Contemporary Issues in Uterine Serous Carcinoma

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Overview

• Incidence and etiology of endometrial carcinoma
• Classification of endometrial carcinoma:
  – (Type I and II) Histology and Molecular
• Uterine serous carcinoma (USC):
  – molecular, IHC and precursors lesions
• Differential diagnosis of USC –
  – other high grade endometrial carcinomas
• Benign mimickers of USC

Gynecologic Cancers

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine</td>
<td>49,560</td>
<td>8,190</td>
</tr>
<tr>
<td>Ovarian</td>
<td>22,240</td>
<td>14,030</td>
</tr>
<tr>
<td>Cervical</td>
<td>12,340</td>
<td>4,030</td>
</tr>
<tr>
<td>Vulvar</td>
<td>4,700</td>
<td>990</td>
</tr>
<tr>
<td>Vaginal &amp; Other</td>
<td>2,890</td>
<td>840</td>
</tr>
<tr>
<td>Total</td>
<td>91,730</td>
<td>28,080</td>
</tr>
</tbody>
</table>

ACS Statistics 2013

Endometrial carcinoma: a snapshot

• 48,000 new EMC cases in USA in 2012
  – 82% 5-year survival (2002-2008)
  • 84% Caucasian ancestry
  • 59% African ancestry
  – 25-35% high grade
  – 17% high stage (FIGO III/IV)
  – 17% DOD

SEER 2012

Obesity in America

A Health Care Epidemic

Endometrial Cancer Risk Factors

Risk Ratio Estimated for Certain Factors Correlated with Endometrial Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
<tr>
<td>Overweight (age 50-59)</td>
<td></td>
</tr>
<tr>
<td>20-50</td>
<td>3</td>
</tr>
<tr>
<td>&gt;50</td>
<td>10</td>
</tr>
<tr>
<td>Nulliparity vs 1 child</td>
<td>2</td>
</tr>
<tr>
<td>Nulliparity vs 5 children</td>
<td>5</td>
</tr>
<tr>
<td>Late menopause (&gt;52 or later vs &lt;49)</td>
<td>2.4</td>
</tr>
<tr>
<td>Diabetes by personal history</td>
<td>2.7</td>
</tr>
<tr>
<td>Unopposed estrogen use</td>
<td>6</td>
</tr>
<tr>
<td>Tamoxifen therapy</td>
<td>2.2</td>
</tr>
<tr>
<td>Sequential oral contraceptive use</td>
<td>7</td>
</tr>
<tr>
<td>Combination oral contraceptive use</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Type I</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Unopposed estrogen</td>
<td>Present</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Pre- and peri-menopausal</td>
</tr>
<tr>
<td>Precursor lesion</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>Low</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td>Variable, often minimal</td>
</tr>
<tr>
<td>Histologic subtypes</td>
<td>Endometrioid, mucinous</td>
</tr>
<tr>
<td>Behavior</td>
<td>Indolent</td>
</tr>
<tr>
<td>Genetic alterations</td>
<td>PTEN mutation</td>
</tr>
<tr>
<td></td>
<td>Microsatellite instability</td>
</tr>
<tr>
<td></td>
<td>K-ras mutation</td>
</tr>
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</table>

Endometrial cancer classification inspired by Bokhman

**Re-Classification of Endometrial Carcinoma Based on Molecular**

- **Cluster 1**: POLE ultramutated
- **Cluster 2**: microsatellite Unstable hypermutated
- **Cluster 3**: copy-number low
- **Cluster 4**: copy-number high (serous-like).
Endometrial carcinoma TCGA subgroups: what’s important?

- Serous-like signature is unfavorable
- POLE signature is highly favorable

Type I

- Endometrioid adenocarcinoma
  - Villo glandular
  - Secretory
  - Endometrioid adenocarcinoma with squamous differentiation.
- Mucinous carcinoma
Type II

Closer to reality

High-grade endometrial carcinoma

- Serous
- Clear cell
- FIGO grade 3 endometrioid
- Undifferentiated
- Carinosarcoma/MMMT
- High-grade, NOS

Uterine Risk Factors

**Grade of the Tumor**

- Depth of Myometrial invasion
- Tumor size
- Cervical Stromal invasion
- Lymphovascular space invasion

*Different high-grade endometrial carcinomas represent different disease entities*

- Staging
- Adjuvant therapy
- Hereditary cancer risk (i.e. Lynch)
- Targeted therapy
- Protocol eligibility/trial design

Uterine Serous Carcinoma
Uterine Serous Carcinoma

• 10% of endometrial carcinoma

• ~ 40% of all endometrial cancer-related death

• First established as a distinct entity in 1981-1982 by Lauchlam and Hendrickson

  – Unlike typical endometrial carcinoma:
    • Frequently have extra-uterine disease
    • More lymphovascular space invasion

Uterine Serous CA: Epidemiology/Behavior

• Aggressive tumor

  – ~55% of USC present as stage III and IV
  – Progression free survival of 65, 37 and 0% for stages II, III and IV

Uterine Serous CA: Epidemiology/Behavior

• Higher incidence reported in AA women with higher mortality rates.

• Associated with history of breast cancer, including those treated with Tamoxifen.
  – Association with BRCA 1

Survival after an Endometrial Cancer Diagnosis, by Race and Type

Uterine Serous CA: Epidemiology/Behavior

• Race: Higher incidence reported in AA women with higher mortality rates.

• Associated with history of breast cancer, including those treated with Tamoxifen.
  – Association with BRCA 1

Uterine Serous CA: Morphology

• Papillary pattern
• Glandular pattern
• Solid pattern
  – characterized by discordance between:
    • architecture, well differentiated (papillary or glandular pattern)
    • nuclear morphology, high grade

The Many Faces of Endometrial Serous Carcinoma
Uterine Serous CA Molecular Advances

• High rates:
  – TP53 mutations
  – Her-2/neu gene amplification
  – PIK3CA mutations
  – FBXW7 mutations
  – PPP2R1A mutations
  – CHD4 somatic mutations

Patients with USC have demonstrated germline mutations in BRCA1 in 2% of the nonfounder population ~ suggests an association with hereditary breast and ovarian cancer

Genetic counseling should be recommended to these patients


Discriminating Uterine Serous Carcinoma from High Grade Ovarian and Fallopian Tube Serous Carcinoma by Whole Genome Expression


Background: The morphologic and molecular similarities amongst uterine serous carcinoma (USC), high grade ovarian serous carcinoma (OGC) and fallopian tube serous carcinoma (FTSC) are well known. The aim of our study was to analyze and highlight the differences at the molecular level.

Design: We retrieved 24 cases of primary high grade USC (n=8), FTSC (n=8) and OGC (n=8) age and stage matched from our pathology database. We measured whole-genome mRNA expression in all formalin-fixed paraffin (FFPE) specimens. Total RNA was isolated and mRNA quantity and quality was estimated using a Nanodrop (Wilmington) spectrophotometer. Further sample processing and gene expression profiling was done using an Illumina Human Whole-Genome HT Assay Kit. A total of 25,000 annotated genes derived from RefSeq were measured. A level determined significant differential gene expression.

Results: High grade (OGC) and (FTSC) did not show any significant difference in mRNA expression supporting the concept of similar cell of origin and development pathway in both. At the same time USC was distinct. 1,746 genes were differentially expressed (p<0.05) for both uterine versus ovarian and uterine versus fallopian. Significant pathway analysis of the resulting gene set indicated significant pathway-level differences, listed in

Conclusions: Understanding molecular differences between these diseases might help in identifying some of the clinical differences, prognostic biomarkers and targeted treatment to improve USC outcomes.

Uterine Serous CA: IHC
**Uterine Serous CA: IHC**

- Overexpression of p53:
  - ~90% of USC
  - ~75% of EIC
  - Secondary to p53 gene mutation

- Diffuse P16
- Positive Ki-67
- May express Her2-neu
- Positive PTEN
- Negative ER/PR
- Recently: IMP 3
  - oncofetal protein, insulin-like growth factor II mRNA-binding protein 3 (diffuse cytoplasmic expression)
Precursor lesions of Uterine Serous CA

- Endometrial Intraepithelial Carcinoma

Endometrial Intraepithelial Carcinoma (EIC)

- Putative precursor lesion for serous carcinoma
- Other names:
  - Carcinoma In Situ (CIS) - (should not be used)
  - Uterine Surface Carcinoma (USC)
  - Serous Intraepithelial Carcinoma
Endometrial Intraepithelial Carcinoma: EIC

• EIC is different from EIN (Endometrial Intraepithelial Neoplasia).
• Arises in atrophic endometrium and may be missed.
• p53 ~ 75% of EIC

EIC-microscopic

• Lines the surfaces and glands of the atrophic endometrium.
• Replacement of the endometrial epithelium by malignant cells but with preservation of the normal architecture.
• No confluent glands.
• No stromal desmoplasia/invasion.
• Serous features:
  – Markedly atypical, enlarged, vesicular nuclei.
  – Prominent nucleoli.
  – Mitosis and apoptosis.
  – Prominent hobnail morphology

Endometrial Intraepithelial Carcinoma, EIC

• Uterine serous surface carcinoma
• Minimal uterine serous carcinoma (Less than 1 cm in greatest dimension)
• Noninvasive serous carcinoma

• Share many features at the level of
  – Morphology
  – Molecular biology
  – Clinical behavior and management

Zheng et al, 2005
No differences in term of outcome: EIC, Minimal uterine serous carcinoma (Less than 1 cm), Uterine surface carcinoma or non-invasive USC

Uterine Serous Carcinoma

- Retrospective multi-institutional review:
  - 55/236 cases with no myometrial invasion
  - 40/236 cases with tumor <1cm in size
- FIGO Stage distribution in patients with no myometrial invasion
  - I: 44 (80%)
  - II: 1 (1.8%)
  - IIIA: 1 (1.8%)
  - IVB: 9 (16.4%)
- Behavior of ‘small tumors’ (<1cm)
  - 10% with outer myometrial invasion
  - 10% had LN metastases

2. Winer I et al, Gynecol Oncol 2013

Arising in a Polyp

Stage I Noninvasive and Minimally Invasive Uterine Serous Carcinoma

Objective: The aim of this study was to determine if comprehensive surgical staging in a subset of pathologically confined disease or minimally invasive (≤5 mm) uterine serous carcinoma (USC) was feasible. "Total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and peritoneal cytology sampling was completed in 30% (12/40) of the patients with Stage I disease. There was no difference in survival in the comprehensive surgery group compared to those receiving minimal surgery, suggesting that additional lymphadenectomy is not necessary in this clinical setting."

- p53

Stage I Non-invasive USC

Clinical and Pathologic Characteristics of Serous Carcinoma Confined to the Endometrium: A Multi-institutional Study

1. Andrew Sasson, MD, Small Mert, MD, Abou R. Mousa, MD, Saadoun Basdouguzi, MD, Hader M. More, MD, Ira S. Young, MD, MD, Marlin R. Nace, MD, Yaar Huseen, MD, Fatma Qureshi, MD, Khim Hasko, MD, Fadul Tahmeen, MD, Beba Abdo, MD, Daniel S. Schiff, MD, MD, Michele L. Cote, MD, Koen K. Van de Vusse, MD, MD, Robert T. Meek, MD, Esther Oliva, MD, and Renu A. Kliman, MD
Management of EIC

Same as non invasive serous carcinoma

Diagnosis of EIC → patient should undergo surgical staging at the time of diagnosis.

EIC is not an “in situ” malignant neoplasm

• It is not an “in situ” malignant neoplasm
  – associated with high stage and fatal outcome even in the absence of endometrial stromal, myometrial or vascular invasion
  – “carcinoma in situ” is misleading for the surgeon, who may under treat the patient

Differential Diagnosis

• Endometrioid carcinoma
  – Villoglandular
  – Endo CA with small nonvillous papillae

Differential Diagnosis
Gland forming serous carcinoma

- Glandular tumor lacking confirmatory endometrioid features in the presence of diffuse, severe nuclear atypia
- Not FIGO G2 endometrioid carcinoma

Gland forming serous carcinoma

- Not FIGO G2 endometrioid
- Supporting evidence:
  - TP53 mutation
    - No PTEN, DNA MMR
  - Unfavorable clinical outcomes (like serous CA)

Serous vs CCC

- Morphology overlaps significantly, but Fadare criteria might discriminate
- Genotype and, possibly, IHC differ
  - ARID 1A
  - DNA MMR
  - +/- p53, WT1, HNF
- Extensive clinical data are lacking, but Fadare’s data suggest significant differences

Endometrioid FIGO 3, Carcinoma

molecular signatures and immunophenotype

- Endometrioid
  - Mutations: PTEN, PIK3CA, ARID 1A, DNA MMR, KRAS, CTNNB1, TP53
  - IHC: aberrant PTEN, ARID 1A, DNA MMR, β-catenin, p53


<table>
<thead>
<tr>
<th>TABLE 1. Refinements to WHO Diagnostic Criteria for the Diagnosis of FIGO Grade 3 Endometrioid and Serous Carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endometrioid FIGO</strong></td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
</tr>
<tr>
<td>Architecture</td>
</tr>
<tr>
<td>Cell shape and cytoplasm</td>
</tr>
<tr>
<td>Nuclear features</td>
</tr>
</tbody>
</table>

Tumors displaying hybrid features were categorized as “morphologically ambiguous.”
Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers


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Endometrioid vs CCC

- Morphology overlaps significantly, but Fadare criteria might discriminate
- No distinctive genotypic or IHC features
- No convincing differences in clinical outcomes, except, possibly, relative chemoresistance in CCC

Endometrial carcinomas with solid architecture:
FIGO G3 endometrioid vs solid serous carcinoma
Morphological ambiguity:

• Sources of diagnostic discrepancies:
  – Serous vs CCC
  – Endometrioid vs CCC
  – Intratumoral heterogeneity
    • R/O MMMT
    • Mixed epithelial carcinoma

Mixed Serous Carcinoma

• One third of USC coexist with other subtypes of uterine carcinoma
  – Endometrioid
  – Clear cell
  – Neuroendocrine carcinoma

  • Trophoblastic differentiation has been reported
**Mixed serous-endometrioid CA**

- In patients with early-stage disease, even 10% of serous component has a worse prognosis compared to grade III, endometrioid CA
- Very important to document any serous component

_Boruta et al., Cancer_. 2004 Nov 15;101(10):2214-21

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**P53 in mixed EC**

_Courtesy of Dr. Crump_

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**Morphology of carcinosarcoma (MMMT)**

- Biphasic neoplasm
  - Epithelial component: serous>G3 endometrioid>ugly carcinoma NOS>G2 endometrioid
  - Sarcomatoid component: pleomorphic spindle cell sarcoma; heterologous sarcoma (i.e. rhabdo)
De-differentiated endometrial carcinoma

- Combined differentiated endometrioid carcinoma and undifferentiated carcinoma
- Not FIGO G3, MMMT, Adenosarcoma, Combined neuroendocrine CA

Supporting evidence:
- No high grade glandular EMC component
- Highly unfavorable clinical outcomes (worse than MMMT-homol)
- Aberrant DNA MMR


High-grade EMC: clinical features

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Risks</th>
<th>Age (&gt;65 yr)</th>
<th>Hi (III/IV) stage</th>
<th>Median survival</th>
<th>Metastatic sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>70%</td>
<td>70%</td>
<td>40 mo</td>
<td>Pelvis, LN, peritoneum</td>
<td></td>
</tr>
<tr>
<td>MMMT-homol</td>
<td>70%</td>
<td>70%</td>
<td>40 mo</td>
<td>Pelvis, LN, peritoneum</td>
<td></td>
</tr>
<tr>
<td>MMMT-heterol</td>
<td>70%</td>
<td>70%</td>
<td>20 mo</td>
<td>Pelvis, LN, peritoneum</td>
<td></td>
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<tr>
<td>FIGO G3</td>
<td>?</td>
<td>50%</td>
<td>30%</td>
<td>&gt;60 mo</td>
<td>Pelvis, LN</td>
</tr>
<tr>
<td>CCC</td>
<td>?</td>
<td>50%</td>
<td>40-50%</td>
<td>&gt;60 mo</td>
<td>Pelvis, LN</td>
</tr>
</tbody>
</table>

High-grade EMC: clinical features

Risks: 
- No high grade glandular EMC component
- Highly unfavorable clinical outcomes (worse than MMMT-homol)
- Aberrant DNA MMR

Is Subspecialty Sign-Out Better for Classifying Uterine Endometrioid Carcinomas?

Sumi Thomas MD, Yaser Hussein MD, Sudeshana Bandyopadhyay MD, Michele Cote PhD, Oudai Hassan MD, Eman Abdulaleel MD, Baraa Alish MD, Hui Guan MD, Robert Soslow MD, Rouba Ali-Fehmi MD

Wayne State University School of Medicine, Detroit, MI
Memorial Sloan Kettering Cancer Center, New York, NY

70 and 65 G3EC cases were identified from Wayne State University (WSU) (general surgical pathology sign-out) and Memorial Sloan Kettering Cancer Center (MSK) (subspecialty sign-out) respectively. 2 GYN pathologists reviewed slides, classified according to sub-type and grade into G3EC group or reclassified group.
• Agreement rate between original diagnosis and review diagnosis was higher at MSK than WSU (83% vs. 64%; \( P=0.02 \))
• Overall agreement rate of cohorts combined was 73%
• Mixed endometrioid and serous carcinoma was the most common misclassified subtype (44%).

Differential Diagnosis

• **Endometrial Metaplasias:**
  – Papillary syncytial *metaplasia*
  – Hobnail *cell metaplasia*
  – Eosinophilic (pink cell) *metaplasia*

Endometrial Metaplasias

– *Hobnail cell metaplasia*

Hobnail Metaplasia: A Worrisome Mimic of Carcinoma
“Shedding” Endometrium With Features Worrisome for a Serous Neoplasm

Papillary syncytial metaplasia

Endometrial Metaplasias

• Eosinophilic (pink cell) metaplasia
Future Horizons

- Understanding the molecular basis of endometrial carcinoma may impact classification, prognosis and treatment

Incidence and etiology of endometrial carcinoma

Classification of endometrial carcinoma:
- (Type I and II) Histology and Molecular

Uterine serous carcinoma (USC):
- molecular, IHC and precursors lesions

Differential diagnosis of USC –
- other high grade endometrial carcinomas

Benign mimickers of USC

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