Controversies in the Pathology of the Endometrium

Professor Mike Wells
University of Sheffield
Amman, Jordan
November 2013
ENDOMETRIAL CANCER

• increasing in incidence:
  – epidemic of obesity
  – increasing elderly population
• most managed by hysterectomy and BSO
• crucially dependent on the histopathology report
• role of lymphadenectomy remains very controversial
Endometrial adenocarcinoma

Low grade endometrioid

High grade serous
Endometrioid carcinoma
Genetic alterations

PIK3CA 30%
Microsatellite instability 20-30%
K-ras 10-30%
PTEN 30-60%
FGFR2 10-20%
Beta-catenin 28-35%
Non-endometrioid carcinoma

Genetic alterations

- C-erbB2: 26%
- Cyclins: 26-42%
- E-cadherin: 90%
- p16: 40%
- p53: 90%

Courtesy of Xavier Matias Guiu
Sources of high circulating oestrogen

- **Endogenous** –
  - obesity
  - polycystic ovary syndrome
  - oestrogen secreting ovarian tumour
    (granulosa cell tumour)
- **Exogenous** –
  - oestrogen replacement therapy
Intraendometrial adenocarcinoma in polycystic ovary syndrome
PTEN

• tumour suppressor gene – 10q23.3
• inactivated (LOH/mutation) in up to 83% of endometrial adenocarcinomas – early event
• PTEN null glands seen in normal proliferative endometrium by immunohistochemistry
Endometrial intraepithelial neoplasia

*PTEN* mutations  55%

*PTEN* null  63%
COWDEN’S SYNDROME

- rare autosomal dominant
- **germline mutations of** *PTEN*
- multiple hamartomas
- increased risk of breast and thyroid cancer
- increased risk of endometriat hyperplasia and carcinoma
Monte et al Joint loss of PAX2 and PTEN expression in endometrial precancers and cancer Cancer Res 2010

- PAX2 is required for embryonic uterine development
- loss of PAX2 with neoplastic progression is similar to PTEN
- loss in normal endometrium increases with age
- coincident loss of PTEN and PAX2 in only 21% of normal endometrium
- coincident loss increases with neoplastic progression: precancer 31%; carcinoma 55%
Volume Percentage Stroma (VPS): light circles are outer perimeter of gland epithelium.
ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA

• volume percentage stroma < 55%
• cytological changes
• >1mm diameter
• exclude cancer, polyps, secretory endometrium, artefact etc
Papillary syncytial metaplasia
Papillary syncytial metaplasia superimposed on endometrial intraepithelial neoplasia
Reproducibility of classification of endometrial endometrioid glandular proliferations

Ordi et al, *Histopathology* 2013

- 9 gynaecological pathologists
- 3 classifications:
  - WHO, EIN & European Working Group
- poor interobserver agreement (28-59%)
- reproducibility improved with a two tier classification of benign vs atypical/carcinoma (69-72%)
Exceptions to hysterectomy in EIN

• in young women with polycystic ovary syndrome
• in women who wish to preserve reproductive function
• poor operative risk – obesity and/or multiple medical problems
Grading of *endometrioid* endometrial adenocarcinoma  
FIGO

- Grade 1 - \( \leq 5\% \) solid growth
- Grade 2 – 6-50\% solid growth
- Grade 3 - > 50\% solid growth

the overall grade of architecturally G1 or G2 tumours is increased by 1 if there is notable nuclear atypia

Zaino (1995) – modify the architectural grade only in the presence of severe nuclear atypia
Grading of endometrioid endometrial adenocarcinoma

• aim - to identify a low risk group who do not benefit from lymphadenectomy or adjuvant therapy
• FIGO grading is arbitrary and lacks rigour
• binarised FIGO grading is most reproducible:
  
  G1 & 2 = low grade
  G3 = high grade
LOW GRADE CYTOLOGICAL ATYPIA
HIGH GRADE CYTOLOGICAL ATYPIA
ENDOMETRIOID ADENOCARCINOMA WITH SMALL NON-VILLOUS PAPILLAE

- intraglandular or surface small papillae
- papillae consist of buds of cells with abundant cytoplasm
- other features of endometrioid adenocarcinoma
- may be areas of more usual endometrioid carcinoma
- usually low cytological grade
- no difference in behaviour from typical endometrioid adenocarcinoma
- may mimic serous carcinoma
- may be misdiagnosed as hyperplasia (often no glandular confluence)
Epithelial-mesenchymal transition

- MELF (MICROCYSTIC ELONGATED FRAGMENTED)
  - common pattern of myometrial invasion in endometrioid adenocarcinomas
  - usually associated with fibromyxoid stromal reaction
  - out-pouchings from typical invasive glands
  - flattened epithelium, microcysts
  - elongation and fragmentation of glands
  - may get single invasive cells (CKs may be useful)
Endometrial adenocarcinoma

Low grade endometrioid
High grade serous
Endometrial intraepithelial carcinoma
“Minimal uterine serous carcinoma”

- serous carcinoma limited to endometrium (superficial serous carcinoma) and without stromal invasion (endometrial intraepithelial carcinoma)
- associated with extrauterine tumours in 45% of cases – recent evidence suggest that this is metastatic disease (Hui et al Mod Pathol 2005; 18: 75-82)
- ovarian serous carcinoma – WT-1 diffuse strong nuclear positivity
- uterine serous carcinoma - WT-1 negative
Mixed endometrioid and serous adenocarcinomas occur more frequently than suggested by the literature - ?
related to
de-differentiation of endometrioid tumours – p53 immunohistochemistry has practical application
**Immunohistochemical profile of endometroid vs serous endometrial adenocarcinoma**

<table>
<thead>
<tr>
<th>ENDOMETRIOID</th>
<th>SEROUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 –</td>
<td>p53 +</td>
</tr>
<tr>
<td>ER +</td>
<td>ER -</td>
</tr>
<tr>
<td>PTEN –</td>
<td>PTEN +</td>
</tr>
<tr>
<td>p16 -</td>
<td>p16 +</td>
</tr>
</tbody>
</table>
## Endocervical or endometrial adenocarcinoma?

<table>
<thead>
<tr>
<th></th>
<th>Endocervical adenocarcinoma</th>
<th>Endometrial adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimentin</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Oestrogen receptor</td>
<td>+ Focal</td>
<td>++</td>
</tr>
<tr>
<td>CEA</td>
<td>++</td>
<td>+ Focal</td>
</tr>
<tr>
<td>p16</td>
<td>++ 100%</td>
<td>+ &lt;50%</td>
</tr>
<tr>
<td>CD10</td>
<td>+ 33% limited luminal</td>
<td>77% cytoplasm, membrane or both</td>
</tr>
<tr>
<td>HPV</td>
<td>66%</td>
<td>-</td>
</tr>
</tbody>
</table>
Vascular invasion in endometrial cancer
Lymphatic vascular invasion

Vascular invasion in endometrial cancer
Vascular invasion in endometrial cancer
Recurrence free survival

Vascular invasion in endometrial cancer
Role of lymphadenectomy in endometrial cancer – deficiencies in published studies
(recent ASTEC & PORTEC II trials)

• done in patients with a low risk of lymphatic involvement
• short follow-up period
• selective not systematic lymphadenectomy
• too few nodes removed
• para-aortic lymphadenectomy not done
Role of lymphadenectomy in endometrial cancer

• Combined pelvic and para-aortic lymphadenectomy improves survival in patients at intermediate/high risk
• Only beneficial to those at highest risk of lymphatic metastases
• 27% of those at intermediate or high risk had positive nodes

(Todo et al Lancet 2010; 375: 1165-1172)
Role of radiotherapy in endometrial cancer

- Conventionally two main indications for adjuvant radiotherapy:
  - > 50% myometrial invasion
  - cervical involvement

- Increasing tendency to withhold radiotherapy until recurrence actually occurs (even for 2009 FIGO stages IB & II)