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Target Volume Heterogeneity Index, a Potentially Valuable Metric in IMRT Prostate Cancer Treatment Planning

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Abstract

Purpose/Objectives: Heterogeneity index (HI) has been described in the literature as a tool for evaluating dose gradients within a planning target volume (PTV). HI may be expressed as D1/D95 where D1 and D95 equal the dose encompassing 1% and 95% of the target volume. The purpose of this study is to evaluate the effect of target volume dose heterogeneity on dose received by local organs at risk in the treatment of low and intermediate risk prostate cancer.

Materials/Methods: Treatment plans were reviewed for 157 patients with low or intermediate risk prostate cancer treated with dose-escalated radiation therapy between 6/2007 and 2/2012. Patients treated in the post-operative setting or receiving pelvic nodal irradiation were excluded. Patients were treated with either standard intensity modulation (IMRT) using 7 or 8 fields or 2-arc volumetric modulated arc therapy (VMAT). All patients had daily image-guidance. PTV HI (D1/D95) and dose-volume histogram (DVH) data at 8 dose levels for rectum and bladder were recorded. Patients were categorized into two groups (low HI or high HI) with respect to median index score. A two-tailed t-test was used to test for differences in dose received by rectum and bladder for the two groups.

Results: For the 157 plans evaluated, mean PTV volume was 164cc and mean prescription dose was 7833cGy. Median HI was 1.04 (range 1.0-1.08). Low HI (≤1.04) was found to correlate with significantly lower rectal V50 (p=0.02), V55 (p=0.01), V60 (p=0.01), V65 (p=0.01), and V70 (p=0.01). There was no significant correlation with dose received by bladder at any dose level. HI was similar for patients treated with standard IMRT and VMAT (p=0.85).

Conclusions: Target volume HI ≤ 1.04 is associated with more favorable rectal doses at clinically relevant dose-levels. We believe HI may serve as a valuable metric in prostate cancer treatment planning. Further work is needed to correlate these dosimetric findings with clinical outcomes.

Keywords: Heterogeneity; Prostate; Toxicity; Rectum

Introduction

Background

Dose-escalated radiation therapy has been widely adopted in the treatment of prostate cancer [1,2]. Following definitive radiation therapy, biochemical progression free survival (bPFS) for low risk prostate cancer is greater than 83% at 10 years [1] and cancer specific survival at 8 years approaches 99% [2]. Given the excellent prognosis and expected survival rates following treatment of prostate cancer with radiation therapy, an emphasis should continue to be placed on techniques to limit dose to adjacent organs and to decrease acute and late toxicity.

Intensity modulated radiation therapy (IMRT) has allowed for advancement of the field in this direction. Zelefski et al, for example, observed significantly decreased acute and late rectal toxicity with IMRT as compared with 3-D conformal historical controls while maintaining comparable bPFS [3]. In another study comparing these two modalities, risk of grade 2 rectal bleeding was reduced from 10% to 2% with the use of IMRT [4]. Beyond the implementation of IMRT in the treatment of prostate cancer, several studies have explored optimal beam angle selection and inverse planning prioritization in order to decrease dose to organs at risk including bladder, rectum, femoral heads, and penile bulb [5,6].

Using inverse planning algorithms, priorities are often assigned to these organs at risk in order to minimize incidental dose. Because of the proximity of the rectum to the prostate and this organ's relative radiosensitivity, dose constraints to this organ must be respected. The importance of rectal dose constraints has been clinically validated. Important dose-constraints that have previously been explored include rectal volume receiving at least 30 Gray less than 80% (V30Gy< 80%), V40Gy <65%, V50Gy <55%, V60Gy <40%, V65Gy <30%, V70Gy <15%, and V75Gy <3% [7].

Heterogeneity index (HI) has been described in the literature as a tool for evaluating dose gradients within a planning target volume (PTV) in other treatment sites [8,9]. HI may be expressed as D1/D95

where D1 and D95 equal the dose encompassing 1% and 95% of the target volume [9]. The purpose of this study is to evaluate the effect of target volume dose heterogeneity on dose received by local organs at risk in the treatment of low and intermediate risk prostate cancer (Figure 1). We hypothesize that with decreasing target dose heterogeneity, lower doses to bladder and rectum will be observed.

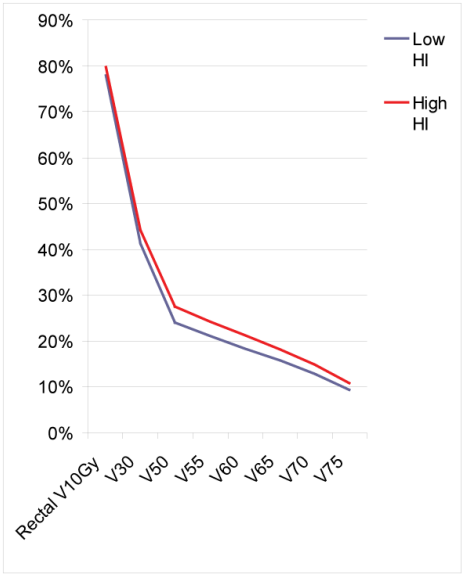

Figure 1: Percent rectal volume receiving dose (Gray) differences in rectal dose/volumes by group; HI= Heterogeneity Index, VxGy=Percent of organ volume receiving xGy or more

Methods

Following Institutional Review Board approval, patient charts, including consultation notes, treatment planning records, and completion summaries were reviewed for 157 patients with low or intermediate risk prostate cancer treated from June 2007 through February 2012 at our institution. All patients were treated with dose-escalated radiation therapy (7740-7920cGy). Patients treated in the post-operative setting, with high-risk disease, or receiving pelvic nodal irradiation were excluded from this analysis given significant variability for these patients' target volumes.

Clinical target volume (CTV) had been defined as the prostate gland only for patients with low risk disease and prostate plus proximal seminal vesicles (generally the proximal 1 cm) for patients with intermediate risk disease. Planning target volume (PTV) margin ranged from 0.8 to 1.0 cm in all directions except posteriorly where margin was limited to 0.5 cm, though these margins could be individually tailored. Patients were treated with either 7 or 8-field IMRT or 2-arc VMAT (359.8 degree arcs). All treatment planning was performed using Eclipse treatment planning software version 8.6 or 8.9 and plans were subsequently exported to Mosaic version 2.3. All patients had daily image-guidance with ultrasound, orthogonal films plus fiducial markers, or cone-beam computed tomography. Most patients were treated by a single radiation oncologist (JM) regardless of treatment facility.

DVH data including PTV volume, PTV heterogeneity index (D1/D95), rectal and bladder V10Gy, V30Gy, V50Gy, V55Gy, V60Gy, V65Gy, V70Gy, and V75Gy were recorded for each plan. Patients were categorized into two groups (low HI or high HI) with respect to median index score. A two-tailed t-test was used to test for differences in dose received by rectum and bladder for the two groups.

Results

Patient characteristics

For the 157 plans evaluated, mean PTV volume was 164cc and mean prescription dose was 7833cGy. Patients in the two groups were similar in age, T stage, Gleason score, pretreatment PSA, and National Comprehensive Cancer Network risk level (Table 1).

	Low HI Number (%)	High HI Number (%)	*p*
Age			0.656
<70 years	48 (65)	51 (61)	
70 years or older	26 (35)	32 (39)	
T Stage			1.000
1a-2a	73 (99)	81(98)	
2b	1 (1)	2 (2)	
Gleason Score			0.829
score <7	22 (30)	26 (31)	
score =7	52 (70)	57 (69)	
PSA			0.605
<10	63 (85)	73 (88)	
10 - 20	11 (15)	10 (12)	
NCCN Risk			0.718
low risk	27 (36)	28 (34)	
intermediate risk	47 (64)	55 (66)	
Modality			0.63
RA	18 (24)	23 (28)	
IMRT	56 (76)	60 (72)	
Mean PTV Volume	160cc	168cc	0.304

Table 1: Patient Characteristics, Baseline patient characteristics; HI=Heterogeneity Index; NCCN= National Comprehensive Cancer Network; RA=Rapid Arc Volumetric Modulated Arc Therapy; IMRT= Intensity Modulated Radiation Therapy; PTV= Planning Target Volume

Dosimetric Findings

Median HI was 1.04 (range 1.0–1.08). Low HI (≤1.04) correlated with significantly lower average rectal V50Gy (p=0.02), V55Gy (p=0.01), V60Gy (p=0.01), V65Gy (p=0.01), and V70Gy (p=0.01). Differences in rectal V10 Gy (p=0.33), V30Gy (p=0.18), and V75Gy (p=0.08) failed to reach statistical significance. There was no significant correlation with dose received by bladder at any dose level; bladder V10 Gy (p=0.86), V30Gy (p=0.58), V50Gy (p=0.37), V55Gy (p=0.38), V60Gy (p=0.40), V65Gy (p=0.45), V70Gy (p=0.52), and V75Gy (p=0.79). (Table 2). Additionally, HI was similar for patients treated with standard IMRT and VMAT (p=0.85).

Rectal Volumes	V10	V30	V50	V55	V60	V65	V70	V75
Low HI	78% +/- 2%	41% +/- 1%	24% +/- 1%	21% +/- 1%	18% +/- 1%	16% +/- 1%	13% +/- 1%	9% +/- 1%
High HI	80% +/- 1%	44% +/- 2%	28% +/- 1%	28% +/- 1%	21% +/- 1%	18% +/- 1%	15% +/- 1%	11% +/- 1%
P value	0.33	0.18	0.02	0.01	0.01	0.01	0.01	0.08
Bladder Volumes	V10	V30	V50	V55	V60	V65	V70	V75
Low HI	80% +/- 2%	46% +/- 2%	28% +/- 1%	25% +/- 1%	23% +/- 1%	20% +/- 1%	18% +/- 1%	15% +/- 1%
High HI	79% +/- 2%	48% +/- 2%	30% +/- 1%	27% +/-1%	24% +/- 1%	22% +/- 1%	19% +/- 1%	15% +/- 1%
P value	0.86	0.58	0.37	0.38	0.40	0.45	0.52	0.79

Table 2: Rectal and Bladder dose/volume reductions noted as a function of target heterogeneity specifically, rectal V50, V55, V60, V65, V70; HI=Heterogeneity Index, VxGy=Percent of organ volume receiving xGy +/- standarad error.

Discussion

In our series we have found target volume HI ≤1.04 to be associated with more favorable rectal doses at clinically relevant dose-levels without compromising dose to the PTV. There was no statistically significant correlation between decreasing HI and bladder dose (Figures 1 and 2).

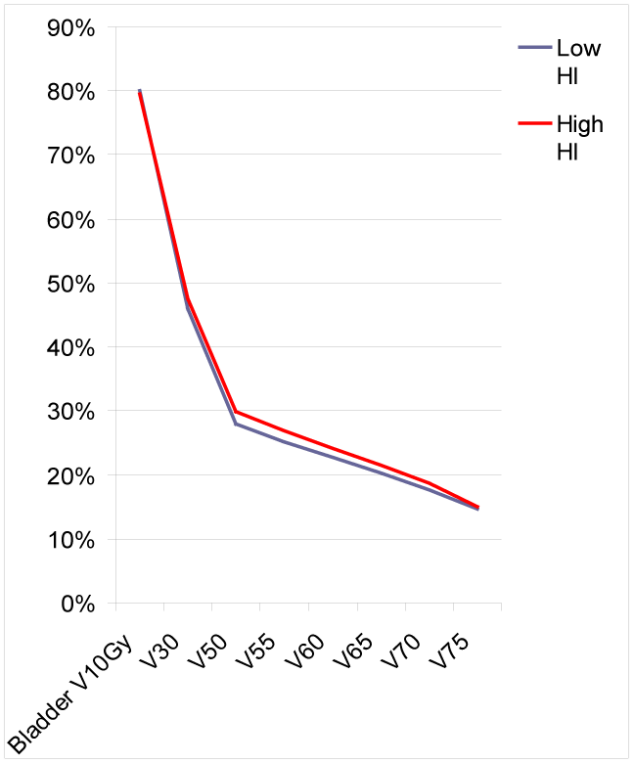

Figure 2: Percent bladder volume receiving dose (Gray) differences in rectal dose/volumes by group; HI= Heterogeneity Index, VxGy=Percent of organ volume receiving xGy or more

To our knowledge, this is among the first dosimetric studies investigating a possible correlation of HI with dose to organs at risk in prostate cancer. Of perhaps most importance, decreased dose to rectum has been shown to translate to improved patient reported quality of life as a function of gastrointestinal dysfunction in the treatment of prostate cancer [10]. For example, in the study by Nguyen et al, patients with anterior rectal wall V60 >54%, reported an average bowel symptom score of 10.6, compared with a lower average score of 5.4 for patients with V60 < 54% (p = 0.04) [10].

This hypothesis-generating study suggests that further investigation into HI as a plan assessment tool may be warranted. Given these findings, we feel that target volume heterogeneity recommendations may be provided in future clinical trials evaluating radiation techniques in the management of prostate cancer.

Further avenues for study include implementation of specific target HI parameters while inverse planning to determine if HI is not only a metric for plan evaluation but may also serve as a planning tool for generating superior plans with decreased dose to rectum.

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