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Three-Tesla Magnetic Resonance and Computed Tomography Imaging in Three-Dimensional Conformal Radiotherapy for Localized Prostate Cancer

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Abstract

Aims and background: we evaluate CT-3Tesla MRI fusion in conformal radiotherapy for localized prostate cancer.Methods: 18 consecutive patients underwent a 3T MRI scan under radiotherapy planning conditions, after the CT scan. Bowel and bladder preparation were prescribed. CT and MR images were automatically fused; prostate and seminal vesicles were contoured on CT and on MRI, organs at risk were defined on CT-MRI fusion. Late rectal and sexual toxicity, differences in target volume between MRI and CT and differences in rectal and penile bulb dose distribution based on CT only or on CT-MRI fusion were evaluated.Results: one patient experienced a late rectal toxicity; no patient had sexual toxicity. The difference between the mean MRI and CT target volumes was statistically significant ($p = 0.0001$ paired Student's t-test). The dose-volume histogram (DVH) analysis shows a significant reduction of the dose received by the rectum and the penile bulb in MRI-plans compared to CT-plans.Conclusions: 3 Tesla MRI scan under radiotherapy planning conditions along with bowel preparation significantly improves the definition of the target volume sparing normal tissue irradiation.

Keywords: Prostate Cancer, 3 Tesla Magnetic Resonance, Computed Tomography, Conformal Radiotherapy

1. Introduction

Prostate cancer is the most common male malignancy in Western countries and the second leading cause of cancer death in men [1,2]. The improvement of the screening has lead to the identification of prostate cancer at an earlier and potentially treatable stage and three dimensional conformal radiation therapy (3DCRT), along with surgery and brachytherapy, are the standard therapies for localized prostate cancer [3-8]. In 3DCRT the accurate delineation of the clinical target volume (CTV) is crucial in particular with intensity-modulated radiation therapy (IMRT), where it is possible to increase the radiation dose to the target volume, sparing at the same time the surrounding normal tissues and minimizing the risk of acute and late complications [9-11]. Computed tomography (CT) scanning is the most common approach to localize the prostate in radical conformal radiotherapy, but it has poorer soft-tissue contrast than magnetic resonance imaging (MRI), in particular when differentiating the prostate gland from the periprostatic soft tissues. Three-Tesla MRI allows excellent morphologic information of prostate, penile bulb anatomy, and of rectum-prostate interface [12-13].

In this study we retrospectively evaluated 3DCRT based on CT-3Tesla MR image fusion, for 18 patients with localized prostate cancer. Differences in CTV (prostate + seminal vesicles) volume between MRI and CT and differences in terms of rectal and penile bulb dose distribution based on CT only or CT-MRI fusion were evaluated as well as late rectal and sexual toxicity.

2. Materials and Methods

Eighteen patients with localized prostate cancer underwent CT-planned radical 3D conformal radiotherapy at the Radiation Oncology Therapy Unit of the University of Rome Tor Vergata; after a 3T MRI scan, under radiotherapy planning conditions, to evaluate the feasibility of CT-3T MRI image registration in order to define

prostate CTV. This study was approved by the hospital ethics committee, and all of the 18 patients were asked to sign a written informed consent agreement regarding the use of a 3T MRI.

Patient characteristics are summarized in **Table 1**. The median age at the time of treatment was 72 years (range 46-78 years); 13 patients were classified as T1c clinical stage, 4 were T2a and 1 patient T2c (TNM, American Joint Committee on Cancer 2002). The median PSA (prostate specific antigen; normal values range between 0 ng/ml and 4 ng/ml) value at diagnosis was 9.39 ng/ml (range 5.21 - 42 ng/ml), and the Gleason score (a grading system that assigns a grade to each of the two largest areas of cancer in the tissue samples, grades range from 1 to 5) was 6 (3 + 3) in 9 patients, 7 (3 + 4) in 2 cases and 7 (4 + 3) in 1 case, 8 (4 + 4) in 5 patients and 9 (4 + 5) in 1 patient; 10 / 18 cases were treated with 6 months hormone-releasing hormone agonist in association with radiotherapy. Nine patients had erectile dysfunction before the start of radiotherapy / hormone therapy, due to age, diabetes and cardio-vascular co-morbidities.

Bowel preparation was obtained suggesting a diet in combination with a daily mild laxative to reduce intestinal gas and obtain a reproducible bowel volume during CT and MRI acquisition and treatment sessions. For bladder preparation patients were asked to empty their bladder for better daily prostate localization.

CT scanning was performed with a GE LightSpeed® Scanner (GE Healthcare Diagnostic Imaging, Slough, UK). The scan was to start at the level of the iliac crests and continue down through the perineum, with a 2.5 mm slice thickness. MRI study took place within 20 minutes after CT scanning and was performed with a 3.0 T Philips Achieva Intera (Philips Medical Systems, Reigate, UK); T2 TSE (turbo-spin eco) weighted images were acquired with the following scan parameters: repetition time (TR) = 1000 ms, echotime (TE) = 90 ms, TSE factor = 16, FOV = 400 x 400 mm, acquisition matrix 304 x 240 reconstructed to 512 x 512, slice thickness 2.5 mm, 50 - 60 slices, number of signal averages (NSA) = 2; total acquisition time: 8 - 10 minutes. Patients were scanned, both for CT and MRI, supine on a flat couch top with the arms on the chest; ankle stocks were used to prevent rotation of the hips, and localizing tattoos were used to maintain a stable position. For 3 T MRI a home-made wood couch insert was used to achieve a flat scan surface.

Table 1. Patients characteristics (n = 18).

	median	range		n. of patients
Age	72 y	46 y - 78 y		
PSA at diagnosis	9.39 ng/ml	5.21 ng/ml - 42 ng/ml		
			T1c	13
T-stage			T2a	4
			T2c	1
			6 (3 + 3)	9
			7 (3 + 4)	2
Gleason score			7 (4 + 3)	1
			8 (4 + 4)	5
			9 (4 + 5)	1
Sexual dysfunction			yes	9
before RT/hormone-therapy				
			no	9
			yes	10
Hormone-therapy				
			no	8

CT and MRI images were exported on Syntegra soft ware (Pinnacle, Philips Medical System, Andover, MA) and the two data sets were automatically fused; Syntegra is a multi-modality image registration software that provides manual and point-based image registration, and three automated methods of gray value-based image registration: cross correlation, local correlation and mutual information. The result of each registration was always checked by a physician, inspecting visually the matching of bony structures and soft tissues.

For each patient the clinical target volume (CTV) and organs at risk (OARs) were outlined by the same radiation oncologist. The target volume irradiated to 66 Gy (CTV_1) consisted of prostate and seminal vesicles; the boost irradiated to 76 Gy (CTV_2) was the prostate only. Planning target volumes (PTV_1 and PTV_2) were generated by an asymmetric expansion of CTVs (6 mm in all directions except at the posterior margin, where a 4 mm expansion was used). The target volumes were delineated on CT images and on MRI images afterwards (**Figure 1**); the CTV contouring for each of the two set of images was performed blindly with respect to the other one.

The rectum was contoured on CT-MRI fusion as solid organ from the 8th slice (2 cm) above the anal verge to the rectosigmoid junction; the bladder was contoured on CT in its entirety. The penile bulb was defined using CT-MRI fusion, as a pear-shaped structure comprising the proximal part of the corpus spongiosum; the femurs were defined on CT.

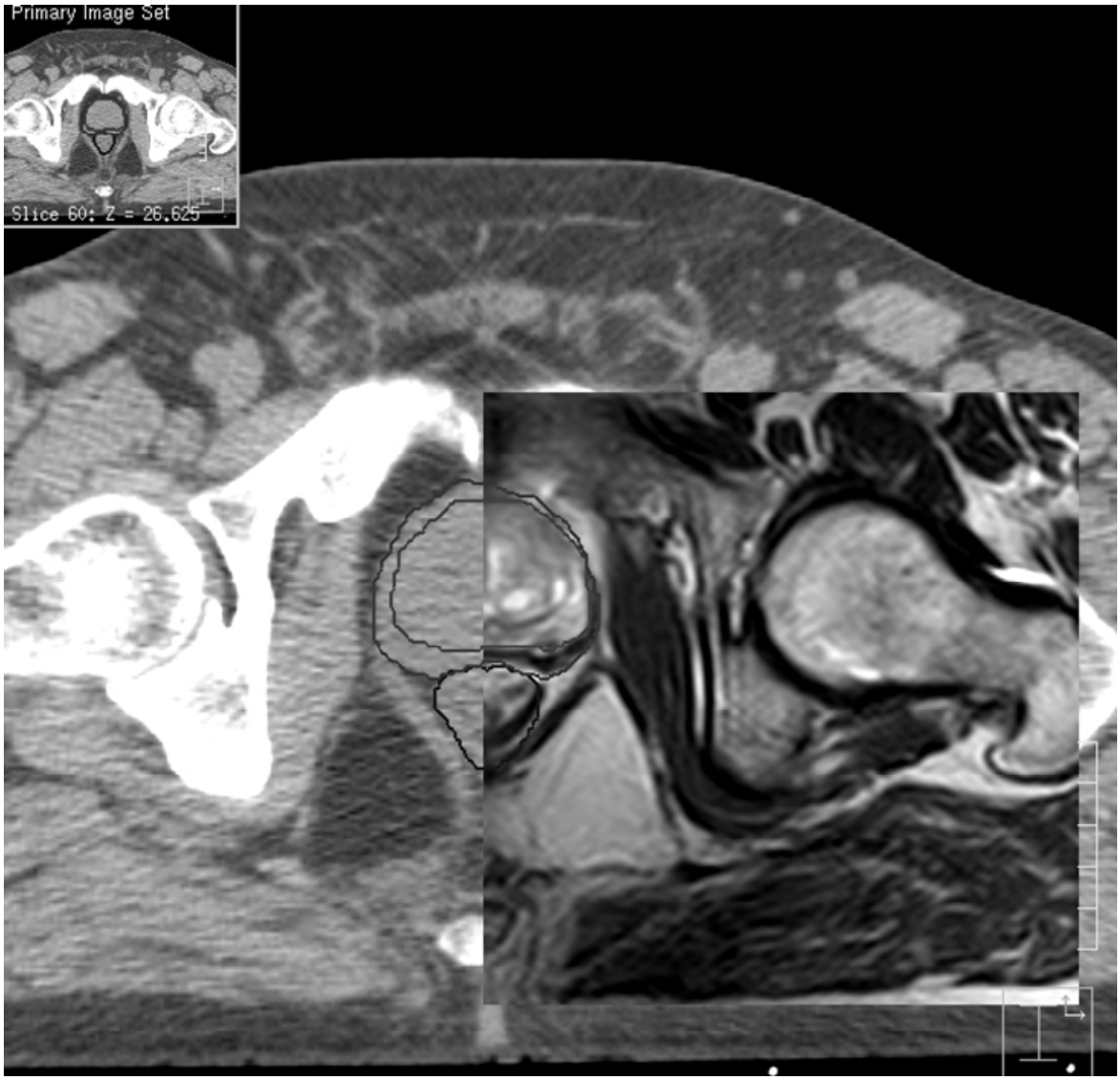

Figure 1. Axial CT- 3T MRI scan fusion. The red line is the MRI-delineated prostate contour, the purple line is the CT-delineated prostate contour and the blue line is the contour of the rectum delineated on CT-MRI fusion.

For each patient, CT images and contours were transferred from Pinnacle to Precise Plan treatment planning system (Elekta Oncology Systems, Crawley, UK) and 3-dimension conformal radiotherapy treatment planning, with a six field arrangement, was obtained. For the purpose of this analysis, two treatment plans were generated for each patient: an MRI-plan based on the MRI-delineated CTV and a CT-plan based on the CT-delineated CTV. For an adequate PTV coverage, it was accepted that the 95% of PTV volume was covered by 95% of the prescribed dose and that the maximum dose did not exceed 107% of the prescribed dose.

The radiotherapy treatment was developed on the MRI-delineated CTVs. Daily fractions of 2 Gy (5 days a week) were delivered with conformal shaped treatment fields (15 MV) using the multi-leaf collimator (MLC; 1 cm leaf width) of an Elekta Precise linear accelerator (Elekta Precise Treatment System Plus™). Two orthogonal portal images were used in order to check set-up alignment; digitally reconstructed radiographs (DRRs), obtained from the CT localization scans, were used as reference images; a matching software was applied to quantify set-up errors between DRRs and portal images.

For biochemical failure definition we referred to the Phoenix definition, revised by ASTRO and RTOG in Phoenix, as a rise in PSA by 2 ng/ml or more above the nadir PSA (defined as the lowest PSA achieved) [14].

Acute rectal toxicity (within 90 days from the start of radiotherapy) and late rectal toxicity were scored by the radiation oncologist, according to the RTOG / EORTC toxicity scale. Erectile function was assessed before radiotherapy and 1 year after the end of radiotherapy, by the 5-item version of the IIEF (International Index of Erectile Function) self-administrated questionnaire [15].

For rectal dose volume histogram (DVH) analysis we compared the values V70, V50 and V40 (defined as the percentage of rectum receiving at least 70, 50 and 40 Gy) obtained from the two treatment plans, the one developed on MRI prostate contour and the other on CT prostate contour.

For penile bulb we compared the mean dose to the 100% of the penile bulb, the D50, D70 and D90 (defined as the dose delivered to the 50%, 70% and 90% of penile bulb volume).

Statistical analysis

Statistical analysis was carried out using a commercial statistical software package (SPSS 9.0; SPSS Inc, Chicago, IL). The data were tested for normality with the Kolmogorov-Smirnov test, and different datasets were compared with paired Student's t tests (two tailed). For survival analysis Kaplan-Meier method was used.

3. Results

All 18 patients received 3D-conformal radiotherapy based on MRI-contoured CTVs. The median and the mean follow-up were 23.71 and 24.22 months respectively (range 15.76-37.16 months).

A G2 acute rectal toxicity was recorded in 5/18 patients and only 1 patient experienced a G2 late toxicity. At the time of analysis the 9 patients sexually active before radiotherapy were still sexually active (median IIEF score for the 9 patients: 20; range 17 - 25), but all referring a reduced ejaculation volume.

As concerns target volume analysis we considered the prostate and seminal vesicles (CTV_1), being CTV_2 included in CTV_1. In all patients, except one, the contoured volume of the prostate and seminal vesicles was larger on CT than on MRI (**Table 2**); the difference between the mean MRI and CT volumes (58.1 ± 27.5 cc for MRI CTV_1 vs 73.7 ± 33.8 cc for CT-CTV_1) was statistically significant ($p = 0.0001$, paired Student's *t*-test).

The mean volume of the rectum was 46.94 ± 9.66 cc (range: 31.21 - 63.56 cc); and the mean volume of the bulb of the penis was 6.93 ± 1.79 cc (range: 4.4 cc-9.7 cc).

Table 3 shows the rectum dose-volume-histograms (DVHs) parameters, for the total dose of 76 Gy, from treatment plans based on CT-PTVs and on MRI-PTVs: the volume of rectum receiving a dose ≥ 70 Gy, 50 Gy, 40 Gy is significantly reduced in MRI-plans compared to CT-plans ($p < 0.05$, paired Student's *t*-test).

In penile bulb DVHs analysis, for the total dose of 76 Gy, the difference in terms of mean dose to the 100% of the volume between MRI-plans and CT-plans (39.14 Gy vs 43.86 Gy) was not statistically significant ($p = 0.1$ paired Student's *t*-test), while there was a statistically significant difference in D50, D70 and D90 values ($p < 0.05$, paired Student's *t*-test), as reported in **Table 4**.

4. Discussion

Our analysis confirmed that MRI-defined CTV (prostate and seminal vesicles) is significantly smaller than the CT-defined one ($p = 0.0001$); this result is based on the better definition on MRI of the prostate, the seminal vesicles and the peri-prostatic tissues anatomy, with a reduction of the 3 major diameters (cranio-caudal; antero-posterior and latero-lateral diameter).

Several studies have demonstrated the gain in prostate volume definition using MRI, with better normal tissue sparing due to the more exact contouring of the target and to the minor interobserver variability [16-18]; these data are mainly based on 1.5T MRI without endorectal

coil. In the study of Debois *et al.* the average prostate volume, in 10 patients irradiated for localized prostate carcinoma, was 51 ± 25 cc on CT while on 1.5T MR it was 35 ± 17 cc (p = 0.004, paired Student's *t*-test) [16]. Rasch *et al.* evaluated the difference between prostate delineation on CT and MR (interscan variation) in 18 patients treated for localized prostate cancer. Three radiation oncologists delineated the prostate on CT and MRI: CT volumes were significantly larger than MRI volumes in 52 of 54 delineations [17]. The significant decrease of the interobserver delineation variability with the use of MRI has been illustrated by Villeirs *et al.* [18]: the retrospective analysis of prostate and seminal vesicles volume, in 13 patients, delineated by three radiation oncologists on CT and on CT + 1T MRI showed that there was a 63.06% reduction of the standard deviation around the mean CTV volume, when 1T MRI was used in addition to CT.

Table 2. Volume comparison between MRI-defined and CT-defined CTV_1 (n = 18).

Patient	MRI-CTV_1 volume (cc)	CT-CTV_1 volume (cc)	
1	93	129.2	
2	62.2	64.2	
3	44.9	52.6	
4	64.5	85.9	
5	60.6	73.8	
6	28.1	26.7	
7	108.2	130.8	
8	53.8	69.4	
9	128.9	150.7	
10	42	42.5	
11	66.4	99.2	
12	50	64.3	
13	34.8	39.6	
14	37.7	56.1	
15	49.7	57.4	
16	32.7	58.9	
17	59.7	75.2	
18	27.8	49.5	
	mean value (cc) ± sd	mean value (cc) ± sd	p value (ref. to paired t-test)
	58.1 ± 27.5	73.7 ± 33.8	0.0001

Table 3. Rectal dose volume histogram comparison (n = 18). P-value refers to paired t-test.

DVH parameter	mean CT volume (cc) ± SD	mean MRI volume (cc) ± SD	p-value
V 70	16.75 ± 5.56	9.78 ± 6.82	0.0010
V 50	36.63 ± 7.87	29.69 ± 8.40	0.0001
V 40	43.69 ± 8.27	37.13 ± 9.82	0.0010

Table 4. Penile bulb dose volume histogram comparison (n = 18). P-value refers to paired t-test.

DVH parameter	CT	MRI	p-value
Mean Dose (Gy) ± SD	43.86 ± 13.16	39.14 ± 12.84	0.106
D90 (Gy) ± SD	15.38 ± 7.8	10.22 ± 6.3	0.024
D70 (Gy) ± SD	27.33 ± 6.11	19.83 ± 5.9	0.015
D50 (Gy) ± SD	46 ± 16.9	39 ± 16.1	0.006

The use of endorectal coil in 1.5T MR prostate imaging resulted in a higher spatial resolution with a significant improvement of anatomic details [19-21]; on the other hand endorectal coils produce changes in shape and volume of the prostate, induced by the pressure on the parenchyma of the gland and may deform the peripheral zone that is typically involved in prostate cancer; the same pressure should be reproduced during the radiotherapy treatment sessions, where endorectal coil should be replaced by an endorectal balloon [22-24]. Finally endorectal coil can result in hyperintense signal intensity near the rectum, the peripheral zone and the neurovascular bundle, making the image interpretation difficult.

Some author made an image quality comparison between 3T MRI and endorectal 1.5T MRI. Sosna *et al.* prospectively compared 20 patients who underwent 3T MRI with 20 patients who had a 1.5T MRI with endorectal coil, in terms of image quality, reporting that image quality at 3T without endorectal coil can be comparable with the one obtained at 1.5T with an endorectal coil [25].

Park *et al.* compared the magnetic resonance imaging quality and local staging accuracy for prostate cancer, using phased-array 3T and endorectal 1.5T MRI. Two groups, each consisting of 54 patients, were retrospectively evaluated: one group underwent 3T MRI using a phased-array coil, the other had 1.5T MRI with endorectal coil. The incidence of MR artefacts was higher in 1.5T than in 3T MRI ($p = 0.00$), and 3T MRI did not show any artefact in 57% of patients, while 1.5T MRI had artefacts in all patients; 1.5T MRI artefacts were the hyperintense signal intensity around the rectum, image distortion from entrapped air and decreasing signal-to-noise ratio (SNR) of remote area from the coil. On the other hand, artefacts at 3T MRI, which are common to 1.5 MRI, are related to bowel peristalsis and patient motion [13].

For these reasons 3T MR image quality may be considered superior to 1.5T MRI and when available may be valuable to better define prostate and seminal vesicles and normal surrounding structures without the evident disadvantages and discomfort due to the use of endorectal coil.

All these efforts obtained apparently two important results: the first one was to better define prostate, seminal vesicles and the rectum and the second one to spare normal tissue irradiation with the improvement of tolerance of the irradiation and evident reduction of rectal toxicity in particular. In this limited number of patients rectal toxicity was almost absent or limited to G2 transitory complaints disappearing within a few weeks from the end of the treatment. Sexual activity may be difficult to assess before and after treatment but the nine patients with an active sexual life before treatment declared to retain potency after the end of the irradiation. Psychological reasons might influence the sexual life of these patients besides tumour or treatment damage to the pudendal structures, but rectal toxicity $\geq$ G2 is always reported as a major problem in all the patients receiving radical treatment for prostate cancer. Different methods may contribute to reduce rectal toxicity and an important one is, at least in our experience, the combination of bowel preparation with the better definition of the organ contours obtained using MR images.

The use of bowel preparation, with a diet and a daily mild laxative, ensures a reproducible rectal volume during CT and MRI acquisition and treatment session. This methodology allows the daily reproducibility of the radiation treatment, avoiding the organ motion due to the rectum repletion hence diminishing prostate dislocation [26,27]. In empty rectum condition the upper tract of the anterior rectal wall is far from the posterior surface of the prostate and seminal vesicles, with evident advantages in the development of the treatment plan. The use of MRI for target volume definition combined with the rectal preparation, for the daily reproducibility of rectal volume and position, allows to reduce the PTV margins, in particular towards the posterior and caudal margins, with less treatment related toxicity [28].

The analysis of rectal dose volume histograms showed a statistically significant reduction of about 40% ($p = 0.001$) of rectum receiving a dose of 70 Gy in MRI-defined treatment plans compared to CT-defined plans. The same results were demonstrated for the rectal volume receiving the dose of 40 Gy and 50 Gy, where plans based on MRI-CTV showed a volume decrease of about 18% and 15% compared with plans based on CT-CTV. Our data are consistent with the results of analogous studies [16,26]; Debois *et al.* [16] found a statistically significant decrease of about 23.8% of the rectum receiving 80% of the prescribed dose for the treatment plans based on MRI delineation compared with the treatment plans based on CT delineation in 8 / 10 patients investigated. Krempien *et al.* showed that the mean dose received by the rectum could be reduced from 74.9% to 64.2% of the prescribed dose using MRI delineation compared with CT delineation of the prostate [29].

The penile bulb is best visualized on T2-weighted MR appearing as an oval-shaped, hyper-intense midline structure under the prostatic apex. An underestimation of the prostatic apex location could lead to a geographical tumour miss, while an overestimation may cause erectile dysfunction due to irradiation of the penile bulb; MRI help to discriminate between the prostate apex and the proximal penile bulb. Erectile dysfunction is a long-term sequela after definitive radiotherapy for prostate cancer

[30]; the irradiation of the proximal penile tissue damage vascular and nervous structures supplying the cavernosus muscle [31]. Merrik *et al.* [32] demonstrated that if the dose delivered with brachytherapy to 50% of the bulb was < 50 Gy, potency was likely to be conserved. In the analysis of Fisch *et al.* a dose to 50% of the bulb < 48.5 Gy was associated with no risk of erectile dysfunction [31]. In the recent issue by Roach *et al.* [33] it is suggested to keep the mean dose to the 95% of the bulb under 50 Gy.

In our experience the bulb of the penis received significant less dose with the treatment plans based on MRI-delineated CTV compared with those based on the CT-delineated CTV. We found that the mean value of D 50 was 46 ± 16.9 Gy in CT-plans radiotherapy versus 39 ± 16.1 Gy in MRI-plans (p = 0.006).

In conclusion in this preliminary experience we proved the feasibility of CT-3T MRI image registration under radiotherapy planning conditions. The results of our analysis showed that 3T MRI improves the definition of the target volume sparing normal tissue irradiation.

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