



Prostate Cancer Imaging & Treatment

Strategies to enable novel diagnostic and therapeutic techniques to flourish

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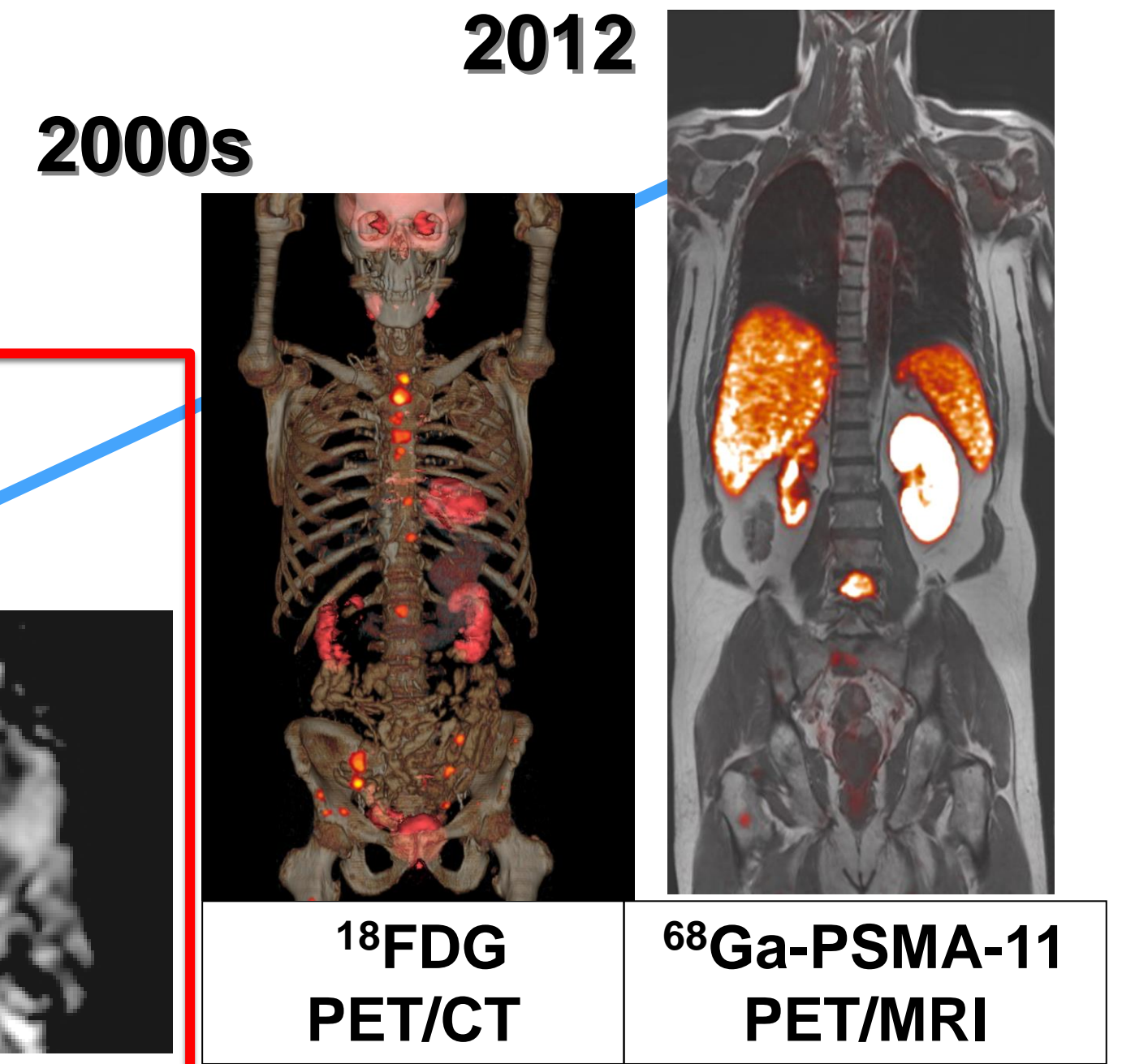
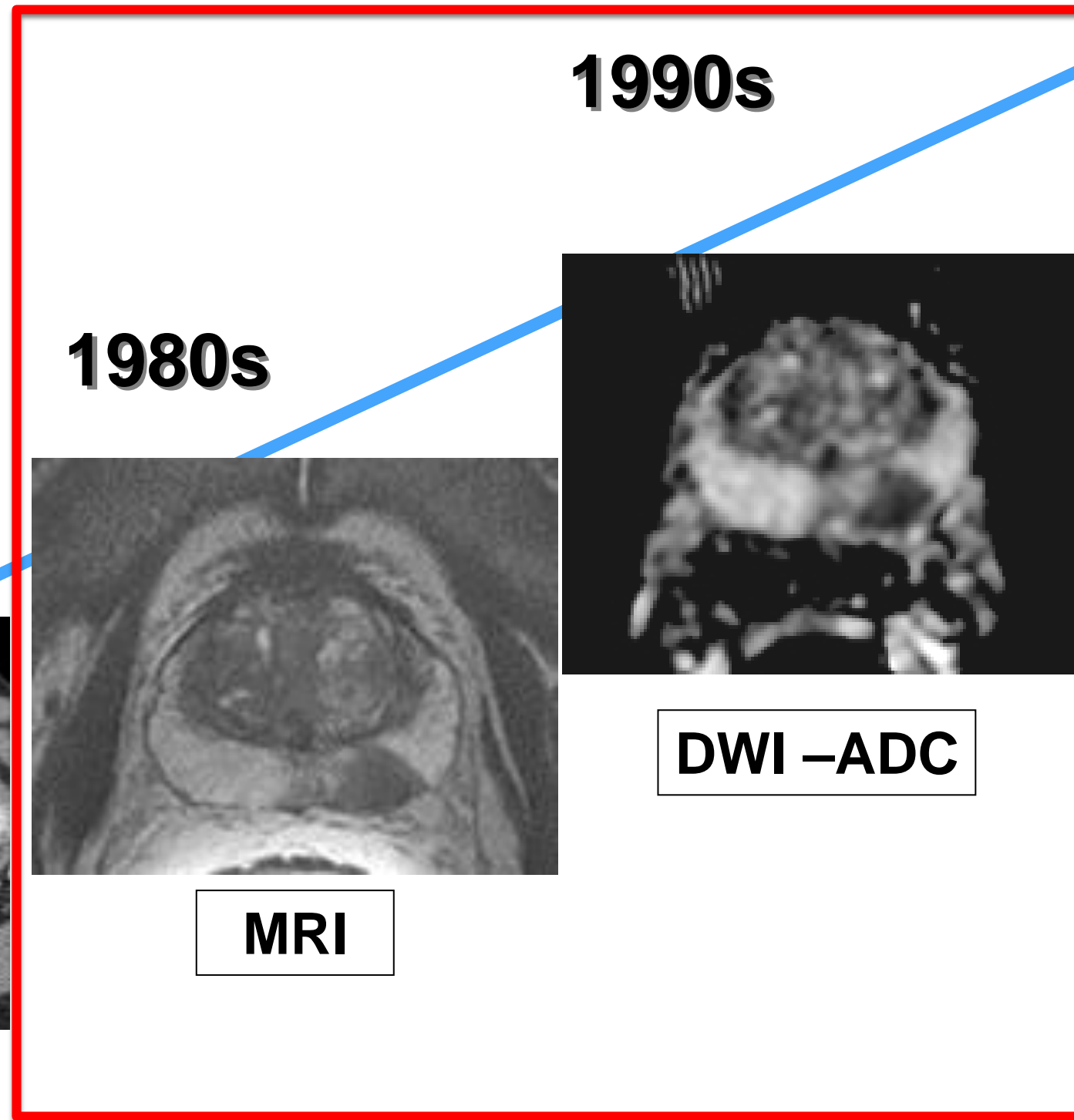
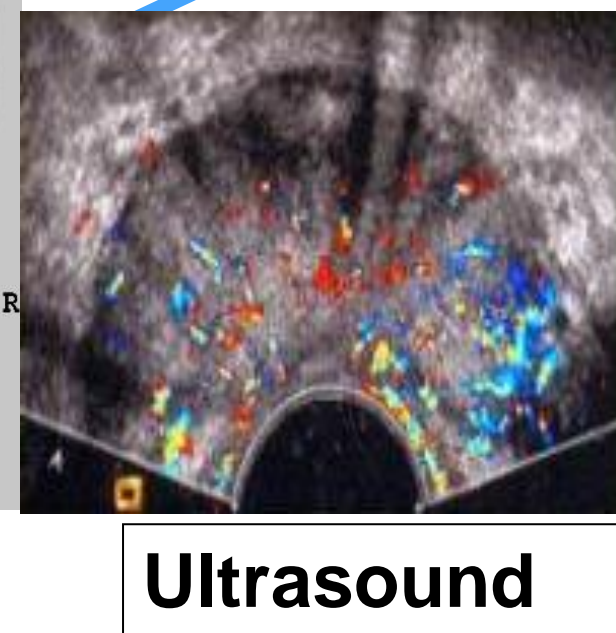
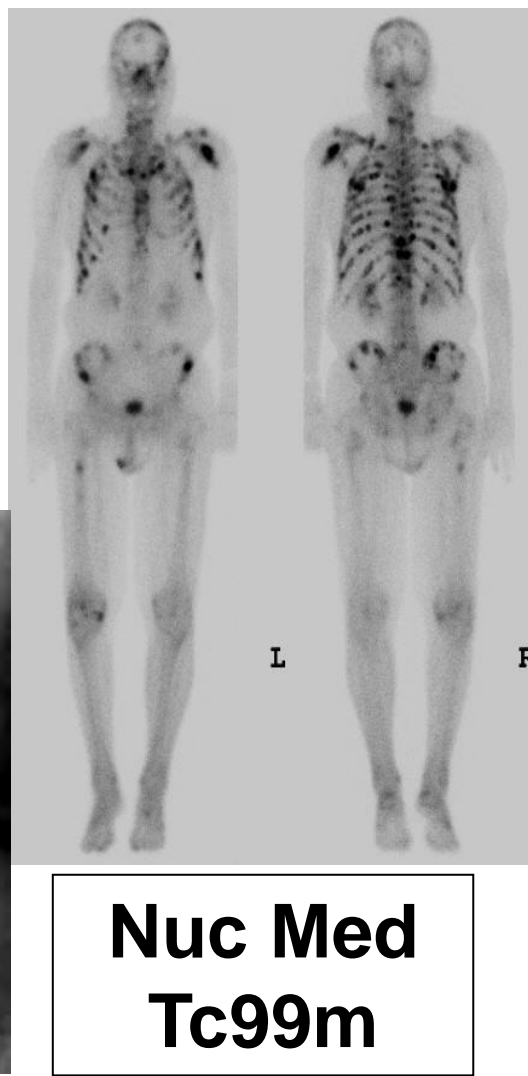
Disclosures

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Imaging Prostate Cancer

From Helpful to Essential

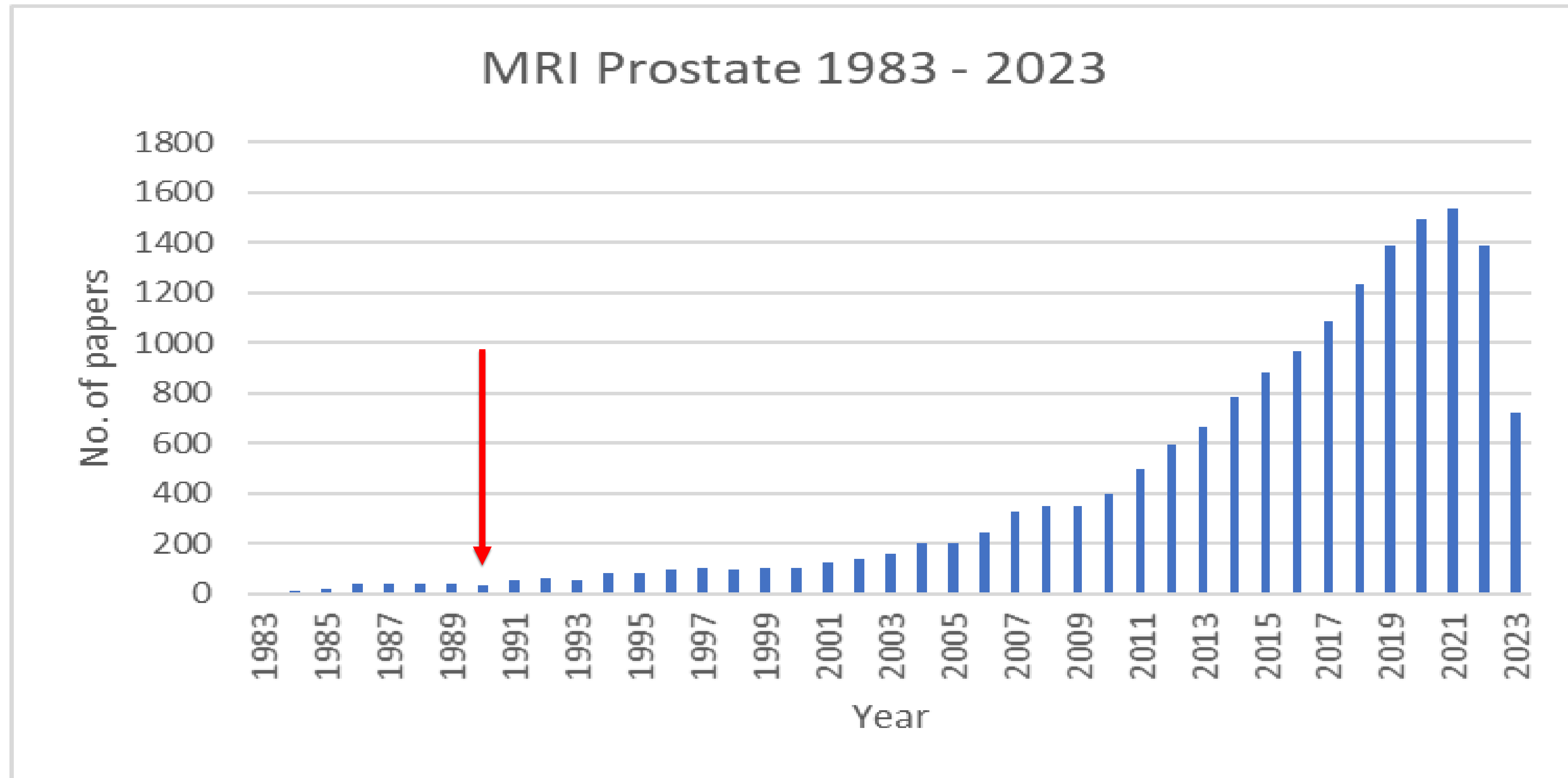
Since 2014 there is an alarming 3% annual increase in PCa incidence driven by the diagnosis of advanced disease



*“Learn from Yesterday,
Live for Today,
Hope for Tomorrow”*
Albert Einstein

Steyn JH, Smith FW: NMR imaging of the prostate; *Br J Urol* 1982

Hricak H, Williams RD: Anatomy and pathology of the male pelvis by MRI; *AJR* 1983



Modality Assessment Before Its Time

Technology, Standardization in Interpretation

NEJM 1990

Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. Results of a **multi-institutional cooperative trial**

“MRI identified ***only 60 percent*** of all malignant tumors measuring ***more than 5 mm*** on pathological analysis, and ***ultrasonography identified only 59 percent.***”

Modality Assessment before its Time

Technology and Knowledge in Interpretation

AJR 1992

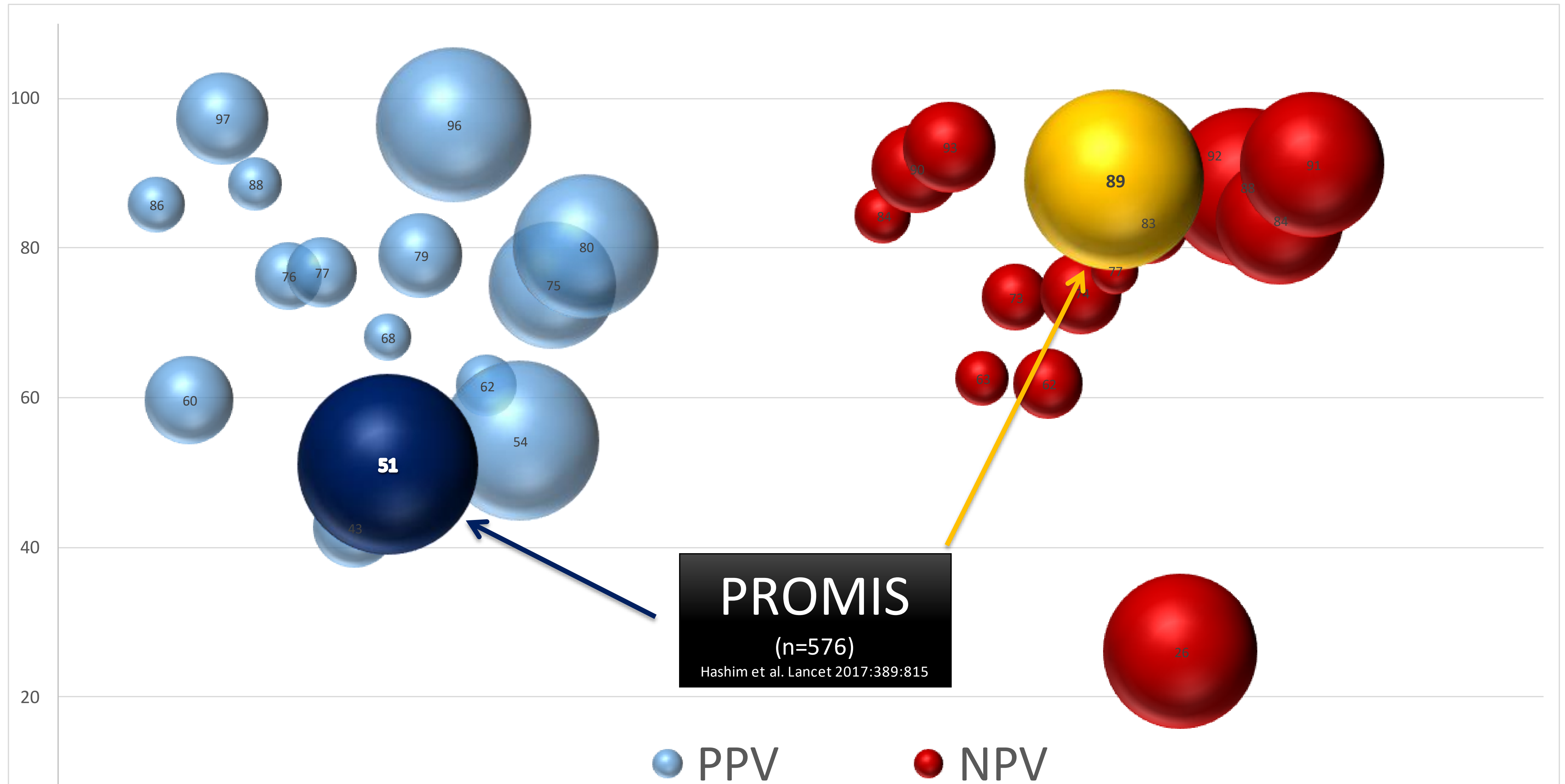
- MR imaging in adenocarcinoma of the prostate: interobserver variation and efficacy for determining **stage C disease**.

“ The average accuracy among four radiologists in determining the **presence of stage C** adenocarcinoma of the prostate from MR images was only ***slightly above a chance guess at .55.***”

Radiology 1994

- Staging of prostate cancer: results of **Radiology Diagnostic Oncology Group** project comparison of three MR imaging techniques.
- “Overall accuracy for conventional body-coil, fat-suppressed body-coil, and endorectal-coil **MR was 61%, 64%, and 54%**, respectively.”

Diagnostic Precision of Prostate MRI



PROMIS
(n=576)
Hashim et al. Lancet 2017:389:815

● PPV

● NPV

Modality Assessment Before Its Time

Lessons Learned

- Technology Assessment before its time (technology needs to be robust and ready for wide dissemination)
- The evaluation team needs to be multidisciplinary (not only multi-institutional)
- The evaluating site personnel needs to be trained/certified; image interpretation needs to be standardized; participating radiologists need to be disease sub-specialized and be a part of MDT

PSMA PET Imaging – *From synthesis to FDA approval*

In **2012** Eder and the Heidelberg group synthesized a ^{68}Ga -labeled PSMA PET compound, which was FDA-approved on **December 1, 2020**

In **2011** Pomper and the John Hopkins group synthesized a ^{18}F -PSMA PET compound, which was FDA-approved on **May 30, 2022**



^{68}Ga PSMA -11 PET

¹⁷⁷Lu - PSMA Radioligand Therapy

First introduced by the German Cancer University, Hospital Heidelberg in 2015

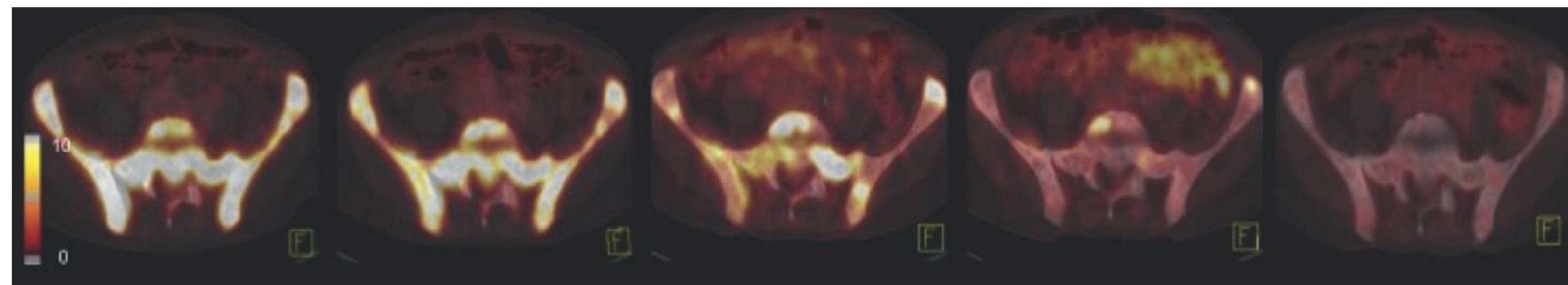
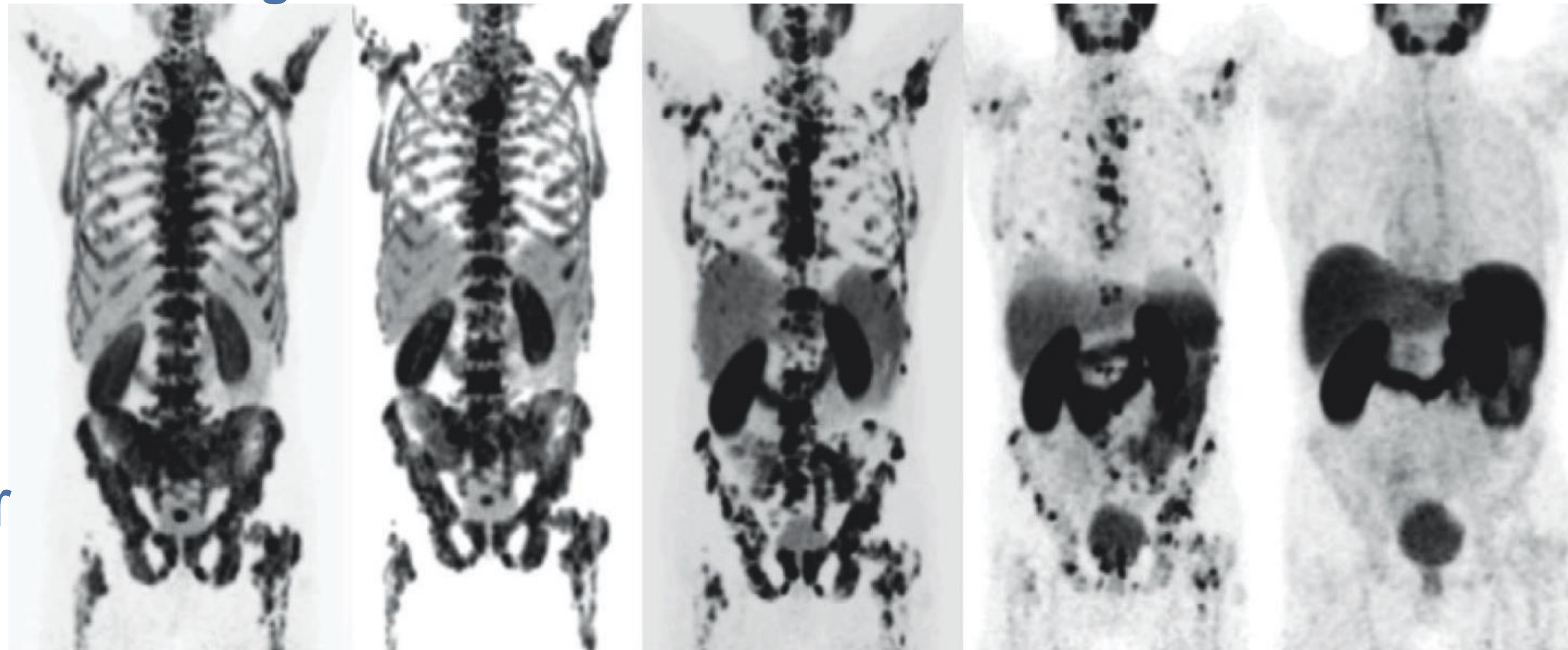
Before therapy
PSA = 755 ng/mL

Cycle 1

Cycle 2

Cycle 3

Cycle 4
PSA < 0.2 ng/mL



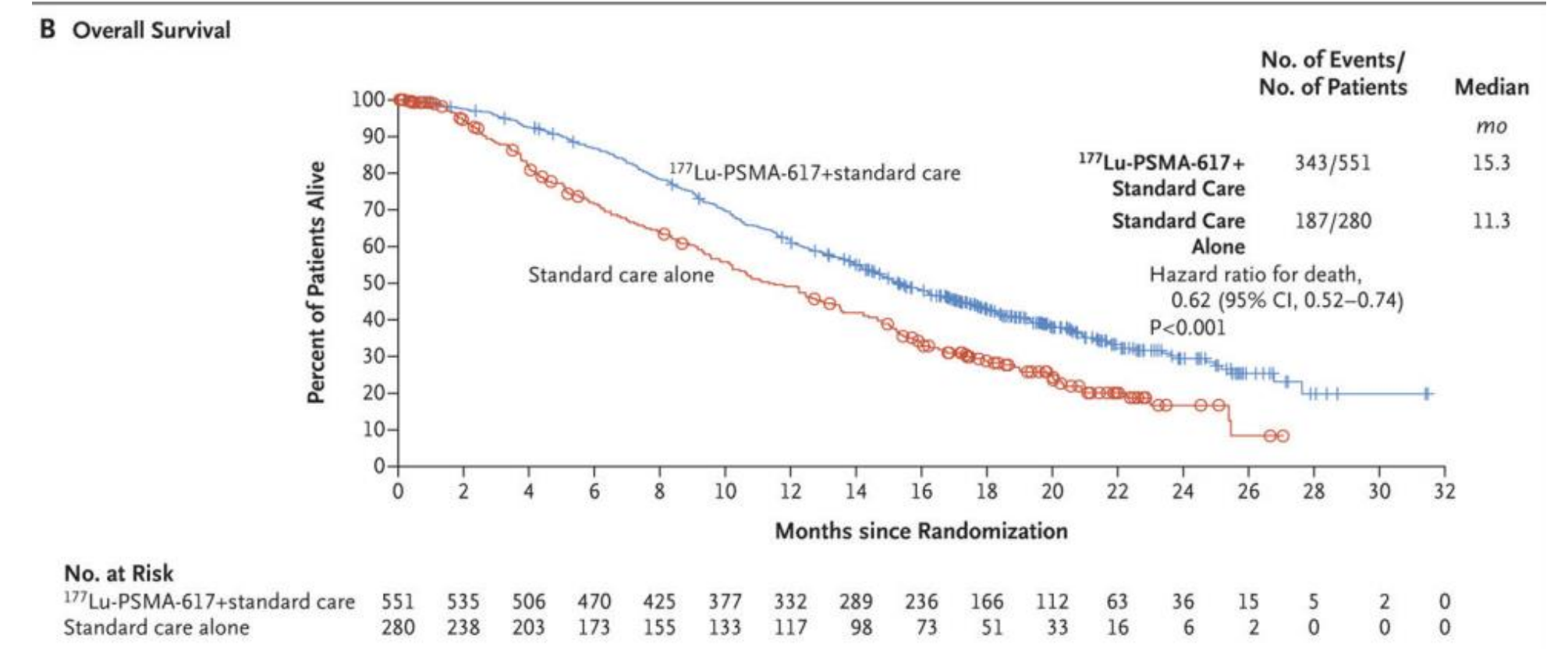
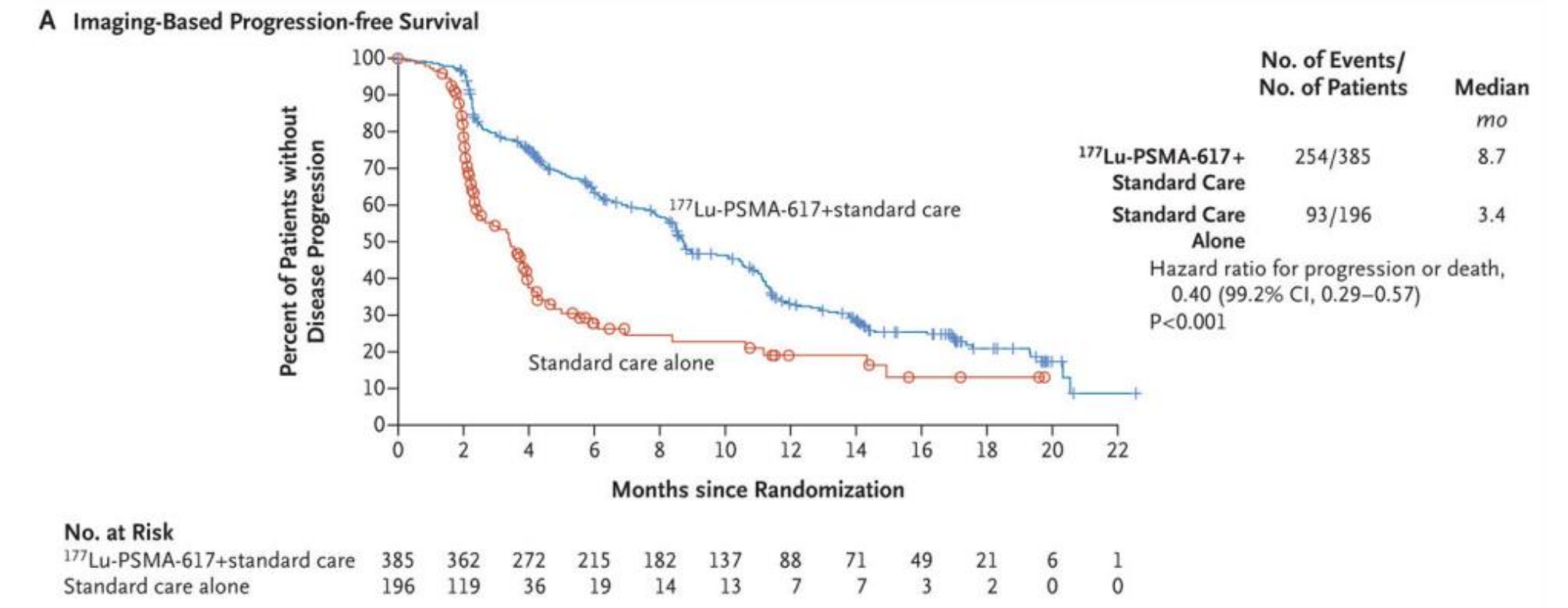
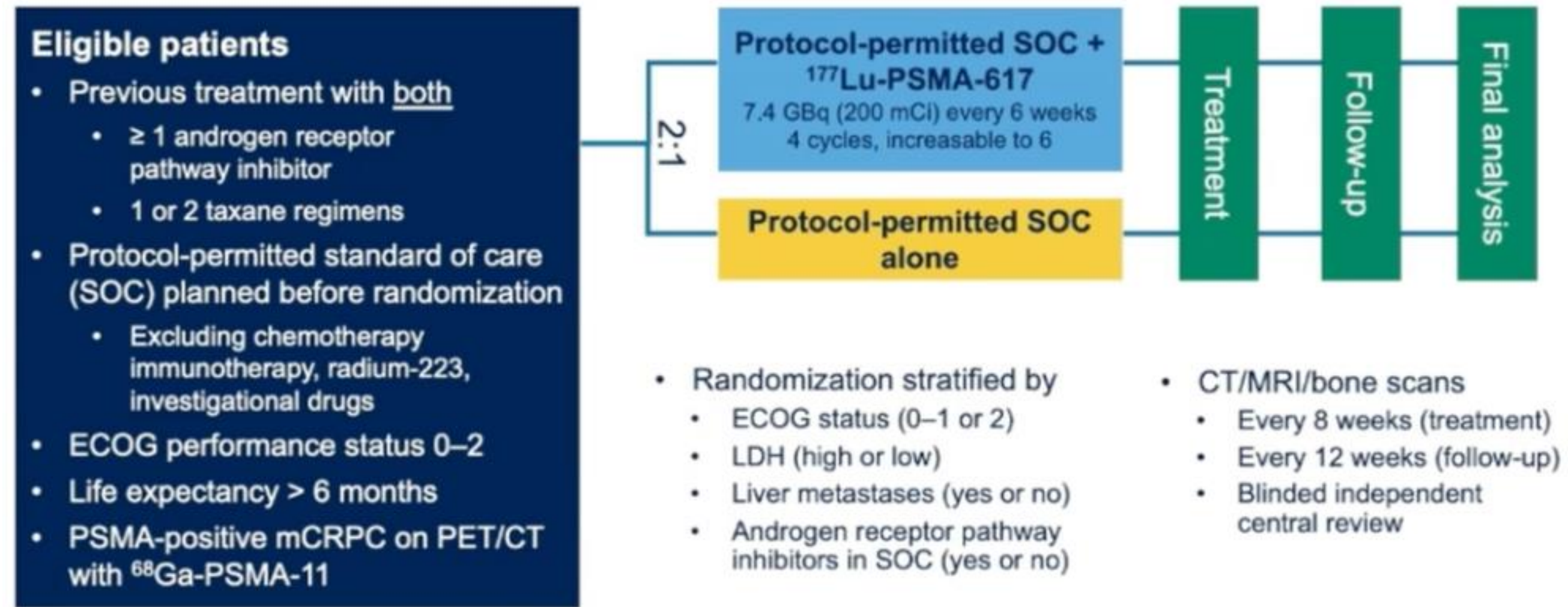
⁶⁸Ga-PSMA-11 PET/CT

Heck et al. J Urol (2016)
Figure 4, edited

71 years old
patient with
metastatic
castration-
resistant
prostate cancer
(mCRPC).

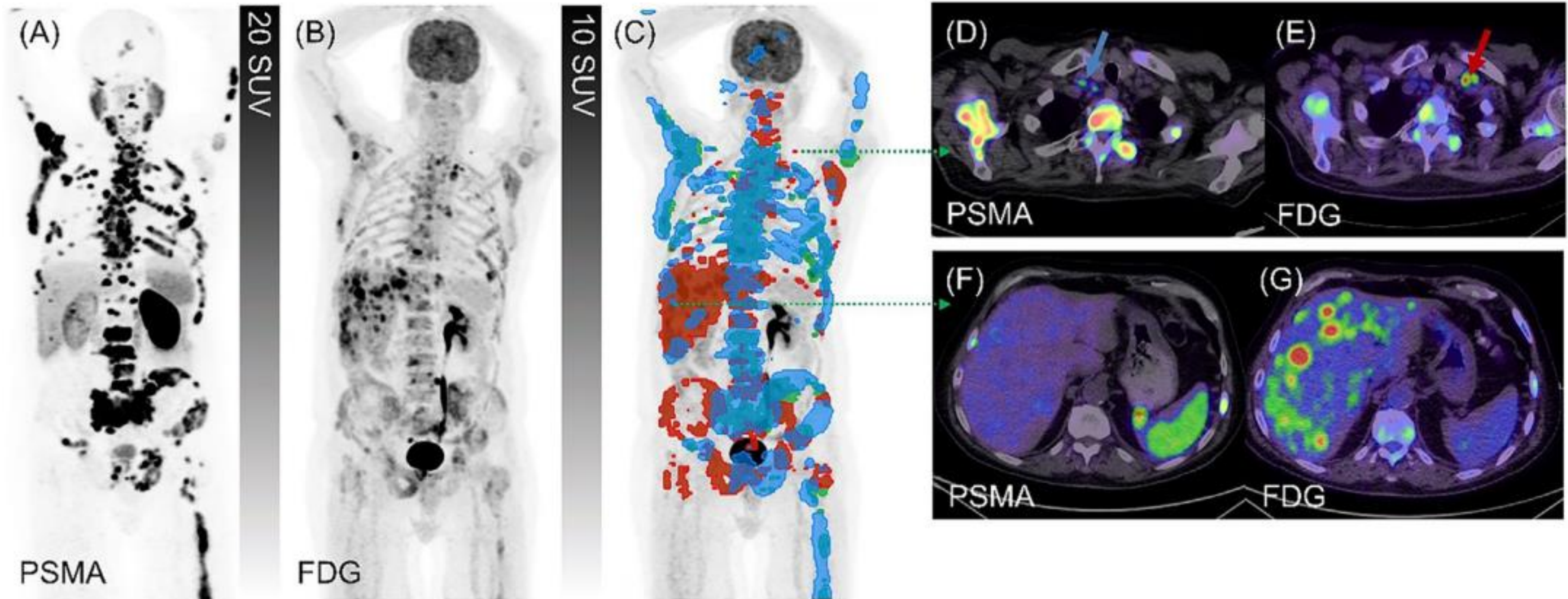
¹⁷⁷Lu-PSMA-617 Radioligand Therapy: VISION Trial

- Phase III VISION trial: 831 patients
- FDA approval of ¹⁷⁷Lu-PSMA-617 for advanced prostate cancer in **3/2022** (7 y. after the first report)



^{177}Lu -labelled PSMA Radioligand Therapy – *Patient Selection*

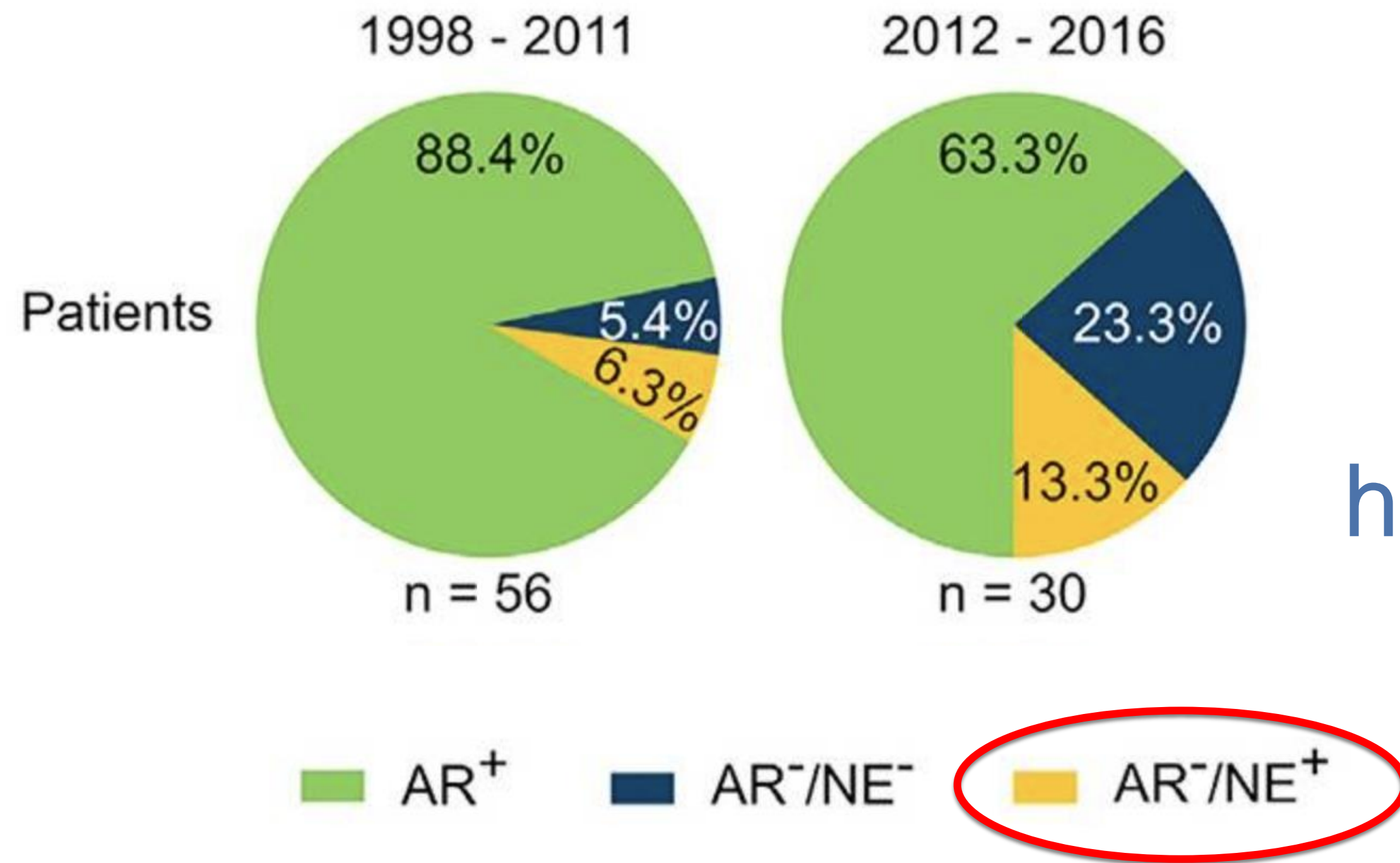
Thang et al., Eur Urol Oncol 2019



- 20-30% of mCRPC patients with low PSMA expression or discordant PSMA/FDG avidity have a poor prognosis, short survival, and are ineligible for ^{177}Lu -labelled PSMA RLT

Understanding Biology of Metastatic Prostate Cancer

Identifying Unmet Clinical Needs



Neuroendocrine Prostate Cancer (NEPC) is biologically lethal, heterogeneous, at present untreatable, and **diagnosed only by Bx.**

Unmet clinical need – In vivo diagnostics of NEPC

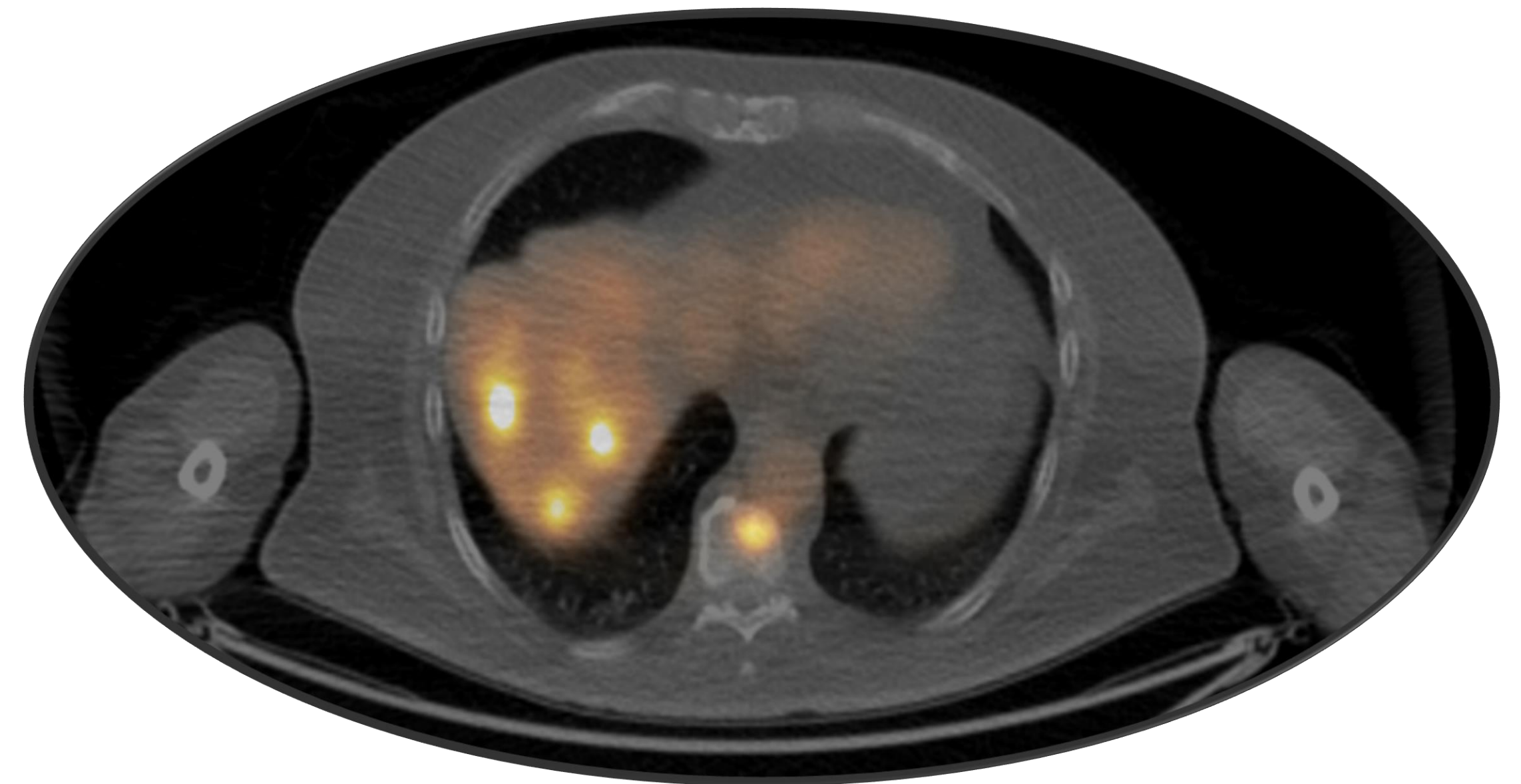
⁸⁹Zr-SC16 PET tracer for in vivo detecting and quantifying tumor DLL3 expression

Clinical Trial: DLL3 expression in SCLC using Zr-89 SC16 PET/CT imaging

*Delta-like ligand 3 (DLL3) is
overexpressed in NEPC*

Puca et al. Sci. Transl. Med. 2019

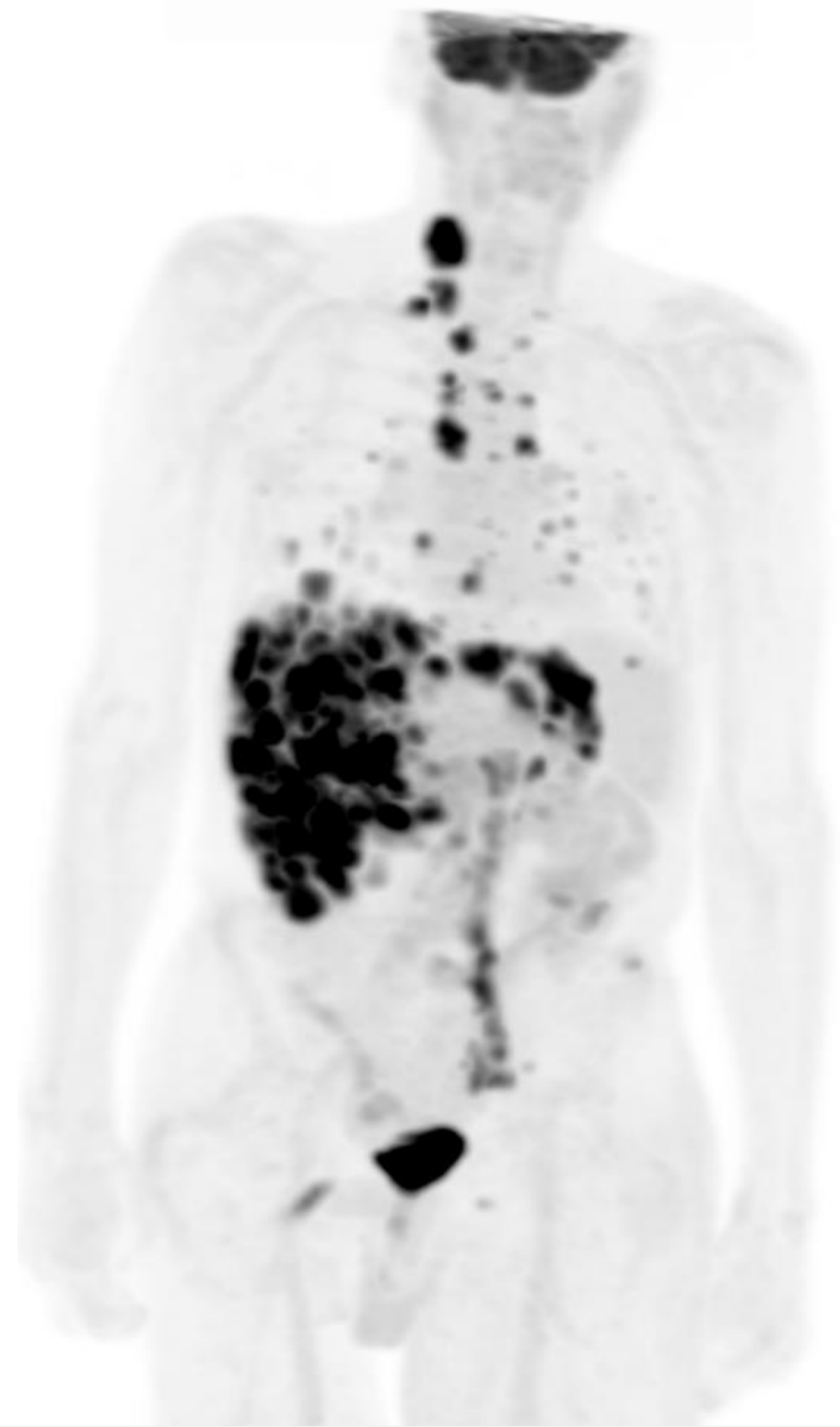
*DLL3 is also overexpressed in
small-cell lung cancer (SCLC)
and large-cell neuroendocrine
carcinoma (LCN)*



Zr-89 SC16 PET/CT - 5 days post tracer
injection; tracer-avid metastases in the liver and
spine in a 70 y. Stage IV SCLC

^{89}Zr -SC16 for detecting and quantifying in vivo tumor DLL3 expression in NE Prostate Cancer

FDG PET



DLL3 PET (3D)



PSMA PET

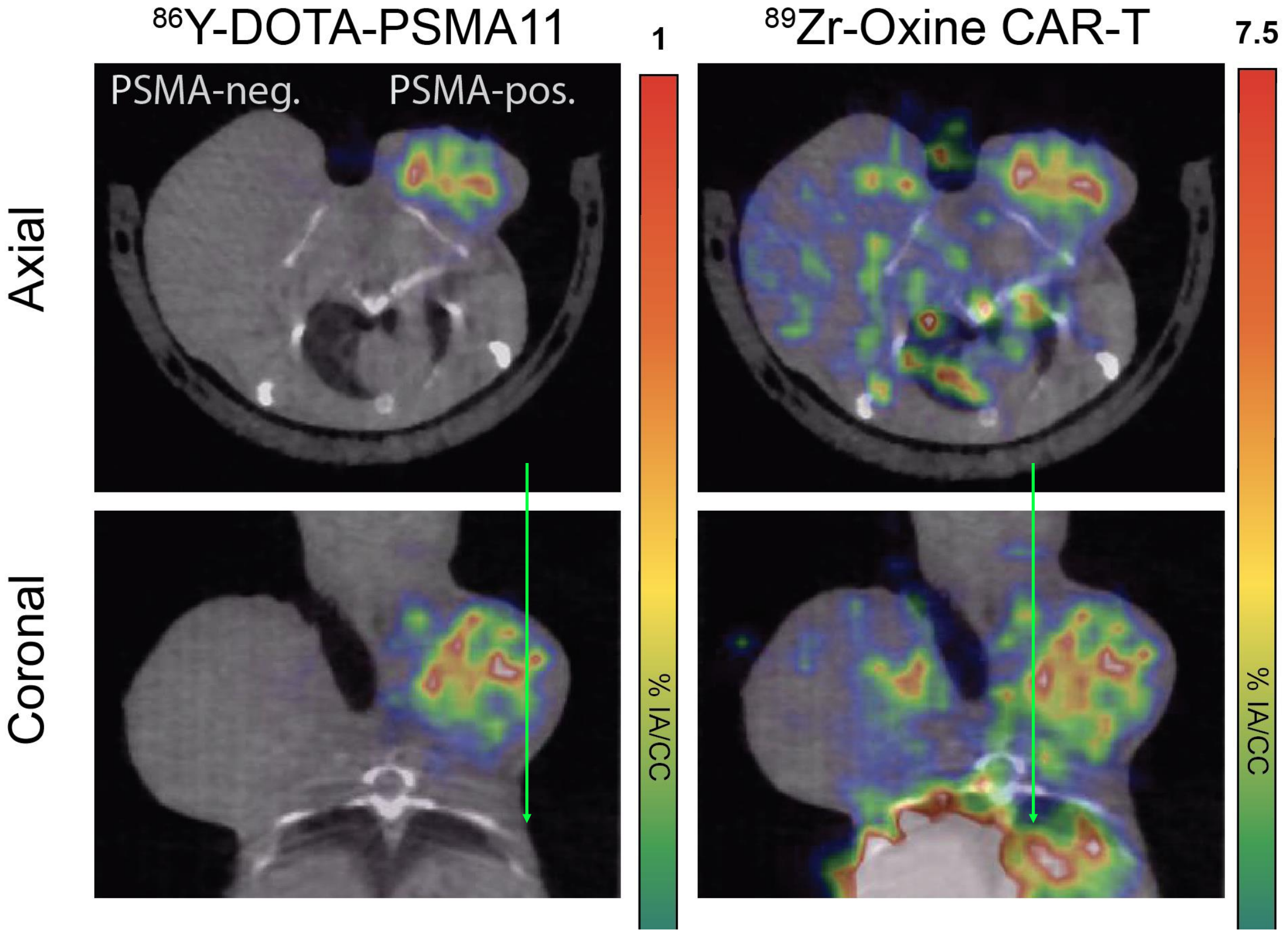
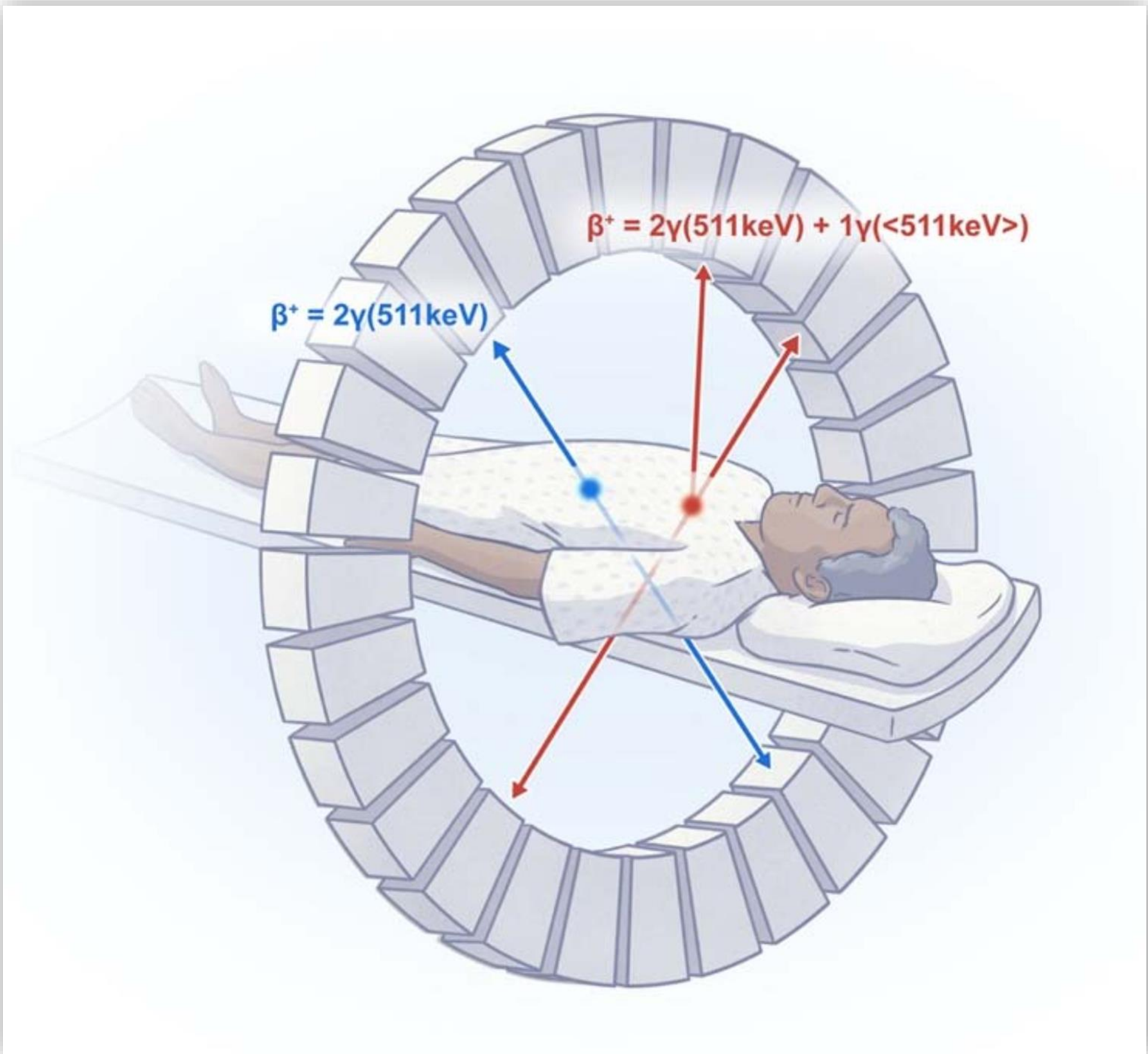


DLL3 PET (3D)



Delta-like ligand 3–targeted radioimmunotherapy for neuroendocrine prostate cancer; Lewis JS, PNAS 2022

Multicolor/ Multitracer PET



^{89}Zr -Oxine-labeled PSMA-targeting CAR-T cells

Prostate Cancer Imaging & Treatment

Strategies to enable novel diagnostic and therapeutic techniques to flourish

***“Learn from Yesterday,
Live for Today,
Hope for Tomorrow”
Albert Einstein***

Thank You!!!

***“Learn from Yesterday,
Live for Today,
Hope for Tomorrow”***
Albert Einstein

Prostate Cancer Imaging & Therapy

Lessons Learned & Looking Forward

- Understanding of the Biology of the disease
- New Imaging technology requires the well design of the prospective study with standardized imaging protocols and defined interpretation guidelines and training of the readers
- Credentialing of the chemist
- Standardize reporting
 1. Preclinical studies and rigorous regulatory assessment
 2. Multi-institutional Global, Multidisciplinary trial
 3. Standardization of interpretation
 4. Biomarkers and Patient selection (biomarkers)
 5. Always looking forward to unmet or emerging clinical needs

Prostate Cancer Imaging & Therapy

Lessons Learned & Looking Forward

- Understanding of the Biology of the disease
 - Looking forward to unmet or emerging clinical needs
-
1. Preclinical studies and rigorous regulatory assessment
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Integrated Diagnostics – *Data Governance*

Academic Medicine:

Culture of collaboration, trust, and sharing?

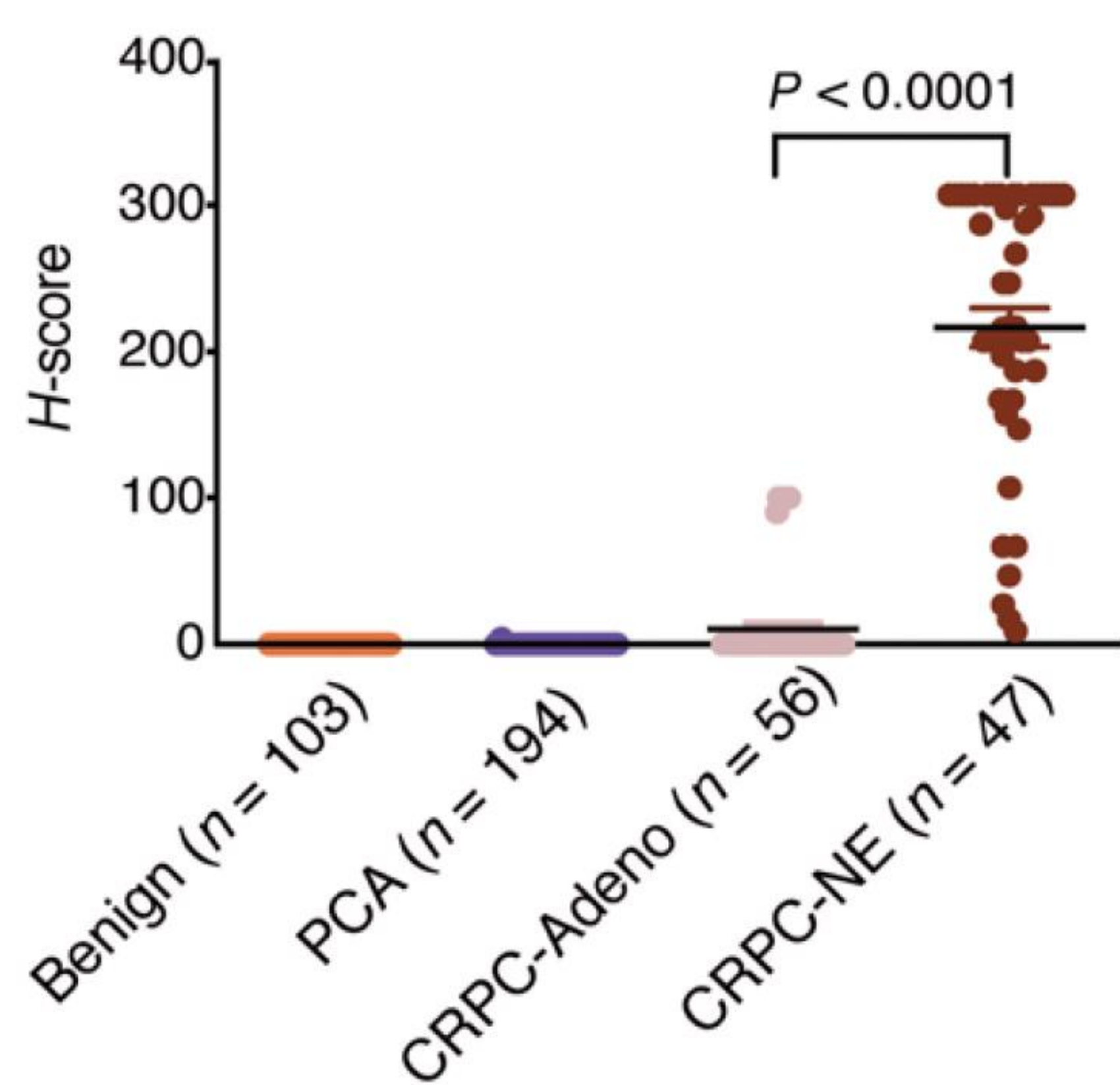


“Culture eats strategy for breakfast.”

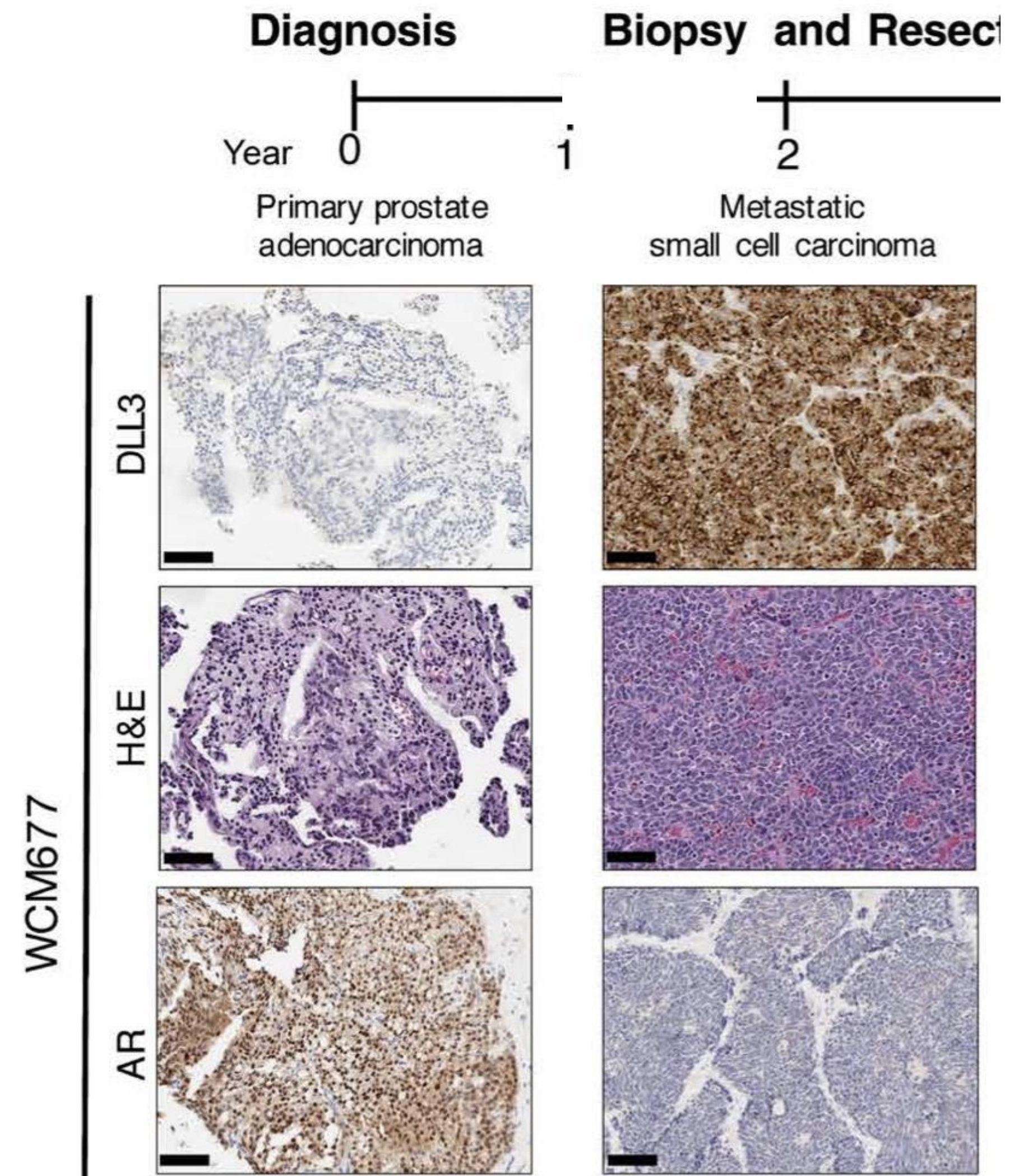
Peter Drucker

Data Sharing Requires Guardrails and Incentives!

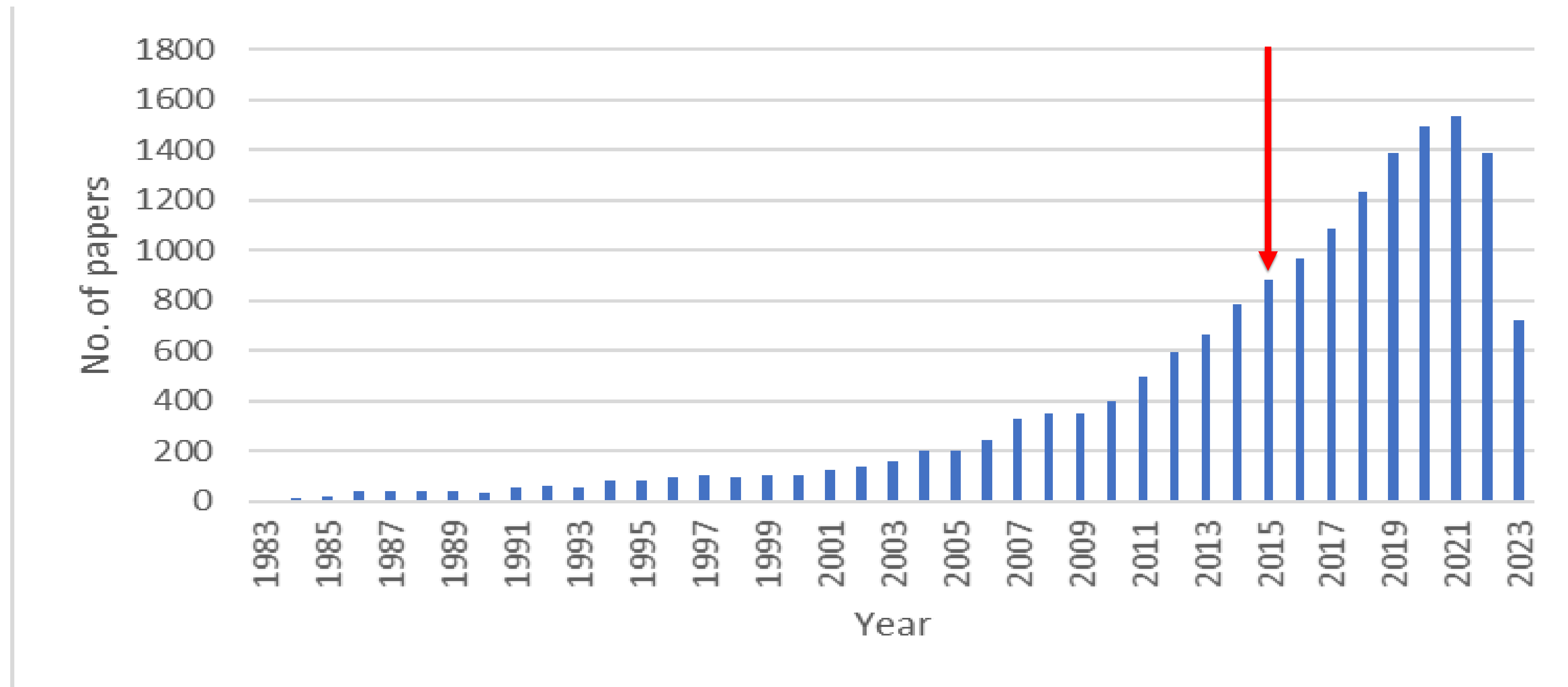
DLL3 expression is observed following androgen deprivation therapy in patients with NEPC



PCa (Adeno Ca): Detectable by AR tracers
 CRPC = Castration-resistant PCa
 NEPC: Not detectable by AR tracers



1982 - July 2023, there are >14,000 Publications on MR of the Prostate



Steyn JH, Smith FW: NMR imaging of the prostate; *Br J Urol.* 1982

Hricak H, Williams RD,: Anatomy and pathology of the male pelvis by MRI; *AJR* 1983

Integrated Diagnostics – *Multifaceted Opportunities*

- ***Clinical:*** “*AI-facilitated Tumor Boards*” - Multidisciplinary & Interdisciplinary workflow organized along disease-specific pathways e.g., MSKCC pilot projects – (Solid tumors: Brain, Neuroendocrine, & Ovary. Liquid tumors: Lymphoma)
- ***Research:*** endless opportunities for new discoveries through annotated & curated large database
- ***Education***
- ***Patient access:*** to data and shared decision making
- ***Health Equity:*** Enabling personalized precision cancer care globally

Towards Precision Oncology

Reducing Medical Errors & Improving Outcomes


Predictors of response to ^{177}Lu - PSMA-617


In 2012 an expert consensus group of the European Society of Urogenital Radiology (ESUR) introduced the version 1 (v1) of the Prostate Imaging Reporting and Data System (PI-RADS)



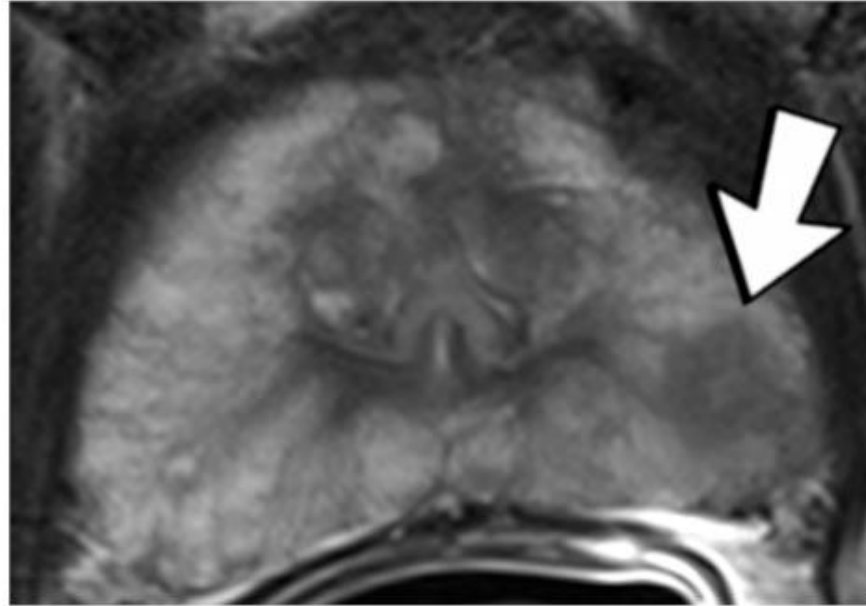
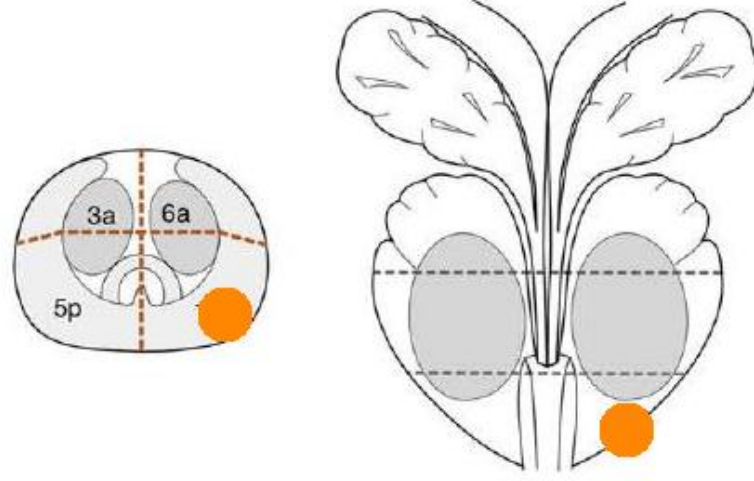


ESUR: PI-RADS (v. 1) version - December 2011

ACR, ESUR, & AdMeTech Found. PI-RADS (v. 2) - March 2019

 Memorial Sloan Kettering Cancer Center

 J. Doe MD | [Logout](#)

John Doe M, 65 y, ID: 0000000000 Current Case Unit: Urology

Timeline	Data Summary	Synopsis	Notes
<ul style="list-style-type: none"> ○ 08/14 Appendectomy [HIS] ○ 08/14 PSA = 1.3 ng/ml [Laboratory Medicine] ○ 07/18 PSA = 22.8 ng/ml [Laboratory Medicine] ○ 08/18 MRI: PI-RADS 5 [Radiology] ○ 08/18 Biopsy: Gl. 4+3 [Pathology] 	<p>Key Image:</p>  <ul style="list-style-type: none"> - PSA density 0.34 ng/ml² - PI-RADS 5 lesion left apical PZ - Probable ECE - Abuts anterior rectum - No evidence for nodal disease [Radiology] - 4/60 cores positive for PCa - Gleason 4+3 - TCCL 16 mm [Pathology] - Patient has prior Hx of prior 	<div style="display: flex; justify-content: space-around;">  </div> <div style="display: flex; justify-content: space-around; margin-top: 10px;"> T3a N0 M0 </div> <div style="background-color: orange; color: white; text-align: center; padding: 5px; margin-top: 10px;">  </div> <ul style="list-style-type: none"> - Moderate cardiovascular risk Agatston Score = 381 (04/18) [Radiology] - Prior MRSA colonization (05/12) [Microbiology] 	<div style="background-color: #eee; padding: 10px; min-height: 150px;"> <p>Add note here ...</p> </div> <div style="background-color: #0056b3; color: white; text-align: center; padding: 5px; margin-top: 10px;">  Save </div>

Standardization in Reporting & User-friendly Dashboard

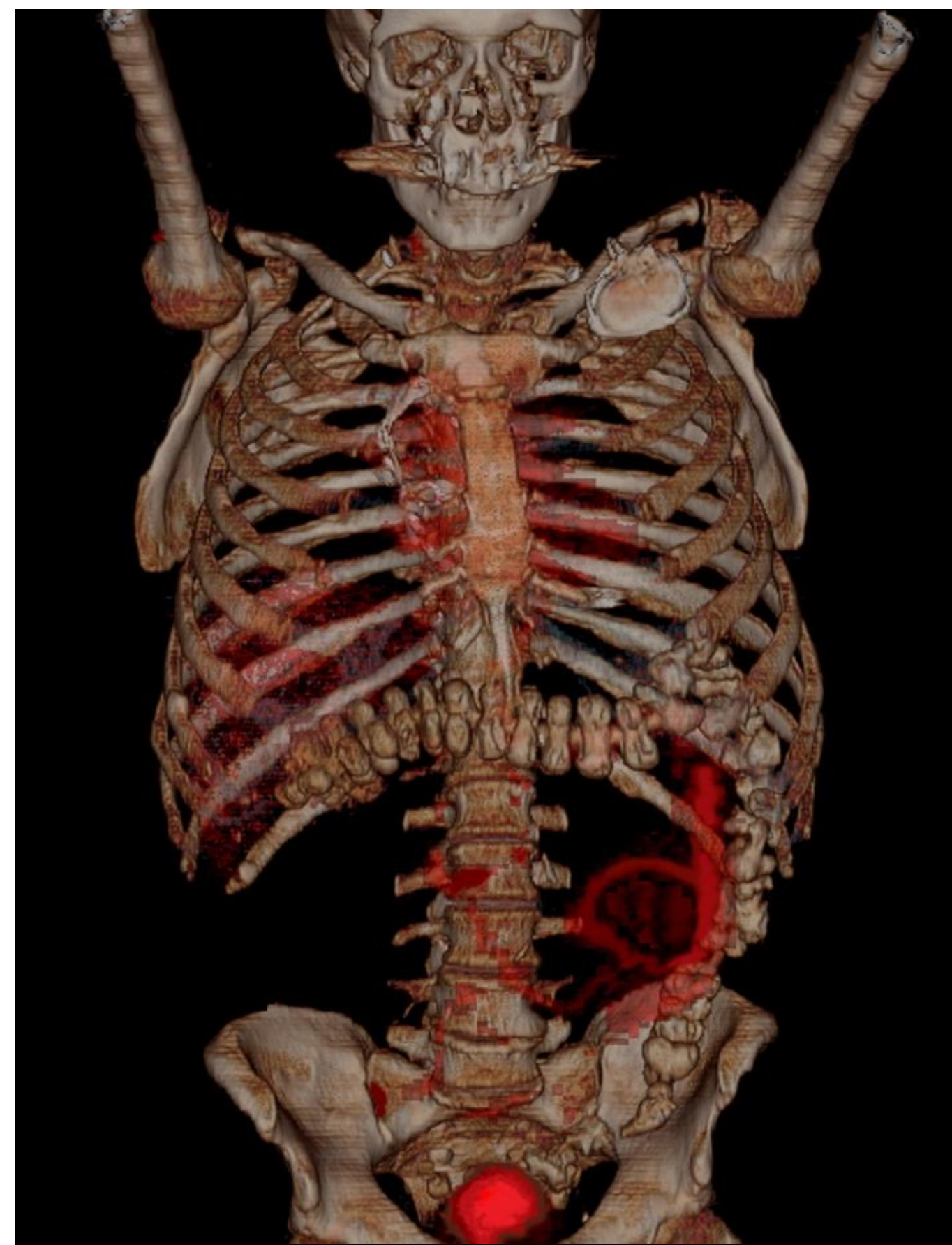
Drug Development for the 21st Century

Targeted Molecular Imaging as a Predictive Biomarker in Clinical Trials

Targeted Imaging / Targeted Therapy



¹⁸F-FDHT PET/CT
Baseline



¹⁸F-FDHT PET/CT
4 wks after Enzalutamide

The majority of patients had recurrence within 12 months**

*Scher et al; Lancet: 2010

** Sawyers et al: Nature Reviews Cancer: 2015



IS3R 2023

Prostate Cancer Imaging & Treatment

Strategies to enable novel diagnostic and therapeutic techniques to flourish

Hedvig Hricak, M.D., Ph.D., Dr.h.c^m

Carroll and Milton Petrie Endowed Chair of Radiology

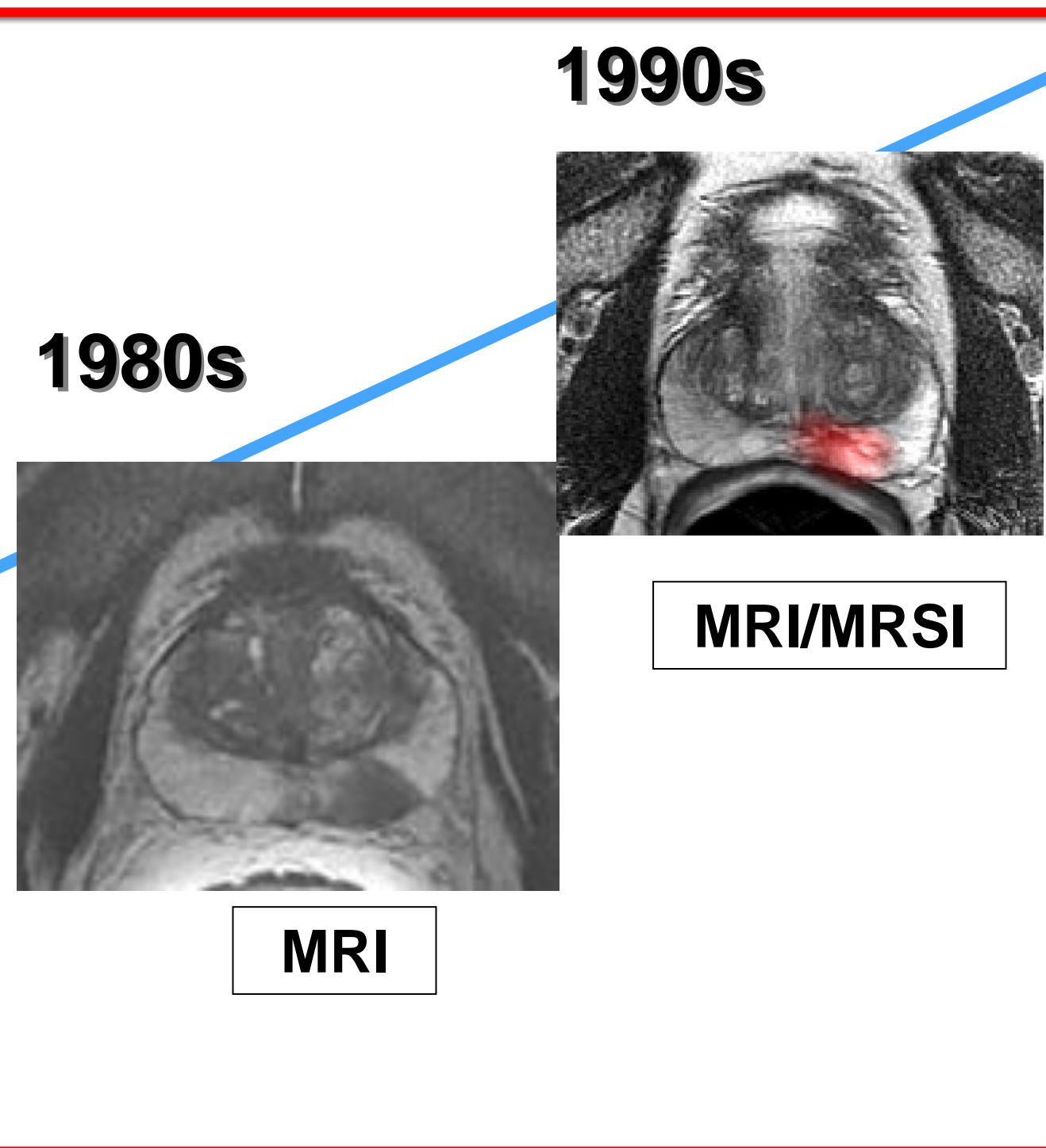
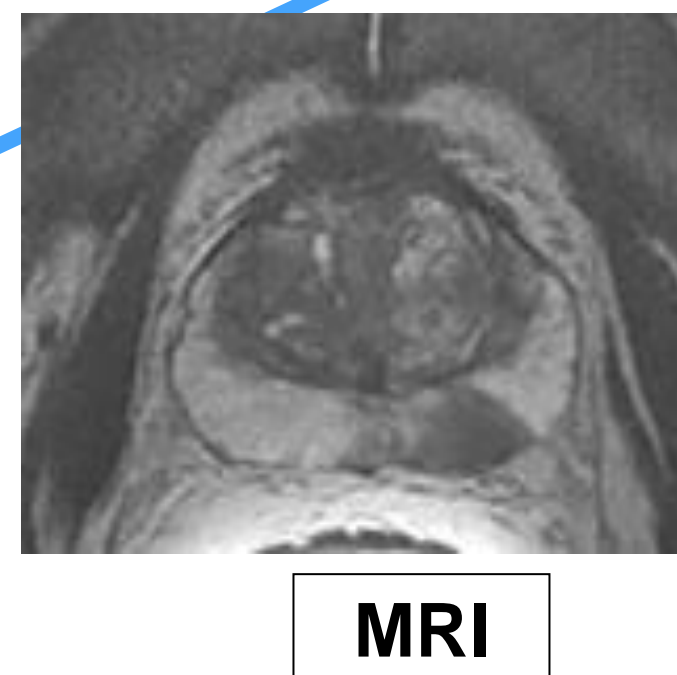
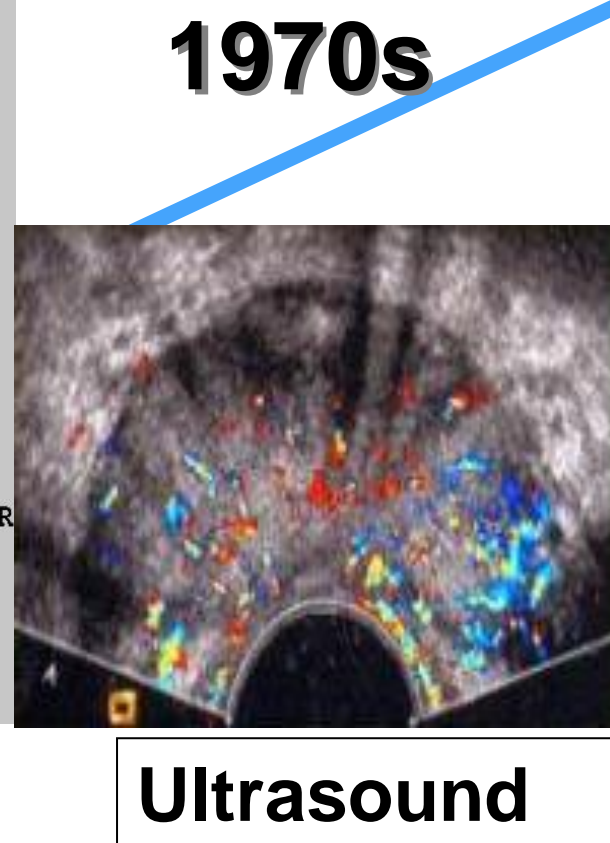
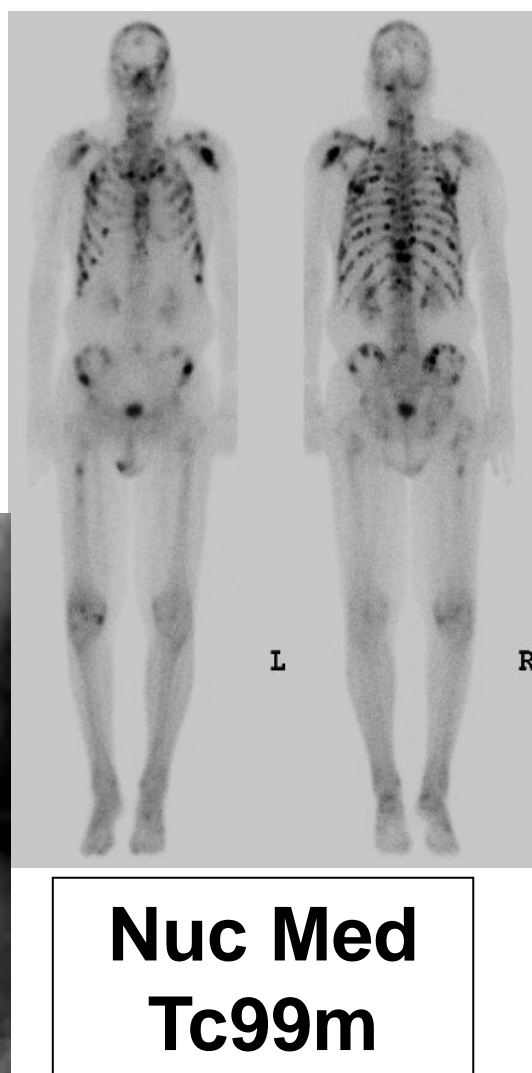
Professor Gerstner Sloan-Kettering Graduate School of Biomedical Sciences

Memorial Sloan Kettering Cancer Center

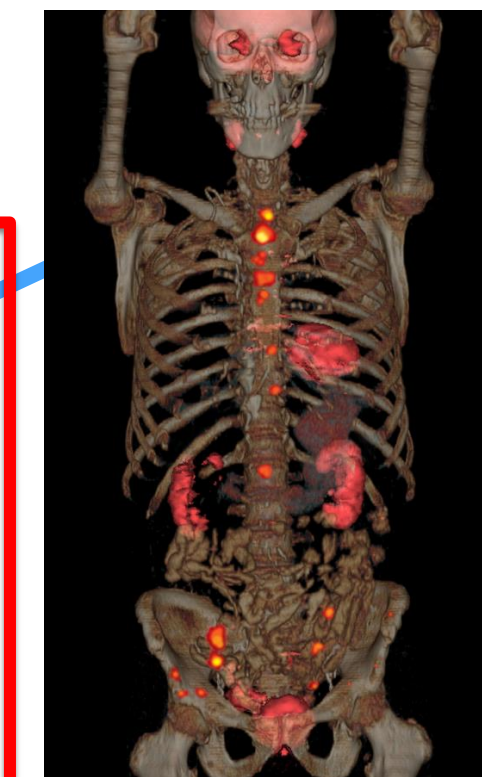
Professor of Radiology, Weill Medical College of Cornell University

Imaging Prostate Cancer

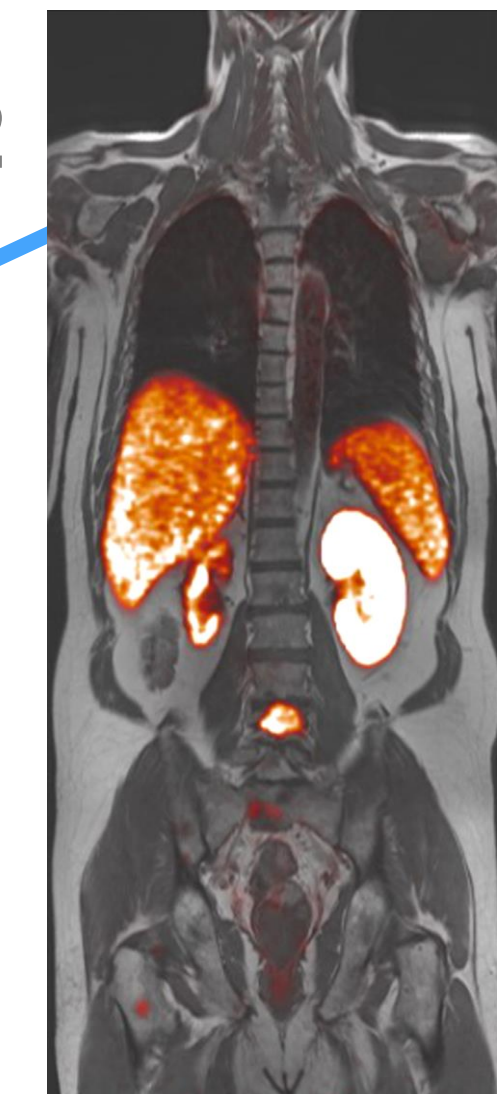
From Helpful to Essential



2000



2012

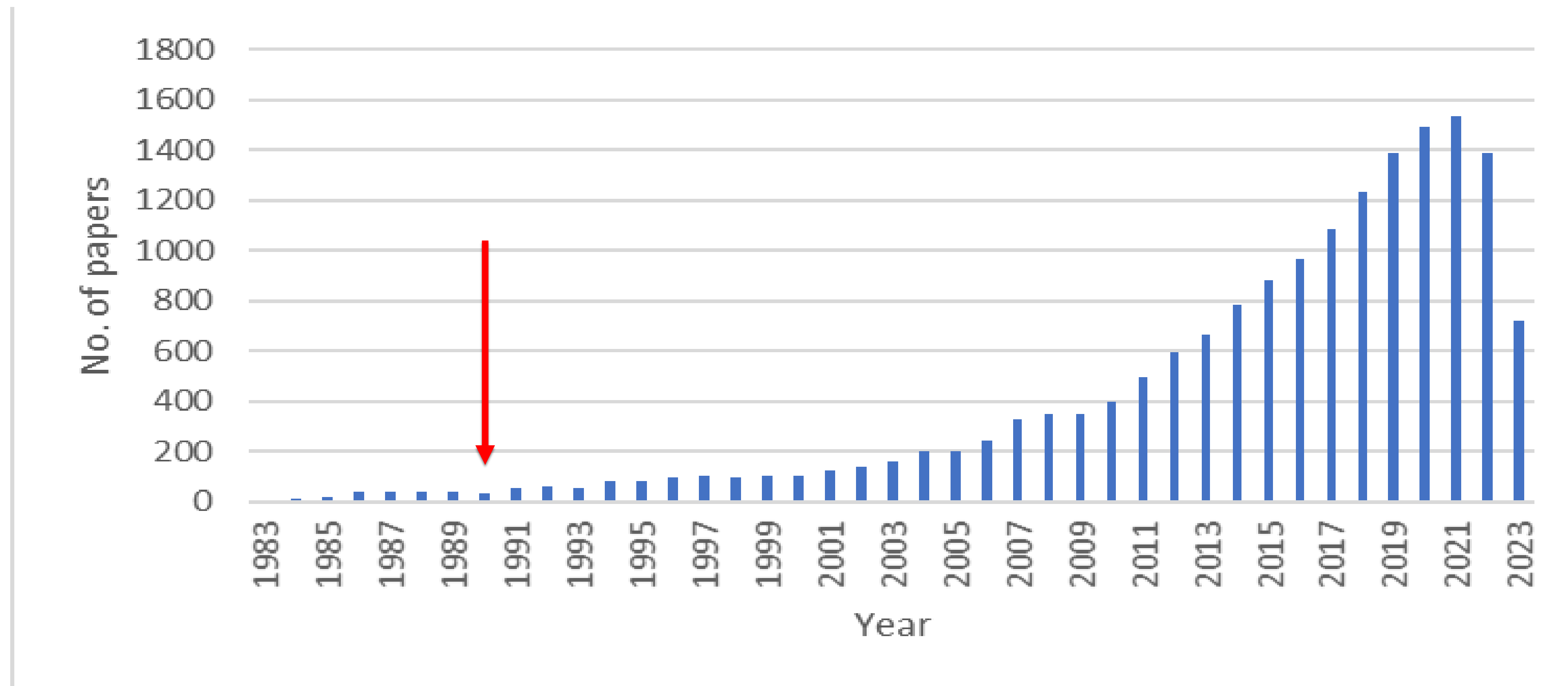


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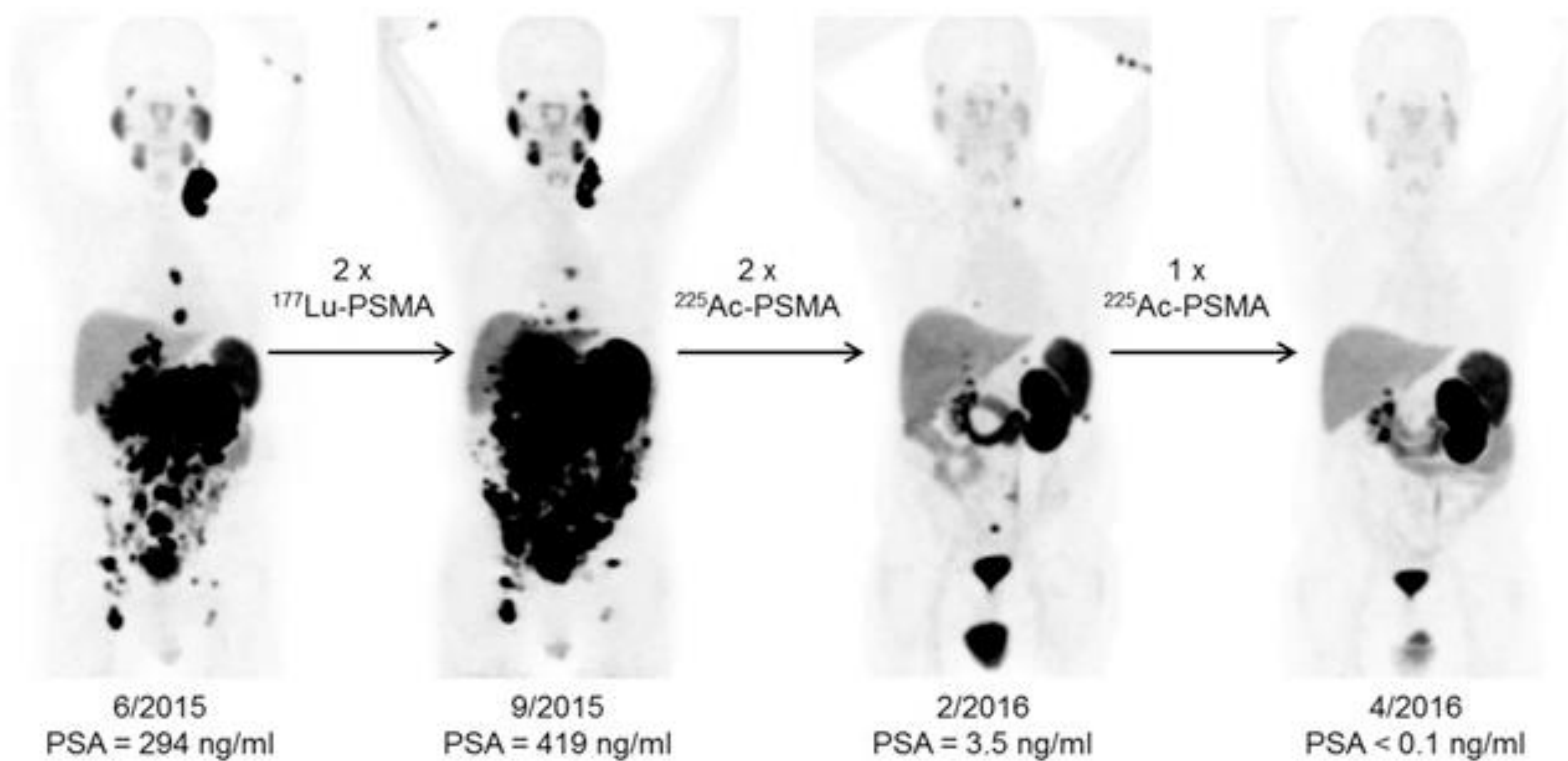
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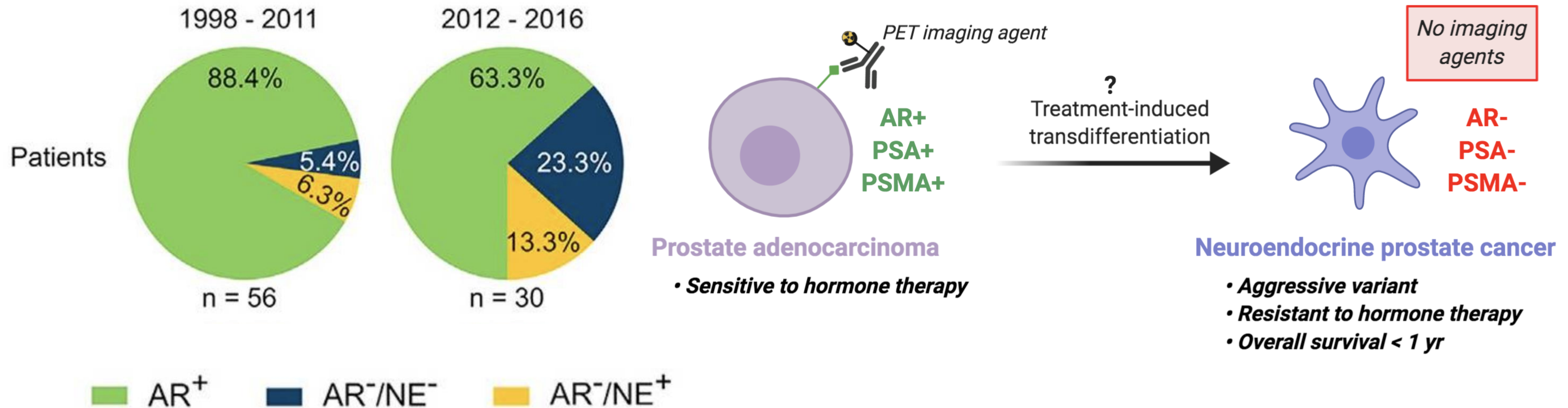


PSMA-directed Alpha Therapy – induces complete remissions *after Lu-177 failures*



Evolving Biology of Metastatic Prostate Cancer

Identifying Unmet Clinical Needs



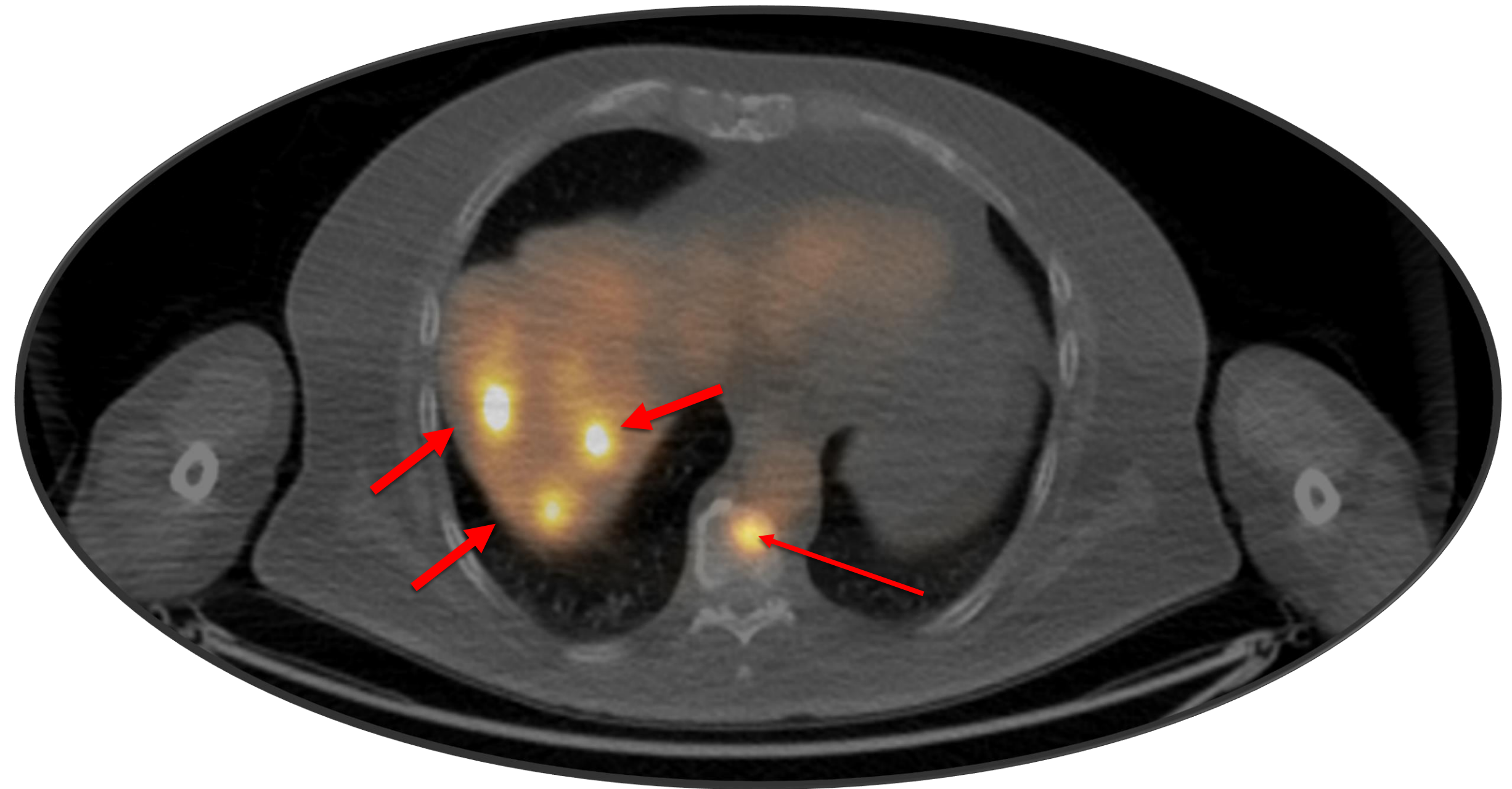
Neuroendocrine Prostate Cancer (NEPC) is biologically lethal, diverse, heterogeneous, and at present untreatable.
Regardless of total tumor burden, overall survival is <1 year!

⁸⁹Zr-SC16 PET tracer for detecting and quantifying in vivo tumor DLL3 expression

DLL3 expression in SCLC – Zr-89 SC16 PET/CT imaging

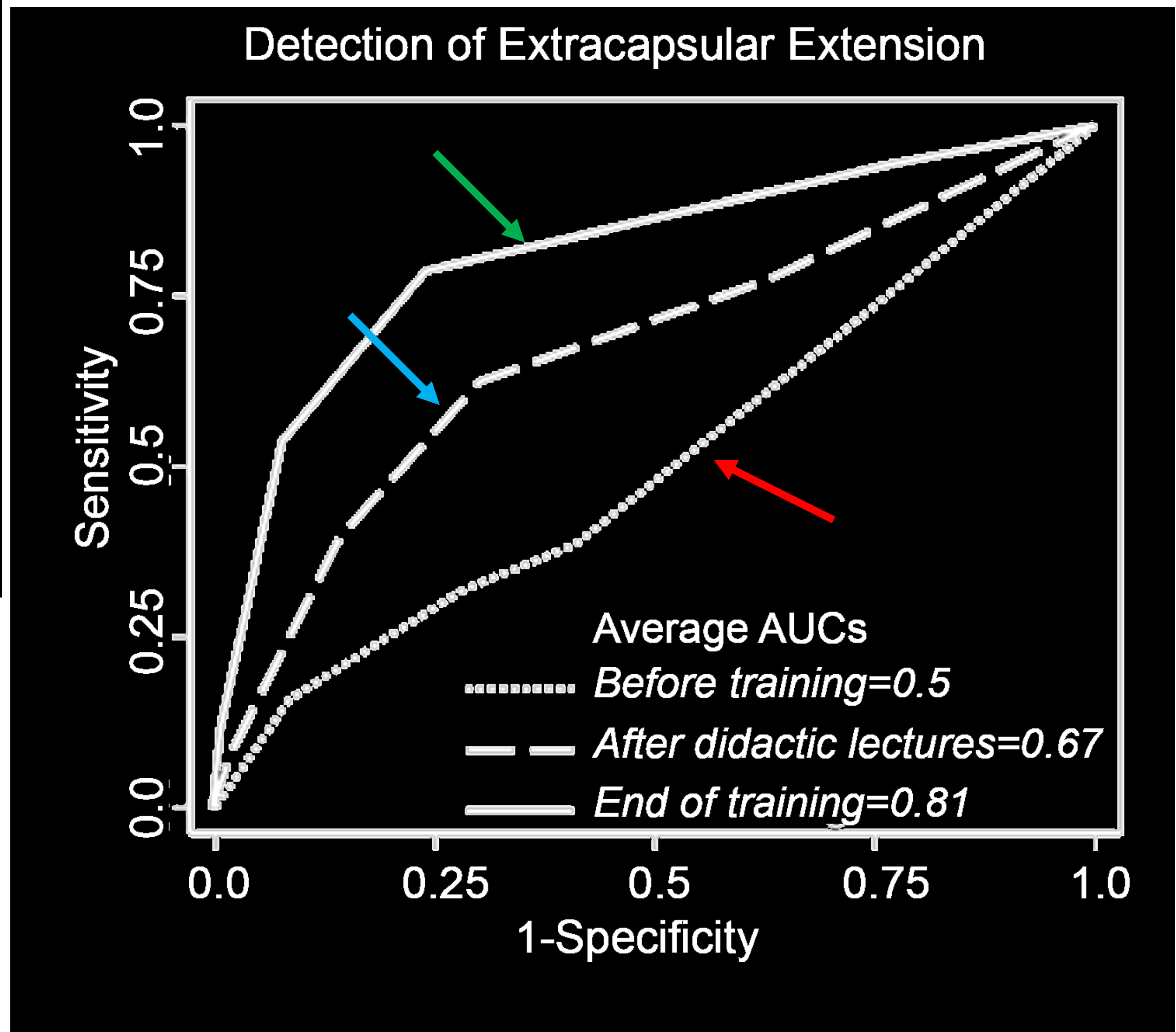
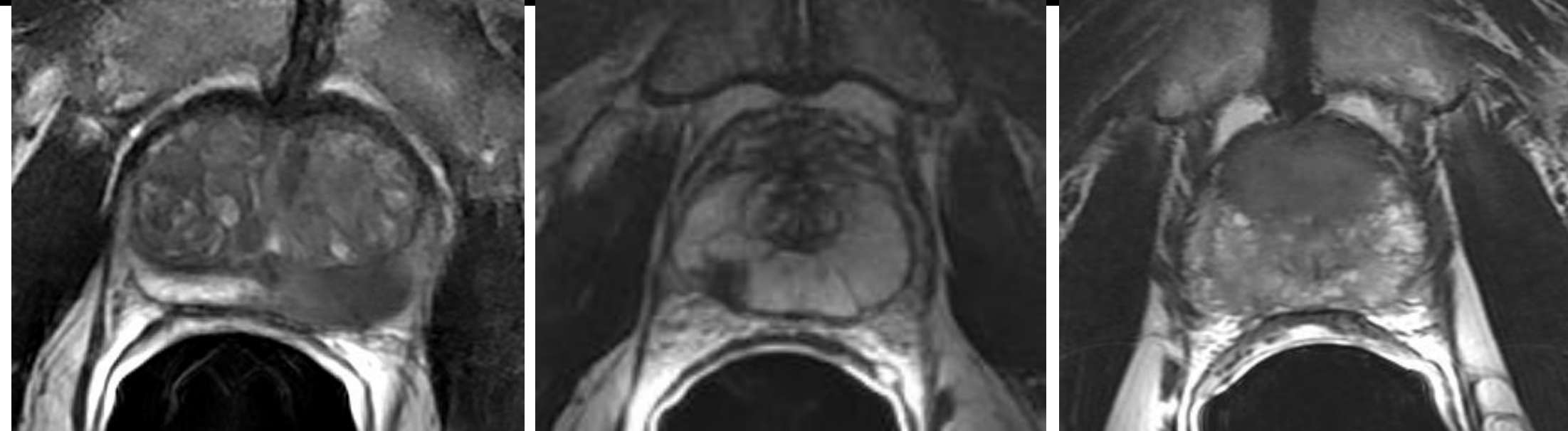
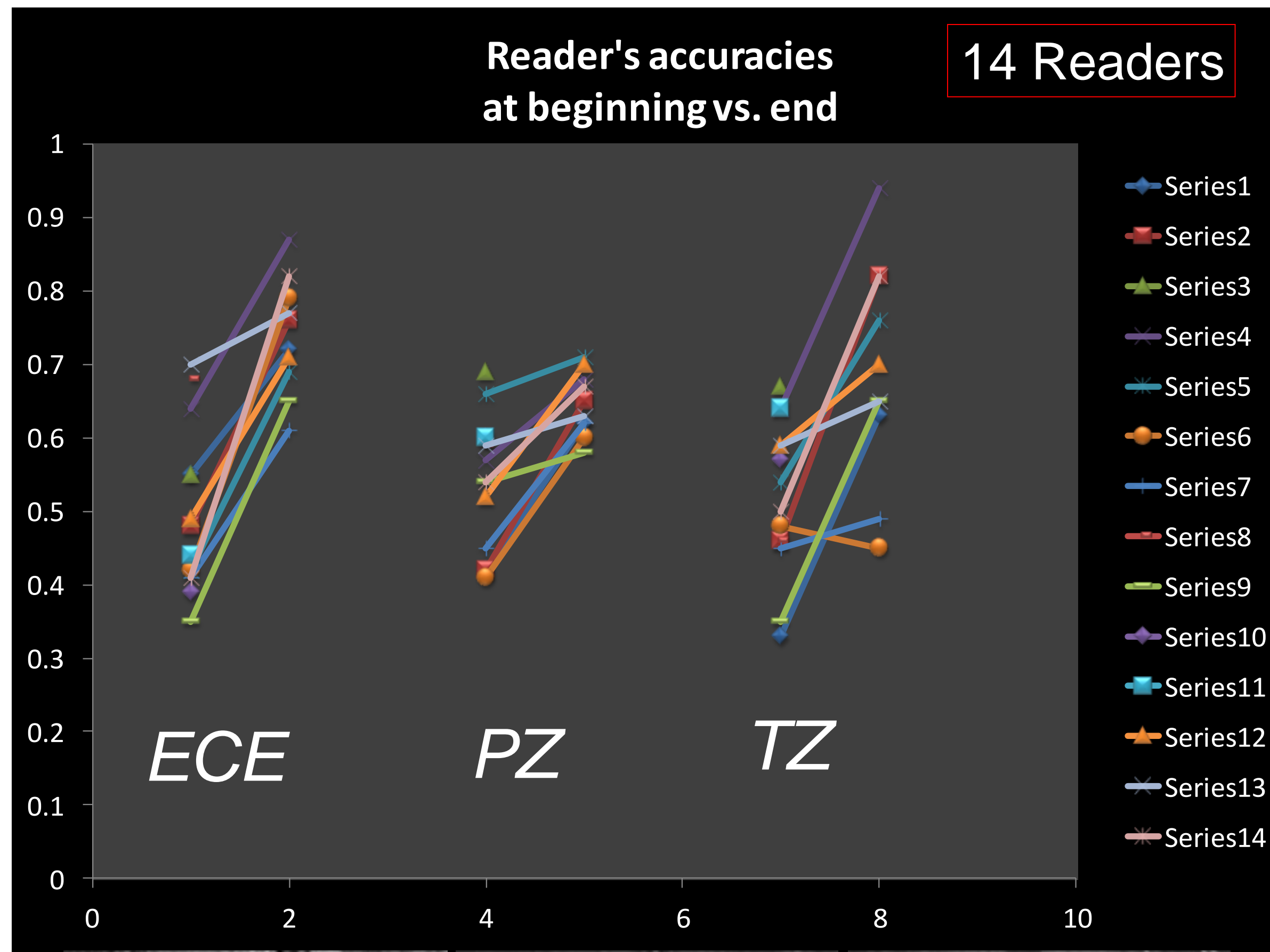
70 y. Stage IV SCLC

Increased expression of delta-like 3 (DLL3) is present in neuroendocrine tumors, including small-cell lung cancer (SCLC), high-grade pulmonary neuroendocrine tumors, and large-cell neuroendocrine carcinoma (LCNEC)



Zr-89 SC16 PET/CT - 5 days post tracer injection
DLL3 tracer-avid metastases in the liver and spine

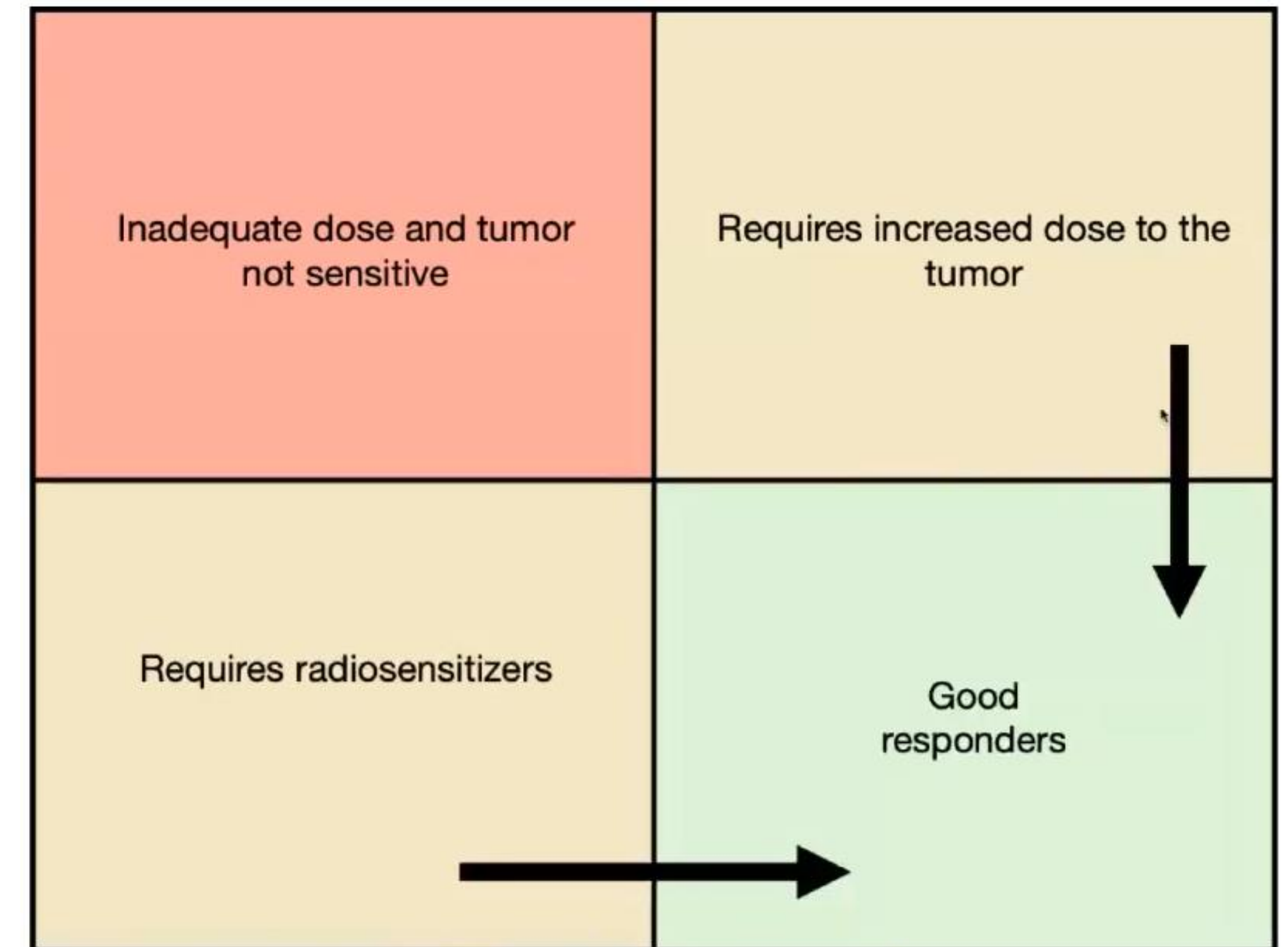
Learning Curve in Reading Prostate MR



O. Akin, C. Reidl et al: European Radiology 2009

Predictors of Response to ^{177}Lu -PSMA-617 RLT

- Response rate 50-60%
- Need for biomarkers to predict response
- Radiation dose - dosimetry
- Tumor sensitivity to radiation
- Level of PSMA expression



Courtesy Doris Leithner NYU

PSMA – PET- Prostate Cancer Molecular Imaging Standardized Evaluation

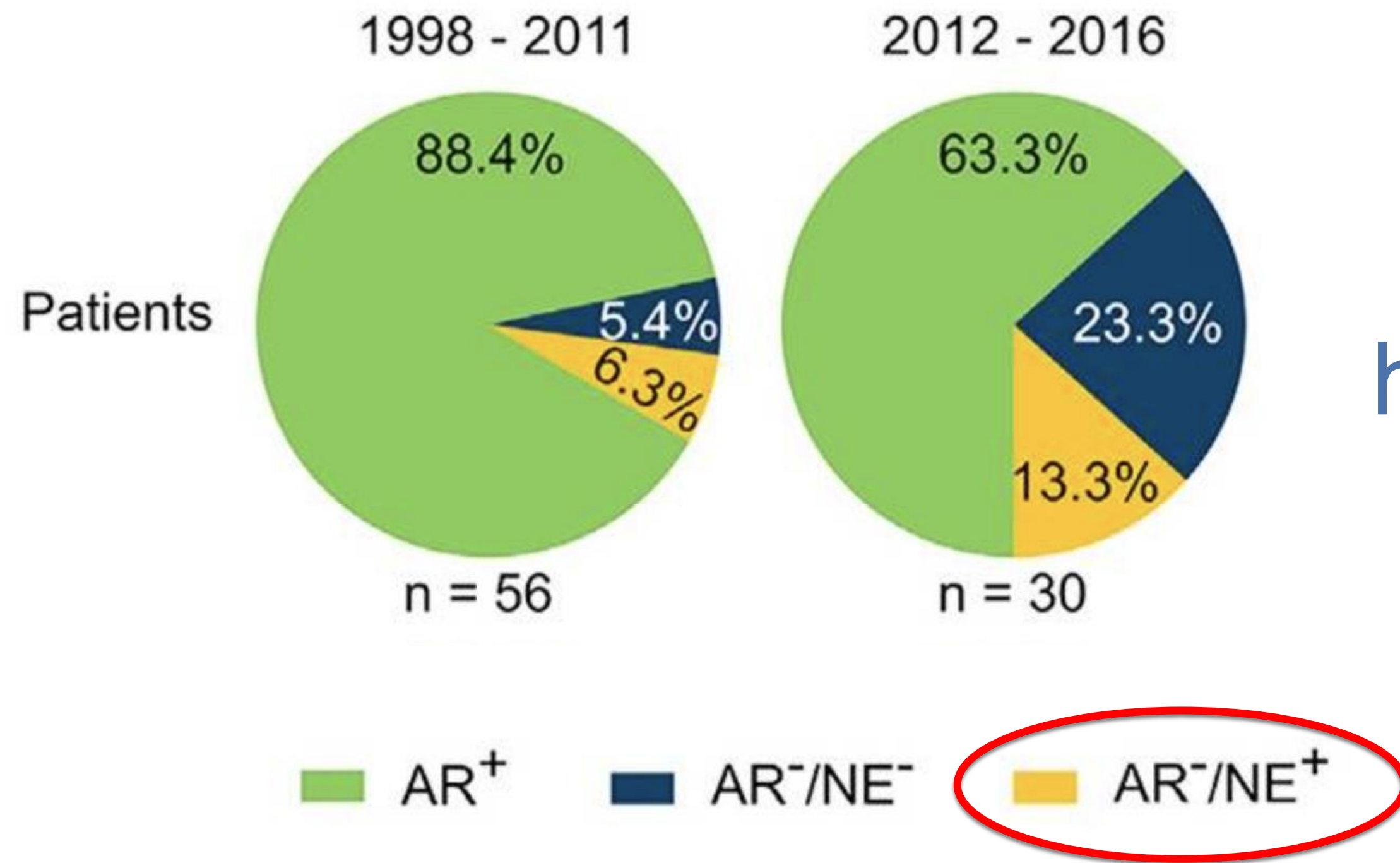
PROMISE criteria for whole-body molecular imaging TNM staging (**miTNM staging**) for PCa disease extent on PSMA-PET

<i>Local tumor (T)</i>		
miT0		No local tumor
miT2		Organ-confined tumor
	u	Unifocality
	m	Multifocality
miT3		Non-organ-confined tumor
	a	Extracapsular extension
	b	Tumor invades seminal vesicle(s)
miT4		Tumor invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic
miTr		Presence of local recurrence after radical prostatectomy
<i>Intrapelvic nodes (N)</i>		
miN0		No positive pelvic lymph nodes
miN1		Single lymph node region harbors lymph node metastases, report location by a standardized template
miN2		Multiple (≥ 2) lymph node regions harbor lymph node metastases, report location(s) by a standardized template
<i>Distant metastases (M)</i>		
miM0		No distant metastasis
miM1		Distant metastasis
	a	Distant lymph node region(s)
	b	Bone(s), additionally report pattern and involved bone(s) in case of unifocal or oligometastatic

Seifert et al.: Prostate Cancer Molecular Imaging Standardized Evaluation Framework Including Response Evaluation for Clinical Trials (PROMISE V2); European Urology May 2023

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Neuroendocrine Prostate Cancer (NEPC) is biologically lethal, heterogeneous, at present untreatable, and **diagnosed only by Bx.**

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Unmet clinical need – In vivo diagnosis of NEPC