Strategies for Typing High-grade Endometrial Carcinomas

C Blake Gilks

Disclosure of Relevant Financial Relationships

USCAP requires that all planners (Education Committee) in a position to influence or control the content of CME disclose any relevant financial relationship WITH COMMERCIAL INTERESTS which they or their spouse/partner have, or have had, within the past 12 months, which relates to the content of this educational activity and creates a conflict of interest. Dr. Blake Gilks declares he/she has no conflict(s) of interest to disclose.

Presentation Outline

• A brief history of classification of uterine cancer
• Is molecular/biomarker-based classification necessary?
• The Cancer Genome Atlas
• Molecular subgroups of endometrial cancer: translating genomics into practice through immunohistochemistry
• Future state?

Corpus vs. Cervix

Combination of distinctive clinical and pathological features = a meaningful category i.e. a distinct disease entity

Histological Typing of Female Genital Tract Tumours:
Corpus Uteri: Epithelial Tumours, Malignant (WHO 1975)

1 Adenocarcinoma
2 Clear cell (mesonephroid) adenocarcinoma
3 Squamous cell carcinoma
4 Adenosquamous carcinoma
5 Undifferentiated carcinoma

Type I vs. Type II EC (1983)
A common cancer, but... a great deal we do not know

Clinical Questions in Endometrial Cancer

- Which women are cured by surgery alone?
- How can we improve stratification of risk of recurrence or death from disease?
- We seem to use the same drugs and surveillance for all. Appropriate?
- Who are candidates for fertility-preserving surgery?
- Who stands to benefit from more extensive staging surgery?

Reproducibility of histotype diagnosis

- Study 1: 56 cases of high-grade endometrial ca reviewed by 3 pathologists: agreement about predominant cell type in 35/56 cases (62.5%)
- Study 2: 116 cases, three reviewers – kappa – 0.62

<table>
<thead>
<tr>
<th>Sign</th>
<th>I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memorial function</td>
<td>Medical history of involuntary uterine bleeding</td>
<td>No disturbances</td>
</tr>
<tr>
<td>Reproductive function</td>
<td>Decreased, frequent infertility</td>
<td>No disturbances</td>
</tr>
<tr>
<td>Onset of symptoms</td>
<td>Older after the age of 50</td>
<td>Older under the age of 50</td>
</tr>
<tr>
<td>Type of reproductive function</td>
<td>Endometrioid</td>
<td>Atypical</td>
</tr>
<tr>
<td>Ovarian status</td>
<td>Hyperplasia of theca internum</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Endometrial background or results of previous surgery</td>
<td>Hyperplasia, precursors</td>
<td>Atrophy</td>
</tr>
<tr>
<td>State of myometrium</td>
<td>Myoma, internal adenomyosis</td>
<td>No changes</td>
</tr>
<tr>
<td>Obesity</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Associated with obesity and/or diabetes mellitus</td>
<td>Absent or not associated with obesity and diabetes mellitus</td>
</tr>
</tbody>
</table>

case 28286

- path 1: 35% Gr1/2, 65% S
- path 2: 100% S vs CC
- path 3: 40% Gr1/2, 60%CC

MAJOR DISAGREEMENT

ER+, p53 abn, PTEN+, p16+
Conclusions

- Assessment of tumor cell type for endometrial carcinoma is inferior to ovarian carcinoma (kappa – 0.89, 94% concordance)
- Diagnostic improvements are needed if tumor cell type is to be used to guide adjuvant treatment

N.B. Reproducibility is equivalent to accuracy for a test where there is no gold standard!!!

- patients given different diagnoses in different centers
- results of studies on natural history provide conflicting results (e.g. clear cell carcinoma)
- impossible to move forward with good studies on molecular pathology or clinical trials of new treatments

Presentation Outline

- A brief history of classification of uterine cancer
- Is molecular/biomarker-based classification necessary?
- The Cancer Genome Atlas
- Molecular subgroups of endometrial cancer: translating genomics into practice through immunohistochemistry
- Future state?

Adjuncts to Morphology in Histotype Dx

- IHC
- Gene mutational analysis
- Gene panels

Immunohistochemical stains for histotype Dx

- ER
- PTEN
- p16
- p53

Currently no uniformity in marker(s) used or how they are interpreted

Gene mutations that correlate with histotype Dx

- PTEN
- ARID1A
- PPP2R1A
- CTNNB1
- TP53

None are both highly sensitive and specific for histotype
Endometrioid/clear cell genotype cases:
- PTEN + ARID1A mutations, or
- PTEN or ARID1A mutations without PPP2R1A and TP53 mutations

Serous genotype cases:
- TP53 and/or PPP2R1A mutations, without ARID1A or PTEN mutations


Conclusions
- This nine gene panel does not allow for a purely molecularly based classification of endometrial carcinoma
- It may prove useful as an adjunct to morphological classification and serve as an aid in the classification of problematic cases

Recommendation:
- In tumors with predominantly or exclusively papillary/villoglandular growth pattern
  - p53 IHC is recommended in cases with more than low-grade nuclear features (intermediate to high-grade) and/or increased mitotic activity
  - Mutated p53 immunostaining ("all or none") suggests serous carcinoma
  - Normal p53 immunostaining suggests non-serous type carcinoma
  - p16 IHC not as useful (emphasis should be placed on p53 IHC result)

The Cancer Genome Atlas (TCGA) characterization of endometrial carcinomas has provided a "gold standard" molecular classification, identifying four groups:
1. Low somatic copy number abnormalities: CN-lo
2. High somatic copy number abnormalities: CN-hi
3. Highly mutated tumors due to mismatch repair enzyme deficiency: MSI
4. Ultramutated tumors due to mutations in polymerase epsilon: POLE

Morphologic Features of MMR ECs

- 52 MSI-H and 50 non-MSI-H ECs
- Assessed tumour infiltrating lymphocytes, Peritumoral lymphocytes, bizarre tumour giant cells, intratumoural heterogeneity, metaplastic changes, Lymphovascular invasion, among others
- TILs and PTLs correlated with MSI-H status

Presenting eligible cases for radiotherapy:

- Low risk: 0 risk factors (17%)
- Intermediate risk: 1 risk factor (26%)
- High risk: >2 risk factors (57%)

Further Direction

- Predictive versus Prognostic?
  - Is POLE EDM a marker of excellent prognosis or is it predictive of a great response to chemotherapy?
  - Only diagnosis of POLE will provide an answer.

Presentation Outline

- A brief history of classification of uterine cancer
- Is molecular/biomarker-based classification necessary?
- The Cancer Genome Atlas
- Molecular subgroups of endometrial cancer: translating genomics into practice through immunohistochemistry
- Future state?

Step Towards a practical molecular classifier:

- MMR IHC versus MSI assay
- p53 IHC, TPS3 mutational testing or FISH for 3 most common loci
- Increase copy number as surrogates for copy number status
- 16 models tested. Winner chosen based on:
  i) Practical/pragmatic
  ii) Ability to discern outcomes

Calling the CN high:
TCGA Mutational Data by Clusters

Note that the clusters were not obtained from the data. Just an overlay.

Figure 1

Institute of Medicine’s Guide to Development of ‘omics based tests

Confirmation cohort n=456

Conf. cohort n=456
Conclusions

• The four molecular groups (POLE, MMR, p53 wt, p53 abn) were associated with significantly different patient outcomes
• Stage, grade, LVI also associated with outcome
• Clinical risk groups (ESMO) and molecular classifier identify different groups/are complimentary

Presentation Outline

• A brief history of classification of uterine cancer
• Is molecular/biomarker-based classification necessary?
• The Cancer Genome Atlas
• Molecular subgroups of endometrial cancer: translating genomics into practice through immunohistochemistry
• Future state?

What about Gr3 Endometrioid Ca?

• T Bosse platform presentation on Monday at 8:15!
• Most MMRd and POLE
• Molecular classifier is prognostically significant

PFS: TCGA classifiers Stage IA and IB

The Immediate Future

We can do all but POLE in daily practice:
• MMRd (MSI, mostly endometrioid but higher grade, neither Type I or Type II, no specific gene mutations or additional IHC)
• p53 abn (CN-hi, Type II, serous and some Gr3 endometrioid, TP53 mut)
• p53 wt (CN-lo, NSMP, Type 1, low-grade (grade 1 or 2) endometrioid)

How to report?

Provide both histotype and molecular classification
Examples:
• Endometrial adenocarcinoma of endometrioid type, grade 1/3; MMRd
• Endometrial adenocarcinoma of serous type; p53 abn
• Endometrial adenocarcinoma of endometrioid type, grade 2/3; p53 wt
Conclusions

• Four types of endometrial carcinoma, not two
• Readily diagnosed in practice EXCEPT for POLE
• Of prognostic significance and correlate with clinical findings
• Add information beyond that of histotype (available based on the biopsy specimen)
• More reproducible than histotype

Acknowledgements:

University of British Columbia & Genetic Pathology Evaluation Centre
• Cheng Han Liu, MD, PhD
• Mary-Kloech, MD (now Univ of Saskatchewan)
• David G Hunston, MD
• Julie Krong, MD
• Melissa E McGrath, PhD
• Jessica R McAlpine, MD
• Barbara H, MD
• Sam Soung, MD

Memorial Sloan Kettering Hospital, New York
• Ben Davidson, MD
• University of Birmingham
• Raji Ganesan MD
• University of Lleida
• Xavier Mattes-Gass, MD

Massachusetts General Hospital, Boston
• Esther Oliva, MD
• Beth Harrison, MD
• University of Illinois Hospital
• Guangming Han, MD (now Surrey Memorial Hosp)
• Maryke Robboshana, MD

Norwegian Radium Hospital, Norway
• Ben Davidson, MD
• University of Birmingham
• Raji Ganesan MD
• Xavier Mattes-Gass, MD
• University of Lleida
• Melbourne Memorial Hospital, Melbourne
• David G Hunston, MD
• Mary-Kloech, MD (now Univ of Saskatchewan)
• University of Toronto, Ontario
• Guangming Han, MD (now Surrey Memorial Hosp)
• Maryke Robboshana, MD

University of Calgary, Alberta
• Marisa R Nucci, MD
• University of Lleida
• Raji Ganesan MD
• University of Birmingham
• Manchester Memorial Hospital, Manchester
• Beth Harrison, MD

University of British Columbia & Genetic Pathology Evaluation Centre
• Cheng Han Liu, MD, PhD
• Mary-Kloech, MD (now Univ of Saskatchewan)
• David G Hunston, MD
• Julie Krong, MD
• Melissa E McGrath, PhD
• Jessica R McAlpine, MD
• Barbara H, MD
• Sam Soung, MD

Massachusetts General Hospital, Boston
• Esther Oliva, MD
• Beth Harrison, MD
• University of Illinois Hospital
• Guangming Han, MD (now Surrey Memorial Hosp)
• Maryke Robboshana, MD

Norwegian Radium Hospital, Norway
• Ben Davidson, MD
• University of Birmingham
• Raji Ganesan MD
• Xavier Mattes-Gass, MD
• University of Lleida
• Melbourne Memorial Hospital, Melbourne
• David G Hunston, MD
• Mary-Kloech, MD (now Univ of Saskatchewan)
• University of Toronto, Ontario
• Guangming Han, MD (now Surrey Memorial Hosp)
• Maryke Robboshana, MD

University of Calgary, Alberta
• Marisa R Nucci, MD
• University of Lleida
• Raji Ganesan MD
• University of Birmingham
• Manchester Memorial Hospital, Manchester
• Beth Harrison, MD