DIAGNOSTIC DILEMMAS IN REPORTING OF ENDOMETRIAL CARCINOMAS

W Glenn McCluggage
Belfast
TO DISCUSS

• issues in typing of endometrial cancers
• distinction between endometrial and cervical adenocarcinoma (PITFALLS IN IMMUNO PANEL)
• MELF pattern of myometrial invasion
• assessment of lymphovascular invasion
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%
• ICON 5- poor
RECENT STUDY ON REPRODUCIBILITY OF OVARIAN CARCINOMA TYPING

- excellent agreement
- participants had training in modern criteria
- important for subtype specific ovarian cancer treatments/ personal and family history risk
- good marker- WT1
- CONTRAST WITH UTERINE CARCINOMA
OVARIAN HIGH GRADE SEROUS CARCINOMA
WT1 in PSEUDOENDOMETRIOID AREAS IN HIGH GRADE SEROUS CARCINOMA
WT1 in CLEAR CELL AREAS IN HIGH GRADE SEROUS CARCINOMA
WT1 IN TRANSITIONAL-LIKE AREAS IN HIGH GRADE SEROUS CARCINOMA
UNDIFFERENTIATED OVARIAN CARCINOMA

WT1
PROBLEMS WITH TYPING OF ENDOMETRIAL ADENOCARCINOMA

- low grade endometrioid carcinoma versus serous carcinoma (immunohistochemistry of value)
- typing of “high grade” endometrial carcinomas (immunohistochemistry of limited value)
- clear cells in endometrial carcinomas (immunohistochemistry of limited value)
- surface changes on “low grade” endometrial carcinomas (immunohistochemistry of limited value)
- undifferentiated endometrial carcinoma (immunohistochemistry of some value)
ENDOMETRIOID ADENOCARCINOMA

• many have a papillary architecture
• usual type, villoglandular, with small non-villous papillae, surface changes
PAPILLARY VARIANTS OF ENDOMETRIOID CARCINOMA
ENDOMETRIOID ADENOCARCINOMA WITH SMALL NON-VILLOUS PAPILLAE

- intraglandular or surface small papillae
- papillae consist of buds of cells
- may be areas of more usual endometrioid carcinoma
- usually low cytologic grade
- no difference in behaviour from typical endometrioid adenocarcinoma
- may mimic serous carcinoma
- may be misdiagnosed as atypical hyperplasia since often no glandular confluence
Serous Carcinoma

- NOT PAPILLARY SEROUS CARCINOMA
- purely glandular variant exists
- solid variants
USC- RELATIVELY SUBTLE NUCLEAR ATYPIA
DIFFERENT PATTERNS IN USC
SEROUS- DIFFERENT PATTERNS
SOLID VARIANT OF SEROUS
IMMUNOHISTOCHEMISTRY- SEROUS VERSUS LOW GRADE ENDOMETRIOID

- use a panel
- interpret along with morphology
- immunohistochemistry quite useful (overlap in some cases)
IMMUNOHISTOCHEMISTRY

- p53
- ER
- p16
- HMGA2 (expressed more commonly in serous than endometrioid)
- PTEN (lost in many low grade endometrioid carcinomas; preserved in serous carcinomas)
- IMP3 (expressed more commonly in serous than endometrioid)
CLASSIC IMMUNOPHENOTYPE

- low grade endometrioid- ER diffuse +ve, p53 wild-type, p16-ve/patchy
- serous- ER-ve, p53 diffuse +ve, p16 diffuse +ve
CLASSIC UTERINE SEROUS CARCINOMA
Low Grade Endometrioid Versus Serous

p53

ER

p16
SUBTLE SEROUS CARCINOMA (in polyp)- may be misdiagnosed as atypical hyperplasia
SUBTLE SEROUS CARCINOMA (in polyp)
SUBTLE SEROUS CARCINOMA (in polyp)

p53

p16
SEROUS EIC (in polyp)
Problems

• grade 3 endometrioid carcinomas (some, but not all, exhibit a “serous” immunophenotype)
• mixed tumours (? not uncommon)
• overlapping immunophenotypes
• interpretation of immunohistochemistry (especially p53)
GRADE 3 ENDOMETRIOID CA

p53  
p16
MIXED TYPE 1 AND TYPE 2 (USUALLY ENDOMETRIOID AND SEROUS)

• WHO 10% rule (NOW CHANGED)
• type 2 may evolve from type 1 cancer via p53 mutation (dedifferentiation)
• prognosis (? dependent on % of type 2 cancer)
• report any amount of type 2 and categorise as mixed
• overlapping clinical, morphological, immunohistochemistry, molecular
• IMMUNOHISTOCHEMISTRY OFTEN NOT OF VALUE- p53 intermediate, ? true mixed tumours
MIXED SEROUS-ENDOMETRIOID

p53

p16
MIXED SEROUS-ENDOMETRIOID

p53
ER

- classically low grade endometrioid carcinoma diffusely positive and serous carcinoma negative
- reality - many/most serous carcinomas are ER positive (new antibodies/retrieval methods; different spectrum of serous carcinomas)
ER/PR IN UTERINE SEROUS CARCINOMA - PR BETTER DISCRIMINATOR THAN ER
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)
- most normal tissues and tumours exhibit focal, weak, heterogenous staining (“wild-type” staining)
- 2 types of aberrant p53 staining (predictive of mutation)
p53- “all or nothing staining of diagnostic importance”

mutation type

wild type
UTERINE SEROUS CARCINOMA

- Tp53 mutation is definitional
- don’t need immunohistochemistry in classical cases
- in problematic cases, if p53 is not aberrant- not serous carcinoma
- ? are we now overdiagnosing serous carcinoma or mixed carcinoma with serous component (contrast to prior where serous carcinomas were missed)
p16

• most uterine serous carcinomas diffusely positive (nothing to do with HPV)
• classically uterine endometrioid carcinomas said to be negative
• reality- many endometrioid carcinomas positive- can be focal or quite diffuse but still patchy (mosaic pattern)
p16 in endometrioid cancer mosaic
HMGA2

- Histopathology 2012;60;547-553.
- 91% serous carcinomas positive (usually diffuse); 37% endometrioid carcinomas positive (usually focal)
- HMGA2 more likely to be positive in serous than in grade 3 endometrioid
- useful as part of panel
- ovarian serous carcinoma also positive
HMGA2 in SEROUS CARCINOMA
HIGH GRADE ENDOMETRIAL CARCINOMAS

• not the same as type 1 and 2
• grade 3 endometrioid, serous, clear cell, carcinosarcoma, undifferentiated, mixed
• significant interobserver variability in classification (classification of endometrial carcinomas much more problematic than classification of ovarian carcinomas)
• immunohistochemistry of limited value (many are p53 aberrant, p16 diffuse)
• distinct molecular alterations between different types- ? useful in problematic cases (TCGA- 20-30% of endometrioid carcinomas have molecular profile of serous)
IS IT IMPORTANT TO DISTINGUISH BETWEEN DIFFERENT TYPES OF HIGH GRADE ENDOMETRIAL CARCINOMA?

• undifferentiated carcinoma and carcinosarcoma- poor prognosis
• grade 3 endometrioid versus serous- literature conflicting (may be because of different diagnostic criteria)
• serous may be worse prognosis only in early stage disease
• serous more likely to disseminate to abdomen; grade 3 endometrioid to nodes
• serous more likely to disseminate with only superficial myometrial invasion
• NEED ACCURATE CLASSIFICATION IF SUBTYPE SPECIFIC TRIALS/TARGETTED THERAPIES ARE TO WORK
INTEROBSERVER VARIABILITY

- AJSP- Gilks, Oliva, Soslow
- 56 cases diagnosed as “high grade” endometrial carcinoma
- 62% - agreement between all 3
- 36% - major disagreement (subtype or even whether high grade carcinoma was present)
- no consistent pattern between observers
- major problems- serous v clear cell; serous v grade 3 endometrioid (comparisons with ovary)
- need for molecular tools/ development of better markers
CLEAR CELLS IN ENDOMETRIAL CARCINOMAS- A REAL PROBLEM

• true clear cell carcinoma (or mixed tumour with clear cell component)
• clear cell change in serous adenocarcinoma
• secretory variant of endometrioid adenocarcinoma
• clear cell change in squamous elements of endometrioid adenocarcinoma
• non-specific clear cell change in endometrioid adenocarcinoma
• ? effects of progestogens
• clear cell areas in endometrioid carcinomas sometimes have a solid appearance and mimic clear cell carcinoma
• IMMUNOHISTOCHEMISTRY OF LIMITED VALUE (possible exception is clear cell areas in serous carcinoma)
UTERINE CLEAR CELL CARCINOMA

• very uncommon (beware before make diagnosis)
• possibly 2 types
• classic type
• type related to serous carcinoma (serous with clear cells- may be diagnosed as either but should probably call serous)
CLEAR CELL CARCINOMA
IMMUNOHISTOCHEMISTRY OF CLEAR CELL CARCINOMA

- variable (because of different criteria)
- often ER negative and p53 wild-type
- variant related to serous carcinoma is p53 aberrant
- hepatocyte nuclear factor 1 beta is proposed new marker (but recent observations suggest that not specific - “clear cells” may be positive)
CLEAR CELLS IN ENDOMETRIOID CARCINOMA
SECRETORY VARIANT OF ENDOMETRIOID CARCINOMA
SEROUS WITH CLEAR CELL FEATURES

p53

p16
CHANGES ON SURFACE OF UTERINE ADENOCARCINOMA

- low grade endometrioid or mucinous type
- especially likely to be sampled on biopsy
- micropapillary or microglandular architecture
- may look like papillary syncytial metaplasia
- may look like cervical microglandular hyperplasia (caution before diagnosing cervical MGH in endometrial biopsy in postmenopausal woman)
- may be mistaken for component of serous/clear cell carcinoma