Ovarian Serous Tumours

Trupti Mandalia

Royal Devon and Exeter Hospital

Classification

- Serous
- Endometrioid
- Clear cell
- Mucinous
- Brenner

Type 1

- Endometrioid – CTNNB1, PTEN
- CCC –ARIDIA, PIK3CA
- LGSC – KRAS, BRAF
- Mucinous – KRAS

Type 2

- Serous – p53, BRCA

Majority of stage 3 and 4 disease presentation HGSC or LGSC

HGSC much more common than LGSC (17:1)

The remainder of types usually stage 1 and less commonly stage 2

What's new? -Serous

LGSC and HGSC two distinct tumour types

-not two grades of one neoplasm

-different pathogenesis, different molecular signatures, different prognosis

Micropapillary variant of SBT is now considered – noninvasive LGSC

Invasive implants – LGSC

Low grade Serous tumours

- Adenoma – Borderline- carcinoma pathway well established and understood

SBT- morphology (>10%)

Hierarchical branching/ Stratification

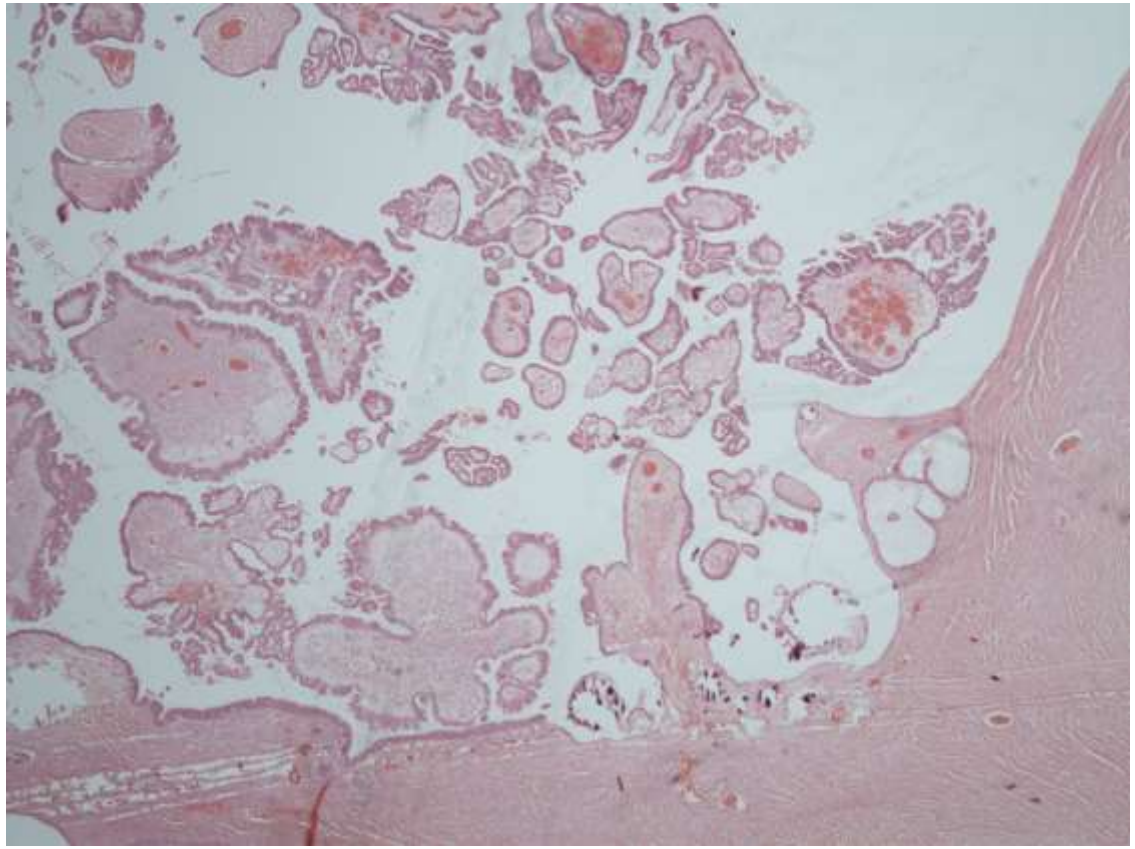
Epithelial tufts

Exfoliation

Mild to moderate nuclear atypia

Occasional mitoses

Absence of destructive stromal invasion



Low grade serous tumours -challenges

- Benign → Borderline → Low grade serous carcinoma

- 1) how much proliferation is enough to justify BL over benign
- 2)Issues with micropapillary pattern
- 3)Identification of microinvasion
- 4)SBT vs LGSC
- 5)Implants

SBT

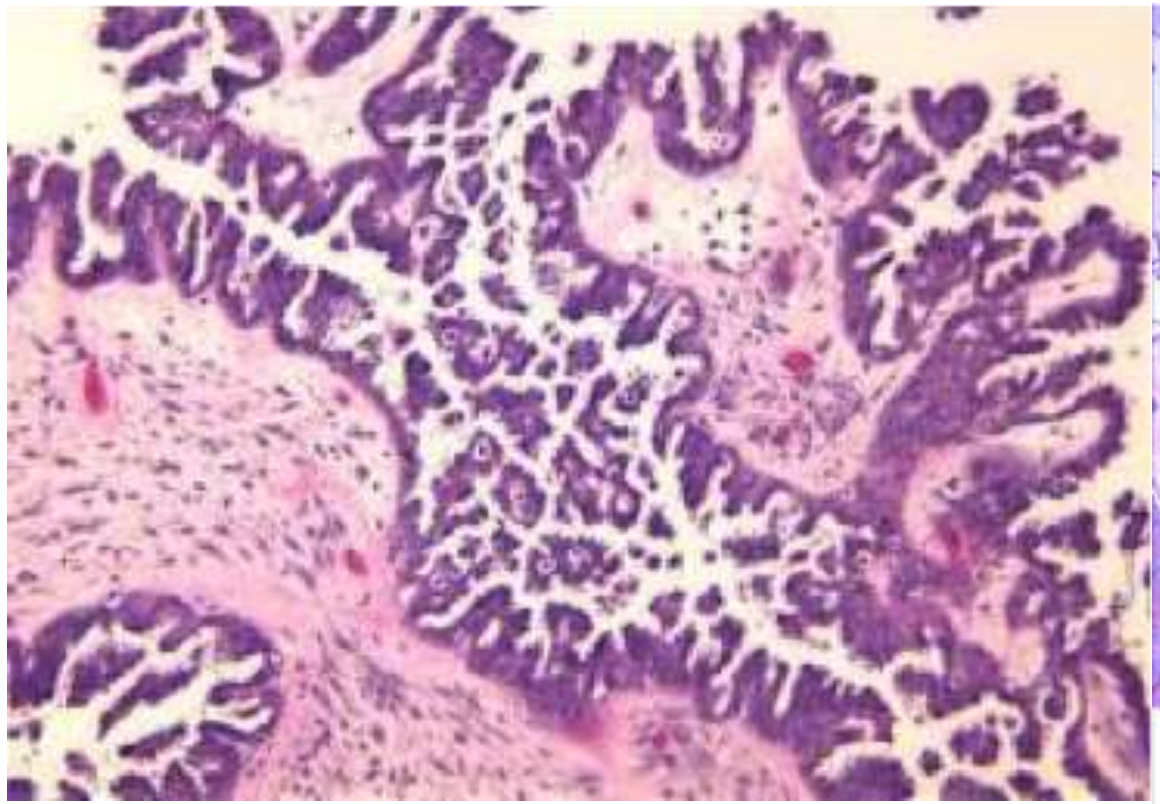
- Bilateral – 30-40%
- Advanced stage 30-40%
- 4^{th} and 5^{th} decade
- Elevated ca125
- Transformation to HGSC very rare

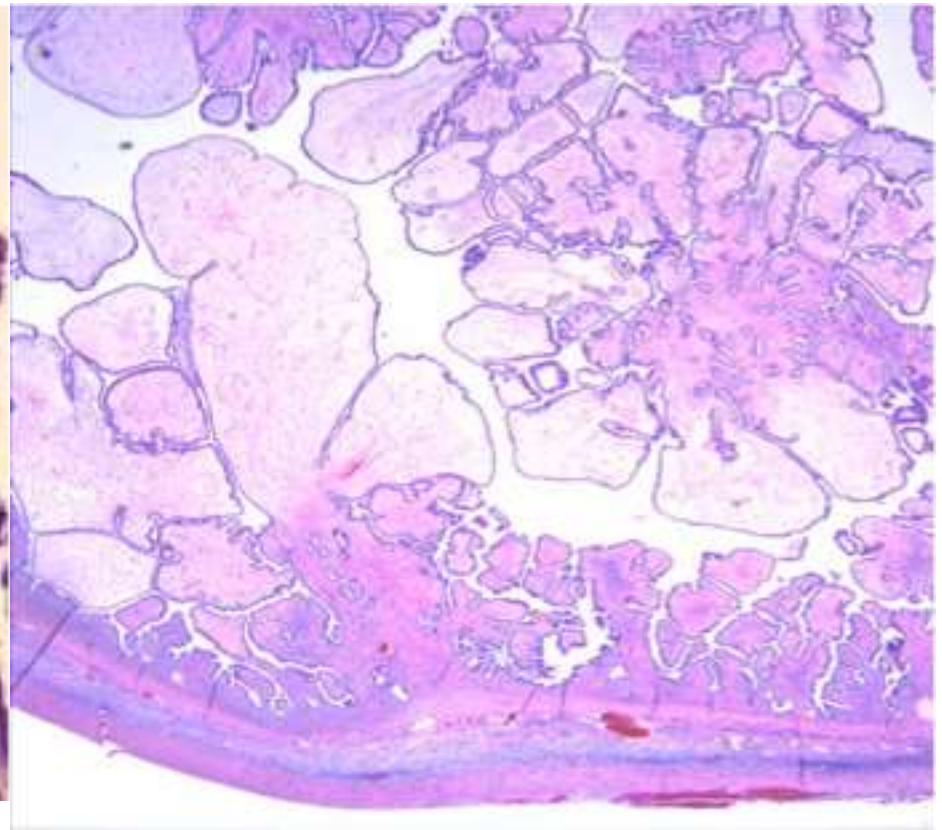
SBT

- 3-10% risk of recurrence
- Recurrence usually as SBT or LGSC
- High grade transformation rare but described (second mutation involving Tp53)
- NO specific immunohistochemical or molecular markers to predict prognosis

LGSC –molecular features

- KRAS or BRAF mutation (genes of MAPK pathway)
- KRAS and BRAF are mutually exclusive
- No p53 mutation





Micropapillary (Now renamed – noninvasive LGSC WHO 2014)

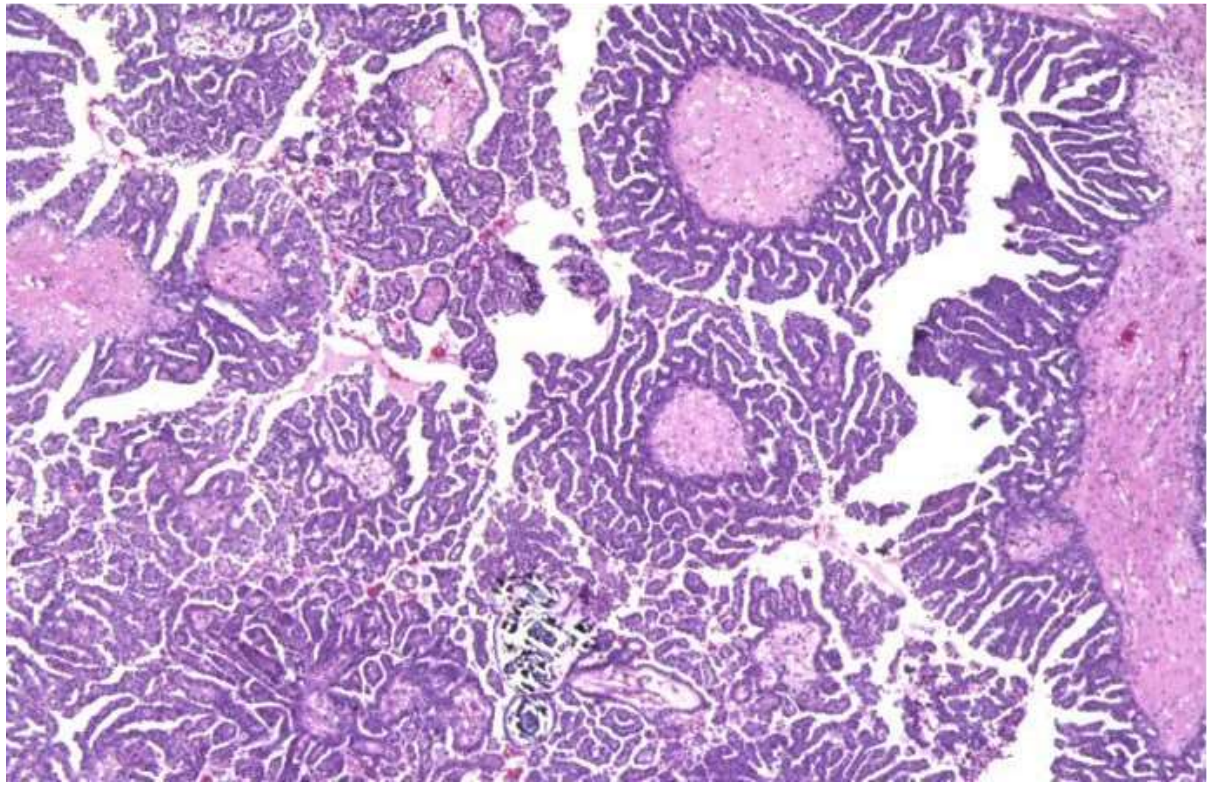
5 times taller than wide papillae

>5mm continuous extent

Comprises 10-12% of SBT

Invasive implants more common

Prognosis is related to type of implants



Micropapillary

1) Extensive sampling of tumour
2) Extensive sampling of omental tissue even if looks normal macroscopically (at least 10 sections –my practice)
3) Prognosis depends on the stage and implant morphology

   - stage 1 excellent prognosis

   -stage 2 and 3 excellent prognosis if no invasive implants

   - invasive implants (presence and frequency) –poorer prognosis

Implants

Noninvasive implants – epithelial and desmoplastic

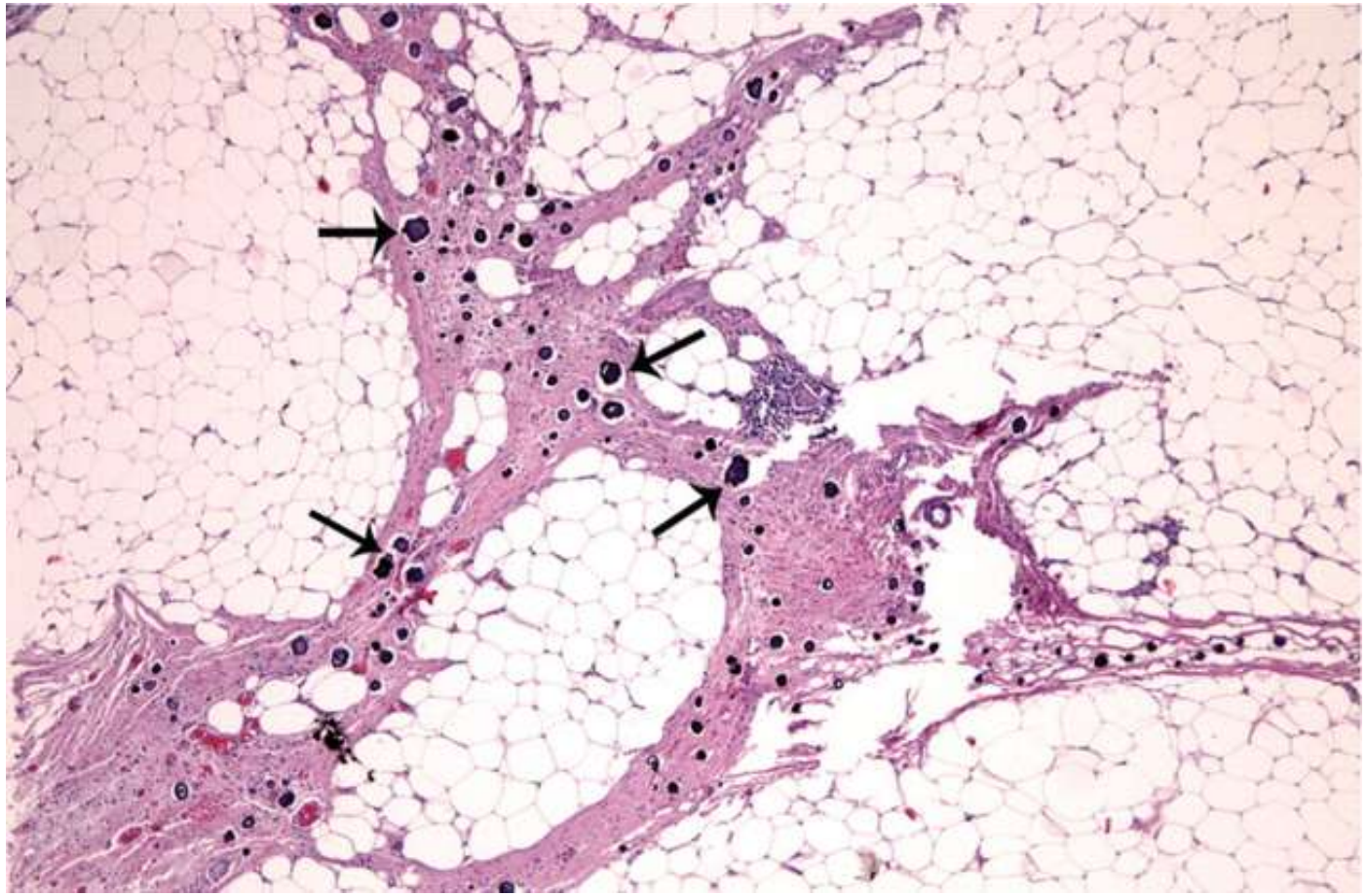
Invasive implants = LGSC

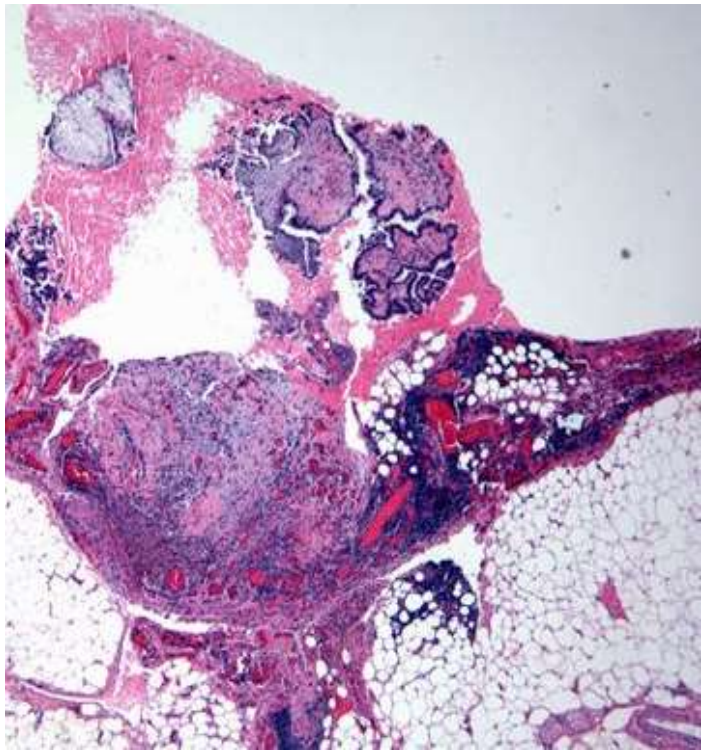
30-40% are associated with implants

<15% are invasive

SBT with invasive implants are now classified as LGSC (WHO 2014)
Associated with significantly shorter survival

Implants - morphology





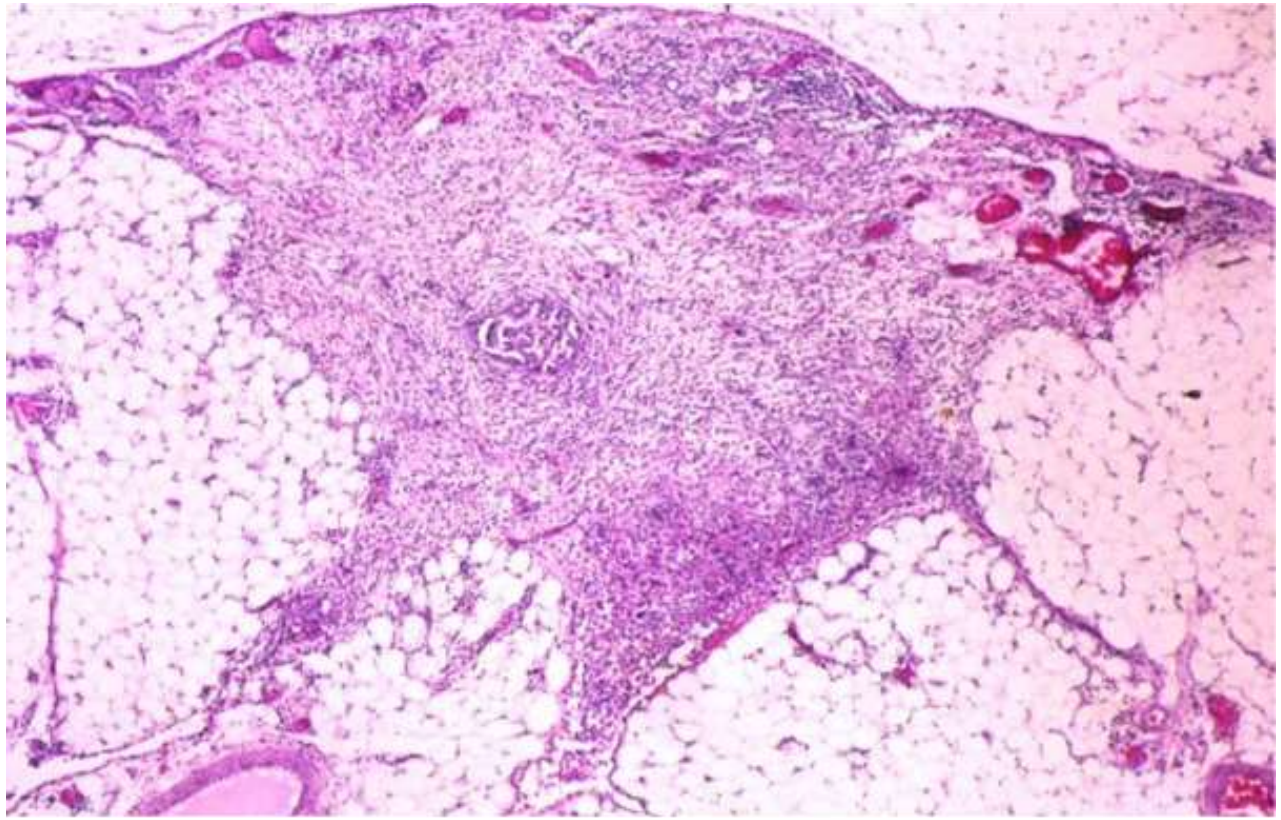
Located on the surface without invasion of underlying tissue

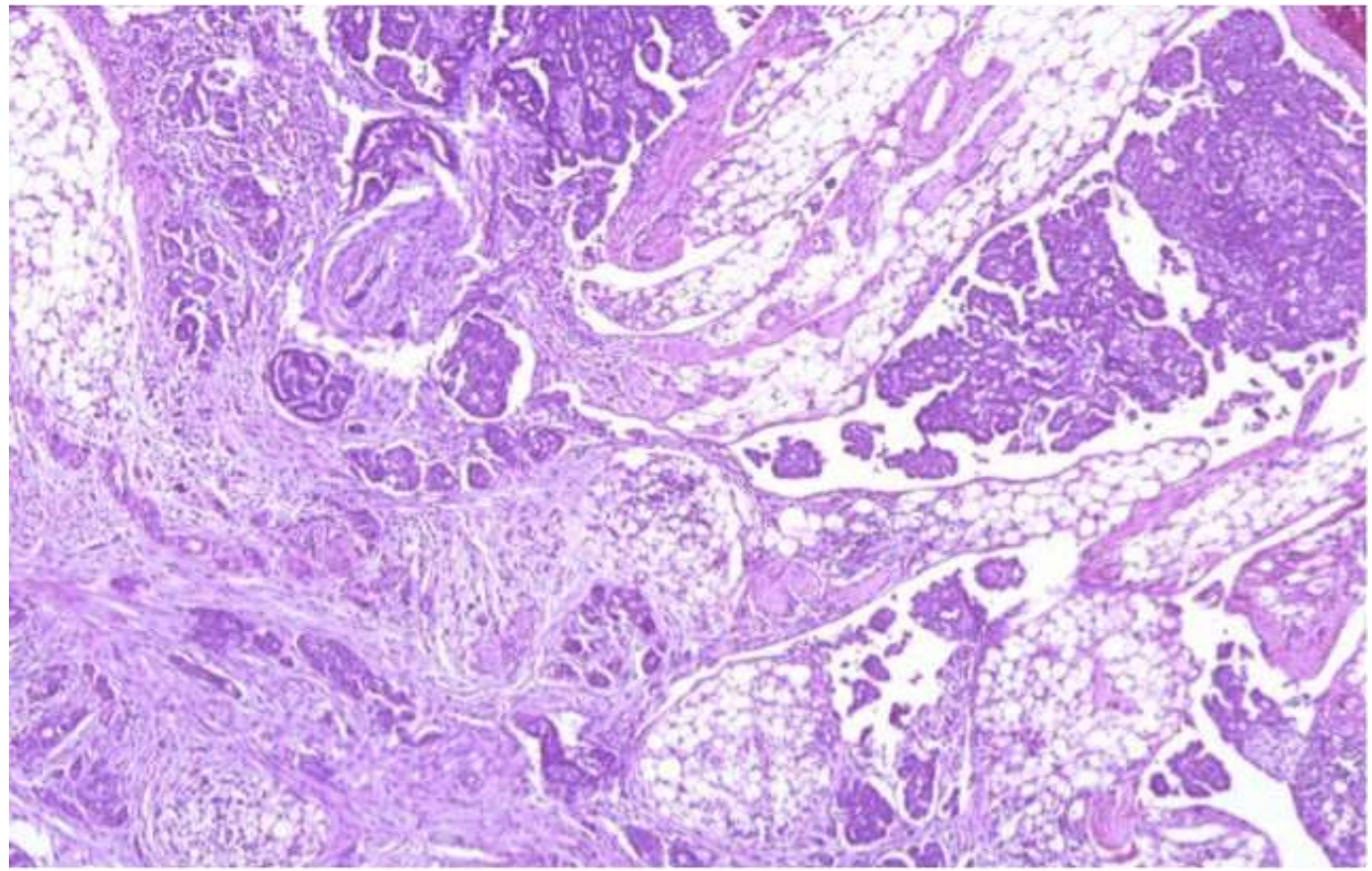
May extend into septa of omentum

Glands lioned by mildly atypical cells

Abundant fibrous/granulation like tissue

Implants - morphology





Lymph node involvement

Seen in 20-25% of SBT
Paraaortic, obturator, iliac nodes
Mainly in sinuses
Significance uncertain

Microinvasion in SBT

- Two types

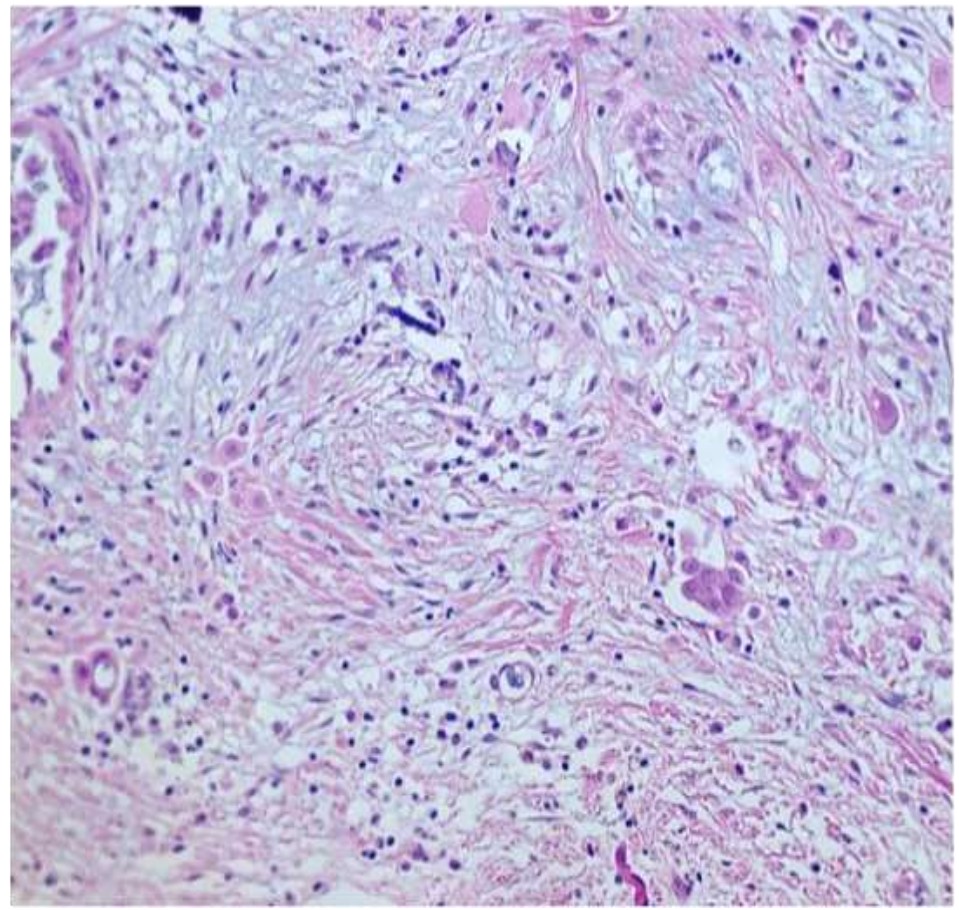
  single cells or small clusters with eosinophilic cytoplasm

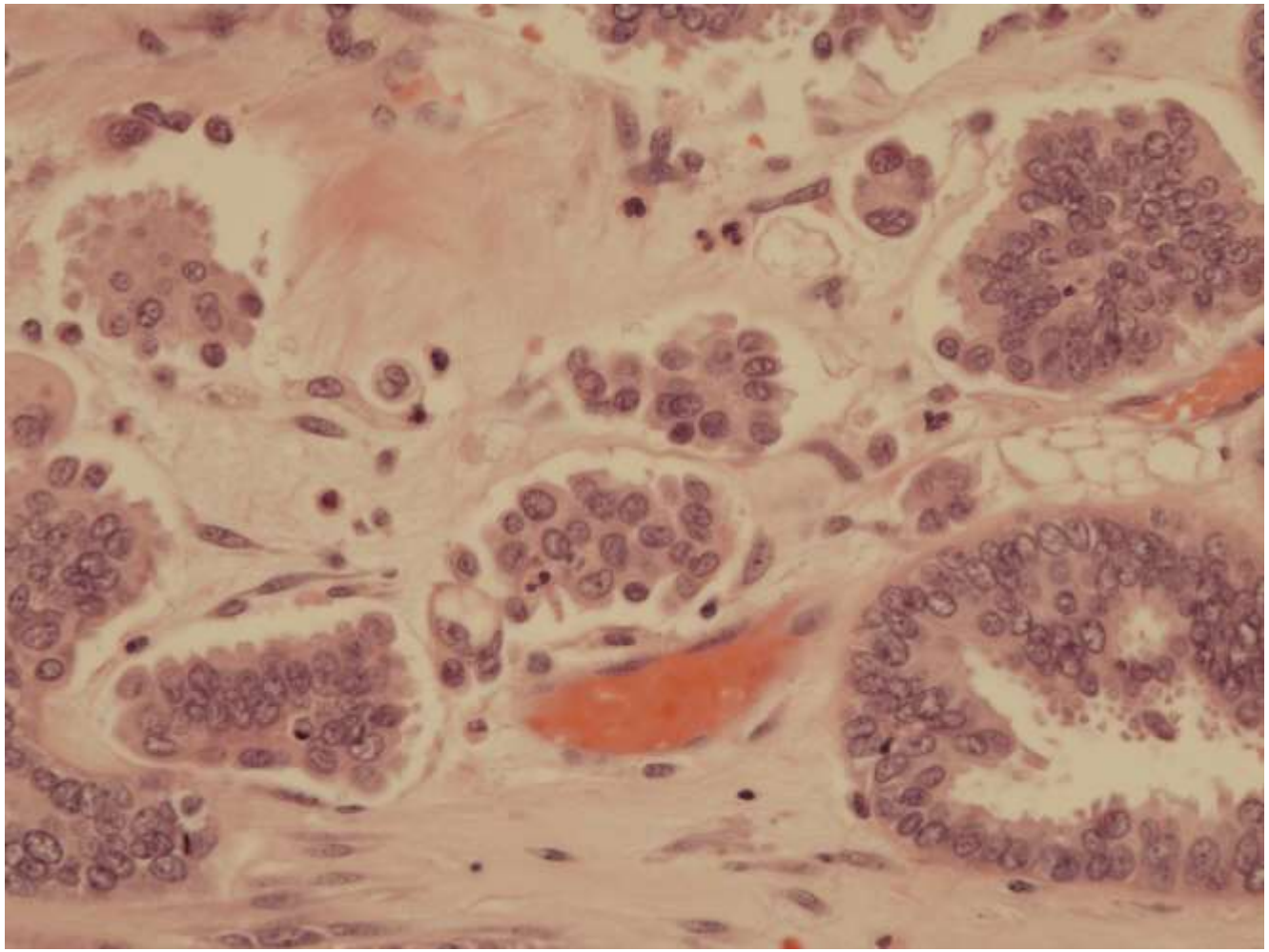
  small papillary clusters

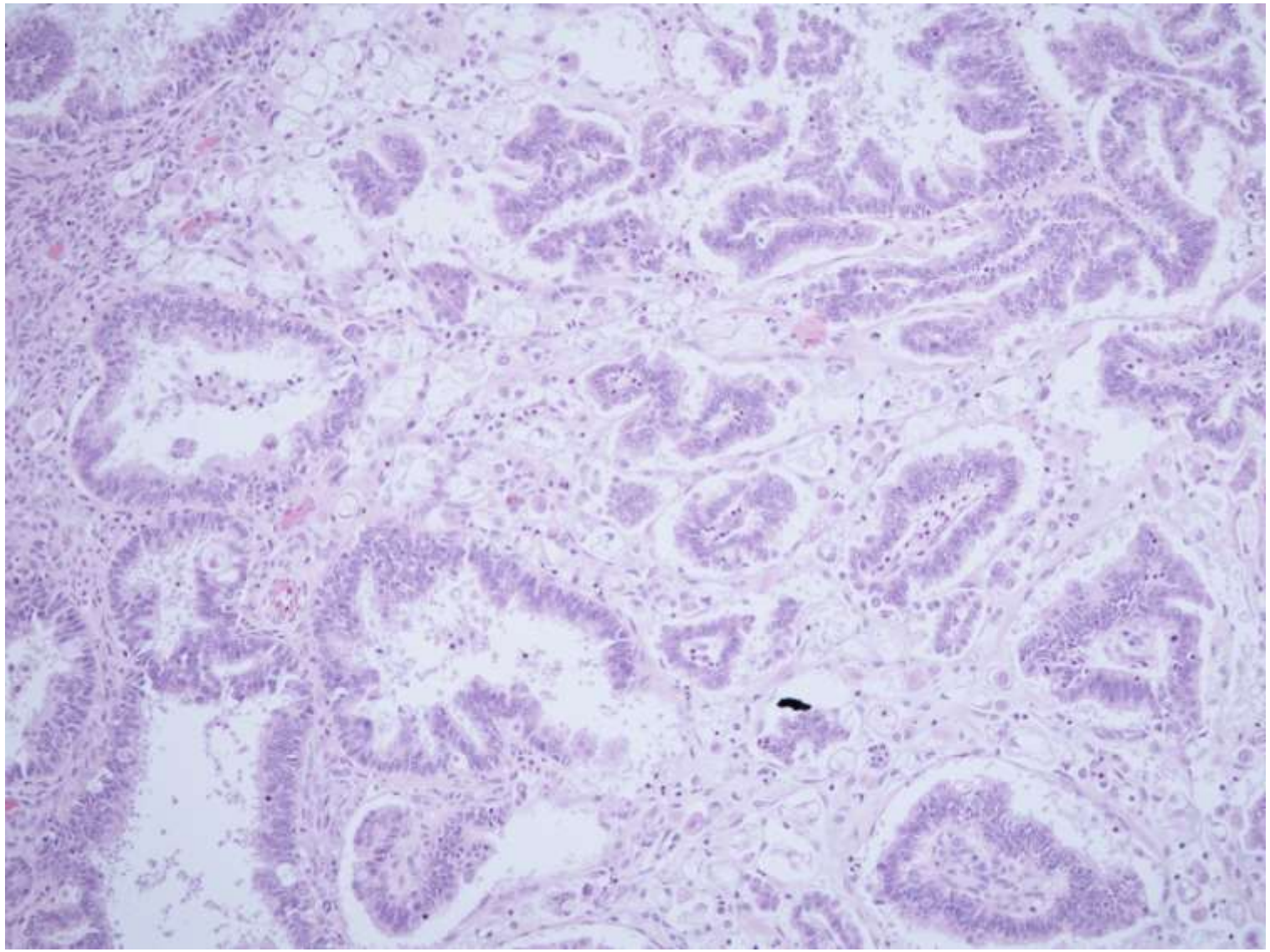
  < 5mm across (multiple foci allowed)

No adverse effect on prognosis

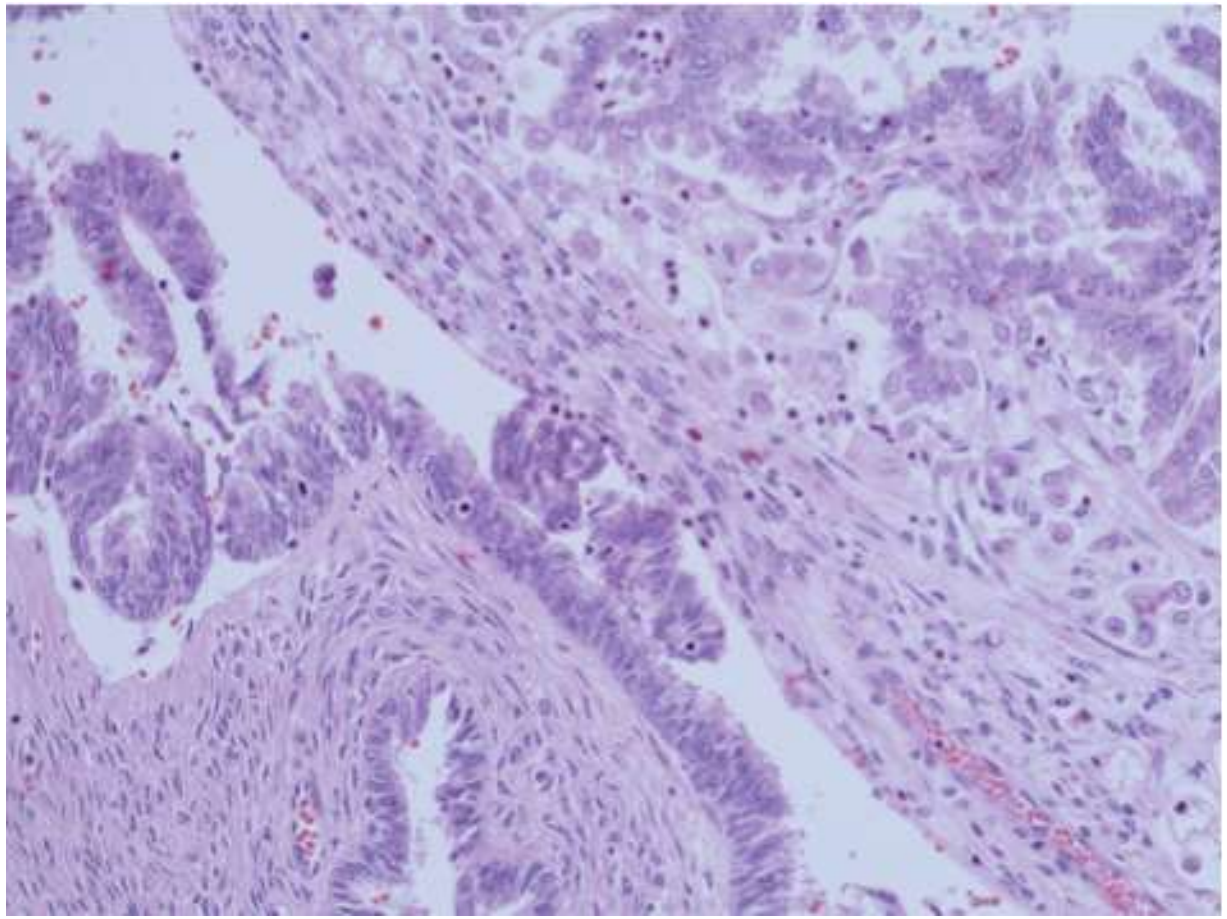
Ki 67 – low







LGSC



LGSC

Complex back to back architecture
Little intervening stroma
Frank stromal invasion

Slowly progressing
Usually high stage at presentation
Chemoresistant
BRAF mutation -slightly better prognosis

Staging of SBT

- Staged as carcinoma
- Noninvasive implants are included in staging of SBT and LGSC
- If only invasive disease is extraovarian than indicate sites and volume of invasive component

D/D

- Endometrioid ca (low grade) - WT1 negative, asso with endometriosis
- Seromucinous carcinoma - Wt1 negative, Endometriosis, mixed morphology
- Endosalpingiosis vs implants

Take home…

SBT

prognosis is mainly decided by the presence and type of implants

Micropapillary variant is reclassified as LGSC, noninvasive type

Invasive implants are reclassified as LGSC

Extensive sampling is the key to correct diagnosis/assessment

HGSC –pathogenesis

- Most cases arise from distal fallopian tube
- STIC –precursor lesion
- DOES NOT ARISE from borderline tumour
- P53 –early event in molecular pathway

    -almost 100% p53 mutated (IHC- 5%wild type)

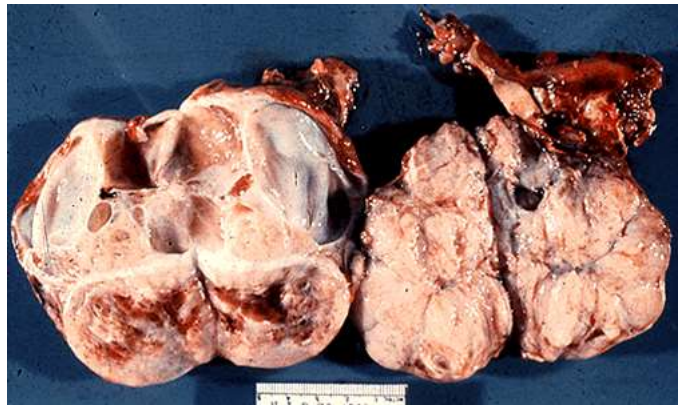
BRCA mutation – (25%) hypermethylation or germline

No BRAF or KRAS

HGSC

- Most common 70-80%
- high stage (stage 3-4) disease presentation common
- Hysterectomy for ovarian mass or omental biopsy in radiologically high stage disease
- Tp53 mutation almost in 100% cases (IHC -95%)

Gross examination

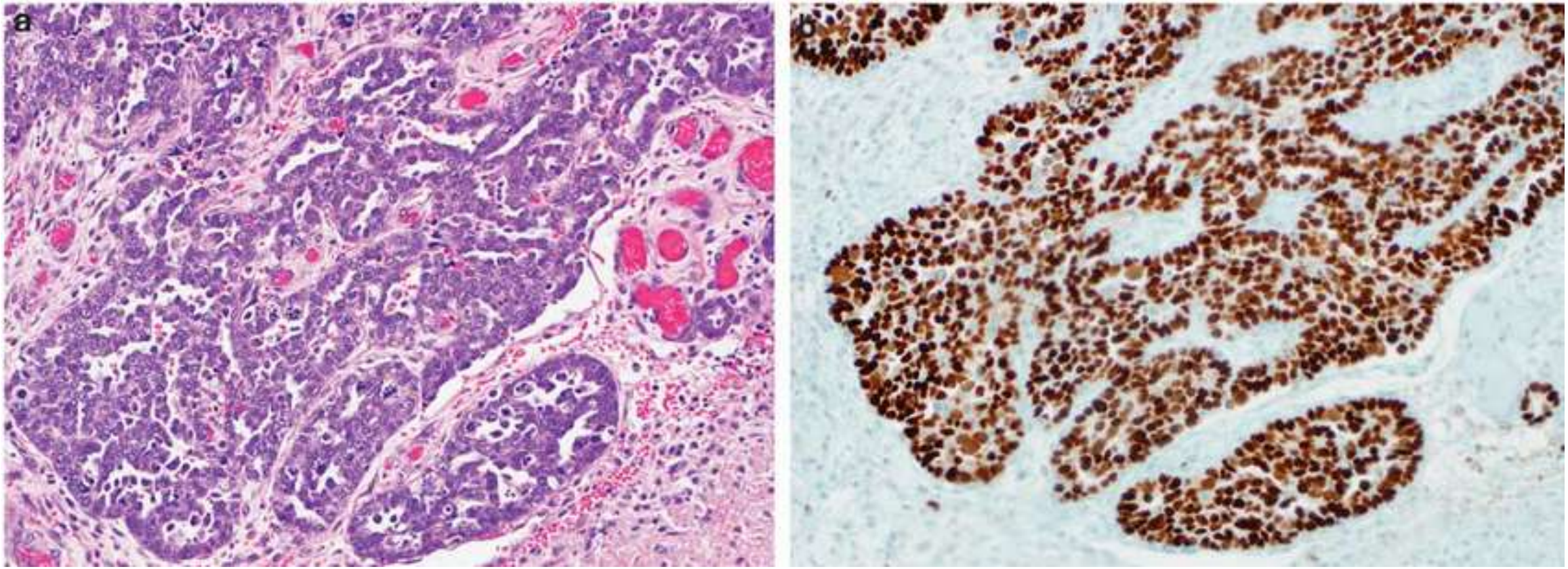


HGSC morphology

- Severe nuclear atypia
- Numerous mitoses (>12/10HPF)
- Tumour giant cells

Morpholgy

- Papillary
- Solid
- Pseudoendometrioid
- TCC-like
- microcystic
- Clear cell
- mixed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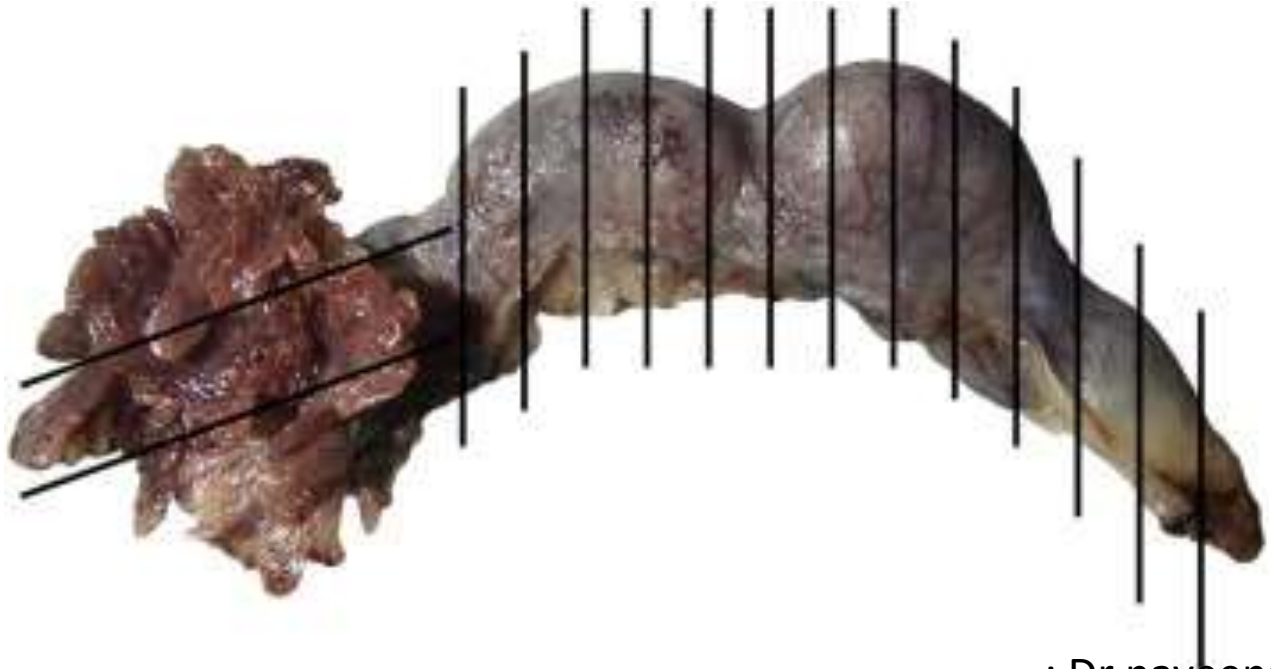
- Frequency of STIC in HGSC
- Very high in risk reducing salpingo-oophorectomy (RRSO) specimens
- Sporadic cases: Huge variation in literature, 28-61% in recent meta analysis

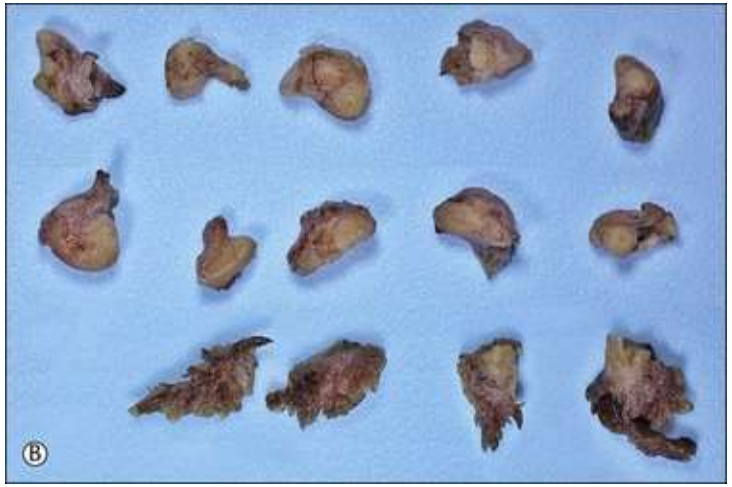
Depends on

1)sampling (SEE-FIM sectioning and extensive examination of the fimbriated end protocol)

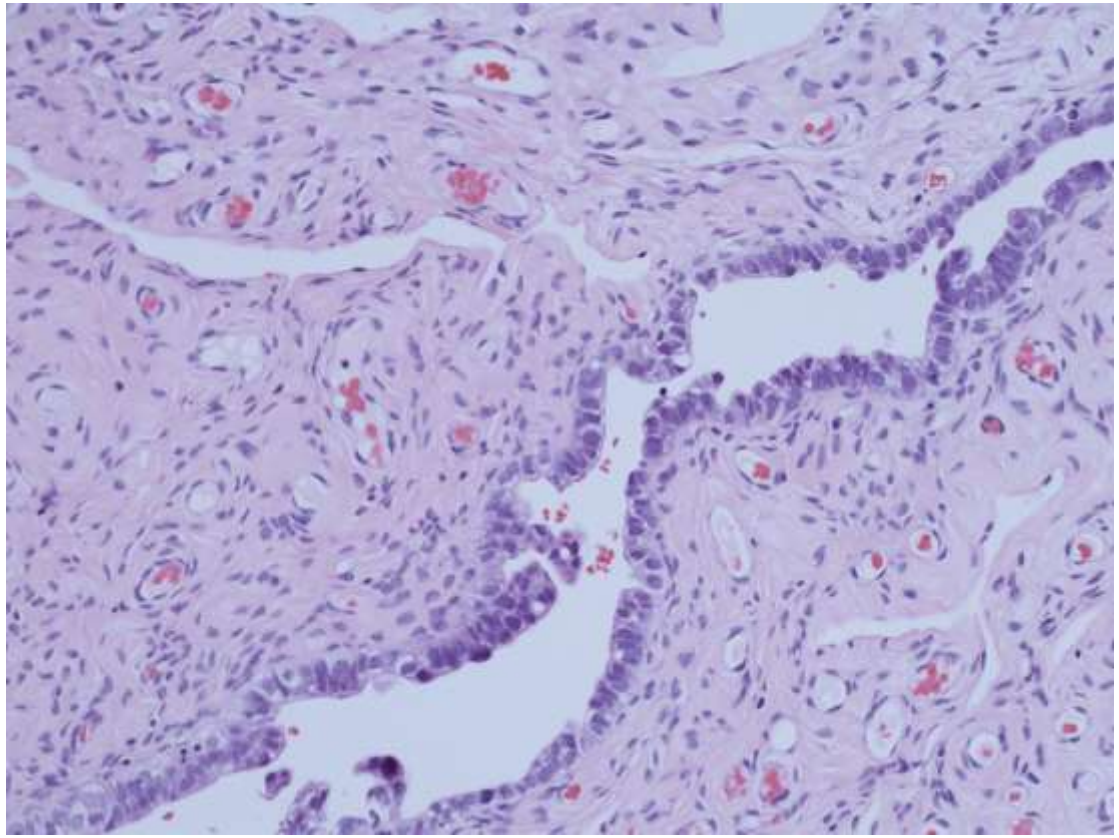
2)Diagnostic criteria used

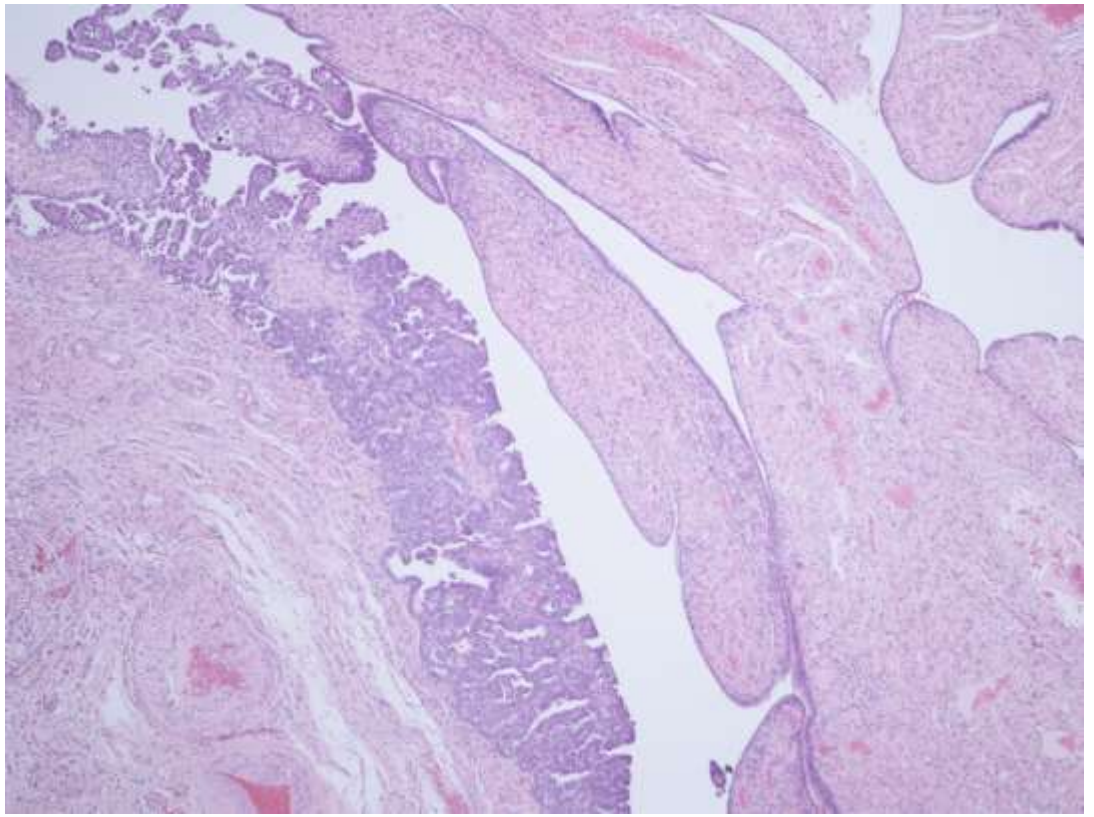
SEE FIM – all HGSC, all HR

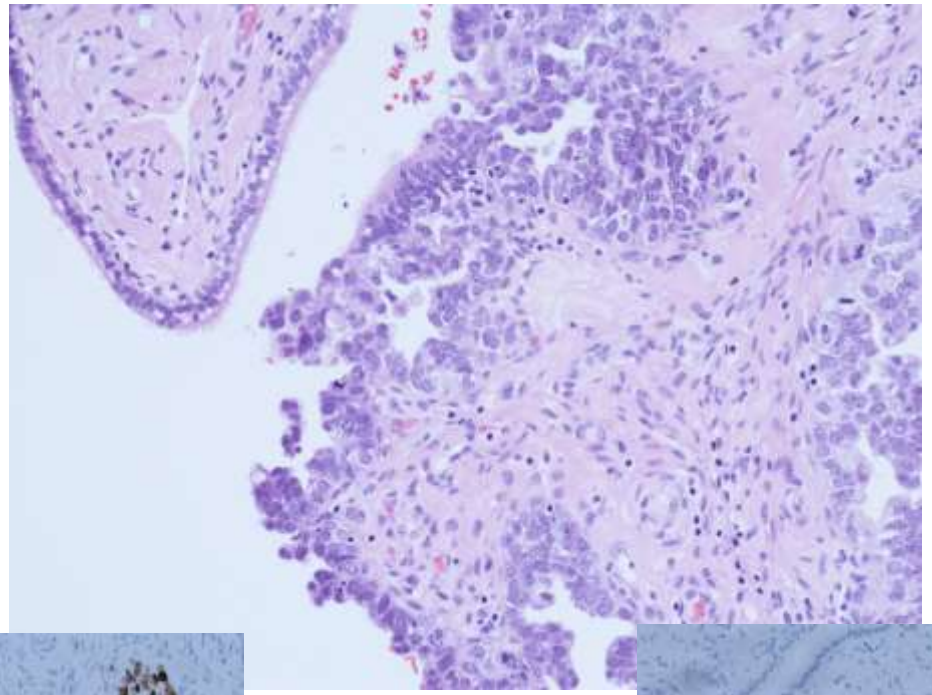


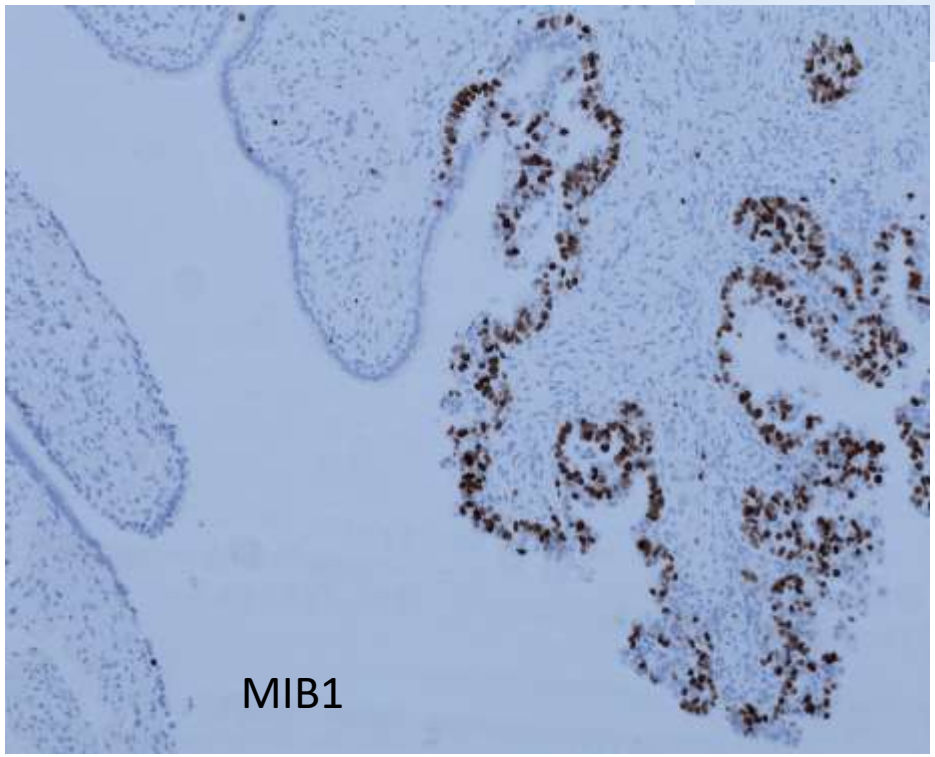


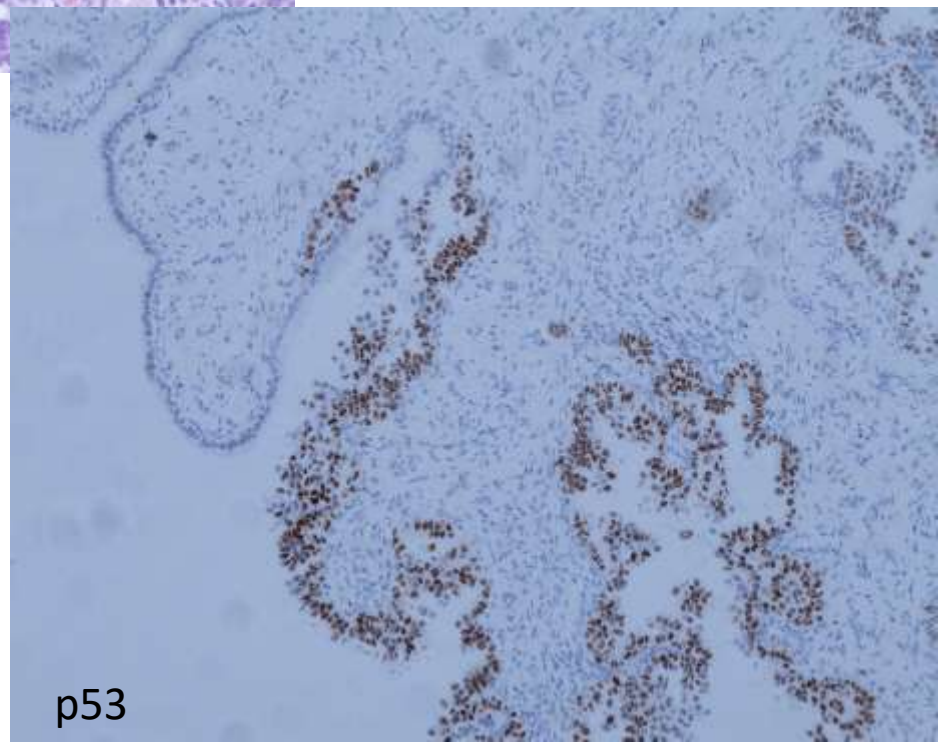
: Dr naveena singh, Royal Barts and london hospital) BAGP meeting)








MIB1

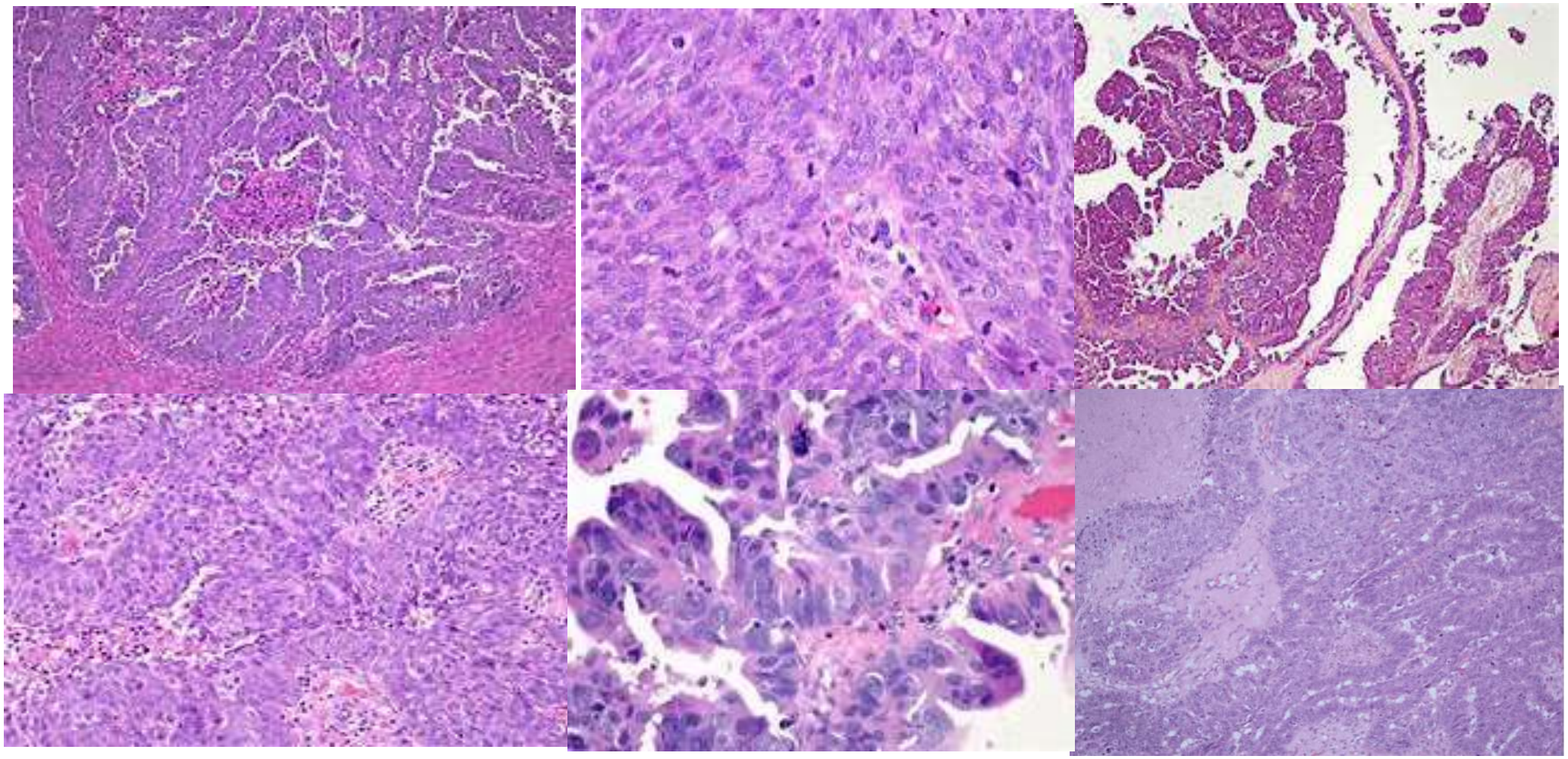

p53

Site assignment in HGSC

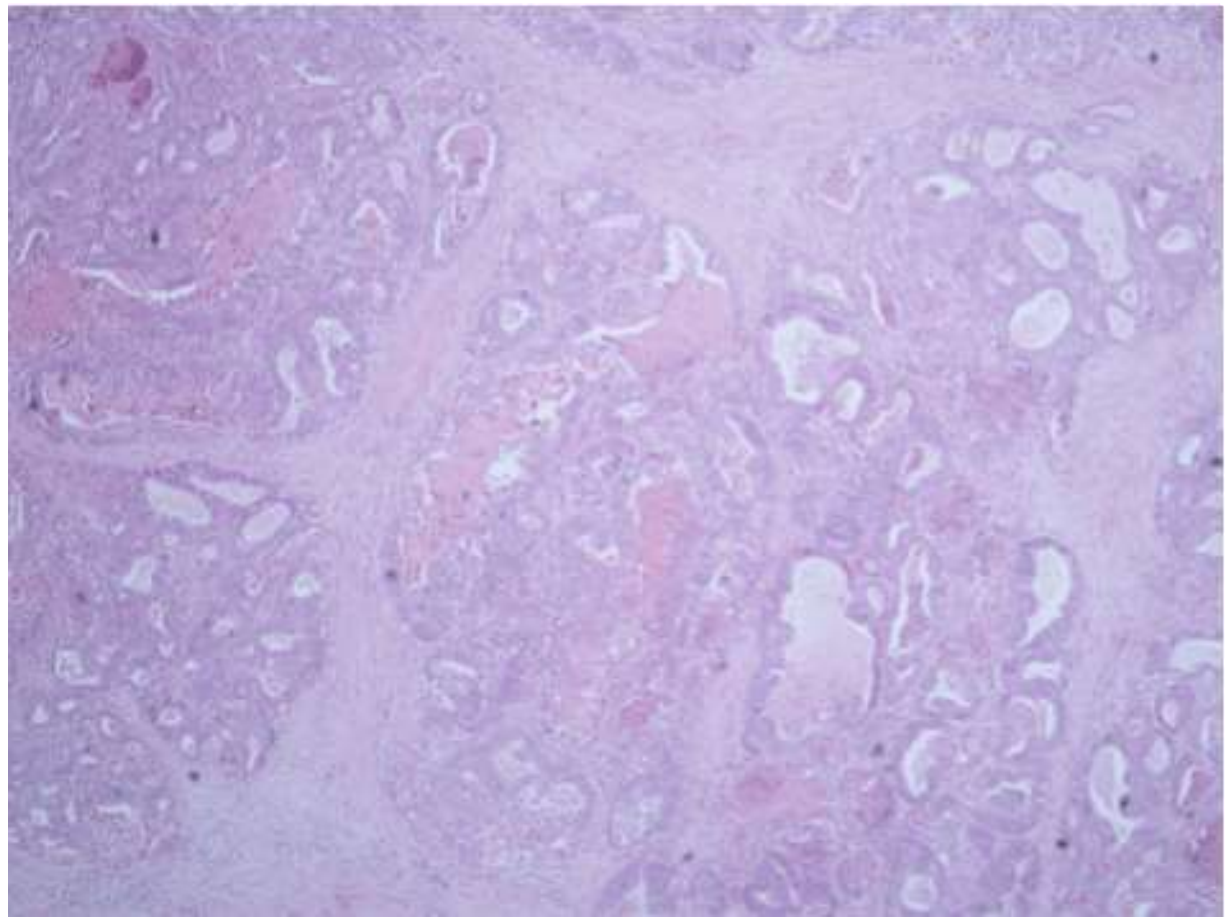
- TUBAL, in the presence of: – STIC, tubal Invasive mucosal carcinoma and/or tube is incorporated into tubo-ovarian mass
- OVARIAN, in the absence of tubal involvement as above
- PERITONEAL, in the absence of gross or microscopic involvement of tubes (mucosal) and ovaries
- UNDESIGNATED: genuine uncertainty between uterine vs tubo-ovarian

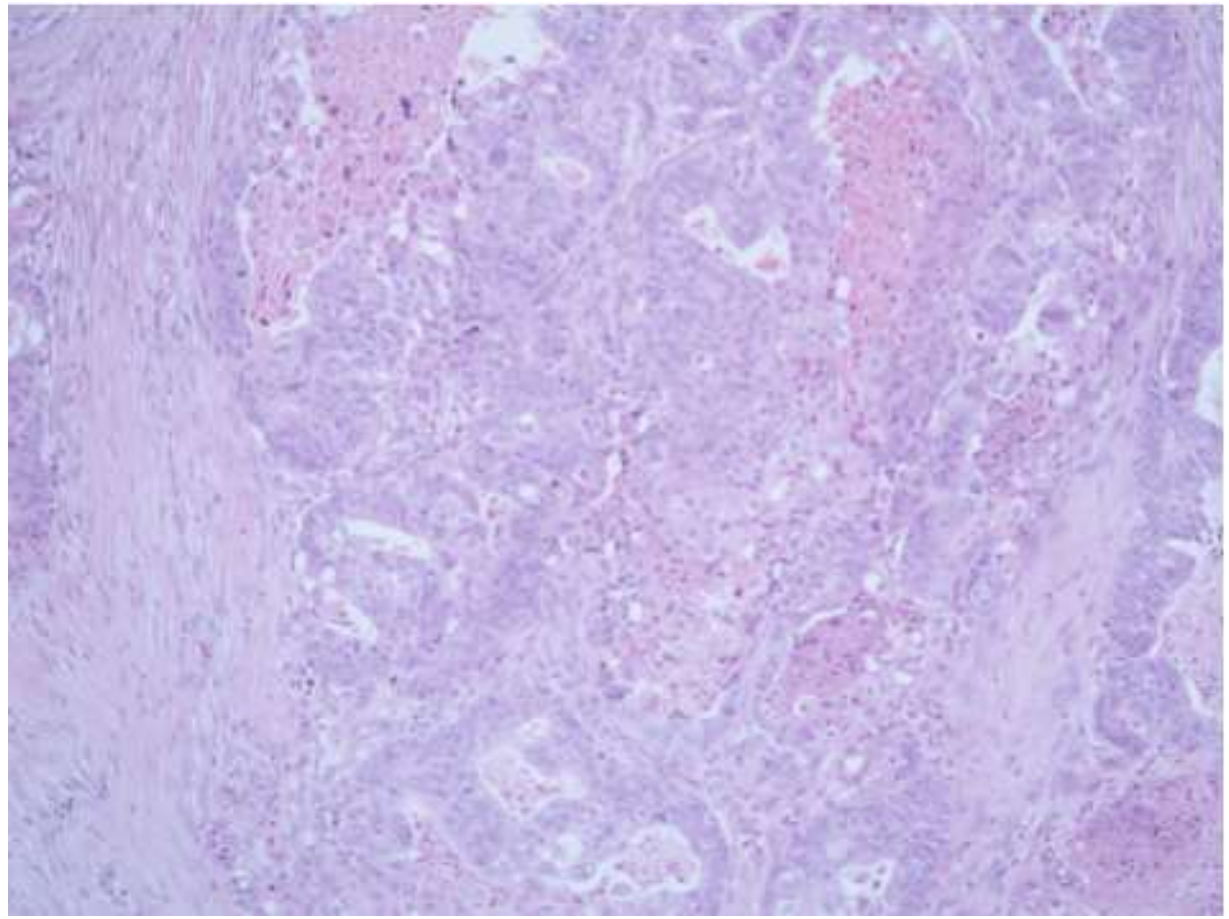
- STIC is not secondary/metastatic in majority of cases
- STIC can spread to peritoneal surfaces without invasion at the primary site

HGSC morphology –diagnostic challenge

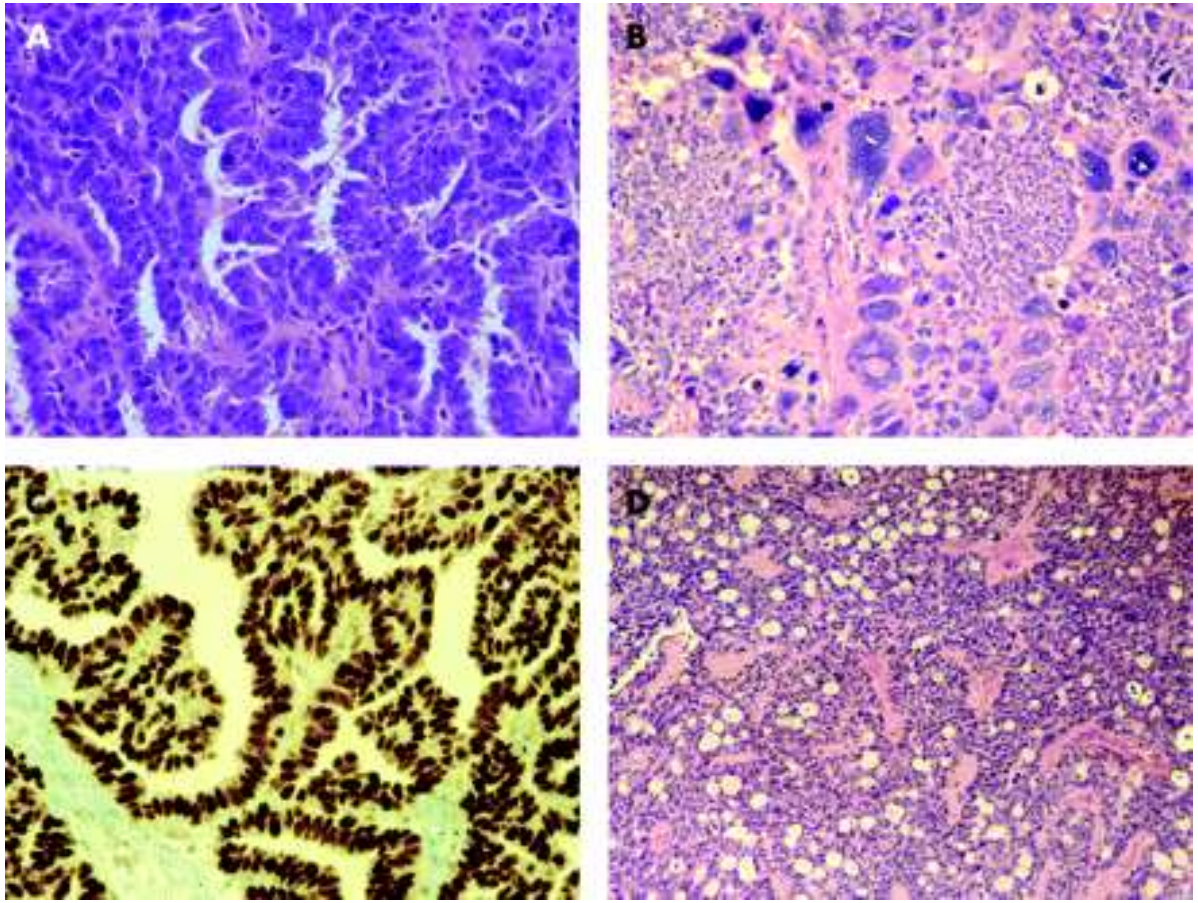


- Pseudoendometrioid pattern – D/D endometrioid ca
- Solid pattern –D/D endometrioid ca, undifferentiated ca
- Transitional pattern- malignant Brenner tumour





HGSC vs Endometrioid (WT1)



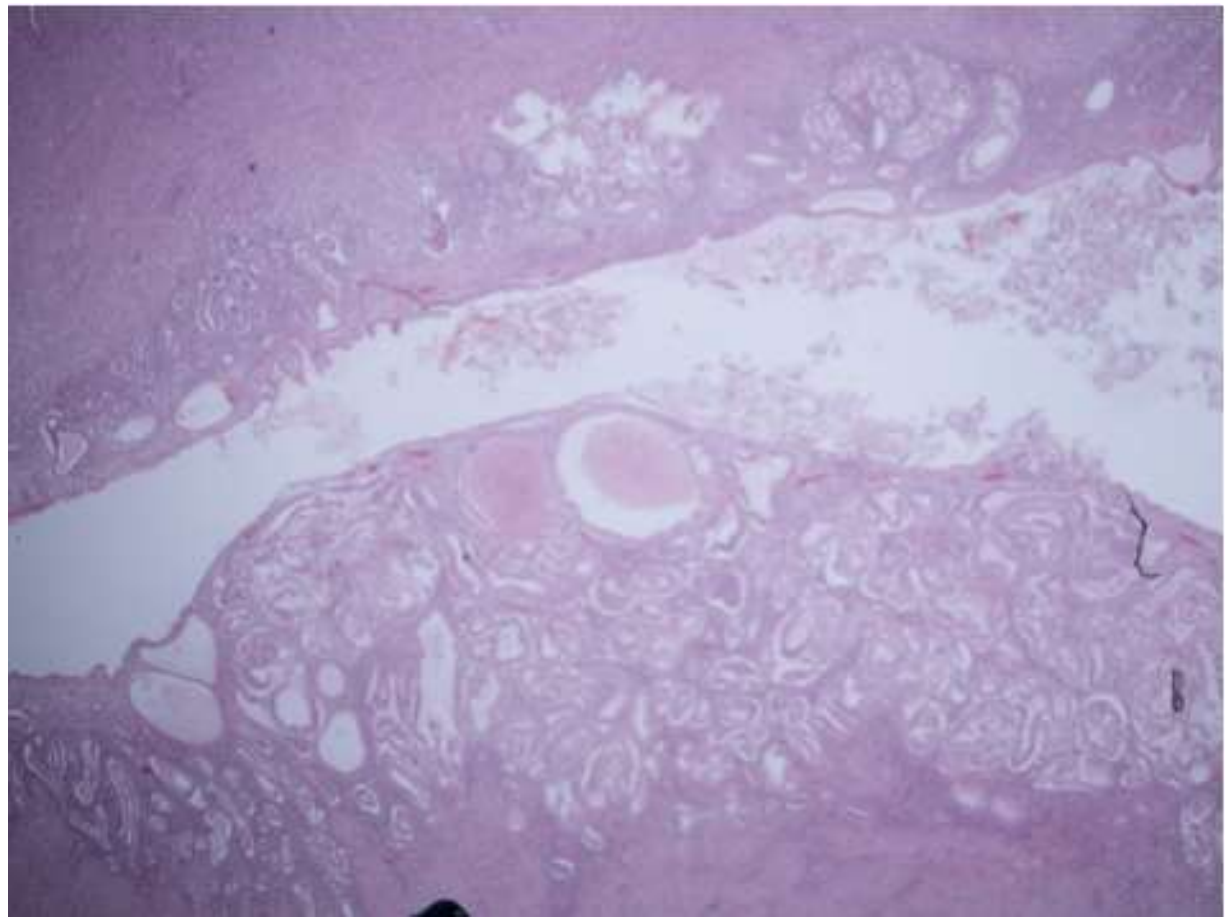
HGSC and HG endometrioid

Presence of STIC supports HGSC

Endometrioid-

Low grade endometrioid areas, endometriosis, squamous metaplasia

- P53 wild type
- WT1 –negative or very focal and weak (low grade can be positive)
- P16 patchy
- MMR helpful (if abnormal)



MSI associated tumours

Peritumoural and/or intratumoural lymphocytes

Mixed morphological patterns

Undifferentiated morphology

Synchronous carcinoma

Lynch syndrome –endometrioid carcinoma

MSI tumours have better outcome

More responsive to RT

Eligible for immune checkpoint inhibitor Rx

Candidates for progesterone Rx(not oestrogen driven)

- IHC panel (PMS2, MLH1, MSH6, MSH2)
- Or MSI (PCR)

If abnormal

- Advise germline mutation testing

HGSC VS CCC

- Clear cell change not uncommon in HGSC
- Mixed tumours almost never occur
- Look out for STIC or endometriosis
- IHC helpful
- P53, p16, WT1, ER
- CCC (triple negative??)

Endometriosis associated ovarian tumours

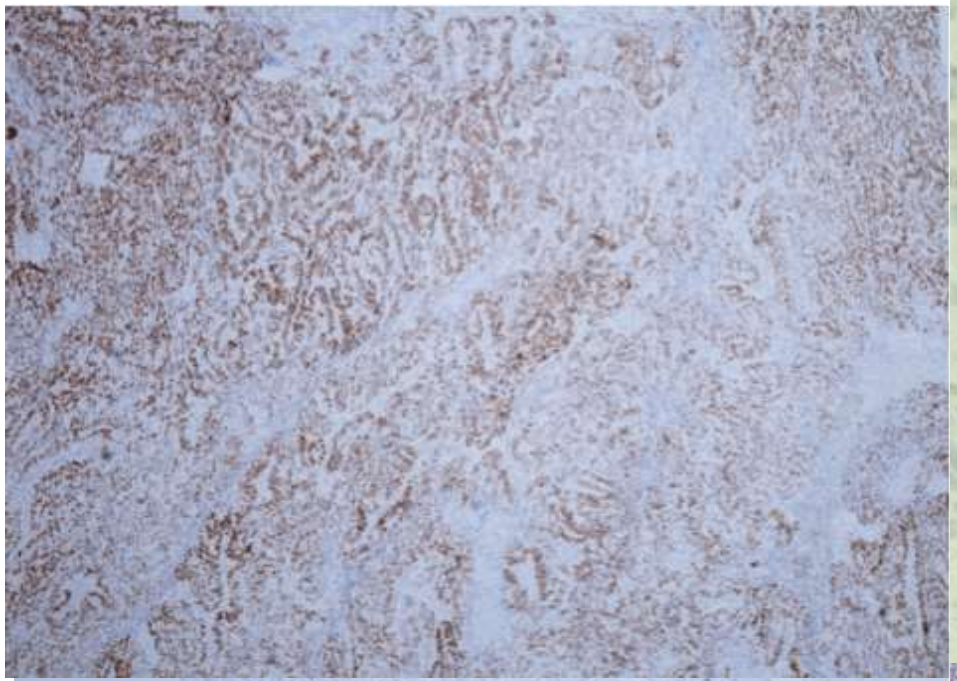
- Endometrioid ca
- Seromucinous ca
- CCC

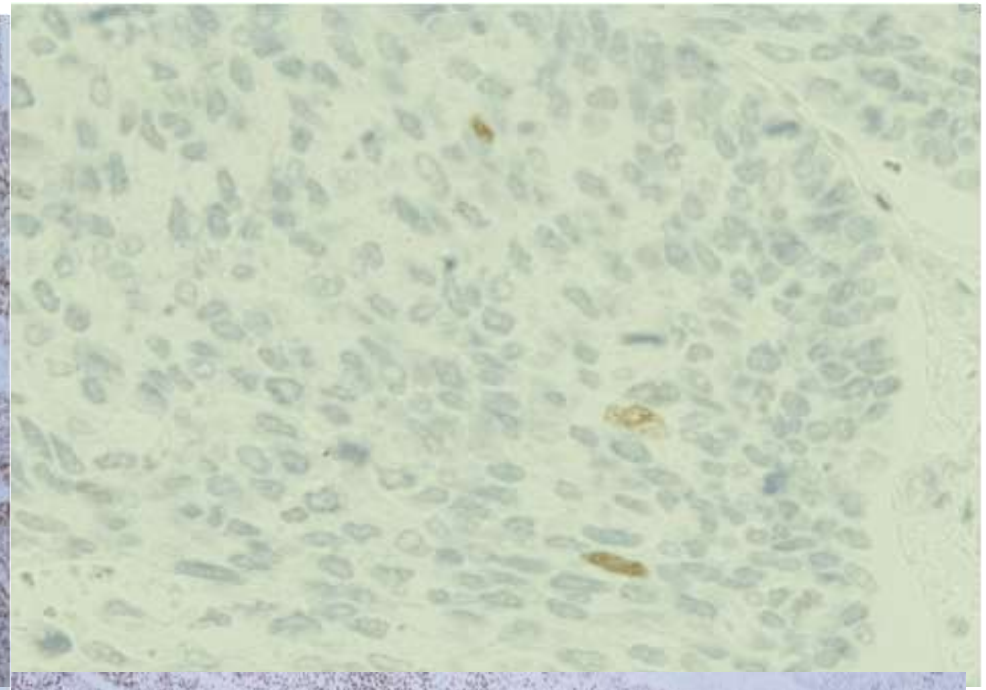
Importance of block selection/grossing – take sections from cystic areas

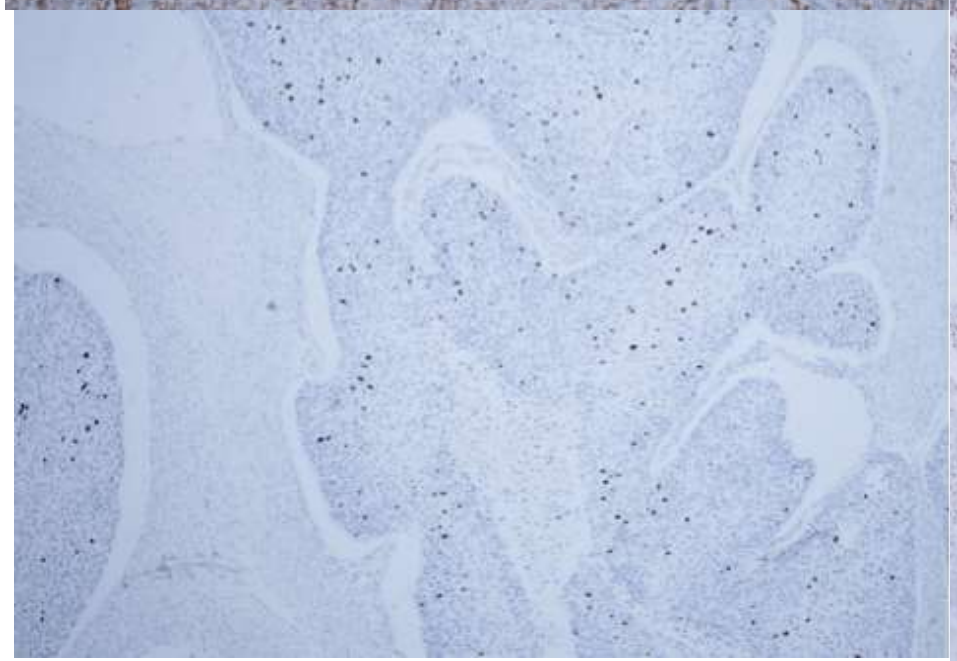
p53

- Interpretation is challenging
- Diffusely positive or completely negative – both staining patterns represent aberrant phenotypes
- Do not report as positive or negative but

  - overexpression-mutation type
  - null staining (mutation type)
  - patchy staining/focal staining -wild type

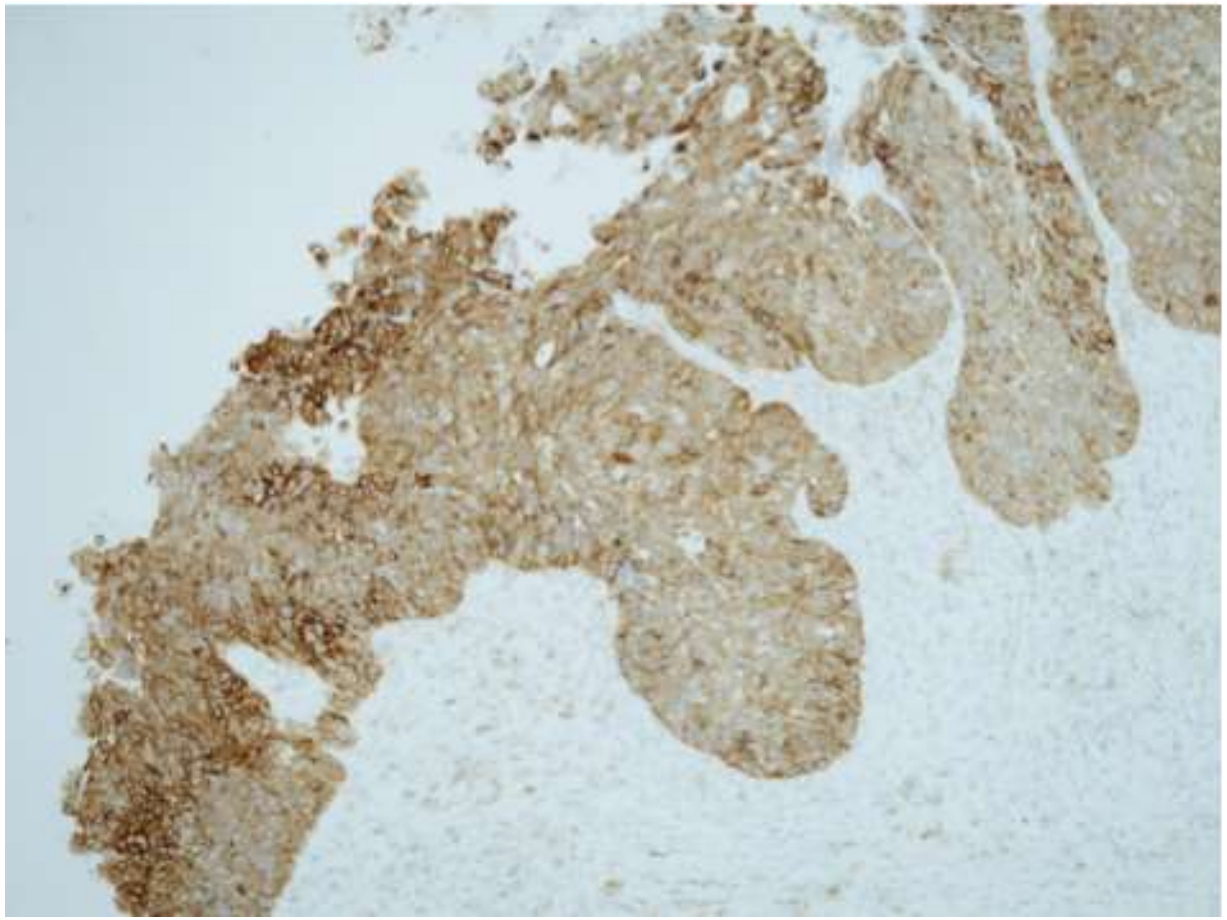






P16

- Diffuse block positivity in 60%
- Cytoplasmic and nuclear
- Lack of block staining – of little value
- Metastatic ca of cervical origin to be excluded



Reporting…….

WT1

- Most are positive
- Not entirely specific
- Also positive in mesothelial cells
- WT1 negative HGSC – raise the possibility of uterine origin

HGSC vs LGSC

- Usually not a problem
- In small biopsies – may be difficult
- Also some LGSC show diffuse nuclear atypia and vice versa some HGSC may not show diffuse atypia and may show prominent papillary architecture
- P53 – single most important marker, p16 also useful

D/D of HGSC

- HGSC and EC –
- WT1, p53, p16, MMR
- HGSC and CCC-
- p53, p16, WT1,ER
- HGSC and undifferentiated ca-
- p53 and p16
- HGSC and LGSC –
- p53, MIB1, p16

Importance of typing

- HGSC chemosensitive (CCC, LGSC and mucinous are not)
- Personalised medicine
- Genetic counselling

    HGSC – bRCA1, BRCA2

    Endometrioid ca and clear cell ca – Lynch syndrome

Ovarian carcinoma grading

- Serous –low grade and high grade (2 different types)
- Endometrioid –like uterine endometrioid
- Clear cell- high grade (by convention)
- Mucinous- like endometrioid
- Seromucinous- as for endometrioid

post treatment histology

- 90% HGSC present at stage III/IV
- First line platinum based chemo (NACT) followed by debulking surgery – completion of chemo (standard treatment)
- Response – ca125, imaging (RECIST-response evolution criteria in Solid tumours)

Histological response; Chemotherapy Response Score

- CRS 1: No or minimal tumour response (mainly viable tumour with no or minimal regression-associated fibro-inflammatory changes, limited to a few foci)
- CRS 2: Appreciable tumour response with residual tumour, both readily identified
- CRS 3: Complete or near-complete response (mainly regression associated fibro-inflammatory changes with minimal (or nodules up to 2mm OR no residual tumour identified)

- Good histological response +increased PFS and OS
- CRS 3 identifies patients with low probability of platinum resistant disease
- Ca125 does not predict CRS
- Omental sections are scored
- Simple and reproducible

BRCA

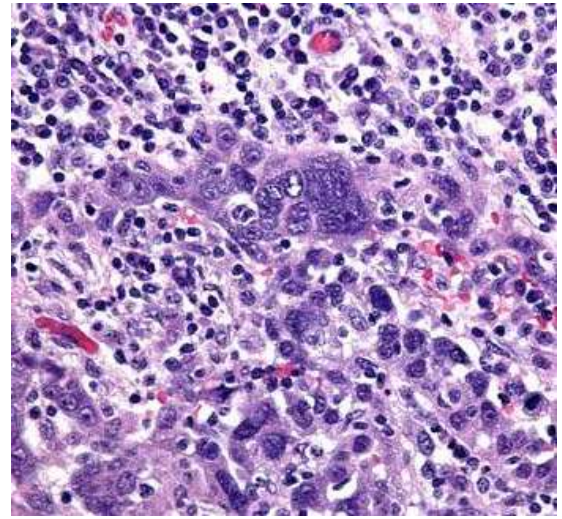
Breast cancer risk increases from 12 to 75%

Ovarian cancer from 1.4% to 25-40%

Increased risk of breast and ovarian malignancy for family members

HGSC and BRCA

- 22 to 25% of HGSC with BRCA
- Morphology –SET pattern
- TIL
- Non infiltrative pattern of omental disease
- Platinum and PARP inhibitor sensitive



Take home…

- HGSC and LGSC –completely different diseases
- D/D from other HG carcinoma important due to management, follow up and familial implications
- SEE-FIM protocol is important to look for small STIC lesions
- Site of origin for HGSC is now a requirement
- P53, WT1, p16 most important IHC markers in D/D
- P53 and p16 – standardization of interpretation