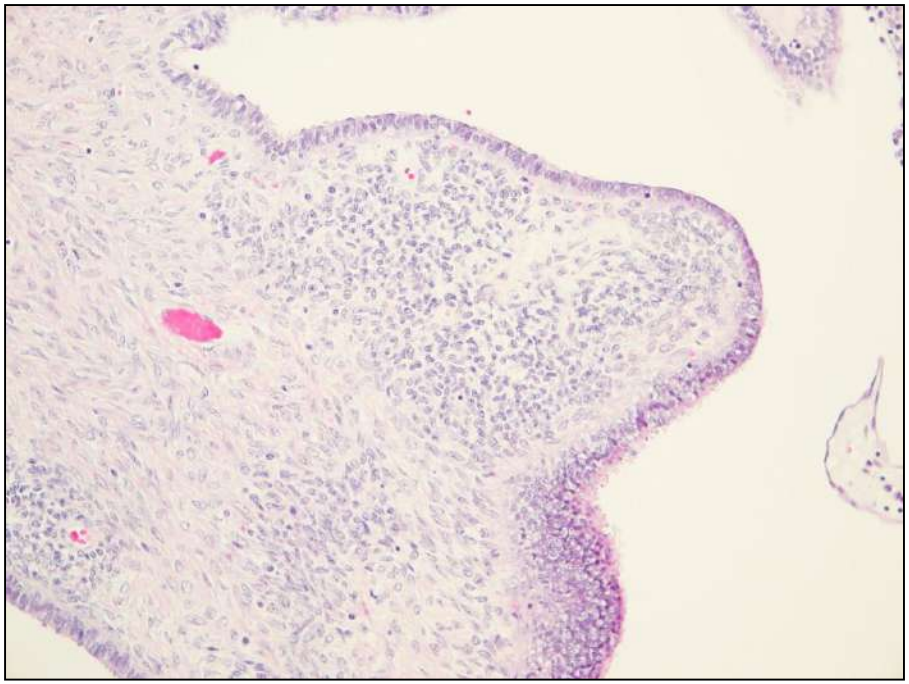
Endometriosis-associated tumors

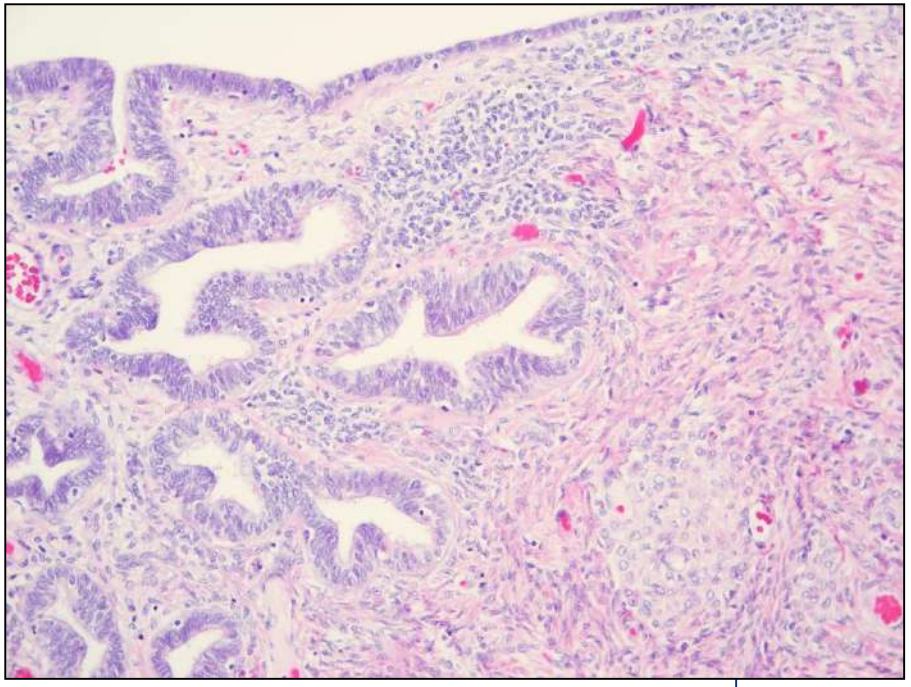
- Endometrioid carcinoma (EC)
- Clear cell carcinoma (CCC)
- Seromucinous tumors
- Low-grade serous carcinoma (LGSC)
- Carcinosarcoma
- Adenosarcoma
- Endometrial stromal sarcoma (ESS)

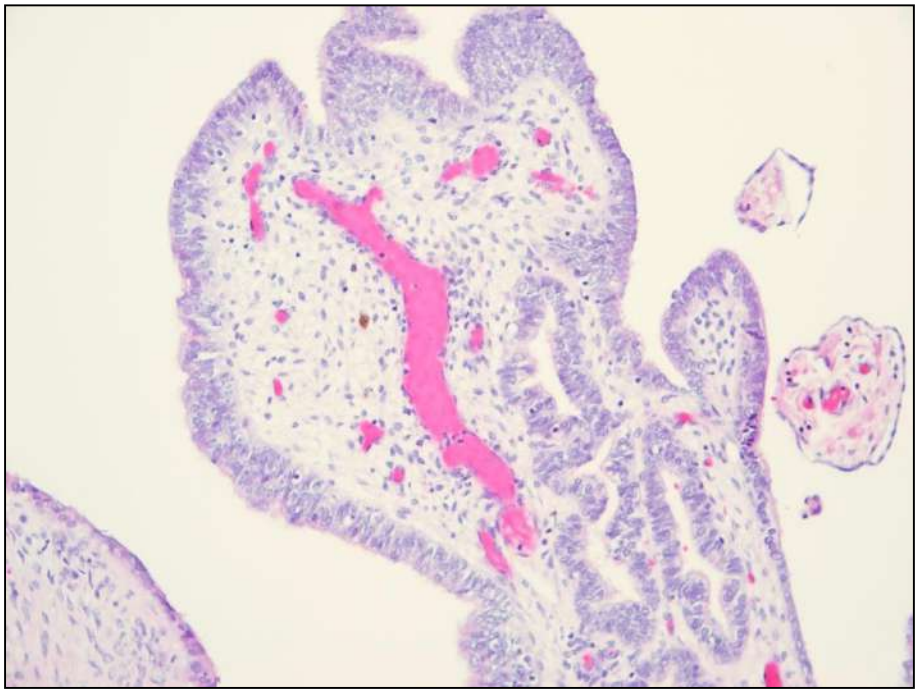


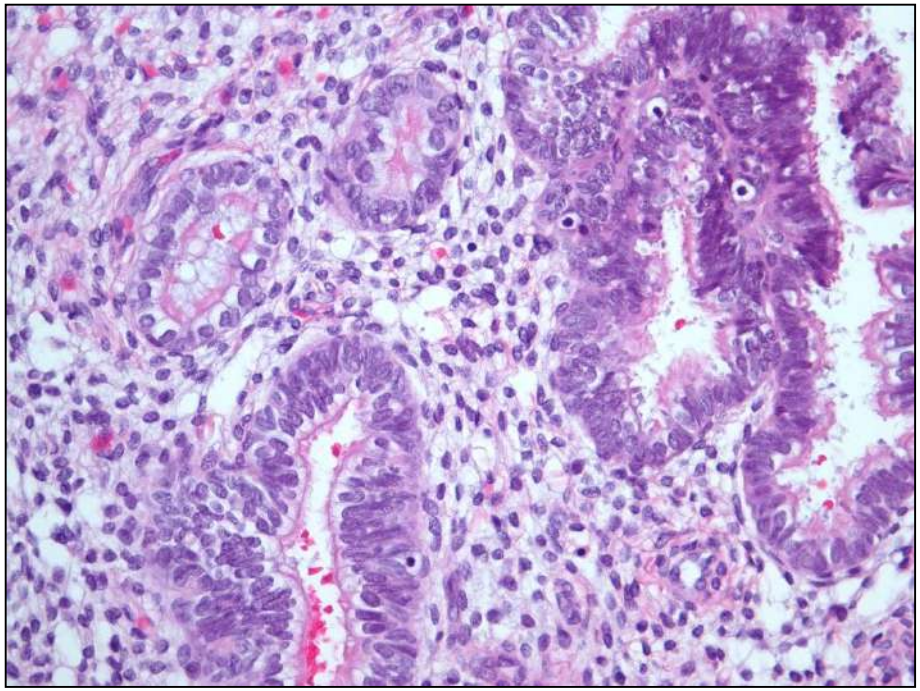


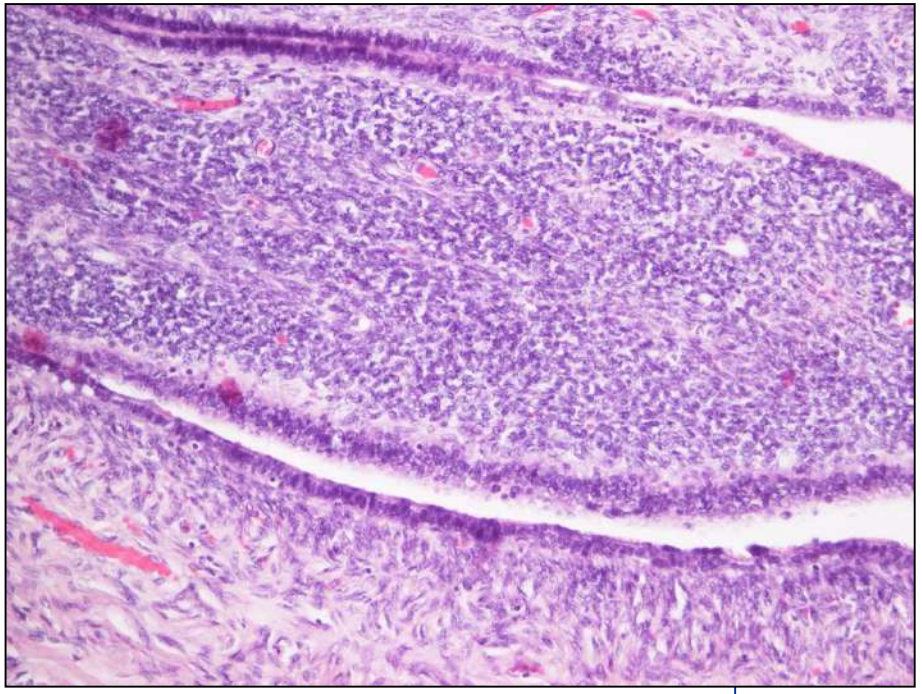


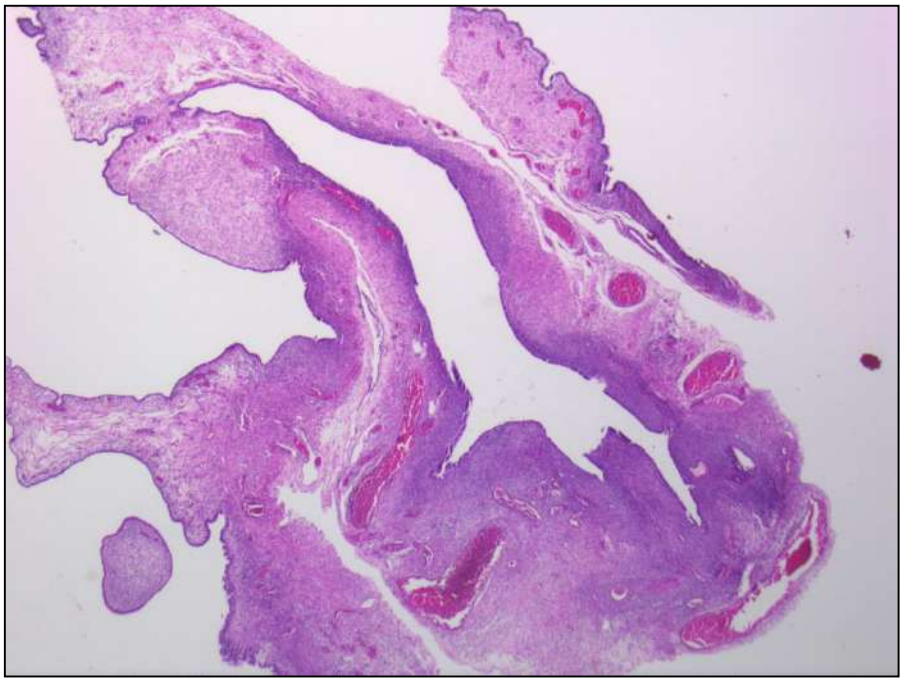




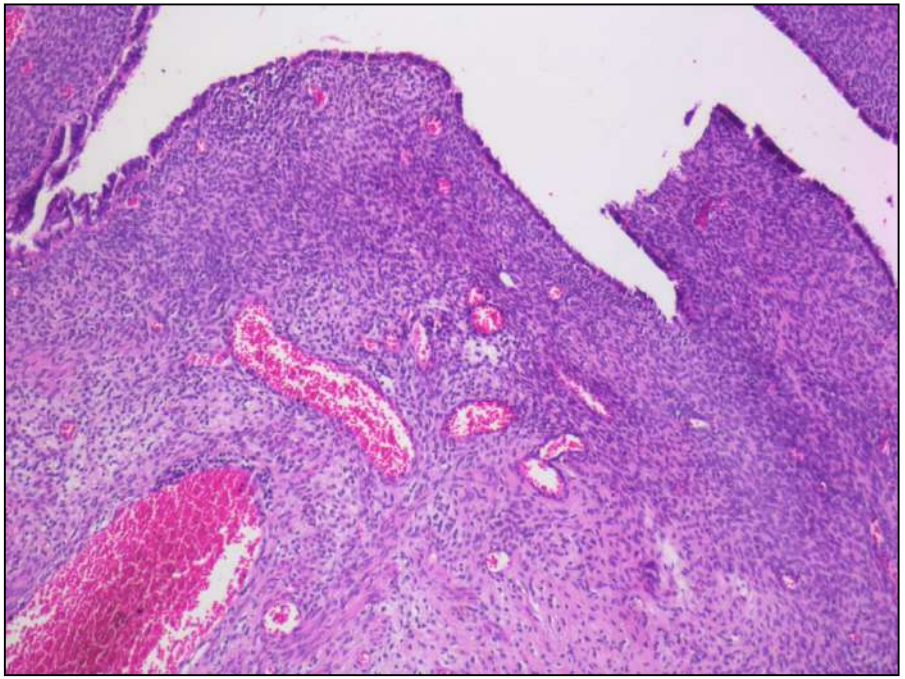


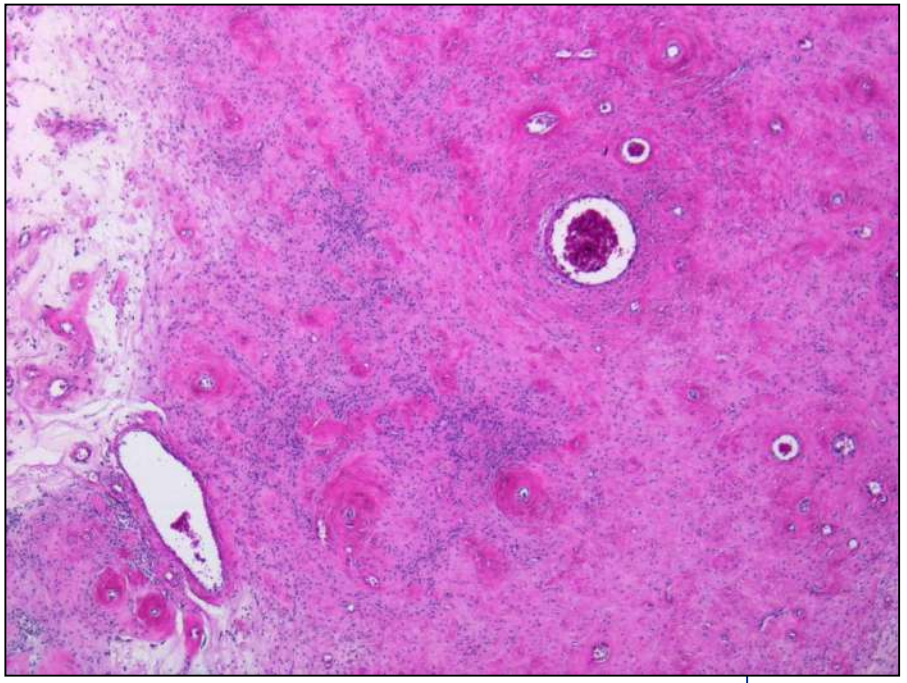


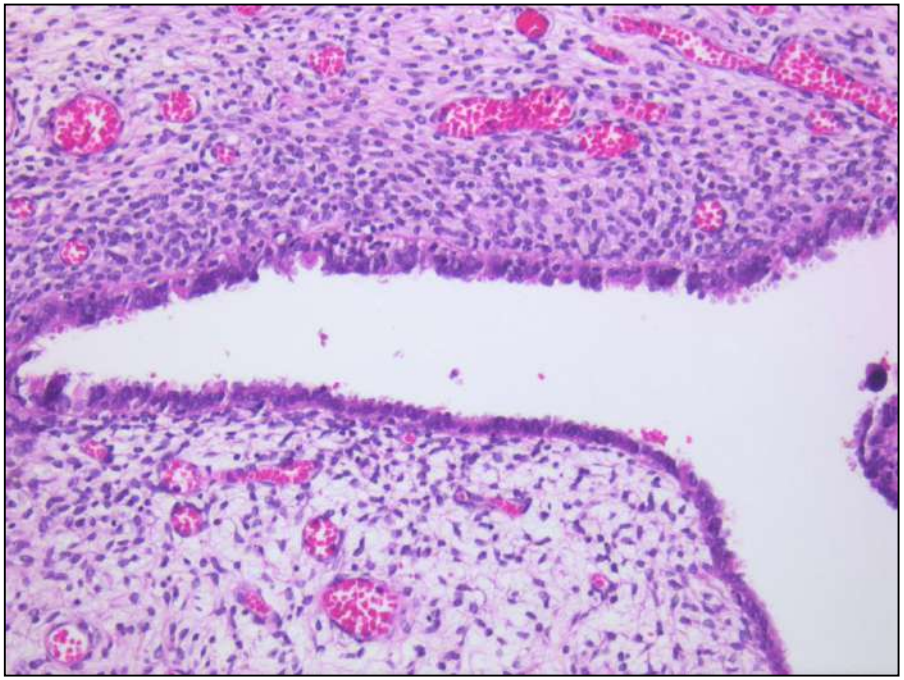


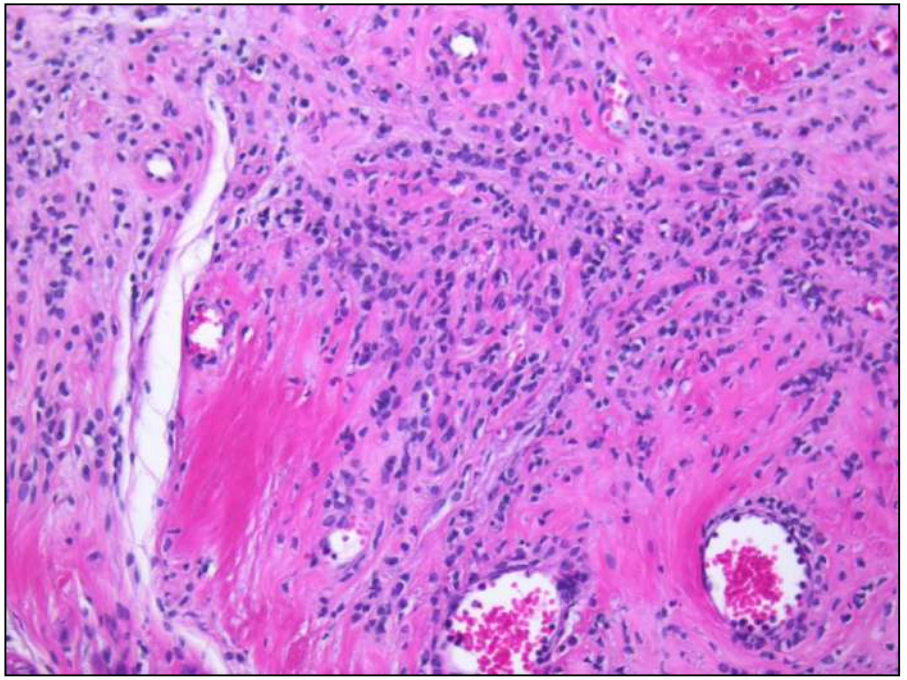




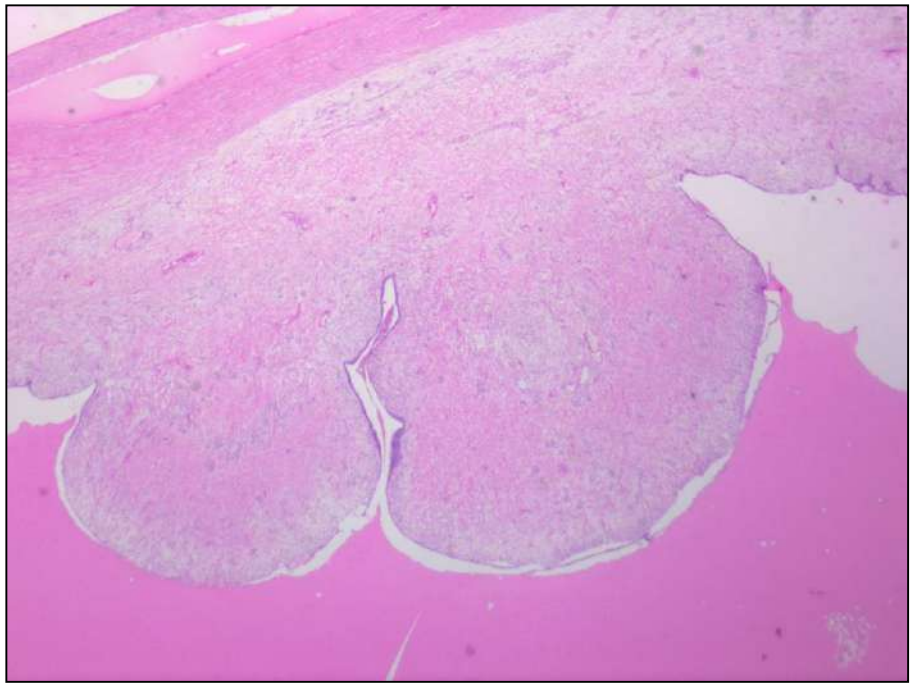


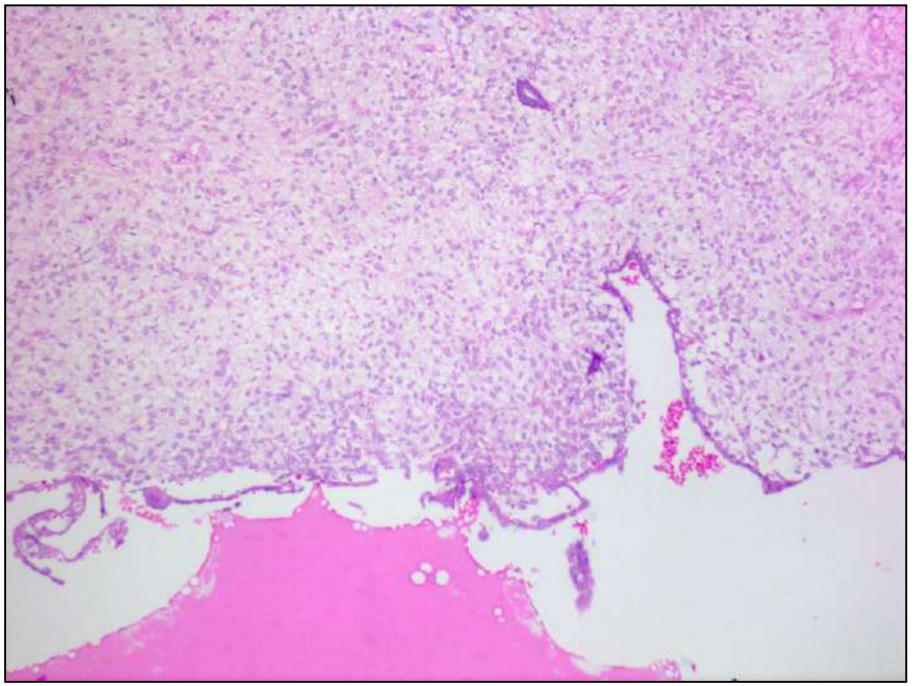


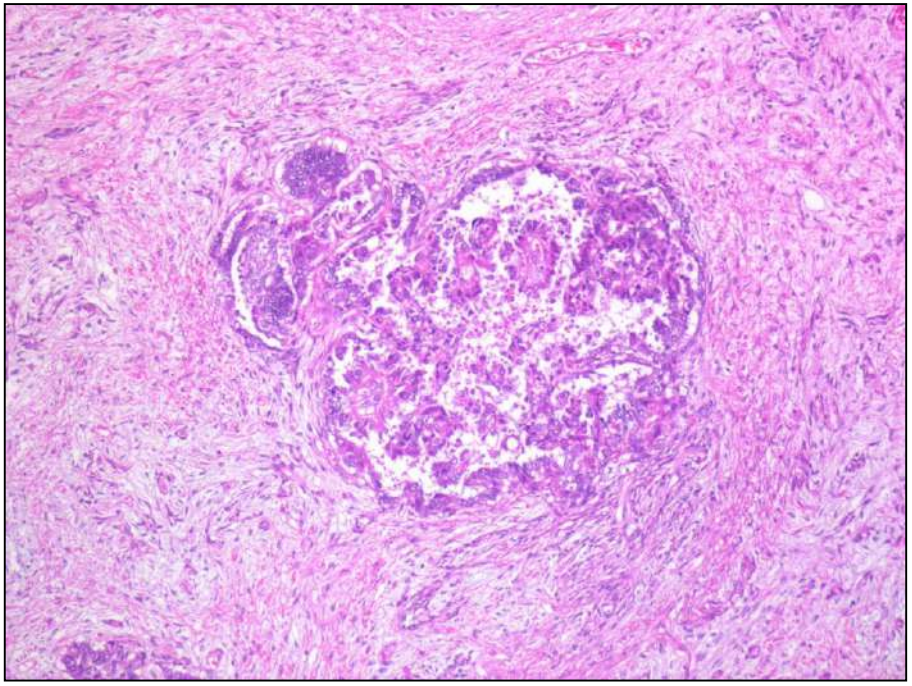


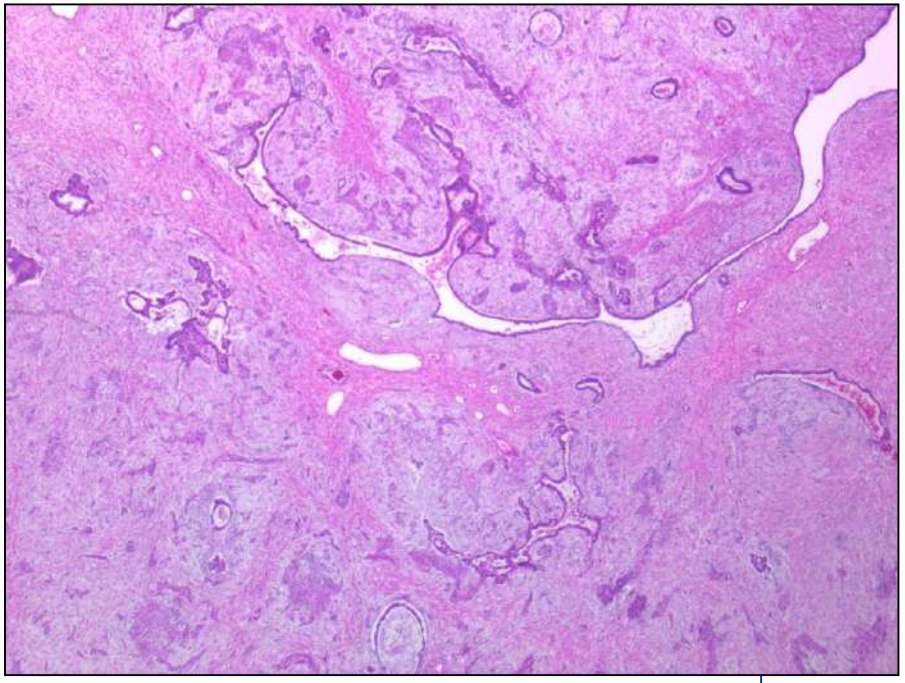


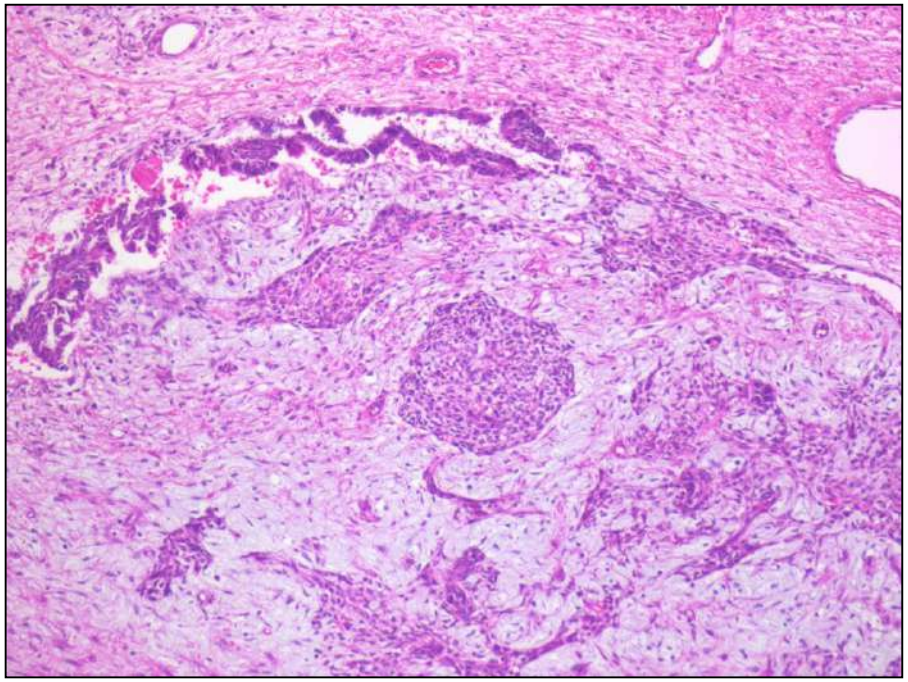
Oslo universitetssykehus

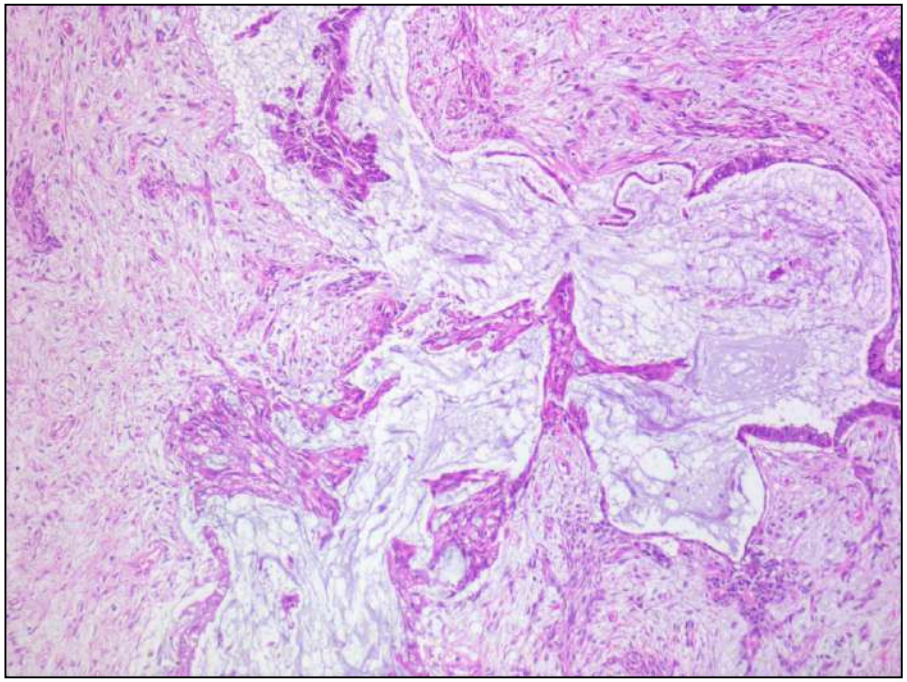


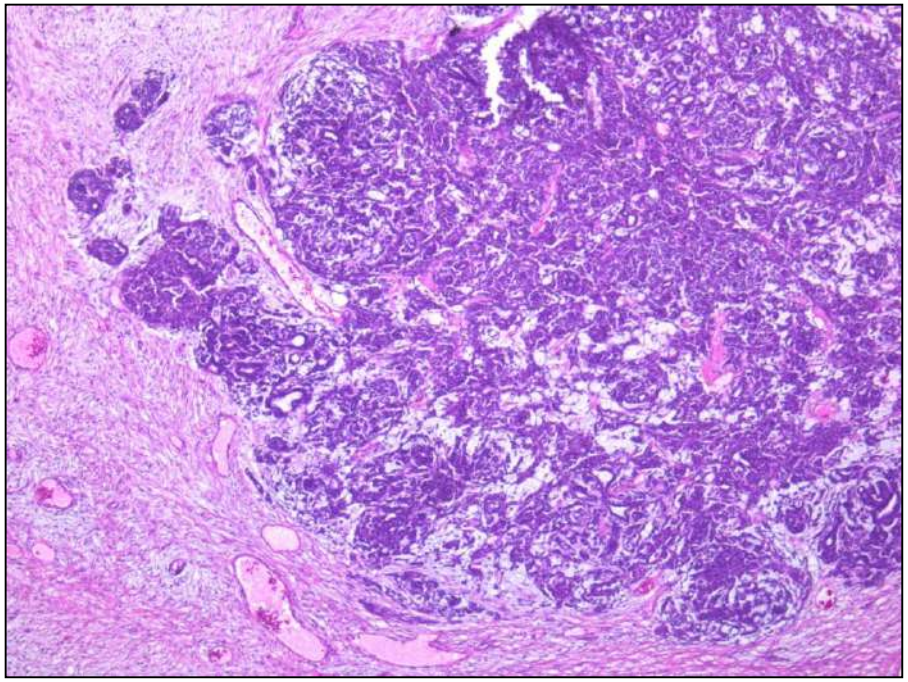


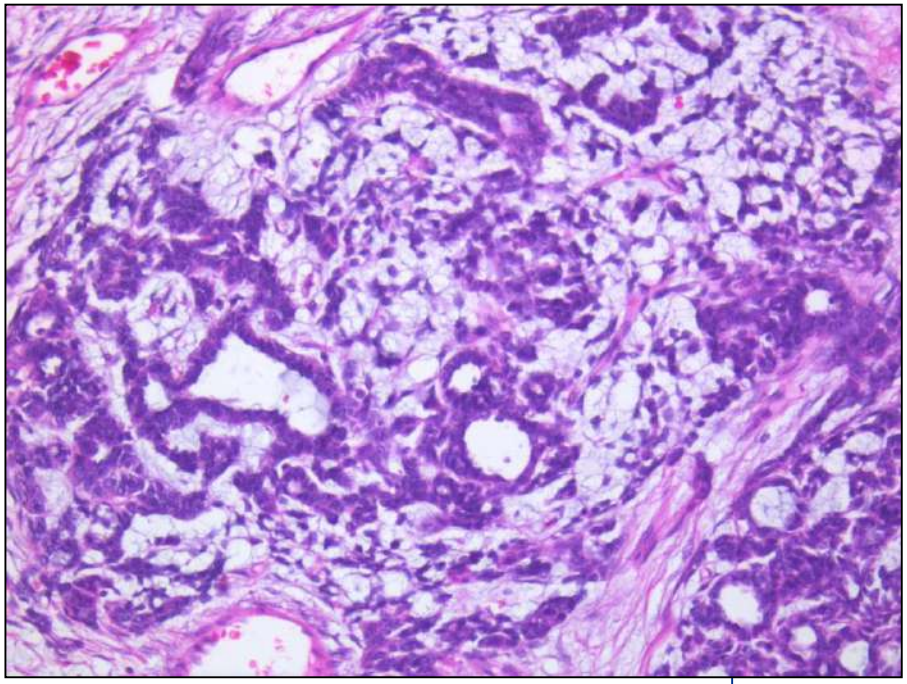


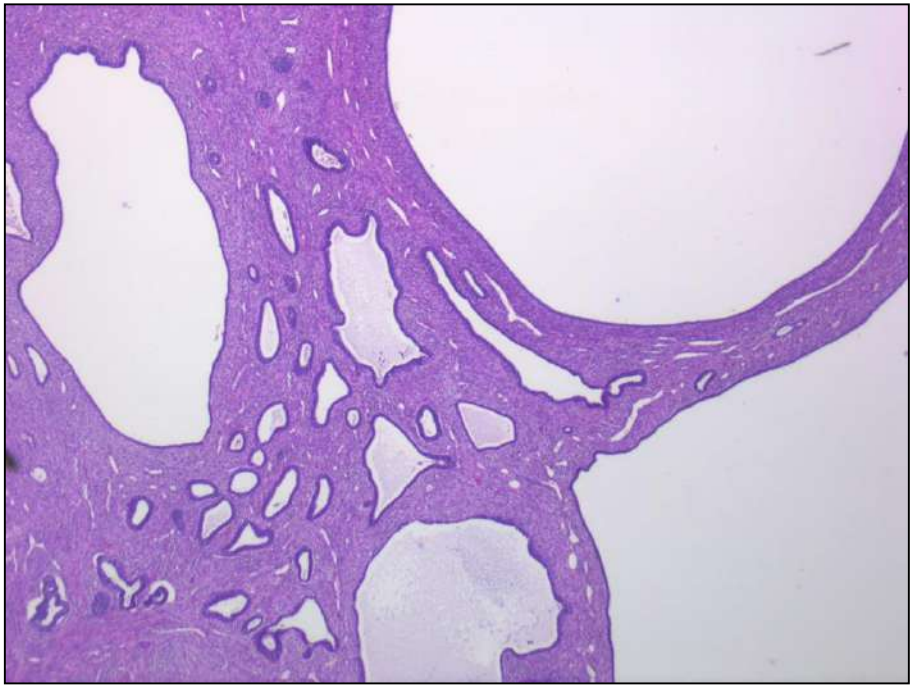


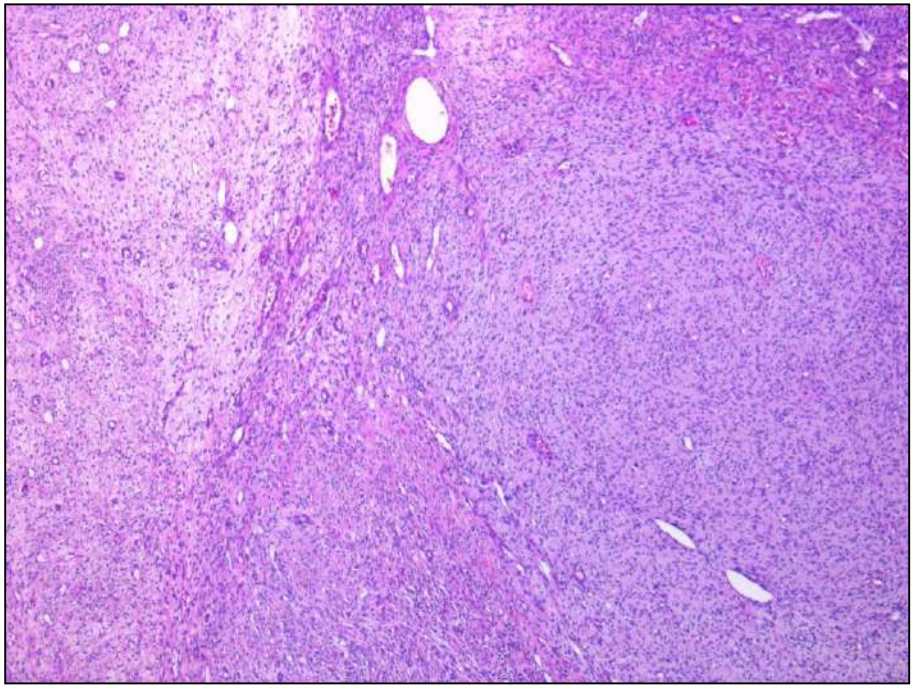


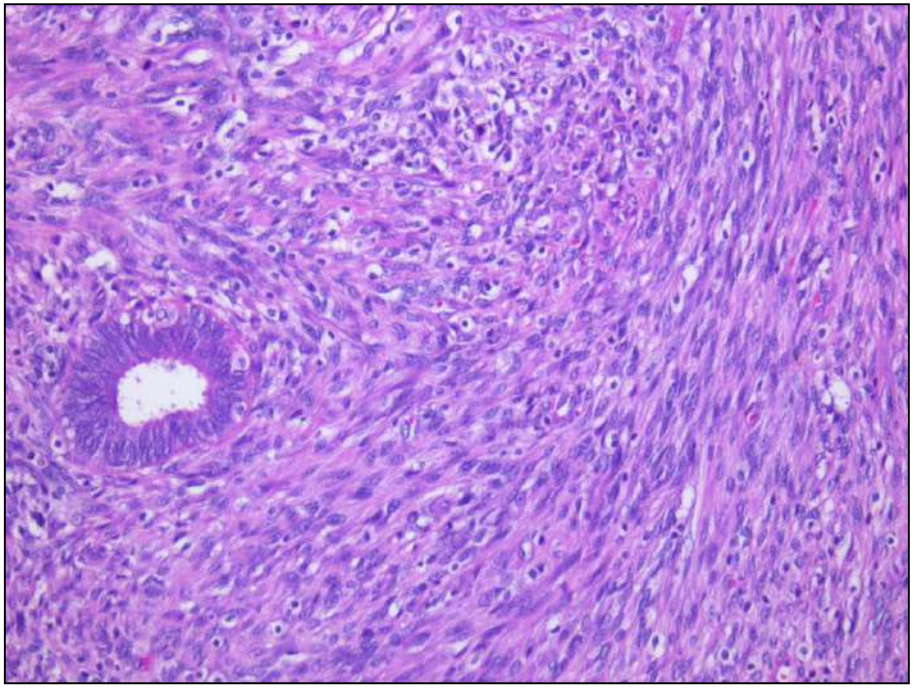


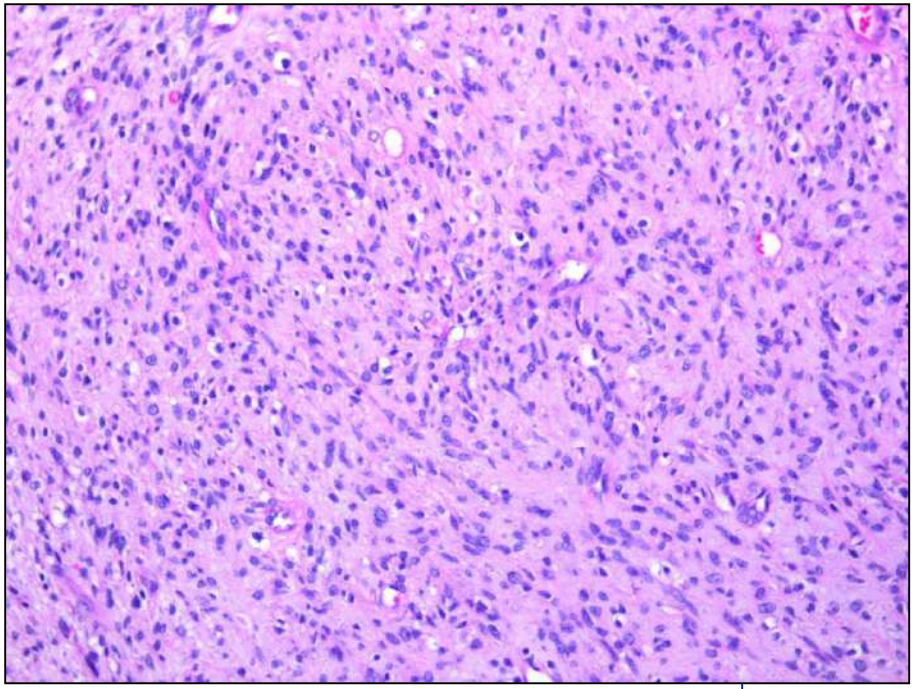


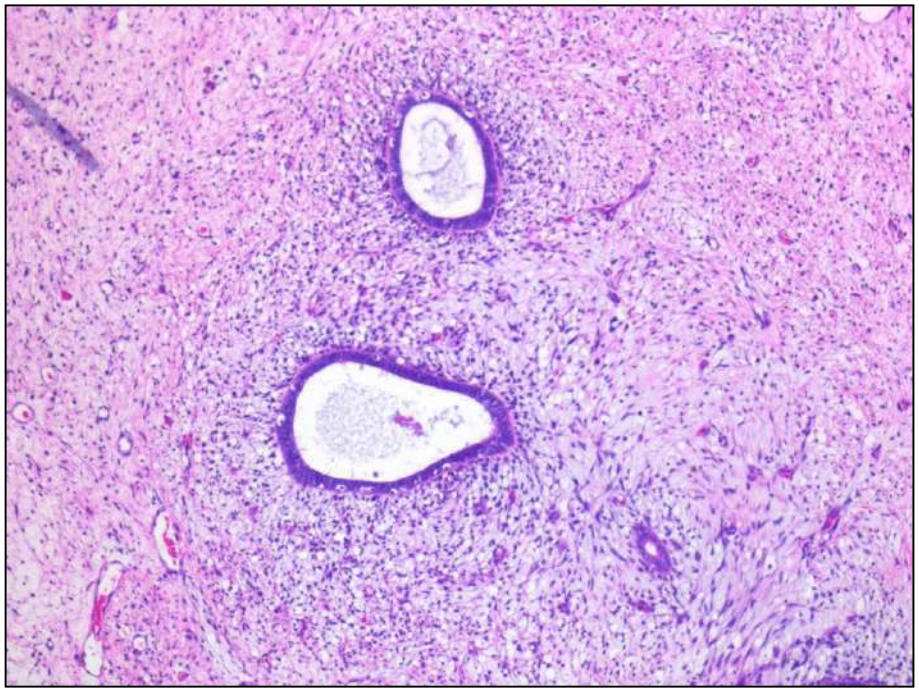


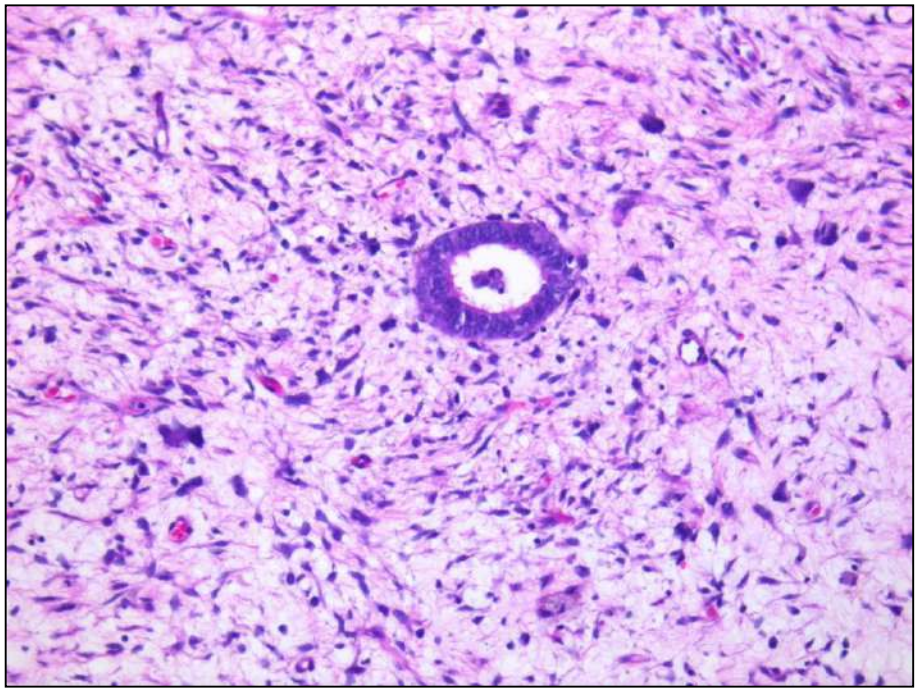


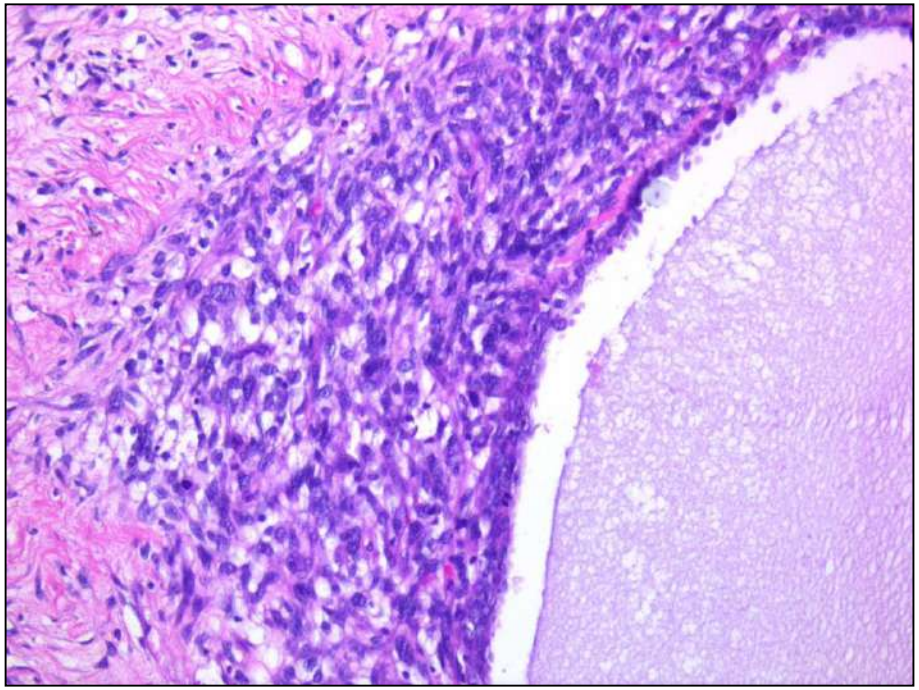












Oslo universitetssykehus

Take-home message

- Endometriosis is infrequently associated with neoplasia, predominantly carcinoma
- Endometriosis is of multi-factorial etiology
- Progression to neoplasia occurs through atypical endometriosis
- Molecular events underlie progression from endometriosis to neoplasia

Thank you for your attention



Oslo universitetssykehus