TCGA Results for Endometrial Cancer

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The face of clinical trials is changing
Types of endometrial cancer

- **Endometrioid (low grade)**
- **Serous (high grade)**
- **Serous vs Endometrioid**
  - More solid
  - Less glandular
  - Higher grade nuclei
  - Greater N:C ratio
  - Loss of polarity

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@LevineMD
Poor Interobserver Reproducibility in the Diagnosis of High-grade Endometrial Carcinoma

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Abstract: Patients with high-grade subtypes of endometrial carcinoma (grade 3 endometrioid, serous, clear cell, or carcinosarcoma) have a relatively poor prognosis. The specific subtype may be used to guide patient management, but there is little information on the reproducibility of subtype diagnosis in cases of high-grade endometrial carcinoma. Fifty-six cases diagnosed as a high-grade subtype of endometrial carcinoma were identified from the pathology archives of Vancouver General Hospital. All slides for each case were reviewed independently by 3 pathologists, who diagnosed the specific tumor subtype(s) and assigned the percentage of each subtype for mixed tumors. Agreement between observers was categorized as follows: major disagreement in 4 cases (4/56, 7.1%). In 20 of 56 (35.8%) cases there was a major disagreement; in 17 (30.4%) of these cases there was no consensus about the major subtype diagnosis, whereas in 3 (5.4%) cases there was disagreement about whether a component of high-grade endometrial carcinoma was present. In the final case, all 3 reviewers diagnosed the case as low-grade endometrioid carcinoma, disagreeing with the original diagnosis of high-grade carcinoma. The most frequent areas of disagreement were serous versus clear cell (7 cases) and serous versus grade 3 endometrioid (6 cases). Immunostaining results using the 5-marker immunohistochemical panel were then used to adjudicate in the 6 cases in which there was disagreement between reviewers with respect to serous versus endometrioid carcinoma, and these supported a diagnosis of serous carcinoma in 3 of 6 cases of endometrial carcinoma.

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TCGA Research Network
BCR Pipeline – Endometrial

- Received: 937
- Shipped: 523
- Awaiting Shipment: 8
- Total Shipped/Pending: 531

- Received at BCR: 871 cases
- Pathology QC: Pathology Pass: 740 cases
- Molecular QC: Molecular Pass: 576 cases
- Genotype/Final Review: Shipped: 523 cases
- Awaiting Shipment: 8 cases
- Held: 37 cases
- Initial Screen Failures: 66 cases
- Pathology Failures: 131 cases
- DQ Molecular: 164 cases
- DQ Genotype: 8 cases

The Cancer Genome Atlas
TCGA: The Pipeline for Comprehensive Characterization

Tissue Sample

- Pathology QC
- DNA & RNA Isolation, QC

Sequencing

Data Storage at DCC & CGHub

Expression, CNA & LOH, Epigenetics

Integrative Analysis

GDAC

Comprehensive Characterization of a Cancer Genome

3 months 2 years ~90d

SNP 6.0 ~45d
Methylation ~60d
miRNAseq ~105d
mRNAseq ~120d
DNAseq Exome ~180d

~12-24 months

The Cancer Genome Atlas
Sample criteria limit ‘askable’ questions

- Newly diagnosed, untreated, invasive tumors
- Snap frozen, <60min to LN2
  - ~50 mg wet weight
- Pathology review of contributed tissue
- ≥60% tumor cells, ≤20% necrosis
- Matched germline DNA
- Select clinical annotation
- IRB approval for TCGA use and general data sharing
- MTA without retention of IP
ENDOMETRIAL RESULTS

CANCERGENOME.NIH.GOV

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Copy number alteration clusters

Andrew Cherniack, Broad

The Cancer Genome Atlas
24% of high-grade endometrioid tumors cluster with serous tumors (serous-like)

Andrew Cherniack, Broad

The Cancer Genome Atlas
Extended 1q analysis

- Clinically relevant analysis of TCGA data
- Significantly decreased PFS for 1q amp’d group
  - Independent of standard histopathology
  - Within stage I pts
- Limited by 26 mos f/u
- Remarkable
  - Endometrioid 1q subset

- Itai Pashtan, Andrew Cherniack, Broad

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Mutation spectrum

Very high background mutation rate; ~100-500 / Mb

High background mutation rate; ~10-20 / Mb

Low background mutation rate; ~2-3 / Mb

Hypermutators associated with MSI and MLH1 DNA promoter methylation

- Cyriac Kandoth and Li Ding, WashU
- Niki Schultz, Nils Weinhold, MSKCC
SMGs – Significantly Mutated Genes

The Cancer Genome Atlas
Progression free survival

Serous – poorest PFS
No difference between MSI and MSS groups
No events in small POLE group
Copy number spectrum

- MSI, MLH1 meth, Few SCNA, high mutation rate
- MSS, Few SCNA, very high mutation rate
- MSS, Few SCNA, Low mutation rate
- MSS, Many SCNA, Low mutation rate

- Cyriac Kandoth and Li Ding, WashU
- Niki Schultz, Nils Weinhold, MSKCC
Integrated features

- All endometrioid, PTEN mutations, few TP53 mutations
- All endometrioid, PTEN mutations, no TP53 mutations
- TP53 mutations, few PTEN mutations, high grade tumors, serous and some endometrioid

- Cyriac Kandoth and Li Ding, WashU
- Niki Schultz, Nils Weinhold, MSKCC
• Extensive activation of CTNNB1 through novel mechanism; different than CRC cancer
• New SOX17 hotspot mutations identified

Niki Schultz, Nils Weinhold, MSKCC
PI3K/AKT – most active in endometrial cancer

b. PI3K pathway

- **PI3CA**
  - 55% 53% 47%
  - Proliferation, cell survival, translation

- **PIK3R1**
  - 40% 34% 13%

<table>
<thead>
<tr>
<th>Gene</th>
<th>Homozygous deletion</th>
<th>Somatic mutation</th>
<th>Hypermethylated (95%)</th>
<th>Endometrioid low mutation rate (92%)</th>
<th>Serous-like (60%)</th>
</tr>
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<tbody>
<tr>
<td>PTEN</td>
<td></td>
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<tr>
<td>PIK3R1</td>
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<tr>
<td>PI3CA</td>
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- **PIK3CA**

- **PIK3R1**
The endometrial cancer pathway

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J Clin Oncol 29:3278-3285. © 2011
Multiplatform molecular similarities among ovarian serous, uterine serous, basal like breast

Andrew Cherniack, Hui Shen, Wei Zhang, Chris Benz, Peter Laird, Yuexin Liu, Christina Yau
Mutation frequencies vary across tumors

The Cancer Genome Atlas
The Cancer Genome Atlas Pan-Cancer analysis project


Background Mutation Frequencies

Mutation frequencies, spectra, and contexts across 12 cancer types

Distribution of mutations in 127 SMGs across Pan-Cancer cohort

Emerging landscape of oncogenic signatures across human cancers

Giovanni Ciriello, Martin L Miller, Bülent Arman Aksoy, Yasin Senbabaoglu, Nikolaus Schultz & Chris Sander

Comments

• Genomic landscape (from TCGA or other sources) will form backbone for clinical trial design of targeted agents with defined mechanism
  – Selection vs. stratification
  – Intelligent trials (with biospecimens)
• Expected alterations do not result in response to targeted agents with defined mechanisms of action
  – Endometrial phase II trials of mTORi
• Properly designed clinical trials will allow us to learn about mechanisms of response and resistance