Received:
11 January 2019

Revised:
19 March 2019

Accepted:
21 March 2019

<https://doi.org/10.1259/bjr.20190056>

Cite this article as:

de Leon J, Jameson MG, Rivest-Henault D, Keats S, Rai R, Arumugam S, et al. Reduced motion and improved rectal dosimetry through endorectal immobilization for prostate stereotactic body radiotherapy. *Br J Radiol* 2019; **92**: 20190056.

FULL PAPER

Reduced motion and improved rectal dosimetry through endorectal immobilization for prostate stereotactic body radiotherapy

¹JEREMIAH DE LEON, MBBS FRANZCR, ^{2,3,4}MICHAEL G JAMESON, PhD, ⁵DAVID RIVEST-HENAULT, PhD, ²SARAH KEATS, BSc, ²ROBBA RAI, MSc, ²SANKAR ARUMUGAM, PhD, ⁶LEE WILTON, BSc, ²DIANA NGO, BN MCaHaemN, ^{2,3,4}GARY LINEY, PhD, ⁴DANIEL MOSES, MBBS FRANZCR, ⁵JASON DOWLING, PhD, ^{6,7}JARAD MARTIN, MBChB BSc PhD DMed, FRANZCR GAustMS and ^{2,4}MARK SIDHOM, MBBS FRANZCR

¹Illawarra Cancer Care Centre, Wollongong, Australia

²Liverpool Cancer Therapy Centre, Liverpool, Australia

³Ingham Institute for Applied Medical Research, Liverpool, Australia

⁴Faculty of Medicine, University of New South Wales, Australia

⁵Australian e-Health Research Centre, CSIRO, Herston, Australia

⁶Calvary Mater Newcastle, Newcastle, Australia

⁷School of Medicine and Public Health, University of Newcastle, Newcastle, Australia

Address correspondence to: Dr Michael G Jameson
E-mail: michael.jameson@health.nsw.gov.au

Objective: PROMETHEUS (ACTRN12615000223538) is a multicentre clinical trial investigating the feasibility of 19 Gy in 2 fractions of stereotactic body radiotherapy (SBRT) as a boost technique for prostate cancer. The objective of this substudy was to evaluate intrafraction motion using cine MRI and assess the dosimetric impact of using a rectal displacement device (RDD).

Methods: The initial 10 patients recruited underwent planning CT and MRI, with and without a RDD. Cine MRI images were captured using an interleaved T2 HASTE sequence in sagittal and axial planes with a temporal resolution of 5.2 s acquired over 4.3 min. Points of interest (POIs) were defined and a validated tracking algorithm measured displacement of these points over the 4.3 min in the anteroposterior, superior-inferior and left-right directions. Plans were generated with and without a RDD to examine the impact on dosimetry.

Results: There was an overall trend for increasing displacement in all directions as time progressed when

no RDD was *in situ*. Points of interest remained comparatively stable with the RDD. In the sagittal plane, the RDD resulted in statistically significant improvement in the range of anteroposterior displacement for the rectal wall, anterior prostate, prostate apex and base. Dosimetrically, the use of a RDD significantly reduced rectal V16, V14 and D_{max}, as well as the percentage of posterior rectal wall receiving 8.5 Gy.

Conclusion: The RDD used in stereotactic prostate radiotherapy leads to reduced intrafraction motion of the prostate and rectum, with increasing improvement with time. It also results in significant improvement in rectal wall dosimetry.

Advances in knowledge: It was found that the rectal displacement device improved prostate stabilization significantly, improved rectum stabilization and dosimetry significantly. The rectal displacement device did not improve target volume dosimetry.

INTRODUCTION

Dose escalation in prostate cancer radiotherapy has been shown to improve biochemical control in all risk groups.¹ It is estimated that doses as high as 86.5 to 95.5 Gy are required to achieve prostate cancer ablation.² Such dose escalation must be balanced against the potential of increased gastrointestinal and genitourinary toxicity.

In a systematic review of randomized trials of radiotherapy for prostate cancer Vogelius and Bentzen reviewed the data

from >10,000 men with prostate cancer to estimate the α/β ratio.³ They estimated the α/β ratio was 1.2 Gy [(95% confidence interval (CI) (0.8–1.7))] assuming no effect from overall treatment time and 2.7 Gy (95% CI 1.6–3.8) if it were postulated 0.31 Gy was lost daily.³ Given a low estimated α/β ratio it was postulated by Brenner and Hall that hypofractionation may be efficacious for prostate cancer.⁴ Hypofractionation in prostate radiotherapy has been shown by multiple randomized controlled trials to be equivalent to longer course radiotherapy in terms of overall survival,

albeit with differing toxicity profiles.^{5–7} These trials have recently been reviewed in the context of moderate hypofractionation by Martin *et al*.⁸

High dose rate brachytherapy (HDR) is well established as a means to deliver such high doses while limiting dose to surrounding normal organs. Early attempts to emulate HDR doses using external beam radiotherapy (EBRT) techniques such as intensity modulated radiotherapy have proven inferior to HDR.⁹

Stereotactic body radiotherapy (SBRT) techniques allow target doses matching that of brachytherapy to be achieved whilst maintaining similar organ at risk dose volume histogram (DVH) constraints. Studies using this technique have shown comparable early biochemical control and toxicity rates.¹⁰

PROstate Multicentre External beam radioTHERapy Using a Stereotactic boost (PROMETHEUS), a multicentre Phase II trial (ACTRN12615000223538), primarily aims to determine the feasibility and safety of an escalating SBRT boost dose in intermediate and high risk prostate cancer.¹¹ To achieve this, a rectal displacement device (RDD) is required in the trial protocol. We hypothesize that the RDD would lead to reduced rectal doses resulting in lower gastrointestinal toxicity, as well as improved intrafraction prostate and organ at risk (OAR) stability. We report the outcomes of a sub study of PROMETHEUS, which examined the impact of rectal displacement on dosimetry and intrafraction motion using cine Magnetic Resonance Imaging (cine MRI).

METHOD

This study was approved by local ethics committees at both recruiting institutions. The initial 10 patients enrolled into the trial from the (Liverpool Cancer Therapy Centre, Sydney) were included in this study. All patients had biopsy-confirmed intermediate or high risk prostate cancer defined as T2b–T4, PSA >10 ng ml⁻¹ and/or Gleason Score ≥ 7.

Simulation and planning details

Bladder filling consisted of patients consuming 600 ml of water 1 h prior to simulation. After the initial two patients, indwelling catheters were subsequently used to accurately reproduce bladder filling in SBRT imaging and treatment. Patients were also advised to remain nil by mouth for the morning of the planning scan and

had an enema administered 1 hr prior to simulation to ensure their bowels were completely evacuated.

All patients underwent planning CT (Brilliance Big Bore, Philips Medical Systems, Nederland B.V.) and 3 T MRI (Magnetom Skyra, Siemens Healthcare, Erlangen) in the supine position with and without the RDD (Rectafix[™], Scanflex Medical AB, Täby, Sweden) *in situ* (Figure 1). The RDD was inserted into the rectum and downward pressure applied, thereby displacing the rectum posteriorly away from the prostate. The RDD was then fastened to the vertical locking column. A T₂ weighted MRI was acquired and registered to the CT data set for anatomical contouring of the prostate ± base of seminal vesicles, which was the clinical target volume (CTV). All scans were contoured by a single investigator. A planning tumour volume (PTV) expansion of 5 mm was applied in all directions except posteriorly, which was 3 mm. 19 Gy in 2 fractions was prescribed to the CTV D98% for the SBRT phase, with 46 Gy in 23 fractions subsequently planned for a fractionated external beam component without the RDD (not reported here). OARs included the rectum, bladder and femoral heads.

Motion analysis

At simulation a cine MRI sequence was captured using an interleaved T2 HASTE sequence with and without the RDD. The sequence was interleaved capturing the sagittal and axial planes with a temporal resolution of 5.2 s acquired over 4.3 min (giving 50 frames), the average time for a single SBRT volumetric modulated arc therapy (VMAT) fraction employing two arcs at a standard dose rate of 600MU/minute.

Points of interest (POIs) were defined on the sagittal slice including prostate apex, prostate base, anterior mid-prostate and posterior mid-prostate. Mid-prostate points represent the most anterior and posterior prostate points respectively defined at the slice midway between the prostate apex and base. Rectal POIs were the anterior inferior rectum and posterior inferior rectum, anterior mid-rectum and posterior mid-rectum, anterior superior rectum and posterior superior rectum. The inferior rectal points were in line with the prostate apex, mid-rectal points with the mid-prostate and superior rectal points were in line with the prostate base. They represent the most anterior and posterior points of the rectum at these slices. POIs defined on the axial slice were anterior prostate, posterior prostate, left prostate, right prostate, anterior rectum, posterior rectum, left rectum and right rectum (Figure 2). A validated tracking algorithm (described

Figure 1. Example of patient #3 sagittal view (a) with RDD, (b) without RDD and (c) the Rectafix[®] RDD. Bladder, yellow; Prostate, blue; Rectum, tan; PTV, red; RDD, rectal displacement device.

Figure 2. (a) Sagittal plane through the prostate showing the location of the tracking markers; 1, prostate apex; 2, anterior mid-prostate; 3, prostate base; 4, posterior mid-prostate; 5, anterior inferior rectum; 6, anterior mid-rectum; 7, anterior superior rectum; 8, posterior superior rectum; 9, posterior mid-rectum; 10, posterior inferior rectum. (b) Axial plane through prostate showing the location of the tracking markers; 11, posterior prostate; 12, right prostate; 13, anterior prostate; 14, left prostate; 15, posterior rectum; 16, right rectum; 17, anterior rectum; 18, left rectum.

below) measured displacement of these points over the 4.3 min in the anteroposterior (AP), superior–inferior and left–right directions.¹²

Displacement of each point was analyzed using the 2.5% trimmed range, which represents the range of movements from the 2.5 percentile to the 97.5 percentile as described by Gill et al.¹³ The 2.5% trimmed range was used as it captures 95% of displacements while eliminating extreme outliers caused by imaging or tracking noise.

The trimmed range was calculated for the entire 4.3 min. To analyze the effect of time on displacement, the trimmed range was calculated for the intervals of 0–1, 0–2, 0–3 and 0–4 min.

Automated tracking of points and contours

The anatomical points manually defined on the first MRI image of each cine MRI were automatically tracked and propagated through all frames. The DICOM images were first imported, temporally sorted, and divided into axial and sagittal sets. Then each frame was denoised, histogram-normalized, and deformably registered to the first frame of the sequence using a diffeomorphic demons algorithm.¹⁴ Finally, the anatomical points were back-propagated to each frame using the corresponding registration deformation vector field. It has one smoothing parameter that permits the smoothness of the final solution to be adjusted. Using the first patient data set this parameter was adjusted by visually comparing the tracking results with the corresponding manually defined points at frame numbers 25 and 50. The smoothing parameter was set at the beginning of the study and kept constant thereafter for all cine MRIs.

Dose comparison

The RDD data set was planned to a boost dose of 19 Gy in two fractions by a single investigator using a VMAT technique and the patients were treated based on this plan. Subsequently, the non-RDD data set was planned by the same investigator

with the planning priority of matching coverage achieved in the RDD plan. Dosimetric comparison between RDD and non-RDD was performed using DVH data. All planning constraints and protocol variation definitions are detailed in [Supplementary Material 1](#), structure definitions were according to the PROMETHEUS protocol.¹¹

Statistical analysis

Dependent *t* tests were used to test differences between arms with significance set as $p = 0.05$. Descriptive statistics were calculated for the motion and dosimetric parameters. Data analysis was performed using SPSS (v. 20.0. Armonk, NY: IBM Corp.)

RESULTS

Displacement

The 2.5% trimmed range displacement (Euclidean distance) results over all cine imaging frames are provided with summary statistics in [Table 1](#). For the sagittal images, the average 2.5% trimmed range (at $t = 4.3$ min) of displacement the prostate apex with and without the RDD was 0.82 ± 0.82 vs 1.02 ± 1.20 mm. Average prostate base displacement was 0.71 ± 0.52 vs 1.07 ± 0.94 mm with and without the RDD.

The average 2.5% trimmed range of displacement in the sagittal images with and without the RDD of the anterior and posterior mid-rectum were 1.02 ± 1.42 vs 1.17 ± 1.23 mm and 0.82 ± 0.37 vs 0.90 ± 0.97 mm, respectively. The average 2.5% trimmed range of displacement in the AP direction with and without the RDD of the anterior and posterior inferior rectum were 0.59 ± 0.34 vs 1.12 ± 0.88 mm and 0.84 ± 0.47 vs 1.01 ± 0.65 mm respectively.

Displacement with time

[Figures 3 and 4](#) show the average displacement of the prostate and rectum over time in all directions.

Table 1. Displacement summary statistics in mm for each point labelled in Figure 2.

	RDD					Non-RDD				
Prostate	Min	Max	Median	Mean	Std	Min	Max	Median	Mean	Std
1	0.05	3.60	0.59	0.82	0.82	0.11	6.33	0.57	1.02	1.20
2	0.04	4.76	0.51	0.93	1.11	0.02	5.71	0.41	0.89	1.33
3	0.04	2.37	0.58	0.71	0.52	0.06	3.73	0.73	1.07	0.94
4	0.07	7.67	0.54	1.16	1.93	0.06	8.46	0.69	1.39	2.02
11	0.06	1.81	0.60	0.67	0.42	0.08	2.51	0.83	0.93	0.62
12	0.05	1.58	0.56	0.62	0.35	0.05	1.72	0.53	0.58	0.36
13	0.08	1.50	0.54	0.61	0.32	0.03	1.72	0.36	0.48	0.40
14	0.05	1.61	0.57	0.64	0.38	0.03	1.56	0.48	0.60	0.43
Rectum										
5	0.03	1.26	0.58	0.59	0.34	0.07	3.74	0.83	1.12	0.88
6	0.05	5.79	0.60	1.02	1.42	0.07	5.82	0.73	1.17	1.23
7	0.03	5.17	0.61	0.96	1.24	0.05	6.53	0.84	1.35	1.58
8	0.06	1.29	0.56	0.58	0.30	0.05	4.91	0.56	0.87	1.02
9	0.07	1.64	0.83	0.82	0.37	0.05	4.28	0.58	0.90	0.97
10	0.03	2.20	0.84	0.84	0.47	0.07	2.54	0.84	1.01	0.65
15	0.05	1.36	0.81	0.74	0.37	0.05	2.18	0.53	0.63	0.38
16	0.06	0.84	0.43	0.43	0.19	0.05	1.63	0.44	0.51	0.31
17	0.07	1.33	0.60	0.65	0.33	0.04	2.53	0.72	0.87	0.60
18	0.04	0.99	0.33	0.39	0.23	0.06	1.98	0.44	0.52	0.34

RDD, rectal displacement device.

The average displacement of the prostate apex, prostate base, mid and inferior anterior rectum increased in the AP direction with increasing time with and without the RDD (graphs for all tacking points available in appendix). Statistically significant differences were seen at 3 and 4 min for both prostate apex and base.

The average AP displacement of the posterior rectum in the mid and inferior regions increased with time. Significant differences with and without the RDD were seen from 1 min on for both mid and inferior rectum. There was no statistically significant change in SI displacement. The largest displacement recorded was for Patient 2 without the RDD where a large movement of 3.5 mm followed by drift of the prostate apex was recorded ([Supplementary Material 1](#)).

Dosimetry

There was no statistically significant difference in coverage in both RDD and non-RDD plans, an example is shown in [Figure 5](#). However, all 10 non-RDD plans had major protocol violations compared to two RDD plans. RDD plans resulted in a statistically significant reduction in rectal wall dose including D_{max} , posterior wall dose and rectal mucosa D_{max} ([Supplementary Material 1](#) and [Figure 6](#)).

DISCUSSION

Cine MRI has been shown to be a useful tool to assess intrafraction motion, as it allows the acquisition of multiple images in a defined time frame with good soft tissue definition. Its

use in measuring intrafraction prostate motion has been well published.^{13,15,16} This is the first study using cine MRI to analyze the impact of rectal immobilization on intrafraction motion in the stereotactic prostate radiotherapy setting through directly comparing it to intrafraction motion without any immobilization device. The RDD was well tolerated, with none of these patients unable to proceed with planning and subsequent treatment. The logistical impact of using the RDD was not prohibitive and it could be used in a community setting. Recruitment to the PROMETHEUS trial was not adversely impacted by the prospect of the RDD and was likely helped by reducing the number of fractions and avoiding brachytherapy.

The impact on setup time was not specifically measured as part of this study, but the use of an RDD did increase the time required to initially insert the device and position the patient. Inserting the RDD required the oncologist to be present at treatment. Other rectal separation options such as hydrogel spacers are injected through the perineum under general anaesthetic, usually when fiducial markers are implanted. Once in place the hydrogel does not impact on setup time.

SBRT as a means of dose escalation is increasingly utilized in the treatment of prostate cancer with the literature reporting high rates of biochemical control.¹⁷ A major hurdle in delivering such high doses is the resultant dose to surrounding OARs. The use of a RDD to facilitate high dose delivery has been examined by

Figure 3. Average displacement of all prostate points over time. Area contained within braces indicates significant difference between RDD and nonRDD. Shaded areas represent 1σ , red, SI; green, LR; blue, AP; black, vector length. AP, anteroposterior; LR, left-right; RDD, rectal displacement device; SI, superior-inferior.

Nicolae et al.¹⁸ They reported their experience using a similar RDD in SBRT prostate radiotherapy analyzing intrafraction motion through comparison of pre- and post-treatment cone beam CT and dosimetric comparison. As outlined in their discussion, prostate gland motion may not be uniform or linear over the treatment duration, and using pre- and post-imaging to assess intrafraction motion may not truly represent displacement during treatment. The reported three-dimensional displacement was 1.83 ± 0.75 mm with less than 5% of all measurements ≥ 2.87 mm.

The results of this study are different from that of Vanhanen et al.¹⁹ who report opposite findings for the use of a RDD. They found that the use of a RDD compared to no RDD increased the amount of time the prostate spent at displacements of 1, 2, 3, 4, 5 and 6 mm significantly. The reasons for this opposite effect observed are not clear but the method of measurement differs between our studies. The reported study used RayPilot[®] electromagnetic tracking which consists of a single transmitter implanted in the prostate and receiving system overlaid on the couch. This system provides a single measurement point for the prostate as compared to our study which analyzed nine anatomical locations on the prostate using cine-MRI. Vanhanen et al also analyzed prostate motion with and without RDD on treatment rather than in a pre-treatment imaging session as in the current study.

The results presented in this manuscript show increased intrafraction stability with the RDD. A strength of the current study is that multiple points in the prostate and rectum were analyzed in terms of displacement. By doing this it was possible to highlight exactly where, anatomically, the RDD resulted in greater stability. The method also accounted for any organ deformation. The results show that all prostate and rectal points achieved reduced intrafraction motion with the RDD in the AP direction. We found that this reduction was statistically significant in the prostate apex and base and in the lower and mid rectum.

With the close anatomical relationship between the prostate apex and rectal points, it can be hypothesized that by stabilizing the rectum some stabilization of the prostate can be achieved. Gas and other material in the rectum can impact on prostate stability. The Dennonvilliers' fascia is a membrane of complex connective tissue between the prostate and rectum that connects the two organs,²⁰ therefore, stabilizing the rectum may stabilize the prostate. There was a different impact of the RDD for axial versus sagittal measurement points. This is attributable to the axial and sagittal planes measuring different anatomical positions within the pelvis. The sagittal measurements cover a range of points in the sup/inf direction where the axial represents only a single slice. AP movement is clinically the most relevant, as the separation between prostate and anterior rectal wall often drives radiotherapy planning to ensure adequate coverage and acceptable rectal dosimetry. Reducing

Figure 4. Average displacement of all rectum points over time. Area contained within braces indicates significant difference between RDD and nonRDD. Shaded areas represent 1σ , red, SI; green, LR; blue, AP; black, vector length. AP, anteroposterior; LR, left-right; RDD, rectal displacement device; SI, superior-inferior.

intrafraction motion allows greater certainty that DVH results achieved at planning are delivered during treatment. Given the reduction in motion achievable with the use of an RDD it may also be possible to reduce the margin required in the nonRDD setting, further reducing rectal dosimetry and toxicity.

The relationship between time and intrafraction motion was also analyzed. The results show that prostate and rectal displacement from the starting position increases with time, which is consistent with published literature.²¹ It was found that without a RDD,

displacement increased almost linearly over the 4.3 min time frame. In comparison, with the RDD, displacement remained approximately stable over the 4.3 min. The reduction in displacement was most pronounced again in the AP direction of the inferior and mid-rectal walls as well as the prostate apex and base, the difference reaching significance from around 2 min. Based on this, it would indicate that the faster treatment can be delivered, the less intrafraction motion would be a factor. Quicker treatments are currently achievable with advances in treatment technology such as a flattening filter free delivery where a roughly fourfold increase in efficiency is possible with 10 FFF compared to 6 MV. The total beam on time also depends on modulation and therefore a fourfold increase in efficiency may not be realized. When treating without an RDD intrafraction imaging between arcs or tracking could be used to increase confidence in targeting.^{22,23} Overall, although it was discovered that the RDD reduced intrafraction motion, displacement greater than 3 mm was rare in both cohorts. This is within PROMETHEUS CTV to PTV expansion of 5 mm in all directions except posteriorly which is 3 mm.¹¹

We found that when dosimetrically matched to target organ coverage, the RDD led to statistically and clinically relevant reduction in rectal doses. All non-RDD plans failed to meet protocol rectal DVH constraints (see [Supplementary Material 1](#)). This improvement was secondary to the physical separation between the prostate and rectum created by the immobilisation device.

Figure 5. Example of Patient #3 dosimetry with and without RDD. Bladder, yellow; prostate, blue; Rectum, tan. RDD, rectal displacement device.

Figure 6. Rectal wall DVH with and without rectal immobilization device. DVH, dose volume histogram.

POI registration error was estimated using two methods. First, the position of tracked POIs were compared with new manual point identification (by the same observer) at frame 25 and frame 50. Using this method, we found an average difference of 1.4 ± 0.9 mm ($\mu \pm \sigma$) on the axial plane and of 2.5 ± 1.7 mm on the sagittal plane. These values amount for both registration accuracy and intra observer point identification differences. In particular, it was found that the position of fiducial point was especially hard to define on the sagittal plane in the SI direction reason of the less salient anatomic landmarks, which explain in part the larger differences values observed for the sagittal plane. Second, the tracked POI were rendered on the sequence of images and their position validated by a trained observer. The position of the points was deemed to be satisfactory.

These results indicate a benefit with the use of RDDs in prostate stereotactic radiotherapy. Within the PROMETHEUS trial, patients may also be treated using an interstitial hydrogel as opposed to the external RDD studied here. This polymer is injected through the perineum into the space between the rectum and prostate under trans-rectal ultrasound guidance. A separate randomized trial has validated the use of hydrogel in improving patient reported outcomes.²⁴ Furthermore, a separate

PROMETHEUS substudy has shown similar dosimetry achievable with either a RDD or Hydrogel, suggesting it is the rectal separation rather than specific method through which this is achieved which is beneficial.²⁵

Limitations of the current study include the small sample size, uncertainty in automatic point tracking and anatomical point placement. The limited sample size was based on initial recruitment to the PROMETHEUS trial and what was feasible to contour and analyze. The point tracking algorithm relies on the quality of the deformable image registration between frames and may be impacted by poor image quality or large anatomical differences. The dosimetric data reported here are based on the planning image which does not include delivery uncertainties. Future work could include an examination of the impact of displacement reduction on delivered dose of using a RDD.

CONCLUSION

The RDD improves prostate and rectal intrafraction stability as assessed by cine MRI. This improvement increases with treatment time. Furthermore rectal dosimetry was significantly improved with the RDD. The improvement in stability could potentially translate into reduced margins, further sparing OARs.

REFERENCES

- Trada Y, Plank A, Martin J. Defining a dose-response relationship for prostate external beam radiotherapy. *J Med Imaging Radiat Oncol* 2013; **57**: 237–46. doi: <https://doi.org/10.1111/1754-9485.12008>
- Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009; **74**: 1405–18. doi: <https://doi.org/10.1016/j.ijrobp.2008.10.091>
- Vogelius IR, Bentzen SM. Dose response and fractionation sensitivity of prostate cancer after external beam radiation therapy: a meta-analysis of randomized trials. *Int J Radiat Oncol Biol Phys* 2018; **100**: 858–65. doi: <https://doi.org/10.1016/j.ijrobp.2017.12.011>
- Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999; **43**: 1095–101. doi: [https://doi.org/10.1016/S0360-3016\(98\)00438-6](https://doi.org/10.1016/S0360-3016(98)00438-6)
- Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year Outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016; **17**: 1047–60. doi: [https://doi.org/10.1016/S1470-2045\(16\)30102-4](https://doi.org/10.1016/S1470-2045(16)30102-4)
- Lee WR, Dignam JJ, Amin M, Bruner D, Low D, Swanson GP, et al. NRG oncology RTOG 0415: a randomized phase III non-inferiority study comparing two fractionation schedules

- in patients with low-risk prostate cancer. *American Society of Clinical Oncology* 2016;.
7. Catton CN, Lukka H, Gu C-S, Martin JM, Supiot S, Chung PWM, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol* 2017; **35**: 1884–90. doi: <https://doi.org/10.1200/JCO.2016.71.7397>
 8. Martin JM, Supiot S, Keall PJ, Catton CN. Moderately hypofractionated prostate external-beam radiotherapy: an emerging standard. *The British Journal of Radiology* 2018; **58**: 20170807. doi: <https://doi.org/10.1259/bjr.20170807>
 9. Deutsch I, Zelefsky MJ, Zhang Z, Mo Q, Zaider M, Cohen Gil'ad, et al. Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT. *Brachytherapy* 2010; **9**: 313–8. doi: <https://doi.org/10.1016/j.brachy.2010.02.196>
 10. Paydar I, Pepin A, Cyr RA, King J, Yung TM, Bullock EG, et al. Intensity-modulated radiation therapy with stereotactic body radiation therapy boost for unfavorable prostate cancer: a report on 3-year toxicity. *Front Oncol* 2017; **7**(6 Pt 2): 5. doi: <https://doi.org/10.3389/fonc.2017.00005>
 11. Richardson M, Sidhom M, Gallagher S, Grand M, Pryor D, Bucci J, et al. Prostate multicentre external beam radioTHERapy using a stereotactic boost: the prometheus study protocol. *BMC Cancer* 2018; **18**: 588. doi: <https://doi.org/10.1186/s12885-018-4511-6>
 12. Dowling J, Dang K, Fox CD, Chandra S, Gill S, Kron T, et al. Fast cine-magnetic resonance imaging point tracking for prostate cancer radiation therapy planning. *Journal of Physics: Conference Series* 2014; **489**: 012027. doi: <https://doi.org/10.1088/1742-6596/489/1/012027>
 13. Gill S, Dang K, Fox C, Bressel M, Kron T, Bergen N, et al. Seminal vesicle intrafraction motion analysed with cinematic magnetic resonance imaging. *Radiat Oncol* 2014; **9**: 174. doi: <https://doi.org/10.1186/1748-717X-9-174>
 14. Vercauteren T, Pennec X, Perchant A, Ayache N. Diffeomorphic demons: efficient non-parametric image registration. *Neuroimage* 2009; **45**(1 Suppl): S61–S72. doi: <https://doi.org/10.1016/j.neuroimage.2008.10.040>
 15. Ghilezan MJ, Jaffray DA, Siewerdsen JH, Van Herk M, Shetty A, Sharpe MB, et al. Prostate gland motion assessed with cine-magnetic resonance imaging (cine-MRI). *Int J Radiat Oncol Biol Phys* 2005; **62**: 406–17. doi: <https://doi.org/10.1016/j.ijrobp.2003.10.017>
 16. Padhani AR, Khoo VS, Suckling J, Husband JE, Leach MO, Dearnaley DP. Evaluating the effect of rectal distension and rectal movement on prostate gland position using cine MRI. *Int J Radiat Oncol Biol Phys* 1999; **44**: 525–33. doi: [https://doi.org/10.1016/S0360-3016\(99\)00040-1](https://doi.org/10.1016/S0360-3016(99)00040-1)
 17. King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol* 2013; **109**: 217–21. doi: <https://doi.org/10.1016/j.radonc.2013.08.030>
 18. Nicolae A, Davidson M, Easton H, Helou J, Musunuru H, Loblaw A, et al. Clinical evaluation of an endorectal immobilization system for use in prostate hypofractionated stereotactic ablative body radiotherapy (SABR). *Radiat Oncol* 2015; **10**: 122. doi: <https://doi.org/10.1186/s13014-015-0426-4>
 19. Vanhanen A, Kapanen M. The effect of rectal retractor on intrafraction motion of the prostate. *Biomed Phys Eng Express* 2016; **2**: 035021. doi: <https://doi.org/10.1088/2057-1976/2/3/035021>
 20. Furubayashi N, Nakamura M, Hori Y, Hishikawa K, Nishiyama K-I, Hasegawa Y. Surgical considerations in regard to Denonvilliers' fascia. *Oncol Lett* 2010; **1**: 389–92. doi: <https://doi.org/10.3892/ol.00000069>
 21. Langen KM, Willoughby TR, Meeks SL, Santhanam A, Cunningham A, Levine L, et al. Observations on real-time prostate gland motion using electromagnetic tracking. *Int J Radiat Oncol Biol Phys* 2008; **71**: 1084–90. doi: <https://doi.org/10.1016/j.ijrobp.2007.11.054>
 22. Arumugam S, Sidhom M, Truant D, Xing A, Udovitch M, Holloway L. Variable angle stereo imaging for rapid patient position correction in an in-house real-time position monitoring system. *Phys Med* 2017; **33**: 170–8. doi: <https://doi.org/10.1016/j.ejmp.2016.12.014>
 23. Keall P, Nguyen DT, O'Brien R, Booth J, Greer P, Poulsen P, et al. Stereotactic prostate adaptive radiotherapy utilising kilovoltage intrafraction monitoring: the TROG 15.01 spark trial. *BMC Cancer* 2017; **17**: 180. doi: <https://doi.org/10.1186/s12885-017-3164-1>
 24. Hamstra DA, Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. *Int J Radiat Oncol Biol Phys* 2017; **97**: 976–85. doi: <https://doi.org/10.1016/j.ijrobp.2016.12.024>
 25. Wilton L, Richardson M, Keats S, Legge K, Hanlon M-C, Arumugam S, et al. Rectal protection in prostate stereotactic radiotherapy: a retrospective exploratory analysis of two rectal displacement devices. *J Med Radiat Sci* 2017; **64**: 266–73. doi: <https://doi.org/10.1002/jmrs.238>