CURRENT CHALLENGES IN PROSTATE CANCER:

ROLE OF PSMA PET

&

ACCURATELY DEFINING “NEUROENDOCRINE” PROSTATE

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Role of PSMA PET in Prostate Cancer

- Men who are initially diagnosed with prostate cancer with *risk for metastatic disease*

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- *Biochemical Recurrence (rising PSA after definitive therapy)*

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Role of PSMA PET in Prostate Cancer

- Men who are initially diagnosed with prostate cancer with *risk for metastatic disease*
- *Biochemical Recurrence (rising PSA after definitive therapy)*
- *Defining eligibility for Lu-PSMA*
- *There is no data for the use of PSMA PET to define treatment failure in metastatic castration resistant prostate cancer (mCRPC)*

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Role of PSMA PET in Prostate Cancer

- Men who are initially diagnosed with prostate cancer with *risk for metastatic disease*
- *Biochemical Recurrence (rising PSA after definitive therapy)*
- *Defining eligibility for Lu-PSMA*

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What is Biochemical Recurrence?

- Rising PSA after surgery and/or RT with curative intent
- Negative TC99 and CT Scan
- Highly variable and often indolent course

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Case Study

- 63 yo male with Gleason 8(4+4) localized prostate cancer
- Treated with RT in 2011 with curative intent
- Recurrent PSA (BCR) in 2016, neg Tc99 and CT imaging
- By 2019 his PSA was 29. CT and Tc99 remained negative. PSA Doubling time was 17 months.
- He had a PSMA scan as part of a study…

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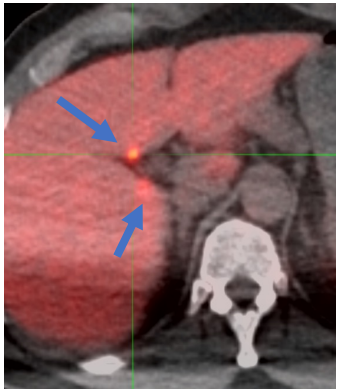
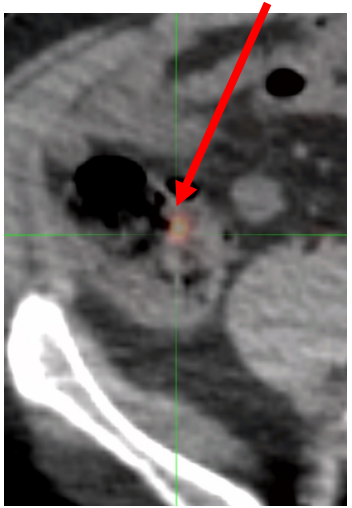
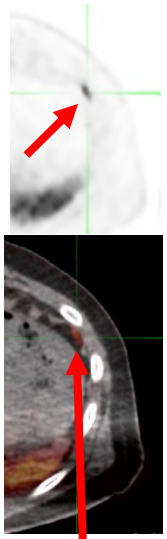
PSA =29 in 2019



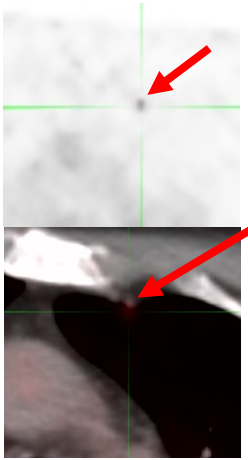
Representative liver foci without CT correlate

Representative R colon focus

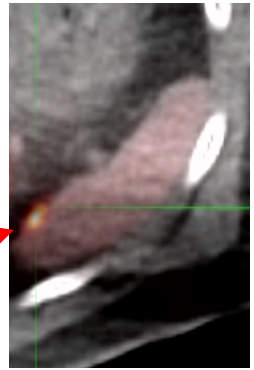




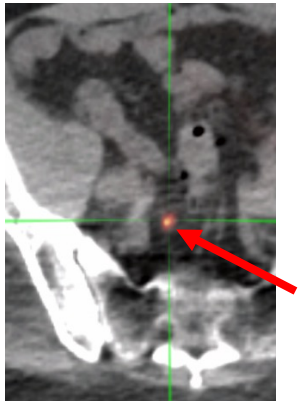
Representative mesenteric focus without CT correlate



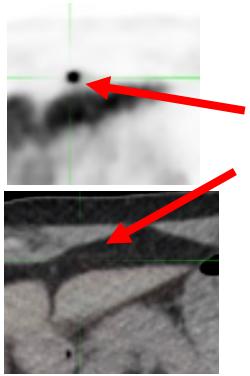
3mm L int mammary node



Focus in spleen without CT correlate



6mm presacral node



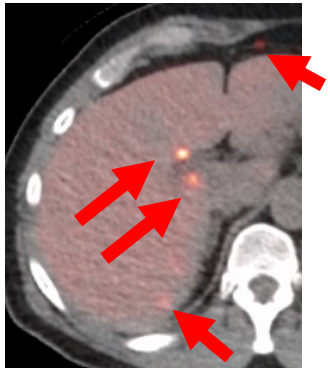
Representative mesenteric focus anterior to liver without CT correla

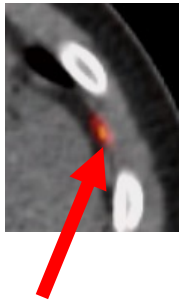
PSA Doubling Time is 17 months

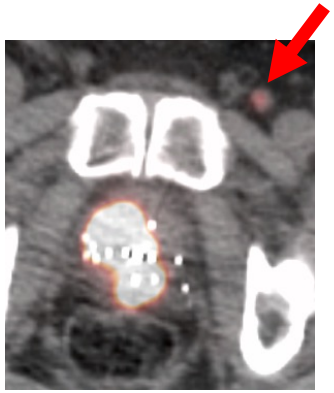
Madan RA et al. JCO 2022

PSA 49.5 ng/mL in August 2021

8-26-2021 PSMA scan with new and increased foci in pleural, peritoneal and mesenteric membranes

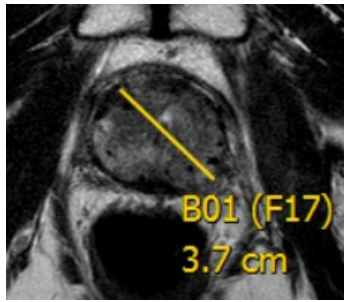






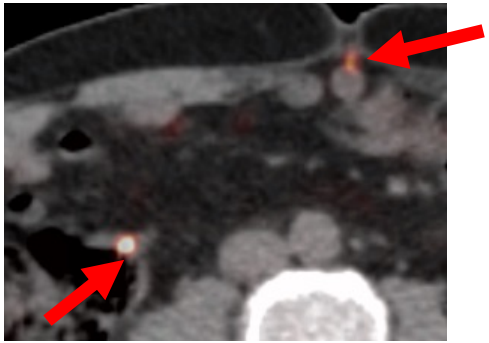
Diffuse uptake again in prostate and SVs. Increased in L ing LN and other pelvic LNs.

MRI 8-26-2021

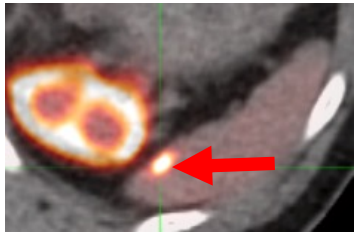


Lesion throughout the prostate

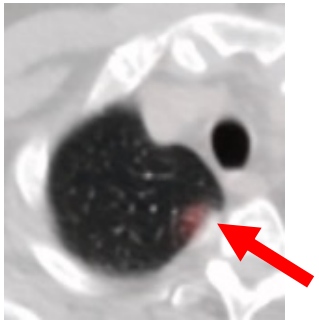
NIH score: High



Foci in umbilicus and colonic mesentery



Splenic focus, likely serosal surface



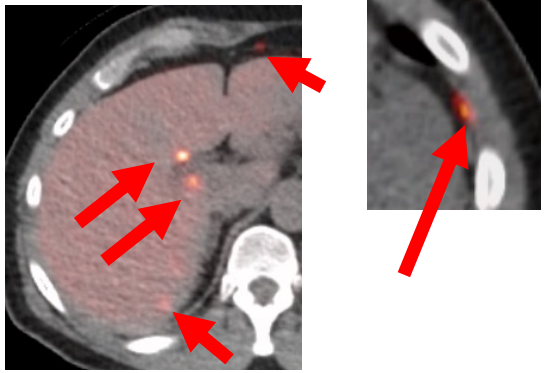
Foci in right upper lung pleural opacity

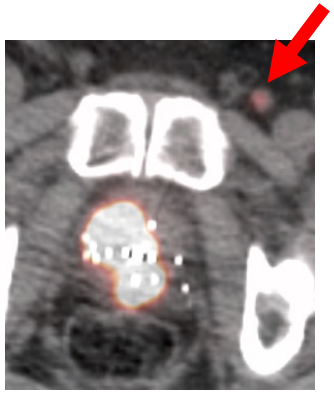
Madan RA et al.
J Clin Oncol 2022

PSA 49.5 ng/mL in August 2021

CT and Tc99 Still Negative!!!!

8-26-2021 PSMA scan with new and increased foci in pleural, peritoneal and mesenteric membranes





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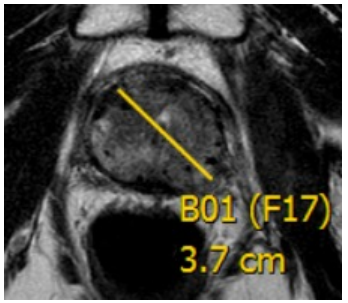

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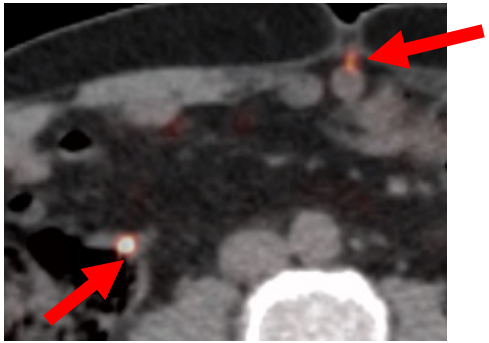

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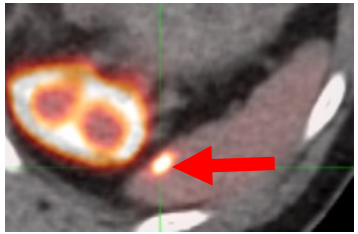

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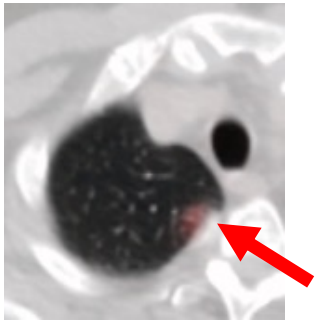

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PSMA Scans Will Change How We See Recurrent Prostate Cancer (BCR)

- But should it change how we treat recurrent disease (i.e. BCR)?

- Changes in technology will only change the urge to treat!

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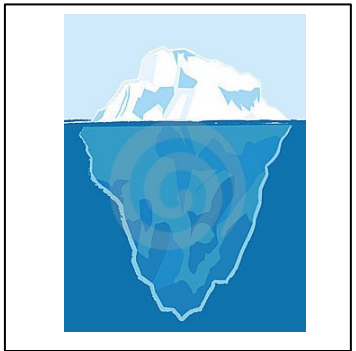
PSMA Scans Will Change How We See Recurrent Prostate Cancer (BCR)

- But should it change how we treat recurrent disease (i.e. BCR)?
- Changes in technology will only change the urge to treat!
- PSMA scans still do not show all of the disease



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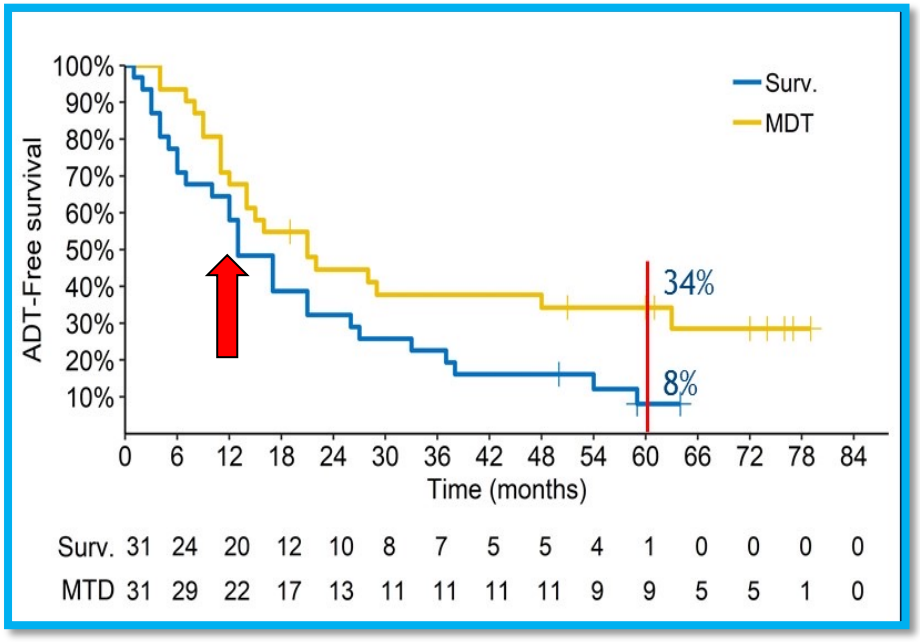
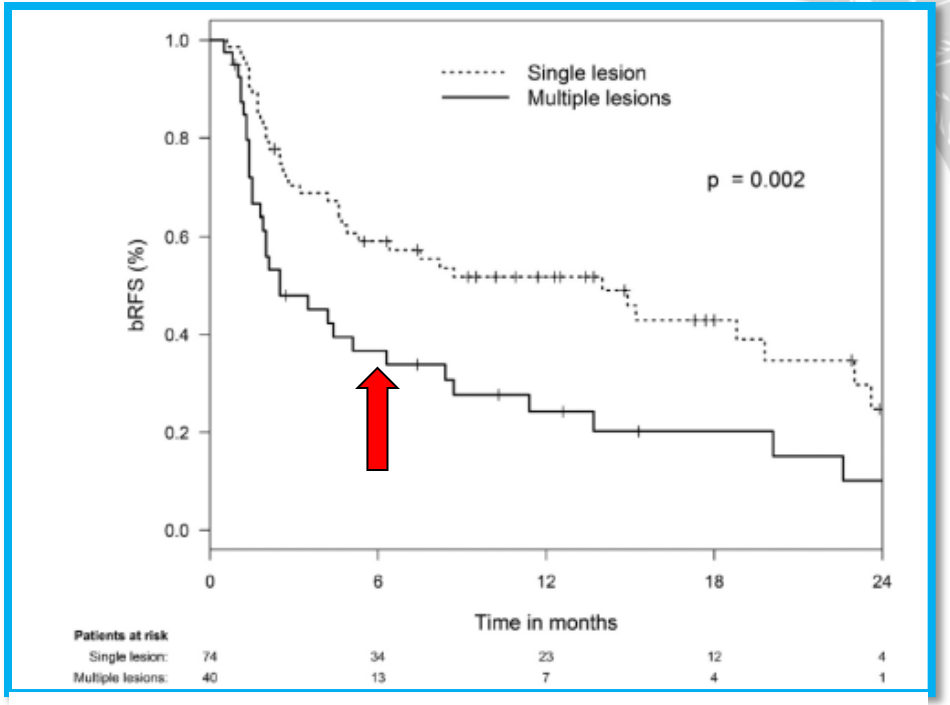
PSMA PET Directed Therapy in BCR



- STOMP Trial, up to 3 lesions
- Within 1 year ~30% are on ADT (60% @ 2 years)

(Ost et al. ASCO GU 2020)



- N= 114, PSMA + lesions treated with radiosurgery
- >60% Biochemical failure at 6 months if 1+ lesion

(Horn, T et al Euro Urol 2020)

Metachronous/Biochemically Recurrent Prostate Cancer (CT and Tc99 Neg, PSMA +)

Long term outcomes of STOMP and ORIOLE

SBRT vs observation phase 2 trials

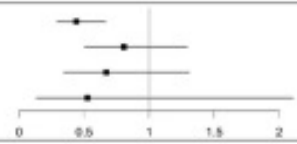
Both Trials only enrolled pts with 1-3 lesions on PET

N= 116

PFS = PSA rise of 25% with a min of 2.0

Figure 2: Time to event outcomes of MDT vs. Observation

Outcome	MDT median time to event (months, 95% CI)	Observation median time to event (months, 95% CI)	HR (95% CI)	p value
PFS	11.9 (8 – 18.3)	5.9 (3.2 – 7.1)	0.44 (0.29 – 0.66)	<0.001
rPFS	18.3 (12 – 36)	17 (13 – 22.8)	0.81 (0.50 – 1.29)	0.37
CRPC	NR (62 – NR)	63 (53.9 – NR)	0.67 (0.34 – 1.31)	0.24
OS	NR (84 – NR)	NR (73 – NR)	0.53 (0.13 – 2.11)	0.36



Time to event outcomes demonstrate improvements in PFS with MDT over observation, but no differences in rPFS, time to CRPC, or OS.

MDT: metastasis directed therapy, CI: Confidence interval; HR: Hazard ratio, PFS: Progression free survival; rPFS: radiographic progression free survival; CRPC: castration resistant prostate cancer; OS: overall survival; NR: Not reached

"That's it. That's the data…

So why are we doing so much SBRT outside of trials… it puzzles me."

Dr. Piet Ost, Radiation Oncologist, ESMO 2022

** Small numbers and short follow-up may limit rPFS and OS data*

Slide Presented by Dr. P. Ost, ESMO 2022

Deek et al. JCO 2022

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“Wouldn’t it be *swell* if we had a biomarker that could predict outcomes…”

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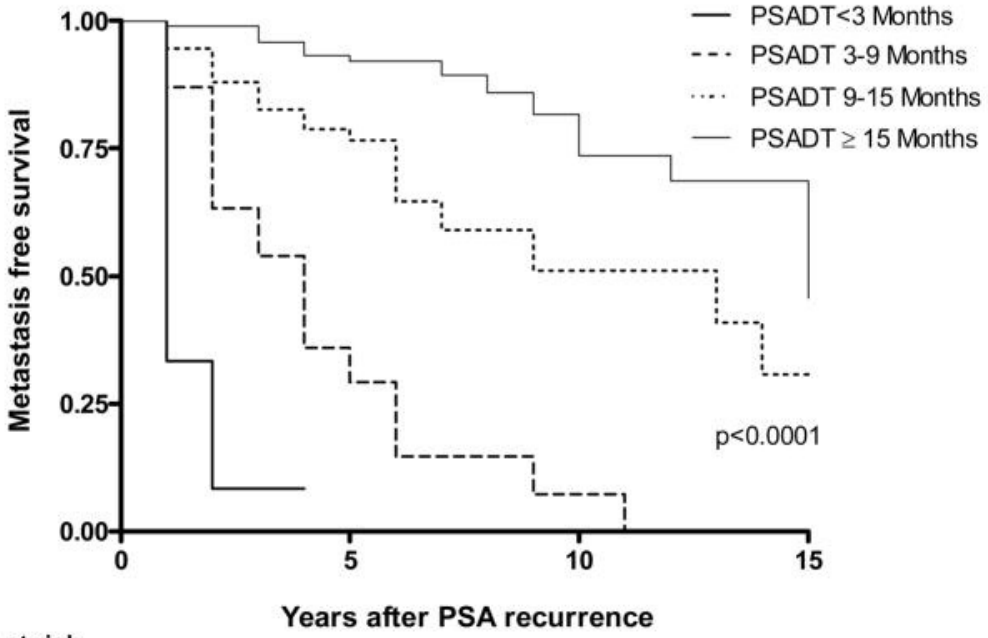
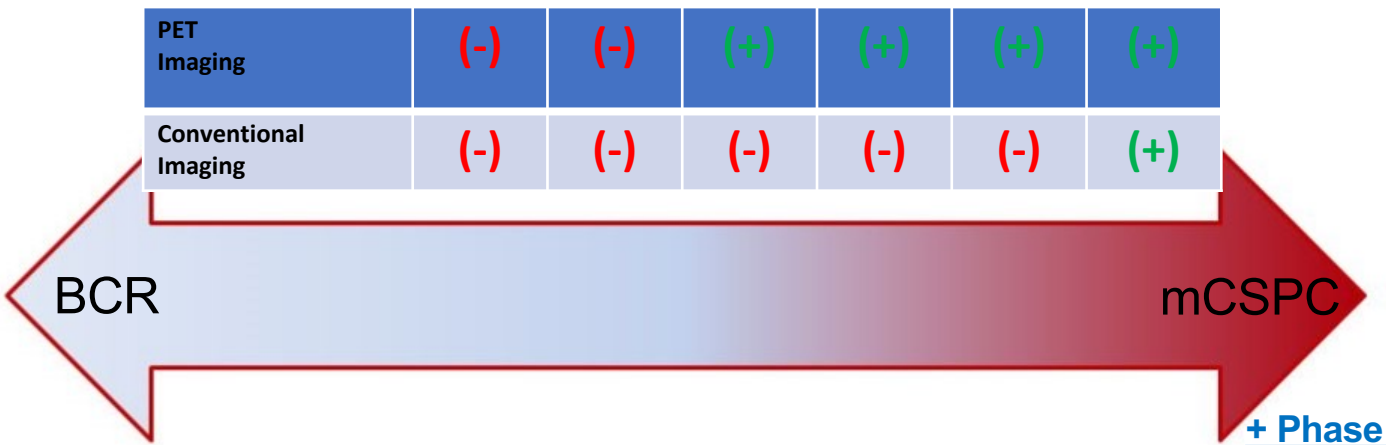
PSADT and Time to Metastasis on CT or Tc99 Scan



Number at risk				
PSADT < 3 Month	46	0	0	0
PSADT 3-9 Month	106	16	2	0
PSADT 9-15 Month	86	37	11	1
PSADT ≥ 15 Month	212	86	30	3

Antonarakis et al. BJUI 2012

PSMA PET and the *Continuum* of BCR to mCSPC



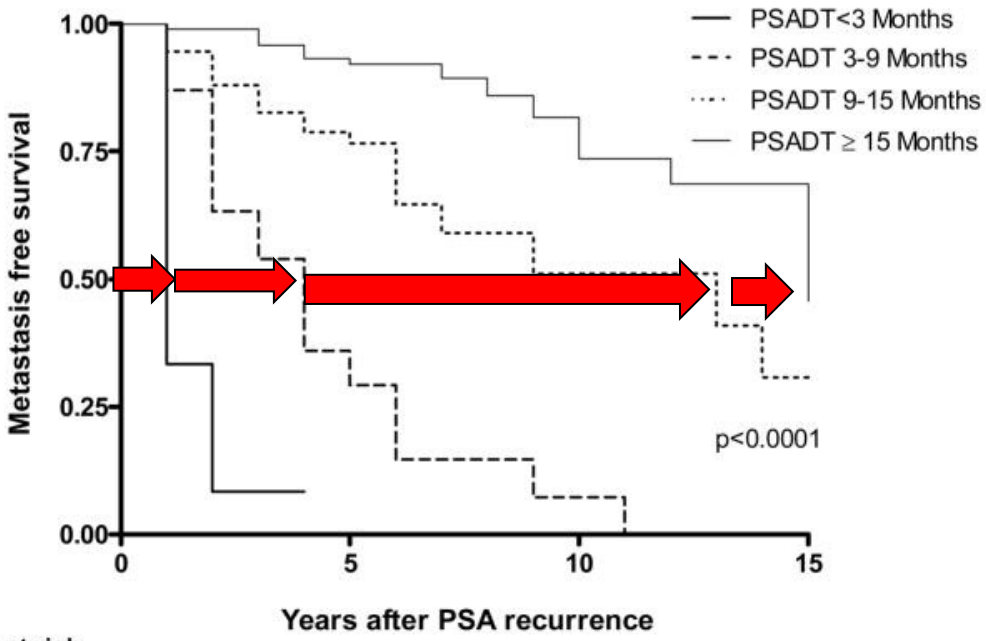
Negative Data for ADT
ELAAT/TOAD trial
(Loblaw et al, ASCO 2018)

STAMPEDE
ADT + Abi subset
>3% of 1,976 pts
(Attard, Lancet 2022)

+ Phase 3*
CHAARTED
ENZAMET
LATTITUDE
PEACE1
(*PET Imaging Not Evaluated)
Recurrent Pts a Minority

Adapted from Kase AM et al, Cancers 2022

PSMA Scans Will Lead to Over Treatment



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With New Technology Comes Great Responsibility: Prostate-Specific Membrane Antigen Imaging in Recurrent Prostate Cancer

Ravi A. Madan, MD[1]; Esther Mena, MD[2]; Liza Lindenberg, MD[2]; and Peter L. Choyke, MD[2]

Prostate-specific antigen (PSA) is both a blessing and a curse for prostate cancer. It is a blessing because it makes prostate cancer one of the few cancers with a reliable serum biomarker, but it is also a curse because it can drive overdiagnosis and overtreatment in newly diagnosed disease and also because it creates anxieties for men with recurrent disease.[1] In patients previously treated with radiation or surgery for localized prostate cancer, 30%-40% will experience a rise in PSA, an initial signal of recurrent disease.[2,3] With an estimated 1.4 million men diagnosed each year worldwide, this could mean approximately 500,000 will be detected with recurrent disease.[4] Given the ability of PSA to detect even low levels of recurrent disease, this often creates a vexing scenario where men have biochemical evidence of disease for years, but no anatomic evidence of disease on conventional imaging with computed tomography (CT) or Technetium-99m (Tc99) bone scans. The recent

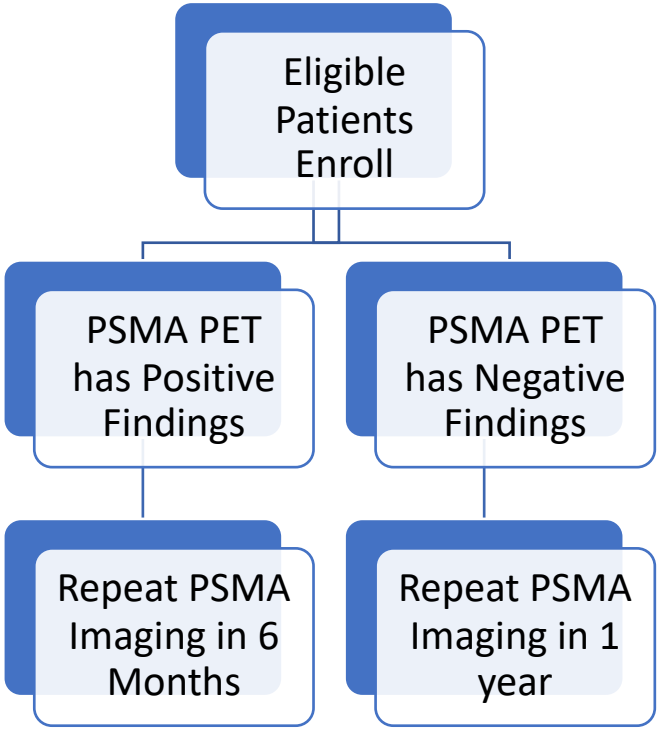
The ability to stage primary prostate cancer more accurately will be a critical new tool for determining if surgery or radiation with androgen deprivation therapy (ADT) is appropriate when evaluating the curability of a given patient. PSMA PET will be used to limit morbidity of futile surgical resections in patients with known metastatic disease or perhaps select patients for whom a clinical trial may be most appropriate.[8] Studies need to be done to evaluate how systemic ADT affects findings on a PSMA scan in patients undergoing radiation to their primary tumor within their prostate. In addition, new imaging strategies, such as PSMA PET, may increase the efficacy of salvage options for these patients by identifying those who are the best candidates for such interventions. There will be hope among patients and physicians alike that the identification of oligometastatic findings on a PSMA scan may be successfully treated with tailored focal radiation. This optimism should be tempered by the fact that

Madan RA et al.
J Clin Oncol 2022

This is no Prospective Data on the Evolution PSMA+ Disease in BCR

PSMA Natural History Study Design

ClinicalTrials.gov Identifier: NCT05588128



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Eligibility

Inclusion Criteria

- History of primary treatment for prostate cancer (either surgery or radiation).
- PSA ≥ 0.50
- Testosterone >100
- Age ≥18 years.
- The ability of a subject to understand and the willingness to sign a written informed consent document

- **Exclusion Criteria**
- Evidence of soft tissue disease on CT scan or MRI as clinically indicated) (lymph nodes up to 1.5 cm in the shortest dimension are allowed).
- Evidence of bone lesions on Tc99 bone scan.
- Prostatectomy within 1 year before entering the study.
- ADT within the 6 months before entering the study
- Systemic therapy for prostate cancer within the 6 months before entering the study

ClinicalTrials.gov Identifier: NCT05588128

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NEUROENDOCRINE PROSTATE CANCER

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Neuroendocrine Prostate Cancer (NEPC)

- What is this? And Why do we need to define it?
- Are Neuroendocrine & Small Cell Prostate Cancer the same thing?
- Does every “NEPC” get treated Platinum+Etoposide?

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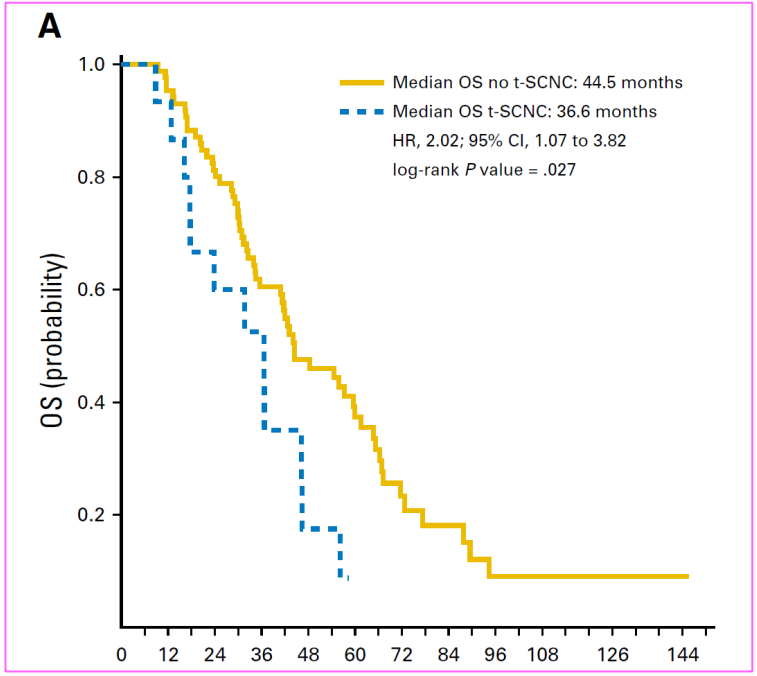
VOLUME 36 · NUMBER 24 · AUGUST 20, 2018

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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



"…small-cell neuroendocrine prostate cancer is present in nearly one fifth of patients with mCRPC and is associated with shortened survival."

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“Proposed” Neuroendocrine “Markers”

Table 1. Neuroendocrine markers

Commonly used in clinical practice	Chromogranin
	Synaptophysin
	Neuron specific enolase
	CD56
Typically not used in clinical practice	Cytochrome b561
	Synaptic vesicle protein 2 (SV2)
	Vesicular monoamine transporters (VMAT)
	Synaptobrevin
	Syntaxin
	SNAP-25
	Rab3 Vesicle associated membrane proteins

Parimi, V et al. Am J Clin Exp Urol 2014

Proposed Genomic Definition:

- RB loss
- P53 mutation

Clinical Findings that Raises Fear of Neuroendocrine Prostate Cancer and Lead to NE Staining:

- “Low” PSA
- Soft tissue disease
- Short Response to ADT/anti-androgen

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Are All Neuroendocrine Prostate Cancer The Same?

Table 2. Neuroendocrine differentiation in the prostate

	Type	Subtypes
Benign	Benign neuroendocrine cells	Neuroendocrine cells in benign prostates
Malignant	Neuroendocrine carcinoma	Small cell (neuroendocrine) carcinoma
		Large cell (neuroendocrine) carcinoma
	Carcinoid tumor	Carcinoid tumor
	Adenocarcinoma with neuroendocrine differentiation	Conventional adenocarcinoma
		• Diffuse
		• Focal
		Paneth cell differentiation
		• Focal

"Prostatic adenocarcinomas with scattered foci of neuroendocrine immunohistochemical expression are designated under prostatic adenocarcinoma with neuroendocrine differentiation (PCND). PCND can present as untreated primary pathology or more commonly as a post ADT and androgen receptor inhibition resistance phenomenon."

Histologically focal neuroendocrine differentiation ranges from 10 to 100% in prostate adenocarcinomas treated by ADT. (Epstein JI, Am J Surg Pathol 2014)

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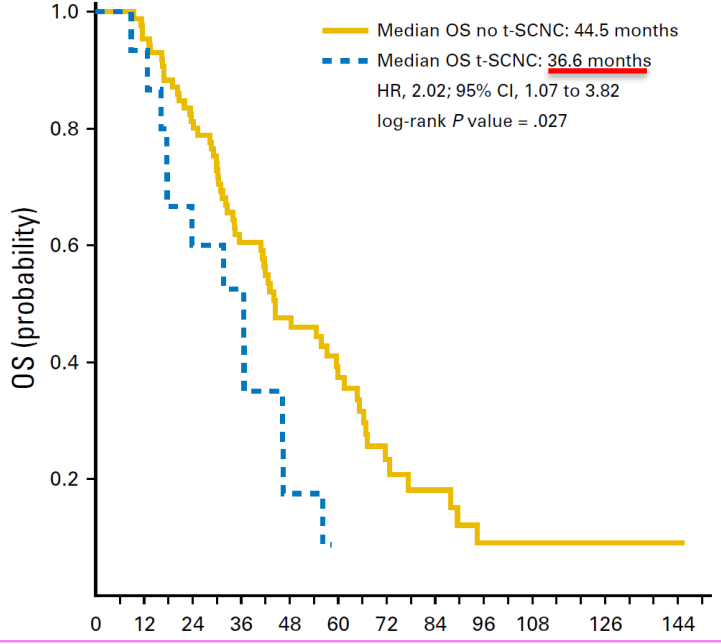
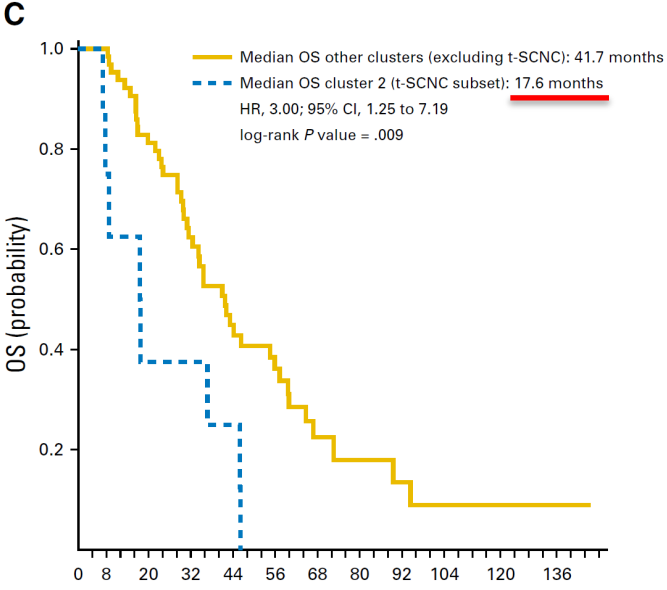
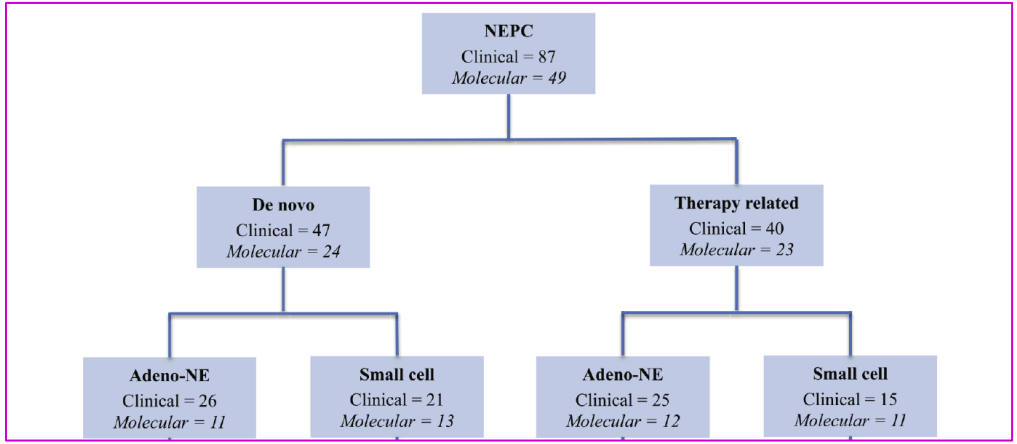




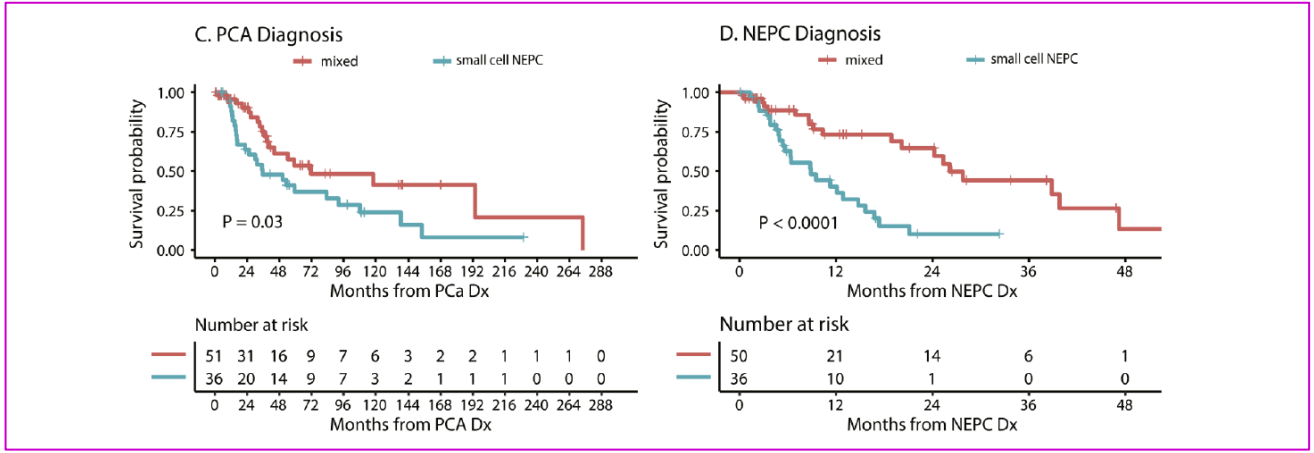
"Patients whose biopsy fell within the small-cell–enriched cluster 2 on unsupervised hierarchical clustering likewise had worse survival"

Clinical features of neuroendocrine prostate cancer

Vincenza Conteduca[a,b,c], Clara Oromendia[d], Kenneth W. Eng[e,f], Rohan Bareja[e,f], Michael Sigouros[a], Ana Molina[a,e], Bishoy M. Faltas[a,e], Andrea Sboner[e,f], Juan Miguel Mosquera[e,g], Olivier Elemento[e,f], David M. Nanus[a,e], Scott T. Tagawa[a,e], Karla V. Ballman[d], Himisha Beltran[a,b,*] Eur J Cancer. 2019



Small Cell Prostate Cancer is significantly worse than "Mixed Adeno-NE"



Are All Neuroendocrine Prostate Cancer The Same?

Table 2. Neuroendocrine differentiation in the prostate

	Type	Subtypes
Benign	Benign neuroendocrine cells	Neuroendocrine cells in benign prostates
Malignant	Neuroendocrine carcinoma	Small cell (neuroendocrine) carcinoma
		Large cell (neuroendocrine) carcinoma
	Carcinoid tumor	Carcinoid tumor
	Adenocarcinoma with neuroendocrine differentiation	Conventional adenocarcinoma
		• Diffuse
		• Focal
		Paneth cell differentiation
		• Focal

Parimi, V et al. Am J Clin Exp Urol 2014

Small Cell Prostate Cancer

- 2% of all prostate cancer
- Can be de novo or arise years after diagnosis
- PSA is often absent
- Rapid often soft tissue progression
- Best treated with a platinum-based regimen
- Expected survival is 12-18 months

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Small Cell Neuroendocrine Prostate Cancer is a Conflation of Terms

Prostate Cancer Adenocarcinoma with Neuroendocrine Features

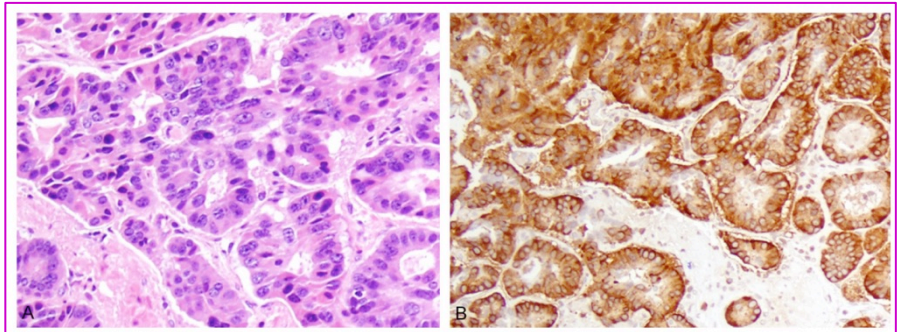

Figure 5. Prostatic adenocarcinoma with neuroendocrine differentiation on H&E (A) which is confirmed by strong positive staining for chromogranin (B).

Small Cell

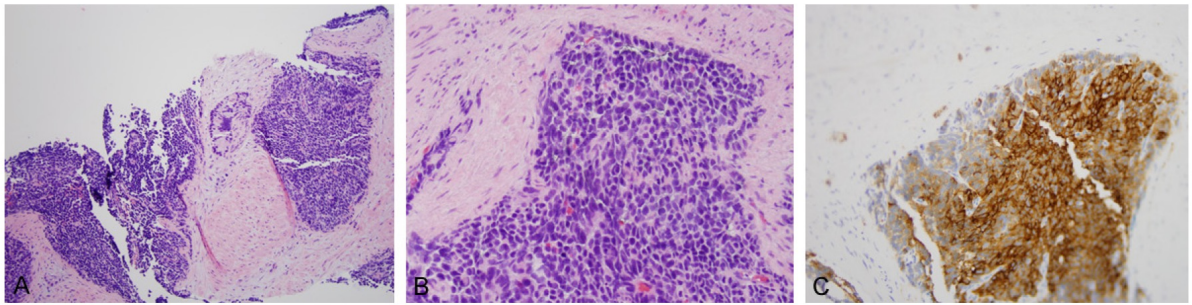

Figure 2. Small cell carcinoma of the prostate seen on a needle core biopsy (A). Similar to pulmonary counterpart, these tumor cells display characteristic "small blue cell" appearance (B), confirmed by neuroendocrine marker synaptophysin (C).

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Parimi, V et al. Am J Clin Exp Urol 2014

JCI The Journal of Clinical Investigation

Deciphering the enigma of neuroendocrine prostate cancer

Fatima Karzai, Ravi A. Madan

J Clin Invest. 2022;132(21):e164611. https://doi.org/10.1172/JCI164611.

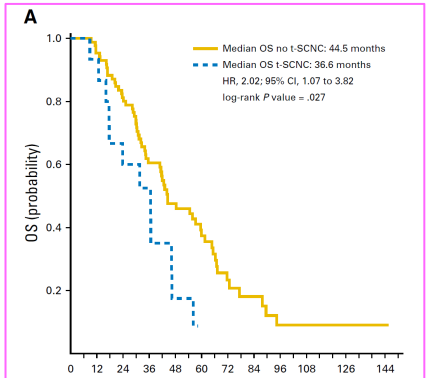
Commentary

Despite the clinical advances in managing metastatic prostate cancer in the last 20 years, treatments for patients with metastatic disease only offer a brief respite from disease progression, especially after first-line therapies. Research into treatment resistance has defined a subset of patients with neuroendocrine differentiation of their prostate adenocarcinoma. Although neuroendocrine findings in conjunction with prostate adenocarcinoma can be seen in pathology samples at all stages of disease, the neuroendocrine variant of prostate cancer associated with poor outcomes occurs in approximately 20% of men with advanced disease. In this issue of *JCI*, Zhao, Sperger, and colleagues present data for a promising biomarker platform that can detect neuroendocrine prostate cancer after serial sampling of patients' blood with a high degree of sensitivity and specificity. This assay will be tested in several current and future trials to better define its potential clinical role and perhaps provide a greater understanding of neuroendocrine prostate cancer itself.

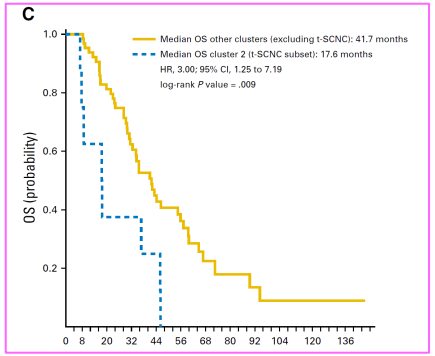
"Although adenocarcinoma of the prostate with neuroendocrine differentiation may respond to platinum-based therapies, it is not immediately clear at what point in this lineage transformation standard prostate therapies, such as androgen receptor targeting, need to be abandoned for a small-cell regimen. Prematurely curtailing standard prostate cancer therapies in patients diagnosed with adenocarcinoma with neuroendocrine features in favor of a purely small-cell regimen may lead to increased toxicity and thus diminished survival."

Small Cell Neuroendocrine Prostate Cancer is a Conflation of Terms

- Small Cell Prostate Cancer
  - Very rare (2% of prostate cancer)
  - Often PSA=0
  - Rapid disease course
  - Requires therapy with a platinum-based regimen



Small Cell is driving worse outcomes reported in "NEPC"



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Small Cell Neuroendocrine Prostate Cancer is a Conflation of Terms

- Small Cell Prostate Cancer
  - Very rare (2% of prostate cancer)
  - Often PSA=0
  - Rapid disease course
  - Requires therapy with a platinum-based regimen

- Adenocarcinoma with Neuroendocrine Features
  - Can be seen at diagnosis or after ADT
  - May not be associated with a rapid disease course
  - May still respond to standard prostate cancer therapies

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THANK YOU!

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