Tumour biopsy in men with metastatic prostate cancer: What should the pathologist report?

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Taxonomy of disease
Common Molecular Alterations in Prostate Cancer

Most Common PCA Specific mutations

Tomlins et al, Science 2005

Common Somatic Alteration in Localized Prostate Cancer

- **PIK3CA**
- **ZNF595**
- **SCN11A**
- **FOXA1**
- **C14orf49**
- **NIPA2**
- **THSD7B**
- **CDKN1B**
- **PTEN**
- **TP53**
- **SPOP**
Most Common Recurrent Point Mutation in Prostate Cancer: SPOP mutations affect substrate binding

Blattner et al., Cancer Cell 2017 (in press)

Barbieri, Baca et al., Nature Genetics 2012
Mutations Enriched in CRPC

Enriched:
- AR
- MYC
- PTEN
- TP53
- RB1
- BRCA2

Depleted:
- SPOP

Van Allen, Schultz, IDT et al., unpublished
Prostate Cancer Resistance on Androgen Deprivation Therapy (ADP)

**Work around**
- Reactivate AR
- ARmut
- AR SV

**New route**
- Adopt New pathway
- wnt PI3K/AKT

**Indifference**
- Lineage plasticity
- True AR independence

AR+  AR+/−
A model of progressive reprogramming

Androgen-dependent, AR⁺
In castrate-resistant prostate cancer (luminal epithelial adenocarcinoma), cells express and depend upon androgen receptor (AR⁺) for growth.

Androgen-indifferent, AR⁺/−
After treatment with an AR antagonist, cells with altered RB1 and TP53 are selected. Factors including SOX2 and EZH2 contribute to dedifferentiation and plasticity.

Androgen-independent, AR⁻
Cells established are most often reprogrammed to the neuroendocrine lineage that is resistant to enzalutamide.

Comment by Kelly and Balk, Science 2017
Clinical Considerations for the pathology interpretation of a mPCA Biopsy

• **No systematic study yet to address:**
  – Morphology for mCRPC
  – Association between pathology and **clinical outcome** (response to treatment/disease progression)
  – Association between pathology and **genomic/transcriptomic** findings
SU2C-PCF Prostate Dream Team Leaders and Principals
Multi-institutional study workflow

Clinical sites
- UW, RM-ICR, UM, DFCI, MSKCC, BIDMC, Weill-Cornell, Karmanos

Pathology data coordination
- Weill-Cornell

Sequencing
- UM
- Broad Institute

Data analysis
- UM
- Broad Institute

Clinical data integration
- PCCTC, MSKCC

Precision Medicine Tumor Board (PMTB)

Data visualization
- cBio portal
- MSKCC

Integrative Clinical Genomics of Prostate Cancer
Robinson et al., 2015, Cell
Pathology Protocol for Evaluation of metastatic CRPC Biopsy

Frequently only rare tumor cells are available for analysis

[Images: HE, x40 and ERG, x20]

Mosquera et al., SU2C/PCF Protocol
Pathology review workflow

All Participants

- Retrieve all H&E frozen sections
- Retrieve a subset of FFPE slides (aim: ~20%)
- Independent review: each case reviewed by at least two pathologists

Weill Cornell Medicine

- Slides centralized at Weill Cornell
- Slide scanning (Aperio, 40X)
- Cases integrated into Profiler (an online slide review interface)

- Consensus review of discordant cases
- Data analysis
- Correlation with molecular findings
# Workshop Attendees: mCRPC Pathology

<table>
<thead>
<tr>
<th>First Name</th>
<th>Last Name</th>
<th>Organization/Institution</th>
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<tbody>
<tr>
<td>1</td>
<td>Juan Miguel</td>
<td>Weill Cornell</td>
</tr>
<tr>
<td>2</td>
<td>Brian</td>
<td>Weill Cornell</td>
</tr>
<tr>
<td>3</td>
<td>Gustavo</td>
<td>University of Texas Health Science Center</td>
</tr>
<tr>
<td>4</td>
<td>Martin</td>
<td>Vancouver Prostate Centre</td>
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<tr>
<td>5</td>
<td>Mahul</td>
<td>Cedars Sinai</td>
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<tr>
<td>6</td>
<td>Larry</td>
<td>University of Washington</td>
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<tr>
<td>7</td>
<td>Victor</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
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<tr>
<td>8</td>
<td>Jaioti</td>
<td>David Geffen School of Medicine at UCLA</td>
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<tr>
<td>9</td>
<td>Scott</td>
<td>University of Michigan Medical School</td>
</tr>
<tr>
<td>10</td>
<td>Jonathan</td>
<td>Johns Hopkins University</td>
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<tr>
<td>11</td>
<td>Tamara</td>
<td>Johns Hopkins Medical Institutions</td>
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<tr>
<td>12</td>
<td>Chris</td>
<td>University of Texas MD Anderson Cancer Center</td>
</tr>
<tr>
<td>13</td>
<td>Misha</td>
<td>Weill Cornell Medical College</td>
</tr>
<tr>
<td>14</td>
<td>Mark</td>
<td>Weill Cornell Medical College</td>
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</table>

Proposed Morphologic Classification of Prostate Cancer With Neuroendocrine Differentiation.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Usual high grade prostatic adenocarcinoma (no apparent neuroendocrine differentiation)</td>
</tr>
<tr>
<td>B</td>
<td>Usual high grade prostatic adenocarcinoma with apparent neuroendocrine differentiation</td>
</tr>
<tr>
<td>C</td>
<td>Pure small cell neuroendocrine carcinoma</td>
</tr>
<tr>
<td>D</td>
<td>Pure large cell neuroendocrine carcinoma</td>
</tr>
<tr>
<td>E</td>
<td>Mixed neuroendocrine carcinoma - acinar adenocarcinoma</td>
</tr>
<tr>
<td>F</td>
<td>Paneth cell-like neuroendocrine differentiation</td>
</tr>
<tr>
<td>G</td>
<td>Intermediate Atypical Carcinoma</td>
</tr>
<tr>
<td>H</td>
<td>Other (including no tumor or atypical cells)</td>
</tr>
</tbody>
</table>

Profiler: an online interface for slide review

Dropdown menus and text fields for review parameters

Profiler: an online interface for slide review

Adjustable magnification on whole slides (up to 40X)
Diagnosis

Usual prostatic adenocarcinoma

Adenocarcinoma with neuroendocrine differentiation apparent on H&E

Small cell neuroendocrine carcinoma

Used classification:

Additional proposed parameters

• Tumor content in sample
  - Tumor purity (%)
  - Overall tumor quantity (moderate, scant, abundant)

• **Nuclear pleomorphism** (moderate, minimal, severe)

• **Prominent nucleoli** (yes, no)

• **Special features** (squamous, sarcomatoid, other...)

• **Inflammation** (minimal, moderate, severe)
Nuclear pleomorphism

Moderate
Most frequent

Minimal
Bland nuclei
Possible overlap with IAC

Severe
Uncommon
Correlation with genomic findings?
Intermediate Atypical Carcinoma (IAC)

- 29% of mCRPC
- Median OS = 19.1 months
  (small cell ca. = 12.8 mo., adenocarcinoma = 25.8 mo.)

*WCDT, Small et al., ASCO 2016, USCAP 2017*
Specific challenges of frozen sections

Quality
- e.g. bone biopsies

Morphology
- e.g., what are the criteria for Intermediate Atypical Carcinoma on frozen section?
Preliminary observations

- Review cohort: 288/405 (71%) SU2C patients; 314 slides in total (all frozen sections)

- Based on first 385 replies from 6 reviewers:
  - the agreement rate for diagnosis was 79%
  - neuroendocrine differentiation was called in 10% of cases

* “Other”: includes “carcinoma NOS”, “atypical cells” and “no apparent tumor cells on H&E”.
West Coast Dream Teams at ASCO 2017

Robinson, IDT, Cell 2015
Small, WCDT, ASCO 2016
Huang, WCDT, USCAP 2017
West Coast Dream Teams at USCAP 2017

Huang, WCDT, USCAP 2017

- AdCa: 30%
- IAC: 29%
- SCNC: 13%
- Mixed: 28%
West Coast Dream Teams at USCAP 2017

Adenoca  Intermediate Atypical Ca  Small Cell Neuroendocrine

IAC express AR (80%), survival intermediate between AdCa and SCNC, and distinct 50 gene signature
Compared characteristics of pathology reviews from both Teams

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>West Coast Dream Team</th>
<th>International Dream Team</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abi/Enza-resistant patients</td>
<td>Some biopsies before Abi/Enza</td>
<td></td>
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<tr>
<td>Reviewed material</td>
<td>FFPE</td>
<td>Frozen sections</td>
</tr>
<tr>
<td>IHC used in review?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>% NEPC (without IAC)</td>
<td>12% (small cell carcinoma)</td>
<td>~ 4% (preliminary review)</td>
</tr>
<tr>
<td>% IAC</td>
<td>29%</td>
<td>TBD</td>
</tr>
<tr>
<td>Tumor enrichment method</td>
<td>Laser capture microdissection</td>
<td>Macrodisssection or none</td>
</tr>
<tr>
<td>Sequencing tests performed</td>
<td>RNA-seq</td>
<td>WES and RNA-seq</td>
</tr>
</tbody>
</table>
Clinical Considerations for the pathology interpretation of a mPCA Biopsy

• When a pathologist tells a clinician there are NE features the clinician routinely thinks:
  A) this tumor is more aggressive and the patient will have a shorter rPFS and OS;
  B) this patient will probably not respond to hormone therapy and should probably get platinum based chemo;
  C) there is more likely to be visceral disease, etc.

• What is the clinical relevance of CRPC with NE features? Does this even matter?

• Important considerations: Do they do badly? Are they treatment refractory? Are they AR negative? RB lost?

De Bono and SU2C team, On Going Conversation
Clinical Considerations for the pathology interpretation of a mPCA Biopsy

• Optimal pathology from FFPE material – best morphology and ability to perform IHC/WES
• Morphology as per Consensus Classification* (note: we do not know the meaning of NE features and do NOT suggest that it excludes AR modulating therapies.
• NO Gleason grading!

Clinical Considerations for the pathology interpretation of a mPCA Biopsy

• Frozen material useful for RNAseq and organoid growth

• Possible ancillary studies include: AR, PSMA, PSA*, RB, TP53 (missense mutations), PTEN, NE (CD56/Synaptophysin, Chromogranin, NSE)

Research grade

* Is it prostate???
Future (near and far)

- cfDNA
- Orgnaoids
- RNAseq from FFPE
- Proteomics/metabolomics /epigenetics
- Whole Genome Sequencing

mCRPC Workshop Part II

• Review cases from multiple studies (WCDT, IDT, and others)
• Develop blinded consensus
• Explore for clinical and molecular associations
• Representation from multiple institutions
• Develop practical guidelines for evaluation including reference images and recommendations for use of IHC & molecular studies.