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ORIGINAL ARTICLE

MRI target delineation may reduce long-term toxicity after prostate radiotherapy

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ABSTRACT

Background and purpose. Aiming for minimal toxicity after radical prostate cancer (PC) radiotherapy (RT), magnetic resonance imaging (MRI) target delineation could be a possible benefit knowing that clinical target volumes (CTV) are up to 30% smaller, when CTV delineation on MRI is compared to standard computed tomography (CT). This study compares long-term toxicity using CT or MRI delineation before PC RT.

Material and methods. Urinary and rectal toxicity assessments 36 months after image-guided RT (78 Gy) using CTC-AE scores in two groups of PC patients. Peak symptom score values were registered. One group of patients (n = 72) had standard CT target delineation and gold markers as fiducials. Another group of patients (n = 73) had MRI target delineation and a nickel-titanium stent as fiducial.

Results. At 36 months no difference in overall survival (92% in both groups, p = 0.29) or in PSA-relapse free survival was found between the groups (MRI = 89% and CT = 94%, p = 0.67). A significantly smaller CTV was found in the MRI group (p = 0.02). Urinary retention and frequency were significantly reduced in the MRI group (p = 0.03 in the matter of both). The overall urinary and rectal toxicity did not differ between the two groups.

Conclusion. MRI delineation leads to a significantly reduced CTV. Significantly lower urinary frequency and urinary retention toxicity scores were observed following MRI delineation. The study did not find significant differences in overall urinary or rectal toxicity between the two groups. PSA-relapse survival did not differ between the two groups at 36 months.

Radiotherapy (RT) plays a key role in today's treatment of prostate cancer (PC). In several randomised trials dose escalation has shown to improve the biochemical control, but it is also followed by an increase in toxicity [1–3]. RT-related toxicity in PC most commonly involves the urogenital and gastrointestinal systems. Development of these toxicities is related to both the radiation dose to and the volume of normal tissue irradiated during the therapy [4,5]. Day-to-day changes in patient position and variations in prostate position during the course of radiation are considered as sources of treatment errors. Prostate displacements of more than 10–15 mm have been documented [6]. To account for these positional changes a margin is added to the clinical target volume (CTV) to assure sufficient dose coverage of the targeted tumour volume. This, however, increases the risk of over dosage of normal tissue and thereby toxicity. The use of prostate markers enables a more exact target location and makes margin reduction possible [7]. Novel techniques like daily image-guided radiotherapy (IGRT) are widely used combined with prostate fiducials for daily prostate position verification and correction. This has led to a reduction in the observed toxicity [8,9].

Currently, the most used method is implanted gold markers (GM) combined with treatment planning on computed tomography (CT). This method, however, has been shown to lead to an overestimation of the prostate volume. Volumes up to 30% larger have been found on CT when compared to target delineation on MRI [10–12]. CT-MRI image

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fusion-based treatment planning allows more accurate prediction of the target volume [13,14]. The CT-MRI co-registration can be done in several ways – on bony landmarks, with endorectal coil or by intraprostatic fiducial markers. Despite this, MRI-based planning has not yet replaced CT planning for routine PC RT. Studies are needed to evaluate whether the reduction in CTV on MRI is followed by a clinical relevant reduction in the long-term toxicity without compromising treatment failure.

The aim of this historical follow-up study was to evaluate the late (36 month) urinary and rectal toxicity among men with localised or locally advanced PC treated with RT at the Department of Oncology, Aalborg University Hospital between 2007 and 2009. Comparisons were made between the standard treatment (planning CT/GM) and a new treatment modality using MRI delineation, CT-MRI co-registration and a Nickel-Titanium (Ni-Ti) stent as prostate marker [15].

Material and methods

Patient population

Included in this non-randomised historical follow-up study were patients with localised or locally advanced PC (T1-T3N0M0) who completed RT with curative intent at the Department of Oncology, Aalborg University Hospital between March 2007 and May 2009. During this period, a group of 100 patients participated voluntarily in a phase III trial evaluating a Ni-Ti stent for MRI-CT co-registration and as fiducial marker (MRI-group) [15]. Another consecutive group of 102 PC patients had standard planning CT and GMs as fiducials during the same period (CT-group).

The patients were identified through searches in the patient radiation databases at the Department of Oncology, Aalborg Hospital.

Reasons for exclusion were death, biochemical failure (PSA nadir + 2 ng/ml) and inability to read and understand the questionnaires in Danish. The study was approved by the Regional Committee for Medical Research Ethics.

Toxicity assessment

All eligible men received a mailed invitation to participate in the study including information about the study, a consent form and a questionnaire. All participants completed and returned the consent form and questionnaire in a prepaid envelope.

The patients that returned the consent form and questionnaire were contacted for a telephone interview and toxicity regarding urinary and rectal symptoms was assessed. All the patients were contacted by one doctor or one research nurse.

The late toxicity assessment was made for the individual patient three years after his RT. Late complications were defined as those developing ≥ 6 months after RT completion. Peak toxicity scores were registered, even in the case of full recovery. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE) version 4.0. Rectal symptoms included stool frequency, stool incontinence, rectal pain, proctitis, rectal pain and rectal bleeding. Urinary symptoms included frequency, urgency, incontinence, dysuria, urinary retention and haematuria.

Data regarding clinical parameters like Gleason score, tumour stage, presenting PSA level, prostate volume, medications and co-morbidity (including haemorrhoids) were retrieved from the medical hospital records.

Treatment

Men with medium and high risk disease according to the D'Amico classification [16] received neo-adjuvant endocrine treatment with either LHRH analogues or non-steroidal anti-androgens for three months before irradiation. Endocrine treatment was continued during irradiation and for a limited period thereafter, usually for one year according to the recommendations in Denmark at that time.

Patients had fiducials inserted in the prostate before dose planning imaging. Fiducials were either three GMs or a Ni-Ti prostate stent. All patients had a planning CT scan (spiral scan slice thickness 2.5 mm). Patients with the prostate stent inserted had an additional planning MRI scan performed (1.5T or 3T MR T2 weighted images slice thickness 3 mm, TR: 5320 ms, TE: 94.96 ms, FOV: 300×300 mm^2, matrix: 382×224). The CTV was defined as the prostate gland. In case of seminal vesicle invasion or risk of invasion (Partin tables) [17], the CTV was defined as the prostate gland plus the proximal third part of the seminal vesicles. For patients in the CT group the CTV was outlined on the planning CT alone. Patients in the MRI group had CTV outlined on the MRI scan. The MRI scan was co-registered to the planning CT using manually inserted landmarks on the inserted stent. The CTV outlined on MRI was subsequently copied to the planning CT before dose calculation.

A planning target volume (PTV) was created using an isotropic PTV to CTV margin of 5 mm. Treatment planning was based on a 3D conformal technique with five conformal fields at gantry angles 0, 90, 140, 220 and 270 degree. Multi leave collimators were fitted until the 95% isodose encompassed the PTV. A dose of 2 Gy was prescribed to 100% isodose. Using 6 MV x-rays a total dose of 78 Gy was given in 39 fractions. The

following constraints were used for normal tissue. Rectum V70 ≤ 25% (maximum 25% of the rectal volume should receive maximum 70 Gy). V60 ≤ 50% and dorsal part of rectum received a maximum dose of 65 Gy. For the bladder V70 ≤ 35% and V60 ≤ 50% was used. For the femoral heads v52 ≤ 10% was used. Patients were treated lying supine with a knee and feet fixation. Using the inserted fiducials daily stereoscopic x-ray images were matched within 1–2 mm of CT reference digital reconstructed radiogram (DRR) images. After matching patients were automatically repositioned using the ExacTrac system with Robotics from Brainlab. The final position was verified daily using a new set of x-ray images before treatment was given.

Statistical methods

Comparisons between participants and non-participants were made using the t-test or Mann-Whitney test for continuous variables and χ^2 or Fisher's exact test for categorical variables. These statistical tests were also used comparing patient characteristic and late toxicity scores between the CT and MRI treatment groups. We calculated time time-to-event curves from the end of RT, using Kaplan-Meier estimates. Log-rank statistics was applied to test differences in survival and PSA-relapse free survival between the groups. The CT group was used as a reference when comparing the two treatment groups. P-values are two-sided and statistical significance was set at 5%. Univariate and multivariate logistic regression was used for subgroup analysis. The data were analysed using STATA v11 (Stata statistical software version 11; StataCorp).

Results

Two hundred and two patients underwent curatively intended RT during the defined period. A total of 145 men returned the consent form and participated in the study. There were no significant differences between participants and non-participants with regard to patient characteristics or tumour characteristics except that T-stages were higher in the group of participants (p = 0.05) (data otherwise not shown). Patient flow is shown in Figure 1.

Follow-up time for all participants was 36 months. Baseline patient characteristics are presented in Table I. The two groups were comparable in the matter of age, Gleason score, pre-treatment PSA, inclusion of seminal vesicles in CTV, smoking, diabetes and medications. Higher T-stages and risk classification were present in the MRI group. No significant difference in overall survival was found at 36 months (CT group = 92% and MRI group = 92%, p = 0.29). The PSA failure free survival did not differ significantly either (CT group = 94% and MRI group = 89%, p = 0.67).

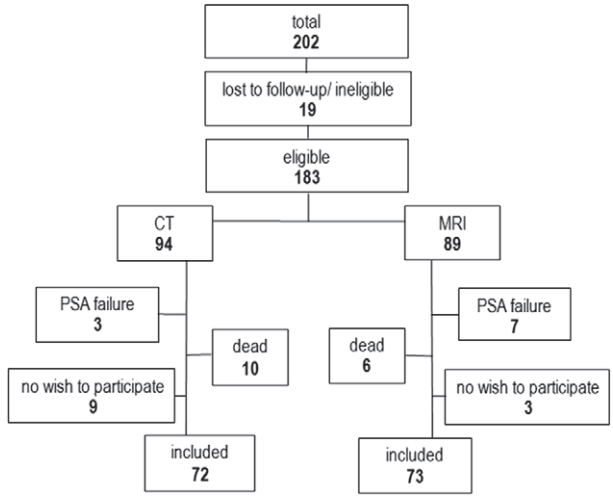

Figure 1. Patient flow. Fourteen were lost to follow-up (11 from the Faroe Islands, three from other Danish regions). Ineligible were two patients because of non-standard RT treatment, two because of language problems, one because of PSA failure during RT (metastatic disease). PSA failure = nadir + 2 ng/ml.

The prostate volume was found to be 21.5% smaller in the MRI group than in the CT group with mean volumes of 40.9 cm^3 and 52.1 cm^3, respectively (p = 0.02). In general the late side effects within the first three years after RT were few and mild in both groups. No grade 3 toxicity was registered. The results for the peak toxicity scores concerning rectal and urinary symptoms are presented in Tables II and III, respectively. Comparisons between the maximum overall scores of late rectal and urinary toxicities observed are made in Table IV, these do not differ significantly between the groups (p = 0.4 and 0.5, respectively).

With regard to rectal symptoms, grade 2 toxicity was registered only concerning "rectal bleeding" and in only four patients in total. The one patient from the MR group with grade 2 rectal bleeding was subsequently diagnosed with ulcerative colitis subsequent the RT. No significant differences were found concerning rectal symptoms between the two groups. There was no influence of age, T-stage, Gleason score, pre-treatment PSA, seminal vesicles irradiation, anticoagulants, smoking or statin-use on the development of rectal symptoms.

Urinary toxicity was predominantly manifested as increased frequency and urgency symptoms requiring α-blocker medications. No difference in overall urinary toxicity was found. Looking at the specific toxicity a statistically significant difference between the two groups was found with respect to "frequency" and "urinary retention" (p = 0.03 in the matter of both). No correlation was found between overall urinary toxicity and CTV. No apparent influence of age, T-stage, Gleason score, pre-treatment PSA, anticoagulants, smoking or

Table I. Patient characteristics.

	MRI	CT	
Age (range)	70.5 (62–80)	70.1 (58–78)	p = 0.5
T-stage (%)			
T1	9 (12)	26 (36)	p = 0.003
T2	28 (38)	14 (19)	
T3	36 (49)	31 (43)	
T4	0	1 (1)	
Gleason score (%)			
6	11 (15)	3 (4)	p = 0.19
7	52 (71)	58 (81)	
8	5 (7)	6 (8)	
9	4 (5)	5 (7)	
10	1 (1)	0	
Risk (d'Amico classification) (%)			
Low	4 (5)	1 (1)	p = 0.02
Intermediate	18 (25)	33 (46)	
High	51 (70)	38 (53)	
Pretreatment PSA			
Mean (range)	15.5 (4.1–67)	14.6 (0.6–67)	p = 0.23
Seminal vesicles in CTV (%)	9 (12)	10 (14)	p = 0.78
Hormonal therapy (%)	69 (95)	69 (96)	p = 0.19
Nicotine (%)	17 (23)	15 (21)	p = 0.79
Diabetes (%)	10 (14)	11 (15)	p = 0.44
Use of antikoagulantia (%)	10 (14)	9 (13)	p = 0.83
Haemorrhoids (%)	5 (7)	4 (6)	p = 0.75
Medications			
No drugs	12 (16)	13 (18)	p = 0.92
< 5 different drugs	45 (62)	42 (58)	
Polyfarmaci (≥ 5)	16 (22)	17 (24)	

diabetes on the development of urinary symptoms was seen.

Discussion

To our knowledge, this is the first report to compare toxicity in patients with localised or locally advances PC treated with IGRT using target planning delineation on either MRI or CT. The comparison is of value in that both groups were treated with the same radiation dose and with similar margins for the PTV. The difference between the two groups, were whether the target planning was based on MRI or CT delineation and whether a three-dimensional Ni-Ti stent or three GMs were used as fiducials for daily positioning verification. We observed, as expected, a smaller CTV volume in the MRI-delineated prostates. The CTV was correlated to a reduction in overall rectal toxicity but not correlated to a reduction in overall

Table II. Rectal toxicity.

	Grade	MRI	CT	Total	
Diarrhoea	0	68	63	131	p = 0.3
	1	5	9	14	
	2	0	0	0	
Faecal incontinence	0	68	68	136	p = 0.7
	1	5	4	9	
	2	0	0	0	
Proctitis	0	68	67	135	p = 0.9
	1	5	5	10	
	2	0	0	0	
Rectal bleeding	0	53	44	97	p = 0.3
	1	19	25	44	
	2	1	3	4	
Rectal pain	0	73	72	145	
	1	0	0	0	
	2	0	0	0	

Table III. Urinary toxicity.

	Grade	MRI	CT	Total	
Haematuria	0	66	67	133	p = 1.0
	1	6	5	11	
	2	1	0	1	
Frequency	0	47	36	83	p = 0.03
	1	16	30	46	
	2	10	6	16	
Urinary retention	0	70	61	131	p = 0.03
	1	3	11	14	
	2	0	0	0	
Urethral pain	0	69	70	139	p = 0.7
	1	4	2	6	
	2	0	0	0	
Urgency	0	40	43	83	p = 0.7
	1	23	21	44	
	2	10	8	18	
Incontinence	0	68	66	134	p = 0.9
	1	5	5	10	
	2	0	1	1	

Table IV. Late overall rectal and urinary toxicity.

Grade	MRI (n = 73)		CT (n = 72)		p-value
	n	%	n	%	
Rectal					
0	46	63	39	54.1	0.4
1	26	35.6	30	41.7	
2	1	1.4	3	4.2	
Urinary					
0	29	39.7	25	34.7	0.5
1	32	43.8	38	52.8	
2	12	16.4	9	12.5	

urinary toxicity. However, the number of patients that experienced urinary frequency and urinary retention differed significantly between the two groups. The overall incidences of both late rectal and urinary toxicities showed a trend towards less toxicity in the MRI group though not significant.

Late grade 2 urinary toxicity was observed in 16.4% (MRI) and 12.5% (CT) of the patients. These results are consistent with the results in resent publications like those of Zelefsky (10.4%, IGRT, 86.4 Gy) [18] and Crehange (7%, IMRT, 74–78 Gy) [19]. With regard to late grade 2 rectal toxicity our findings at 1.4% (MRI) and 4.2% (CT) are also comparable with Zelefsky (1%) and Crehange (1.2 %).

The contouring variation seen with MRI is lower than with CT because of the superior distinction of the prostate from adjacent structures on MRI. However, with training, these structures can many times be recognised on CT scans as well [11]. This may explain that we have found a difference of "only" 21.5% between the MRI-delineated prostate volumes and the CT-delineated volumes, whereas others have found differences above 30%. The similar toxicities between the two groups found in this study may also be a result of this.

Albeit we did not observe a reduction in late rectal toxicity, this might be explained by the low rectal toxicity incidence with IGRT in general. A larger patient population would be required to demonstrate a difference in rectal toxicity between the groups. The strong correlation between CTV and rectal bleeding and the finding of a smaller CTV in the MRI group in this study sustain this theory. Other studies have evaluated rectal dose-volume histograms and found consistent results on the dose-volume effect on the probability of developing rectal bleeding [20,21]. Both the absolute and the percentage of rectal volume receiving the highest doses (>60 Gy) are correlated with rectal bleeding [22]. As the CTV increases a larger volume of the rectum is at risk of high dose irradiation thus explaining the increased risk of rectal bleeding.

There is a delicate balance between the aim of maximum accuracy and PTV margin reduction to avoid normal tissue toxicity, and the risk of missing microscopic extra prostatic tumour extension as consequence of irradiated target volume reduction. The exact incidence and extent of microscopic disease remains uncertain because of imaging modalities limitations, but is known to be correlated with certain pre-treatment characteristics like PSA, T-stage and Gleason score [23]. A recent study from Heemsbergen et al. [24] has reported fewer clinical failures for high-risk PC patients treated with rectangular fields, compared to conformal fields underlining the above mentioned problem. Patient recruitment took place in the period 1994–1996, thus in another era. Imaging modalities have improved significantly since and androgen deprivation therapy in combination with RT is standard treatment of high-risk PC patients today. However, the authors raise a relevant question: Maybe margins can be too tight, thus compromising clinical failure and in the end survival. In that case higher toxicity rates would be acceptable, if the patients gain in terms of prolonged survival.

Limitations of this study include the relatively short follow-up time and that it is a historical follow-up design. A prospective design, especially with baseline assessments before RT, would be preferable to evaluate changes in late toxicity. In the matter of long-term toxicity registrations, some of the symptoms may be due to undetected co-morbidity progression. This may be particularly relevant in an elderly patient population like PC patients. Age-matched control groups are known to be affected by significant urinary problems [25]. These considerations are, however, of less significance in this study, as we compared two patient groups with similar baseline assessments.

This study includes a relatively low number of patients. Furthermore, we observed a very low number of patients with $\geq$ grade 2 toxicity, and this limits the statistical power.

MRI delineation and MRI-CT co-registration is today feasible as part of IGRT treatment for PC. We have presented the first data from our institution reporting 36-month toxicity after RT using MRI delineation for target planning. The effect of MRI delineation will require further confirmation with future prospective studies on more patients with longer follow-up time to evaluate the clinical relevance in terms of possible toxicity reduction. MRI delineation using the stent as fiducial is a costly and time consuming procedure, and therefore only recommendable if relevant toxicity reduction is obtained.

Future perspectives using the Ni-Ti stent as fiducial might also include sparing of the urethra. Dose exposure to the urethra and bladder neck attributes to the urinary toxicities. Urethra sparing with IMRT have so far been considered controversial because of

concerns for under dosage of the periurethral tissue. A theoretical study suggests preserved tumour control using the Ni-Ti stent as fiducial combined with IMRT [26].

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