Neuroendocrine Neoplasms of The Prostate
Morphologic & Molecular Features

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USA
Disclosures

• **TERT** Promoter Mutations in Urothelial Neoplasia

• **UroSEEK;CancerSEEK; PapSEEK**
  Methods and Materials for Assessing and Treating Cancer
  Patents: (US16/250,703) (PCT/US2018/045669)

• **Genentech** Advisory Pathology Board
Disclosures

J. Epstein and G. Netto
Differential Diagnosis in Genitourinary System
Overview

- Background
- WHO 2016 Classification of NE Tumors of Prostate
- Molecular Alterations in Prostate NE Neoplasms
Background

• Normal Prostate has NE cells (most among GU organs)

• Prostate NE tumors of are very rare

• IHC in “usual” prostate adenocarcinoma (PCA) will delineate scattered NE cells in almost all cases
  • No prognostic significance

• Majority of prostate NE tumors are found in association with usual PCA component

• Classifications of NE neoplasms across organs: does one size fit all?
### WHO classification of tumours of the prostate

<table>
<thead>
<tr>
<th>Epithelial tumours</th>
<th>8140/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glandular neoplasms</td>
<td></td>
</tr>
<tr>
<td>Acinar adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Atrophic</td>
<td></td>
</tr>
<tr>
<td>Pseudohyperplastic</td>
<td></td>
</tr>
<tr>
<td>Microcystic</td>
<td></td>
</tr>
<tr>
<td>Foamy gland</td>
<td></td>
</tr>
<tr>
<td>Micronodular (colloid)</td>
<td></td>
</tr>
<tr>
<td>Signet ring–like cell</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic giant cell</td>
<td></td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>8572/3</td>
</tr>
<tr>
<td>Prostatic intrastitial neoplasia, high–grade</td>
<td>8140/2</td>
</tr>
<tr>
<td>Intraductal carcinoma</td>
<td>8552/2</td>
</tr>
<tr>
<td>Ductal adenocarcinoma</td>
<td>8550/3</td>
</tr>
<tr>
<td>Cribriform</td>
<td>8201/3</td>
</tr>
<tr>
<td>Papillary</td>
<td>8200/3</td>
</tr>
<tr>
<td>Sclerotic</td>
<td>8230/3</td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>8120/3</td>
</tr>
<tr>
<td>Squamous neoplasms</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>8560/3</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
</tr>
<tr>
<td>Miscellaneous tumours</td>
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<tr>
<td>Cystadenocarcinoma</td>
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<tr>
<td>Nephroblastoma</td>
<td>8960/3</td>
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<tr>
<td>Rhabdoid tumour</td>
<td>8963/3</td>
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<tr>
<td>Germ cell tumours</td>
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<tr>
<td>Clear cell adenocarcinoma</td>
<td>8310/3</td>
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<tr>
<td>Melanoma</td>
<td>8720/3</td>
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<tr>
<td>Paraganglioma</td>
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<tr>
<td>Neuroblastoma</td>
<td>9500/3</td>
</tr>
<tr>
<td>Metastatic tumours</td>
<td></td>
</tr>
<tr>
<td>Tumours of the seminal vesicles</td>
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<tr>
<td>Epithelial tumours</td>
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<tr>
<td>Adenocarcinoma</td>
<td>8140/3</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
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</tbody>
</table>

### Neuroendocrine tumours

<table>
<thead>
<tr>
<th>Neuroendocrine tumours</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Adenocarcinoma with neuroendocrine differentiation</td>
<td>8574/3</td>
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<tr>
<td>Well-differentiated neuroendocrine tumour</td>
<td>8240/3</td>
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<tr>
<td>Small cell neuroendocrine carcinoma</td>
<td>8041/3</td>
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<td>Large cell neuroendocrine carcinoma</td>
<td>8013/3</td>
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<td>Angiosarcoma</td>
<td>9120/3</td>
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<tr>
<td>Synovial sarcoma</td>
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<tr>
<td>Inflammatory myofibroblastic tumour</td>
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<td>Cholesteatoma</td>
<td>9160/3</td>
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<td>Undifferentiated pleomorphic sarcoma</td>
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<td>Solitary fibrous tumour</td>
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<tr>
<td>Solitary fibrous tumour, malignant</td>
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<td>Hemangiomata</td>
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<td>Granular cell tumour</td>
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<td>Haematolymphoid tumours</td>
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<td>Follicular lymphoma</td>
<td>9690/3</td>
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<tr>
<td>Mantle cell lymphoma</td>
<td>9670/3</td>
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<tr>
<td>Metastatic tumours</td>
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</tr>
</tbody>
</table>

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (9174). Behaviour is coded 'S' for benign tumours, 'M' for unspecified borderline or uncertain behaviour, 'I' for carcinoma in situ, and grade '1' for intrastitial neoplasia and '2' for malignant tumours.

The classification is modified from the previous WHO classification (7664A), taking into account changes in our understanding of these lesions.
Proposed Morphologic Classification of Prostate Cancer With Neuroendocrine Differentiation

Jonathan I. Epstein, MD,*†‡ Mahul B. Amin, MD,§ Himisha Beltran, MD,‖ Tamara L. Lotan, MD,*‡
Juan-Miguel Mosquera, MD, MSc,¶## Victor E. Reuter, MD,** Brian D. Robinson, MD,¶##
Patricia Troncoso, MD,†† and Mark A. Rubin, MD¶##

Usual prostate adenocarcinoma with NE differentiation
Adenocarcinoma with Paneth cell NE differentiation
Carcinoid tumor
Small cell carcinoma
LCNEC
Mixed (small or large cell) NE carcinoma—acinar adenocarcinoma
Neuroendocrine Tumors of Prostate
WHO 2016

- Adenocarcinoma with Neuroendocrine Differentiation
- Adenocarcinoma with Paneth cells-like Neuroendocrine Differentiation
- Well differentiated Neuroendocrine Tumors (Carcinoid)
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- Large Cell Neuroendocrine Carcinoma
Typical adenocarcinoma of prostate (PCA) with NE differentiation only demonstrated on IHC

PSA(+) in usual PCA component but variable in NE cells

No PGx significance (most studies)

Not recommended to routinely use NE IHC stains in otherwise morphologically typical PCA
Proposed Morphologic Classification of Prostate Cancer With Neuroendocrine Differentiation

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Am J Surg Pathol 2014
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• Small Cell Neuroendocrine Carcinoma
• Large Cell Neuroendocrine Carcinoma
Adenocarcinoma with Paneth cells-like Neuroendocrine Differentiation

- Typical PCA with proportions of cells with **eosinophilic granules**
- SYN/Chromo (+)
- Neurosecretory granules by EM
- **Bland** cytology
- Frequently contain **cords and nests**
Prognostic Significance of Paneth Cell-like Neuroendocrine Differentiation in Adenocarcinoma of the Prostate

Ecaterina F. Tamas, MD* and Jonathan I. Epstein, MD†‡

Am J Surg Pathol 2006
36 cases
- Paneth cell-like NE patchy or diffuse
- OC: 10/16 (62.5%)
- Positive MG: 6/16 (37.5%)

- BCR free: 92%
- 5/6 “Gleason pattern 5” architecture had no evidence of progression @ 46 months

- Tumors with diffuse Paneth cell-like cells → not assigned Gleason Grade
- Comment: Favorable prognosis
Variant of prostatic adenocarcinoma with Paneth cell–like neuroendocrine differentiation readily misdiagnosed as Gleason pattern 5

Jeffrey S. So MD\textsuperscript{a}, Jennifer Gordetsky MD\textsuperscript{a}, Jonathan I. Epstein MD\textsuperscript{a,b,c,*}
Variant of prostatic adenocarcinoma with Paneth cell–like neuroendocrine differentiation readily misdiagnosed as Gleason pattern 5☆

Jeffrey S. So MD^a, Jennifer Gordetsky MD^a, Jonathan I. Epstein MD^a,b,c,*

- Nests and cords
- Deeply amphophilic cytoplasm
- Rare Paneth cell–like eosinophilic granules
- IHC : NE markers (+)
- Favorable outcome
PCA with Paneth Cell-Like Neuroendocrine Differentiation

• Bona fide higher grade component should be graded

• When reporting “Prostate cancer with Paneth cell-like neuroendocrine differentiation” clearly state **NOT** small cell carcinoma
Neuroendocrine Tumors of Prostate
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• Large Cell Neuroendocrine Carcinoma
Well Differentiated Neuroendocrine Tumor (Carcinoid)

Very Strict Definition
- Analogous morphology to carcinoid in other organs
- Originates in prostate (not urethra/bladder)
- NE markers (+) AND PSA (-)

- Only 5 cases reported !!!
Carcinoid-Like PCA
Neuroendocrine Tumors of Prostate
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- Large Cell Neuroendocrine Carcinoma (LCNEC)
Large Cell Neuroendocrine Carcinoma (LCNEC)

• Not recognized in 2004 WHO classification

• Rare neuroendocrine tumor variant (total 15 in literature)

• Largest series of 7 cases published in 2006
Large Cell Neuroendocrine Carcinoma of Prostate

A Clinicopathologic Summary of 7 Cases of a Rare Manifestation of Advanced Prostate Cancer

Andrew J. Evans, MD, PhD,* Peter A. Humphrey, MD, PhD,† Jay Belani, MD,‡ Theodorus H. van der Kwast, MD,§ and John R. Srigley, MD||

AJSP 2006
6/7 cases had history of 2-3yr hormone Rx and showed hormone Rx effect
LCNEC was incidentally diagnosed in palliative TURP in 5 cases

IHC
- Positive CD56, CD57, chromogranin A, synaptophysin and AMACR
- High (>50%) MIB1 and p53
- Focal/weak positivity for PSA and negative AR

F/U: All 6 patients died of metastatic disease within 1yr (range: 3 to 12) after platinum based ChemoRx

? Clonal progression under the selection pressure of hormonal Rx
# Large Cell Neuroendocrine Carcinoma of Prostate

A Clinicopathologic Summary of 7 Cases of a Rare Manifestation of Advanced Prostate Cancer

Andrew J. Evans, MD, PhD,* Peter A. Humphrey, MD, PhD;† Jay Belani, MD;‡ Theodorus H. van der Kwast, MD,§ and John R. Srigley, MD¶

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Initial Diagnosis</th>
<th>PSA at Initial Diagnosis (ng/mL)</th>
<th>Initial Treatment</th>
<th>Interval to LCNEC Diagnosis</th>
<th>LCNEC Diagnostic Procedure</th>
<th>PSA at LCNEC Diagnosis (ng/mL)</th>
<th>Chemotherapy After LCNEC Diagnosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>Gleason 10/10; TURP 1998</td>
<td>N/A</td>
<td>ADT(^<em>(\times 3 \text{ y})</em>)</td>
<td>3y</td>
<td>TURP (urinary obstruction and hematuria)</td>
<td>3.66</td>
<td>Palliative mitoxantrone</td>
<td>DOD; bone, lymph nodes, mets</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>Gleason 7/10; Needle biopsy 1998</td>
<td>10.5</td>
<td>WW ((\times 3 \text{ y}) then ADT(\times 2 \text{ y}))</td>
<td>5y</td>
<td>TURP (urinary obstruction)</td>
<td>&lt; 0.05</td>
<td>Carboplatin, VA-16</td>
<td>DOD; lung, liver, brain, mets</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>Needle biopsy 1989</td>
<td>N/A</td>
<td>RP (ADT(\times 2 \text{ y}) post-RP)</td>
<td>12y</td>
<td>Biopsy of pelvic mass</td>
<td>N/A</td>
<td>N/A</td>
<td>Palliative XRT Lost to F/U</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>Gleason 7/10; Needle biopsy 1992</td>
<td>23.2</td>
<td>ADT(\times 2 \text{ y})</td>
<td>4y</td>
<td>TURP (urinary obstruction)</td>
<td>&lt; 0.2</td>
<td>Carboplatin, VP-16</td>
<td>DOD; bone mets</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>Gleason 8/10; Needle biopsy 1997; positive lymph nodes</td>
<td>29.7</td>
<td>ADT(\times 2 \text{ y})</td>
<td>2y</td>
<td>TURP (urinary obstruction)</td>
<td>&lt; 0.2</td>
<td>Carboplatin, VP-16</td>
<td>DOD; bone mets</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>Gleason 5/10; Needle biopsy 1996 – no mention of NE differentiation</td>
<td>4.3</td>
<td>RP; de novo LCNEC</td>
<td>de novo LCNEC</td>
<td>de novo LCNEC</td>
<td>&lt; 0.1</td>
<td>Carboplatin, VP-16</td>
<td>DOD; pelvic mass post-RP and brain mets</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>Gleason 8/10; Needle biopsy 19; positive lymph nodes</td>
<td>68.0</td>
<td>ADT(\times 2 \text{ y})</td>
<td>2y</td>
<td>TURP (urinary obstruction)</td>
<td>9.90</td>
<td>Palliative mitoxantrone</td>
<td>DOD; bone mets</td>
</tr>
</tbody>
</table>
Morphology
• Solid sheets/ribbons
• Abundant amphophilic cytoplasm
• Large nuclei with coarse chromatin
• Prominent nucleoli
• Brisk mitotic activity
• Necrosis
De novo large cell neuroendocrine carcinoma of the prostate, case report and literature review

Gabriel Acosta-Gonzalez¹, Jia Qin², Rosemary Wieczorek²,³, Jonathan Melamed¹, Fang-Ming Deng¹, Ming Zhou¹, Danil Makarov⁴, Fei Ye⁵, Zhiheng Pei³, Matthew R Pincus²,³, Peng Lee¹,³,⁴
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- Small Cell Neuroendocrine Carcinoma
- Large Cell Neuroendocrine Carcinoma
Small Cell Neuroendocrine Carcinoma (SCC)

• Unique histological, immunohistochemical & clinical features

• Differs from Gleason pattern 5 PCA

Should not be assigned Gleason Grade
NCCN Guidelines Version 3.2018
Prostate Cancer

**SYSTEMIC THERAPY FOR M1 CRPC**

- Small cell
  - Consider brain MRI with and without contrast

- Visceral metastases
  - Consider biopsy

- Adenocarcinoma
  - Docetaxel\(^{mm}\) (category 1)
  - Enzalutamide\(^{f}\) (category 1)
  - Abiraterone\(^{f}\) with prednisone
  - Clinical trial
  - Mitoxantrone with prednisone\(^{mm,uu}\)
  - Other secondary hormone therapy\(^{f}\)

**SUBSEQUENT THERAPY**

- Chemotherapy
  - Cisplatin/etoposide\(^{mm,xx}\)
  - Carboplatin/etoposide\(^{mm,xx}\)
  - Docetaxel/etoposide\(^{mm,xx}\)
  - Clinical trial

- Docetaxel\(^{mm}\) (category 1)
  - If not previously received:
    - Abiraterone\(^{f}\) with prednisone
    - Enzalutamide\(^{f}\)
  - Pembrolizumab for MSI-H or dMMR (category 2B)
  - Clinical trial
  - Other secondary hormone therapy\(^{f}\)
  - Best supportive care

**Prior therapy enzalutamide/abiraterone\(^{ss}\)**

- Progression\(^{dd}\)
  - Prior therapy docetaxel

**Prior therapy abiraterone\(^{f}\)**

- Abiraterone\(^{f}\) with prednisone (category 1)
- Cabazitaxel\(^{mm}\) (category 1)
- Pembrolizumab for MSI-H or dMMR (category 2B)
- Clinical trial
- Docetaxel rechallenge
- Mitoxantrone with prednisone\(^{mm,uu}\)
- Other secondary hormone therapy\(^{f}\)
- Best supportive care

---

\(^{f}\) See Principles of Androgen Deprivation Therapy (PROS-F).

\(^{dd}\) Workup for progression should include chest x-ray or chest CT, bone imaging.
Clinical/Demographic Features

- 95 cases
- Patient age (44 - 92 years old; mean: 69 y)
- Median serum PSA 4.0 ng/mL (up to 1896 ng/mL)

- Advanced stage at diagnosis: >90% stage T3 & T4
- Soft tissue/visceral and osteolytic bone mets
- Castration resistant
- Platinum based ChemoRX

- Most SCC lack paraneoplastic symptoms
  - majority of prostate ca with clinically evident ACTH and ADH hormone production are SCC
Small Cell Carcinoma (SCC)

Morphology

- Classic “oat cell” (64%)
  - High N/C
  - High mitotic activity
  - Nuclear molding
  - Necrosis (geographic and/or apoptosis)

- “intermediate cell” variant

- Other features
  - Giant bizarre cells
  - Indian filing
  - Rosette/glandular/tubular formation
  - Desmoplasia
SCC
“intermediate” variant
SCC
“intermediate” variant
SCC
“intermediate” variant
SCC
“intermediate” variant
DDx

SCC vs 5+5=10
5 + 5 = 10
5+5=10
Majority (88%) expresses at least 1 neuroendocrine marker (SYN, CHROM, CD56)

Prostate differentiation markers in SCC component:
- 19% positive PSA
- 28% positive P501s
- 25% positive PSMA
- 60% of cases NEG for all 3

TTF-1 positive in 50% of cases

Ki67 High (>70%)
Relation to Adenocarcinoma (PCA)

• **Prior** diagnosis of PCA in up to 35% of cases; median 18-50 months before SCC

• **Pure SCC** in 70% cases at diagnosis

• **Mixed** small and acinar adenocarcinoma (30%)
  • SCC component is **dominant** (80% of the tumor)
  • **Gleason score ≥ 8** in 85% of cases
  • two components **intermixed** in majority of cases
SCC with Challenging/Equivocal Morphology
Prostatic NE Neoplasms Pathogenesis

- Practically **ALL PCA** have NE cells (including **PIN**)

- NE cells in usual PCA are the origin of NE Neoplasms

- Castrate Resistant Prostate Carcinoma (**CRPC**)  
  - Clonal progression under selective pressure of hormonal Rx

- Majority originates through **trans-differentiation** from usual PCA

Fine S. Mod Path 2018
The Molecular Taxonomy of Primary Prostate Cancer


- Comprehensive molecular analysis of 333 primary prostate carcinomas
- Seven subtypes defined by ETS fusions or mutations in SPOP, FOXA1, and IDH1
- Substantial epigenetic heterogeneity, including a hypermethylated IDH1 mutant subset
- Presumed actionable lesions in the PI3K, MAPK, and DNA repair pathways
Prostatic NE Neoplasms
Molecular Alterations

• *TMRSS2-ERG/ETS Fusion* (50%)
• *PTEN* loss

• *AR* mutations and amplifications

• *MYCN* amplification (65-86%)
• *AURKA* amplification
  • PGx/ Target of Rx
  • PCA with Paneth-Like Cell NE differentiation
    (45% express *AURKA*)

• *TP53* mut (60%)
• Expression of Stem Cell markers *NANOG / POU5F1 / SOX2*
Rb Loss Is Characteristic of Prostatic Small Cell Neuroendocrine Carcinoma

Hsueh-Li Tan¹, Akshay Sood¹, Hameed A. Rahimi¹, Wenle Wang¹, Nilesh Gupta², Jessica Hicks¹, Stacy Mosier¹, Christopher D. Gocke¹,³, Jonathan I. Epstein¹,³,⁴, George J. Netto¹,³,⁴, Wennuan Liu⁵, William R. Isaacs³,⁴, Angelo M. De Marzo¹,³,⁴, and Tamara L. Lotan¹,³

Clin Cancer Res 2013
Cyclin D1 Loss Distinguishes Prostatic Small Cell Carcinoma from Most Prostatic Adenocarcinomas

Harrison Tsai¹, Carlos L. Morais¹, Mohammed Alshalahfa², Hsueh-Li Tan¹, Zaid Haddad², Jessica Hicks¹, Nilesh Gupta³, Jonathan I. Epstein¹,4,5, George J. Netto¹,4,5, William B. Isaacs⁴,5, Jun Luo⁵, Rohit Mehra⁶, Robert L. Vessella⁷, R. Jeffrey Karnes⁸, Edward M. Schaeffer⁴,5, Elai Davicioni², Angelo M. De Marzo¹,4,5, and Tamara L. Lotan¹,4
### Table 1: Overview of Clinicopathologic Characteristics of PD-L1—Positive and PD-L1—Negative Tumors

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>PD-L1−</th>
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<th>PD-L1+</th>
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</thead>
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<tr>
<td></td>
<td>Cases, n</td>
<td>n</td>
<td>%</td>
<td>n</td>
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<td><strong>Primary tumors</strong></td>
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<tr>
<td>Acinar adenocarcinoma</td>
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<td>469</td>
<td>92.3</td>
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<td>Grade group</td>
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<td><strong>Stage</strong></td>
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<td>T2</td>
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<td>T3B</td>
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<td><strong>Lymph node status</strong></td>
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<td>428</td>
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<td>N1</td>
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<td>32</td>
<td>7.0</td>
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<td><strong>Prostatic duct adenocarcinoma</strong></td>
<td>24</td>
<td>20</td>
<td>83.3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Small cell carcinoma</strong></td>
<td>7</td>
<td>4</td>
<td>57.1</td>
<td>3</td>
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<tr>
<td><strong>Distant metastases (mCRPC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rapid autopsies</td>
<td>29</td>
<td>20</td>
<td>69</td>
<td>9</td>
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<tr>
<td>Biopsies</td>
<td>28</td>
<td>19</td>
<td>67.9</td>
<td>9</td>
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Comprehensive Evaluation of Programmed Death-Ligand 1 Expression in Primary and Metastatic Prostate Cancer

CONCLUSIONS

- Prostate NE tumors are rare but important variants to recognize given their unique management implications

- Morphology should trigger the diagnosis and work up (NE markers)
- Loss of PSA/NKX3.1/p501S
- IHC should not be performed in “usual” PCA (lacks PGx role)

- Loss of CyclinD1 and RB1 with p16 expression are helpful when traditional NE markers are non contributory

Merci Beaucoup!
Prostatic Carcinoma with Diffuse NE Differentiation

- Tumors do not fit other categories: WDNEC/SCC/LCNEC
- Overlapping features of SCC and Gleason Pattern 5
- “Amphicrine carcinoma” cytologic but not architectural features of LCNEC and co-expressing PSA and NE markers
Neuroendocrine tumors of the prostate

Samson W Fine

Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Modern Pathology (2018) 31, S122–S132
2016 WHO classification of prostatic neuroendocrine tumors

- Adenocarcinoma with neuroendocrine differentiation
- Adenocarcinoma with Paneth cell-like neuroendocrine differentiation
- Well-differentiated neuroendocrine tumor (carcinoid tumor)
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (9174). Behaviour is coded (5) for benign tumours. (1) for unspecified, benign, or uncertain behaviour, (2) for carcinoma in situ, and grade (3) for infiltrative neoplasms and (4) for malignant tumours. The classification is modified from the previous WHO classification (7564A), taking into account changes in our understanding of these lesions.
Variant of prostatic adenocarcinoma with Paneth cell–like neuroendocrine differentiation readily misdiagnosed as Gleason pattern 5:

Jeffrey S. So MD*, Jennifer Gordskys MD, Jonathan I. Epstein MD

*Human Pathology (2014) 45, 2388–2393

Tumor conventionally would have resulted in assigning a Gleason pattern 5 for the primary or secondary pattern. Ten cases were entirely composed of the Paneth cell–like component. Architectural patterns included the following: nest and cord–like architecture (n = 4; 36.4%), nests only (n = 6; 54.5%), and cords only (n = 1; 9.1%). All 11 cases had amphophilic cytoplasm. Among the 11 cases, 7 had rare granules, 1 had 10% of the cells with granules, and 3 had no granules. Within the Paneth cell–like feature component, rare nucleolar prominence was seen in only 4 (36.4%) of 11 cases. Eight cases were diffusely positive for chromogranin and synaptophysin, 2 for chromogranin only, and 1 for synaptophysin only. In the 3 cases where performed, Ki-67 showed a very low rate of less than 5%. The keys to recognizing these cases are as follows: (1) nests and cords in a small focus, (2) deeply amphophilic cytoplasm with careful search in most cases revealing rare Paneth cell–like eosinophilic granules, (3) indistinct nucleoli, and (4) immunohistochemical staining for neuroendocrine markers. Based on follow-up from prior studies and the current work, these tumors appear to have a favorable prognosis. The importance of recognizing this variant of adenocarcinoma with Paneth cell–like differentiation is that if