Short-term and Long-term Changes in Urinary Function in Prostate Cancer Patients Treated with IMRT: Effect of Real-time Tumor Tracking

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Purpose/Objectives

The primary objective of our study was to compare treatment-related urinary function changes in two groups of patients treated for prostate cancer: patients treated with IMRT in conjunction with Calypso real-time tumor tracking system and patients treated with IMRT utilizing implantable fiducial gold markers with CBCT for image guidance.
We also describe the impact of pretreatment urinary function on post-treatment IPSS trends and evaluate the impact of fractionation regimen on the effects of real-time tracking.

Materials/Methods

We retrospectively reviewed medical records of patients treated for prostate cancer between July 2007, when Calypso was introduced at our Department, and April 2011. We enrolled all patients who were curatively treated with IMRT for histologically confirmed cancer of the prostate gland with either Calypso beacons or gold fiducials. Subjects were treated with either standard (sIMRT, 78 Gy, 2 Gy / fx) or hypofractionated (hIMRT, 70 Gy, 2.5 Gy / fx) regimen by the same physician and using the same treatment-planning guidelines. We recorded IPSS, nocturia, and use of medicines at pre-treatment and every 6 months post-treatment for 24 months. Repeated-measures analysis of variance was performed to assess within-group changes compared to pre-treatment; linear mixed models were fit to assess differences by treatment group after adjusting for potential covariates.

Results

Table 1. Patient and treatment characteristics.

	Calypso n = 174	Gold n = 87
Age, median (range)	66 (50-90)	65 (47-82)
BMI, mean (SD)	28.4 (4.2)	36.0 (5.5)
Prostate volume, mean (SD)	37.7 (22.4)	39.5 (20.5)
PSA, mean median	11.9 7.3	12.0 7.3
Clinical Stage – no. (%) T1 T2 T3 T4	78 (45) 69 (40) 26 (15) 1 (<1)	39 (45) 37 (43) 9 (11) 1 (1)
Treatment regimen – no. (%) sIMRT hIMRT	107 (61) 67 (39)	56 (64) 31 (36)
ADT, duration > 6 mo – no. (%)	73 (42)	40 (46)

There were no significant differences in demographic characteristics according to tumor tracking modality. Except for a higher BMI in the Gold group, other patient and treatment characteristics were similar between the cohorts. Age was a significant covariate in nocturia but not in IPSS trend analysis. BMI and prostate volume turned out to be non-confounders. The mean pretreatment IPSS was 10.0 (SD = 7.9) in Calypso and 12.6 (SD = 8.4) in Gold cohort. The corresponding median values were 7.0 (0 to 34.0) and 11.0 (0 to 30.0). 27% of Calypso men and 42% of Gold men had pretreatment IPSS ≥ 15.

Posttreatment trends differed depending on the pretreatment urinary symptom severity: IPSS trended up in patients with good to moderate urinary function at baseline, while it decreased in subjects with moderate to severe pre-RT symptoms. The mean values of the groups differed by over a half pretreatment standard deviation throughout the follow-up.
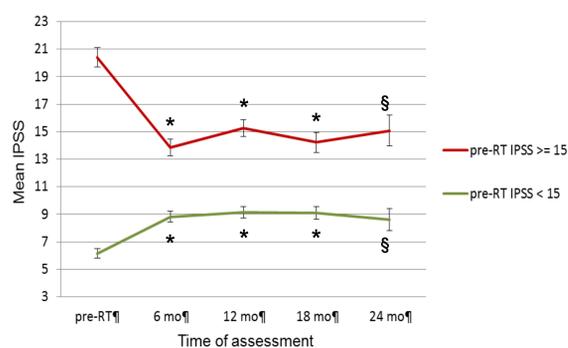
Figure 1. IPSS trends by pre-RT urinary function (all 261 patients). Variance within both groups was significant (Greenhouse-Geisser, p < 0.001). The bars represent standard errors (Delta-method). Data points that differed significantly (at p < 0.01 to account for Bonferroni adjustment) from pre-RT values are marked with asterisks (*), and data points at which p = 0.02 are marked with section marks (§). Paragraph symbols (¶) designate time points at which mean scores differed between treatment groups by more than a half pretreatment standard deviation.

Results cont.

Analysis with mixed linear models showed a significant difference in posttreatment trends of mean IPSS between Calypso and Gold cohorts in sIMRT group (p = 0.006) but not in hIMRT. In sIMRT subjects with a pretreatment IPSS < 15, the mean pre-RT scores were very similar between the cohorts. After the RT, Gold patients experienced an earlier and greater increase in the scores compared to Calypso men (Figure 2a). A significant difference between the trends persisted up to 18 months of follow-up, and the maximal difference between the means reached 5.1 points (p = 0.004), at 12 months (Table 2). This difference was 1.5 pre-RT standard deviation, corresponding to a large clinical effect size. The maximum individual patient median rises, seen around 18 months, were 2.8 (-9 to 15) and 5.5 (-5 to 14) points in Calypso and Gold cohorts respectively and differed significantly ($\chi 2$= 4.1, p = 0.04). By 24 months, there was no significant difference by tracking modality between the median IPSS rises ($\chi 2$ = 0.04, p = 0.8), and the contrasts of mean IPSS vs. pretreatment were no longer significant regardless of tracking method.
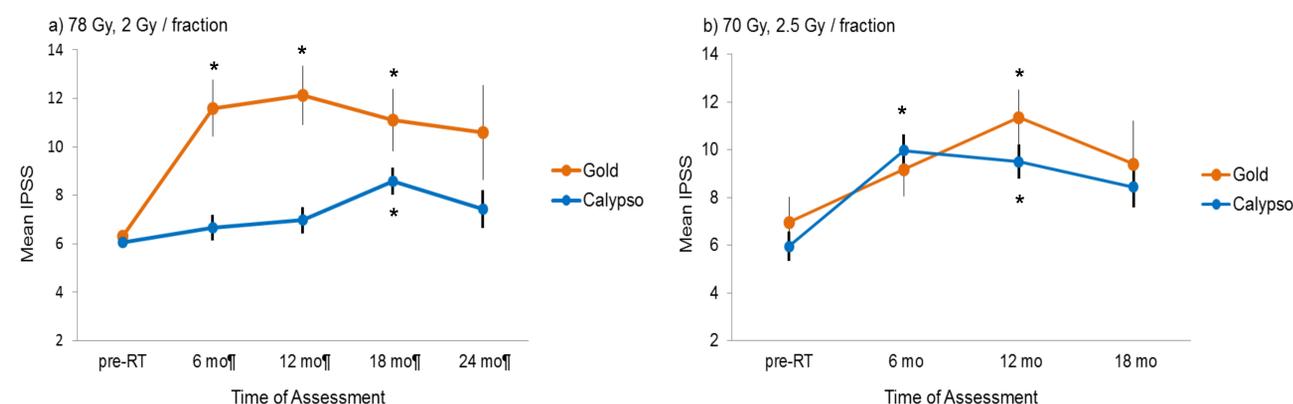

Figure 2a & 2b. Changes in the mean IPSS over time by tumor tracking modality in patients without poor baseline urinary function (pretreatment AUA BPH score < 15) treated with standard IMRT (a) and hypofractionated IMRT (b) regimens. The bars represent standard errors. Data points that differed significantly (at p < 0.01 to account for Bonferroni adjustment) from pre-RT values are marked with asterisks (*). Paragraph symbols (¶) designate time points at which mean scores differed between treatment groups by more than a half pretreatment standard deviation.

Table 2. Repeated-measures analysis of variance in IPSS, by tumor tracking modality, among men without poor urinary function at baseline (pretreatment IPSS < 15).

	sIMRT						hIMRT				
	Mean (95% Confidence Interval)					P*	Mean (95% Confidence Interval)				P*
	Pre-RT	6 mo	12 mo	18 mo	24 mo		Pre-RT	6 mo	12mo	18 mo	
Calypso	6.1 (5.1 – 7.0)	6.7 (5.7 – 7.7)	7.0 (5.9 – 8.0)	8.6 (7.4 – 9.7)	7.4 (5.9 – 9.0)	0.03	5.9 (4.7 – 7.2)	10.0 (8.7 – 11.3)	9.5 (8.1 – 10.9)	8.4 (6.7 – 10.1)	0.02
Gold	6.3 (4.2 – 8.4)	11.6 (9.3 – 13.9)	12.1 (9.8 – 14.5)	11.1 (8.6 – 13.6)	10.6 (6.8 – 14.4)	0.03	7.0 (4.9 – 9.1)	9.2 (7.0 – 11.4)	11.3 (9.1 – 13.6)	9.4 (5.9 – 12.9)	0.11

* ANOVA, Greenhouse-Geisser adjustment

In subjects with a pretreatment IPSS ≥ 15, post-RT mean scores in both cohorts remained decreased relative to the baseline. The maximum individual patient median drop was -7.5 (-30 to 11) and -8 (-25 to 2) points in Calypso and Gold cohorts respectively; however, this difference was not significant.

Overall, the 261 men experienced a significant increase in nocturia scores by the end of treatment: an individual patient mean increase was 1.08 (95% CI: 0.8 – 1.3) and median increase was 1.0 (-8.5 to 8). However, no significant difference by tracking method was observed. At baseline, 24% of Calypso and 34% of Gold patients in the sIMRT group used an alpha-receptor antagonist (p = 0.2). By the end of treatment, the respective prevalence values increased to 46% and 66%, and the difference by tumor tracking method became significant (p = 0.01). Among sIMRT subjects with a pretreatment IPSS < 15 who didn't use an alpha-blocker before RT, 39% of Calypso patients and 63% of Gold patients needed to start one at some point during the RT (p = 0.04). However, no significant difference in medication use was found during the follow-up.

Conclusion

Real-time tracking was associated with a reduced need for α-blockers during the RT and reduced post-treatment increase in urinary symptoms in men with pre-RT IPSS < 15. This difference was not only significant but had a large clinical effect size; however, it was present only with sIMRT but not with hIMRT regimen. Further studies are needed to investigate effects of dose regimen on clinical benefits of real-time tracking.

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