Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

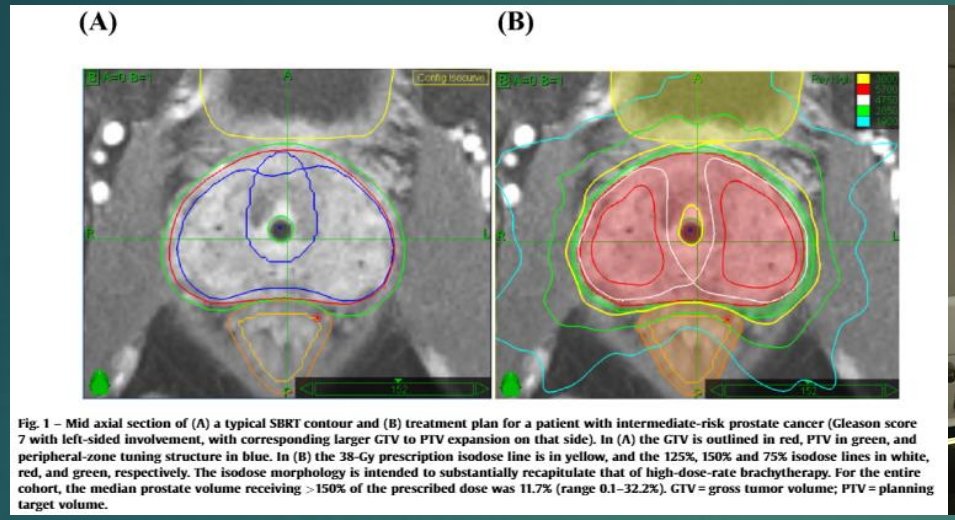


Fig. 1 – Mid axial section of (A) a typical SBRT contour and (B) treatment plan for a patient with intermediate-risk prostate cancer (Gleason score 7 with left-sided involvement, with corresponding larger GTV to PTV expansion on that side). In (A) the GTV is outlined in red, PTV in green, and peripheral-zone tuning structure in blue. In (B) the 38-Gy prescription isodose line is in yellow, and the 125%, 150% and 75% isodose lines in white, red, and green, respectively. The isodose morphology is intended to substantially recapitulate that of high-dose-rate brachytherapy. For the entire cohort, the median prostate volume receiving ≥150% of the prescribed dose was 11.7% (range 0.1–32.2%). GTV = gross tumor volume; PTV = planning target volume.

Eligibility Requirements (for CK SBRT salvage protocol)

> 2 years since their original RT course

Biopsy proof of recurrence is mandated in the protocol

Radiologically NED beyond the prostate

No complications > grade 1 from their prior RT course

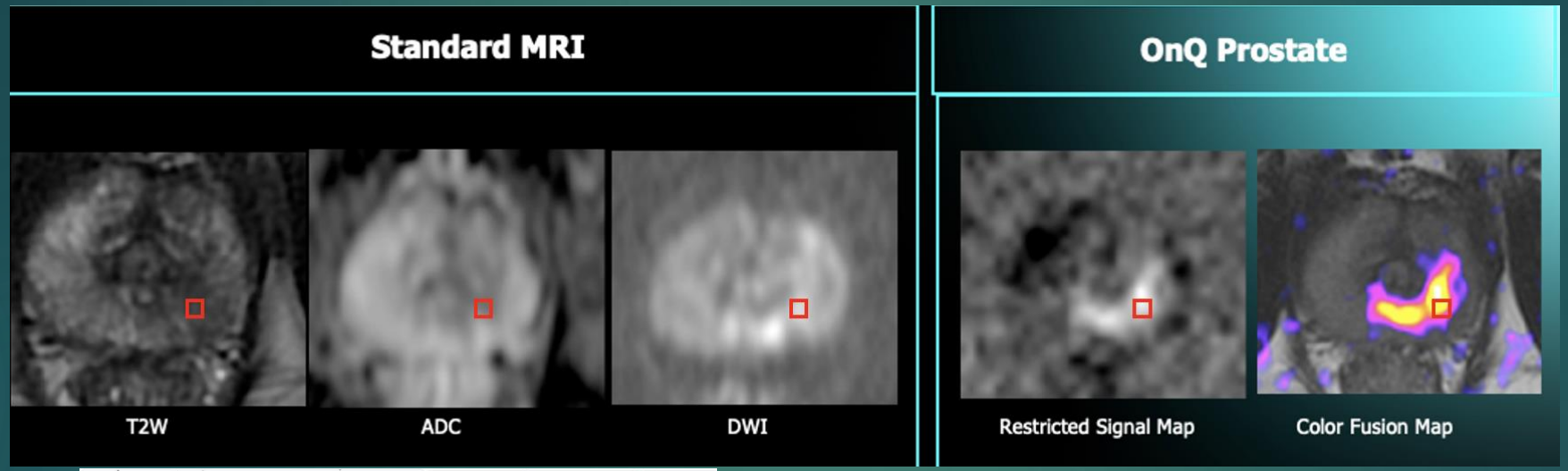
In 2007 . . . . (when this protocol was written . . .)

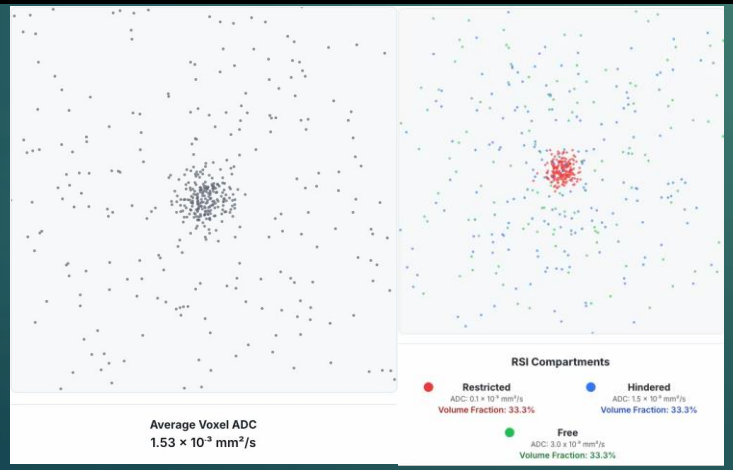
PSMA PET/CT . . . hadn't been invented . .

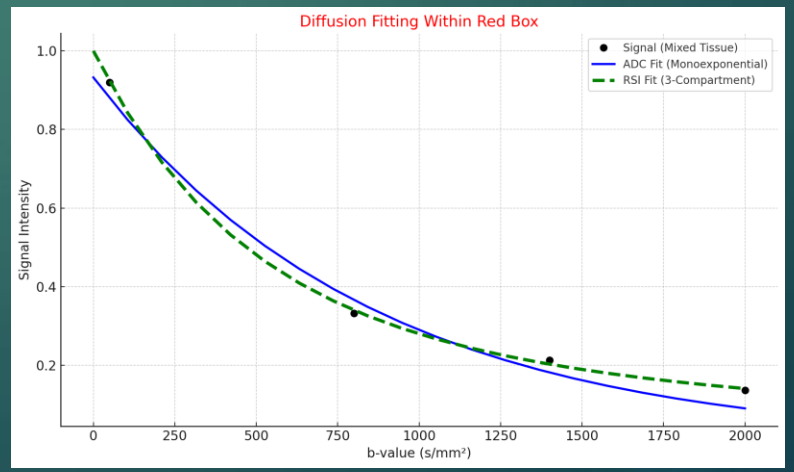
My favorite MRI sequence (RSI) . . Hadn't been invented

Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

- **Chapter One:**
- **"New and improved" MRI . . .**







Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

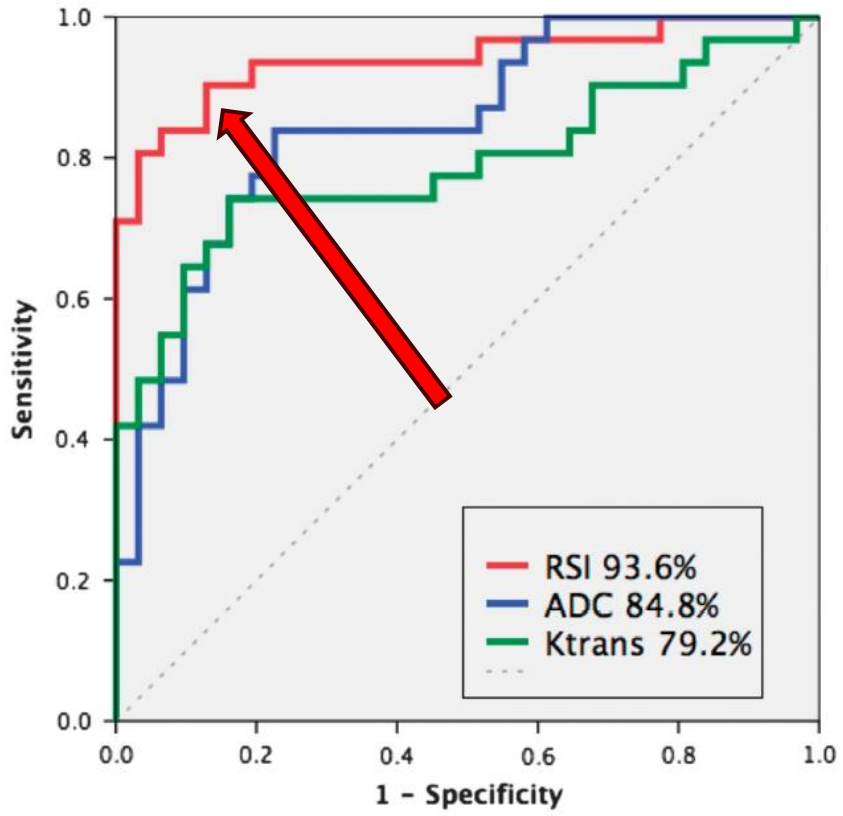


Figure 3. Receiver-operating characteristic (ROC) curves demonstrating performance of restriction spectrum imaging (RSI)-magnetic resonance imaging *z*-score, conventional ADC values and K^{trans} for the quantitative discrimination of prostate cancer from normal peripheral zone. Respective areas under the ROC curve are listed in the legend.

ORIGINAL ARTICLE

In vivo prostate cancer detection and grading using restriction spectrum imaging-MRI

KC McCammack[1], CJ Kane[2,7], JK Parsons[2,7], NS White[1], NM Schenker-Ahmed[1], JM Kuperman[1], H Bartsch[1], RS Desikan[1], RA Rakow-Penner[1], D Adams[3], MA Liss[4], RF Mattrey[1], WG Bradley[1], DJA Margolis[5], SS Raman[5], A Shabaik[3], AM Dale[1,6] and DS Karow[1]

BACKGROUND: Magnetic resonance imaging (MRI) is emerging as a robust, noninvasive method for detecting and characterizing prostate cancer (PCa), but limitations remain in its ability to distinguish cancerous from non-cancerous tissue. We evaluated the performance of a novel MRI technique, restriction spectrum imaging (RSI-MRI), to quantitatively detect and grade PCa compared with current standard-of-care MRI.

METHODS: In a retrospective evaluation of 33 patients with biopsy-proven PCa who underwent RSI-MRI and standard MRI before radical prostatectomy, receiver-operating characteristic (ROC) curves were performed for RSI-MRI and each quantitative MRI term, with area under the ROC curve (AUC) used to compare each term's ability to differentiate between PCa and normal prostate. Spearman rank-order correlations were performed to assess each term's ability to predict PCa grade in the radical prostatectomy specimens.

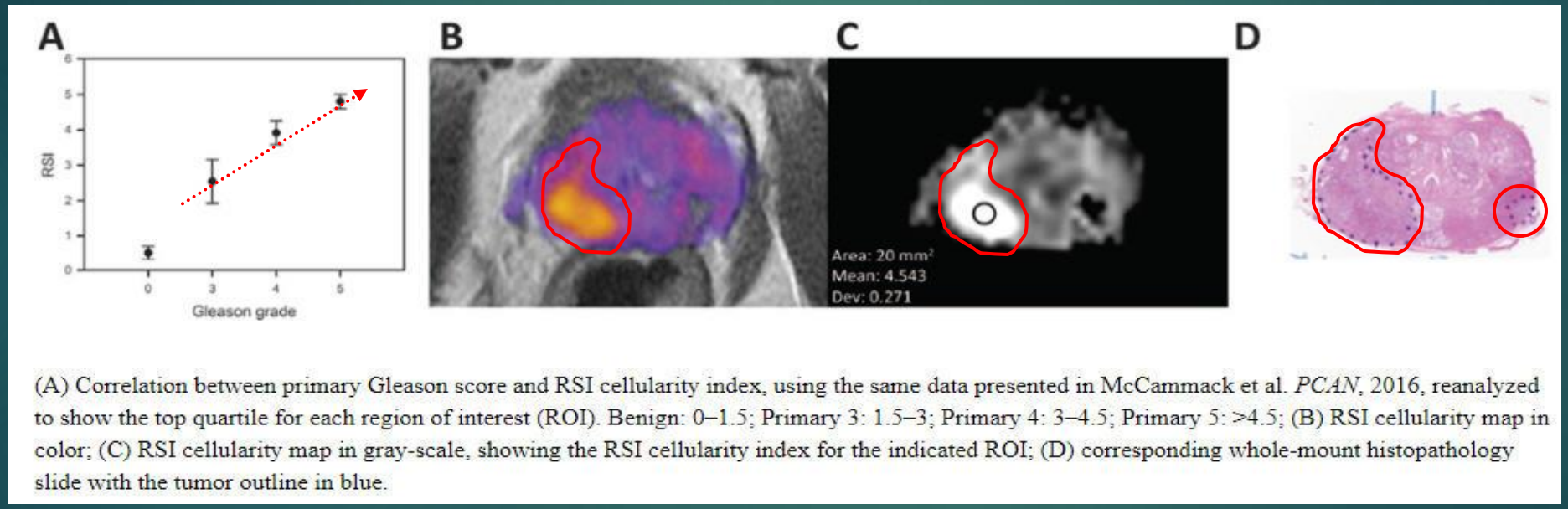
RESULTS: RSI-MRI demonstrated superior differentiation of PCa from normal tissue, with AUC of 0.94 and 0.85 for RSI-MRI and conventional diffusion MRI, respectively ($P = 0.04$). RSI-MRI also demonstrated superior performance in predicting PCa aggressiveness, with Spearman rank-order correlation coefficients of 0.53 ($P = 0.002$) and −0.42 ($P = 0.01$) for RSI-MRI and conventional diffusion MRI, respectively, with tumor grade.

CONCLUSIONS: RSI-MRI significantly improves upon current noninvasive PCa imaging and may potentially enhance its diagnosis and characterization.

Prostate Cancer and Prostatic Diseases (2016) **19,** 168–173; doi:10.1038/pcan.2015.61; published online 12 January 2016

Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

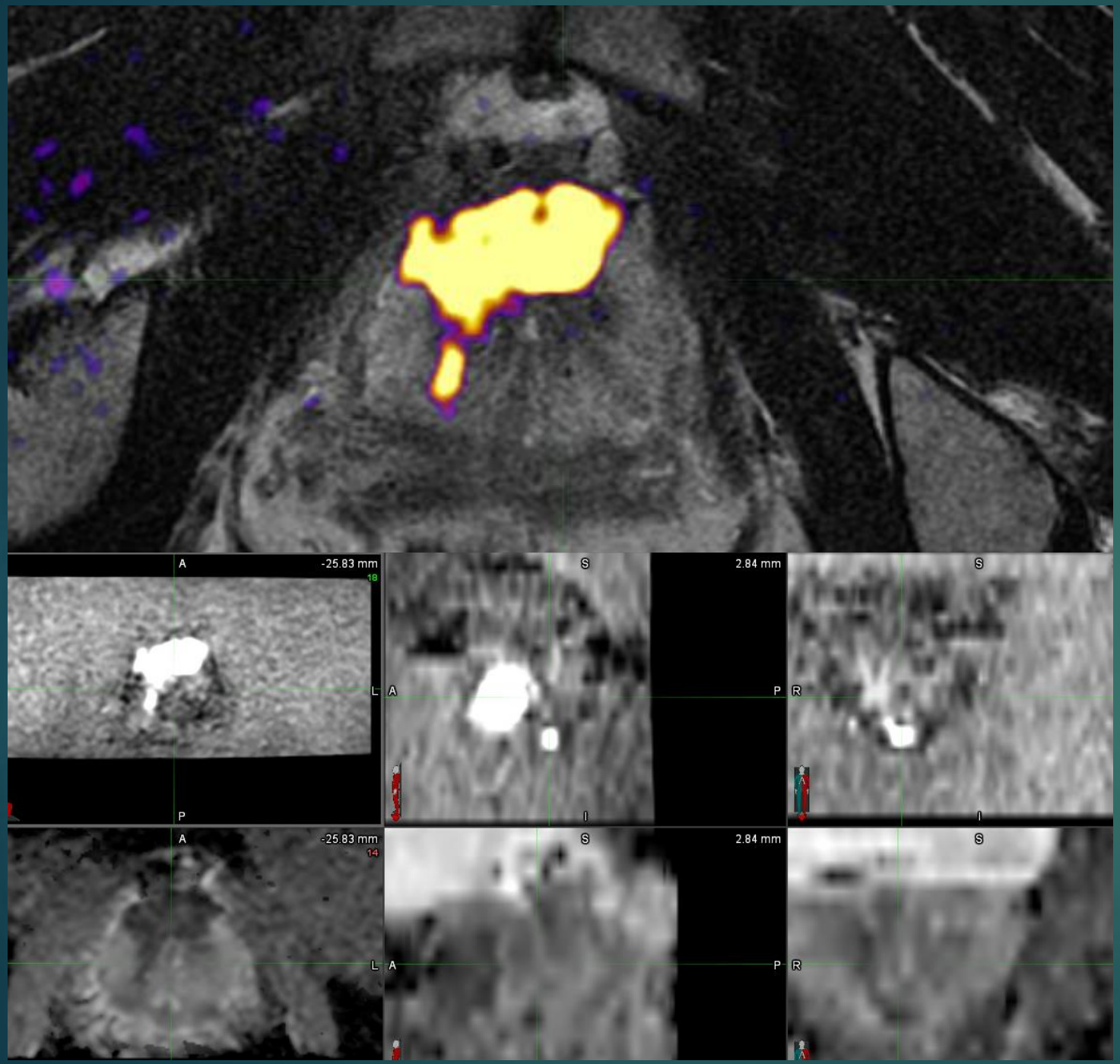
- **Chapter One:**
- **"New and improved" MRI . . .**

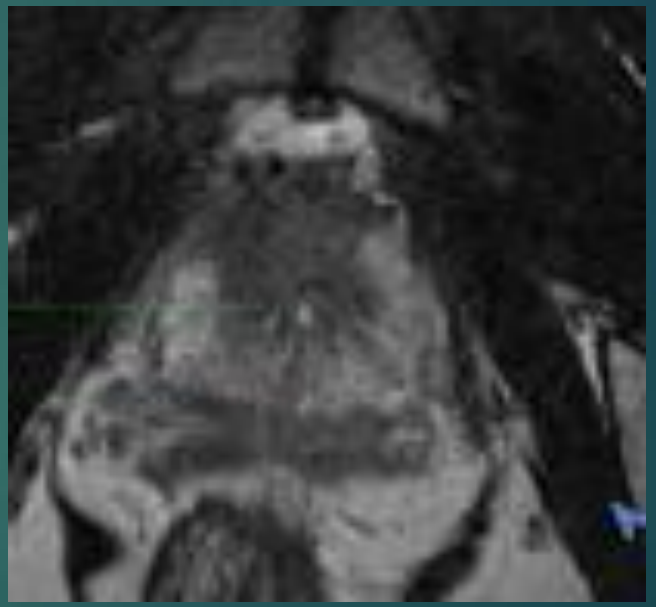


(A) Correlation between primary Gleason score and RSI cellularity index, using the same data presented in McCammack et al. *PCAN*, 2016, reanalyzed to show the top quartile for each region of interest (ROI). Benign: 0–1.5; Primary 3: 1.5–3; Primary 4: 3–4.5; Primary 5: >4.5; (B) RSI cellularity map in color; (C) RSI cellularity map in gray-scale, showing the RSI cellularity index for the indicated ROI; (D) corresponding whole-mount histopathology slide with the tumor outline in blue.

Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

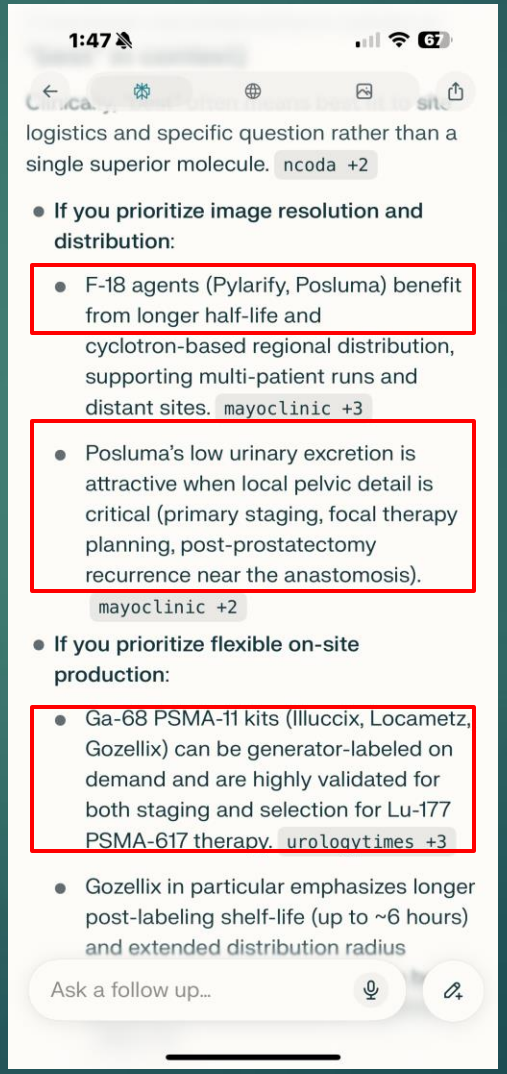
- So, RSI MRI appears to be the first described MRI sequence with sensitivity/specificity in the range of 90%, for differentiating prostate cancer from "normal peripheral zone"
- RSI specificity is less in transitional zone, as BPH nodules may also restrict diffusion
  - (just as "sensitive" in TZ, but could be highlighting nodular BPH in some cases, instead of cancer)
- The RSI signal intensity is positively correlated with Gleason grade
  - Higher Gleason grade lesions are apparently more restrictive of intracellular water movement
  - "The RSI trend then: "brighter the signal, the higher the Gleason score"
  - Also, In grayscale, the RSI is inverted vs the ADC map (RSI signature is "white" while ADC signal is "black")
- NOTE: if RSI is not available, ADC maps do closely recapitulate the RSI signal, just not as "sharply"

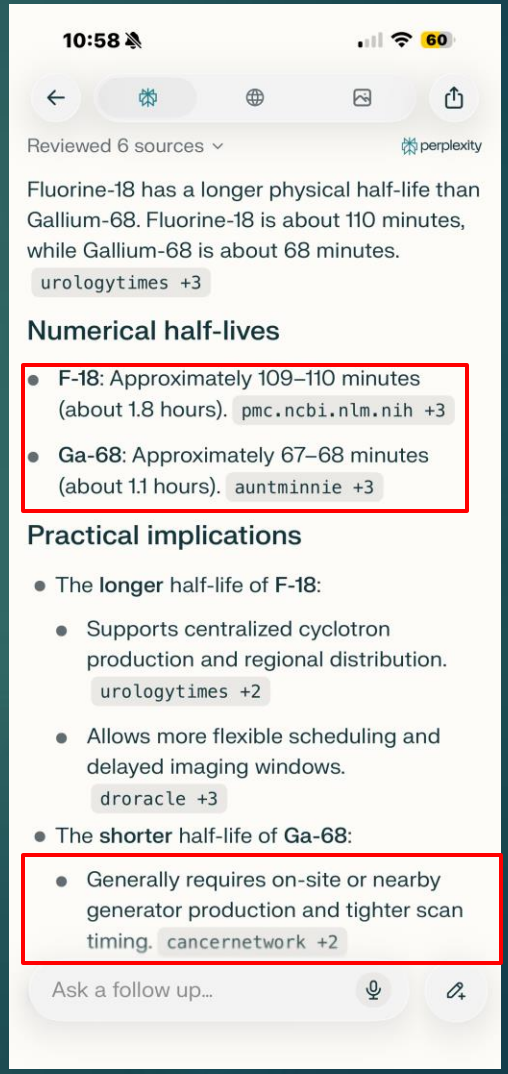

A
-25.83 mm
18
L
P
S
A
I
2.84 mm
P
S
R
I
A
-25.83 mm
14
L
S
A
P
2.84 mm
S
R



Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

- What about PSMA PET/CT???
  - Hmm . .
  - Let's ask "AI" . . (Perplexity)





Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

- What about PSMA PET/CT???

Eur J Nucl Med Mol Imaging. 2024 Dec 27;52(5):1642–1648. doi: 10.1007/s00259-024-07021-0

Three-dimensional spatial localization and volume estimation of prostate tumors using ^{18}F-PSMA-1007 PET/CT versus multiparametric MRI

Guocheng Huang [1], Patrick Albers [1], Nikhile Mookerji [1], Tyler Pfanner [2], Amaris Hui [2], Rohan Mittal [3], Stacey Broomfield [1], Lucas Dean [1,4], Blair St Martin [1,4], Niels-Erik Jacobsen [1,4], Howard Evans [1,4], Yuan Gao [3], Ryan Hung [2], Jonathan Abele [2], Peter Dromparis [3], Joema Felipe Lima [5], Tarek A Bismar [5,6], Evangelos Michelakis [7], Gopinath Sutendra [7,8], Frank Wuest [8,9], Wendy Tu [2], Benjamin A Adam [3], Christopher Fung [2], Sunita Ghosh [8], Alexander Tamm [2,6,#], Adam Kinnaird [1,4,6,8,9,✉,#]; The Next Generation Trial Investigators

Author information · Article notes · Copyright and License information

PMCID: PMC11928431 PMID: 39725694

134 patients w pre-op MRI and pre-op PSMA PET/CT, prior to RP

Conclusion

^{18}F-PSMA-1007 PET/CT outperforms MRI for determination of three-dimensional spatial localization and volume of prostate tumors. These findings support the use of ^{18}F-PSMA-1007 PET/CT prior to definitive treatment of localized prostate cancers.

Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

- What about PSMA PET/CT???

Prostate. 2024 Sep 30;85(1):48–57. doi: 10.1002/pros.24799

Head-to-head comparison of GA-68 PSMA PET/CT and multiparametric MRI findings with postoperative results in preoperative locoregional staging and localization of prostate cancer

Mustafa Dinckal [1], Kasim Emre Ergun [2,✉], Mustafa Serdar Kalemci [2], Ezgi Guler [3], Recep Tokac [4], Süleyman Ordu [2], Nahit Ogut [2], Semiha Ozgul [5], Ozgur Sanli [6], Sait Sen [7], Burak Turna [8]

Author information · Article notes · Copyright and License information

PMCID: PMC11609967 PMID: 39345022

68 patients w preop MRI and pre-op PSMA PET/CT, prior to RP

Results

mpMRI demonstrated higher sensitivity in detecting extraprostatic extension (EPE) and bladder neck invasion (BNI) compared to Ga-68 PSMA PET/CT (83% vs. 44% and 29% vs. 17%, respectively). Conversely, Ga-68 PSMA PET/CT showed higher sensitivity in detecting seminal vesicle invasion (SVI) and lymph node metastasis (LNM) (75% vs. 55% and 50% vs. 30%, respectively). When both methods were combined, sensitivity increased in detecting both EPE and SVI. The index tumor localization in mpMRI and Ga-68 PSMA PET/CT was

Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

- What about PSMA PET/CT???

Adv Radiat Oncol. 2025 Jun 9;10(8):101821. doi: 10.1016/j.adro.2025.101821

Comparative Analysis of ^{68}Ga-Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography and Multiparametric Magnetic Resonance Imaging for Gross Tumor Volume Delineation in Radiation Therapy Planning of Prostate Cancer

Hamed Bagheri [a], Seied Rabi Mahdavi [b,*], Parham Geramifar [c], Ali Neshasteh-Riz [a], Masoumeh Sajadi-Rad [a], Habibollah Dadgar [d], Hossein Arabi [e], Habib Zaidi [e,f,g,h,*]

Author information · Article notes · Copyright and License information

PMCID: PMC12282173 PMID: 40697967

25 patients w pre-op MRI and pre-op PSMA PET/CT, prior to Radiotherapy

The average ± SD GTV-MRI and GTV-PET were 5.468 ± 11.6 cm^3 and 11.136 ± 14.3 cm^3, respectively, with the GTV-PET being significantly larger than the GTV-MRI ($P = .003$). GTV-

Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

- What about PSMA PET/CT???

Mol Imaging Biol. 2021 Sep 14;24(1):50–59. doi: 10.1007/s11307-021-01650-9

Incremental Impact of [^{68} Ga]Ga-PSMA-11 PET/CT in Primary N and M Staging of Prostate Cancer Prior to Curative-Intent Surgery: a Prospective Clinical Trial in Comparison with mpMRI

Florian Szigeti [1], Gregor Schweighofer-Zwink [2], Matthias Meissnitzer [3], Cornelia Hauser-Kronberger [4], Wolfgang Hitzl [5,6,7], Thomas Kunit [8], Rosemarie Forstner [3], Christian Pirich [2,#], Mohsen Beheshti [2,✉,#]

Author information · Article notes · Copyright and License information

PMCID: PMC8760214 PMID: 34519966

Intraprostatic IL of the high-risk patients showed significantly higher SUVmax than those in patients with intermediate risk for distant metastases ($n = 48$; median: 17.84 vs. 8.77; $p = 0.02$).

81 patients w pre-op MRI and pre-op PSMA PET/CT, prior to Radiotherapy

Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

- What about ~~PSMA~~ Fluciclovine (AKA "Axumin") PET/CT???

Radiol Imaging Cancer. 2022 Feb 25;4(2):e210091. doi: 10.1148/rycan.210091

^{18}F-Fluciclovine versus PSMA PET Imaging in Primary Tumor Detection during Initial Staging of High-Risk Prostate Cancer: A Systematic Review and Meta-Analysis

Divya Yadav [1], Hyunsoo Hwang [1], Wei Qiao [1], Rituraj Upadhyay [1], Brian F Chapin [1], Chad Tang [1], Ana Aparicio [1], Maria A Lopez-Olivo [1], Stella K Kang [1], Homer A Macapinlac [1], Tharakeswara K Bathala [1], Devaki Shilpa Surasi [1,✉]

Author information · Article notes · Copyright and License information

PMCID: PMC8965534 PMID: 35212559

Conclusion

^{18}F-fluciclovine and PSMA PET demonstrated no statistically significant difference in diagnostic accuracy in primary tumor detection during initial staging of high-risk prostate cancer.

?!!??!?

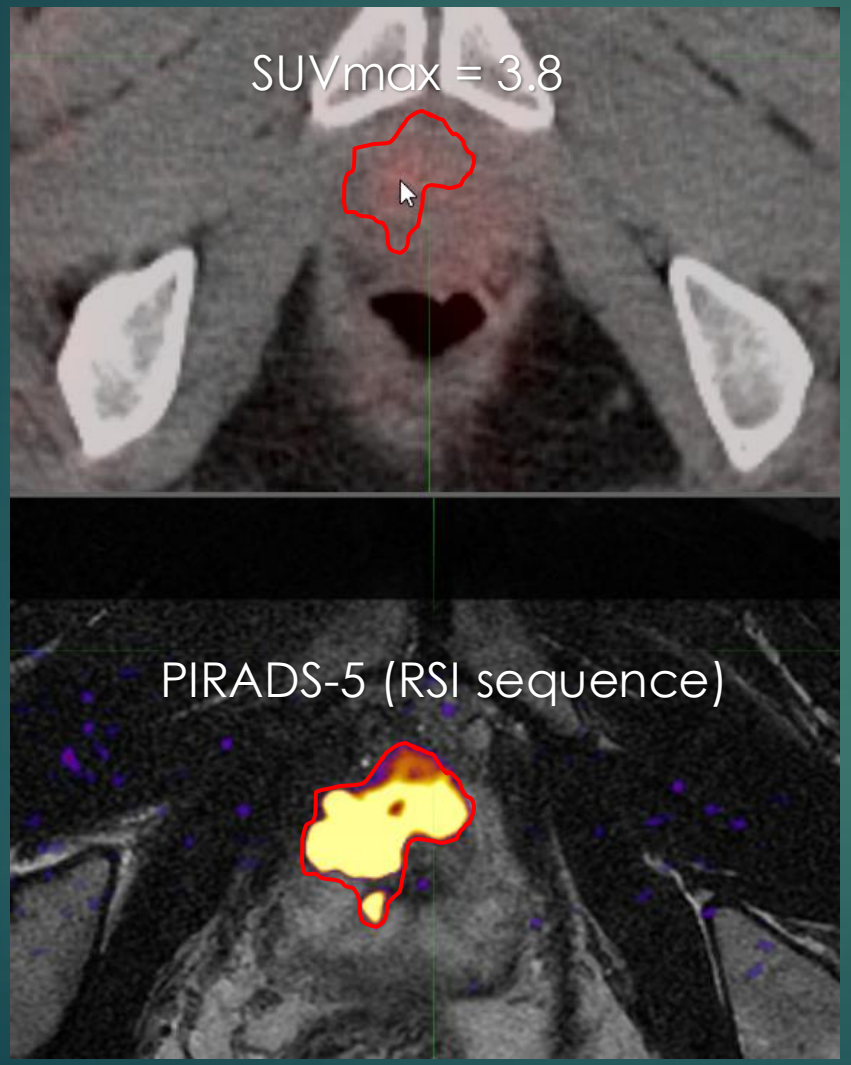
Possible practical concept:

- If PSMA PET/CT is "(-)" when it shouldn't be, at least some patients will have a "(+)" Axumin PET/CT study

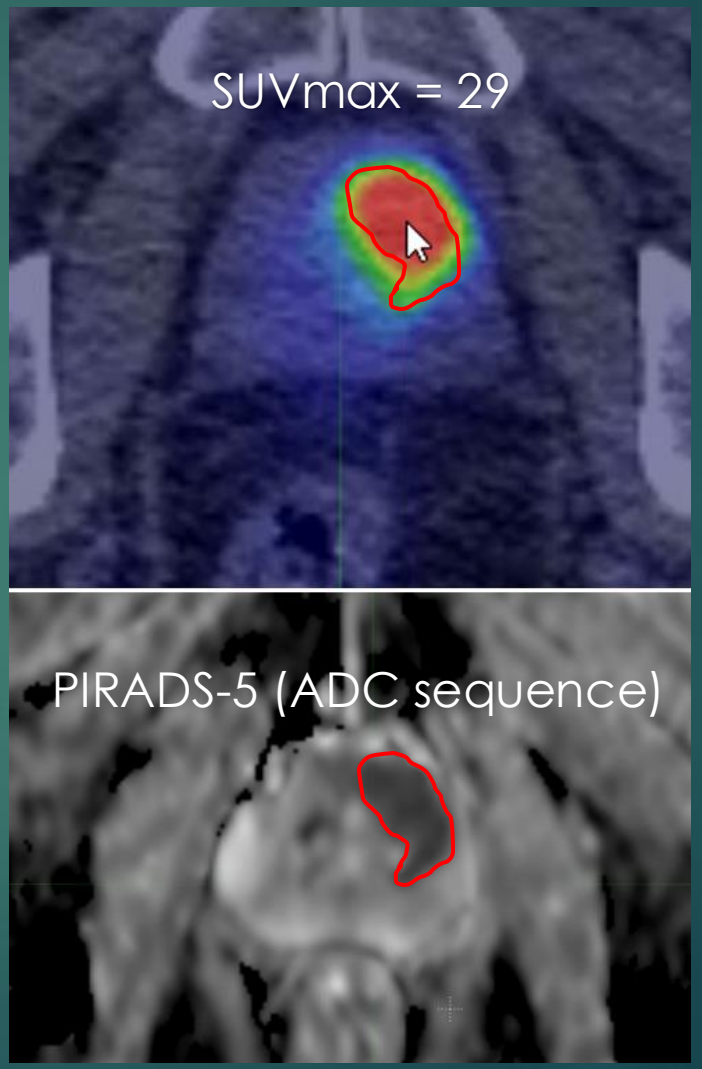
- "AI" (Perplexity) says "(+) Axumin PET/CT w (-) PSMA PET/CT" happens two times out of 100 . .

Two "high-risk" cases w PSMA PET/CT and MRI correlation; both studies are "NED beyond the prostate"

Case 1



Case 2



Do both of these "NED beyond the prostate" PSMA results have the same predictive value?!?

Head to head comparison in an advanced, high-risk case, w multi PSMA (+) pelvic LNs . .

Different "advanced" case, PSMA PET/CT wins "hands down" . . Better definition of his primary tumor, AND, it was the study that proved the multi (+) LNs . .

So regardless what "literature and/or experience" may say, there is VARIABILITY when it comes to any specific individual, to say the least . . .

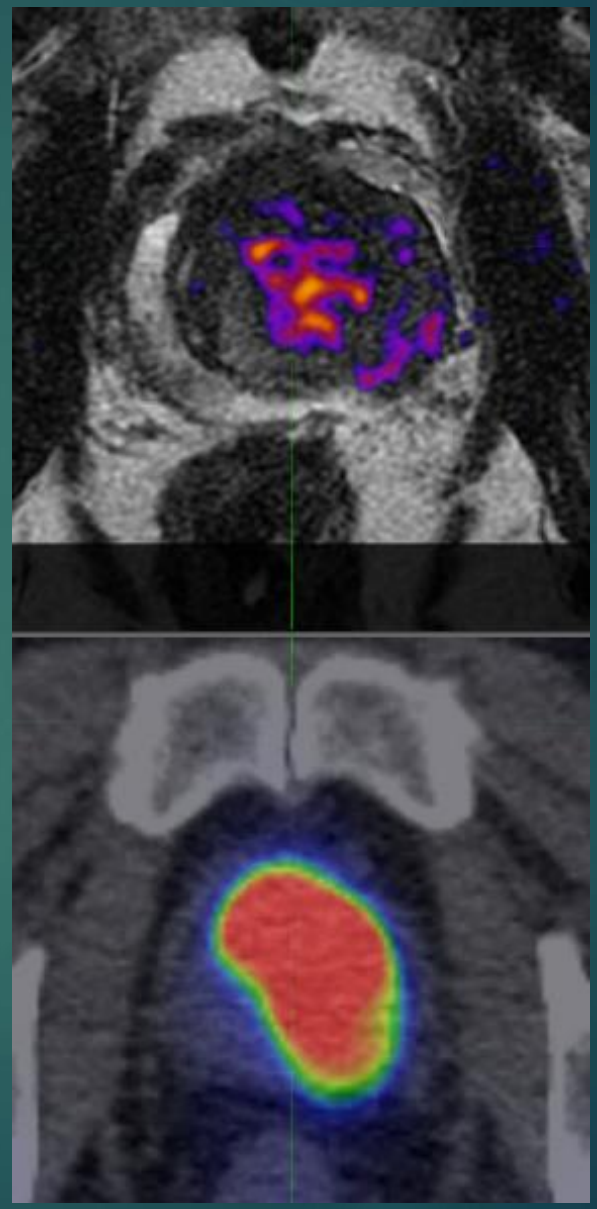
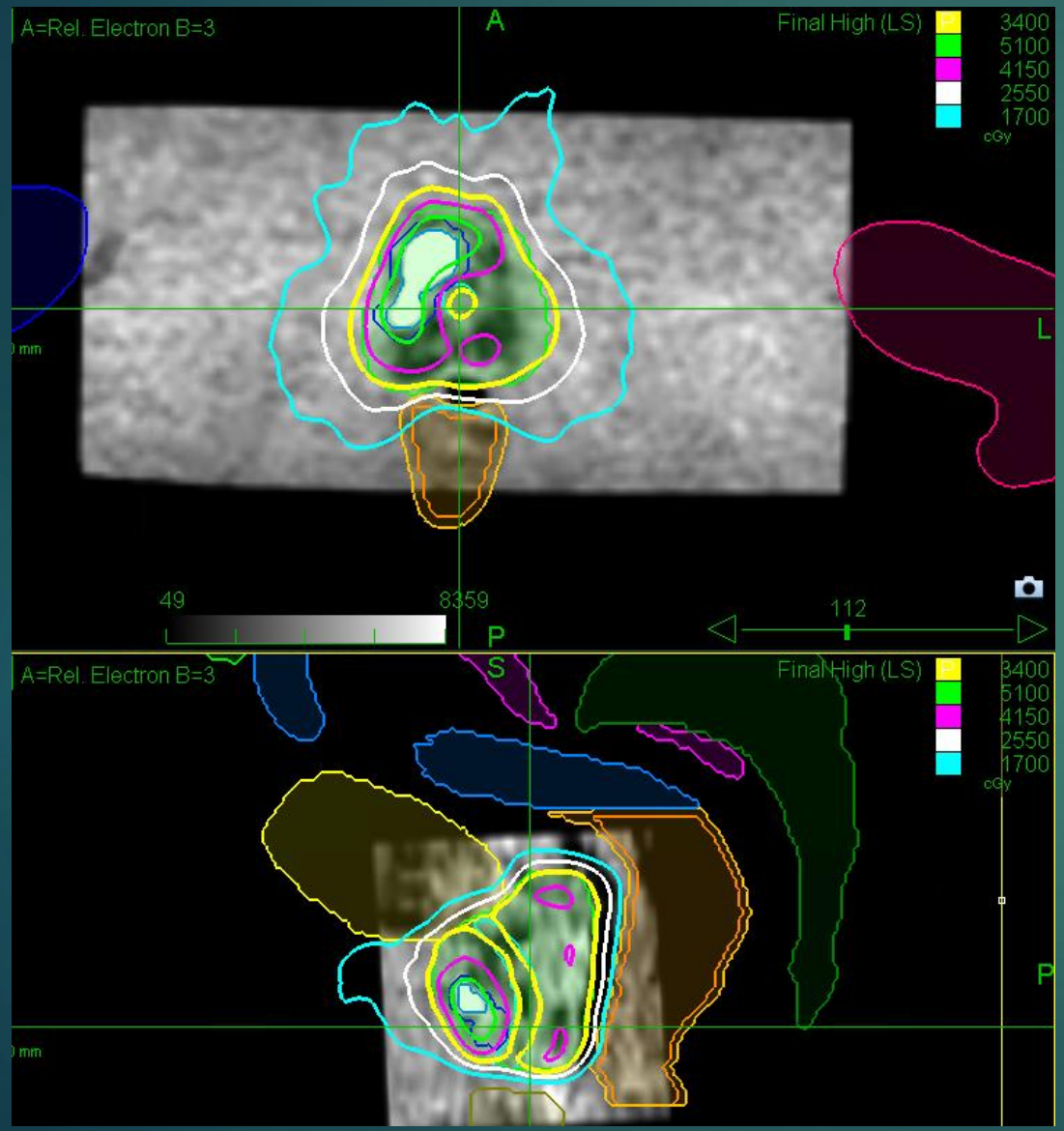
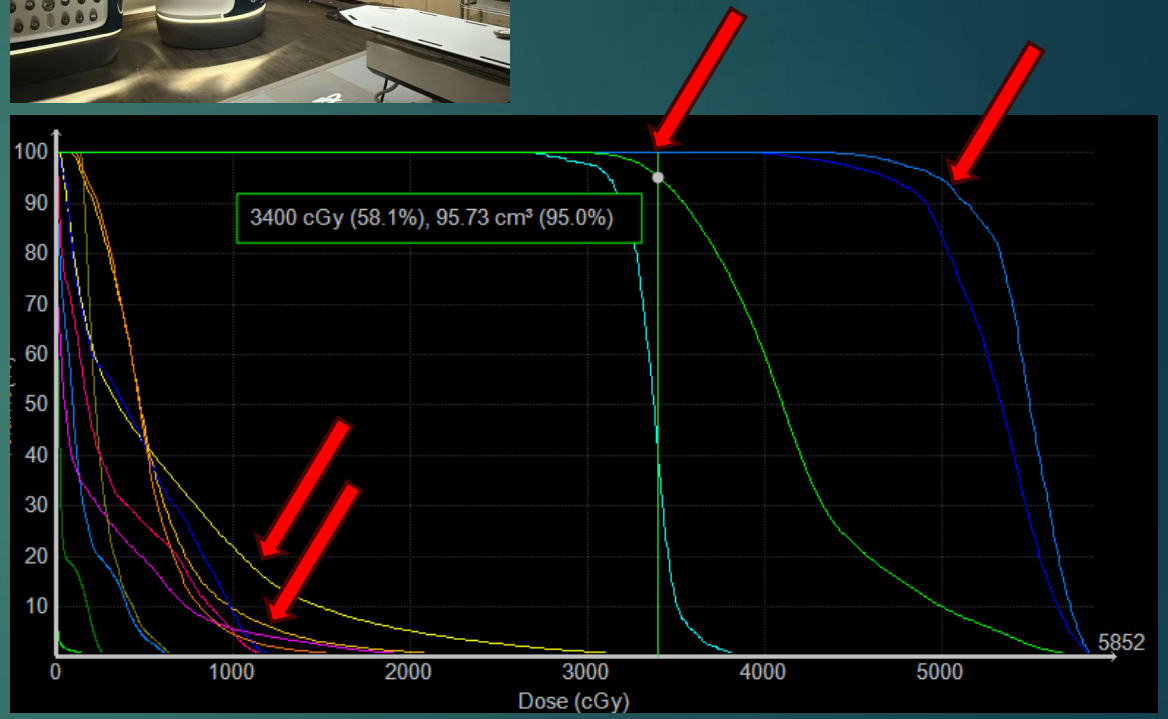
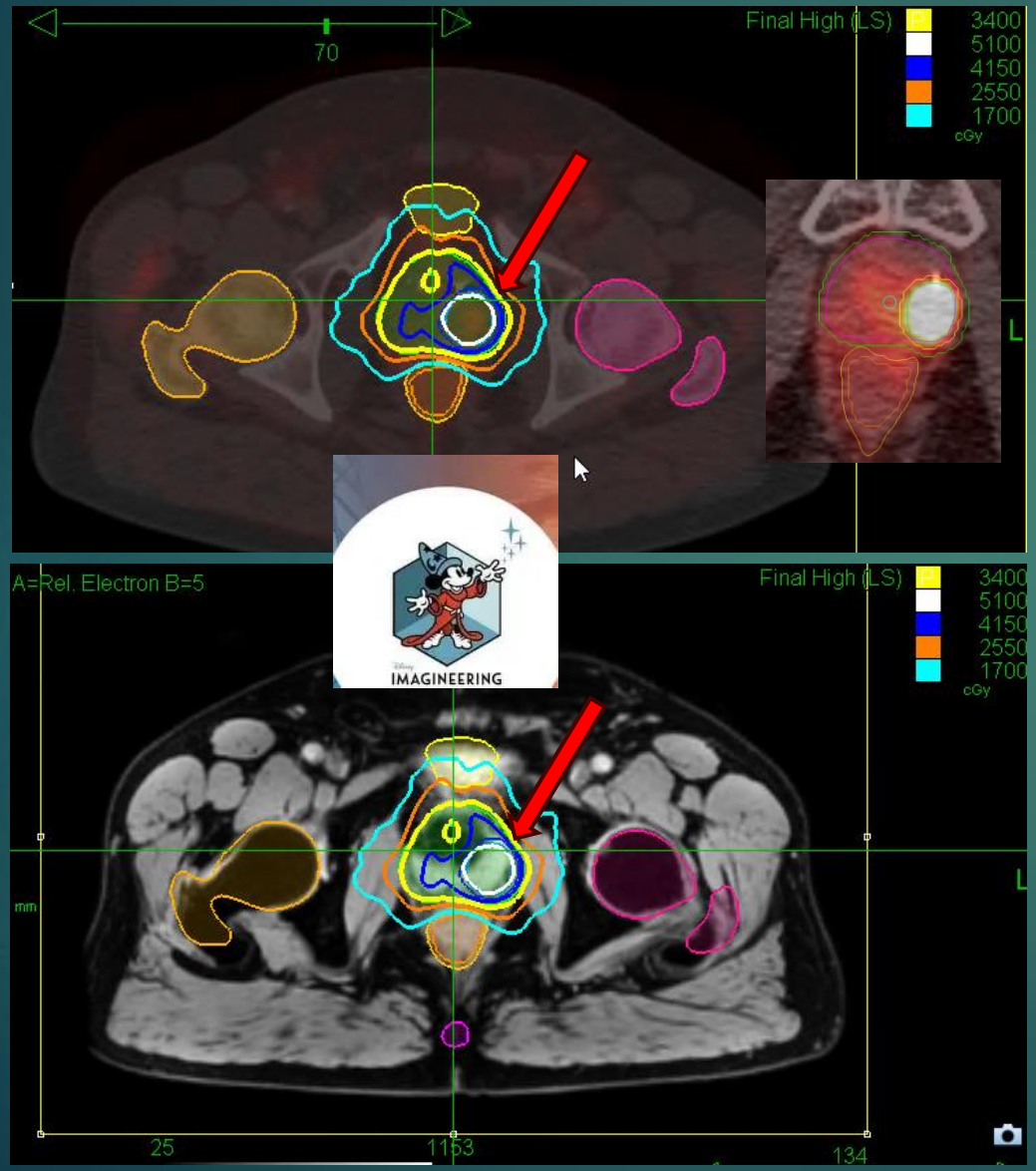


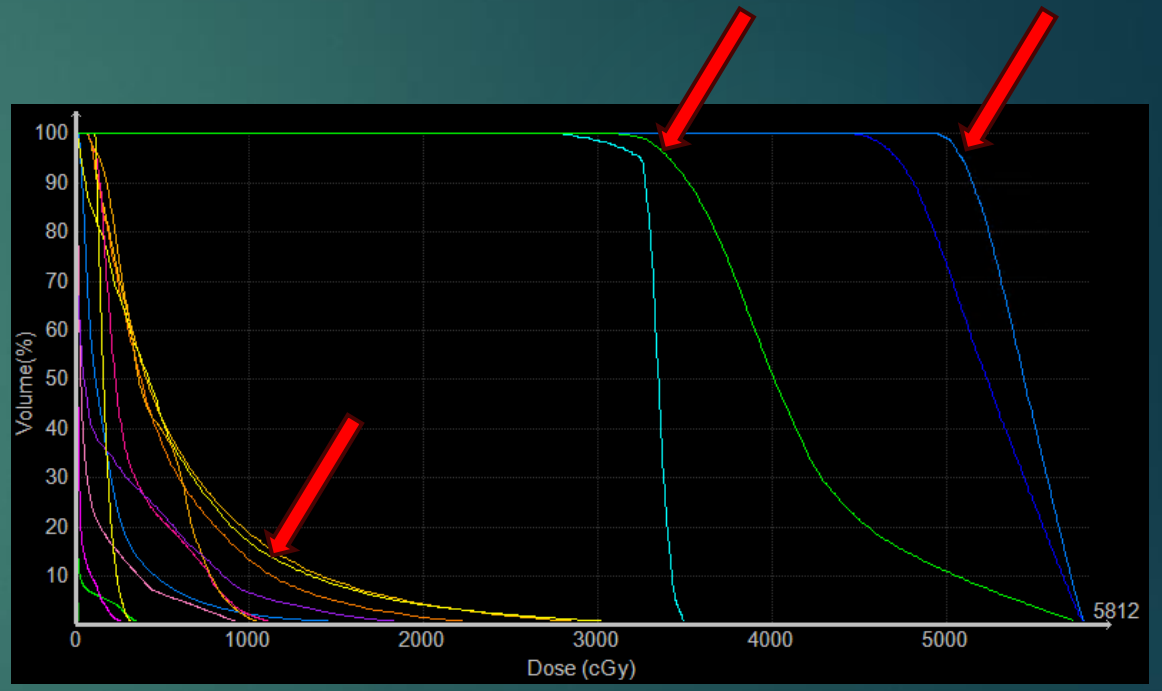
Image-Guided SIB; RSI MRI (Grayscale version)



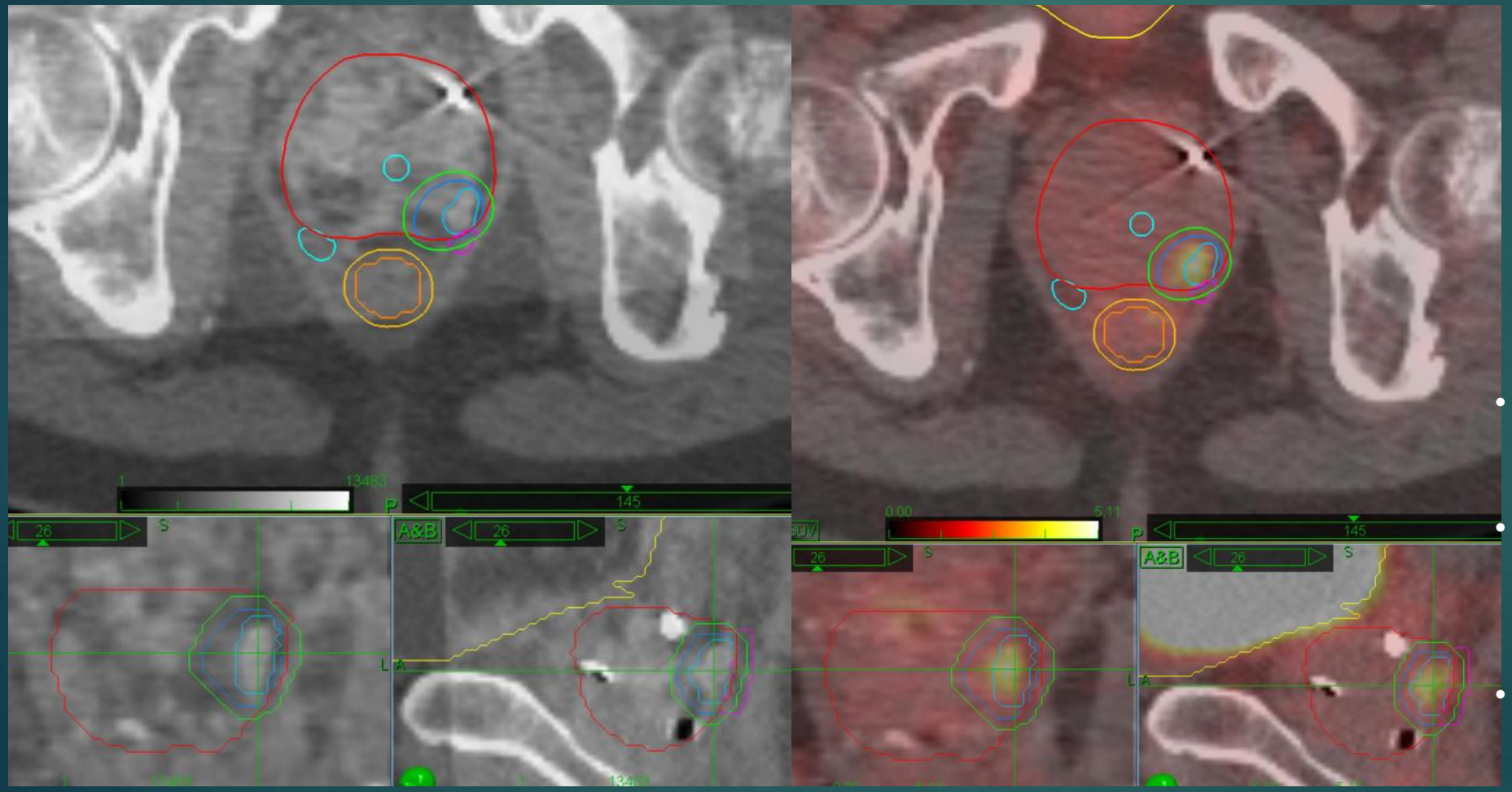


MRI = PIRADS-1; No lesion seen (MRI image severely degraded by Urolift struts); Image-guided SIB by PSMA PET



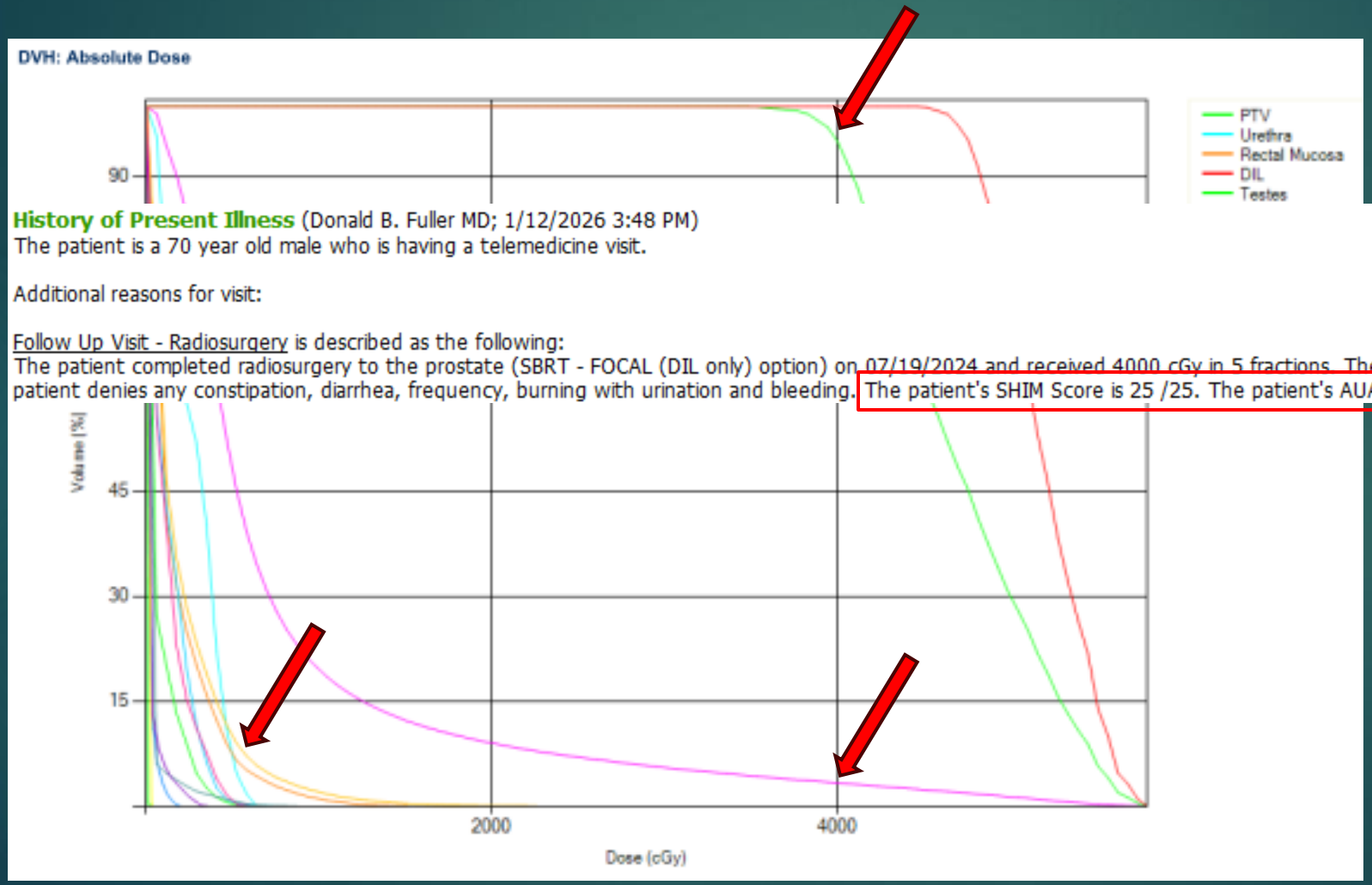


Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")



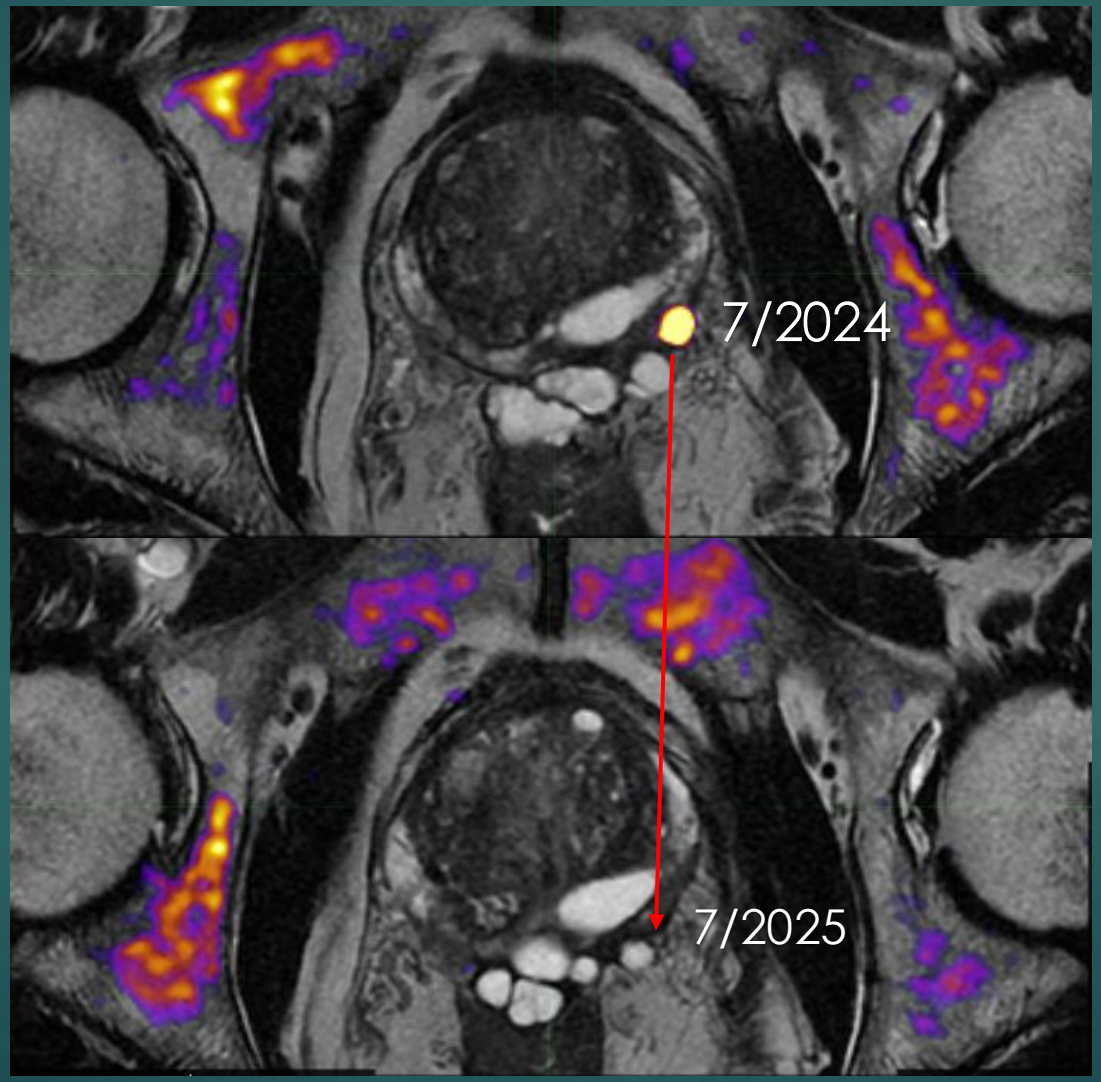
- CYBERKNIFE is well suited for "FOCAL" (PRIMARY tx . .)
- Fiducial moves in tandem w the lesion; allows sub-mm accurate tracking
- Multiple Modalities may be imported into the planning process

Role of Biopsy, MRI, and PSMA PET/CT in Guiding Salvage RT ("What the F#$$ am I treating?")

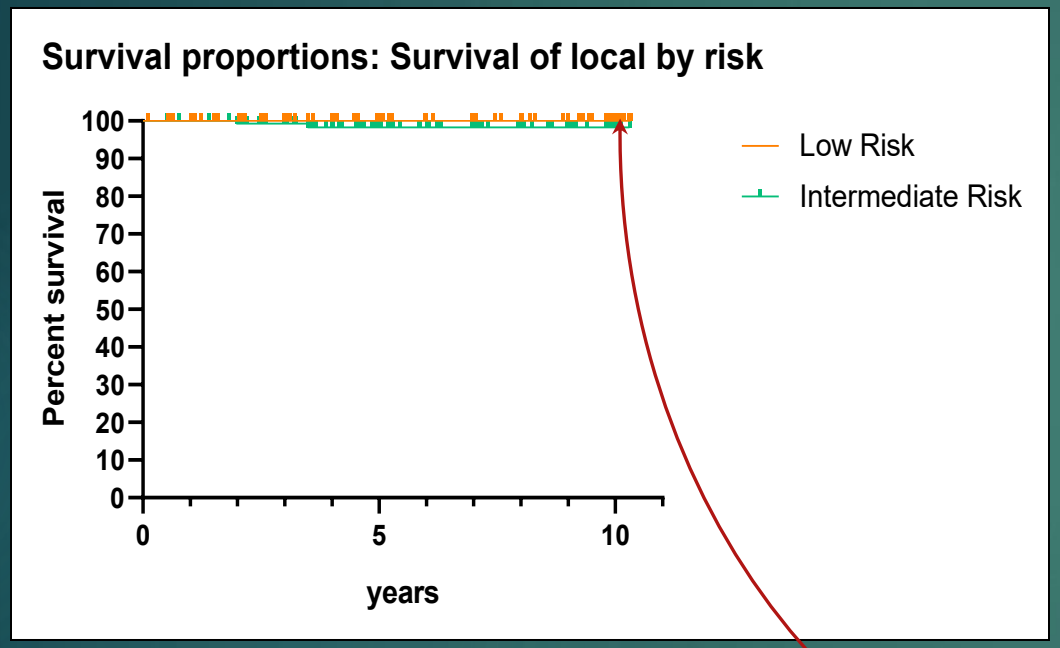


- CYBERKNIFE is well suited for "FOCAL"
- Fiducial moves in tandem w the lesion; allows sub-mm accurate tracking
- Multiple Modalities may be imported into the planning process

Does advanced imaging allow the possibility of FOCAL SBRT for NON-recurrent prostate cancer???

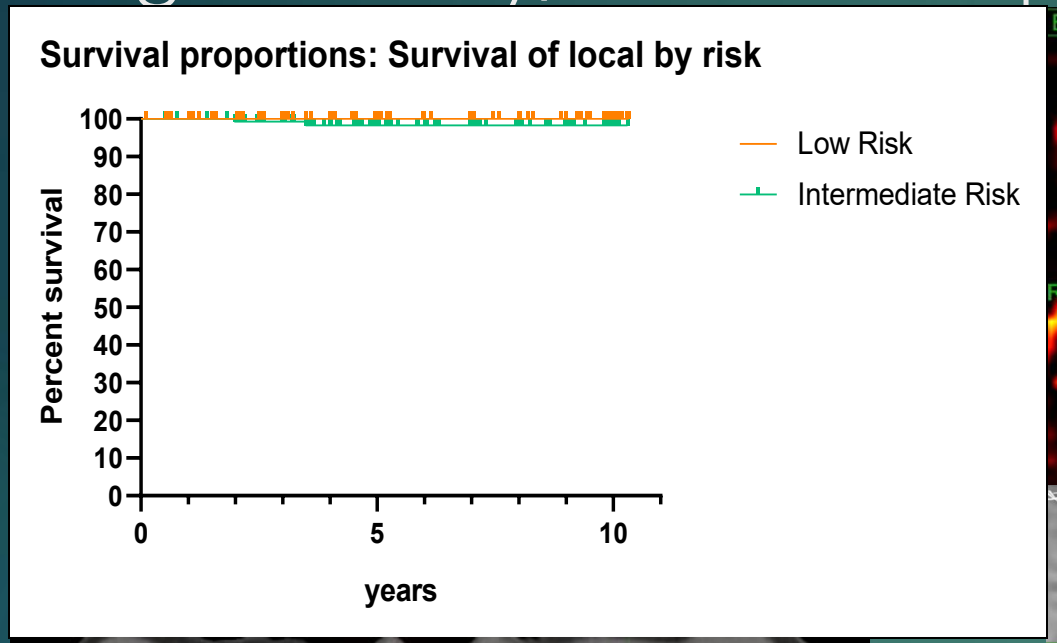


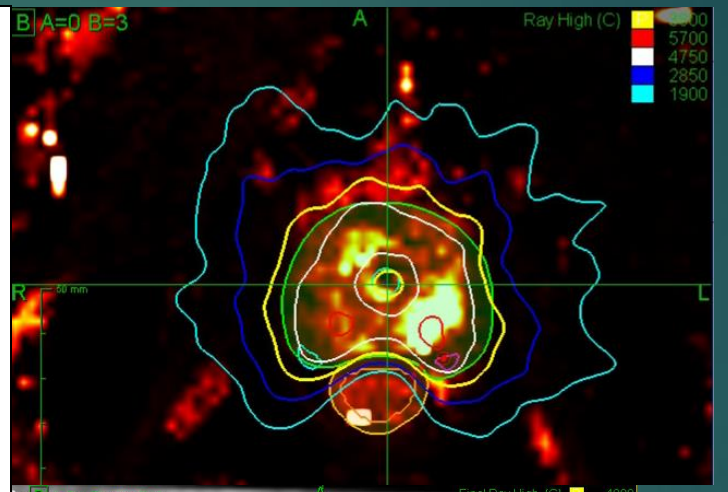
VIRTUAL HDR CYBERKNIFE RADIOSURGERY FOR LOCALIZED PROSTATIC CARCINOMA: A PHASE II STUDY

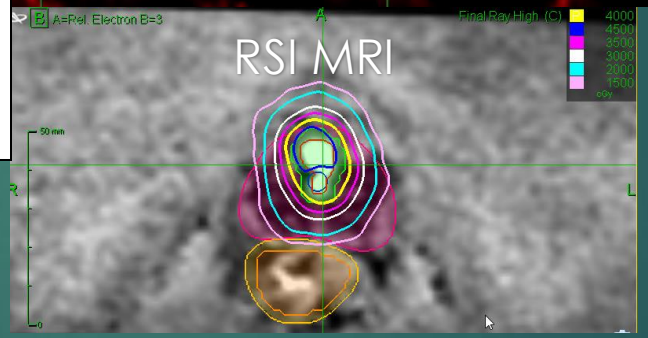


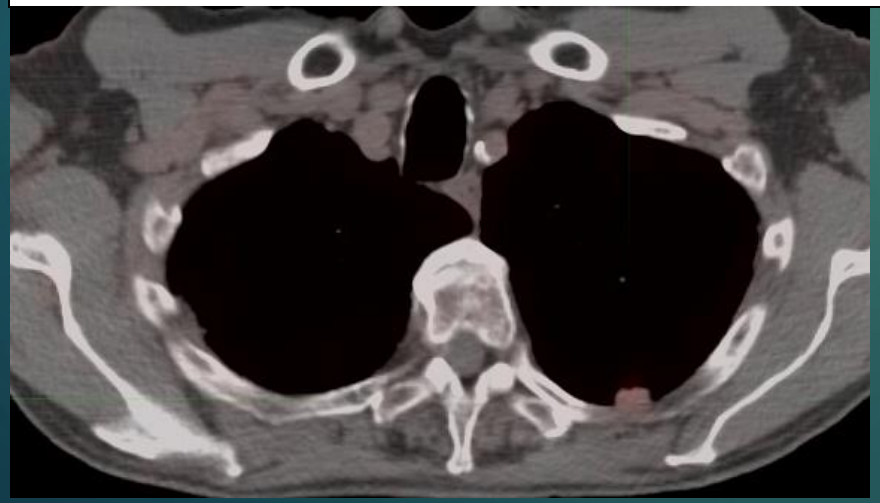
- **10 year result (3,800cGy/4 fx)**
  - High Dose "HDR-Like" Prostate SBRT: PSA 10-Year Results From a Mature, Multi-Institutional Clinical Trial. **Front. Oncol., 29 July 2022**
    Sec. Radiation Oncology
- **Accuray Sponsored multi-institutional study**
  - **Low and int risk**
  - **18 institutions; 257 pts enrolled**
- **Local Control – 99% at 10 years**
- **This regimen is "Locally ablative" to 10 years**

ER – A magnificently otherwise healthy 80yom w localized "high volume" Gd Gp 3 prostate cancer; Treated w "original 38 Gy/4 fx CK SBRT protocol"

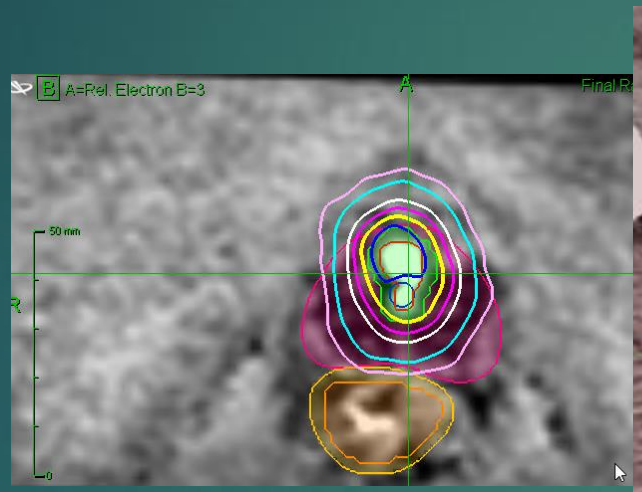




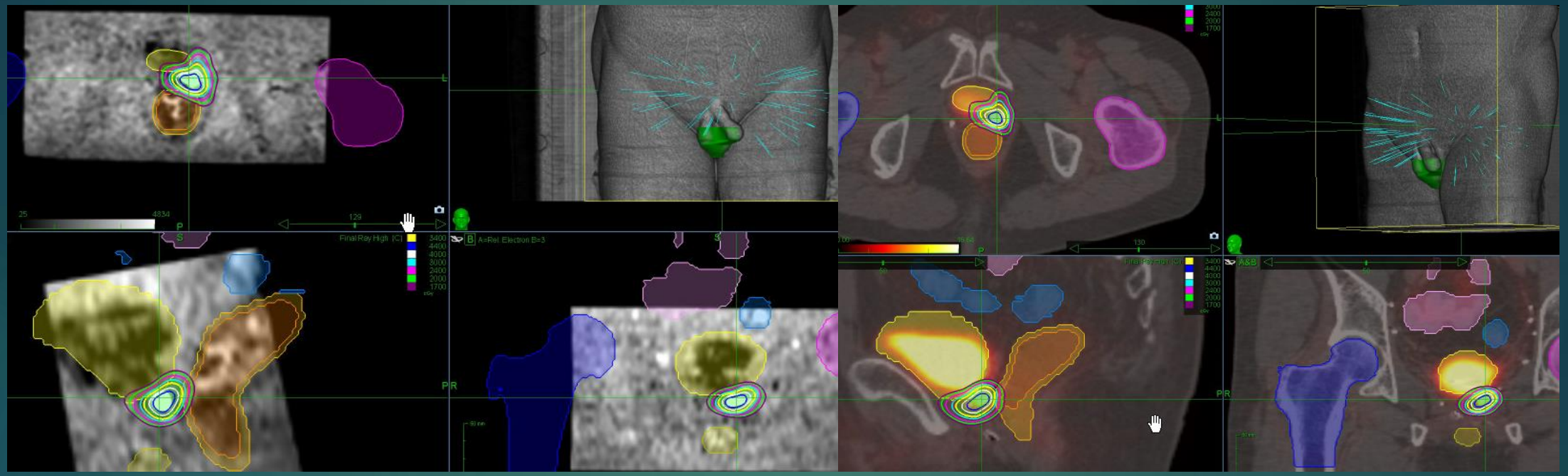




ER – A magnificently otherwise healthy 80yom w localized "high volume" Gd Gp 3 prostate cancer; Treated w "original 38 Gy/4 fx CK SBRT protocol"



NC – A magnificently otherwise healthy 78yom w local relapse 21 years after RP and 20 years after post-op 3DCRT to the prostate bed; Treated w 3,400cGy/5 fx to recurrent lesion w 2 mm margins

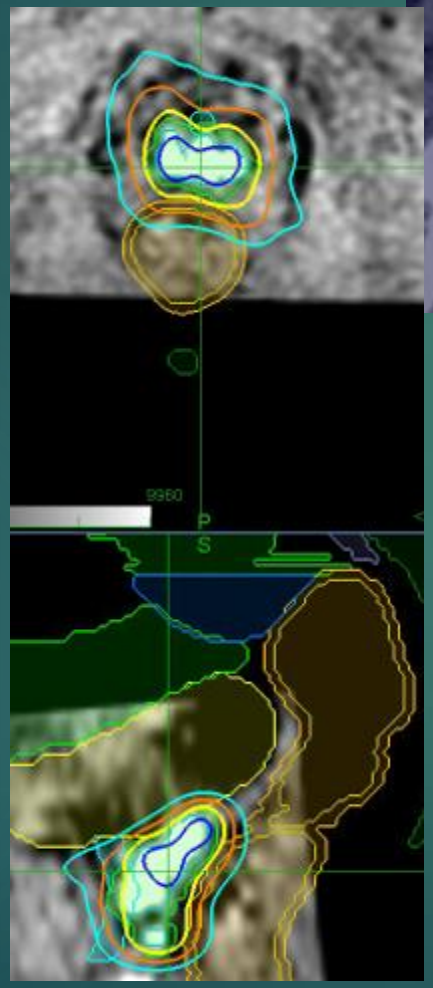


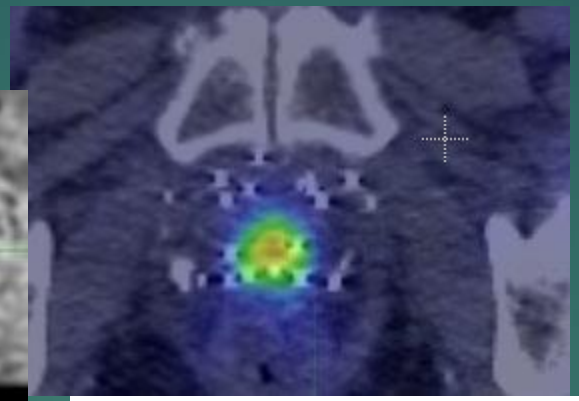
PSA nadir is < 0.1 ng/mL;
GU and GI toxicity is grade 0!

Reasons for this "perfect" outcome:

1) 20 year interval post-prior RT
2) PSA remained "low" at relapse
3) PTV = 2.23 cc! (1 teaspoon = 5 cc)
4) Perfect PSMA PET/CT/MRI concordance

TH – A very nice 80yom w local recurrence, 14 years after 103^Pd brachytherapy plus Prostate IMRT





Post-brachytherapy SBRT salvage is another of our "higher toxicity risk" scenarios, however, this man was "hormone resistant localized" so we still gave it a go – PTV = RSI MRI volume (+) 2 mm; Toxicity at one month is grade 1 GU, improving . .

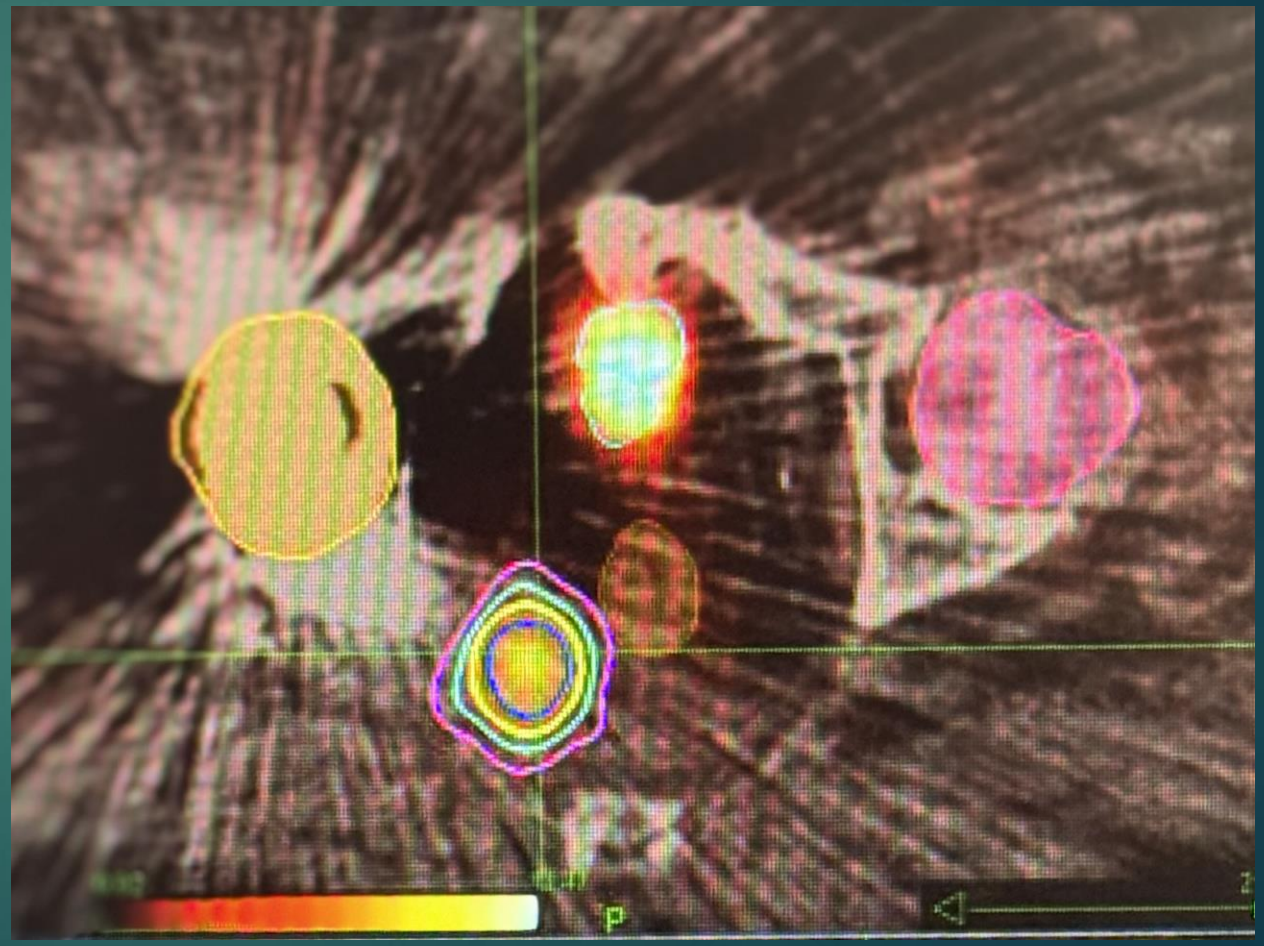
Diagnostic Studies History (Donald B. Fuller, MD; 1/22/2026 4:02 PM)
Labs - PSA 2011 (Pre-RT); 17.33 ng/mL
2011 - Prostate IMRT (tomotherapy) + 103^Pd brachytherapy boost - 4,500cGy + 10,000cGy (Oklahoma City)
8/12/2012 - 0.59 ng/mL (nadir)
4/12/2017 - 9.36 ng/mL
Lupron
8/4/2017 - 0.8 ng/mL
1/15/2018 - 45 mg Lupron
4/3/2018 - 0.8 ng/mL
10/8/2018 - 0.6 ng/mL
3/26/2019 - 0.7 ng/mL
2/4/2025 - 4.2 ng/mL
5/30/2025 - 4.4 ng/mL
7/15/2025 - 3.6 ng/mL
12/10/2025 - CK SBRT salvage
1/13/2026 - 2.2 ng/mL
Labs - Testosterone 4/3/2018 - 12 ng/dL
10/8/2018 - 4 ng/dL
3/26/2019 - 11 ng/dL
2/4/2025 - 14 ng/dL
5/30/2025 - 7 ng/dL
7/15/2025 - 10 ng/dL
1/13/2025 - 11 ng/dL

And what about good, old-fashioned "prostate bed RT" for rising PSA?

90 yo retired MD

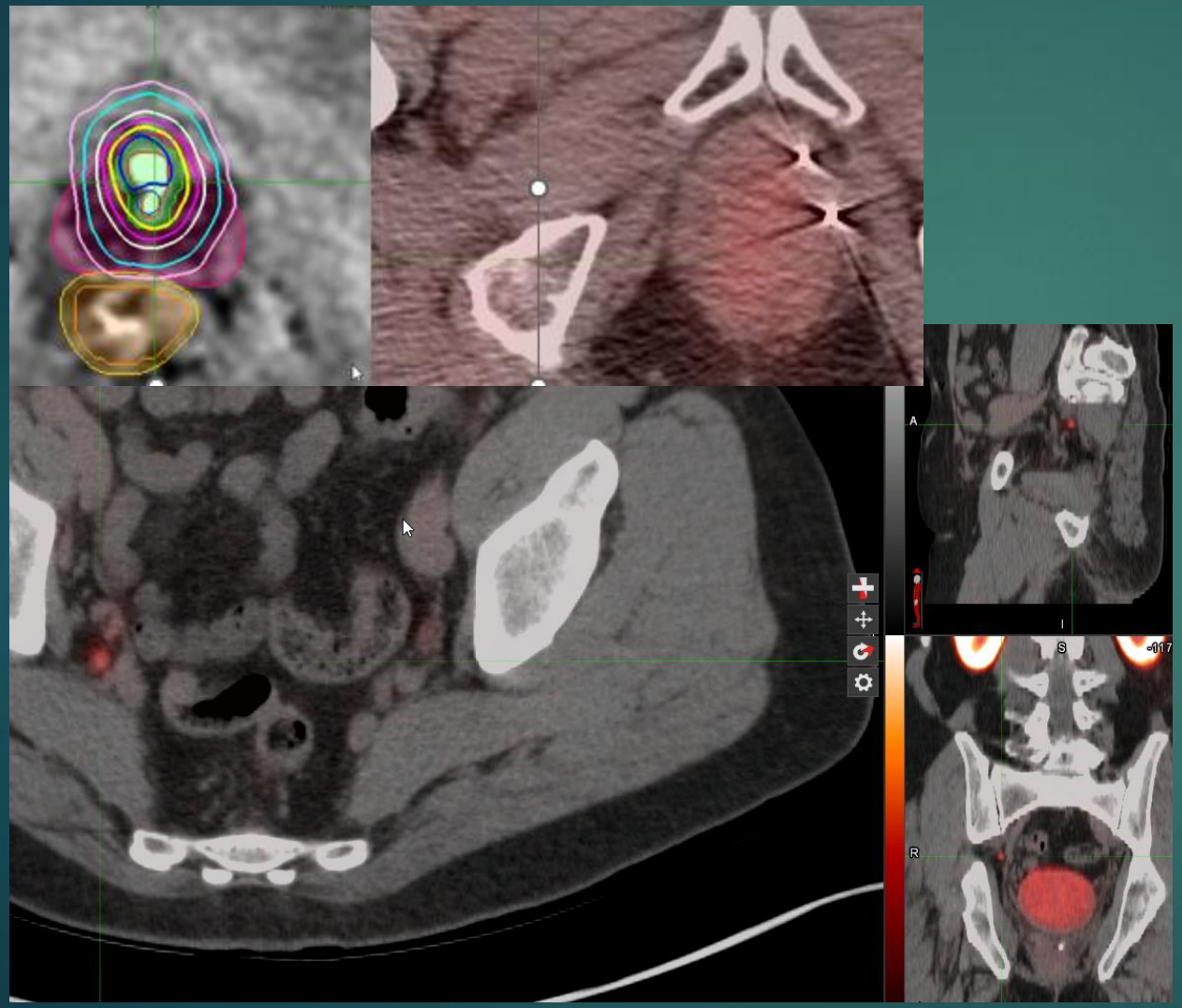
- RALRP 2012 (GI 4+3)(No adjuvant RT)
  - PSA nadir < 0.1 ng/mL for years
  - PSA began rising ~ 2020 → 3.7 ng/mL by 2024
  - 2024: PSMA PET/CT (+) for a solitary hypermetabolic L internal iliac LN

Diagnostic Studies History (Donald B. Fuller, MD; 3/26/2025 11:28 AM)
Labs - PSA 12/2022 - 0.8 ng/mL
4/26/2024 - 1.9 ng/mL
9/10/2024 - 3.7 ng/mL
12/20/2024 - SBRT focal L pelvic LN (no ADT)
2/28/2025 - 0.1 ng/mL



- We did not do "prostate bed IMRT"
- We did CK SBRT "pop" the PSMA (+) LN . .
  - 40 Gy/5 fx; LN (+) 2 mm
- PSA response is "satisfying"
  - Toxicity is grade 0
  - Completed tx in a week
  - If we ever do need to tx the "prostate bed" - I submit that we still could! . .
- NEW imaging . . Breaks . . OLD paradigms!
  - (Use it to its highest capability!)

Basic Imaging Take Home Conclusion:

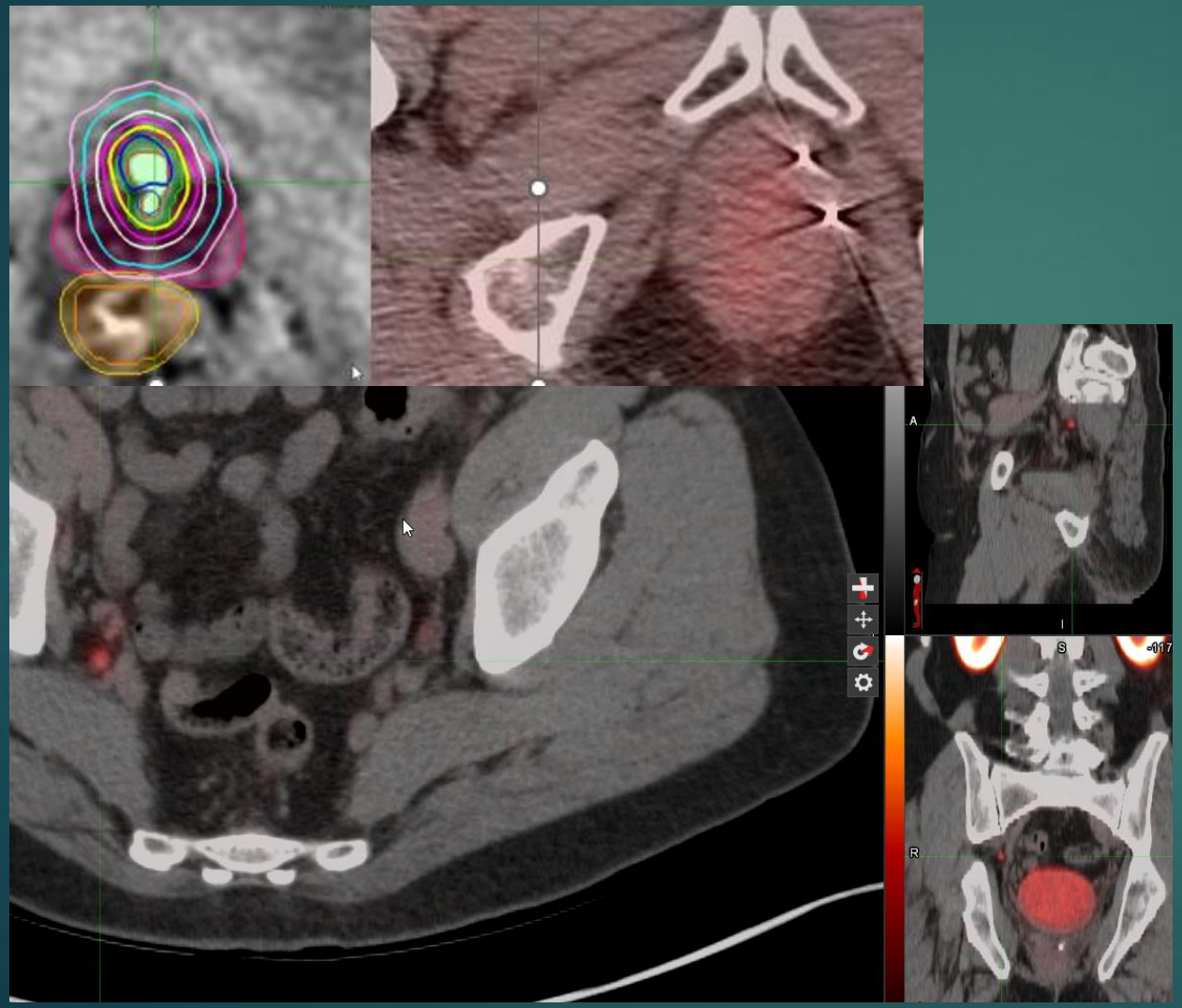


<u>My own opinion FWIW</u> . .

- For intraprostatic disease mapping, RSI MRI typically, though not always, outperforms any flavor of PET/CT
- ("poor man's "RSI" = "ADC map")

- For LNs and distant sites, that opinion is exactly reversed
  (i.e. – they are "complimentary studies")

Basic Imaging Take Home Conclusion:



My own opinion FWIW . .

- FINALLY; Imaging is so good now, that "out of the box" management is no longer so "out of the box" . . e.g.
- Re-irradiating a radiation failure
- Primary "focal" approaches
- Targeting a "PSMA (+) LN only" instead of irradiating the "entire prostate bed" in selected cases . . (Or instead of starting the dreaded "ADT" . . .)
- BOTH imaging modalities combined, outperform either, individually . . . They are "complimentary"

Thank You

DONALD B. FULLER, MD
RADIATION ONCOLOGIST
UNIO HEALTHCARE