PATHOLOGY AND BIOLOGY OF EARLY EPITHELIAL OVARIAN CANCER AND RARE OVARIAN TUMOURS

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TO DISCUSS

- General comments about epithelial ovarian carcinoma
- Changes to WHO 2014
- Pathogenesis and molecular events in epithelial ovarian carcinoma
- Molecular developments in uncommon/ rare ovarian neoplasms

OVARIAN EPITHELIAL CARCINOMA (WHO 2014)- 5 major histotypes

- **low grade serous**
- **high grade serous**
- **mucinous**
- **endometrioid**
- **clear cell**
- Brenner
- seromucinous
- undifferentiated

RECENT POPULATION BASED (WASHINGTON / BRITISH COLUMBIA)

- 68-71% serous (17-18:1 ratio HGSC to LGSC)
- 3% mucinous
- 9-11% endometrioid
- 12-13% clear cell
- 1% transitional
- 6% mixed

LOW STAGE (I/II) VERSUS HIGH STAGE (III/IV)

	I/II	III/IV
serous	36%	88%
clear cell	26%	5%
endometrioid	27%	3%
mucinous	8%	1%

DIFFERENCES FROM PREVIOUS STUDIES

- increase in serous
- decrease in endometrioid
- marked decrease in mucinous
- reversal of endometrioid and clear cell ratio

REASONS FOR DECLINE IN MUCINOUS CARCINOMAS

- exclusion of secondaries
- pseudomyxoma peritonei (PMP) - usually appendiceal origin
- redefinition of criteria for borderline mucinous (intraepithelial carcinoma)
- VARIABILITY STILL EXISTS BETWEEN BORDERLINE AT UPPER END OF SPECTRUM AND MUCINOUS CARCINOMA WITH EXPANSILE INVASION

REASONS FOR INCREASE IN SEROUS AND DECREASE IN ENDOMETRIOID

- Recognised that many neoplasms that were previously diagnosed as high grade endometrioid are actually HGSC (WT1)

TYPING OF OVARIAN CARCINOMA

- at present typing of some/ limited therapeutic significance
- treatment traditionally more dependent on stage and grade
- NOW DIFFERENT THERAPY FOR DIFFERENT OVARIAN CANCER TYPES (surgery, traditional chemotherapy, targetted therapies)
- ongoing trials regarding alternative therapeutic agents in clear cell, mucinous and low grade serous carcinoma (chemoresistant neoplasms)

DIFFERENTIAL DIAGNOSIS AFFECTING MANAGEMENT

- Core biopsies- low grade versus high grade serous carcinoma (chemo versus surgery)
- Resections- low grade versus high grade serous carcinoma (chemo versus no chemo)
- Biopsies of unresectable tumours- low grade versus high grade serous carcinoma (chemo versus hormonal therapy)
- HGSC versus endometrioid (BRCA versus Lynch testing)
- HGSC versus clear cell carcinoma (BRCA versus Lynch testing)
- HGSC versus low grade endometrioid carcinoma (management and BRCA versus Lynch testing)

OTHER REASONS FOR ACCURATE TYPING

- carcinoma grading (differs between different types)
- screening, personal and family history risk (BRCA, Lynch)
- clear cell and mucinous histology (although rare) are independent predictors of poor outcome in advanced stage
- ? need for lymphadenectomy in stage I ovarian carcinoma

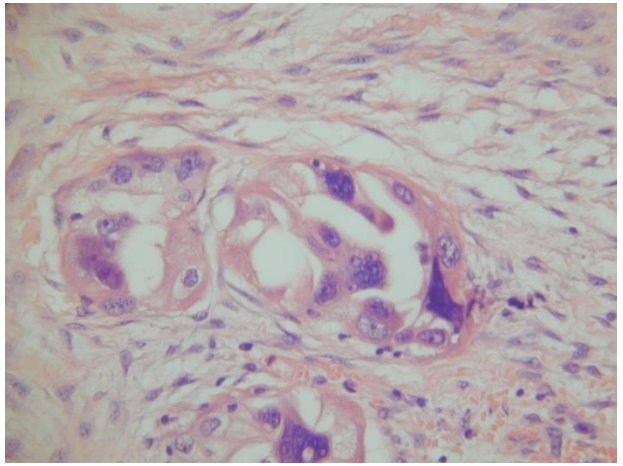
OVARIAN CARCINOMA GRADING- INTERNATIONAL COLLABORATION ON CANCER REPORTING

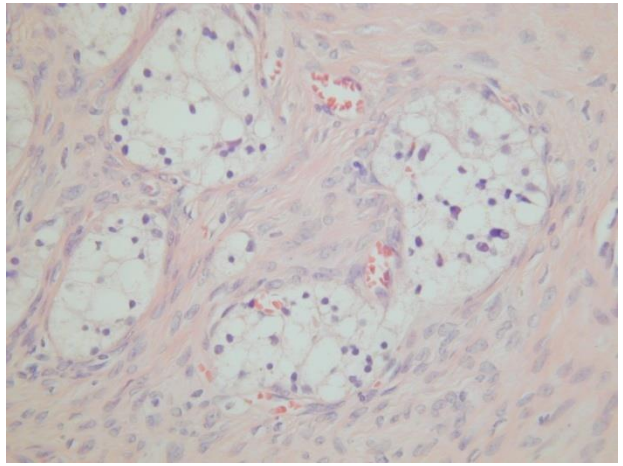
- **serous- low grade and high grade (2 different types)**
- **endometrioid- like uterine corpus**
- **clear cell- automatically high grade**
- mucinous- as for endometrioid
- seromucinous- as for endometrioid

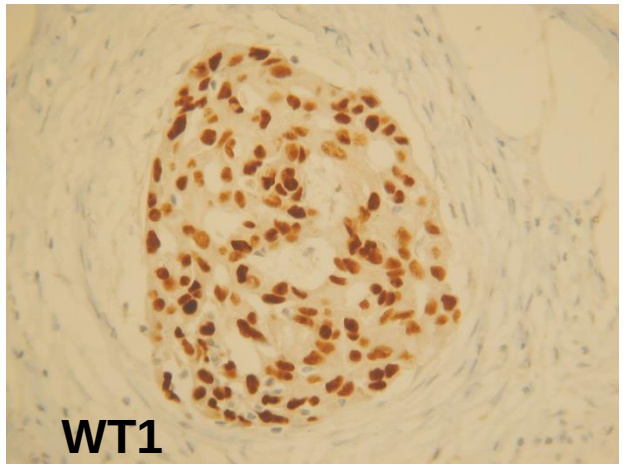
POST-CHEMOTHERAPY

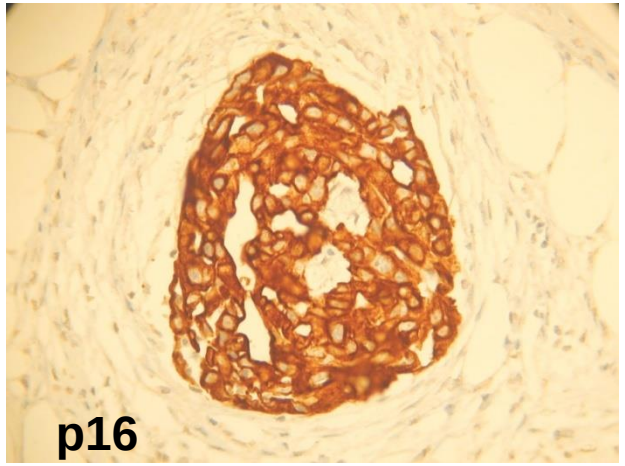
- up-front chemotherapy sometimes administered (poor operative risk, stage IV, lot of upper abdominal disease, miliary disease etc)
- MAY BE DIFFICULT TO TYPE UNLESS MINIMAL OR NO RESPONSE (markers still useful)
- require pre-chemotherapy biopsy (not just ascitic fluid) for typing of carcinoma and to have tissue available for studies/targetted and personalised treatments

POST CHEMO









REPRODUCIBILITY OF OVARIAN CARCINOMA TYPING

- Brugghe et al (IJGC, 1995) - 61%
- Bertelsen et al (IJGC, 1993) - 72% (serous and endometrioid); 86% (mucinous); 100% (clear cell)
- Baak et al (AQCH, 1986) - significant variation
- Cramer et al (APLM, 1987) – suboptimal
- Lund et al (APMIS, 1991) – 68%
- Sakamoto et al (Gynecol Oncol, 1994) -53%

RECENT STUDY ON REPRODUCIBILITY OF OVARIAN CARCINOMA TYPING

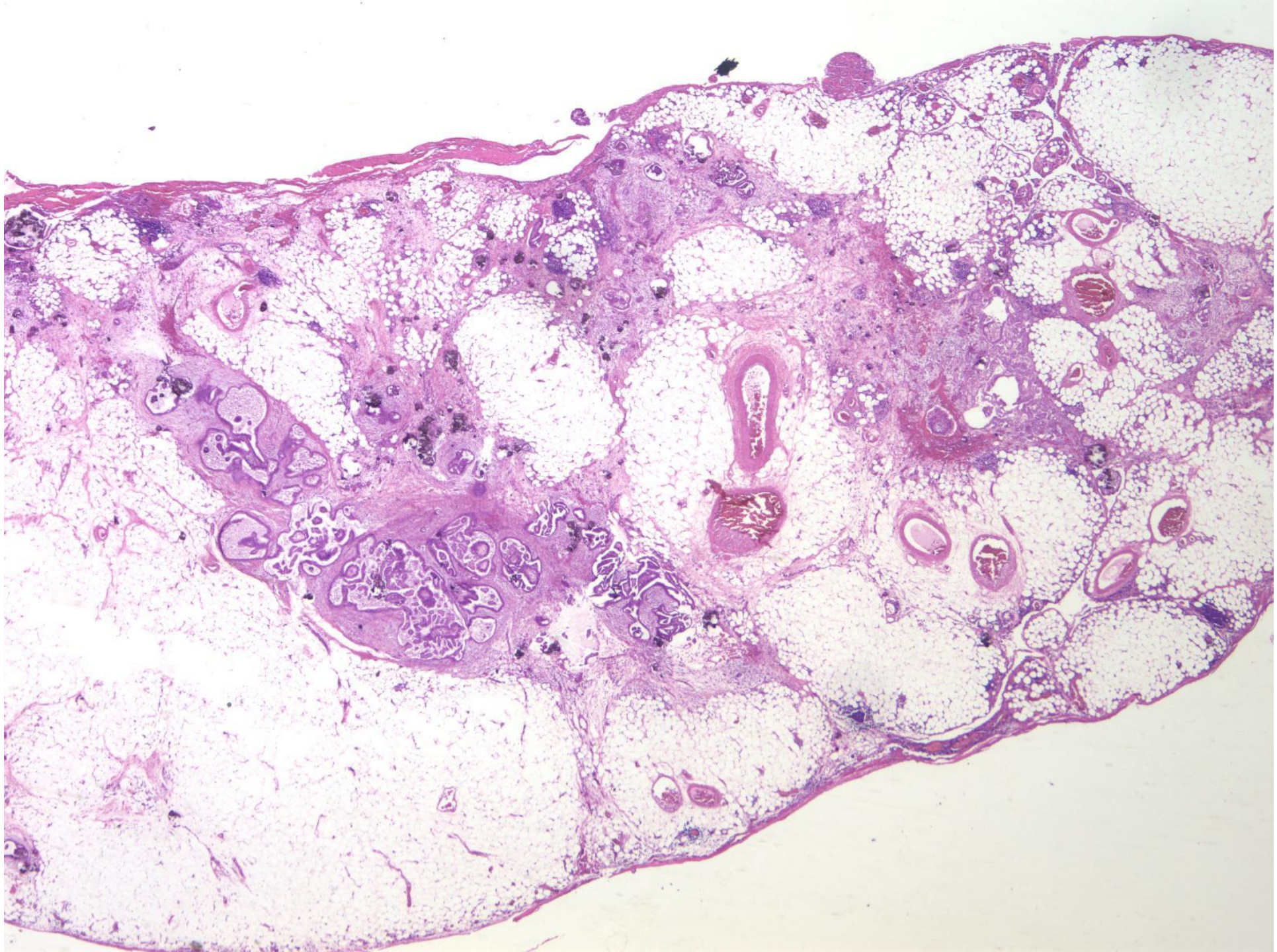
- Koebel et al, Am J Surg Pathol 2010;34;984-93.
- excellent agreement
- participants had training in modern criteria
- important for subtype specific ovarian cancer treatments
- CONTRAST WITH UTERINE CARCINOMA
- good marker- WT1

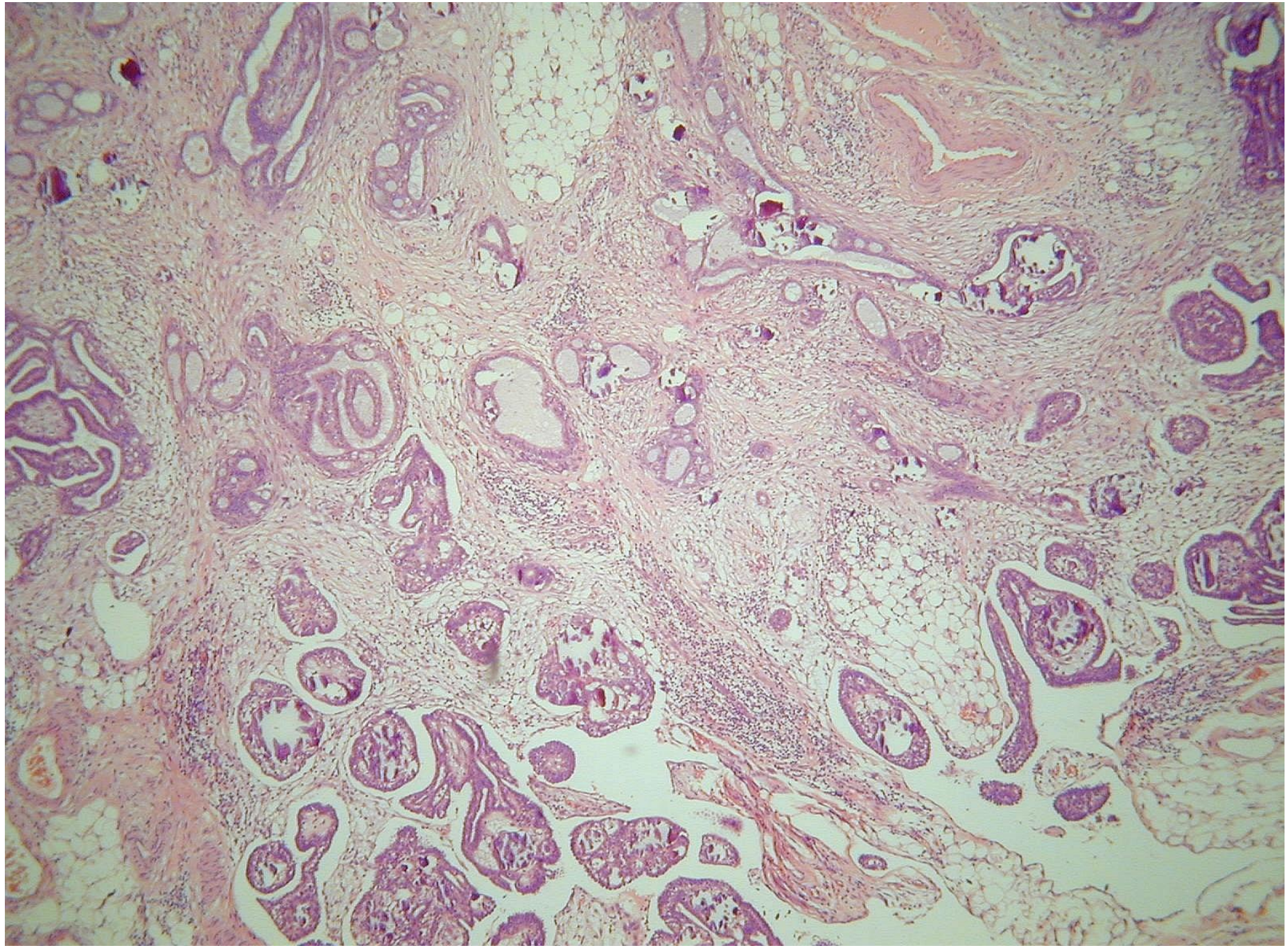
WHO 2014-OVARY AND FALLOPIAN TUBE- CHANGES

- Epithelial tumours
  - benign tumours- cystadenoma and adenofibroma
  - changes related to borderline tumours
  - categories of low grade and high grade serous carcinoma
  - transitional carcinoma dropped
  - no category of mixed carcinoma
  - new category of seromucinous tumour

CHANGES RELATED TO BORDERLINE TUMOURS

- Borderline/ atypical proliferative are synonymous
- Micropapillary variant of serous borderline/ non-invasive low grade serous carcinoma are synonymous
- Non-invasive implants- just call “implants” (in practice I still divide into epithelial and desmoplastic)
- Invasive implants- call LGSC (in practice, I do both)





TRANSITIONAL CARCINOMA

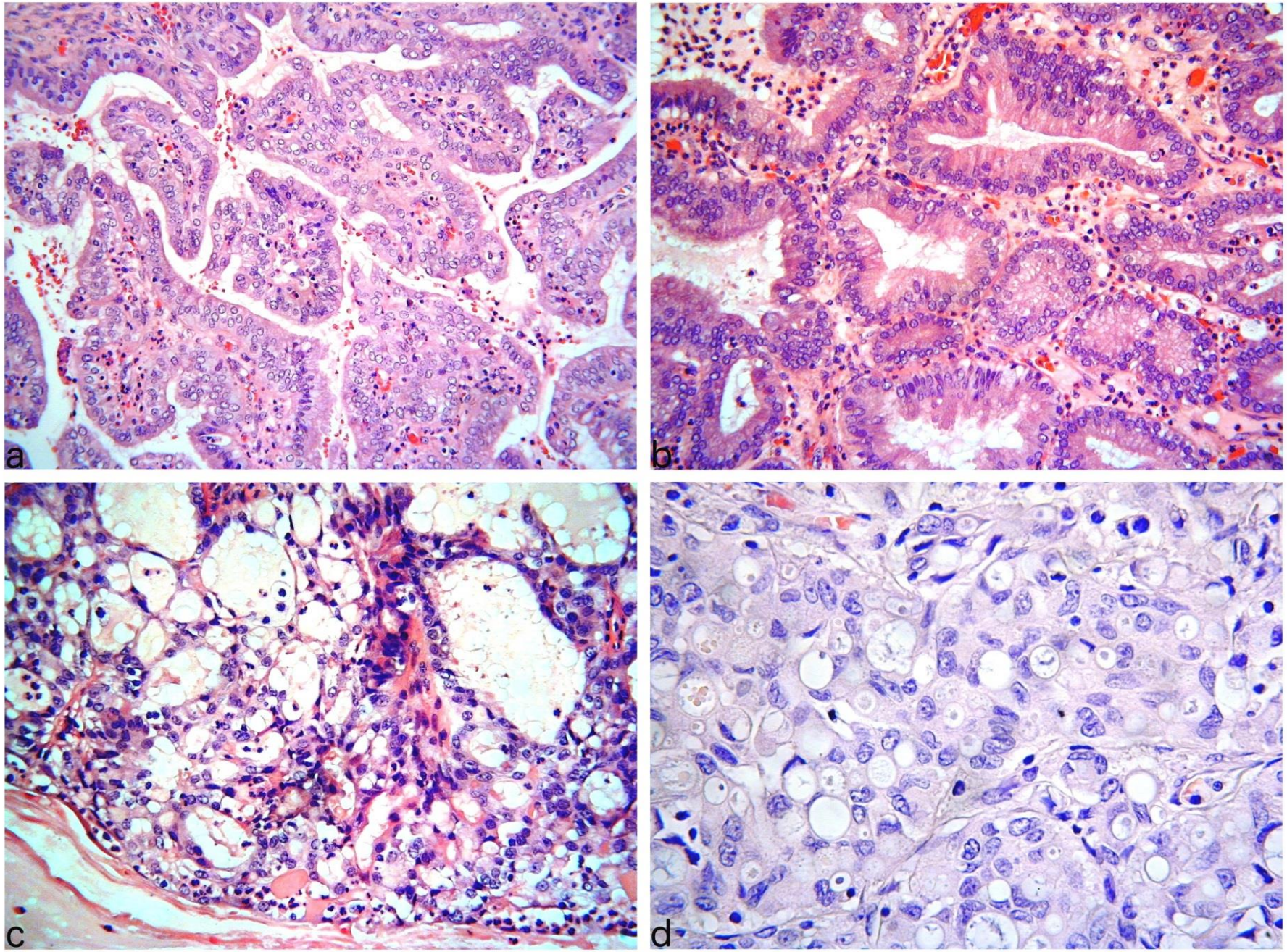
- dropped from WHO 2014
- most are variants of high grade serous (“transitional-like”) (more typical areas if sample well; omental metastases may look like high grade serous; WT1 positive; aberrant p53)
- some are variants of endometrioid carcinoma (transitional-like morphology)
- still categories of benign, borderline and malignant Brenner

SEROMUCINOUS TUMOURS

- new separate category in WHO 2014
- cystadenoma/adenofibroma; borderline/ atypical proliferative; carcinoma
- borderline most common (previously known as Mullerian/ endocervical mucinous; mixed epithelial) (admixture of cell types)
- association with endometriosis

SEROMUCINOUS CARCINOMA

- uncommon (1 large series- AJSP 2015; 39; 983-992- 19 cases) (16 unilateral, 3 bilateral)
- admixture of cell types- often serous-like, mucinous, endometrioid, squamous, clear cell, eosinophilic, signet ring
- usually low grade (13, 5, 1- grade 1, 2, 3 respectively; grade like endometrioid cas- ICCR and paper)
- usually expansile invasion/ occasionally infiltrative
- 15, 1, 3- stage 1, 2, 3 respectively
- **endometriosis (10 cases)**; borderline component (10 cases)
- **? more in common with endometrioid rather than mucinous carcinomas or low grade serous carcinomas**
- overlap with endometrioid carcinomas with mucinous differentiation
- MGH-like areas, polymorphs
- good prognosis (7 of 8 with follow up alive, 1 with stage 3 disease died)
- **GRADE AS FOR ENDOMETRIOID ADENOCARCINOMAS**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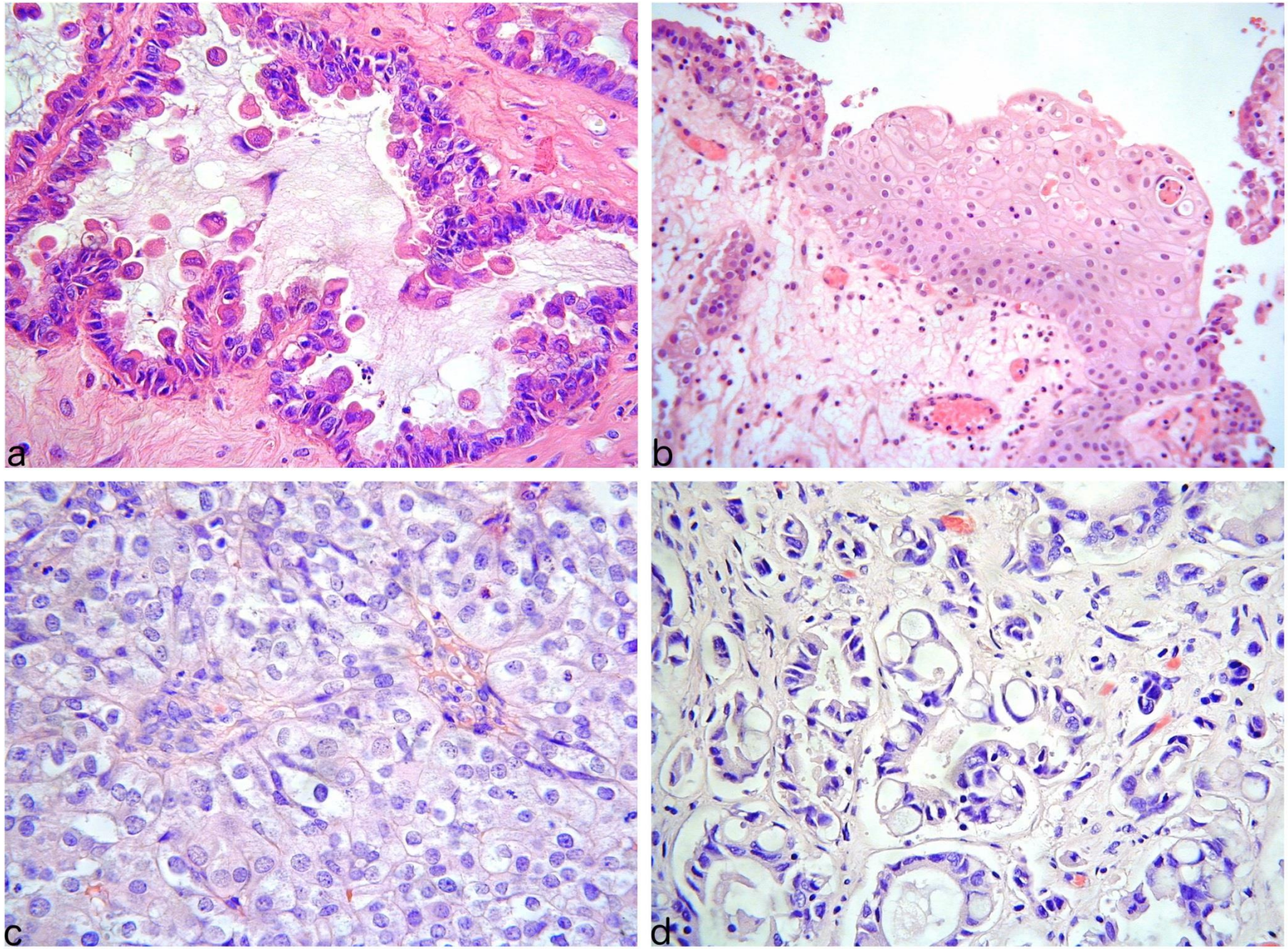
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AJSP – IN PRESS- PMID 28125452

- Morphologic Reproducibility, Genotyping, and Immunohistochemical Profiling Do Not Support a Category of Seromucinous Carcinoma of the Ovary
- 32 cases from 2 centres diagnosed as seromucinous carcinoma
- Marked interobserver variability in diagnosis
- Immunphenotyping and genotyping (targetted NGS looking for mutations in genes commonly mutated in “ovarian” cancers) showed most segregated with endometrioid carcinomas (72%) and some with low grade serous carcinomas (25%)
- SUGGEST TO DISCONTINUE CATEGORY OF SEROMUCINOUS CARCINOMA AND TO USE ANCILLARY STUDIES TO CATEGORISE

“OVARIAN” SEROUS CARCINOMA (OSC) – RECENT DEVELOPMENTS

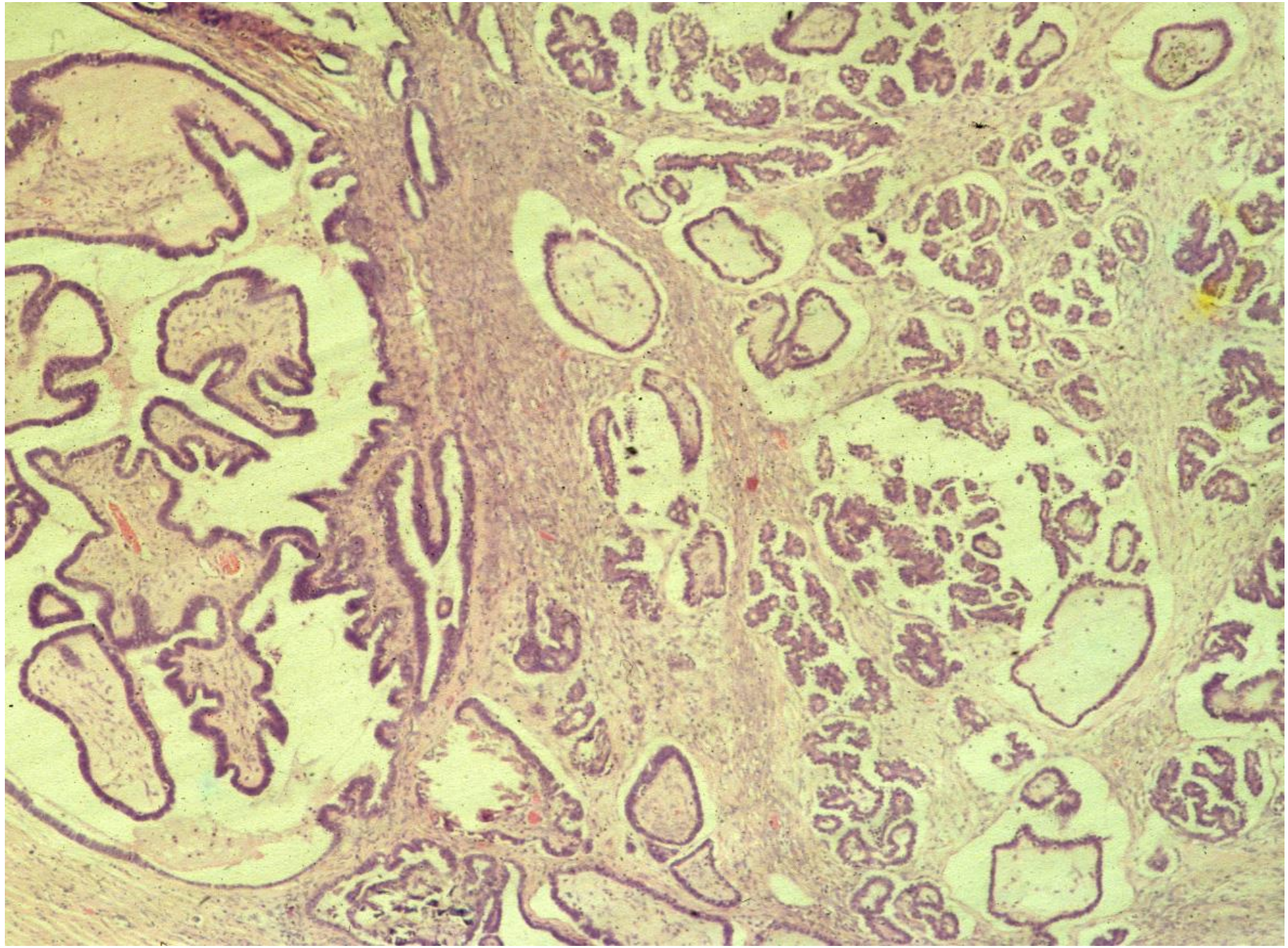
- two distinct tumour types (called low grade and high grade OSC)
- not two grades of same neoplasm
- different neoplasms with different underlying pathogenesis, molecular events, behaviour, prognosis
- high grade **much** more common than low grade (approx 17-18:1)
- use instead of traditional grading schemes

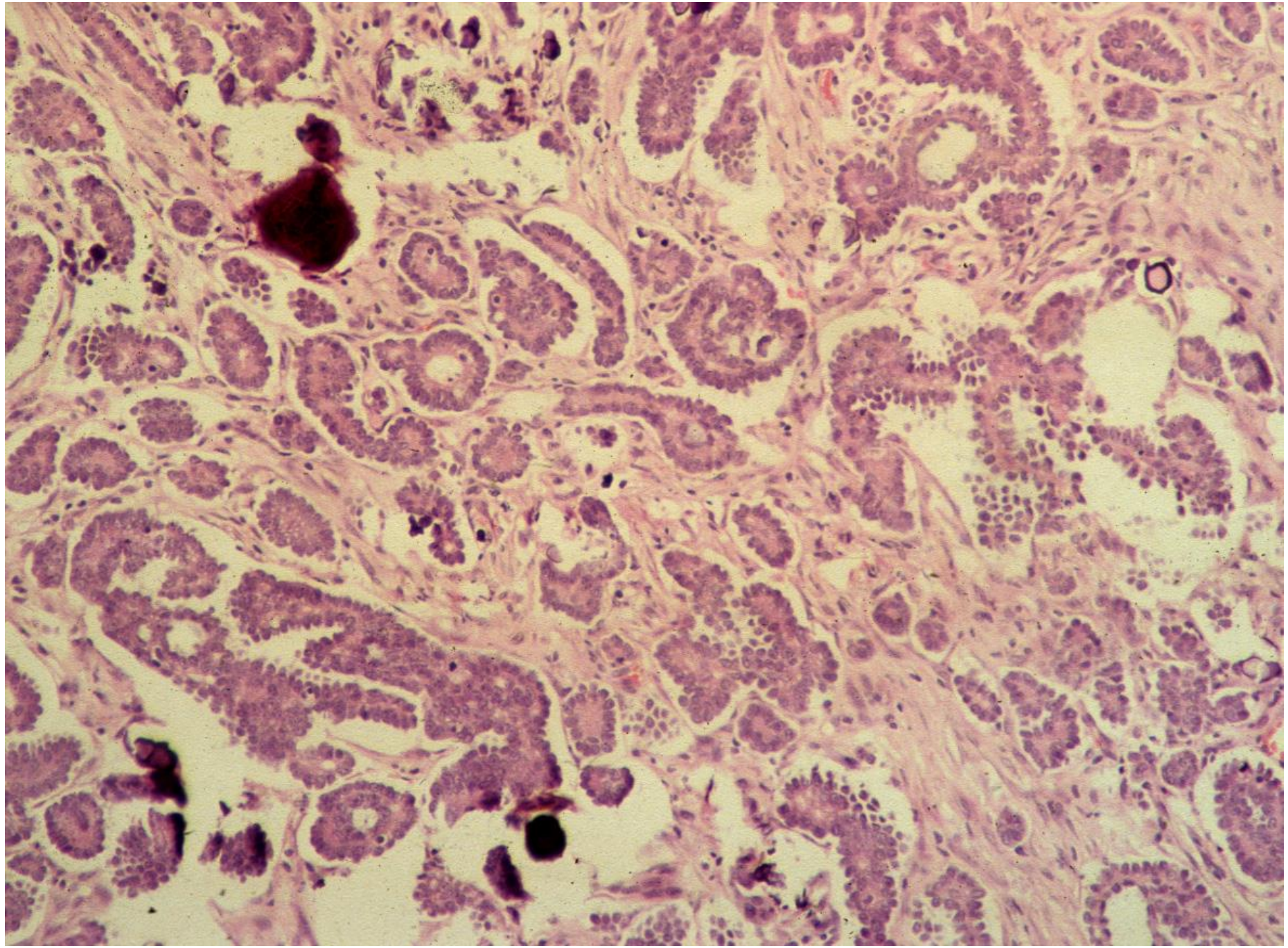
PATHOGENESIS (LOW GRADE SEROUS)

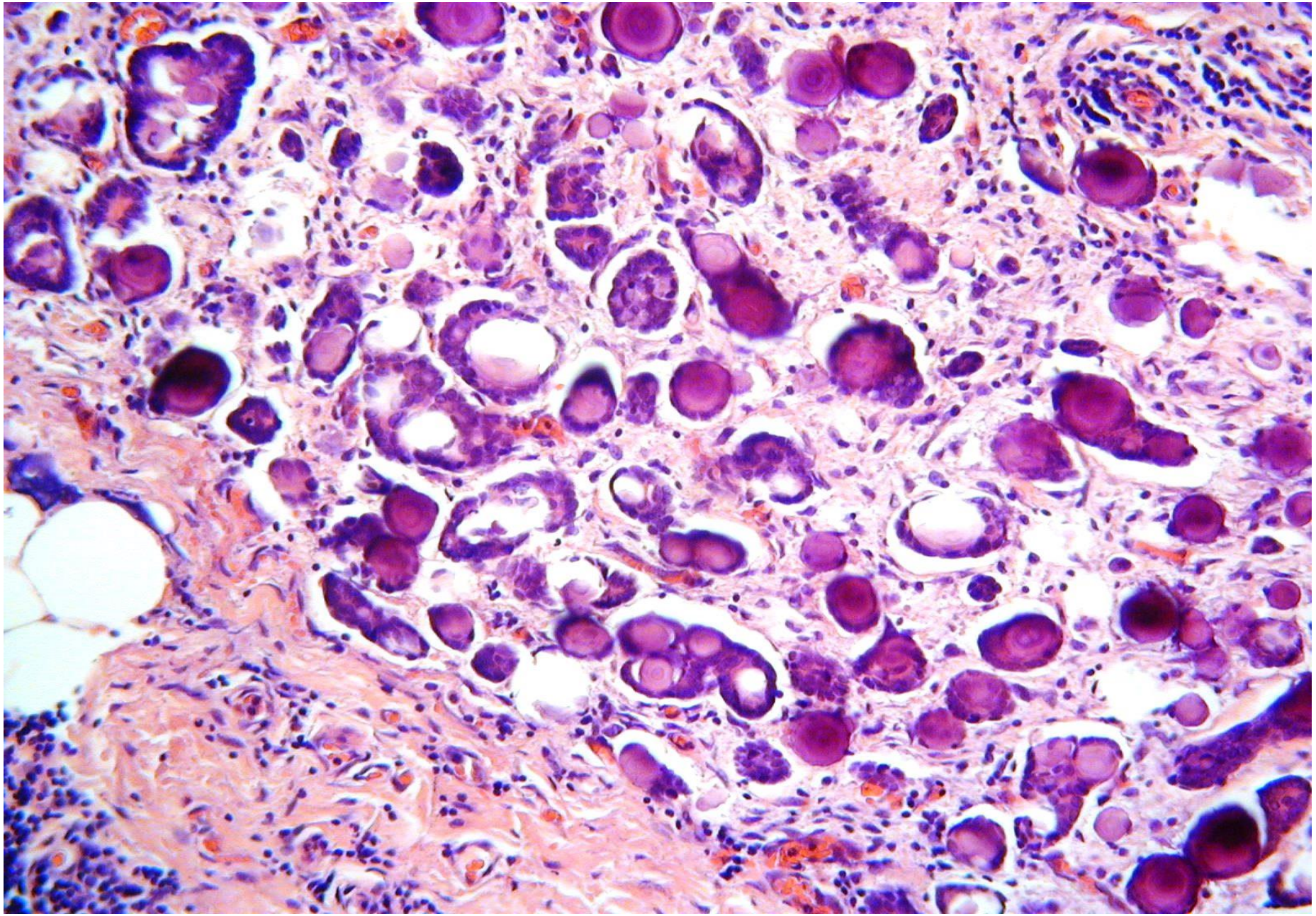
- low grade arise from pre-existing benign and borderline tumour (probably not all cases)
- micropapillary variant of serous borderline may be intermediate stage in development of low grade serous carcinoma
- well-defined adenoma-carcinoma sequence

MOLECULAR (LOW GRADE SEROUS)

- Mutations in genes associated with MAPK pathway (**KRAS** or BRAF mutations in approximately half (sometimes early in evolution – mutations found in benign and borderline tumours; identical mutations in borderline and malignant areas in same tumour)
- KRAS and BRAF mutations are usually mutually exclusive; equivalent effect on tumorigenesis
- no *Tp53* mutations/abnormalities







Psammocarcinoma- LGSC with many psammoma bodies

PATHOGENESIS (HIGH GRADE SEROUS)

- traditionally thought to arise directly from ovarian surface epithelium or epithelium of cortical inclusion cysts; **now clear that most cases arise from epithelium of distal fallopian tube**
- **precursor lesion is serous tubal intraepithelial carcinoma (STIC)**
- doesn’t arise from borderline tumour

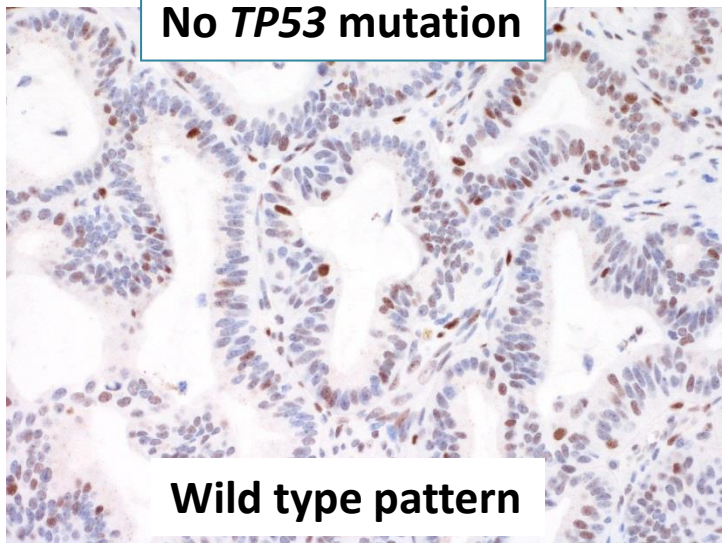
MOLECULAR (HIGH GRADE SEROUS)

- *Tp53* mutations (early in evolution-seen in early microscopic tumours eg BRCA1/2) (p53 dysfunction, usually mutation, found in almost 100% high grade serous using stringent methods) (IJGP; Vang and Soslow and others in press: PMID 26166714)
- recent study (about 5% of HGSC with *Tp53* mutations exhibit wild-type immunoreactivity)
- BRCA1/2 abnormalities (germline or somatic mutations or hypermethylation)
- no BRAF and only occasional KRAS mutations

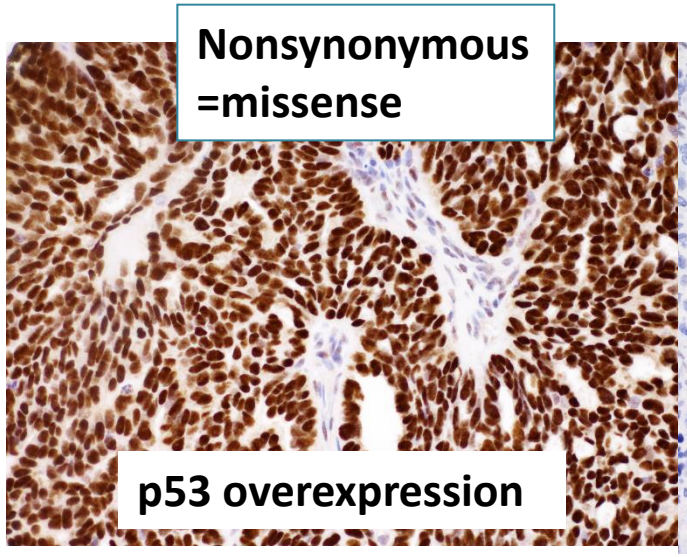
p53

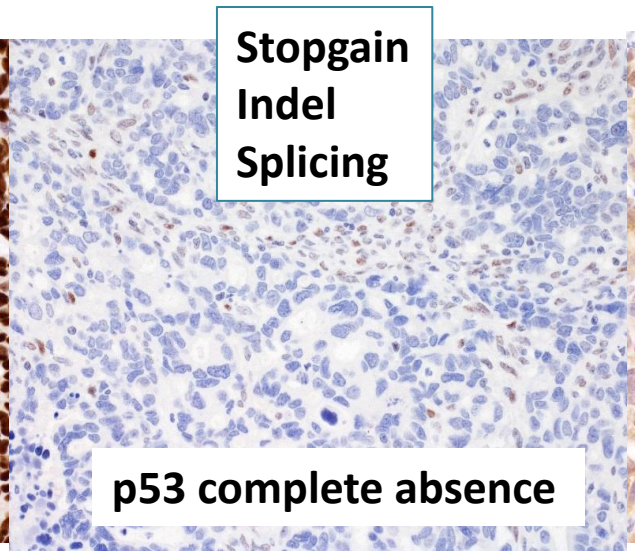
- p53 immunohistochemistry- lot of confusion
- only consider positive/significant if diffuse strong nuclear immunoreactivity (75-80% cells suggested- associated with missence mutation)
- p53 null consistent with serous carcinoma (different type of mutation (nonsense) or deletion resulting in truncated protein which is not detected by immunohistochemistry)
- third pattern of mutation-type staining- cytoplasmic (rare pattern)
- most normal tissues and tumours exhibit focal, weak, heterogenous staining (“wild-type” staining) (usually <50%) (**about 5% of HGSCs with Tp53 mutation exhibit wild-type staining**)
- DON’T REPORT AS POSITIVE OR NEGATIVE- REPORT AS “WILD-TYPE” or “MUTATION-TYPE”
- OCCASIONALLY DIFFICULT TO INTERPRET (“wild-type” at upper end; negative “mutation-type” versus “wild-type”)

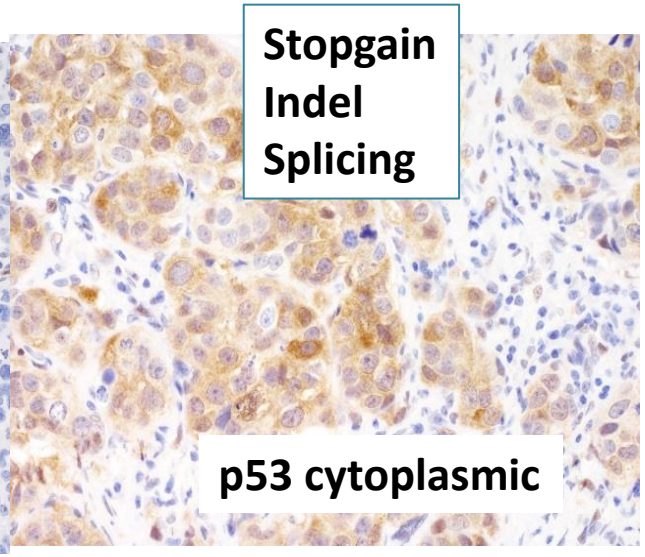
Interpretation of p53 immunohistochemistry



Normal







abnormal; mutation-type

J Pathol Clin Res 2016;2:247

p53 immunohistochemistry pattern and interpretation

Pattern	p53 IHC Interpretation	*TP53* mutation type	% in HGSC
		***TP53* MUTATION ABSENT**	
Wild type	Normal	No mutation	0
		***TP53* MUTATION PRESENT**	
Overexpression	Abnormal	Non-synonymous (missense); also in-frame deletion, splicing	66%
Complete absence/ null	Abnormal	Indels, stopgains, splicing mutations	25%
Cytoplasmic	Abnormal	Indels and stopgains with disruption of the nuclear localization domain	4%
Wild type	Normal*	Truncating mutation	5%

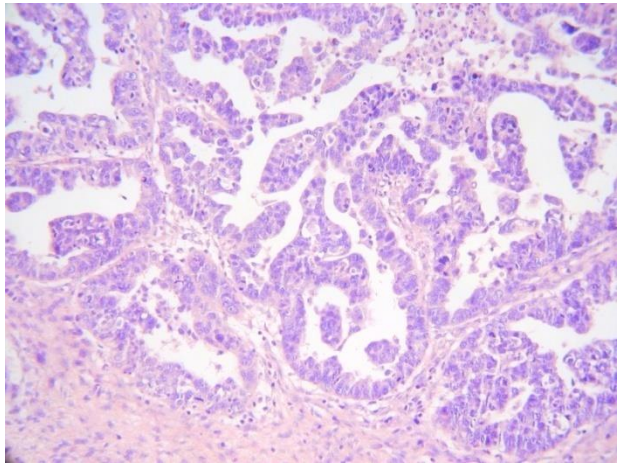
HGSC- high-grade serous carcinoma

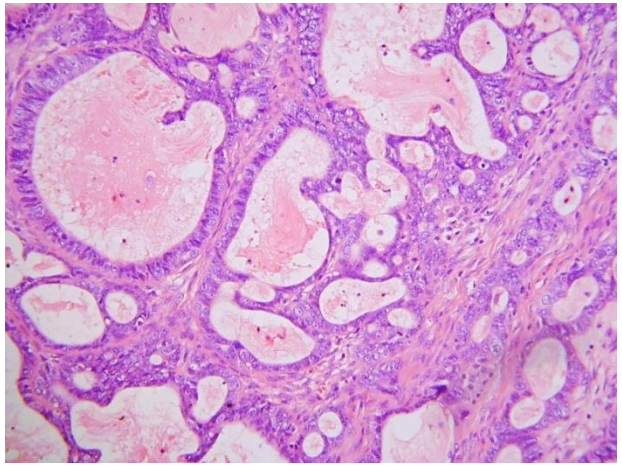
2016: www.thebagp/resources

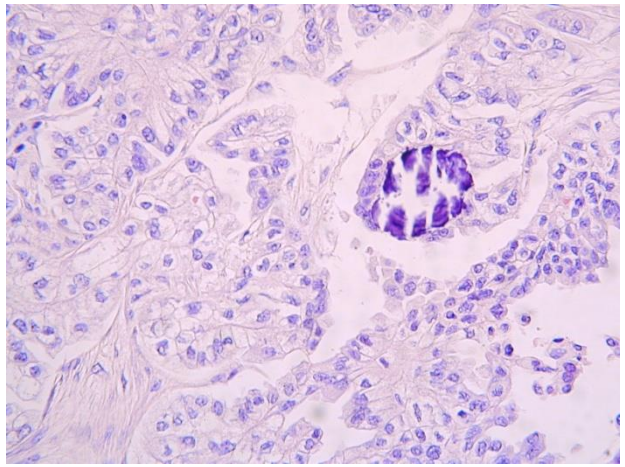
CLINICAL BEHAVIOUR- LGSC and HGSC

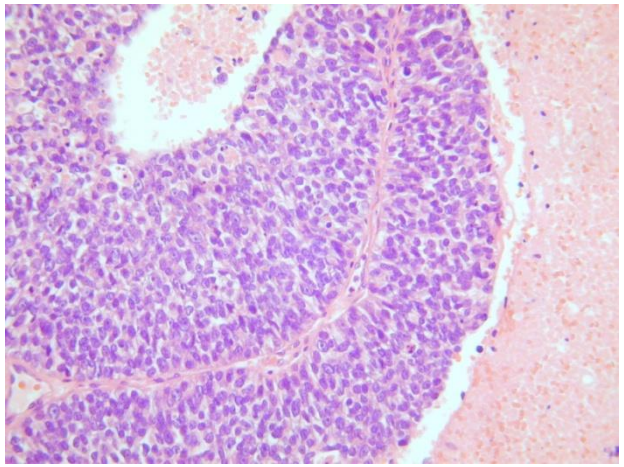
- LGSC (mean 52) younger than HGSC (mean 62)
- HGSC poor prognosis (usually presents at advanced stage, responds well initially to chemo but usually recurs; occasional long term survivors)
- LGSC more indolent (good prognosis for early stage; advanced stage- patients usually die of tumour) (IJGP 2013; 32; 529-535- stage 2-4, <30% survival at 10 years; not significantly different to HGSC); (AJSP 2016;40;627-635; 5 year survival 62.3% LGSC, 43.9% HGSC but no survival difference at 10 years)

OVARIAN HIGH GRADE SEROUS CARCINOMA

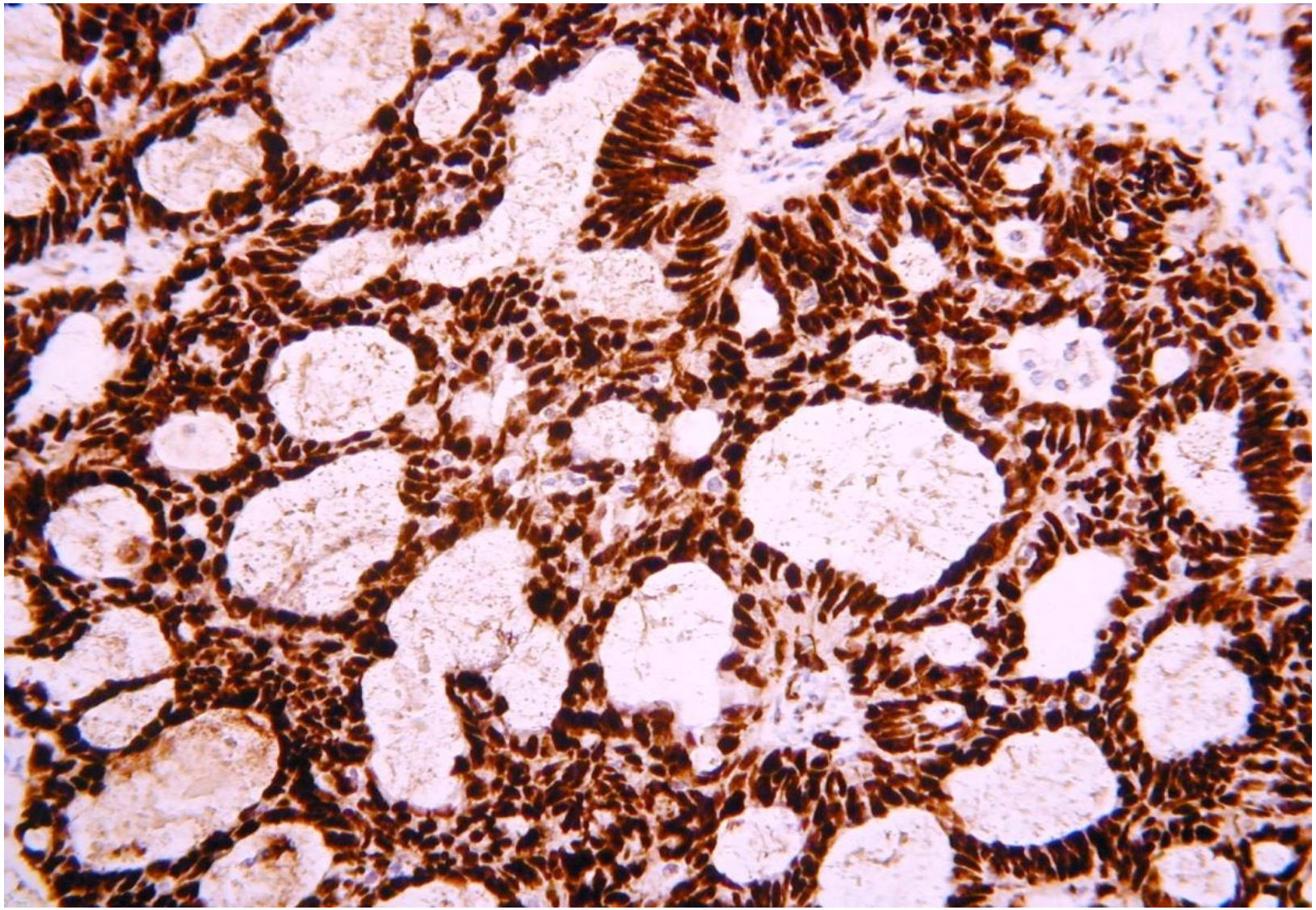




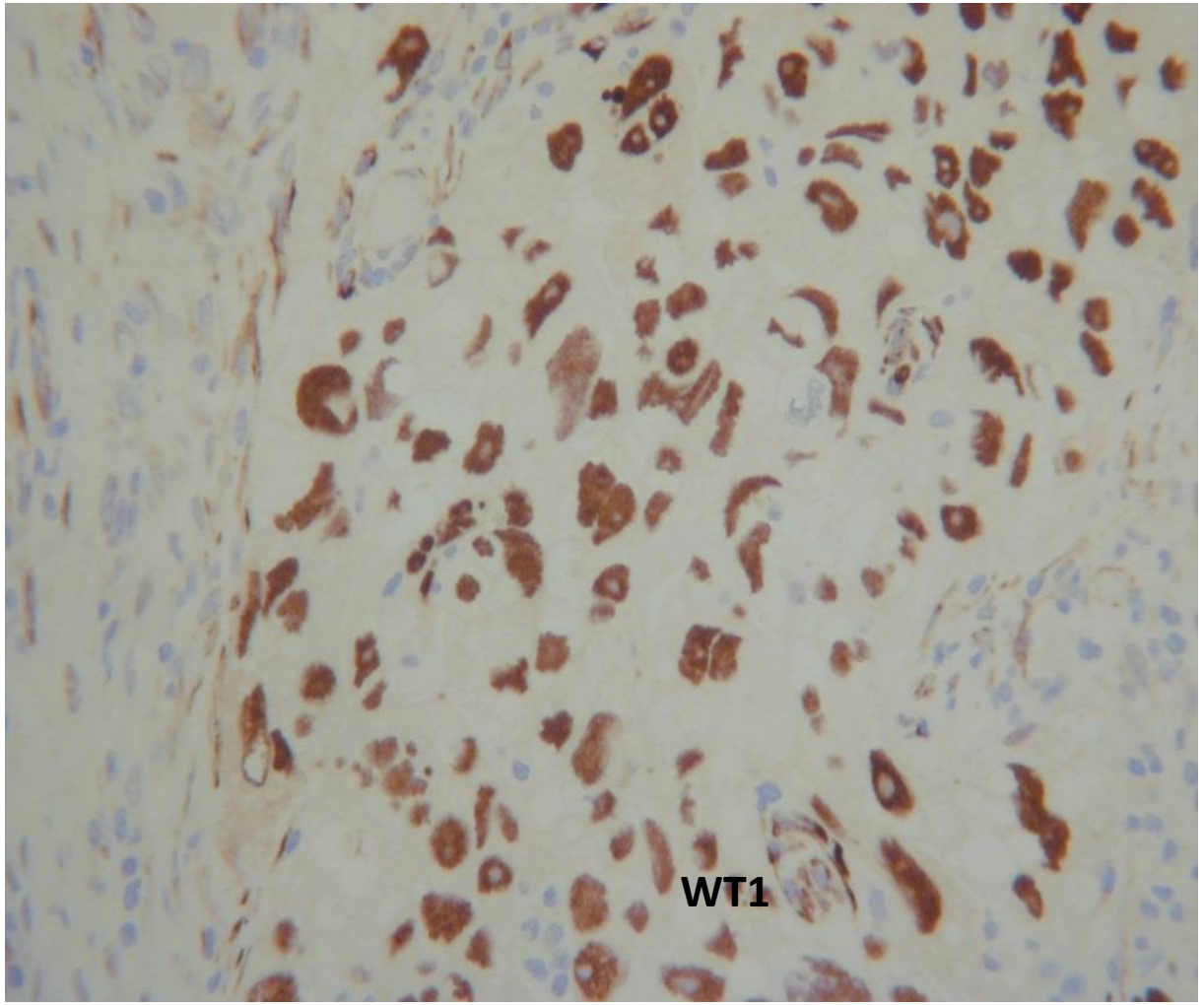




WT1 in PSEUDOENDOMETRIOID AREAS IN HIGH GRADE SEROUS CARCINOMA



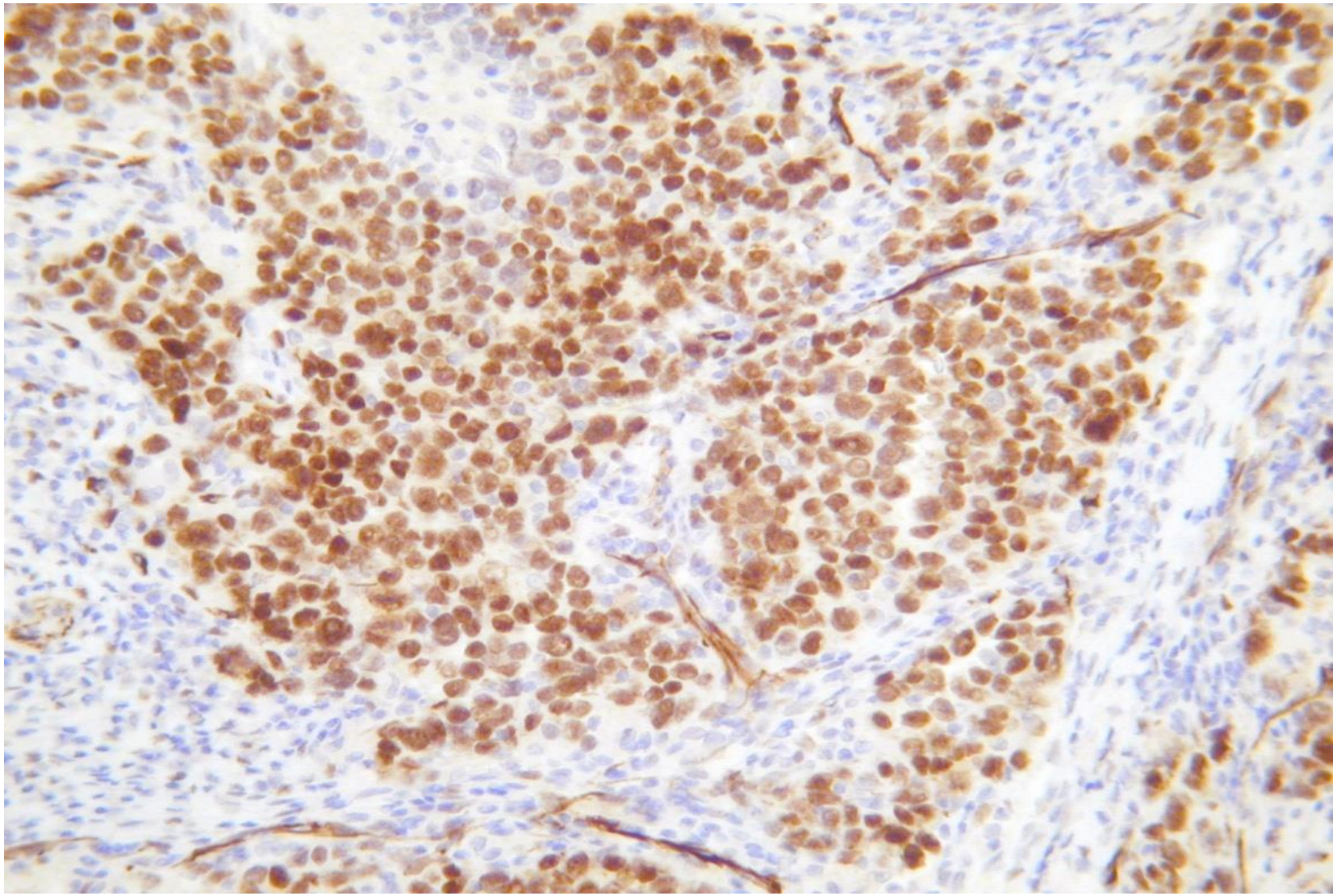
WT1 in CLEAR CELL AREAS IN HIGH GRADE SEROUS CARCINOMA



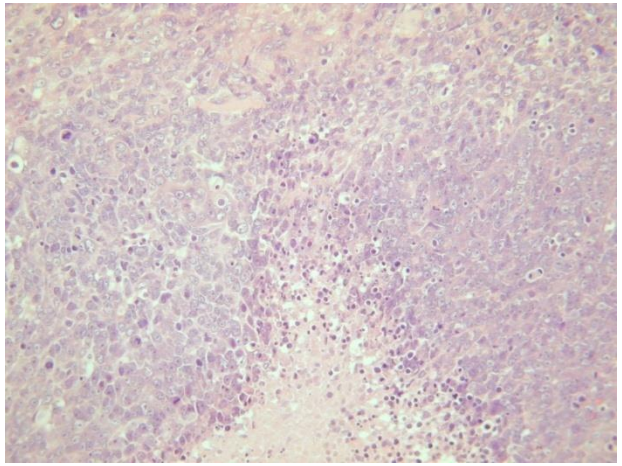
p53

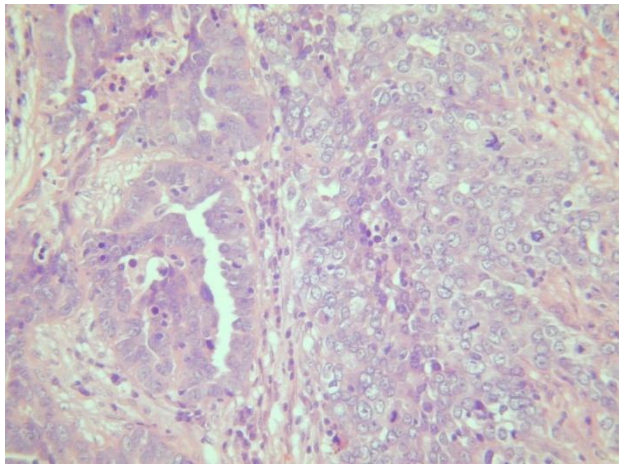
WT1

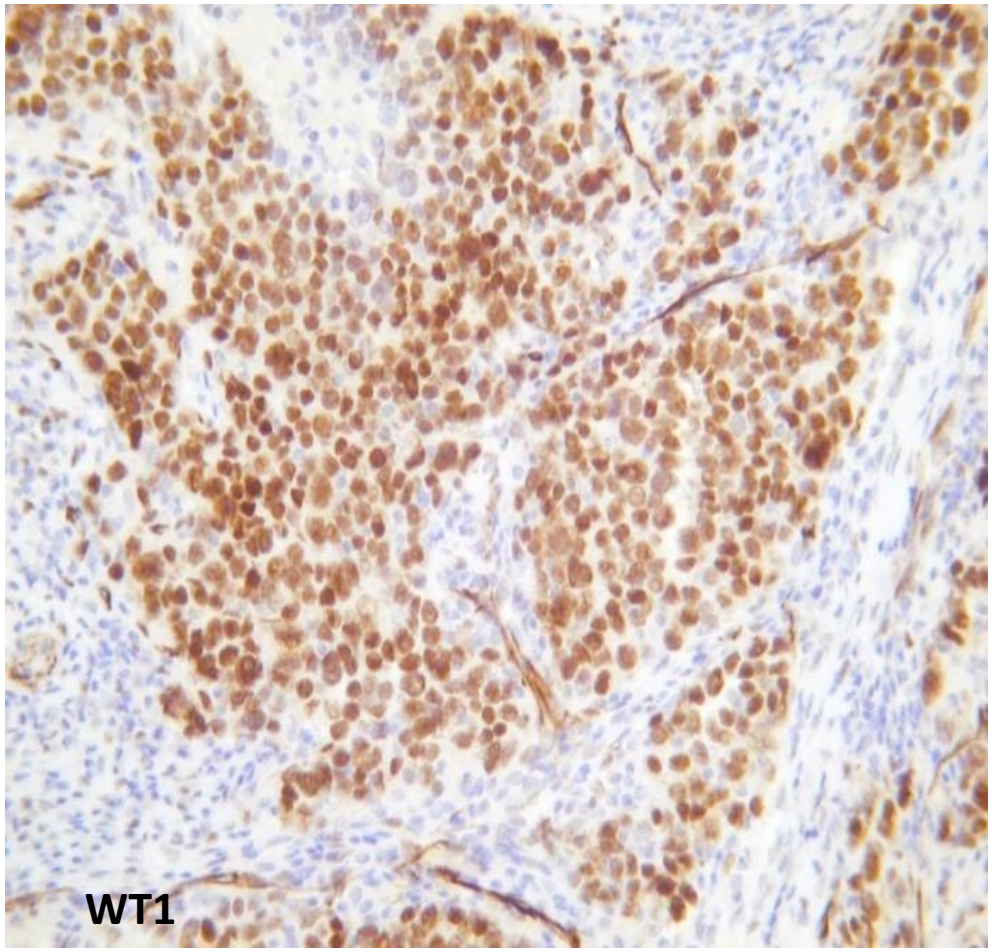
WT1 IN TRANSITIONAL-LIKE AREAS IN HIGH GRADE SEROUS CARCINOMA



UNDIFFERENTIATED OVARIAN CARCINOMA







MIXED OVARIAN CARCINOMAS

- historically quite common (up to 10-20%)
- most commonly historically reported were mixed serous/ endometrioid; mixed serous/clear cell; mixed serous/undifferentiated (mostly variants of high grade serous carcinoma- doubtful if these combinations exist)
- occasionally get mixed endometrioid/ clear cell (association with endometriosis)
- occasionally others
- CATEGORY DROPPED FROM WHO 2014

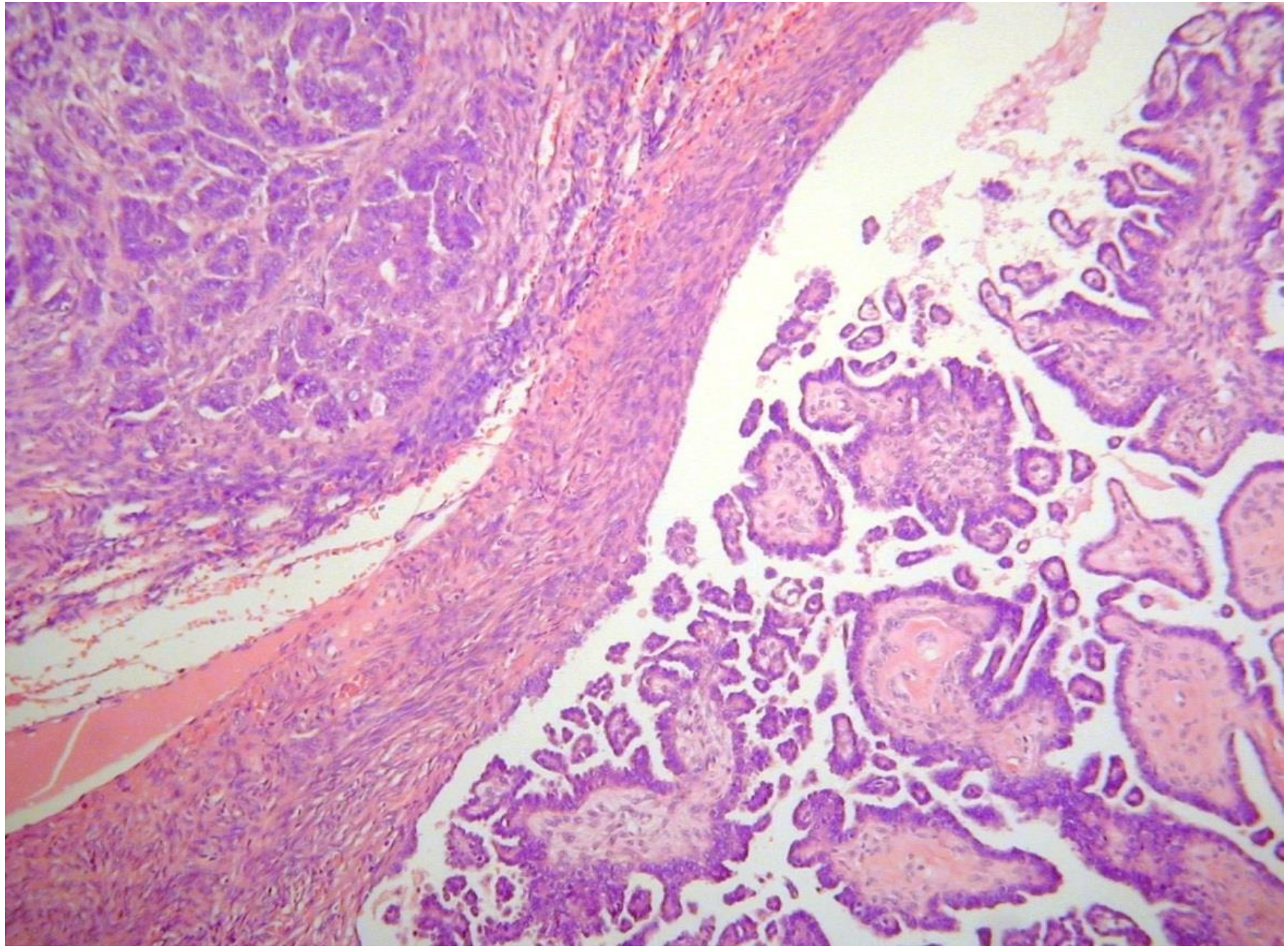
Mixed Ovarian Carcinomas

- Improved recognition of types has virtually abolished mixed tumours
  - 15 of 871 cases reviewed (1.7%) by H/E using modern diagnostic criteria
- 22 cases thought to be mixed were investigated further by immunohistochemistry and molecular testing
- Only 13 true mixed carcinomas when immunohistochemistry and molecular data incorporated
- Mixed carcinomas account for less than 1% of ovarian carcinomas

Mackenzie et al. Am J Surg Pathol 2015; 39: 1548-1557

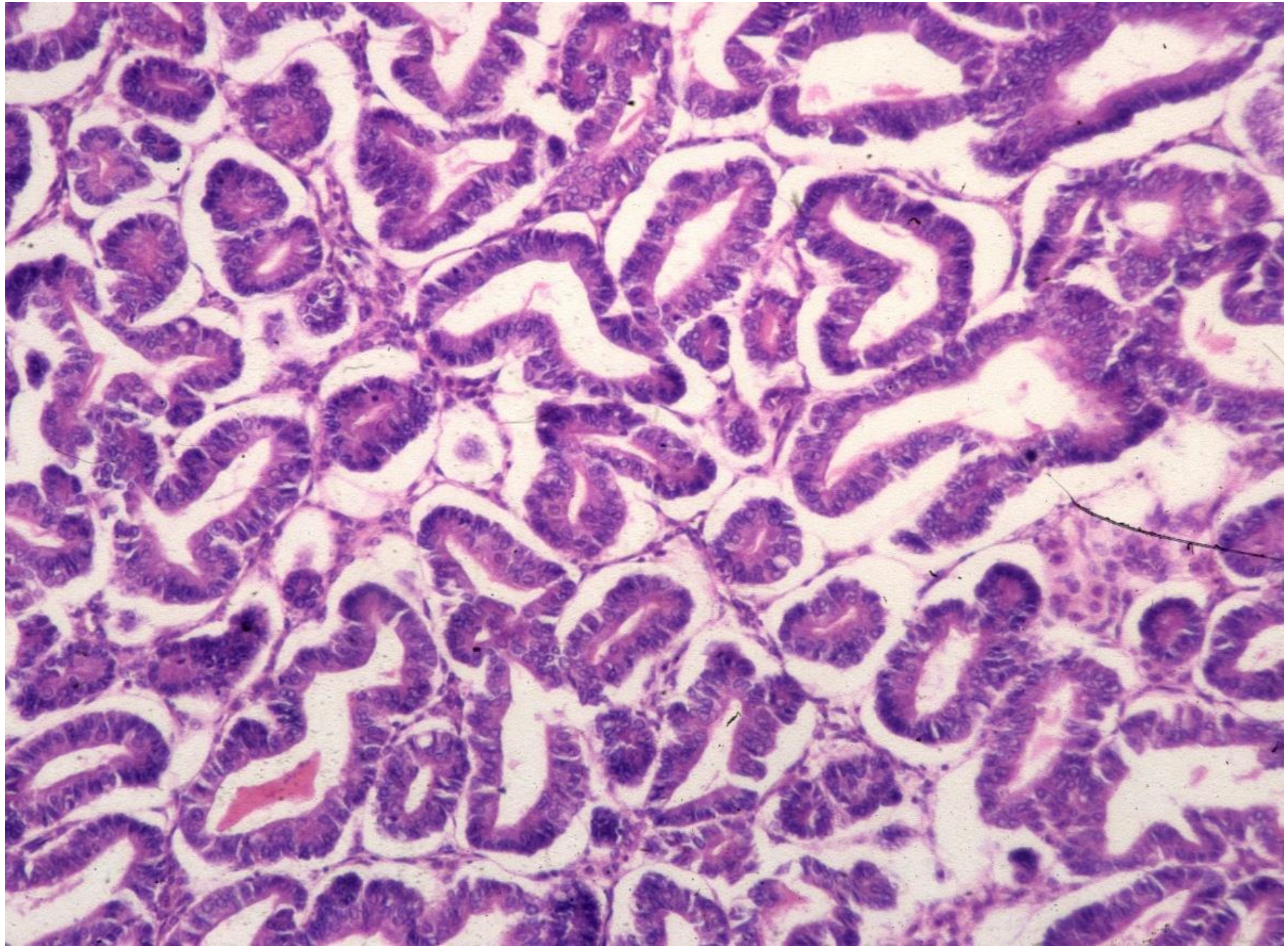
TRANSFORMATION LOW GRADE INTO HIGH GRADE

- rare (AJSP 2012; 36; 368-375) (serous borderline or low grade serous ca)
- can be misdiagnosed (bigger nuclei in low grade serous)
- can transform to HGSC, anaplastic carcinoma, carcinosarcoma
- p53 immunohistochemistry NOT reliable in such cases (often not *TP53* mutated)



ENDOMETRIOID ADENOCARCINOMA

- usually, but not always, low grade and stage
- high grade and high stage relatively uncommon but do occur
- generally good prognosis
- high grade tumours occur but relatively uncommon and previous tendency to overdiagnose
- often arise in endometriosis (or endometrioid adenofibroma)



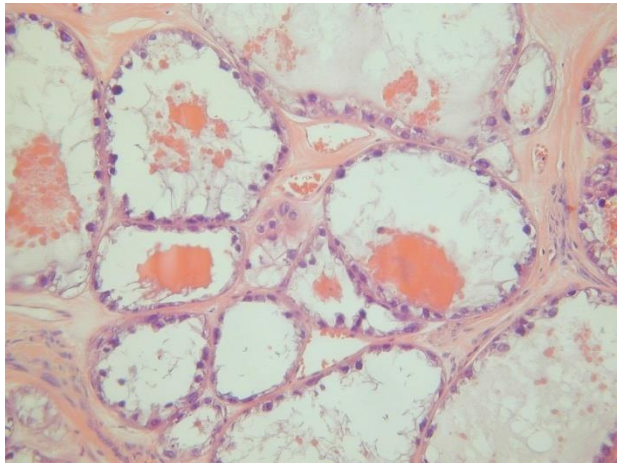
MOLECULAR EVENTS IN OVARIAN ENDOMETRIOID CARCINOMA

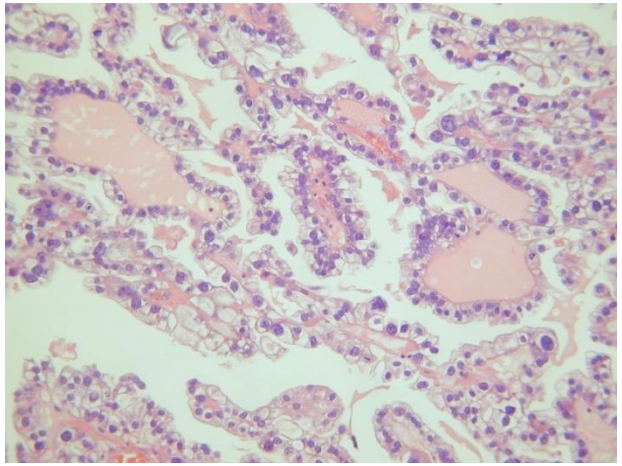
- **SIMILAR TO UTERINE ENDOMETRIOID**
- *PTEN* mutations
- *K-RAS* mutations
- microsatellite instability
- β *catenin* mutation
- *PIK3CA* mutations
- *TP53* mutations in some high grade (? secondary event)
- *ARID1A* mutations

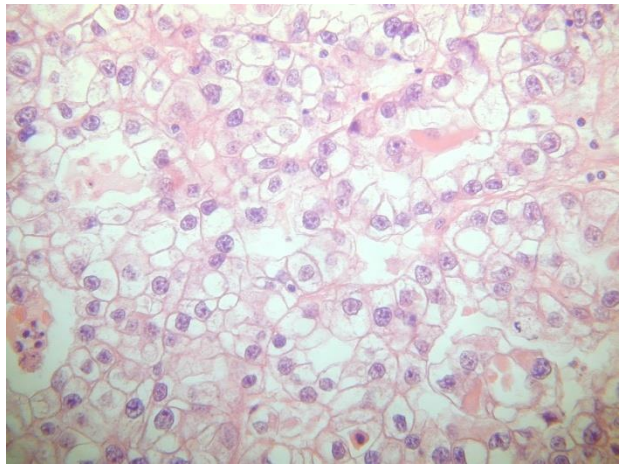
CLEAR CELL CARCINOMA

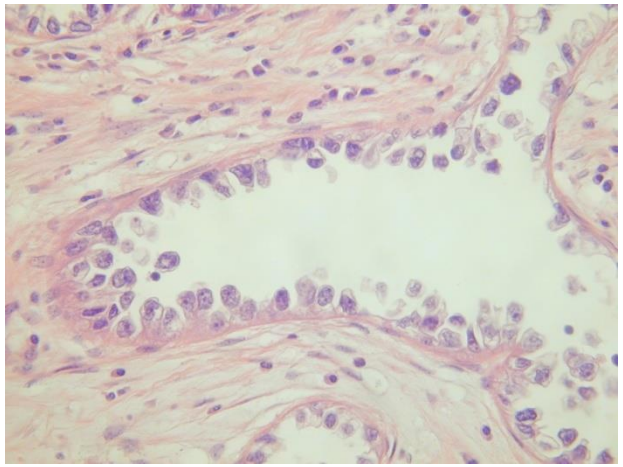
- classically admixture of patterns
- get clear cells in serous and endometrioid carcinomas (previous tendency to misdiagnose as clear cell or mixed carcinoma)
- majority arise in endometriosis (sample well) (endometriosis in ovary may be subtle)
- may sometimes be associated benign or borderline adenofibroma

CLEAR CELL CARCINOMA









GRADING OF CLEAR CELL CARCINOMA (ICCR)

- automatically grade 3
- often mitotically inactive and relatively low architectural and cytological grade (risk of undergrading) (may be reason for poor chemoresponsiveness)

MOLECULAR EVENTS

- low prevalence of *TP53* mutations (<5%)
- *PTEN* mutations
- *ARID1A* mutations
- microsatellite instability
- similar genetic events to endometrioid carcinomas

ENDOMETRIOSIS- ASSOCIATED OVARIAN NEOPLASMS

- Endometrioid
- Clear cell
- Seromucinous
- Mixed endometrioid and clear cell

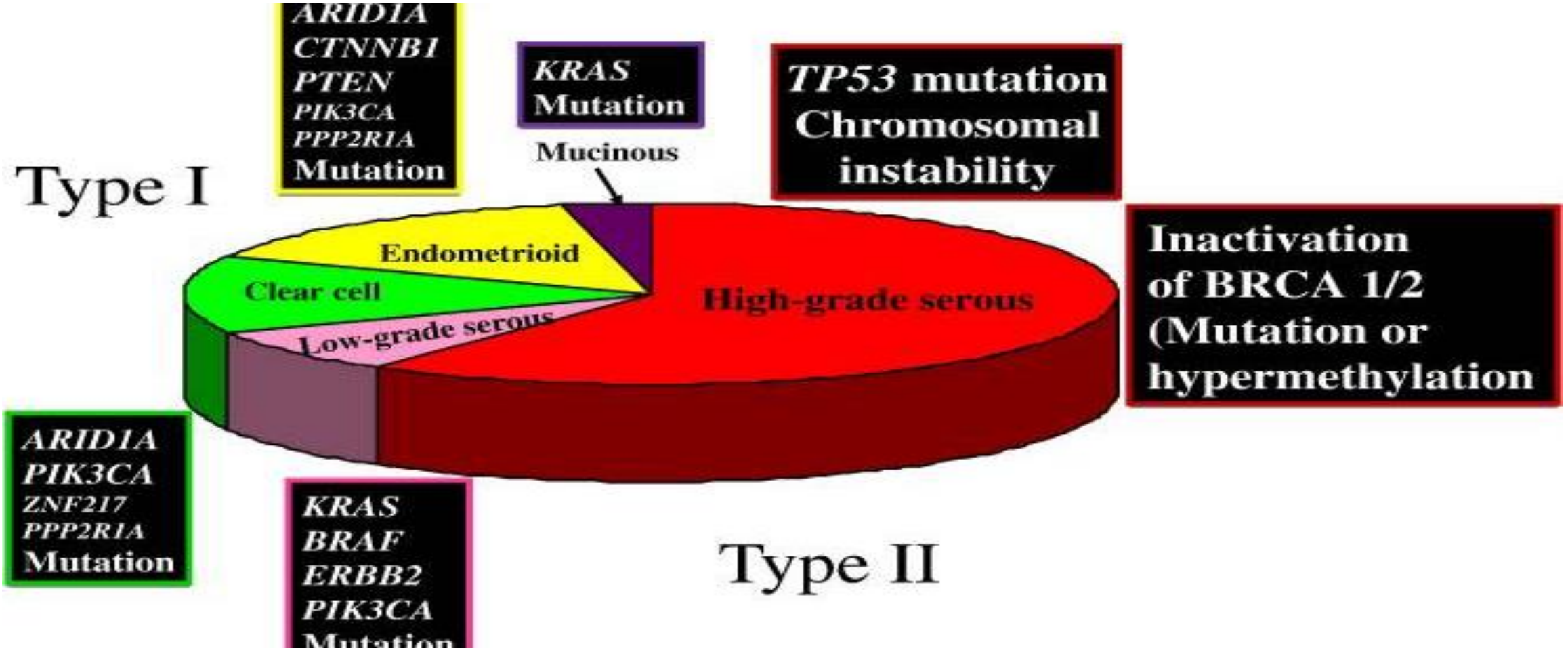
Ovarian Mucinous Tumours (Intestinal Type)

- cystadenoma/ adenofibroma
- cystadenoma with focal epithelial proliferation (<10%)
- borderline tumour (≥10%) (arbitrary and not widely practised)
- borderline with intraepithelial carcinoma
- borderline with microinvasion
- microinvasive carcinoma
- adenocarcinoma

PATHOGENESIS

- continuum from benign-malignant (adenoma-carcinoma sequence)
- K-RAS mutations common (occur early in pathway)
- HER2 overexpressed/amplified in significant percentage of mucinous carcinomas (19% in recent study) (may be treatment option in recurrent tumours)
- *Tp53* mutation occurs in minority of ovarian mucinous carcinomas
- minority arise in teratomas (may exhibit upper or lower intestinal differentiation)
- association with Brenner tumours (recent proposal that most arise from Walthard's rests)

Epithelial Ovarian Carcinoma Subtypes



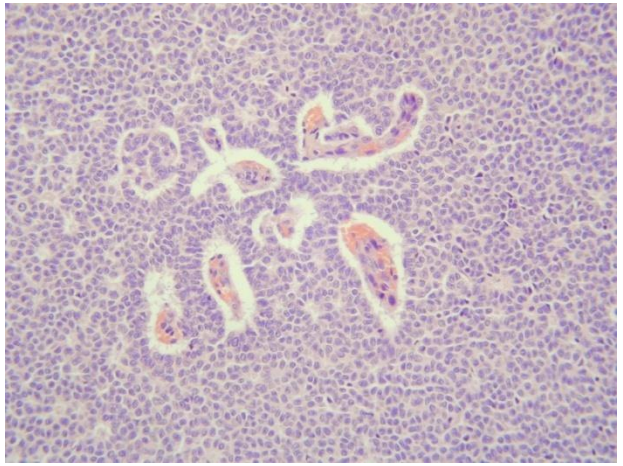
DOES OVARIAN CARCINOMA EXIST?

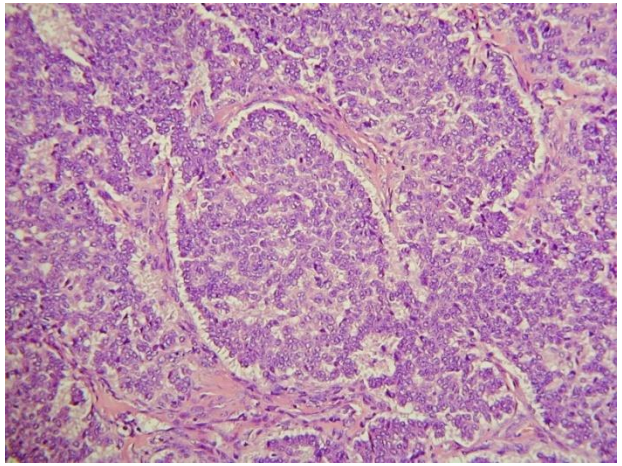
- serous (high and low grade)- ? from fimbria of tube
- mucinous - ? from teratomas or Walthard's rests at tubo-peritoneal junction
- endometrioid and clear cell- from uterus (endometriosis-mostly due to retrograde menstruation)
- ? ONLY TRUE PRIMARY OVARIAN NEOPLASMS ARE GERM CELL AND SEX CORD-STROMAL TUMOURS (similar to testis)

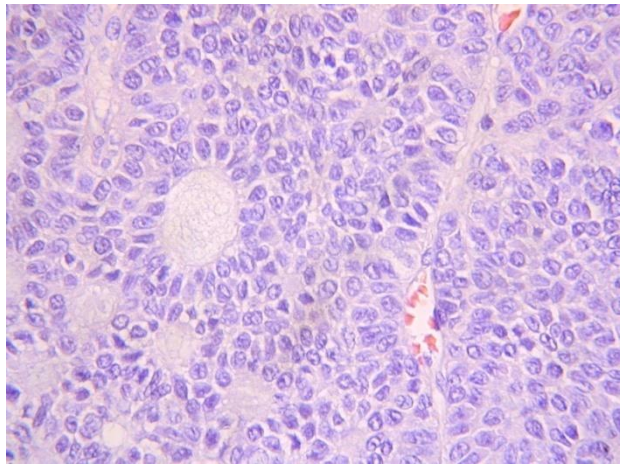
MOLECULAR EVENTS IN ADULT GRANULOSA CELL TUMOUR (AGCT)

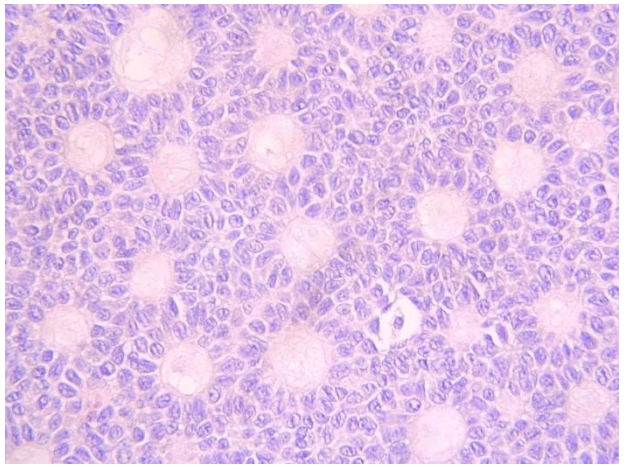
- **somatic** missence FOXL2 mutation recently described in about 95% of AGCT
- only uncommonly found in other sex cord-stromal neoplasms
- VERY SPECIFIC AND SENSITIVE MOLECULAR MARKER OF AGCT **(? outdoes morphology in problematic cases)**
- may be useful in confirming AGCT in problematic cases (important in prognostication given different behaviour)
- mutation not found in epithelial neoplasms

TYPICAL AGCT









UNUSUAL FEATURES OF AGCT- FOXL2 MUTATION TESTING OF VALUE

- cystic variants
- pseudopapillary variants
- luteinised variants
- diffuse/ spindle cell variants
- variants where cytology/architecture is not typical
- “anaplastic” variants
- immunohistochemical markers no use in separating different sex cord-stromal tumours (FOXL2 immunohistochemistry of no value)
- PROGNOSTICALLY IMPORTANT TO MAKE CORRECT DIAGNOSIS OF AGCT

MOLECULAR EVENTS NOW BEING ELUCIDATED IN OVARIAN SEX CORD-STROMAL TUMOURS AND OTHER UNCOMMON NEOPLASMS

- *FOXL2* mutations- adult granulosa cell tumour
- *DICER1* mutations in Sertoli-Leydig cell tumour
- *SMARCA4/ BRG1* mutations in SCCOHT

SERTOLI LEYDIG TUMOUR

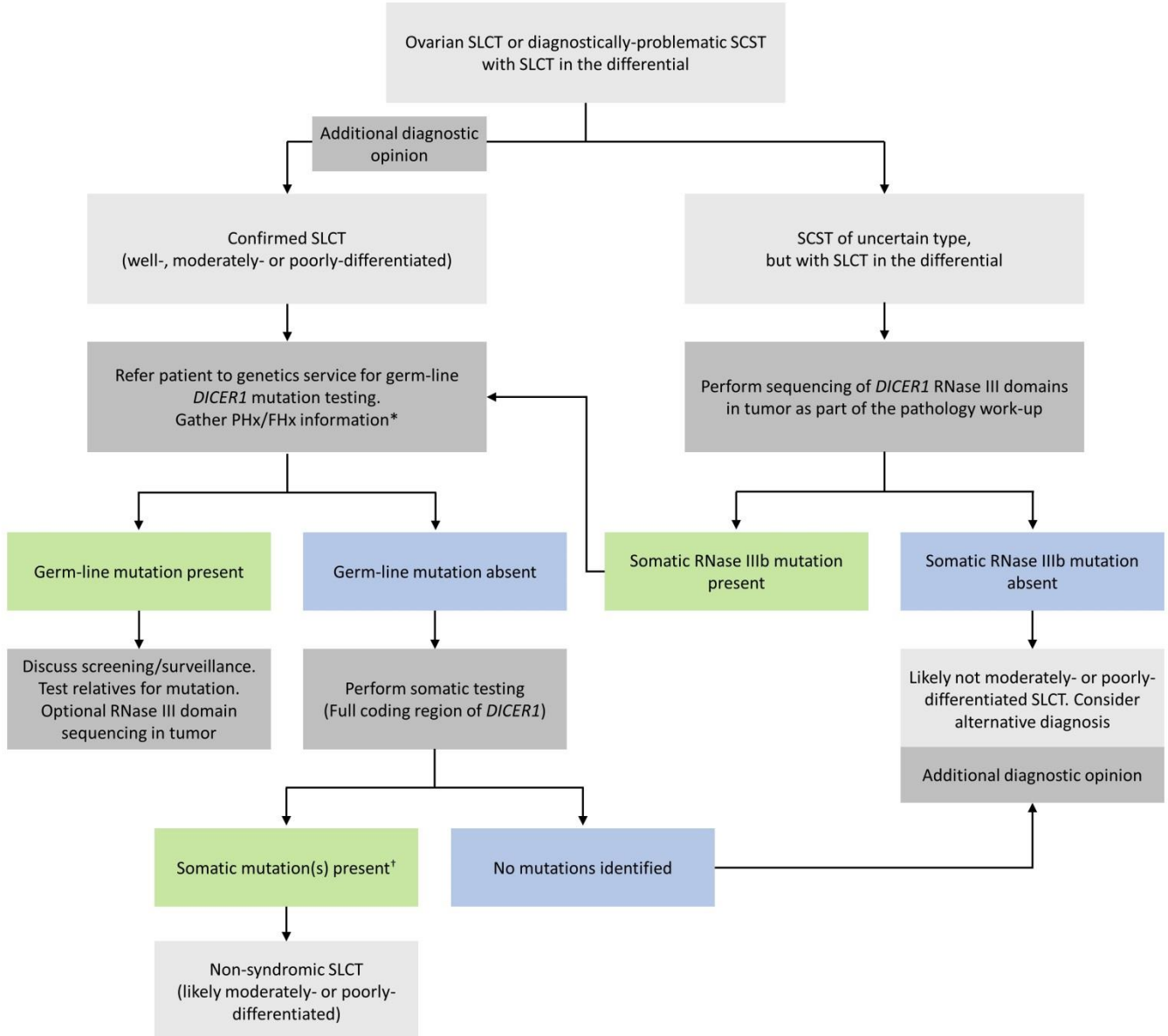
- *DICER1* mutations in approximately 60% of Sertoli Leydig tumours (mostly somatic but not uncommonly germ line mutations)
- association with cervical embryonal rhabdomyosarcoma, thyroid goitres, thyroid carcinomas, cystic nephroma, pleuropulmonary blastoma and other embryonic tumours (*DICER1* mutations found in all these tumour types) (germline mutations) (DICER1 syndrome)

JOURNAL OF CLINICAL PATHOLOGY 2007; 60; 326-328

- A case in which an embryonal rhabdomyosarcoma of the cervix and an ovarian Sertoli-Leydig cell tumour of intermediate differentiation occurred in a 13-year-old girl is described. Although initially considered as a chance association, a review of the literature showed the co-occurrence of these two uncommon neoplasms in three previous cases. The reason for this association, which is thought to be more than coincidental, is not known, although an underlying genetic abnormality is a possibility.

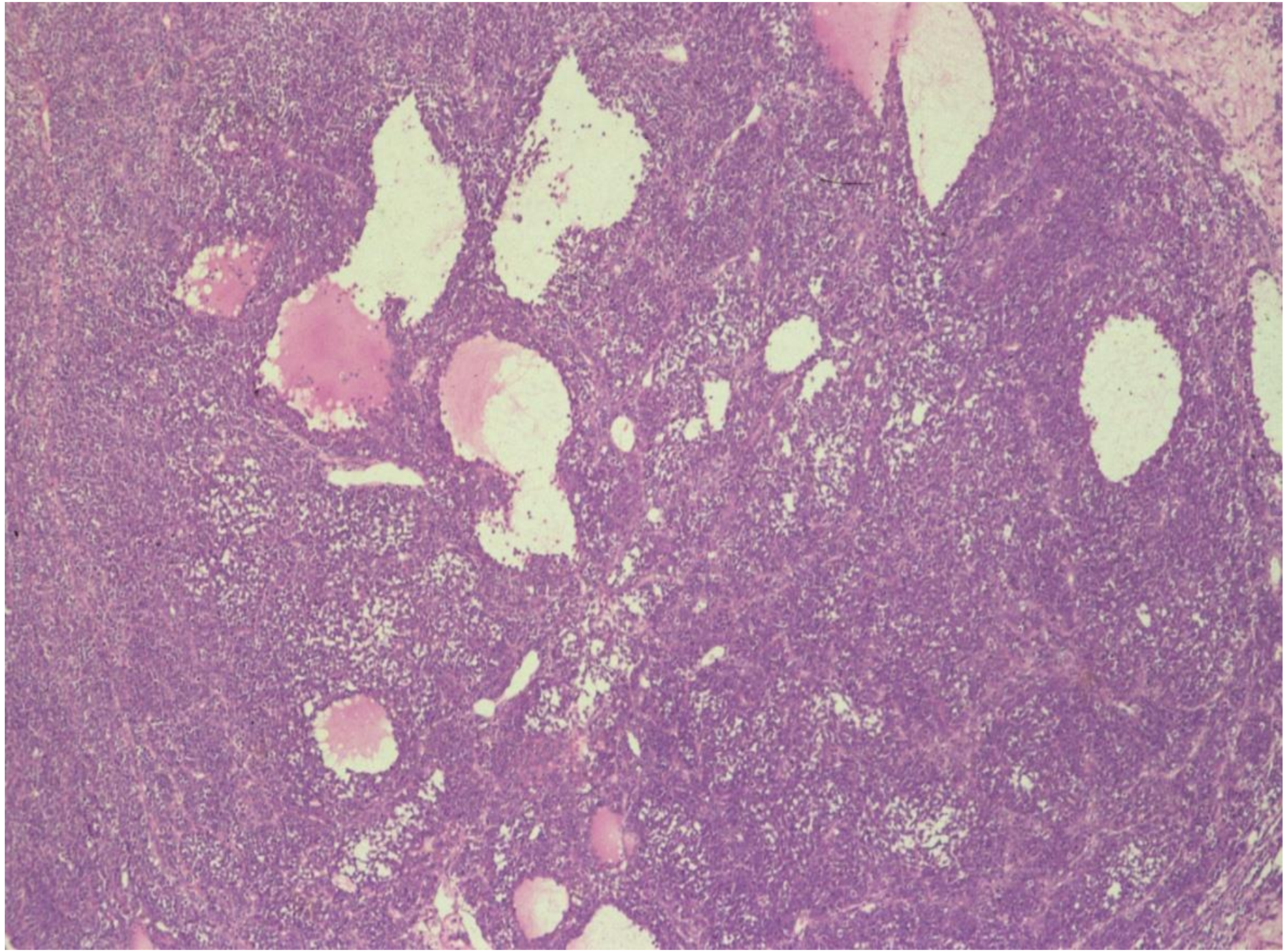
DICER1 in SLCTs

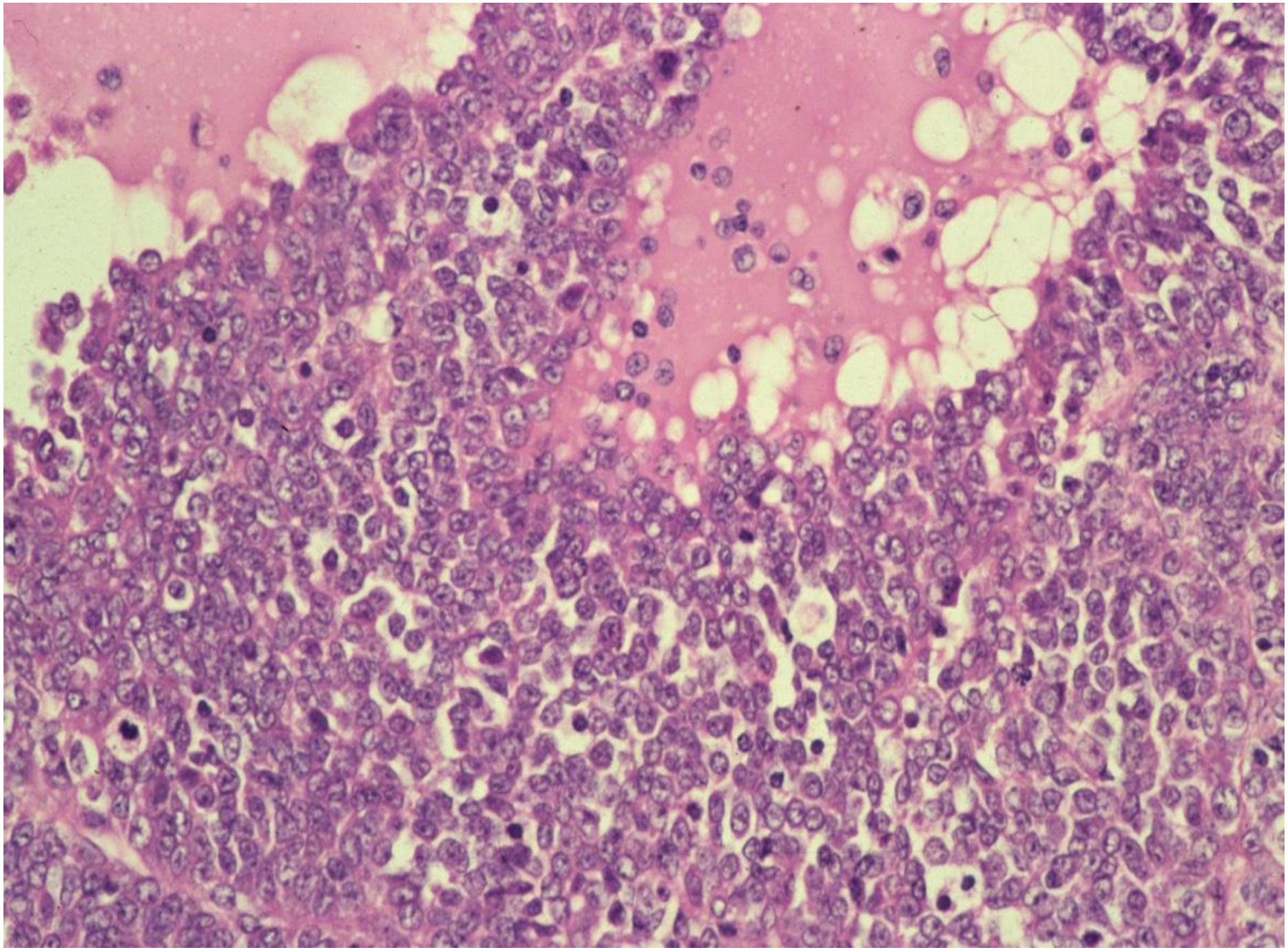
- Study submitted for publication
- All moderate-poorly differentiated *DICER1* mutation positive (may be useful in diagnosis- ? Occasional other sex cord-stromal tumours contain mutation- ? Misdiagnosed SLCTs)
- All well differentiated *DICER1* wild-type
- Suggests that 2 different tumour types
- We suggest that all patients with moderate-poorly differentiated SLCTs undergo genetic testing to look for germline mutations

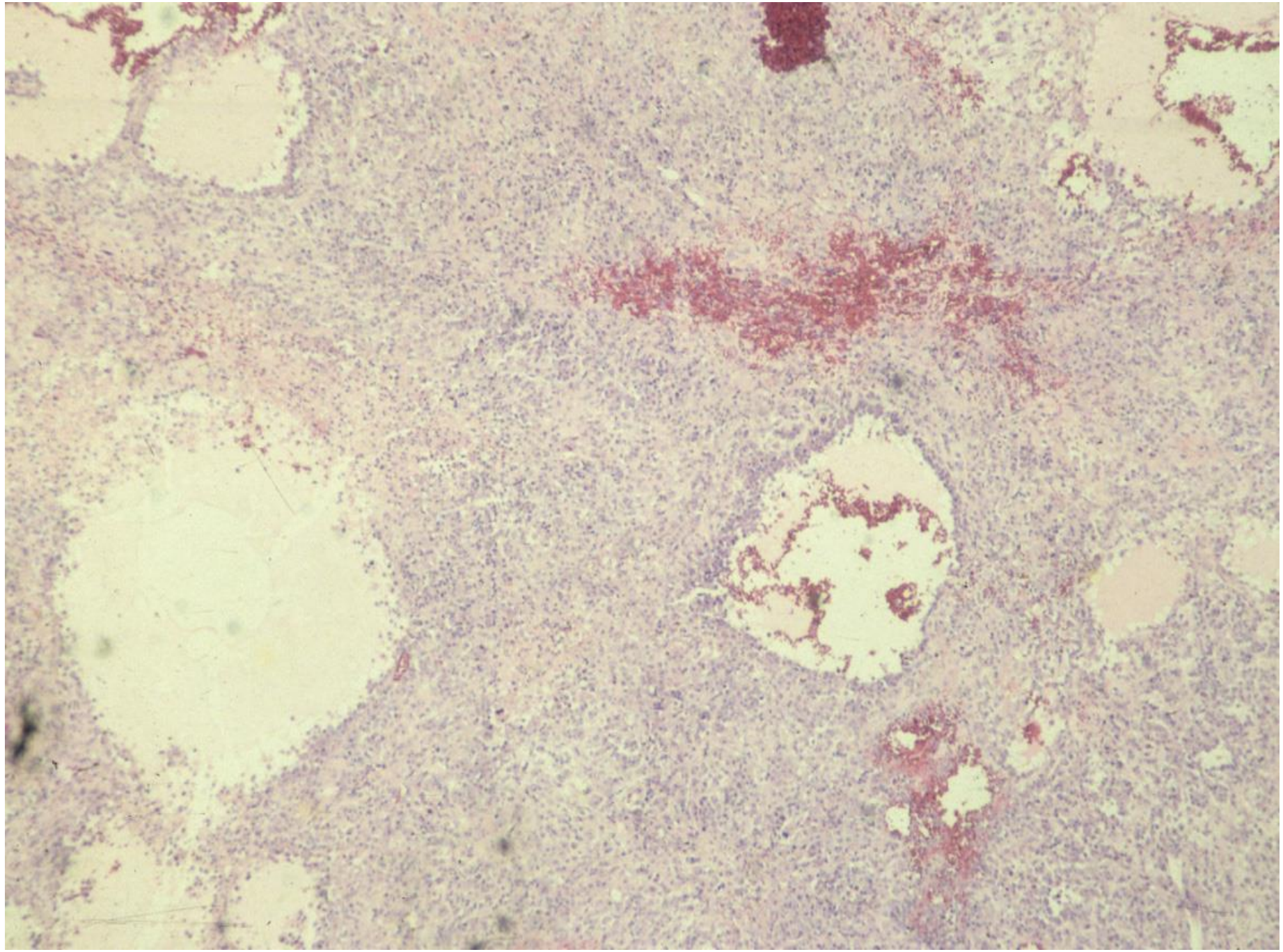

Ovarian SLCT or diagnostically-problematic SCST with SLCT in the differential
Additional diagnostic opinion
Confirmed SLCT (well-, moderately- or poorly-differentiated)
SCST of uncertain type, but with SLCT in the differential
Refer patient to genetics service for germ-line *DICER1* mutation testing. Gather PHx/FHx information*
Perform sequencing of *DICER1* RNase III domains in tumor as part of the pathology work-up
Germ-line mutation present
Germ-line mutation absent
Somatic RNase IIIb mutation present
Somatic RNase IIIb mutation absent
Discuss screening/surveillance. Test relatives for mutation. Optional RNase III domain sequencing in tumor
Perform somatic testing (Full coding region of *DICER1*)
Likely not moderately- or poorly-differentiated SLCT. Consider alternative diagnosis
Additional diagnostic opinion
Somatic mutation(s) present†
No mutations identified
Non-syndromic SLCT (likely moderately- or poorly-differentiated)

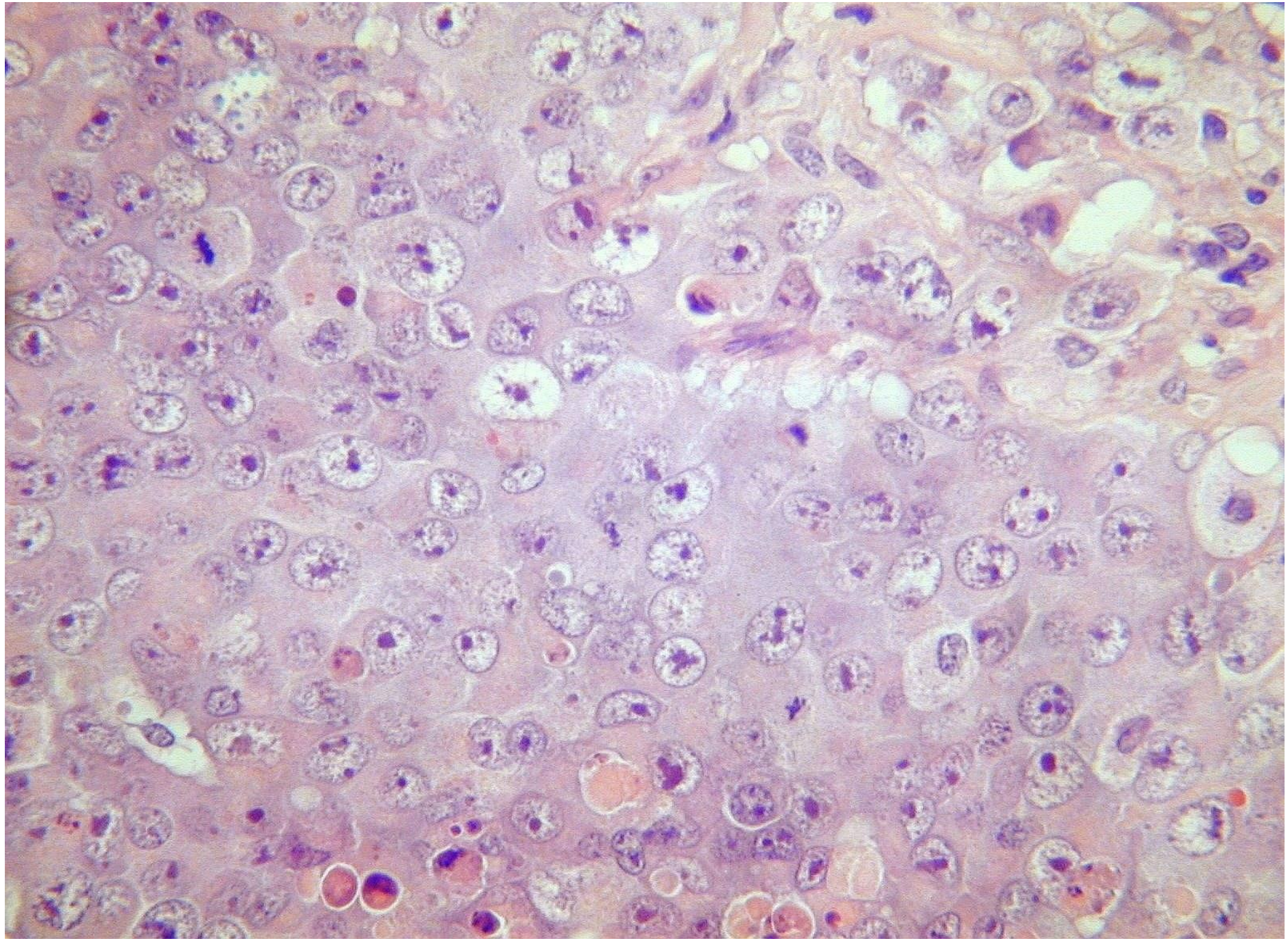
SMALL CELL CARCINOMA OF OVARY OF HYPERCALCAEMIC TYPE- SCCOHT

- usually young females (peak in 2nd and 3rd decades)
- may occur in older females (large series of 150 cases; AJSP 1994;18;1102-1116; age 9-43; average 24 years)
- hypercalcaemia in two-thirds
- usually unilateral ovarian tumour
- rare familial cases (may be bilateral)
- extremely aggressive with poor prognosis









Small Cell **Carcinoma** of **Hypercalcaemic** Type- MISNOMER

- Small- cells not always small
- Carcinoma- no proof that epithelial neoplasm
- Hypercalcaemic- serum calcium only elevated in 2/3 cases

HISTOGENESIS- SCCOHT

- unknown (WHO 2014- categorise among miscellaneous ovarian neoplasms)
- epithelial, germ cell, sex cord and neuroendocrine origin suggested
- never (until recently) described in association with another neoplasm

IMMUNOHISTOCHEMISTRY

- no specific marker (immunohistochemistry of limited value)
- most (not all) WT1 positive (usually diffuse nuclear positivity)
- many other markers may be positive- usually focal- CD10, calretinin, EMA, cytokeratins, CD56; sometimes “mutation- type” p53
- hormone receptors, inhibin negative

DIFFERENTIAL DIAGNOSIS (**small cell or large cell tumour**)

- ovarian small cell carcinoma of pulmonary (neuroendocrine) type
- metastatic small cell carcinoma
- ovarian sex cord-stromal tumour (AGCT, JGCT, SLCT)
- desmoplastic small round cell tumour (DSRCT)
- PNET/Ewing family of tumours
- endometrial stromal sarcoma
- malignant melanoma
- undifferentiated carcinoma
- rhabdomyosarcoma, neuroblastoma, haematopoietic neoplasms
- germ cells tumours

- MANY OF THESE NEOPLASMS OFTEN OCCUR IN YOUNG FEMALES, ARE HIGHLY AGGRESSIVE AND REQUIRE SPECIFIC TREATMENTS

RECENT DEVELOPMENTS

- 3 papers in Nature Genetics 2014
- *SMARCA4/BRG1* mutated in about 98% of SCCOHT (somatic or **germline** mutations) (up to 40-50% have germline) (others mostly have *SMARCB1* mutations)
- *SMARCA4/BRG1* (2%) and *SMARCB1/INI1 (98%)* mutated in virtually all malignant rhabdoid tumours and atypical teratoid/ rhabdoid tumours of CNS
- *SMARCA4* and *SMARCB1* are core members of SWI/ SNF complex

nature genetics

Germline and somatic *SMARCA4* mutations characterize small cell carcinoma of the ovary, hypercalcemic type

Leora Witkowski[1–3,26], Jian Carrot-Zhang[3,4,26], Steffen Albrecht[5], Somayyeh Fahiminiya[3,4], Nancy Hamel[1,6], Eva Tomiak[7], David Grynspan[8], Emmanouil Saloustros[9], Javad Nadaf[3,4], Barbara Rivera[1,3], Catherine Gilpin[7], Ester Castellsagué[1,3], Rachel Silva-Smith[1,2], François Plourde[1,2], Mona Wu[1,3], Avi Saskin[3], Madeleine Arseneault[4], Rouzan G Karabakhtsian[10,25], Elizabeth A Reilly[10], Frederick R Ueland[10], Anna Margiolaki[9], Kitty Pavlakis[11], Sharon M Castellino[12], Janez Lamovec[13], Helen J Mackay[14], Lawrence M Roth[15], Thomas M Ulbright[15], Tracey A Bender[15], Vassilis Georgoulias[9], Michel Longy[16], Andrew Berchuck[17], Marc Tischkowitz[18], Inga Nagel[19], Reiner Siebert[19], Colin J Stewart[20], Jocelyne Arseneau[21], W Glenn McCluggage[22], Blaise A Clarke[23], Yasser Riazalhosseini[3,4], Martin Hasselblatt[24], Jacek Majewski[3,4] & William D Foulkes[1–3,6]*

IS SCCOHT A FORM OF MALIGNANT RHABDOID TUMOUR?

- Clinical similarities (young, aggressive neoplasms)
- Morphological similarities (rhabdoid and non-rhabdoid cells)
- Molecular similarities (*SMARCA4, SMARCB1*)
- **SCCOHT is a form of malignant rhabdoid tumour (could be renamed malignant rhabdoid tumour of the ovary) (but SCCOHT terminology is well established)**

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INVITED PERSPECTIVE

No small surprise – small cell carcinoma of the ovary, hypercalcaemic type, is a malignant rhabdoid tumour

William D Foulkes,[1,2,3]* Blaise A Clarke,[4] Martin Hasselblatt,[5] Jacek Majewski,[2,6] Steffen Albrecht[7] and W Glenn McCluggage[8]

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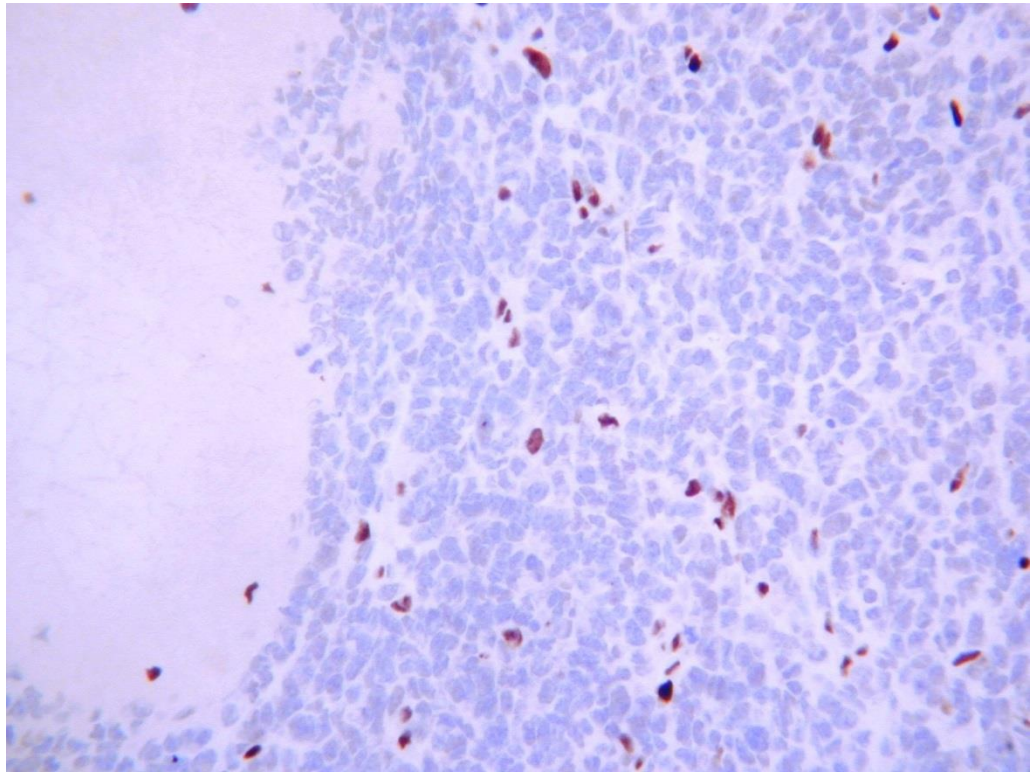
SMARCA4 (BRG1) IMMUNOHISTOCHEMISTRY

- Loss of nuclear staining in SCCOHT secondary to mutation
- **Very useful marker of SCCOHT**
- Retention of nuclear staining in almost all mimics

SMARCA4/ BRG1 IMMUNOHISTOCHEMISTRY



DIAGNOSTIC/GENETIC TESTING ALGORITHM FOR SCCOHT

- 1. Have the tumour reviewed by a gynaecological pathologist and the diagnosis confirmed (this may necessitate SMARCA4/ BRG1 immunohistochemical staining)
- 2. Once the diagnosis is confirmed, counsel the patient for germline SMARCA4 sequencing
- 3. In the case of a germline mutation, consider removal of the unaffected ovary in unilateral SCCOHT if only one ovary has been removed
- 4. In the case of a germline mutation, test family members for mutation (? Role of prophylactic oophorectomy)
- 5. In the case of no germline mutation, if appropriate according to age and clinical context, retain unaffected ovary in unilateral SCCOHT

PAPER IN PRESS- PMID 28130795

- 2 cases of SCCOHT in association with teratomas
- Several similar cases reported in literature
- SUGGESTS THAT SCCOHT MAY BE A PRIMITIVE GERM CELL TUMOUR ARISING FROM A TERATOMA

CASE 1 ASSOCIATED WITH TERATOMA