Borderline tumours of the ovary, carcinomas & fallopian tube pathology.

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Outline

• WHO classification of borderline tumours
• Molecular pathology
• Morphology
• Implants
• Frozen section
• Low grade serous carcinoma
• Cut up
• High grade serous ca & Fallopian tube pathology
WHO Classification of borderline tumours

- Serous borderline tumour/Atypical proliferative serous tumour
- Serous borderline tumour – micropapillary variant/Non invasive low grade serous ca
- Mucinous borderline tumour/Atypical proliferative mucinous tumour
- Clear cell, Brenner, Seromucinous borderline tumours/Atypical proliferative tumours
Stage

- FIGO Staging
- MDT discussion
CUT UP (ovary, fallopian tube and omentum)

- Ovary – weigh and measure (and photograph)
- Identify components of specimen (if in doubt check with Clinician/ask another pathologist)
- Ink/not ink (appropriate use of ink)
- Assess capsule – intact or not (important for staging)
- Adequate fixation – slice at 1cm intervals
- Describe – solid, cystic papillary areas and measure
- Adequate clinical info – past history, histo/cyto, markers, intraop findings, neoadjuvant treatment etc
Cut up

- Photograph cut surface
- 1 block/cm of maximum tumour dimension (provided not simple cyst etc) – see mucinous tumour recommendations later.
- Block description (what have you sampled)
- Include capsule in block sampling
- Ovaries and fallopian tubes for BRCA, Lynch etc – process all tissue (SEE FIM protocol)
- Lymph nodes – process all tissue if not obviously involved
Cut Up

• Peritoneal biopsies – describe and process separately
• Omentum – describe and measure any deposits, adequate sampling “swiss roll” – if obvious tumour 2/3 blocks. If no tumour 4-6 blocks/”swiss rolls”
• Appendix usually submitted for mucinous tumours – describe, measure, ink margins, process all tissue especially if pseudomyxoma.
Cut up and Reporting

- Minimum dataset – see Rcpath website
- Best to describe individual specimens with summary at the bottom
- Always consider you may refer case so cut up, block taking and findings should be easy for specialist review to understand.
Borderline Tumours/APT criteria

- Epithelial proliferation greater than seen in benign tumours of the same cell type
- Destructive or obvious stromal invasion is not present
- Histology: cellular stratification, detached cell clusters, nuclear atypia (not marked), mitotic activity
- **NO** destructive stromal invasion
- <10% proliferation – cystadenoma/adenofibroma with focal proliferation
Borderline tumours (BT)/Atypical proliferative tumours (APT)

- Synonyms: - Tumour of borderline malignancy, Borderline tumour, Tumour of low malignant potential (not recommended), Atypical proliferative tumour. Preferred terminology– (BT/APT)
Behaviour of Borderline Tumours

• True borderline – neither clinically benign nor overtly malignant
• Morphology – architectural complexity without malignant cytology/invasion. Not morphologically malignant nor benign
• Implants
Prognosis

• Stage
• Debulking surgery success
• Implant type (important in predicting clinical outcome)
• Morphology (controversial) – micropapillary architecture, microinvasion.
SBT (image R. Soslow presentation)
SBT/APST

• Macro
Histology of Serous Borderline tumours

- Macro – typically cystic tumours >5cm, surface component, bilateral in 1/3 of patients, papillary tumour lining
- Micro – papillary proliferation with hierarchical branching (large to progressively small terminating in epithelial tufts), cuboidal to columnar cells with cilia, clear cells can be seen, hobnail cells with eosinophilic cytoplasm
- Molecular – KRAS, BRAF mutations, few chromosomal abnormalities. Similar to low grade serous ca (high grade serous ca -TP53 and chromosomal abnormalities)
Serous BT
SBT
SBT
SBT
Microinvasion in SBT/APST

- One or more foci <5mm in any dimension/<10 square mm
- Pink cells in spaces
- No stromal/minimal stromal response
- Micropapillary/crribiform nests
- Outcome usually similar to SBT/APST however:
  - Some reports of adverse outcome, and
  - Destructive stromal invasion <5mm is a “microinvasive carcinoma”
Microinvasion
Micropapillary architecture in Implants/BST.

- Increased recurrence
- Associated with invasive implants (low grade serous ca)
Micropapillary morphology
Frozen section

• If micropapillary pattern present, avoid unequivocal diagnosis of borderline tumour on frozen section.
SBT micropapillary variant/Non invasive low grade serous ca

- Non invasive tumour with non-hierarchichal branching architecture featuring micropapillary and/or cribriform patterns
- Micropapillae 5x taller than wide
- No stromal cores in micropapillae
- Micropapillae emanate directly from large often fibrotic papillae
- Cells cuboidal to polygonal with high N/C ratio, more atypia compared with usual SBT
BST micropapillary variant

- Mitotic index low but higher than SBT/APST
- Can be purely cribriform/mixed micropapillary & cribriform
- Can co-exist with usual SBT
- Diagnosis of non invasive low grade serous ca requires at least one confluent area of micropapillarity measuring 5mm in one dimension and increased nuclear atypia.
- Tumours with less = SBT/APST with focal micropapillary features
Implants

- Borderline tumour with peritoneal disease = implant
- Low grade serous carcinoma with peritoneal disease = metastatic carcinoma not implants
- Implant types – invasive, non-invasive and indeterminate
- Implants described in serous tumours and seromucinous tumours.
- Implants predict patient outcome in patients with high stage ovarian SBT
Implant types

• Invasive – fat or muscle invasion
• Non-invasive – tumour stroma prominent, desmoplastic, no invasion of fat or muscle
• Indeterminate/indefinite for invasion (probably invasive)
• Autoimplant.
• NB: diffuse high grade cytology = carcinoma
Implant assessment

- No fat or muscle invasion = implant
- Fat or muscle invasion = invasive implant (i.e. low grade serous carcinoma)
- Marked cytologic atypia present = carcinoma
- Micropapillary architecture present = ?invasive carcinoma/non invasive low grade serous carcinoma
- Implant biopsy without underlying stroma = probably non invasive.
Implant assessment

- Invasive implant - ideally 2 pathologists required, of which one should be an experienced Specialist Gynaecology pathologist
- Consider obtaining a second opinion
Lymph node involvement

- Approx 30% of Stage III SBT show lymph node involvement.
- Lymph node involvement is not usually of any prognostic significance.
- Watch out for mimicks of lymph node involvement – mesothelial hyperplasia, mullerian inclusions, endosalpingiosis etc.
Proposed new terminology for implants

• Ovarian borderline tumour + peritoneal disease = implants (Complete Minimum dataset with provisional FIGO stage for histology report)
• Ovarian borderline tumour + invasive peritoneal disease = metastatic low grade serous carcinoma with associated serous borderline tumour.
Why change to terminology for invasive implants?

- Non invasive implant survival (10yr) approx 95%
- Invasive implant survival (10-20yr) – 33-50%
- Stage III low grade serous carcinoma survival (10-20yr) – 25-50%
- Patient outcome for “invasive implants” similar to low grade serous carcinoma = same disease.
Non invasive implant
Non invasive implant
Non invasive implant?
Non invasive implant
Non invasive implant
Non invasive implant/indeterminate?
Non invasive implant
Non invasive implant
Non invasive desmoplastic implant
Implant? – no, this is a deposit of mucinous adenocarcinoma
Mucinous adenocarcinoma deposit
Invasive implant morphology

- **Low power** destructive tissue invasion associated with varying degrees of stromal response.
- Destructive tissue invasion = unequivocal irregular, haphazard infiltration into normal tissue structures.
- Cells resemble cytology of low grade serous ca
- Infiltrating tumour shows: glands with bridging/papillary proliferation/small solid epithelial nests, single pink cells, gaping glandular structures.
Invasive implant. Low power assessment.
Invasive implant
Invasive/indeterminate implant?
CT guided core biopsies and small laparoscopic biopsies

- Exercise caution when reporting serous tumours in small biopsies.
- Use immunohistochemistry to guide low grade or high grade.
- MDT discussion
- Obtain specialist opinion
Therapy

- Surgical
- Hormones
- Chemotherapy
- Target therapy e.g. MEK inhibitors for invasive implants/low grade serous carcinoma.
Summary

- SBT/APST – hierarchical branching papillae
- Implants predict outcome
- Invasive implants – imply low grade serous ca, 2 pathologists to confirm otherwise send to Specialist
- Indefinite for invasion – get another opinion
- Microinvasion/Lymph node involvement – no change to prognosis
- Micropapillary morphology – think non-invasive low grade serous ca (seek opinion if not sure)
- Refer to RCPath data set for cut up & reporting
- If in doubt find a GYN Pathologist for opinion.
Seromucinous borderline tumour (SMBT)

• Proliferative epithelial tumour with more than one Mullerian epithelial type – serous and endocervical common. Others – endometrioid, clear cell, transitional, squamous.

• Synonyms – Endocervical type mucinous BT, Mullerian mucinous tumours (endocervical type, Atypical proliferative (borderline) Mullerian tumour.
SMBT
SMBT
SMBT
SMBT
SMBT
Seromucinous BT

• 15% of all mucinous BT
• Present as FIGO stage 1 but minority higher stage
• Implants and/or lymph node involvement
• 34-44yrs
• Associated with endometriosis in up to 1/3 of cases
• Present with non specific symptoms – adnexal mass
Pathology of Seromucinous BT

- Unilocular smooth surfaced cystic mass 8-10cm
- Papillary excrescences on cyst lining
- Haemorrhagic foci (endometriosis)
- Up to 40% bilateral
- Solid areas occasionally seen.
Histology of Seromucinous BT

- Papillary architecture similar to BST
- Larger papillae, oedematous stroma with neutrophils
- Serous & endocervical cell types/others. Low grade
- No goblet cells
- Cytoplasmic eosinophilia prominent
- Endometriotic cyst may be present
Seromucinous BT

- CK7+, CDX2 and CK20 –
- ER and PR +, WT-1 usually negative (or focal)
- ARID1A mutations
- Seromucinous BT are associated with good outcome even in the presence of peritoneal implants
- Seromucinous ca – uncommon.
Mucinous Borderline tumour (MBT)/Atypical proliferative mucinous tumour

- Proliferative tumours with mild to moderate atypia in gastrointestinal mucin containing epithelium
- No stromal invasion
- Second most common BT
- Age range 13-88yrs, mean 40-49yrs
- Usually unilateral ovarian mass confined to ovary
- No implants, acellular mucin on peritoneal surface sometimes present
Mucinous BT

- Size – several cm to 50cm, mean 21.5cm
- Nearly always unilateral. If bilateral or high stage consider metastases
- Messy cut up but due to heterogenous nature and occult foci of carcinoma, adequate sampling crucial.
- 1 section per cm of greatest tumour dimension in tumours up to 10cm
- >10cm tumour/microinvasion/intraepithelial ca – 2 sections per cm as a minimum.
- Solid areas may be seen
Mucinous BT

- Multiple cysts lined by GI type epithelium including gastric pyloric type epithelium, goblet cells, neuroendocrine cells and occasional paneth cells
- >10% proliferation to qualify as BT
- Varying degrees of epithelial proliferation – tufting, stratification, villous papillae
- Gland rupture with granulomatous inflammation common
- Pseudomyxoma ovarii in 20% of tumours (acellular mucin in stroma)
Mucinous BT

- Intraepithelial ca – marked nuclear atypia confined to epithelium
- Microinvasion – small foci of stromal invasion, mild to moderate atypia, <5mm, can be multiple. If marked cytological atypia in foci of stromal invasion = “microinvasive carcinoma”
- Mural nodules – can be associated with MBT/carcinomas – reactive sarcoma like nodules, anaplastic carcinoma and sarcomatous
MBT
MBT
MBT with IEC
Mucinous BT

- Immunohistochemistry – CK 7 diffuse positive, CK20 variable but less than CK7, CDX2 variable, PAX8 in 50-60% of tumours. ER&PR negative.
- KRAS mutations in 30-75%
- Prognosis good in true BT even with microinvasion with tumour related death<5%
Low grade Serous carcinoma

• Invasive carcinoma
• Majority arise from SBT (“adenoma - carcinoma sequence”)
• Variety of architectural patterns – single cells, small nests, solid, glandular, “mucinous appearance”, macropapillae and micropapillae with haphazard infiltration of stroma
• Less common compared with high grade serous carcinoma
  (20:1 high grade serous ca to low grade ratio)
Low grade Serous carcinoma

• 50-60% cases show KRAS and BRAF mutations
• Closely related to SBT on methylation profiling
• Immuno: WT-1, ER positive. P53 “wild type”. Add mesothelial marker e.g. calretinin to panel to exclude mesothelial neoplasia in small omental/peritoneal biopsies.
• Psamomma bodies frequent, mild to moderate nuclear atypia, no necrosis or multinucleation, mitoses <12/10hpf in worst areas (usually <6/10hpf)
Low grade serous ca arising in BST
Invasive low grade serous ca in BST
Primary mucinous carcinoma

ovary

• 3-4% of all primary ovarian ca.
• Mean age 45yrs.
• Abdominal mass, usually disease confined to ovary. **High stage primary ovarian mucinous carcinoma rare.**
• Advanced stage mucinous carcinoma involving ovaries – usually metastatic disease. MDT review crucial
Histology of primary mucinous ca ovary

- Mixture of benign, borderline and frankly malignant areas
- 2 patterns of invasion- confluent glandular growth pattern/expansile and destructive stromal invasion
- If destructive infiltrative invasion especially if bilateral or >stage 1, consider metastatic carcinoma from extra-ovarian site
- Mural nodules present.
Mucinous ca, papillary expansile
Mucinous ca
Pseudomyxoma Peritonei

- Appendix primary
- Can arise from ovary in the rare setting of a primary ovarian low grade mucinous tumour/neoplasm in association with a teratoma.
High grade Serous carcinoma v Low grade serous carcinoma

• High grade serous ca (HGSC) can mimic low grade serous carcinoma but treatment can be different
• Careful assessment and appropriate use of p53 immunohistochemistry helpful
• The two represent 2 different disease not a continuum however:
• Reports of high grade serous ca arising in low grade serous ca in literature (e.g. AJSP 2012;36;368-375)
High grade serous ca

- >12 mitoses/10 hpf in worst areas
- High grade cytology with multinucleation and pleomorphism, necrosis, psamomma bodies
- However remember high grade serous ca mimick low grade carcinoma
- TP53 mutations – p53 immunohistochemistry useful
Histology of high grade serous carcinoma

- Mophology – papillary/micropapillary, slit-like, glandular, microglandular, microcystic, solid, signet ring cells, oncocytic, clear cells or mixture
- BRCA associated carcinomas – intraepithelial lymphocytes >40/hpf, solid, pseudoendometrioid and transitional morphology (“SET”)
- 30-50% of high grade serous ca harbours BRCA mutations (germline/somatic)
- BRCA associated carcinoma more chemosensitive and respond to PARP inhibitors.
- Different type of metastases in BRCA associated carcinoma
HGSC Fallopian tube
HGSC
HGSC – p53 mutation type
HGSC – WT-1
HGSC – p16
HGSC – CT core biopsy
HGSC
Immunohistochemistry for serous carcinomas

• WT-1, p53, p16, ER, PAX8, PR
• P53 report as “wild” type or mutation type
• Mutation type staining for p53 – null (no staining) or diffuse staining >75-80% nuclear staining.
• TP53 missense mutation - diffuse mutation type staining
• TP53 nonsense mutation with truncated protein – no staining (confirm stain has worked first!!)
Hereditary susceptibility to ovarian ca

• 10% of all primary ovarian ca hereditary
• Of these:
  • BRCA1 70-75%
  • BRCA2 20%
  • DNA MMR 2%
  • Other <5%
STIC – serous tubal intraepithelial carcinoma
Fallopian Tube & STIC

- Bilateral risk reducing surgery (BSO) with SEE FIM protocol (sectioning and extensively examining the fimbriated end of fallopian tube) has identified early stage high grade serous carcinoma
- New model of thinking is that pelvic serous carcinoma arises from fallopian tube in a significant proportion of ovarian and primary peritoneal carcinomas
STIC

• 50-60% of sporadic ovarian high grade serous carcinoma show STIC
• 5-10% of prophylactic BSO show STIC
• Some high grade ovarian ca not associated with STIC
• STIC show mutation type p53 staining similar to high grade serous ca
Diagnosis of STIC

- Morphology – nuclear enlargement, pleomorphism, abnormal chromatin, apoptosis, mitosis, epithelial stratification.
- Low power view
- Immunohistochemistry to aid diagnosis – p53 and Ki-67 (Ki-67 >10%, usually higher)
- Do not use p53 alone – p53 signature
- Do not report any lesion not a STIC
Fallopian tube cut up (SEE FIM protocol)

Transverse sections of the isthmus and ampulla at 2-3mm

Longitudinal sections of the infundibulum and fimbrial segment (distal 20mm)
SEE FIM protocol

Transverse sections of the isthmus and ampulla

Longitudinal sections of the infundibulum and fimbrial segment
STIC v STIL/Normal

- STIC – p53 mutation type staining, Ki-67 >10%
- STIL – p53 +, Ki67 low
- STIL – p53 negative, Ki-67 high
- Normal/reactive – p53 negative, Ki-67 low
Papillary proliferation fallopian tube
P53
Metastatic carcinoma to ovary

- Remember metastases can mimic primary ovarian ca or borderline tumours
- Be alert at all times
- Careful use of immunohistochemistry panels, avoid using single stains
Always think metastasis
Thank you

• Questions/Comments