

Parameters that Predict for High Grade Rectal Toxicity in Prostate Cancer Patients Undergoing Stereotactic Body Radiation Therapy – Analysis of Phase I/II Study at UT Southwestern

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ABSTRACT

Introduction: Conventional radiation therapy (CRT) is a well-accepted option for prostate cancer (Pca) treatment with high disease control rate and low (< 3-5%) risk of rectal toxicity. Stereotactic Body Radiation Therapy (SBRT), unlike CRT, delivers higher doses of radiation in 1-5 fractions, reducing treatment time significantly (from 8-9 weeks to ~ 2 weeks). Benefits of SBRT include improved patient convenience, significant healthcare cost reduction, and a strong biologic rationale for large dose treatment. A dose escalation phase I study (Boike et. al, JCO 2011) established 45-50 Gy in 5 treatments as effective and safe. The phase II study at 50 Gy was recently completed. Interim analysis unexpectedly revealed a significant number of grade 3+ delayed rectal events. We performed a rigorous analysis to determine potential etiology and methods to avoid occurrence of such rectal events.

Methods: Clinical parameters evaluated include tumor stage, Gleason grade, prostate volume, comorbid conditions (diabetes, smoking history, immunosuppression), race, age, and baseline bowel function score. Treatment planning parameters collected and evaluated included rectal wall volume receiving high doses of radiation, target volume size, rectal wall size, and degree of circumferential radiation to the rectal wall. Uni/multivariate analysis and correlative studies were conducted.

Results: 59 low/intermediate risk Pca patients were enrolled in this phase I/II study at UTSW. Median follow-up for all patients is 25.5 months. Tumor control rate is 99% to date. No patients experienced high grade rectal toxicity at 45 and 47.5 Gy, but at 50 Gy 10.8% experienced \geq grade 3 rectal toxicity. Significant parameters were rectal volume receiving 50 Gy, HR of 2.67 (1.25, 5.71), $p=.0113$; rectal circumference irradiated by 24 Gy, 39 Gy and 50 Gy, HR of 1.1 (1.01,1.2) ($p=.03$), 1.2 (1.01, 1.38) ($p=.04$), and 1.22 (1.01, 1.47) ($p=.04$) respectively; and possibly diabetes, HR 6.86 (0.83, 56.8) ($p=.074$). All 4 patients with grade 3+ rectal toxicity had > 3.5 cm³ rectal wall irradiated by 50 Gy. All patients without rectal toxicity had < 3.5 cm³ rectal wall irradiated by 50 Gy.

Discussion: We have determined the absolute threshold dose volume constraint to avoid rectal toxicity for SBRT of Pca. These findings contribute significantly to the radiobiology of bowel tolerance. If anatomy does not permit safe rectal dose constraints, dose reduced SBRT or CRT should be considered. When rectal constraints are met, or when 45-47.5 Gy prescription dose is used, SBRT seems to be a potent, safe, convenient and cost effective treatment for patients with low/intermediate risk Pca.

Table 1. Patient Characteristics

| Characteristics | All Groups | 45 Gy | 47.5 Gy | 50 Gy |
|------------------------|------------------|------------------|-------------------|------------------|
| No. of Patients | 59 | 14 | 8 | 37 |
| Age, years | | | | |
| Median (Range) | 65 (52-82) | 69 (55-82) | 62 (58-70) | 64 (52-80) |
| Hormones | | | | |
| Yes | 6 | 3 | 1 | 2 |
| No | 51 | 10 | 7 | 34 |
| PSA | | | | |
| Median (Range) | 5.7 (1.3-12.4) | 6.6 (3.3-12.4) | 5.7 (2.1-11.5) | 5.4 (1.3-11.4) |
| T Stage | | | | |
| T1c | 41 | 11 (78.6%) | 6 (75%) | 24 (64.9%) |
| T2a | 12 | 1 (7.1%) | 1 (12.5%) | 10 (27%) |
| T2b | 6 | 2 (14.3%) | 1 (12.5%) | 3 (8.1%) |
| Gleason Score | | | | |
| 6 (3+3) | 27 | 3 (21.4%) | 4 (50%) | 20 (54.1%) |
| 7 (3+4) | 21 | 8 (57.1%) | 4 (50%) | 9 (24.3%) |
| 7 (4+3) | 11 | 3 (21.4%) | 0 (0%) | 8 (21.6%) |
| Prostate Size, cm3 | | | | |
| Median (Range) | 32 (12.3-60) | 31.2 (19-60) | 38.35 (19.2-52.4) | 33 (12.3-38.9) |
| Rectal Volume, cm3 | | | | |
| Median (Range) | 36.8 (18.9-85.1) | 41.9 (26.8-66.8) | 31.9 (25.6-58.9) | 36.6 (18.9-85.1) |
| Race | | | | |
| African American | 15 | 1 | 2 | 12 |
| White | 36 | 9 | 6 | 21 |
| Hispanic | 3 | 1 | 0 | 2 |
| Asian/Pacific Islander | 5 | 2 | 0 | 3 |
| Smoking | | | | |
| Current | 9 | 3 | 2 | 4 |
| Past | 20 | 7 | 2 | 11 |
| Never | 30 | 4 | 4 | 22 |
| Diabetes | | | | |
| Yes | 9 | 1 | 2 | 6 |
| No | 50 | 13 | 6 | 31 |

Figure 1. Separation of Toxicity by Volume of Rectum receiving 50 Gy

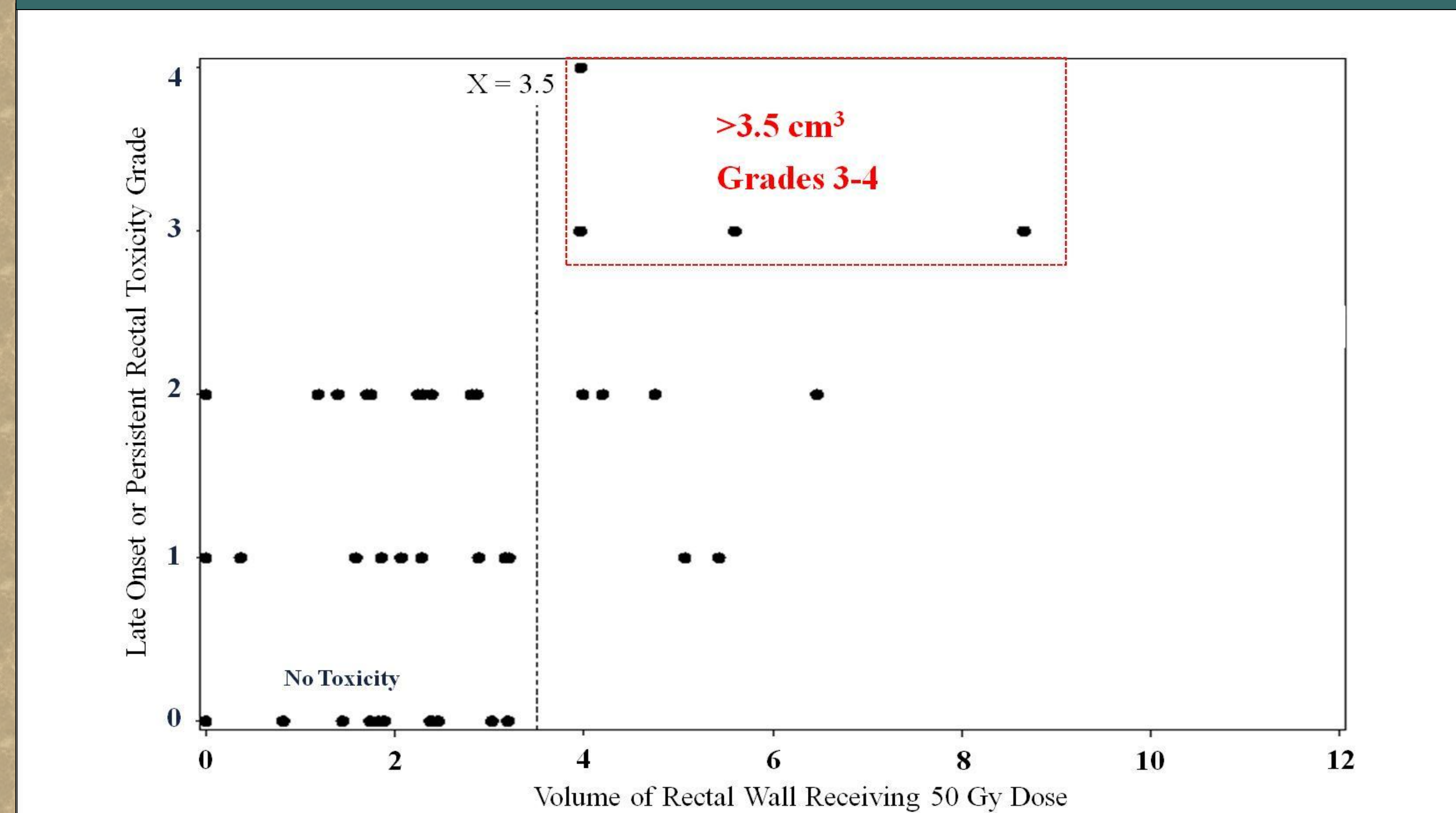


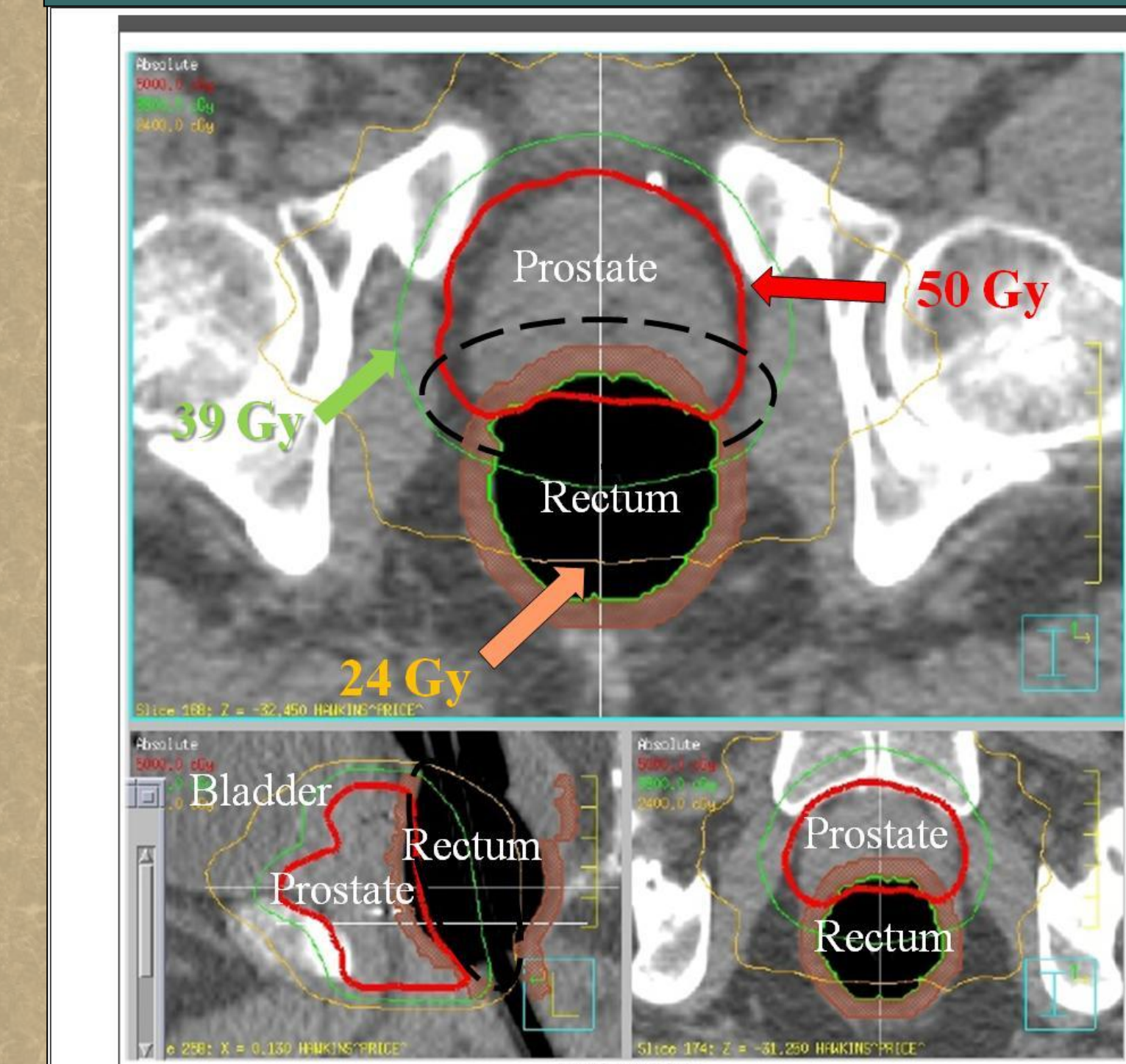
Table 2. Toxicity Data

| | All Patients (n = 59) | | 45 Gy (n = 14) | | 47.5 Gy (n = 8) | | 50 Gy (n = 37) | |
|-------|-----------------------|--------------|----------------|--------------|-----------------|--------------|----------------|--------------|
| Grade | Acute No. (%) | Late No. (%) | Acute No. (%) | Late No. (%) | Acute No. (%) | Late No. (%) | Acute No. (%) | Late No. (%) |
| 0 | 24 (40.7) | 28 (47.5) | 9 (64.3) | 11 (78.6) | 5 (62.5) | 7 (87.5) | 10 (27.0) | 10 (27.0) |
| 1 | 23 (39.0) | 13 (22.0) | 5 (35.7) | 2 (14.3) | 3 (37.5) | 1 (12.5) | 15 (40.5) | 10 (27.0) |
| 2 | 10 (16.9) | 14 (23.7) | 0 (0.0) | 1 (7.1) | 0 (0.0) | 0 (0.0) | 10 (27.0) | 13 (35.1) |
| 3 | 1 (1.7) | 3 (5.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.7) | 3 (8.1) |
| 4 | 1 (1.7) | 1 (1.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.7) | 1 (2.7) |

Table 3. Univariate Analysis

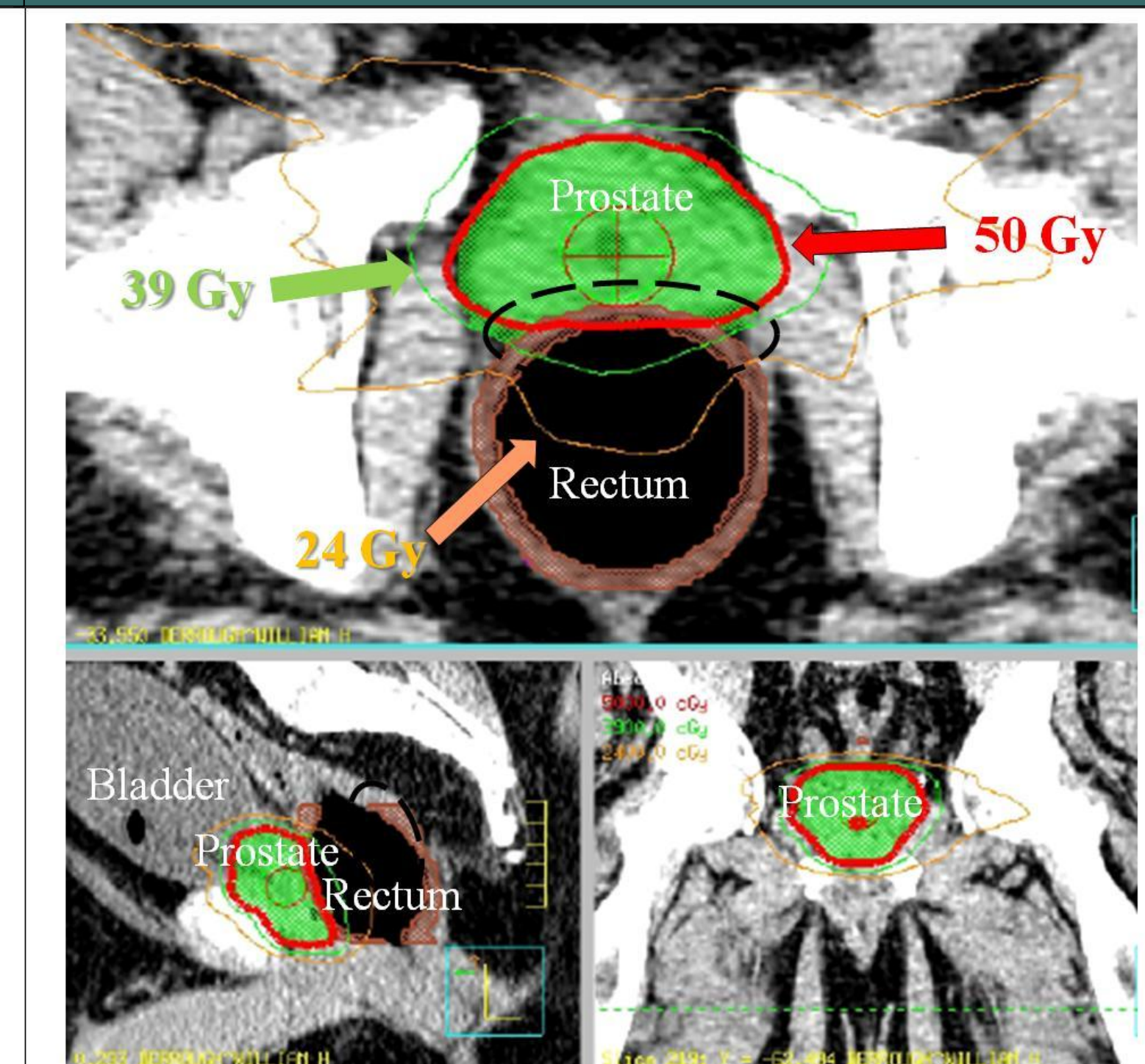
| | Odds Ratio | 95% CI | p-value |
|---|------------|----------------|---------|
| Age | 0.94 | (0.81, 1.09) | .4273 |
| Race | | | 0.1575 |
| African American vs. Caucasian | 20.44 | (0.94, 445.93) | |
| All other vs. Caucasian | 14.6 | (0.49, 431.19) | |
| Gleason Score | | | 0.7054 |
| 3+4 vs. 3+3 | 2.74 | (0.23, 32.43) | |
| 4+3 vs. 3+3 | 2.6 | (0.15, 45.68) | |
| Diabetes | 6.86 | (0.83, 56.8) | .0743 |
| Baseline EPIC Bowel Symptom Score | 1.05 | (0.86, 1.28) | 0.6558 |
| Smoking History * | N/A | N/A | 0.8633 |
| Androgen Deprivation Therapy * | N/A | N/A | 1.0 |
| PTV volume (cm3) | 1.03 | (0.99, 1.07) | 0.1248 |
| Max PTV Length (cm) | 2.12 | (0.56, 8.05) | 0.2695 |
| Max PTV Width (cm) | 5.28 | (0.50, 55.62) | 0.1664 |
| Rectal wall volume (cm3) | 1.03 | (0.96, 1.11) | 0.3466 |
| Max point dose on rectum | 1.01 | (0.997, 1.01) | 0.1981 |
| Anterior rectal volume receiving 40 Gy (cm3) | 2.21 | (1.18, 4.13) | 0.0134 |
| Anterior rectal volume receiving 45 Gy (cm3) | 2.20 | (1.19, 4.08) | 0.0119 |
| % Circumference of Rectum Treated By 24 Gy | 1.1 | (1.01, 1.2) | 0.0265 |
| % Circumference of Rectum Treated By 39 Gy | 1.18 | (1.01, 1.38) | 0.0374 |
| % Circumference of Rectum Treated By 50 Gy | 1.22 | (1.01, 1.47) | 0.0391 |
| Length of inner rectal wall covered by 50 Gy line | 3.03 | (1.27, 7.26) | 0.0126 |
| Volume rectum receiving specified dose (cm3) : | | | |
| 35 Gy | 1.72 | (1.13, 2.62) | 0.0115 |
| 37.5 Gy | 1.84 | (1.15, 2.92) | 0.0103 |
| 40 Gy | 1.95 | (1.18, 3.22) | 0.0095 |
| 42.5 Gy | 2.40 | (1.21, 4.77) | 0.0122 |
| 45 Gy | 2.17 | (1.19, 3.97) | 0.0117 |
| 47.5 Gy | 2.25 | (1.19, 4.24) | 0.0124 |
| 50 Gy | 2.67 | (1.25, 5.71) | 0.0113 |

Fig 2a. Dosimetry of Patient with Grade 3 Rectal Toxicity



Rectal Volume \geq 50 Gy: 5.6 cm³, % Circ. Rectum 24 Gy: 58%, % Circ. Rectum 39 Gy: 40%

Fig 2b. Dosimetry of Patient with Grade 0 Rectal Toxicity



Rectal Volume \geq 50 Gy: 1.9 cm³, % Circ. Rectum 24 Gy: 34%, % Circ. Rectum 39 Gy: 24%