ARRO-Case
High-risk Prostate Cancer

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Clinical Presentation

- HPI: 73-year-old man who presented with elevated PSA trend as below:

January 25, 2018: 9.0
April 29, 2019: 11.8
January 9, 2023: 25.9
January 23, 2023: 28.4
February 21, 2023: 32.9

Clinical Presentation

- **REVIEW OF SYSTEMS**: Daytime urinary frequency, nocturia two times per night
- **PMH/PSH**: Unremarkable
- **MEDICATIONS**: None
- **SH**: Married, wood-worker, no history of tobacco, alcohol, or drug use
- **PE**: No evidence of mass, normal rectal tone. Prostate was non-tender, symmetrical without nodules

I-PSS Baseline

Incomplete Emptying: Not at all

Frequency: Urinate less than every two hours about half the time

Urgency: Half the time it is difficult to postpone urination

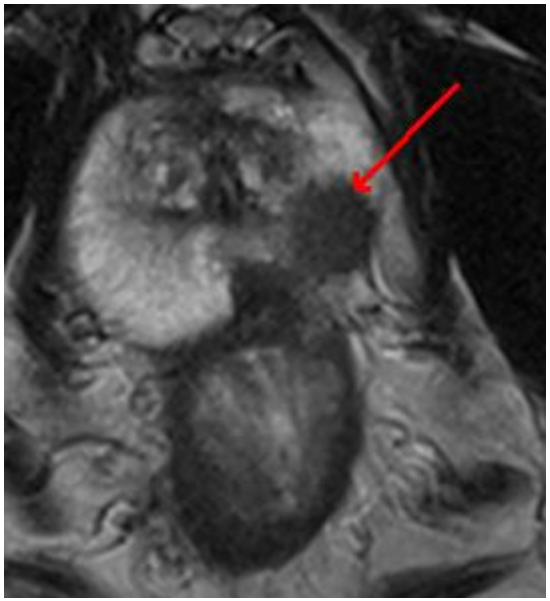
Weak Stream: Not at all

Straining: Not at all

Nocturia: 2 times per night

MRI

- **MRI Prostate** demonstrates PI-RADS 5 2.1 cm lesion in the left posterior peripheral zone at midgland to apex. Suspected left posterolateral extraprostatic tumor extension and involvement of the left neurovascular bundle



Transperineal Fusion Biopsy

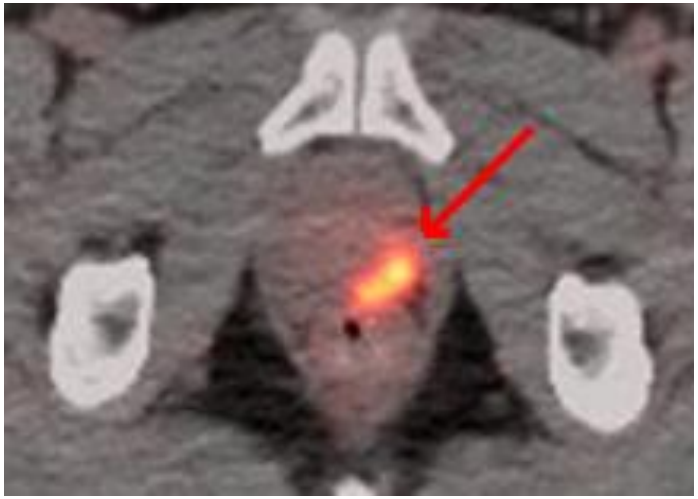
- 13 core biopsy (3 targeted at Region of Interest [ROI] based on MRI)

A) Benign Prostatic Tissue
B) Benign Prostatic Tissue
C) Benign Prostatic Tissue
D) ROI 1, Left Apex 1: Grade Group 4 (GS 4+4=8), involving 90% of submitted tissue
E) ROI 1, Left Apex 2: Grade Group 4 (GS 4+4=8), involving 100% of submitted tissue
F) ROI 1, Left Apex 3: Grade Group 4 (GS 4+4=8), involving 100% submitted tissue
G) ROI 1, Left Apex 4: Grade Group 4 (GS 4+4=8), involving 90% of submitted tissue
H) Benign Prostatic Tissue
I) Grade Group 3 (GS 4+3=7), involving 20% of submitted tissue
J) Grade Group 4 (GS 4+4=8), involving 90% of submitted tissue
K) Grade Group 3 (GS 4+3=7), involving 50% of submitted tissue
L) Benign prostatic tissue
M) Benign prostatic tissue

In total Grade Group 4 (Gleason 4+4=8), with 4/10 cores positive **(all cores in ROI count as 1)**

PSMA PET-CT

- **PSMA PET-CT** demonstrates increased tracer activity within the posterior left peripheral zone of prostate corresponding with suspicious lesion on comparison MRI. No regional or distant metastatic disease



AJCC STAGING[1]

TX – Primary tumor cannot be assessed
T0 – No evidence of primary tumor
T1 – Clinically apparent tumor that is not palpable
- T1a – Tumor incidental histologic finding in 5% or less of tissue resected
- T1b – Tumor incidental histologic finding in more than 5% of tissue resected
- T1c – Tumor identified by needle biopsy found in one or both sides, but not palpable

T2 – Tumor palpable and confined within the prostate
- T2a – Tumor involves one-half of one side or less
- T2b – Tumor involve smore than one-half of one side but not both sides
- T2c – Tumor involves both sides

T3 – Extraprostatic tumor that is not fixed or does not invade adjacent structures
- T3a – Extraprostatic extension (unilateral or bilateral)
- T3b – Tumor invades seminal vesicles
- T4 – Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

T stage based off of DRE

RISK STRATIFICATION [2]

RISK GROUP	Clinical/Pathologic Features		
Very Low	- T1c AND - Grade Group 1 AND - PSA < 10 ng/mL AND - <3 cores positive, <=50% involvement in each core AND - PSA density <0.15 ng/mL/g		
Low	- T1-T2a AND - Grade Group 1 AND - PSA <10 ng/mL		
Intermediate	- Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF): - T2b-T2c, Grade Group 2 or 3, PSA 10-20 ng/mL	**Favorable Intermediate**	- 1 IRF and - Grade Group 1 or 2 AND - <50% biopsy cores positive
		Unfavorable Intermediate	- 2 or 3 IRFs and/or - -Grade Group 3 and/or - >=50% biopsy cores positive
High	- T3a OR - Grade Group 4 or Grade Group 5 OR - PSA > 20 ng/mL		
Very high	- T3b-T4 OR - Primary Gleason pattern 5 OR - >4 cores with Grade Group 4 or 5		

TREATMENT OPTIONS FOR HIGH RISK [2]

- For expected survival >5 years or symptomatic:
  - EBRT + ADT (1.5 – 3 years)
  - EBRT + brachytherapy + ADT (1-3 y)
  - EBRT + ADT (2 years) + abiraterone (for very-risk only)
- For expected survival <5 years and asymptomatic
  - Observation
  - ADT
  - EBRT
- **The patient went on to receive EBRT with concurrent and adjuvant ADT for a total of 2 years.**

SHOULD WE TREAT THE PELVIS?

- **RTOG 9413**[3]
  - Patients were mixed risk with PSA < 100 and risk of LN involvement >15% per Roach formula
  - 4 arms randomizing between neoadjuvant and concurrent ADT versus adjuvant ADT, and prostate only RT versus whole pelvis RT
  - 4-year PFS for prostate-only RT versus whole pelvis (47% versus 54%, p = 0.022)
  - This benefit was lost at later follow up
- **POP-RT** [4]
  - High-risk, N0 prostate cancer with LN risk >20% per Roach formula
  - 80% had PSMA PET
  - Prostate only RT versus whole pelvis RT
  - 5-year bPFS 81% versus 95%
  - 5-year DMFS 89% versus 96%
  - 5-year DFS 77% versus 90%
  - 5-year pelvic recurrence 52% versus 13%

Due to results of POP-RT our institution generally recommends to treat the pelvis in high risk patients.

CAN WE HYPOFRACTIONATE?

SUMMARY OF MODERATE HYPOFRACTIONATION TRIALS					
Author, Institution	**MFU**	**Eligibility**	**Hypofractionated Arm**	**Conventional Arm**	**Outcome**
Hoffman, MDACC [5]	8.4 years	LR-IR	72 Gy / 30 fx	75.6 Gy /42 fx	- 10y bRFS 89.3% versus 76.3% favoring hypofx arm - No diff OS or GI/GU toxicity
Fox Chase [6]	10.2 years	IR-HR	70.2 Gy / 26 fx	76 Gy /38 fx	- 10y biochemical disease failure: 30.6% vs. 25.9%, NS. - IPSS > 12 higher toxicity in hypofx arm
RTOG 0415 [7]	5.8 years	LR	70 Gy / 28 fx	73.8 Gy / 41 fx	- No SS difference in DFS - Hypofx arm more late grade 2 GI toxicity (18.3% versus 11.4%); GU 26.2% versus 20.5%)
CHHiP [8]	5.2 years	All	57-60 Gy / 19-20 Fx	74 Gy / 37 fx	- 60 Gy not inferior to 74 Gy but could not be claimed for 57 Gy - No diff in GI/GU toxicity
PROFIT [9]	6 years	IR	60 Gy / 20 fx	78 Gy / 39 fx	- 5y bF in both arms was 15% (HR 0.96) - Hypofx arm not inferior to conventional - No difference in late GI/GU

Multiple hypofractionation trials have demonstrated equivalent oncologic control with acceptable toxicity

WHAT IS THE EVIDENCE FOR LT-ADT?

- **EORTC 22863** [10]
  - GS 8-10 or T3-T4, N0-N1 (modern high risk and node + patients)
  - EBRT to 70 Gy with concurrent and adjuvant ADT for 36 months versus RT alone
  - 5-year OS 78% ADT versus 62%
  - 10-year OS 58% ADT versus 40%
  - 10-year DFS 48% versus 23%
- **EORTC 22961** [11]
  - Non-inferiority study – 6 months ADT with WPRT + 30 months ADT versus no further ADT
  - 5-year mortality improved with LT-ADT 15% versus 19% with ST-ADT
- **RTOG 9202** [12]
  - Modern high-risk patients (some intermediate)
  - 4 months neoadjuvant and concurrent ADT + WPRT versus 4 months neoadjuvant and concurrent ADT + WPRT + 24 months adjuvant ADT
  - 10-year DFS 22% versus 13%
  - Subanalysis, OS advantage seen in GS 8-10, 32% versus 45%
  - Modern intermediate risk, no difference in 10-year OS

TREATMENT PLANNING

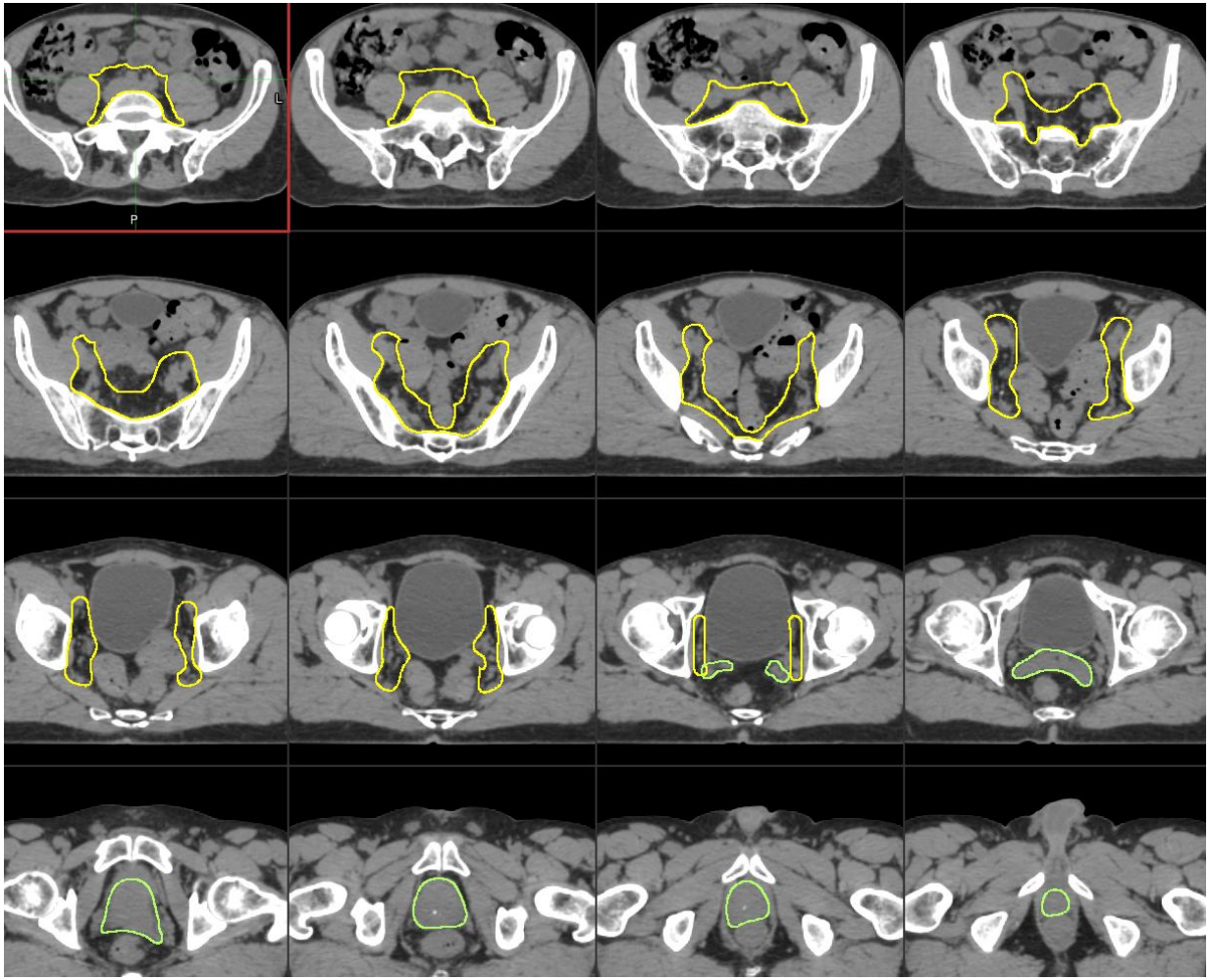
- The patient was treated with hypofractionated EBRT:
  - 70 Gy to the prostate and SV
  - 4760 cGy delivered to the pelvic lymph nodes
  - IMRT
  - Simultaneous Integrated Boost

- Contours were based on NRG guidelines published in 2021

NRG Contouring Guidelines[13]

- **Prophylactic Nodal Contouring:**
  - Commence contours at the bifurcation of the aorta
  - Contour approximately 5-7 mm around each vessel; bowel excluded from nodal CTV contour. Ensure coverage posteriorly in the area between the psoas major and the vertebral body
  - Include prevertebral, presacral, and posterior mesorectal nodes to the bottom of S3
  - Transition from external iliac to the inguinal nodes occurs when the external iliac vessels cross beneath the inguinal ligament into the inguinal canal
  - External iliac contours should typically end when the vessels are completely lateral to the most medial aspect of the acetabulum
- **Prostate and Seminal Vesicles Contouring:**
  - Prostate and proximal 1 cm seminal vesicles contoured with a 5mm expansion posteriorly and 7mm expansion elsewhere

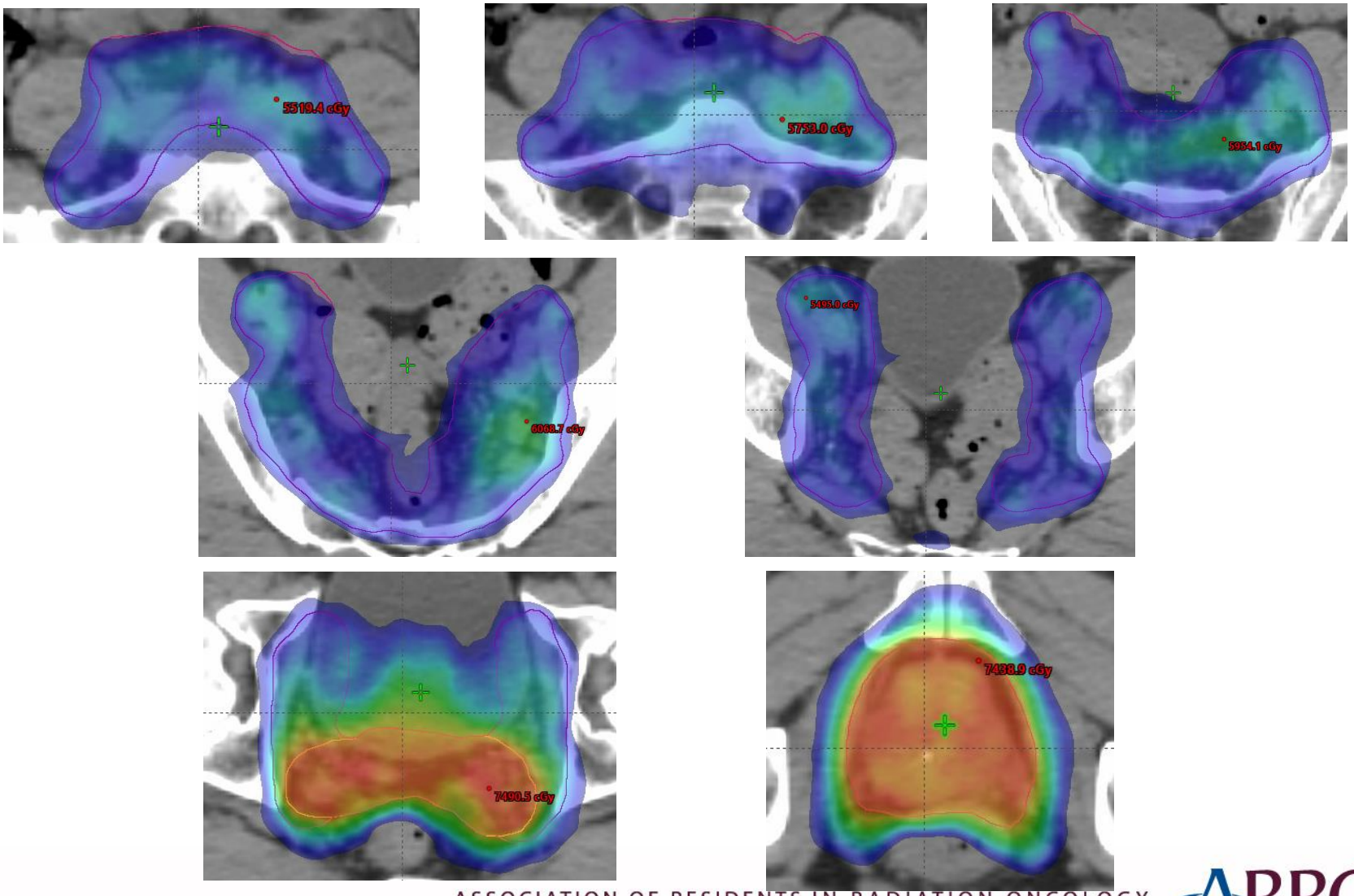
RADIOTHERAPY CONTOURS



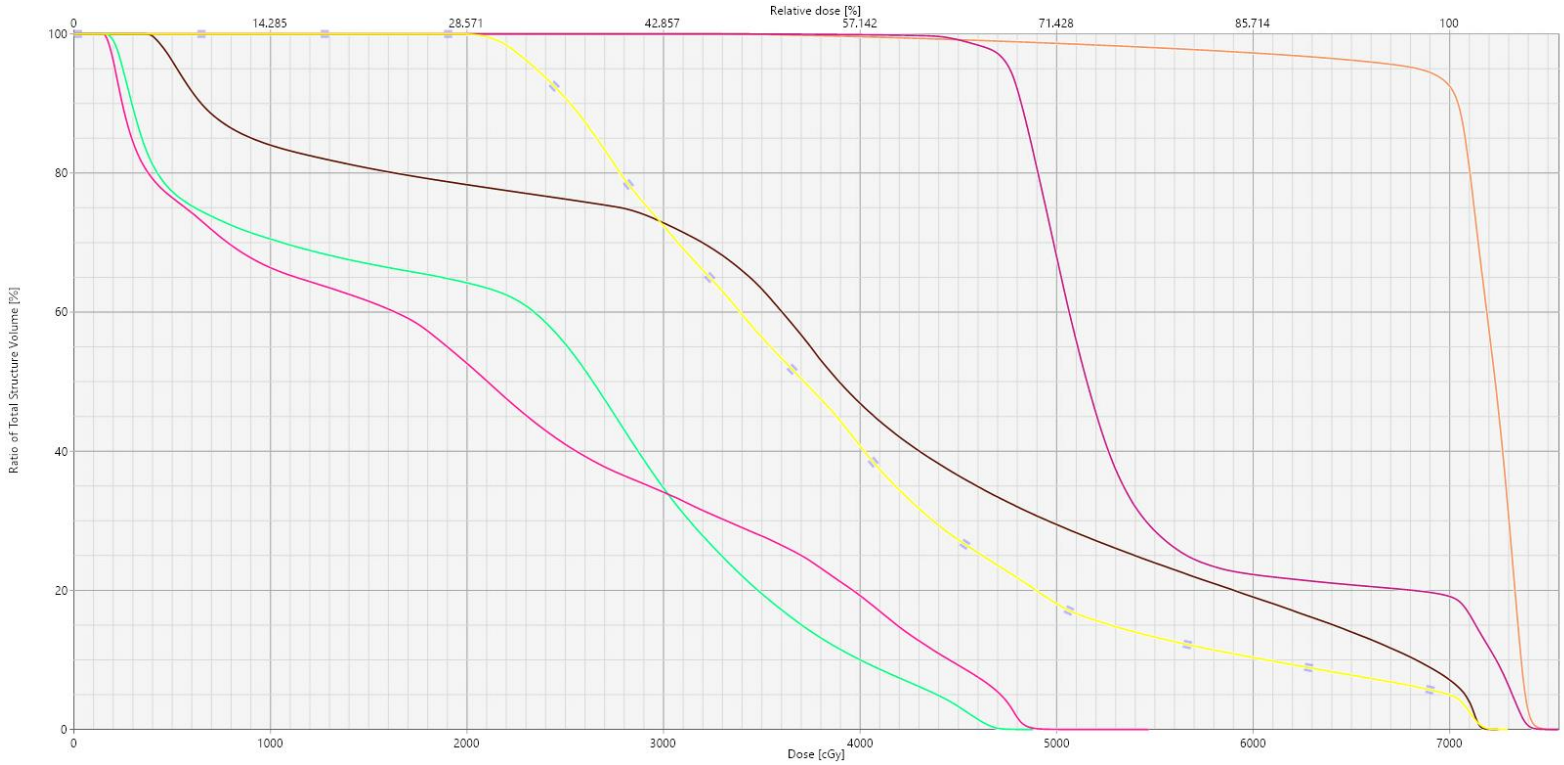
Dose Constraints

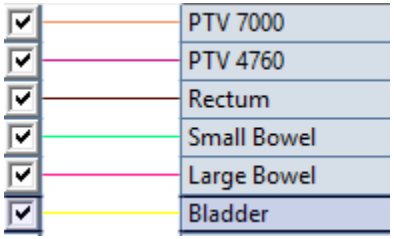
- **Rectum:**
  - V_65 Gy < 15%
  - V_65 Gy < 10cc
  - V_55 Gy <25%
  - V_45 Gy < 45%
- **Bladder:**
  - V_65 Gy < 15%
  - V_55 Gy <25%
  - V_45 Gy < 45%
- **Large Bowel:**
  - D_max = 55 Gy
- **Small Bowel:**
  - D_max < 52 Gy
  - V_46.5 Gy < 2 cc

PLAN EVALUATION



DOSE-VOLUME HISTOGRAM





- PTV_7000 D95% = 97.685% (limited by rectum dose but >95% acceptable)
- PTV_4760 D95% = 100%
- All dose constraints mentioned previously met

TREATMENT COURSE

- He completed RT as described with no treatment breaks
- During the course of RT:
  - Grade 1 genitourinary toxicity (urgency, frequency, nocturia) managed with Ibuprofen/Azo
  - No gastrointestinal toxicity

FOLLOW UP

- 3 month follow up:
  - PSA undetectable
  - Continues on ADT with mild fatigue, erectile dysfunction, decreased libido
  - Genitourinary toxicity has resolved
- Future follow up:
  - PSA every 6 months for 2 years, then annually until 5 years post-treatment
  - PSMA PET-CT if biochemical recurrence (PSA increases >2 above nadir post treatment, or 3 successive increases in PSA)

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