Rapid Communication

Reduction in Patient-reported Acute Morbidity in Prostate Cancer Patients Treated With 81-Gy Intensity-modulated Radiotherapy Using Reduced Planning Target Volume Margins and Electromagnetic Tracking: Assessing the Impact of Margin Reduction Study

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OBJECTIVE To investigate whether patient-reported quality of life after high-dose external beam intensity-modulated radiotherapy for prostate cancer can be improved by decreasing planning target volume margins while using real-time tumor tracking.

METHODS Study patients underwent radiotherapy with nominal 3-mm margins and electromagnetic real-time tracking. Morbidity was assessed before and at the end of radiotherapy using Expanded Prostate Cancer Index Composite (EPIC) questionnaires. Changes in scores were compared between the Assessing Impact of Margin Reduction (AIM) study cohort and the comparator Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROST-QA) cohort, treated with conventional margins.

RESULTS The 64 patients in the prospective AIM study had generally less favorable clinical characteristics than the 153 comparator patients. Study patients had similar or slightly poorer pretreatment EPIC scores than comparator patients in bowel, urinary, and sexual domains. AIM patients receiving radiotherapy had less bowel morbidity than the comparator group as measured by changes in mean bowel and/or rectal domain EPIC scores from pretreatment to 2 months after start of treatment (-1.5 vs -16.0, $P = .001$). Using a change in EPIC score >0.5 baseline standard deviation as the measure of clinical relevance, AIM study patients experienced meaningful decline in only 1 health-related quality of life domain (urinary) whereas decline in 3 health-related quality of life domains (urinary, sexual, and bowel/rectal) was observed in the PROST-QA comparator cohort.

CONCLUSIONS Prostate cancer patients treated with reduced margins and tumor tracking had less radiotherapy-related morbidity than their counterparts treated with conventional margins. Highly contoured intensity-modulated radiotherapy shows promise as a successful strategy for reducing morbidity in prostate cancer treatment. UROLOGY 75: 1004–1008, 2010. © 2010 Elsevier Inc.

Dose escalation with external beam therapy for early-stage prostate cancer results in lower rates of biochemical recurrence,[1-4] although higher doses may increase rates of radiotherapy-related morbidity.[2] Advances in treatment techniques, such as intensity-modulated radiotherapy (IMRT), permit dose escalation while constraining the dose delivered to the rectum and bladder. Rectal dose depends on the margin (ie, radial expansion) added to the clinical target volume (CTV) to create a planning target volume (PTV) that accounts for prostate motion, occurring between (interfraction) and during (intrafraction) daily treatments. Dosimetric modeling studies show that reducing the PTV margin predicts for less rectal toxicity.[5,6]

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Strategies to manage target motion include daily in-room computed tomography, prostate ultrasound, gold fiducial imaging, rectal balloons, and electromagnetic tracking. We undertook a clinical study to determine whether reducing PTV margin results in clinical improvements in patient-reported health-related quality of life (HRQOL).[7]

Electromagnetic localization has been assessed clinically,[8] but this is the first outcomes-based study evaluating the clinical effect of reduced treatment margins. We compared morbidity between enrolled patients and a similarly assessed, contemporary, well-studied cohort of patients (PROST-QA) who underwent prostate IMRT using conventional PTV margins.[9]

MATERIALS AND METHODS

Participants

Patients with localized prostate cancer were enrolled in an institutional review board–approved prospective multi-institutional study (Assessing the Impact of Margin Reduction [AIM]). There were no restrictions on Gleason score, T-stage, pretreatment prostate-specific antigen, or hormonal therapy.

Patients underwent intraprostatic implantation of Beacon transponders (Calypso Medical Technologies Inc., Seattle, WA) and were treated with IMRT to a nominal dose of 81 Gy in 1.8-Gy fractions to the prostate and proximal seminal vesicles, using uniform 3-mm PTV margins with ≥95% PTV coverage by the prescription dose. Radiation Therapy Oncology Group standards were used for structure definition. Treatments were monitored with the Calypso System using a 2-mm intervention threshold. Delivery was paused and/or patients realigned when the threshold was exceeded.

AIM patients (±neoadjuvant hormonal therapy, NHT) and non-NHT comparator patients[9] completed Expanded Prostate Cancer Index Composite (EPIC) questionnaires before and at 2 months after start of radiation (pretreatment and post-treatment, respectively). The timing of the pretreatment assessment for the NHT comparator group differed, so that group was not used. The post-treatment questionnaire response rate was 89% for AIM and 97% for the comparator.

Statistical Analysis

The primary endpoint of the AIM study was patient-reported morbidity associated with radiotherapy. Patients completed the full EPIC questionnaire[7] in writing, at home or in the clinic, per Radiation Therapy Oncology Group guidelines. Reported analyses were restricted to the EPIC 26 subset of questions to permit comparison with the comparator study (questionnaires completed by telephone at home).[9,10]

Differences between pretreatment and post-treatment EPIC scores were compared between AIM and comparator patients in a patient-level regression analysis, accounting for pretreatment score, age, race, education, body mass index, prostate volume, and cancer risk (based on prostate-specific antigen, Gleason score, and T-stage). P values $<.05$ were considered statistically significant. Reported P values are 2-sided.

As described in the comparator study,[9] a clinically relevant change in HRQOL was defined as a difference from pretreatment to post-treatment that exceeded half of the standard deviation of the pretreatment value.[11]

We set target enrollment at a minimum of 50 patients. On the basis of prior experience, we assumed the standard deviation for within-patient pretreatment to post-treatment changes in the EPIC bowel domain score to be approximately 20. With 50 AIM patients and 150 non-NHT comparator patients, the power to detect a difference of 10 between studies is approximately 0.85 with a 2-sample t test at a 0.05 significance level.

RESULTS

Patients

AIM patients had generally less favorable clinical characteristics than comparator patients (Table 1).

Radiotherapy

A total of 61 AIM patients were treated supine and 3 prone. The median prescription dose was 81 Gy (79.8 ± 1.7 Gy). Actual PTV margins were 3 mm uniform (52 patients); 3 mm posterior, 4 mm lateral, 5 mm superior-inferior (3 patients); 4 mm uniform (2 patients); 5 mm uniform (2 patients); and 5 mm uniform to 50.4 Gy followed by 3 mm uniform to 81 Gy (5 patients). Median (standard deviation [SD]) values were PTV maximum dose = 87 Gy (2 Gy), rectalV70 = 10% (4%), rectalV50 = 27% (9%), bladderV70 = 10% (6%), and bladderV50 = 20% (13%). For the comparator group, radiotherapy was delivered according to each center's policies, using high doses of radiotherapy (75.6-79.2-Gy prescription doses in 1.8- to 2.0-Gy fractions) and conventional margins (5-10 mm) with 5- to 7-mm rectal margins (Personal communication with radiation oncologists from comparator centers).

Patient-Reported Morbidity

Table 2 shows the mean EPIC scores for AIM patients (±NHT and non-NHT) and the non-NHT comparator group. For each domain, the AIM cohort had similar or slightly lower pretreatment scores. The post-treatment change in scores for AIM patients was significantly smaller (indicating better HRQOL) than in the comparator group for the bowel and/or rectal domain. In that domain, the decrease in score was 1.5 in the AIM cohort, compared with 16.0 in the comparator cohort (P = .001). The results for the non-NHT group were similar to those for the ± NHT group. The post-treatment change in scores for AIM patients was similar to or better than in the comparator group for the other 3 domains.

AIM patients had no clinically relevant treatment-related worsening of symptoms in 7 of 8 categories, whereas the comparator group showed clinically relevant declines in 3 of 4 categories (Table 2).

Table 3 shows percentages of patients reporting specific bowel and/or rectal symptoms, to provide context for the EPIC scores in terms of patient symptoms. For example, the percentage of patients reporting rectal urgency increased from 3% to 22% in the comparator group but did not increase in the AIM group. Furthermore, the percentage of patients reporting an overall bowel prob-

Table 1. Patient characteristics of the AIM study and comparator study[9] participants

Characteristic	AIM Study (n = 64*)	Comparator Study (n = 153†)	*P*
Enrollment period	September 2008-June 2009	March 2003-March 2006	—
Age			
Median (y)	69	69	.35‡
Range (y)	55-86	47-83	—
Age group, no. (%)	—	—	.08§
<60 y	3 (5)	22 (14)	—
60-69 y	35 (55)	66 (43)	—
≥70 y	26 (41)	65 (42)	—
Race, no. (%)			
White	35 (55)	121 (81)	<.001§
Black	19 (30)	27 (18)	—
Other	10 (16)¶	2 (1)	—
Not reported	0	3	—
College graduate or postgraduate education, no. (%)	27 (43)	77 (50)	.37‖
Mean body mass index (± SD)	28.1 ± 4.6	28.5 ± 5.4	.75‡
Mean prostate volume, mL (± SD)	61.0 ± 25.9	50.0 ± 27.0	≤.001‡
PSA			
Mean (ng/mL)	8.3 ± 6.2	6.8 ± 4.3	—
Median (ng/mL)	6.7	5.8	.04‡
Range (ng/mL)	0.6-36.8	0.5-25.8	—
Group, no. (%)	—	—	.46§
<4 ng/mL	9 (14)	31 (20)	—
4-<10 ng/mL	41 (64)	96 (63)	—
≥10 ng/mL	14 (22)	26 (17)	—
Gleason score on biopsy, no. (%)			
<7	32 (50)	97 (63)	.001‖
7	26 (41)	56 (37)	—
>7	6 (9)	0 (0)	—
Clinical stage, no. (%)			
T1	32 (50)	123 (80)	<.001‖
T2	31 (48)	30 (20)	—
T3	1 (2)	0 (0)	—
Overall cancer severity**, no. (%)			
Low-risk	15 (23)	61 (40)	.003§
Intermediate-risk	41 (64)	88 (58)	—
High-risk	8 (13)	4 (3)	—

AIM, Assessing the impact of margin reduction; PSA, prostate-specific antigen.

* Seventy-seven patients were enrolled and underwent transponder implantation before IMRT. Thirteen were excluded from analyses, 8 did not complete a post-treatment questionnaire, 1 had a questionnaire that was lost in the mail, 2 withdrew for personal reasons, and 2 received whole pelvic radiation. Analyses were based on 64 patients (43 treated without NHT).

† The comparator study included 292 patients treated with IMRT or highly conformal external beam therapy; 153 were treated with IMRT without NHT and formed the comparator group. None received electromagnetic localization.

‡ Wilcoxon's test.

§ χ^2 test.

¶ Categories of race collected in the AIM study were White/Caucasian (not Latino/Hispanic), Black/African American (not Latino/Hispanic), Latino/Hispanic/Mexican-American, Asian/Oriental/Pacific Islander, Native American/Native Alaskan, and other. Categories reported in the comparator study were White, Black, and other. Patients reporting race as Latino, Asian, Native American, and other in the AIM study were combined as other to permit comparison.

‖ Fisher exact test (AIM, n = 63 for College or higher education; comparison was T1 vs T2/3 for Clinical Stage).

** Cancer severity was determined based on the following definition given in the comparator study: low-risk (PSA <10, Gleason score <7, and T1), high-risk (Gleason score >7 or PSA >20), and intermediate-risk (all patients who are not at low- or high-risk).

lem increased from 4% to 20% in the comparator group but did not increase in the AIM group.

COMMENT

This is the first prospective prostate cancer radiotherapy study to report outcomes using reduced PTV margins enabled by real-time tracking. This allowed for continuous management of intrafraction prostate motion, which may be critical when using small margins.[12]

This study was not randomized and used a recent, albeit historical, comparator. Variations in unmeasured characteristics could have influenced the findings. Comparator patients completed questionnaires through telephone, whereas some AIM patients completed questionnaires in the clinic. This could lead to a more favorable outcome for the latter, since patients may be less likely to report their outcome negatively if treating personnel are nearby. A prospective, concurrent trial comparing reduced margins with standard IMRT, using identical administration of EPIC, would address this limitation.

Nonetheless, our comparison is strengthened by several factors. AIM patients had generally less favorable

Table 2. Comparison of patient-reported morbidity between patients in the AIM study (n = 64 for all patients and n = 43 for patients treated only with radiotherapy) and patients in the comparator study[9] treated only with radiotherapy (n = 153)

EPIC Domain and Study (n)	EPIC Score, Mean (SD)* Pretreatment	Post-treatment (2 mon)	Mean Difference† (95% CI)†	*P* ‡	Clinically Meaningful Decline (>0.5 SD)
Bowel/rectal					
AIM ± NHT (63)	90.3 (19.3)	88.8 (17.3)	−1.5 (−7.6, 4.5)	.001	No
AIM non-NHT (41)	91.8 (19.2)	89.8 (17.6)	−1.9 (−9.0, 5.1)	.001	No
Comparator (148)	94.4 (10.8)	78.5 (20.9)	−16.0 (−19.4, −12.5)	—	Yes
Urinary irritation/obstruction					
AIM ± NHT (58)	85.8 (17.3)	79.0 (24.2)	−6.8 (−12.2, −1.3)	.07	No
AIM non-NHT (38)	84.5 (18.0)	80.6 (23.0)	−4.0 (−10.0, 2.1)	.03	No
Comparator (148)	86.6 (14.3)	70.1 (20.7)	−16.5 (−19.8, −13.3)	—	Yes
Urinary incontinence					
AIM ± NHT (61)	89.4 (14.7)	84.4 (21.8)	−5.0 (−9.5, −0.5)	.72	No
AIM non-NHT (43)	93.0 (12.5)	86.3 (21.0)	−6.7 (−12.1, −1.3)	.90	Yes
Comparator (138)	92.5 (13.1)	84.6 (20.5)	−7.9 (−11.0, −4.8)	—	Yes
Sexual					
AIM ± NHT (62)	46.2 (33.5)	43.8 (30.3)	−2.4 (−9.6, 4.9)	.17	No
AIM non-NHT (43)	50.9 (32.1)	50.9 (26.9)	0.0 (−8.6, 8.6)	.04	No
Comparator (133)	63.5 (27.8)	51.5 (30.0)	−12.0 (−15.4, −8.5)	—	No

EPIC, Expanded Prostate Cancer Index Composite; CI, confidence interval; AIM, Assessing the Impact of Margin Reduction; NHT, neoadjuvant hormonal therapy.
* Scores for each domain range from 0 to 100. Higher scores indicate better health-related quality of life.
† Calculated from within-patient differences.
‡ Regression *P* value comparing the pretreatment to post-treatment difference for AIM vs comparator, taking into account pretreatment EPIC score, age, race, college graduate or postgraduate education, body mass index, prostate volume, and cancer risk.

Table 3. Rates of specific bowel and/or rectal clinical symptoms

EPIC Item for Bowel Function	AIM Study (n = 64) Patient % Pretreatment	Post-treatment (2 mo)	Comparator Study[9] (n = 153) Patient % Pretreatment	Post-treatment (2 mo)
Urgency	9	8	3	22
Frequency	3	8	2	22
Fecal incontinence	3	3	1	7
Bloody stools	3	2	2	5
Rectal pain	6	3	5	9
Overall bowel problem	9	6	4	20

EPIC, Expanded Prostate Cancer Index Composite; AIM, Assessing the Impact of Margin Reduction.

clinical and tumor characteristics than comparator patients. Baseline factors known to predict treatment morbidity were taken into account. The radiation dose delivered to AIM patients was the same as or higher than that for comparator patients. Comparator patients were treated at centers of excellence using state-of-the-art IMRT techniques of those institutions and margin definitions that remain widely in use. The outcome metrics represent validated patient assessment tools rather than physician interpretation of complications.

Minimizing dose to normal tissues is a central tenet of radiotherapy. Modeling studies estimate that reducing the PTV margin in prostate cancer radiotherapy from 7 to 3 mm should decrease rectal toxicity by 12%.[6] Our findings support these observations and are consistent with results from a randomized trial, wherein fewer late rectal toxicities were observed with more contoured plans.[13] Patients treated with reduced margins and a nominally higher prescription dose experienced fewer acute adverse HRQOL effects. Given the nature of the comparison, a detailed assessment of normal tissue dose exposure and PTV dose delivery was not done. Therefore, one must be cautious about the robustness of the dose comparison. Nevertheless, given the prescription dose of 81 Gy and the median maximum PTV dose of 87 Gy, it seems unlikely that AIM patients had PTV undertreatment vs comparator patients.

As expected, this benefit is greatest for rectal adverse effects, where narrower margins directly reduce the volume of irradiated rectum. Improvement is somewhat less in the urinary irritation or obstruction domain, which reflects the combined effects of bladder irritability and prostatic obstruction. Bladder irritability may be reduced by margin reduction, but prostatic obstructive symptoms are unlikely to be affected as the entire prostate necessarily remains in-field. Urinary incontinence shows little difference as this is a late treatment effect. Sexual function scores for AIM patients show little or no post-treatment decline, in contrast to comparator patients. Sexual interest may

be better maintained in the absence of bowel and urinary toxicity.

Acute normal tissue damage due to prostate radiotherapy has been shown to predict clinically significant late damage.[14,15] These experiences suggest that the reduction in acute morbidity observed in the AIM study may translate to a reduction in long-term morbidity with longer follow-up.

In conclusion, reducing the PTV margin is an attractive option when prostate motion can be carefully managed during daily radiation treatment, as this reduction can result in decreased acute treatment-related adverse effects. Margin reduction is a logical step in the evolution of IMRT and may support radiotherapy strategies that contribute to better long-term outcomes.

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