Neuroendocrine differentiation of prostate cancer

prof. dr. Louis Libbrecht
Department of Pathology
Cliniques Universitaires Saint-Luc, UCLouvain
Brussels, Belgium

BAU 2018, Terhulpen-La Hulpe

Neuroendocrine (NE) differentiation in prostate carcinoma in different settings

- Neuroendocrine cells in non-cancerous prostate.
- Usual (acinar) prostatic adenocarcinoma with neuroendocrine differentiation.
- Prostatic adenocarcinoma with Paneth cell-like neuroendocrine differentiation.
- Carcinoid tumor.

- Small cell NE carcinoma.
- Intermediate atypical prostate cancer (IAC).
- Mixed acinar-neuroendocrine carcinoma.
- Large cell NE carcinoma.

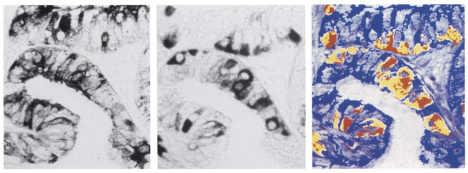


FIGURE 2. Hyperplasia with numerous EP cells. Sequential immunohistochemical demonstration of PSA (left) and ChrA (middle). In the final image PSA deposits appear blue, ChrA appears red, and co-expression of the two antigens appears yellow. (Magnification ×300.)

Basal localisation, between secretory cells.

Within the genitourinary tract, most frequent in prostate.

Most sensitive marker: synaptophysine; normal NE cells are AR negative

Bonkhoff et al. Hum Pathol 1994;25:42-46

Gleason 3+3 usual acinar adenocarcinoma, untreated: 50% of tumoral cells are synaptophysin positive

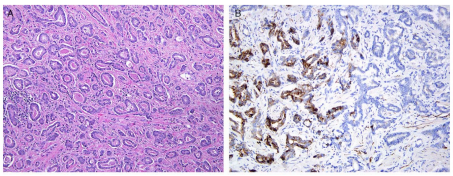


FIGURE 1. A, Adenocarcinoma of the prostate Gleason score 3+3=6. B, Same case as (A) with areas showing positivity for synaptophysin (left) that are indistinguishable in their glandular morphology from areas that are synaptophysin negative (right).

Neuroendocrine differentiation in usual acinar prostatic adenocarcinoma

- Usual acinar carcinoma shows variable, sometimes extensive, positivity for synaptophysin and chromogranine!
- Doing synapto/chromo stainings without considering the morphological features and setting is useless and dangerous.
- **Risk of miscommunication**: clinician asks: is there expression of NE markers? Pathologists does synapto/chromo which is positive and answers: yes. Clinicians concludes this is an aggressive tumor, related to therapy-resistance.

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¶#*

Summary: Currently, as the clinical significance remains uncertain, it is not recommended to routinely use IHC stains to detect any NE differentiation in an otherwise morphologically typical primary adenocarcinoma of the prostate.

AJSP 2014 and current WHO

Adenocarcinoma with Paneth cell-like neuroendocrine differentiation

- Paneth cell-like areas (variable %) can be found in approx. 10% of usual prostatic adenocarcinoma.
- Eosinophilic/amphohilic cells with variable granules, positive for NE markers.
- Considered as low-grade NE differentiation, with favorable prognosis. Cave incorrect scoring as Gleason 5.
- However, recent data show that this tumor type is frequently associated with AURKA amplification, which is also seen in the treatment-resistance setting of NE differentiation towards small cell carcinoma. Meaning unclear.

Paneth Cell-like Change in Prostatic Adenocarcinoma Represents Neuroendocrine Differentiation:

Report of 30 Cases

HARKIRAN ADLAKHA, MD, AND DAVID G. BOSTWICK, MD

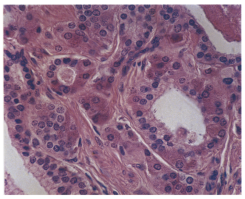


FIGURE 1. Paneth cell-like change in prostatic adenocarcinoma (case no. 20). Note the variable intensity of the eosinophilic granularity in neoplastic cells.

Hum Pathol 1994

Human Pathology (2014) **45**, 2388–2393

ELSEVIER

PAT

www.elsevier.c

Original contribution

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,*]

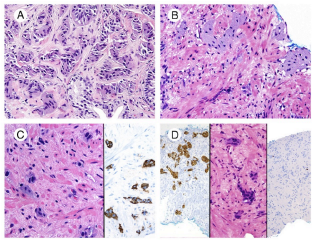


Fig. 2 A, Cords of adenocarcinoma of the prostate with deeply amphophilic cytoplasm lacking eosinophilic granules (hematoxylin and eosin [H&E], ×20). B, Adenocarcinoma with Paneth cell–like change with deeply amphophilic cytoplasm lacking eosinophilic granules and bland nuclei (H&E, ×40). C, Adenocarcinoma with Paneth cell–like change composed of small nests of cells with bland cytology and dense amphophilic cytoplasm (left) and diffuse synaptophysin positivity (right). Left: H&E, ×60; right: synaptophysin, ×60. D, Adenocarcinoma with Paneth cell–like change composed of small nests of cells with bland cytology and dense amphophilic cytoplasm (center), diffuse synaptophysin positivity (left), and low Ki-67 rate (right). Left: synaptophysin, ×20; center: H&E, ×60; right: Ki-67, ×20.

Human Pathology (2014) **45**, 2136–2143

ELSEVIER

PATH

www.elsevier.com

Original contribution

Prostate cancer with Paneth cell–like neuroendocrine differentiation has recognizable histomorphology and harbors *AURKA* gene amplification☆,☆☆,☆☆☆

Kyung Park MD[a], Zhengming Chen PhD[b], Theresa Y. MacDonald BS[a], Javed Siddiqui MS[c,d], Huihui Ye MD[e,f], Andreas Erbersdobler MD[g], Maria M. Shevchuk MD[a], Brian D. Robinson MD[a,h,i], Martin G. Sanda MD[f,j], Arul M. Chinnaiyan MD, PhD[c,d], Himisha Beltran MD[i,k], Mark A. Rubin MD[a,i], Juan Miguel Mosquera MD, MSc[a,i,*]

Carcinoid tumor of the prostate

- Supposed to be prostatic counterpart of typical carcinoid of the lung and well-differentiated neuroendocrine tumor (NET) of the pancreas, etc…
- Extremely rare. Maybe does not exist? Most reported cases represent likely Paneth cell-like change in prostate cancer.
- Rare cases in young patients with MEN syndroma might be bona fide.

Small cell neuroendocrine carcinoma of the prostate: definition

- Typical morphological features (next slide). De novo and in the setting of resistance to AR-targeted therapy.
- Synaptophysin IHC is positive, but sometimes focal and weak, **less than in usual prostatic carcinoma!**
- « **Plasticity gain** » phenotype: aberrant retinoblastoma (pRB) and p53 IHC.
- Luminal marker expression decreases to zero: PSA, AR, NKX3.1 and ERG, **but if TMPRSS2-ERG fusion was present, it remains!**

Tumor type	Adenocarcinoma	SCNC
Cytoplasm	Abundant	Scant
Nuclear chromatin	Clumpy, vacuolated, open chromatin pattern	Fine homogeneous chromatin pattern
Nuclear staining	Light	Dark
Nuclear shape	Some degree of irregularity	Irregular
Nuclear molding	No	Yes
Nucleoli	Prominent macronucleoli	No nucleoli
Crush artifact	No	Yes
Mitotic figures	Rare	Common
Glandular formation	Obvious	No

Aggarwal et al. JCO 2018;36:2492

Development of small cell NE carcinoma: gain of plasticity and neuronal transdifferentiation

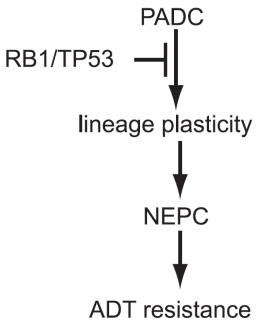
- Small cell carcinoma, probably also de novo cases, arise from transdifferentiation of a tumoral luminal cell, not from normal NE cells.
- **Gain of plasticity** is followed by development of full small cell NE phenotype, **AR indifferent.**
- De novo/primary presentation is rare; prevalence increased in recent times in relation to «escape» from (newer) ARPI treatments.

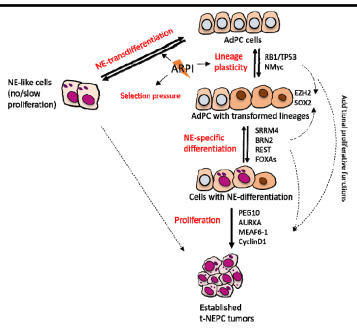
Rb1 and *Trp53* cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance

Sheng Yu Ku,[1*] Spencer Rosario,[1*] Yanqing Wang,[1] Ping Mu,[2] Mukund Seshadri,[1] Zachary W. Goodrich,[1] Maxwell M. Goodrich,[1] David P. Labbé,[3,4] Eduardo Cortes Gomez,[5] Jianmin Wang,[5] Henry W. Long,[3,4] Bo Xu,[6] Myles Brown,[3,4] Massimo Loda,[4,7,8,9] Charles L. Sawyers,[2,10] Leigh Ellis,[1†] David W. Goodrich[1†]

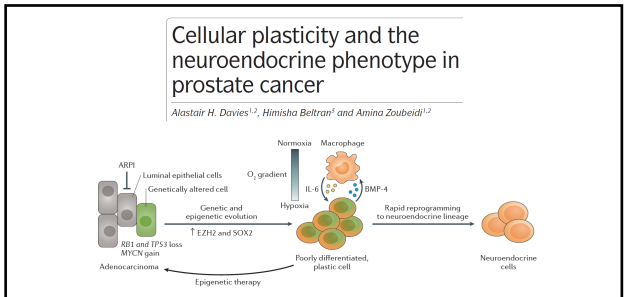
Prostate cancer relapsing from antiandrogen therapies can exhibit variant histology with altered lineage marker expression, suggesting that lineage plasticity facilitates therapeutic resistance. The mechanisms underlying prostate cancer lineage plasticity are incompletely understood. Studying mouse models, we demonstrate that *Rb1* loss facilitates lineage plasticity and metastasis of prostate adenocarcinoma initiated by *Pten* mutation. Additional loss of *Trp53* causes resistance to antiandrogen therapy. Gene expression profiling indicates that mouse tumors resemble human prostate cancer neuroendocrine variants; both mouse and human tumors exhibit increased expression of epigenetic reprogramming factors such as Ezh2 and Sox2. Clinically relevant Ezh2 inhibitors restore androgen receptor expression and sensitivity to antiandrogen therapy. These findings uncover genetic mutations that enable prostate cancer progression; identify mouse models for studying prostate cancer lineage plasticity; and suggest an epigenetic approach for extending clinical responses to antiandrogen therapy.

Science 2017

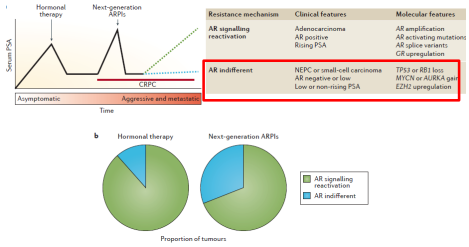




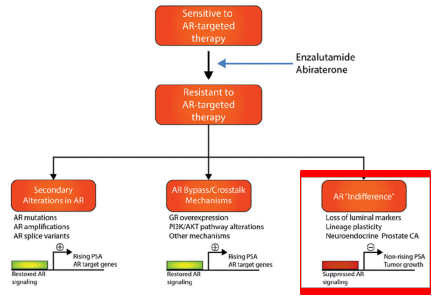
Chen et al. BJU Int 2018;4:560



Davies et al. Nat Rev Urol 2018;15:271



Davies et al. Nat Rev Urol 2018;15:271



Vlachostergios et al. Curr Oncol Rep 2017;19:32

Intermediate atypical prostate cancer

- No uniform definition yet, but important concept.
- Carcinoma « on its way » to small cell NE carcinoma; in the process of transdifferentiation.
- Should show aberrant p53 and pRB pattern on IHC.
- Morphologically intermediate between adenocarcinoma and small cell carcinoma.
- See JCO abstracts, ASCO meetings 2015 and 2016.

Clinical and genomic characterization of metastatic small cell/neuroendocrine prostate cancer (SCNC) and intermediate atypical prostate cancer (IAC): Results from the SU2C/PCF/AACRWest Coast Prostate Cancer Dream Team (WCDT).

Eric Jay Small, Rahul Raj Aggarwal, Jiaoti Huang, Artem Sokolov, Li Zhang, Joshi J. Alumkal, ...
Show More

Abstract Disclosures

Abstract

5019

Background: SCNC and a novel pathologic subtype, IAC, comprise a growing proportion of mCRPC patients resistant to androgen signaling inhibitors such as Abiraterone (Abi) or Enzalutamide (Enz). We sought to characterize these non-adenocarcinoma (adeno) subtypes in a prospective biopsy study. **Methods:** Eligible mCRPC pts underwent a metastasis biopsy (bx), and were followed for clinical outcomes. Tissue was both frozen and formalin fixed/paraffin embedded (FFPE). Independent review of FFPE specimens was undertaken by 3 pathologists. Frozen specimens underwent laser capture micro-dissection prior to RNA sequencing (seq). Machine learning was used to derive histology-specific expression signatures. Signature accuracy was evaluated with leave-pair-out cross-validation and application to an independent data set. **Results:** 226 of 300 planned mCRPC pts (74% resistant to Abi and/or Enz) have undergone bx (including 123 bone, 61 node, and 23 liver bx) with a 78% evaluable biopsy rate. Adeno was identified in 39%, non-adeno in 41% (SCNC in 12%, IAC in 29%), with other mixtures in the remaining 20%. Median overall survival (OS) from time of biopsy for pts with non-adeno histologies was 12.8 months (mos) [IAC OS = 19.1 mos; SCNC OS = 12.8 mos] versus 25.8 mos in adeno pts (n=93). RNAseq data are available from 92 bx

Mixed acinar-neuroendocrine carcinoma

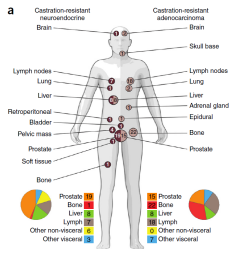
- Abrupt transition, mixture of two populations: NE carcinoma + acinar adenocarcinoma.
- Can be primary/de novo and secondary/treatment resistant setting.
- Unclear why transdifferentiation is sometimes gradually (intermediate atypical carcinoma) and sometimes abrupt (mixed carcinoma).

Small cell NE carcinoma: other molecular features

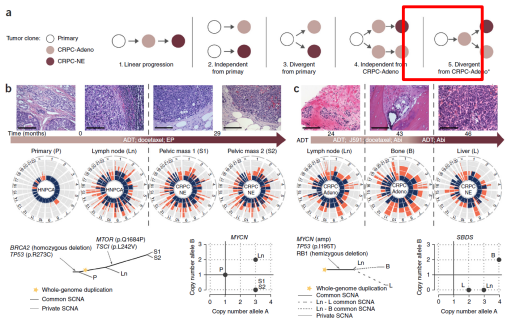
- Upregulation of **EZH2**, SOX2, FOXA2, POU3F2, PDX1,...
- NMYC and AURKA copy number gain.
- No genomic alterations in the DNA repair pathway.
- **Epigenetic modifications (methylation)** play an important role.
- Evolution from adenocarcinoma to small cell NE is divergent clonal.

Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer

Himisha Beltran[1–3,11], Davide Prandi[4,11], Juan Miguel Mosquera[1,2], Matteo Benelli[4], Loredana Puca[1], Joanna Cyrta[1], Clarisse Martin[1], Eugenia Giannopoulou[4], Balabhadrapatruni V S K Chakravarthi[1], Sooryanarayana Varambally[5], Scott A Tomlins[6], David M Nanus[2,3], Scott T Tagawa[2,3], Eliezer M Van Allen[4,10], Olivier Elemento[3,8], Andrea Sboner[1,3,11], Levi A Garraway[4,10,12,13], Mark A Rubin[1,3,5,13] & Francesca Demichelis[1,4,11,14]

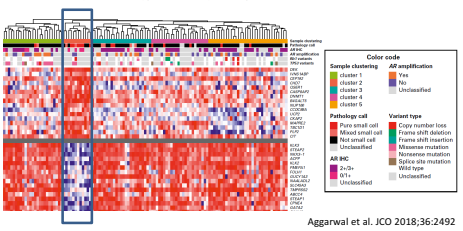


Nat Med 2016



Clinical and Genomic Characterization of Treatment-Emergent Small-Cell Neuroendocrine Prostate Cancer: A Multi-institutional Prospective Study

Rahul Aggarwal, Jiaoti Huang, Joshi J. Alumkal, Li Zhang, Felix Y. Feng, George V. Thomas, Alana S. Weinstein, Verena Friedl, Can Zhang, Owen N. Witte, Paul Lloyd, Martin Gleave, Christopher P. Evans, Jack Youngren, Tomasz M. Beer, Matthew Rettig, Christopher K. Wong, Lawrence True, Adam Foye, Denise Playdle, Charles J. Ryan, Primo Lara, Kim N. Chi, Vlado Uzunangelov, Artem Sokolov, Yulia Newton, Himisha Beltran, Francesca Demichelis, Mark A. Rubin, Joshua M. Stuart, and Eric J. Small



Aggarwal et al. JCO 2018;36:2492

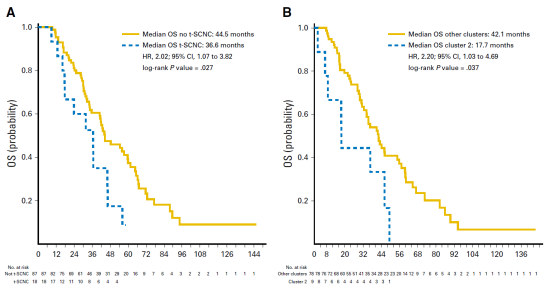


Table 1. Patient Demographics and Clinical Characteristics

Demographic or Characteristic	Total Cohort (N = 202)	Small Cell (n = 27)	Not Small Cell (n = 133)	Inevaluable (n = 42)	P
Metastatic sites of disease at time of biopsy					
Liver	35 (17)	8 (30)	22 (17)	5 (12)	.112 (liver *v* no liver)
Other visceral	38 (19)	4 (15)	29 (22)	5 (12)	
Bone/node only	130 (64)	15 (56)	82 (62)	32 (76)	.257 (overall)
Laboratory values					
PSA, ng/mL	49.5 (0.4-1,657)	64.8 (0.4-1,500)	46.2 (0.4-1,657)	46.0 (0.5-1,444)	.938
Alkaline phosphatase, U/L	96 (20-1,506)	146 (55-1,506)	94 (36-996)	99 (20-1,079)	.212
LDH, IU/L	203 (31-2,643)	235 (150-1,284)	199 (31-2,643)	205 (129-856)	.039
Hemoglobin, g/dL	12.5 (7.8-16.1)	12.5 (8.9-14.4)	12.6 (7.8-16.1)	12.4 (8.0-15.9)	.439
NSE, ng/mL	7.8 (1-90)	11.6 (5-90)	7.1 (1-83)	7.1 (1-79)	< .001
CGA, ng/mL	6.3 (1-198)	7.8 (1-70)	6.0 (1-198)	6.5 (1-23)	.977

core (Fig 2; Data Supplement). The percentage of t-SCNC in the seven mixed cases ranged from 20% to 80%. Detection of t-SCNC was observed at similar proportions by biopsy site, including 14%, 19%, and 14% of evaluable liver, lymph node, and bone metastases, respectively ($P = .76$).

Poly-metastatic patient in the CRPC-setting

- A metastatic site can show any of the following and combinations thereof: acinar adca, intermediate ca, mixed adca-NE and small cell NE.
- There is no strong evidence that a specific organ (bone, visceral,…) is related to one of the tumor types above.
- How to detect the small cell NE? Which metastatic site(s) has to be biopsied? Role of serology and imaging (PSMA, SSTR2?)???

Endocr Relat Cancer. 2018 Oct 1. pii: ERC-18-0226.R3. doi: 10.1530/ERC-18-0226. [Epub ahead of print]

Neuroendocrine differentiation of prostate cancer leads to PSMA suppression.

Bakht MK[1], Derecichei I[2], Li YJ[3], Ferraiuolo RM[4], Dunning MJ[5], Oh SW[6], Hussein A[7], Youn H[8], Stringer KF[9], Jeong CW[10], Cheon GJ[11], Kwak C[12], Kang KW[13], Lamb A[14], Wang Y[15], Dong X[16], Porter L[17].

Author information

Abstract

Prostate-specific membrane antigen (PSMA) is overexpressed in most prostate adenocarcinoma (AdPC) cells and acts as a target for molecular imaging. However, some case reports indicate that PSMA-targeted imaging could be ineffectual for delineation of neuroendocrine (NE) prostate cancer (NEPC) lesions due to the suppression of the PSMA gene (FOLH1). These same reports suggest that targeting somatostatin receptor type 2 (SSTR2) could be an alternative diagnostic target for NEPC patients. This study evaluates the correlation between expression of FOLH1, NEPC marker genes and SSTR2. We evaluated the transcript abundance for FOLH1 and SSTR2 genes as well as NE markers across 956 tumors. A significant suppression of FOLH1 in NEPC patient samples and AdPC samples with high expression of NE marker genes was observed. We also investigated protein alterations of PSMA and SSTR2 in an NE-induced cell line derived by hormone depletion and lineage plasticity by loss of p53. PSMA is suppressed following NE induction and cellular plasticity in p53-deficient NEPC model. The PSMA-suppressed cells have more colony formation ability and resistance to enzalutamide treatment. Conversely, SSTR2 was only elevated following hormone depletion. In 18 NEPC patient-derived xenograft (PDX) models we find a significant suppression of FOLH1 and amplification of SSTR2 expression. Due to the observed FOLH1-supressed signature of NEPC, this study cautions on the reliability of using PMSA as a target for molecular imaging of NEPC. The observed elevation of SSTR2 in NEPC supports the possible ability of SSTR2-targeted imaging for follow-up imaging of low-PSMA patients and monitoring for NEPC development.

A few words on de novo small cell NE cancer

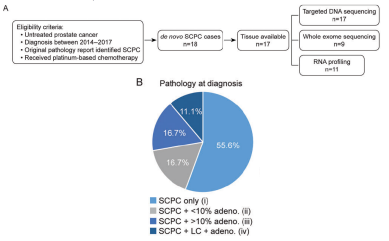
- As for secondary cases, cellular plasticity (p53 and pRB loss) and transdifferentiation also apply.
- Primary and secondary small cell NE cancer has similar RNA profile.
- Frequently presence of intermediate cancer, mixed acinar-NE carcinoma, as in secondary tumors.
- In contrast with secondary small cell NE carcinoma, primary small cell NE carcinoma often shows **involvement of DNA repair genes.**

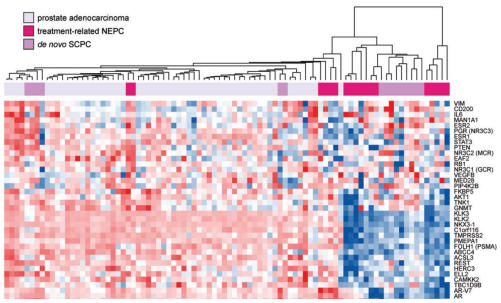
Journal of Pathology
J Pathol 2018; 246: 444–253
Published online 28 August 2018 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.5137

ORIGINAL PAPER

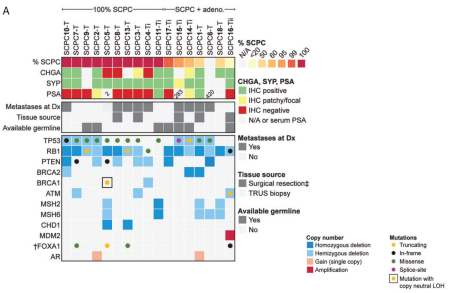
Biallelic tumour suppressor loss and DNA repair defects in *de novo* small-cell prostate carcinoma

Edmund CP Chedgy[1], Gillian Vandekerkhove[1], Cameron Herberts[1], Matti Annala[1], Adam J Donoghue[1], Michael Sigouros[2], Elie Ritch[1], Werner Struss[1], Saki Konomura[1], Janet Liew[1], Sunil Parimi[1], Joanna Vergidis[1], Antonio Hurtado-Coll[1], Andrea Sooner[1], Ladan Fazli[1], Hirotsku Beltran[3], Kim N Chi[1] and Alexander W Wyatt[1]*





DNA repair genes affected



Large cell neuroendocrine carcinoma

- Much rarer than small cell NE carcinoma.
- Frequently mixed with adca (mixed adca-NE carcinoma).
- Sometimes difficult to determine whether a NE carcinoma is small or large, so this is also a setting in which « intermediate type » is used!
- Otherwise, probably very similar to small cell NE in all aspects, but very little data.

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 Bolani, MD,‡ Theodorus H. van der Kwast, MD,§ and John R. Srigley, MD†*

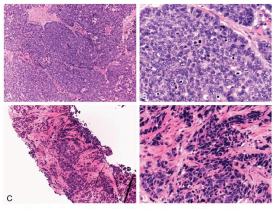


FIGURE 1. Typical hematoxylin and eosin morphology of LCNEC of prostate. A, Solid sheets, ribbons, and nests of cells with areas of peripheral palisading. B, Tumor cells with large, hyperchromatic nuclei with coarse chromatin, and visible nucleoli and pale to amphophilic cytoplasm. C, Typical features of small cell carcinoma of prostate in a representative needle core biopsy are shown for purposes of contrast with LCNEC. D, Small cell carcinoma with small to medium-sized cells with scanty cytoplasm, nuclear molding, and hyperchromatic nuclei with inconspicuous nucleoli.

Am J Surg Pathol 2006

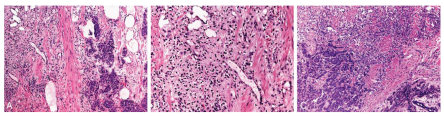
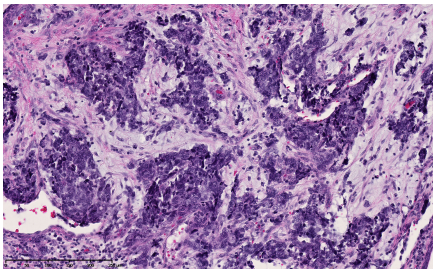


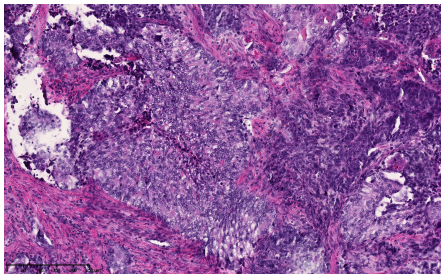
FIGURE 2. A, Admixed foci of conventional prostatic adenocarcinoma showing the morphologic changes expected with ADT. B, Conventional prostatic adenocarcinoma with ADT effects characterized by sheets of tumor cells with clear cytoplasm and shrunken, hyperchromatic nuclei with no nucleoli. C, Transitional areas between LCNEC and conventional carcinoma with ADT effects characterized by poorly formed acinar structures lined by cells with hybrid features.

Some examples

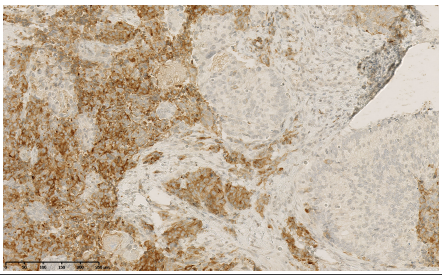
Male, 80 y (17H4852/CW8250E): typical small cell NE carcinoma morphology in a tumor in the ureter in 2017



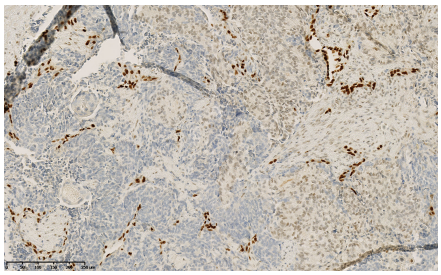
Right part: typical small cell picture
Left: other aspect: too much cytoplasm



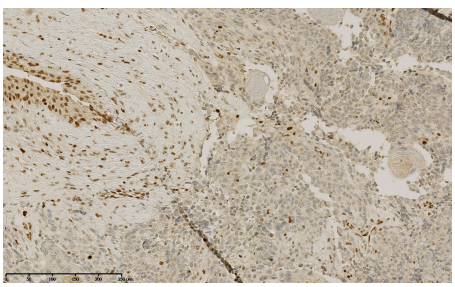
Left part: typical small cell area is synapto+
Right part: other area is synapto-



Left part: typical small cell area is ERG-
Right part: other area faintly ERG+



Both parts show pRB loss

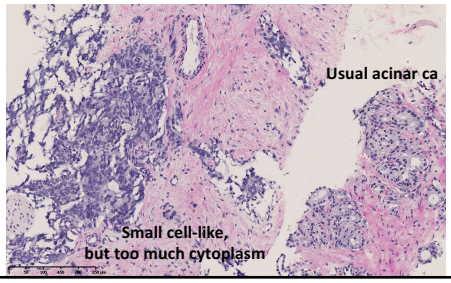


The findings suggest **acinar prostatic carcinoma transformed into small cell NE carcinoma in an ureteral metastasis, with a small «residu» of the original acinar carcinoma with intermediate features.**

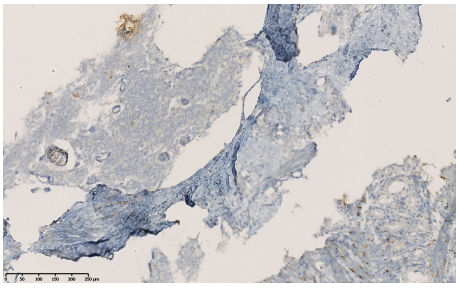
Prostate biopsy 2014:
acinar adenocarcinoma
Additional stainings in 2017 on the 2014 biopsy:
synapto-, ERG strongly+ and loss of pRB.

In 2014 patient was already metastatic and under treatmant with Firmagon and Taxotere.

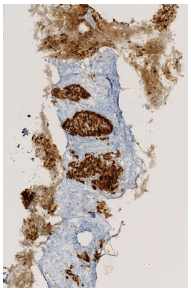
Male, 78 y (17H33905/Mons): prostate biopsies, PSA 83 and bone mets on imaging



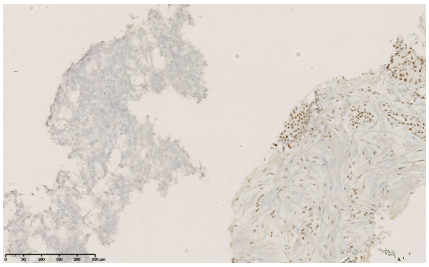
Synapto very faint and focal in the « small cell-like » part



Diffuse overexpression of p53



Loss of pRB (normal glands as internal control on the right)



A small part of this tumor shows classic acinar carcinoma.

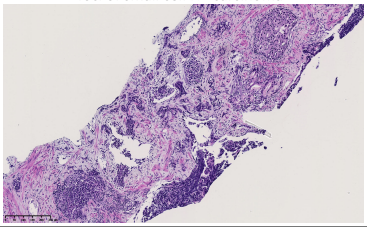
The majority shows the picture of a high grade carcinoma. Some features of small cell ca seem present, but not all morphological features for the diagnosis are there (yet).

There is only focal synaptophysin expression.

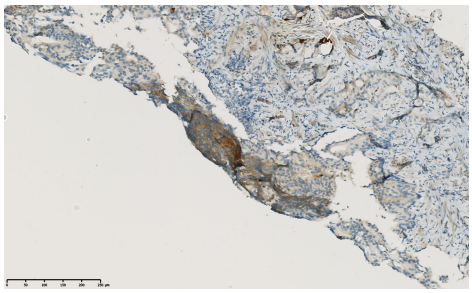
However, there is pRB loss and aberrant p53 expression.

Probably best to consider this as a so-called **intermediate atypical prostate cancer (IAC)**

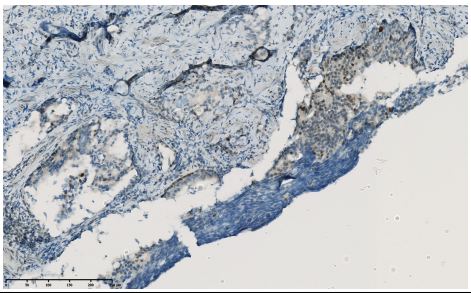
Male, 63 y (18CC1041/76646K): known prostate cancer since 2007, has been treated with RT and CT. Currently has normal PSA and lesion in bladder region. Biopsies of prostate and lesion.
Prostate shows Gleason 9, intraductal carcinoma and foci of small cell NE carcinoma



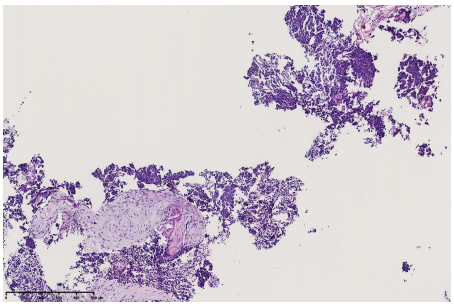
Synaptophysin



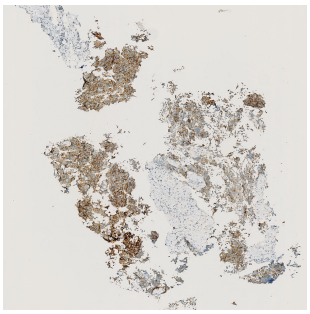
P53: normal heterogeneous expression in the acinar part,
total absence/null phenotype in small cell NE part



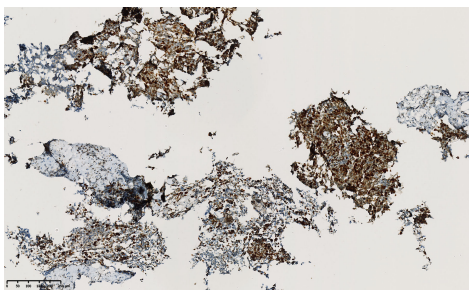
Lesion in the bladder region: 100% small cell NE carcinoma



synaptophysin



P53: overexpression pattern

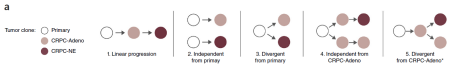


The focus of NE small cell cancer in the prostate shows a
p53 null phenotype

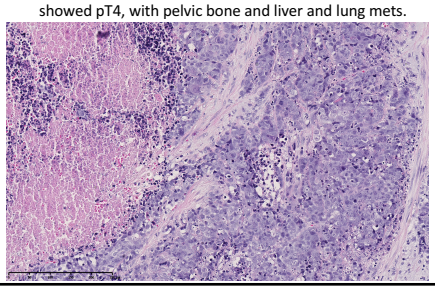
The focus of NE small cell cancer at the bladder shows a
P53 overexpression phenotype

Both pattern means p53 is mutated and non-functional
but:
Different aberrant patterns means different types of mutation in p53

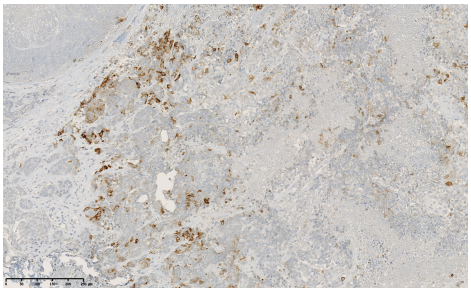
Hence, both foci are different clones that developed seperately from
the acinar carcinoma.
How does this fit in the divergent clonal evolution theory?



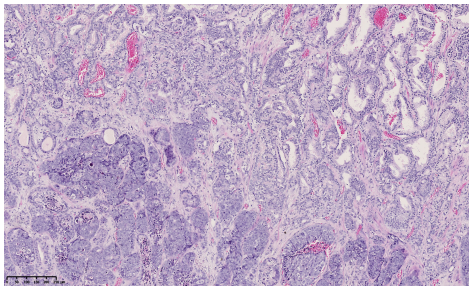
Male, 82 y (17H25472/D32588K): primary/de novo presentation, with obstruction. Fragments from prostate taken to remove obstruction. Imaging after pathological findings showed pT4, with pelvic bone and liver and lung mets.



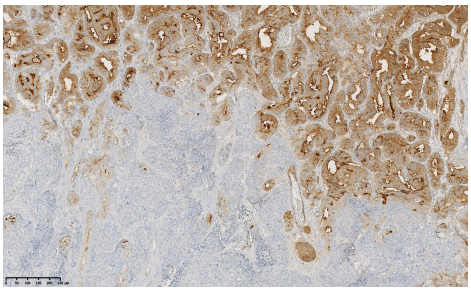
Synaptophysin: multifocal expression



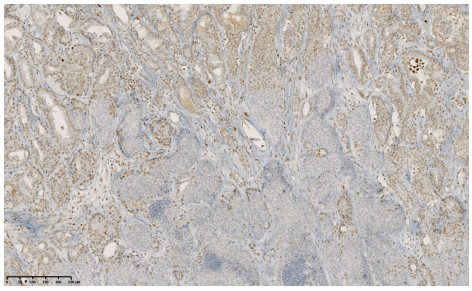
Upper part: acinar, lower part: NE
Abrupt transition



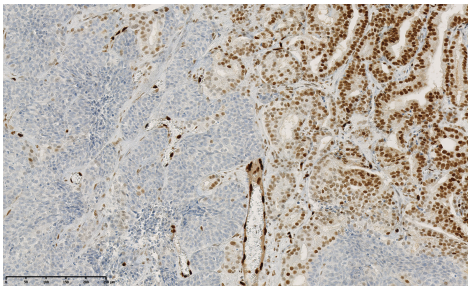
PSA



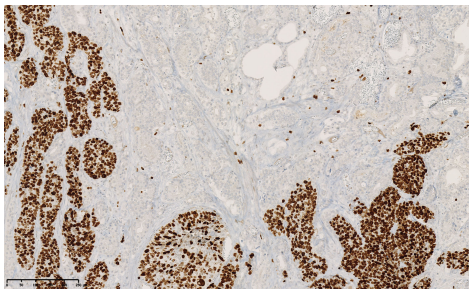
pRB



ERG



Ki-67



A part of this tumor shows the picture of a high-grade NE carcinoma, with features intermediate between large cell and small cell NE carcinoma (« intermediate carcinoma »).

Synaptophysine is focal, less than in some usual adca cases!

The tumor shows abrupt transition between high grade NE carcinoma and usual acinar carcinoma:

Mixed acinar- neuroendocrine carcinoma

This is in a de novo setting!
Why do acinar carcinomas occasionally transdifferentiate « spontaneously » towards NE carcinoma?

New kid on the block…

Human Pathology (2010) 79, 151–159

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Insulinoma-associated protein 1 is a novel sensitive and specific marker for small cell carcinoma of the prostate☆,☆☆

Zhixiang Xin MD[a, 1], Yong Zhang MD[a, 1], Zhou Jiang MD[b], Ling Zhao MD[b], Liancheng Fan MD[a], Yanqing Wang MD[a], Shaowei Xie MD[c], Xun Shangguan MD[a], Yinjie Zhu MD[a], Jiahua Pan MD[d], Qiang Liu MD[b], Yiran Huang MD[a], Baijun Dong MD[a,*], Wei Xue MD[a,*]

Int J Clin Exp Pathol 2017;10(5):5393-5405
www.ijcep.com /ISSN:1936-2625/IJCEP0049690

Original Article

INSM1 is the best marker for the diagnosis of neuroendocrine tumors: comparison with CGA, SYP and CD56

Kosuke Fujino[1,2], Kazuhiro Yasufuku[2], Shinji Kudoh[1], Yamato Motooka[1], Yonosuke Sato[1], Joeji Wakimoto[1], Ichiro Kubota[3], Makoto Suzuki[3], Takaaki Ito[1]