What’s (new) and Important in Reporting of Uterine Cancers

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I have no conflicts of interest to declare

Endometrioid adenocarcinoma

- Grade 1-2 is the archetypal low grade uterine carcinoma
- Arises from atypical hyperplasia (complex atypical hyperplasia/EIN)
- Risk factors – oestrogen++, insulin resistance, LS
- Wide variation in morphology

- High grade carcinomas (common)
- Clear cell
- Immunohistochemistry
- Rarer tumours
- Diagnostic difficulties
- Staging – problems
- Other important considerations when reporting uterine carcinomas

Endometrioid adenocarcinoma

- Grade 1-2 is the archetypal low grade uterine carcinoma
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Differentiating hyperplasia from G1 endometrioid adenocarcinoma

In the absence of myometrial invasion (biopsy, endometrium-confined 1A cancers), diagnosis of adenocarcinoma is based on architecture.

Interobserver variation has been shown to be low in diagnosis of G1 endometrioid adenocarcinoma by expert gynae pathologists (kappa value = 0.83) – Kendall et al, AJSP 1998

Most useful criteria:
- Glandular confluence
- Stromal alterations
- Assessment of atypia in hyperplasia was the most difficult area

Differentiating atypical hyperplasia from G1 endometrioid adenocarcinoma
Endometrioid adenocarcinoma variants (WHO 2014)

- Squamous differentiation
- Secretory variant
- Villoglandular variant
- Ciliated cell variant
- Mucinous carcinoma

＞50% DPAS+ intracytoplasmic mucin

Higher rate of pelvic nodal metastases but no difference in overall survival (Rauh-Hain et al, Am J Clin Onc. 2016)
MELF (Microcystic, elongated and fragmented)

- Particular pattern of invasion in endometrioid adenocarcinomas (generally low grade)
- Typical morphology
- Associated with lymphovascular space invasion
- Can be difficult to delineate (single/small groups of cells overlooked)
Grading endometrioid adenocarcinoma

**FIGO GRADING SYSTEM**

- Grade 1 = <5% solid
- Grade 2 = 5-50% solid
- Grade 3 = >50% solid

Caveat 1: Don’t include morular/squamous differentiation
Caveat 2: Marked nuclear atypia upgrades by one
Immunohistochemistry of endometrioid adenocarcinoma

Mismatch repair immunohistochemistry – more later
Uterine serous carcinoma

- Precursor lesion is endometrial intraepithelial carcinoma
- May be associated with BRCA mutation (de Jonge et al, EJC 2017)
- Generally seen in atrophic background
- (Usually) the epithelial component of carcinosarcoma

Morphology

EIC
**Immunohistochemistry – p53**

**Carcinosarcoma**

- A biphasic tumour in which the epithelial component has undergone epithelial to mesenchymal transition (usually)
- The sarcomatous component can be homologous or heterologous
  - Rhabdomyosarcoma
  - Chondrosarcoma
  - Liposarcoma
- May be useful to comment on the proportion of adenocarcinoma:sarcoma
- Comment on the composition of any metastatic deposits – usually epithelial unless there is extensive rhabdomyosarcomatous differentiation

**Immunohistochemistry cont**
Clear cell carcinoma

- Rare (1-5% of all uterine carcinomas)
- May be associated with Lynch syndrome
- Aggressive

**Immunohistochemistry**

- p53 wild-type
- WT1 negative
- ER negative
- Patchy or block p16
- Napsin often positive (less reliable than in the ovary)

Other rare types

- Indifferentiated/dedifferentiated carcinoma
- Mesonephric carcinoma
- Squamous cell carcinoma
- Neuroendocrine carcinoma
- Peripheral neuroectodermal tumour
- Choriocarcinoma

Mixed carcinomas

- E.g. mixed serous and endometrioid
- There should be at least 10% of the second component (WHO 2014)
- Report all histological subtypes in main body of report, especially if there is a minor high grade component
- Consider underlying genetic abnormality such as MMR deficiency in cases which are difficult to classify
Diagnostic difficulties (subtyping)

Immunohistochemistry can help with:
- Differentiating endometrioid from serous subtypes (usually)
- Differentiating serous from clear cell
- Identifying rhabdomyosarcoma in carcinosarcoma

Immunohistochemistry is not useful for:
- Differentiating atypical hyperplasia from Grade 1 endometrioid carcinoma
- Grading endometrioid carcinoma

IA/IB problems

- Smooth muscle metaplasia within the exophytic part of the tumour can mimic myometrium
- Myometrium may be thinned due to compression by slow-growing tumour
- Tumour in the cornua
- Adenomyosis

Problems with staging/reporting

What problems? It’s so simple!

- Where does the inner half end?
- How do you assess cervical stromal invasion?
- Does cervical glandular involvement matter?
- Does this tumour in the ovary represent metastatic carcinoma or a synchronous primary?
- When is LVSI not LVSI?

Tips

- Tumour by the arcuate vascular plexus indicates outer half
- Try to find tumour adjacent to uninvolved endometrium for accuracy
- Rounded edges may suggest adenomyosis
Cervical stromal invasion

- Longitudinal sections of cervix/LUS are most helpful for accurate detection
- Glandular involvement – does not upstage but may direct adjuvant treatment (depends on centre)

Lymphovascular space invasion

Pseudovascular space invasion

- Robotic and laparoscopic surgery – uterine manipulation
Metastasis versus Synchronous primaries – endometrioid adenocarcinoma

Scully criteria (in the absence of routine genomic sequencing (!) include: histological dissimilarity, no LVSI, superficial myometrial invasion, evidence of precursor lesions (atypical hyperplasia/ovarian endometriosis)

A: Evaluated 10-organ-confined synchronous ovarian/endometrial low-grade endometrioid adenocarcinomas
B: 17/18 demonstrated a clonal relationship

Kommoss et al, AJSP 2017:
- Uterine serous carcinomas can metastasise to tubal epithelium and mimic STIC
- Useful IHC to differentiate includes p53 if divergent patterns (early driving mutation), WT1, ER

Caveat: the reverse can occur (ovarian/tubal primary with secondary uterine involvement)
Other considerations

Tumor Size, an Additional Risk Factor of Local Recurrence in Low-Risk Endometrial Cancer
A Large Multicentric Retrospective Study

Tumor size >25mm was a risk factor for local recurrence.

Other considerations

Sentinel lymph node sampling

- How to assess?
- How to report?
- Significance of ITCs?

Mismatch repair immunohistochemistry

- Who to target?
- Biopsies or resections?
- How to interpret?
- Which patterns are most significant?
Mismatch repair continued...

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Loss of expression</th>
<th>Significance</th>
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<tbody>
<tr>
<td>MLH1</td>
<td>MLH1, PMS2</td>
<td>Sporadic (approximately 50%, promoter methylation), remainder LS.</td>
</tr>
<tr>
<td>PMS2</td>
<td>PMS2</td>
<td>Usually LS.</td>
</tr>
<tr>
<td>MSH2</td>
<td>MSH2, MSH6</td>
<td>Usually LS.</td>
</tr>
<tr>
<td>MSH6</td>
<td>MSH6</td>
<td>Rarest, usually LS.</td>
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Take home messages

- Criteria can be applied to make differentiation between atypical hyperplasia and G1 endometrioid adenocarcinoma more robust and reproducible.
- Staging can be difficult and is crucial for determining adjuvant treatment.
- Consider your policy for mismatch repair testing.

Thank you!

Questions?

Helpful reference: