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Original article

Impact of planning target volume margins and rectal distention on biochemical failure in image-guided radiotherapy of prostate cancer

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ABSTRACT

Background and purpose: A previous study in our department demonstrated the negative impact on freedom from biochemical failure (FFBF) of using too narrow planning target volume (PTV) margins during prostate image-guided radiotherapy (IGRT). Here, we investigated the impact of appropriate PTV margins and rectal distention on FFBF.

Methods and materials: A total of 50 T1-T3N0M0 prostate cancer patients were treated with daily IGRT by implanted markers. In the first 25 patients, PTV margins were 3 mm laterolateral, 5 mm anterioposterior and 4 mm craniocaudal. The subsequent 25 patients were treated with isotropic margins of 6 mm. The rectal cross-sectional area (CSA) was determined on the planning CT. Median follow-up was 61 months.

Results: The overall 5-year FFBF was 83%. A 6 mm PTV margin was related to increased 5-year FFBF on univariate analysis (96% vs 74% with the tighter PTV margins, $p = 0.04$). The 5-year FFBF of patients with a rectal distention on the planning CT was worse compared to those with limited rectal filling (75% for CSA $\geqslant 9\ cm^2$ vs 89% for CSA $< 9\ cm^2$, $p = 0.02$), which remained significant on multivariate analysis ($p = 0.04$).

Conclusion: This retrospective study illustrated the positive impact of PTV margin adaptation and addressed the importance of avoiding rectal distention at time of the planning CT.

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In radiotherapy (RT) of localized prostate cancer, rectal distention on the planning computed tomography (CT) has been clearly shown to be related to a worse freedom from biochemical failure (FFBF) in patients treated without daily image-guided RT (IGRT), independent from classical risk factors such as Gleason score, PSA level and T-stage [1–3]. Prostate IGRT with direct prostate visualization (by means of implanted markers, CT-guided imaging or ultrasound) is an effective tool to avoid geographical miss in patients with rectal distention and has the potential in reducing margins around the clinical target volume (CTV) [4–6]. However, previous data from our department illustrated the potential danger of image guidance techniques as to margin reduction. We reported previously a 5-year FFBF of only 58% in 25 patients in whom inappropriate planning target volume (PTV) margins of 3, 5 and 4 mm in respectively the latero–lateral (LL), anterior–posterior (AP) and craniocaudal (CC) directions were applied for daily positioning by implanted markers [2]. Since January 2008, isotropic PTV margins of 6 mm were considered appropriate to compensate for intrafraction prostate motion during prostate IGRT by implanted markers in our department. The objective of the current retrospective study was to investigate the impact of this margin adaptation on the outcome of prostate cancer patients treated with IGRT by implanted markers at the University Hospital Brussels. In addition, we verified if the use of daily image guidance eliminated the negative impact of a rectal distention at the initial planning CT.

Methods and materials

Patient characteristics

We retrospectively evaluated a total institutional cohort of 50 men with cT1–3N0M0 prostate cancer who were treated consecutively between February 2002 and October 2009 with conformal arc RT ($n = 42$) or intensity-modulated RT (IMRT) ($n = 8$) on the Novalis system with daily IGRT by 3 fiducial gold markers, the latter implanted transrectal with ultrasound guidance. Mean age was 64 years (range, 52–79). Twenty of these patients in addition received concurrent androgen deprivation therapy (ADT). The indication, exact nature and duration of ADT varied depending on the preference of the referring urologist. The distribution of T stage, Gleason score, initial PSA and NCCN risk groups is given in Table 1. Median follow-up was 61 months (range, 30–123).

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Table 1
Disease characteristics of 50 patients.

T stage	Gleason score	Initial PSA	NCCN risk group
1 (19)	2–6 (32)	<10 (21)	Low (10)
2 (21)	7 (12)	10–20 (24)	Intermediate (17)
3 (10)	8–10 (6)	>20 (5)	High-very high (23)

Abbreviations: NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen.
Data in parentheses are number of patients.

Dose and dose–volume constraints

The majority of patients ($n = 38$) received 78 Gy in 2 Gy fractions, 5 patients received 70 Gy in 2 Gy fractions. In the remaining 7 patients, a hypofractionated schedule equivalent to 78 Gy was used in the context of a previously published clinical trial [7–8]. Pencil beam algorithm was used for dose calculation in all patients. The following rectal dose–volume constraints were considered appropriate: $D_{max} = 72.6$ Gy normalized total dose in 2 Gy/fraction (NTD_{2Gy}), rectal $V_{67.4Gy}$ (NTD_{2Gy}) $\leqslant$25% (i.e. $\leqslant$25% of the rectal volume should receive a dose $\geqslant$67.4 Gy) and rectal $V_{57.4Gy}$ (NTD_{2Gy}) $\leqslant$50% (assuming an α/β ratio of 3). For the bladder and femoral heads no specific dose–volume constraints were defined.

Target volumes and margins

Whole pelvic irradiation was not performed as the current group of patients either had a risk of <15% for microscopic lymph node involvement ($n = 34$) or were pN0 ($n = 16$) after laparoscopic lymph node sampling. In patients with a <10% risk of seminal vesicle (SV) involvement the CTV was "prostate only". In the other cases only the proximal half of the SV was delineated as part of the CTV. Risk of microscopic involvement of the SV and pelvic lymph nodes was estimated from the Mayo Clinic data [9–10].

In the first 25 patients who were treated between February 2002 and December 2007, anisotropic PTV margins of 3 mm LL, 5 mm AP and 4 mm CC were applied. Taking into account the negative impact of those tight PTV margins on FFBF [2], isotropic PTV margins of 6 mm in all directions were used in the subsequent 25 patients that were treated from January 2008 until October 2009.

Positioning and treatment

No rectal emptying was done at time of the planning CT or during the actual treatment. Patients were asked to empty the bladder and then to drink 500 ml of water 60 min prior to the planning CT and every treatment fraction, to obtain a reproducible bladder volume. Patients were treated in supine position with conventional head and knee support. Treatment was performed with the Novalis (Brainlab AG, Feldkirchen, Germany) system, consisting of a single energy (6 MV photons) LINAC with an integrated minimultileaf collimator. The patient positioning system has been described in detail previously [11]. Briefly, the positioning involved daily registration of digitally reconstructed radiographs (DRR) from the planning CT with the orthogonal X-rays images taken before every treatment session with a 6 degrees of freedom (6 DOF) registration of the radio-opaque implanted markers. The couch will correct for the translations and vertical rotation, the Robotic Tilt Module (RTM) (Brainlab AG, Feldkirchen, Germany), which is mounted underneath the tabletop, will correct for the longitudinal and lateral rotations. Because it is used on a daily basis, both systematic and random setup error are corrected for. No imaging during treatment was performed.

Evaluation

The "Phoenix" consensus definition (nadir + 2) was used to define biochemical failure [12]. Late side effects were scored using the RTOG/EORTC criteria [13]. FFBF and late toxicity rates were calculated with the Kaplan–Meier method. Multivariate analysis (MVA) was performed with the Cox proportional hazards model. The following five variables were investigated in MVA: NCCN risk group, ADT, dose, rectal cross-sectional area (CSA) on the planning CT and PTV margin. The rectal CSA was here defined as the rectal volume, contoured at the level of the PTV, divided by its length (distance in cm between the first and last slice on which rectal volume was contoured). Based on a previous study assessing the rectal filling status in prostate cancer patients, a CSA of 9 cm^2 was considered to be representative for a rectal distention [14]. Statistical analyses were double-checked with Statview 5.0.1 and Prism 5.0 (GraphPad).

Results

The overall 5-year FFBF was 83% (95% CI 67–92). The 5-year FFBF was 76% (95% CI 52–90) for the high- to very-high risk group compared to 90% (95% CI 63–97) for the intermediate- to low-risk group ($p = 0.10$). Patients in whom a PTV margin of 6 mm was applied ($n = 25$) displayed a statistically significant better FFBF compared to those ($n = 25$) with the tighter PTV margin of 3–5–4 mm (5-year FFBF 96% vs 74%, $p = 0.04$) (Fig. 1A). Of notice, the average CSA did not differ significantly between the group of patients with a tighter margin and those with a 6 mm PTV margin (9.8 ± 4.8 cm^2 vs 8.1 ± 4.0 cm^2). Biochemical failure was significantly worse among patients who presented rectal distention on the planning CT, with a 5-year FFBF of 75% (95% CI 49–89) for patients ($n = 22$) with a CSA $\geqslant 9$ cm^2 whereas 89% (95% 62–97) for patients ($n = 28$) with a CSA < 9 cm^2 ($p = 0.02$) (Fig. 1B). The radiation dose and the addition of androgen deprivation therapy were not significantly related to FFBF on univariate analysis. Interestingly, only the presence of a rectal distention (CSA $\geqslant 9$ cm^2) remained significant on multivariate Cox regression analysis in terms of FFBF ($p = 0.04$). Fig. 2 shows FFBF for the entire cohort divided into 4 subgroups according to their CSA ($\geqslant$9 cm^2 vs <9 cm^2) and PTV margin (3–5–4 mm vs 6 mm). Biochemical control was significantly worse among patients who had rectal distention at time of the planning CT and in whom tight PTV margins were applied by displaying a 5-year FFBF of only 57% in this subgroup ($n = 13$, red curve), compared to a 5-year FFBF of 93% in the group of patients with a 6 mm PTV margin and limited rectal filling at time of the planning CT ($n = 16$, green curve) ($p = 0.001$, log-rank testing). No adverse impact of rectal distention on FFBF was observed when a 6 mm PTV margin was applied ($n = 9$ patients, blue curve). On the other hand, tight PTV margins had no impact on FFBF in case of an empty rectum (CSA < 9 cm^2) at time of the planning CT ($n = 12$, orange curve), but patient numbers are too small to draw firm conclusions. The main message of this subgroup analysis is that rectal distention in the presence of tight PTV margins dramatically affected outcome, reflected by FFBF rates that are even further decreasing to 30% beyond 5 years of follow-up. Lastly, we calculated 5-year grade $\geqslant$3 late gastrointestinal and genitourinary toxicity rates of 2% (95% CI 0–16) and 2% (95% CI 0–14), respectively.

Discussion

The current retrospective study provides evidence of improved outcome after prostate IGRT with the use of adequate safety margins by demonstrating a 22% absolute gain in 5-year FFBF (96% vs 74%) with a PTV margin of 6, 6 and 6 mm in the LL, AP and CC

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