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Prostate radiotherapy

Dose to the inferior rectum is strongly associated with patient reported bowel quality of life after radiation therapy for prostate cancer

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ABSTRACT

Purpose: To evaluate rectal dose and post-treatment patient-reported bowel quality of life (QOL) following radiation therapy for prostate cancer.
Methods: Patient-reported QOL was measured at baseline and 2-years via the expanded prostate cancer index composite (EPIC) for 90 patients. Linear regression modeling was performed using the baseline score for the QUANTEC normal tissue complication probability model and dose volume histogram (DVH) parameters for the whole and segmented rectum (superior, middle, and inferior).
Results: At 2-years the mean summary score declined from a baseline of 96.0–91.8. The median volume of rectum treated to $\geqslant$70 Gy (V70) was 11.7% for the whole rectum and 7.0%, 24.4%, and 1.3% for the inferior, middle, and superior rectum, respectively. Mean dose to the whole and inferior rectum correlated with declines in bowel QOL while dose to the mid and superior rectum did not. Low (V25–V40), intermediate (V50–V60) and high (V70–V80) doses to the inferior rectum influenced bleeding, incontinence, urgency, and overall bowel problems. Only the highest dose (V80) to the mid-rectum correlated with rectal bleeding and overall bowel problems.
Conclusions: Segmental DVH analysis of the rectum reveals associations between bowel QOL and inferior rectal dose that could significantly influence radiation planning and prognostic models.
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Following external beam radiation therapy (EBRT) for prostate cancer, "moderate/severe" gastrointestinal side-effects persist in up to 10% of men typically manifesting as urgency, frequency, pain, incontinence, or bleeding [1]. Extensive research demonstrated rectal dose–volume histogram (DVH) parameters [2–8], including normal tissue complication probability (NTCP) models [9], as a prognostic for physician-scored toxicity. These parameters, however, have not been as carefully studied for patient-reported quality of life (QOL) [10,11], which is a more sensitive and valid indicator of patient satisfaction [12].

In addition, more recent data suggest that radiation dose to the anorectum, as compared to the whole rectum, may exhibit the strongest association with late physician-scored rectal toxicity [13–15,32]. To this end, we sought to evaluate the influence of both whole and segmental rectal DVH parameters on changes in patient-reported bowel QOL [16].

Methods and materials

Study patients

The study cohort included men with clinically localized prostate cancer undergoing definitive EBRT at a single institution from 2004 to 2009 as part of one of three prospective institutional review board approved studies: a randomized phase II trial of urethral sparing intensity modulated radiation therapy and two consecutive QOL studies. Of 114 men treated on these protocols, this analysis was restricted to 90 men with baseline and 2-year post-treatment patient-reported outcome measures.

Outcome measure

Patients completed the Expanded Prostate Cancer Index Composite (EPIC) instrument at baseline, 6, 12, and 24 months [12].

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For the current analysis we have focused on the 24-month timepoint (median 23.9 months [IQR: 23.9–24.0]). The EPIC bowel domain includes 6 items (frequency, urgency, pain, bleeding, incontinence, and overall problem) based upon five responses (no, very small, small, moderate, and big problems) which are transformed to an overall bowel summary score (0–100) [16]. Those with <4-point decline in summary score were considered to have no clinically significant change, those with 4 to <12-points decline a small change, and those with ⩾12-points moderate to severe changes [12]. Individual items were also dichotomized from their original 5-point scale and analyzed by logistic regression controlling for baseline score [11,12].

Treatment and dose–volume parameters

All patients underwent computed tomography planning with a full bladder and an empty rectum and received either three-dimensional EBRT or intensity-modulated EBRT to a dose of 77.7 Gy (interquartile range [IQR]: 75.9–77.7) in 1.8–2.0 Gy fractions. Dose was prescribed to the isodose line encompassing at least 95% of the planning target volume (PTV). The clinical target volume included the prostate (P) for low risk patients, the prostate and seminal vesicles (SV) for intermediate-risk patients, and the pelvic lymph nodes (45 Gy) followed by a boost to the P + SV for high-risk patients. Typically, PTV margins of 0.5 cm were used for patients undergoing daily image-guided RT (IGRT) and 1.0 cm for non-IGRT cases. [17,18]. IGRT consisted of either fiducial markers with daily orthogonal kV imaging or electromagnetic transponders with a 3 mm threshold.

Among the 10 patients receiving pelvic RT, 7 were treated with two sequential IMRT plans to the pelvic lymph nodes and the prostate/seminal vesicles. The 3 other patients were treated with an initial 3D-conformal plan to the pelvis to 45 Gy (1.8 Gy/fx) followed by a boost to the prostate/seminal vesicles utilizing a 7-field 3D-CRT boost in 2 patients and an IMRT boost in 1 patient.

The rectum was contoured as a solid structure [19] from the ischial tuberosities to sigmoid, with planning constraints to keep the volume of rectum receiving ⩾70 Gy (V70) <25% and V50 <50%. NTCP modeling was not utilized in clinical practice at this time. As previously reported, for analysis the rectum was segmented into 3 parts: inferior (ischial tuberosities to 3 cm superior) [20,32], middle (next 3 cm; typically corresponding to the prostate level), and superior rectum (top of middle rectum to sigmoid colon) (Fig. 1A). The median superior rectal segment was 4.3 cm (interquartile range [IQR], 3.3–5.5). The anterior half of the rectal wall (3 mm in thickness) was also contoured for the whole rectum. Small bowel was defined as the peritoneal space from the lowest segment of small bowel or superior aspect of the rectum (whichever was most inferior) up to the iliac crests [19]. The volume and percentage of rectum, anterior rectal wall, rectal segments, and small bowel treated to doses of 25 Gy, 40 Gy, 50 Gy, 60 Gy, 65 Gy, 70 Gy, 75 Gy, and 80 Gy were evaluated. For this analysis a Lyman–Kutcher–Burman NTCP model estimating the risk of Grade ⩾2 rectal toxicity was also evaluated with the following model parameters: $n = 0.09$, $m = 0.13$, and $TD_{50} = 76.9$ Gy [21,22].

Statistical analysis

Associations between mean change in bowel summary score and patient and treatment characteristics were assessed using Analysis of Covariance (ANCOVA). Linear regression modeling for change in bowel score at 2-years from baseline was performed with dosimetric parameters as continuous and dichotomous variables. Individual bowel items were dichotomized as clinically significant *vs.* not (⩾4 *vs.* <4 point decline) and analyzed by logistic regression controlling for the baseline score. Statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC) and the R statistical software package, version 2.13.1 where all *p*-values <0.05 were considered significant. Given the close concordance between differing DVH parameters Akaike information criterion (AIC) [23] and leave one out cross-validation were utilized to identify the rectal DVH parameters that had the strongest associations.

Results

Association between clinical and treatment parameters and patient-reported bowel QOL

At 2 years the mean bowel summary score declined from 96.0 (SEM: 95.2–96.8) to 91.8 (SEM: 90.4–93.2). 59% of patients exhibited a decline <4 points (mean, +3.8 [SEM: −2.6 to +5.0]) reflecting no significant change; 20% had a decline of 4 to <12 points (mean, −5.6 [SEM: −6.1 to −5.1]) representing a small change; and 21% had a decline of ⩾12 points (mean, −25.7 [SEM: −11.9 to −39.5]) representing a moderate to severe change.

Patient and treatment characteristics and their associated change in bowel scores at 2-years are shown in Table 1. Median RT dose was 77.7 Gy (range: 75.6–79.2) with image-guidance in 82%, intensity-modulation in 73%, and pelvic RT in 11%. Only pelvic RT was associated with a decline in bowel function ($p = 0.05$). Acute proctitis (Grade 1–2) and rectal bleeding (Grade 1) during RT were associated with a decline in 2-year bowel QOL, while acute diarrhea (Grade 1–2) was not.

Association between dose-volume parameters and patient-reported bowel QOL

The median V70 for the whole rectum was 11.7% with differences in dose distribution across the rectum such that the median V70 for the inferior, middle, and superior rectum was 7.0%, 24.4%, and 1.3%, respectively. Fig. 1 shows a representative sagittal view of a planning CT (1A) with the segmented rectum (1A) and the overlying radiation dose distribution (1B). Fig. 2 shows the cumulative rectal DVHs as well as the mean DVHs stratified by patient exhibiting declines of <4 points, 4–12 points, and ⩾12 points for the whole (2A–B), superior (2C–D), middle (2E–F), and inferior rectum (2G–H). In patients with a <4 point decline, the mean V40, V70, and V75 of the whole rectum was 32%, 12% and 6%. In comparison these DVH parameters were 36%, 14%, and 8%, for those with a 4–12 point decline, and 46%, 18%, and 11% for those with a ⩾12 point decline. While the mid-rectum received the highest dose, DVH parameters for the inferior rectum demonstrated the greatest prognostic correlation with changes in bowel QOL. Dose to the superior rectum exhibited no measurable association with QOL.

Increasing mean dose, as a continuous variable, correlated with decreased bowel summary score for the whole ($p = 0.03$) and inferior rectum ($p = 0.04$) but not for the middle ($p = 0.14$) or superior ($p = 0.5$) segments. Patients with <4 points decline had a mean dose to the whole rectum of 29.6 Gy (SEM: 27.8–31.4) and to the inferior rectum of 25.2 Gy (SEM: 22.9–27.5). Those with 4–12 and >12 points decline had mean doses of 32.6 (SEM: 29.8–35.4) and 38.6 (SEM: 36.1–41.1) Gy for the whole and 30.9 (SEM: 27.1–34.7) and 37.2 (SEM: 32.4–42.0) Gy for the inferior rectal segment, respectively.

Patients receiving pelvic RT exhibited a decline in bowel function at 2-years ($p = 0.05$). Interestingly, in these patients mean dose to the inferior rectum was significantly higher (42 Gy *vs.* 27 Gy, $p = 0.02$), while there were no differences in mean dose to the whole ($p = 0.3$), middle ($p = 0.5$), superior rectum ($p = 0.9$), or mean NTCP ($p = 0.6$) (Supplemental Table 1).

The results of linear regression modeling for change in bowel QOL are shown (Table 2). There were correlations between the whole rectum and bowel QOL across all doses. By rectal segment,