Radiotherapy and Oncology 119 (2016) 371–380

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

MRI-guided prostate adaptive radiotherapy – A systematic review

A.J. McPartlin [a,1], X.A. Li [b,1], L.E. Kershaw [a], U. Heide [d], L. Kerkmeijer [e], C. Lawton [b], U. Mahmood [c], F. Pos [d], N. van As [f,g], M. van Herk [a], D. Vesprini [h], J. van der Voort van Zyp [e], A. Tree [f,1], A. Choudhury [a,*,1], On behalf of the MR-Linac consortium

[a] The Christie NHS Foundation Trust and Manchester Cancer Research Centre, University of Manchester, Manchester Academic Health Sciences Centre, UK; [b] Medical College of Wisconsin; [c] MD Anderson Cancer Center, Houston, USA; [d] Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital; [e] University Medical Center Utrecht, The Netherlands; [f] Royal Marsden Hospital; [g] Institute of Cancer Research, UK; and [h] Sunnybrook Health Sciences Centre, University of Toronto, Canada

ARTICLE INFO

Article history:
Received 24 February 2016
Received in revised form 8 April 2016
Accepted 9 April 2016
Available online 6 May 2016

Keywords:
Prostate
MRI
MR-Linac
Adaptive radiotherapy
IGRT

ABSTRACT

Dose escalated radiotherapy improves outcomes for men with prostate cancer. A plateau for benefit from dose escalation using EBRT may not have been reached for some patients with higher risk disease. The use of increasingly conformal techniques, such as step and shoot IMRT or more recently VMAT, has allowed treatment intensification to be achieved whilst minimising associated increases in toxicity to surrounding normal structures. To support further safe dose escalation, the uncertainties in the treatment target position will need be minimised using optimal planning and image-guided radiotherapy (IGRT). In particular the increasing usage of profoundly hypo-fractionated stereotactic therapy is predicated on the ability to confidently direct treatment precisely to the intended target for the duration of each treatment.

This article reviews published studies on the influences of varies types of motion on daily prostate position and how these may be mitigated to improve IGRT in future. In particular the role that MRI has played in the generation of data is discussed and the potential role of the MR-Linac in next-generation IGRT is discussed.

Randomised trials have demonstrated that dose escalated radiotherapy improves outcomes for men with prostate cancer [1]. The use of increasingly conformal techniques, such as step and shoot IMRT or more recently VMAT, has allowed this to be achieved whilst minimising associated increases in toxicity to surrounding normal structures [2]. The accuracy of any radiotherapy delivery is however limited by multiple factors: organ delineation, set up error and inter-/intra-fraction organ motion, rotation and deformation [3]. A plateau for benefit from dose escalation using EBRT may not have been reached for some higher risk prostate cancers [4]. To allow further safe dose escalation, the uncertainties in the treatment target must be mitigated using optimal planning and image-guided radiotherapy (IGRT). In particular the increasing usage of profoundly hypo-fractionated stereotactic therapy is predicated on the ability to confidently direct treatment precisely to the intended target for the duration of each treatment [5].

Much work has been carried out over the past 20 years quantifying the degree of prostate motion, rotation and deformation that occurs during a course of radiotherapy, allowing rationalisation of treatment margins based on expansion "recipes" [6]. The use of increasingly sophisticated real time imaging has enabled monitoring of the prostate and OAR's through treatment delivery and has provided extensive data on their behaviour. MRI, with its unrivalled soft tissue delineation, has contributed to these data but has not, as yet, emerged as a routine part of daily radiotherapy delivery. The long anticipated arrival of a fully integrated MR-Linac may change this [7].

The ideal scenario is to guide prostate radiotherapy with MR imaging, identifying the prostate in real time whilst delivering radiation. Two systems (ViewRay and the Elekta MR Linac) hope to demonstrate improvement in patient outcomes with this technique.

This article reviews data on target uncertainties when treating prostate cancer and in particular the work performed using MRI. Available techniques to reduce this uncertainty, and the potential benefits an MR-Linac may offer for IGRT are discussed. These data underpin the clinical work which will be undertaken on the MR-Linac to establish its utility in treating localised prostate cancer.

* Corresponding author at: Dept of Clinical Oncology, The Christie NHS Foundation Trust, Wilmslow Rd, Manchester M20 4BX, UK.
E-mail address: Ananya.choudhury@christie.nhs.uk (A. Choudhury).
[1] These authors contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.radonc.2016.04.014
0167-8140/

Search strategy and selection criteria

References for this review were identified through PubMed with the search terms "prostate", "adaptive", "radiation", "radiotherapy", "motion", "MRI", "MR". The literature review was performed between June and September 2015. The titles/abstracts were screened and full text copies of all potentially relevant studies obtained. References within identified papers were reviewed for relevance. A final reference list was generated on the basis of originality and relevance to the scope of this Review.

Non-MR studies of inter- and intra-fractional prostate motion

The prostate experiences inter- and intra-fractional motion during a course of radiotherapy, as reported from an extensive body of work carried out over the past twenty years (Supplement-Fig. 1). A comprehensive review of early studies indicates that the inter-fraction motion appears to have a standard deviation (SD) of around 1–4 mm, with one study finding motion with SD as high as 7.3 mm [8].

With increasing use of IMRT and consequently increased treatment duration, the significance of intra-fractional motion has grown, with appreciable variation being demonstrated [9–14]. A minority of patients experience more pronounced changes, as illustrated in a series of 427 patients assessed using fiducial markers (FM) and portal imaging, with motion >3 mm in 28% of treatment fractions over a ten minute period [15].

Multiple modalities have been used to demonstrate that two general types of intra-fraction motion are seen: non-resolving slow drift, predominantly in the posterior direction due to rectal changes, and sudden transient motion, largely in the superior and anterior direction, likely a result of peristaltic visceral motion [9,16–18]. Constant assessment also identifies greater intra-fraction motion; one study using Calypso 4-D tracking of 7738 records in 200 patients over 12 min showed the percentage of fractions with prostate shift >2, 3, 5, and 7 mm for >30 s was 56.8%, 27.2%, 4.6% and 0.7% [19]. For the worst 10 patients, 5% of the total, these percentages increased to 91.3%, 72.4%, 36.3% and 6%.

Cohorts of patients assessed using multiple continuous imaging techniques have also found significant proportions experiencing movements >2–5 mm, demonstrating the consistency of this finding within differing imaging modalities [20–23]. Intra-fraction motion has generally been found to be patient specific and predominantly random, although this has been challenged [24–26]. The observation that initial systematic intra-fraction changes can be predictive for subsequent movement may provide some guidance to likely behaviour during therapy [27–29].

Numerous studies have quantified the systematic and random components of inter- and intra-fraction motion to allow application of margin expansion formulas (Tables 1 and 2).

MR studies of inter and intra-fraction motion

The superb soft-tissue contrast and continuous imaging capability of MRI have allowed for confident assessment of inter- and intra- fraction prostate and OAR motion [54–65].

The first work with MRI to quantify prostatic motion used axial cine-MRI on 55 patients to evaluate intra-fraction motion of the rectum and prostate centre of mass every 10 s over a 6–7 min period, representative of a radiotherapy treatment delivery time. This identified a median anterior shift of 4.2 mm, which in 16% of patients was >5 mm [54]. A subsequent study using sagittal and axial cine-MR over 9 min, sampling at 20 s intervals, for 42 patients identified displacement with SD 2.9 mm, 1.5 mm and 3.4 mm in the AP, LR and SI plane [55]. The prostate was identified as tending to return to its original position after large displacements of up to 12 mm, motion which would be missed with pre and post treatment imaging alone [57]. This motion appeared to increase through the course of treatment, perhaps as a consequence of radiation induced toxicity.

More recently intra-fraction prostate motion has been assessed by imaging 47 patients with prostate cancer after instructions to remove rectal gas [63]. Eleven points of interest were determined on axial and sagittal cine-MRI slices and monitored over a total of ten minutes. Displacement was more marked at the base of prostate than apex, likely a result of distal tethering, with mean of means SI and AP displacements of 0.41 mm and 0.86 mm for the former and 0.26 mm and 0.32 mm for the latter.

Continuous MRI has been able to demonstrate that intra-fraction motion increases with treatment time. A study using an open bore MR-scanner for a total of 68 sagittal cine-MRI sequences demonstrated an increasing displacement in the AP and SI planes during treatment with SD of 0.57 mm and 0.41 mm in the first two minutes increasing to 1.44 mm and 0.91 mm in minutes two to four [61]. This increase in motion appears to occur predominantly in the first few minutes of treatment with another study using cine-MRI imaging over 12–15 min finding motion at 3, 5, 10 and 15 min with an SD of 1 mm, 1.3 mm, 2.1 mm and 1.9 mm in the AP plane and 0.7 mm, 1.8 mm, 1.5 mm and 1.6 mm in the SI plane [65].

The increasing intra-fractional motion seen initially over time shows the potential benefit of shortened treatments associated with VMAT compared to that with IMRT. Other studies using non-MR based imaging have also shown this increase and that it is the strongest predictor of observed displacements [18,23,26,66–70]. These increasing movements can contribute 1–2 mm to the required PTV margin [68,71]. Shortened treatment times, such as those achievable by VMAT, have been shown to achieve a marked reduction in the SD of intra-fraction motion [19,50,66].

Stereotactic radiotherapy is challenging both due to the potential increase in treatment time compared to conventional VMAT and the implications of a geographical miss for even a single fraction. The necessity to avoid this obliges caution in margin reduction although it has been shown using Cyberknife that repeat imaging every 60–180 s may be sufficient to allow correction for the increased prostate motion of longer treatments [72]. Even with regular repeat imaging 6-dimensional correction for rotation and translation is required if margins as small as 3 mm are to be achievable.

Deformation and rotation

Many studies of prostatic motion have assumed rigid motion of the prostate. Analyses of prostate changes have shown this to be a simplification although the degree of deformation identified has varied substantially. For example a study comparing the contoured prostate to an average CTV on 8–12 CT images for 19 patients matched for rotation and translation found "real" shape variation, correcting for inter-observer variation, of 1.6 mm at the SV tip and 0.9 mm at the posterior prostate [73]. Another group used three repeat CT scans with prostate and SV contoured and matched to a planning CT and non-rigidly registered to represent deformation [74]. Deformation of the prostate was small ($\leqslant$1 mm) whilst the deformation of SV was up to 2.6 mm SD posteriorly. More marked variation has been suggested; a study matching 200 cone beam CT (CBCT) images for ten patients to planning CT images using B-spline-based deformable registration identified a much larger deformation of the prostate, most marked in the anterior direction with a maximum of 10 mm, 5 mm and 3 mm in 1%, 17% and 76% of

Table 1
Inter-fraction systematic and random motion.

Author	Pt No. (fractions analysed)	Imaging	Inter-fraction motion SD (mm)						Registration	Preparation
			Systematic motion			Random motion				
			AP	LR	SI	AP	LR	SI		
Zelefsky 1999 [30]	50 (200)	CT	2.4	0.6	2.7	1.6	0.5	2.0	Bone	Prone, fleet enema at planning, empty bladder, immobilisation device
Stroom1999 [31]	15 (60)	CT	2.5	0.5	2.7	2.8	0.6	2.5	Bone	Foot and knee support Laxative prior to planning, 1 l fluid 1 h prior to scans
Hoogeman 2005 [32]	19 (209)	CT	2.7	0.3	2.1	2.4	0.4	2.1	Bone	Empty rectum, 250 ml fluid 1 h prior
Schallenkamp 2005 [13]	20 (798)	MV EPID + FM	2.5	2.0	1.9	3.5	1.6	2.0	Bone	Vacuum cradle
De Boer 2005 [33]	15 (255)	MV EPID + FM	2.1	0.8	2.0	1.9	0.7	1.2	Bone	Laxative prior to sim, full bladder
Litzenberg 2006 [34]	11 (–)	EM	1.5	2.2	3.0	5.2	3.4	3.3	Skin markers	Foot and knee support
Van den Heuvel 2006 [35]	10 (270)	MV EPID + FM	3.6	3.4	3.9	5.7	5.7	2.7	Skin markers	Alpha cradle
O'Daniel 2006 [36]	10 (243)	CT	3.9	1.6	3.4	3.6	2.5	2.0	Skin markers	Empty rectum, full bladder at simulation
Soete 2007 [37]	12 (120)	kV EPID + FM	4.3	1.3	4.2	2.8	1.6	2.3	Bone	Head and knee support
Van der Heide 2007 [38]	453 (15855)	MV EPID + FM	4.8	2.2	2.9	3.5	2.0	2.3	Skin markers	Knee, cushion. Bladder emptied 15 min prior to radiotherapy
McNair 2008 [39]	30 (408)	MV EPID + FM	2.5	1.3	1.9	3.1	2.2	2.2	Bone	Ankle/knee support, partially full bladder, empty rectum no prep
Beltran 2008 [40]	40 (1532)	MV EPID + FM	3.5	0.9	3.0	2.8	1.2	2.0	Bone	Not specified
Fiorino 2008 [41]	21 (522)	CBCT	0.3	0.2	0.2	1.0	0.6	0.7	Bone	Leg immobilisation, rectal enema + gas catheter, 250 ml fluid 30 min prior
Byland 2008 [42]	24 (984)	CBCT	2.0	0.7	1.0	2.9	2.0	2.1	Mutual information algorithm	No bladder/bowel prep
Frank 2008 [43]	15 (369)	CT	4.1	0.9	2.9	1.3	0.5	0.6	Bone	Vac-lok bag, enema at sim, 590 ml fluid 30 min prior
Mutanga 2008 [44]	10 (–)	MV/kV EPID	2.9	1.7	4.1	3.2	1.6	2.7	Skin markers	Not specified
Nijkamp 2008 [45]	20 (116)	CBCT	1.8	0.5	1.7	1.9	0.5	1.5	Bone	Empty rectum, 250 ml fluid 1 h prior, dietary advice
Tanyi 2010 [17]	14 (546)	EM	3.4	0.5	2.9	2.5	0.4	2.3	Bone	Not specified
Su 2011 [46]	17 (476)	EM	4.7	2.3	3.4	3.5	3.7	2.7	Skin markers	Not specified
Mayyas 2013 [47]	27 (1100)	CBCT	3.0	2.4	2.7	3.2	2.5	2.2	Skin markers	Empty rectum, partially full bladder
		BAT US	3.3	2.8	3.5	4.1	3.6	3.8		
		kV EPID	3.4	2.6	3.1	2.9	2.4	2.0		
Oh 2014 [48]	17 (546)	CBCT	1.1	1.6	1.9	1.8	2.8	2.4	Skin markers	Knee support, ERB, full bladder
Oehler 2014 [49]	20 (172)	CBCT	1.9	0.6	1.7	1.9	0.9	1.7	Bone	Leg immobilisation, empty rectum with ERB, empty bladder
		kV EPID	1.8	0.8	1.4	2.0	0.9	2.3		

CBCT, cone beam CT; FM, fiducial marker; EM, electromagnetic transponder.

cases [75]. Again SV deformation was larger, with changes in the posterior direction of >5 mm and >3 mm in 7.5% and 44.9% of cases. For this analysis three clinicians delineated contours which were averaged in an attempt to reduce error however the SD of the mean centre of mass of the contours was up to 2.2 mm. It may therefore be that the inferior CBCT image quality, limiting contouring accuracy, contributed to the larger changes identified.

MRI, which may mitigate delineation errors associated with CT imaging, has also been used to assess deformation. A study of 10 patients using sagittal and axial cine MRI of the prostate to assess changes in the volume of contoured prostate over six minutes found similar results to those obtained using CT imaging with a deformation with a SD 1.7 mm in the AP plane shown [76]. Interestingly it has been suggested through tracking points of movement in sagittal MRI imaging that deformation is only seen with a full rectum, and is most marked at the level of mid-prostate [57].

The cause of deformation is due both to mass effect from surrounding structures and as a consequence of treatment itself with the prostate being shown to change in volume during radiotherapy. For example 25 patients underwent MR imaging pre-radiation and at one time point during therapy to assess prostate motion and deformation through treatment [58]. Scans were compared using finite element modelling aligned on the centroid of three FM. An increase in prostate volume by up to 34% was seen in those scanned early in treatment whilst a decrease of up to 24% was seen later in the course. The degree of shrinkage seen over a course of radiotherapy is affected by the use of neo-adjuvant hormone therapy and pre-treatment volume but may be generally of the order of 10–15% [77–80]. This has implications for further development of MR-guided radiotherapy, which can account for the intra-fraction motion described above, but would need further technical developments to adapt for deformation.

The effect of systematic and random inter-fraction rotations on prostate motion has been assessed by various groups using CT, kV and MVCT or EM imaging. These rotations predominate in the sagittal plane and appear to correlate with rectal filling; this moves

Table 2
Intra-fraction systematic and random motion.

Author	Pt No. (fractions analysed)	Imaging	Intra-fraction motion SD (mm)						Treatment time	Preparation
			Systematic motion			Random motion				
			AP	LR	SI	AP	LR	SI		
Beltran 2008 [40]	40 (1532)	MV EPID + FM	0.9	0.6	1.0	1.8	1.3	1.2	2 min	Not specified
Li 2013 [50]	105 (775)	EM	0.5	0.2	0.4	1.1	0.5	1.0	3 min	Not specified
Aubrey 2004 [10]	18 (282)	MV EPID + FM	0.7	0.2	0.4	1.4	0.8	1.0	<5 min	Full bladder, empty rectum
Li 2013 [50]	105 (775)	EM	0.6	0.3	0.5	1.2	0.5	1.1	5 min	Not specified
Choi 2015 [51]	12 (336)	kV EPID + FM	0.3	0.2	0.4	0.6	0.3	0.5	5 min	Ankle immobilisation, enema
Oehler 2014 [49]	20 (52)	CBCT + FM	1.4	0.9	1.4	1.6	1.0	1.4	3–6 min	Leg immobilisation, empty rectum with ERB, empty bladder
Kotte 2007 (15)	427 (11426)	MV EPID + FM	0.6	0.3	0.5	0.9	0.4	0.9	5–7 min	Knee support, empty rectum
Kron 2010 [26]	184 (5778)	kV EPID + FM	0.8	0.5	0.7	1.2	0.8	1.2	<6 min	Not specified
Soete 2007 [37]	12 (120)	MV EPID + FM	0.8	1.3	1.1	1.6	1.4	2.4	7.5 min	Head and knee support
Kron 2010 [26]	184 (5778)	kV EPID + FM	0.9	0.6	0.8	1.2	0.8	1.1	6–9 min	Not specified
Su 2011 [46]	17 (467)	EM	0.6	0.3	0.5	1.9	0.7	1.4	8 min	Not specified
Litzenberg 2006 [34]	11 (–)	EM	2.2	0.7	2.6	0.8	0.2	1.2	8 min	Ankle/knee support, no rectal/bladder prep
Tanyi 2010 [17]	14 (1638)	EM	0.5	0.3	0.7	1.4	0.8	1.3	8–16 min	Not specified
Kron 2010 [26]	184 (5778)	kV EPID + FM	1.3	1.1	1.3	1.3	0.7	1.2	>9 min	Not specified
Mutanga 2012 [27]	108 (2894)	MV EPID + FM	1.1	–	1.0	1.2	–	1.1	11 min	Headrest/knee support, void bladder 30 min prior, laxative at planning
Li 2009 [52]	105 (775)	EM	0.8	0.3	0.8	1.6	0.7	1.4	10–20 min	Not specified
Badakhshi 2013 [53]	13 (427)	kV EPID + FM	0.5	2.0	2.1	1.4	2.2	2.6	14.2 min	Empty rectum + full bladder, head and knee support, foot restraint
Mayyas2013 [47]	19 (–)	EM	1.3	0.6	1.5	2.6	1.4	2.4	20–30 min	Empty rectum, partially full bladder
Quon 2012 [28]	53 (265)	MV EPID + FM	1.4	0.2	1.2	2.4	1.3	2.0	Time not specified	Vac-lok bag, full bladder, empty rectum

CBCT, cone beam CT; EM, Electromagnetic transponder; EPID, Electronic portal imaging device; FM, fiducial marker.

the prostate in the AP direction, causing rotation due to apex tethering [81]. The differing bowel preparations employed by various groups may affect rectal volumes and contribute to the variation in degree of rotation identified.

Intra-fractional rotation has been less well characterised and although appearing smaller, it remains relevant (Table 3). A study using continuous kV imaging with FM during the treatment of 10 patients with prostate cancer found for 35% of treatment time the prostate rotated more than 5° around the lateral axis [82]. These intra-fraction rotations may be clinically significant. For example even with daily translations the intra-fraction rotation during RT can cause significant under-dosing, and margins of 3 mm may be required to account for rotations of up to 5° [72,83]. The significance of prostatic rotation is only likely to increase as treatment margins further reduce.

Relative motion of prostate and seminal vesicles

In high risk disease the likelihood of occult involvement of the SV is increased [88]. It is therefore generally necessary to include this area in the intended CTV for radiotherapy planning. The base of the SV is the region most likely to harbour occult disease, with one pathological series finding disease 2 cm beyond this in only 1% of all patients [89]. This area must therefore be prioritised to receive the full prescribed dose. CT imaging has demonstrated that the SV tips undergo greater inter-fraction movement than the base and consequently larger expansion margins are required if it is clinically necessary to treat its entirety [90,91].

It has been shown that the SV and prostate can behave independently making appropriate expansions to PTV challenging [49,73,92]. The SV volume may vary by as much as 100% during a course of radiotherapy and experience significant independent deformation [78,92]. Inter-fraction SV motion appears more significant than that of the prostate gland with a SD in the order of 2.9–7.3 mm, 1.9–3.1 mm and 2.1–5.5 mm in the AP, LR and SI planes [30,43,79,91,93,94]. Despite direct tumour invasion reducing SV mobility, this motion may remain considerable [95].

Allowing for intra-fractional motion is also problematic. Overall intra-fractional displacement of the SV appears greater than for the prostate and increases over time. In one series using cine-MRI it was found that for 95% of the images SV centroid movement at 3, 5, 10 and 15 min was 4.7 mm, 5.8 mm, 6.5 mm and 7.2 mm respectively in the SI plane and 4.0 mm, 4.5 mm, 6.5 mm and 7.0 mm in the AP plane [65]. The correlation between prostate and SV intra-fraction movement was shown to vary greatly with no relationship between the two for most patients.

Lack of correlation between prostate and SV inter- and intra-fractional motion has implications for the use of prostate tracking devices, such as calypso transponders, when simultaneously treating the SV. Caution must be employed when considering reducing treatment margins on the basis of an assumed confidence about exact CTV location.

Contributing factors to prostate motion

Rectal and bladder volumes

Rectal distension is a major contributor to, and correlates with, prostate motion (Supplement-Fig. 2). This likely relationship was identified in some of the earliest prostate motion analyses [96,97] and subsequent studies have confirmed this association

Table 3
Studies of intra- and inter-fraction rotation.

Author	Pt No. (fractions analysed)	Imaging	Inter-fraction rotation SD (degrees) around each axis						Registration	Preparation
			Systematic			Random				
			AP	LR	SI	AP	LR	SI		
Stroom 1999 [31]	15 (60)	CT	0.8	3.6	1.7	0.9	3.3	1.5	Chamfer match	Laxative prior to simulation. 500 ml 1 h prior to imaging. Knee, foot, arm support
Dehnad 2003 [84]	10 (241)	CT + MV EPID + FM	2.0	4.7	2.7	1.7	3.6	1.9	Prostate COM	Knee support
Aubrey 2004 [10]	7 (348)	MV EPID + FM	2.2	5.6	2.4	2.0	6.1	2.8	Prostate COM	Full bladder, empty rectum
De Boer 2005 [33]	15 (255)	MV EPID + FM	1.5	4.9	1.9	1.6	4.7	1.0	Bone	Laxative prior to simulation, full bladder
Hoogeman 2005 [32]	19 (209)	CT	1.3	5.1	2.2	1.6	3.6	2.0	Chamfer match	Empty rectum
Van der Heide 2007 [38]	234 (8190)	MV EPID + FM	2.8	2.8	2.8	1.7	3.1	2.0	Prostate COM	Empty bladder, knee support
Mutanga 2007 [44]	10 (3382)	kV/MV EPID + FM	1.7	4.9	1.3	1.3	4.2	1.6	Prostate COM	Not specified
Nijkamp 2008 [45]	20 (128)	Weekly CBCT	0.9	2.9	1.0	1.0	3.0	1.1	Bone	Dietary advice, daily mild laxative, empty rectum, 250 ml fluid1 h prior to imaging
Mutanga 2011 [85] (from van der Wielen [74])	21 (84)	CT + FM	2.0	4.3	2.2	1.2	4.5	1.8	Prostate COM	Laxative prior to simulation
Graf 2012 [86]	38 (969)	kV EPID + FM	1.6	4.1	2.3	2.0	3.1	1.8	Bone	Enema prior to simulation, empty rectum, bladder filling, head/knee support foot immobilisation
Smeenk 2012 [87]	15 (576)	EM	2.9	10.2	7.0	1.3	3.9	1.5	EM	Knee support, foot immobilisation
			Intra-fraction rotation SD (degrees) around each axis						Treatment time	
			Systematic			Random				
			AP	LR	SI	AP	LR	SI		
Aubry 2004 [10]	7 (44)	MV EPID + FM	0.3	1.0	0.8	0.6	1.8	1.1	<5 min	Full bladder, empty rectum
Badakhshi 2013 [53]	13 (427)	kV EPID + FM	2.3	2.2	2.4	2.5	5.1	3.5	14.2 min	Full bladder, enema., head and knee support, foot restraint

CBCT, Cone Beam CT; CMO, Centre of Mass; EPID, Electronic portal imaging device; FM, fiducial marker; EM, Electromagnetic transponder.

particularly in relation to AP translation and rotation around the prostate apex [54,55,57,98–100].

This relationship has also been demonstrated with MRI. A small study of seven patients measured the prostate midpoint relative to bony anatomy on pre and post treatment MRI and found variation in rectal filling that correlated strongly with anterior displacement and a lesser correlation between bladder filling and superior motion [56]. A larger study of 42 patients used cine-MRI scans every nine seconds for nine minutes at baseline without any bowel preparation, before CT planning with bowel preparation and at a random point during RT with bowel preparation [58]. This demonstrated rectal gas and stool to be responsible for 74% of identified >3 mm prostate motion. Despite this voiding prior to imaging and bowel preparation did not significantly reduce intra-fraction motion.

Rectal diameter may have a threshold above which its effect on prostate motion becomes more significant. It has been suggested that maximum rectal diameters above 3.5–4.5 cm or mean cross sectional areas $\geqslant 9.5\ cm^2$ at planning imaging are predictive of significant variation in rectal size and prostate position during therapy [101–103].

The increased motion associated with initial large rectal volumes may also negatively influence treatment outcome. In one series of 127 patients those with a mean rectal cross sectional area greater than the group average of 11.2 cm^2 at the time of planning experienced greater biochemical failure rates (HR 3.89) and more toxicity from treatment [104]. Another study examined outcomes for 549 patients, stratified by anorectal volumes $\geqslant 90 cm^3$ at time of planning CT, and found that in patients with a risk of SV involvement >25% those with a larger rectal volume had a 15% reduction in freedom from failure at five years ($p = 0.01$) [105].

Various approaches such as diet modification, bowel regimens (enemas, laxatives, etc.) and immobilising endorectal balloons have been used in an attempt to reduce rectal variation. The evidence for efficacy of these techniques is mixed and a recent systematic review concluded that it was impossible to recommend one particular interventional strategy with further prospective studies required [106]. The use of effective daily image guidance may mitigate any effects of initial rectal distension.

Although the potential effect of rectal volume on prostate motion appears clear, the effects of changes in bladder volume appear at most to be minimal. Various studies have provided some limited evidence suggesting a weak relationship between the two [30,56,100,107] but other groups have failed to find any association [108–111]. It would therefore seem likely that simple bladder filling protocols are sufficient to minimise any bladder volume effects. However, for prone patients or patients with restricted abdominal movement, e.g. due to MR coils, bladder filling may affect prostate motion and such setups should be avoided.

Target delineation

Inter- and intra-operator variation in target delineation, particularly at the SV and apex, can be significant [49,112,113]. This is in part due to poor soft tissue definition on CT imaging making identification of the boundaries of the prostate challenging. It is known that CT delineated prostates are routinely larger than the true anatomical site. One study comparing the CT delineation by six

radiation oncologists with photographic anatomical images found that the contoured prostate was on average 30% larger that the true gland but only included 84% of its volume, such that posterior portions were always missed and anterior normal tissue always included [114]. MRI provides better distinction between adjacent soft tissue structures and has been shown to be superior at identifying the prostate apex, SV and posterior border (Supplement-Fig. 3). Multiple studies have demonstrated a reduction in volume of contoured prostate, of between 30% and 35% in the three largest series, when MR imaging is used to provide addition information for planning [115–117]. These reductions are primarily due to reduced variation at the superior and inferior extent of the prostate and translate into reductions in delivered dose to the rectum [117–120].

This improved soft tissue visualisation on MRI has also been shown to reduce intra- and inter-observer variation in prostate contouring (Supplement-Fig. 4) [115,121]. Using MRI in combination with an education programme it may be possible to reduce this inter-observer variation further [122]. A final benefit from use of MRI for prostate delineation comes from the reduced metal artefact degradation from prosthetic hips which may significantly affect CT imaging and subsequent contour consistency [123]. Good correspondence with MR imaging and prostatectomy specimens has been shown with a correlation coefficient of up to 0.86 [124,125].

Therefore it appears MR-based contouring of the prostate can be done more consistently and with higher fidelity than CT, leading to reduced treatment volumes and radiation to surrounding structures.

Recently work has focused on the use of multi-parametric (MP) MR to identify areas of high grade tumour within the prostate gland [126]. The use of modelling for voxelwise prediction of disease presence on MR imaging has been shown to have promise [127]. Confident identification provides the potential to focus dose intensification to this region, which may be the most likely site of ultimate disease recurrence [128]. MPMR guided targeted dose escalation is the subject of the ongoing phase III FLAME study and results are awaited with interest [129]. It has been shown that the dominant lesion within the prostate can be reliably identified on MP-MR but as yet data on how this region may be affected by prostatic deformation during therapy are scarce and requires future work [130]. In a study using collimator adjustments to account for prostate rotations, patients with and without focal boost were equally sensitive to rotations, indicating a limited effect of prostate rotations on boost dose [131].

Adaptive radiotherapy for inter-fraction motion

The current standard practice to manage inter-fraction variations is to use IGRT by repositioning the patient based on the rigid-body registration of the planning image and the image of the day acquired just before treatment, followed by delivery of the original (unchanged) plan. IGRT addresses the translational motions, including set-up errors, but cannot completely account for the organ deformation, rotation, and independent motion between different organs. The ideal method to fully account for the inter-fractional variations is to adapt the treatment plan based on the anatomy of the day. Such adaptive planning process may be performed in an online or offline manner [132,133]. The offline adaptive process, i.e. using the information from previous treatments to provide feedback for future deliveries, has been used to correct systematic, predictable variations [45,134,135].

Online adaptive radiotherapy (ART), on the other hand, is capable of addressing both systematic and random variations and is the most effective strategy for precisely irradiating concurrent targets that move independently. Online planning must be fast enough to be completed within a few minutes whilst the patient is lying on the table waiting for treatment. Although such fast planning is generally challenging using conventional planning technologies, adaptive re-planning does not need to start completely from scratch. For example, it can start with an initial plan fully optimised from the planning images for the same patient and adapt for the anatomy of the day ('warm start' optimisation). Technologies to facilitate this, such as the quality of in-room imaging, image registration and segmentation, plan optimisation algorithm and computing hardware, are advancing significantly and rapidly. For example, integration of diagnostic-quality MRI in the treatment room, graphic-processing unit (GPU) accelerated auto-segmentation and dose calculation, rapid plan modification algorithms, and plan adaptation based on previous knowledge or a previously-created plan library are among the technology advances that can speed up adaptive planning significantly. In particular, among a number of online planning algorithms [136–139], an online adaptive planning scheme [138] has been developed that features two distinct steps: a) segment aperture morphing (SAM), and b) segment weight optimisation (SWO), and has been used for prostate cancer [140]. It has been demonstrated that the online SAM + SWO scheme can adequately account for all inter-fraction variations and can be completed within 10 min for prostate RT [140]. Alternative techniques for ART of prostate cancer are reported [141–144] and reviewed previously [145,146].

With online ART, a CTV-PTV margin can reach as low as 3 mm, depending mainly on intra-fraction variations. Such a small margin would be highly desirable to reduce treatment-related toxicities and/or to allow dose escalation. Online ART is particularly important for hypo-fractionated RT or SBRT where the penalty of a geographical miss and/or over dosing of normal tissue for a single fraction is significant. However, with such small margins, target definition accuracy becomes much more critical to avoid the risk of compromising clinical outcome [147].

MRI-guided adaptive radiotherapy for inter- and intra-fractional motions

The high soft tissue contrast makes MRI an ideal imaging modality for online ART. MRI-guided RT delivery systems that integrate MR scanners with radiation delivery machines are being introduced into the clinic [148]. For example, ViewRay system (Oakwood Village, OH) combines a 0.35 T MRI scanner with three 60Co sources with multi-leaf collimators (MLC). Integration of a diagnostic MRI scanner with a Linac (MR-Linac) is also under development. The MR-Linac proposed by Lagendijk et al. at the University Medical Center Utrecht [149] that integrates a 1.5 T MRI scanner with a 6 MV Linac is being developed for commercialisation [7]. With CT based IGRT, image quality adversely affects the CTV-to-PTV margins required for targeting and ART, mainly due to the residual uncertainties from the soft-tissue contrast for the image modality [150]. It is anticipated that the residual uncertainty with diagnostic quality MRI will be drastically smaller than those with CT or CBCT, allowing a smaller CTV-to-PTV margin.

The design of the MR-Linac system comprises a 6 MV Linac (Elekta Inc) mounted on a ring around a modified 1.5 T MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands) and an online ART planning system [7]. The system is designed to be able to simultaneously image and irradiate the patient. The radiation beam is shaped by a 160-leaf MLC system and travels through the closed-bore MRI before it enters the patient. The accelerator and MRI are designed to be magnetically decoupled so that the MR images are not distorted by the presence of magnetised accelerator components, and the operation of the accelerator is not hampered by the magnetic field. A series of MR sequences can be

scanned to produce pre-, during- and post-treatment images. Once the MR-Linac is fully developed, the pre- and post-treatment MRI can include both morphological (T1, T2...) and functional (DWI, DCE, etc.) images. The during-treatment MRIs include cine MRI (2D), morphological 3D (e.g., T1, T2) and 4D images.

The online planning system integrated in the MR-Linac should be designed to generate an adaptive plan based on the pre-treatment MRI in the following steps: (1) deformably register the pre-treatment MRI with the planning images, (2) rapidly generate a plan by modifying or re-optimising the original plan or by fast adaptive re-planning to account for the different anatomy based on the registered images, and (3) quickly perform a software-based QA check on the new plan. To be successful the system should complete this 3-step online process within 5 min whilst the patient is still lying on the couch. Then, the new adaptive plan is delivered simultaneously with the during-treatment images acquired.

The MR-Linac system is designed to able to track/monitor organ (e.g., prostate gland) motion in real-time on 2D (cine) MRI during the radiation delivery. Because of superior soft tissue contrast, this tracking should be very accurate and effective. The radiation beam can be paused, via the capability of exception gating, if prostate motion is detected outside a pre-defined range, and can be resumed if the prostate moves back to the range. Alternatively, it is anticipated that with technical enhancements, the radiation beam may be dynamically shaped to trace the prostate motion detected from the cine MRI acquired on the plane perpendicular to the beam orientation. Either way, the intra-fractional variations can be managed effectively, thus the margin required to account for intra-fraction variation can be reduced.

The superior soft tissue contrast along with function/physiological information with MRI will significantly improve the performance and implementation of the online ART strategy (e.g., improved target definition, image registration, auto-segmentation). In addition, with the availability of real-time MR imaging during RT delivery to measure and monitor intra-fraction motion, the motion management techniques (gating or tracking) can be improved. With both inter- and intra-fractional variations being accounted for, the CTV-to-PTV margin may be safely reduced to $\leqslant$3 mm. Because the PTV often overlaps with rectum and bladder, such a drastic reduction in PTV margin should reduce toxicities or allow RT doses to be safely escalated to eradicate the tumour, thus improving treatment outcomes.

Conclusion

Extensive literature demonstrates that substantial inter- and intra-fractional variations occur in radiation therapy for prostate cancer. These variations include translational and rotational motions, deformations, and independent motions between the structures, and consist of both random and systematic components. Whilst the current standard practice of IGRT based on CT or CBCT can only address translational motion, adaptive radiotherapy has the potential to fully account for these variations. The superior soft-tissue contrast and the continuous imaging capability of MRI are highly desirable for the management of inter- and intra-fraction variations. Integration of MRI radiotherapy delivery and ART capability, such as with the MR-Linac, holds the promise to optimise radiotherapy to the prostate. Using this approach the improved delineation of target and OARs in both planning and delivery, will mean inter- and intra-fractional variations may be confidently accounted for, permitting use of a decreased CTV-to-PTV margin.

Source of funding

Not applicable.

Ethics committee approval

Not applicable.

Contribution of authors

McPartlin, Li, Tree, Choudhury contributed equally to the literature review, article selection and manuscript preparation.

Kershaw, van der Heide, Kerkmeijer, Lawton, Mahmood, van As, van Herk, Vesprini, and van der Voort van Zpy all reviewed the manuscript, contributed to its amended final form, and suggested additional references where appropriate.

Conflict of interest

Dr. Tree has received funding from Elekta for a Research Fellow. Elekta and Philips are members of the MR-linac Consortium. Elekta AB financially supports all MR-linac Consortium institutes.

Acknowledgements

Dr. van As and Dr Tree gratefully acknowledge the support of the Royal Marsden/Institute of Cancer NIHR Biomedical Research Centre.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2016.04.014.

References

[1] Kalbasi A, Li J, Berman A, Swisher-McClure S, Smaldone M, Uzzo RG, et al. Dose-escalated irradiation and overall survival in men with nonmetastatic prostate cancer. JAMA Oncol 2015.
[2] Wortel RC, Incrocci L, Pos FJ, Lebesque JV, Witte MG, van der Heide UA, et al. Acute toxicity after image-guided intensity modulated radiation therapy compared to 3D conformal radiation therapy in prostate cancer patients. Int J Radiat Oncol Biol Phys 2015;91:737–44.
[3] Kupelian P, Meyer JL. Image-guided, adaptive radiotherapy of prostate cancer: toward new standards of radiotherapy practice. Front Radiat Ther Oncol 2011;43:344–68.
[4] Eade TN, Hanlon AL, Horwitz EM, Buyyounouski MK, Hanks GE, Pollack A. What dose of external-beam radiation is high enough for prostate cancer? Int J Radiat Oncol Biol Phys 2007;68:682–9.
[5] 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.
[6] van Herk M. Errors and margins in radiotherapy. Semin Radiat Oncol 2004;14:52–64.
[7] Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, Overweg J, Brown KJ, Kerkhof EM, et al. MRI/linac integration. Radiother. Oncol 2008;86:25–9.
[8] Byrne TE. A review of prostate motion with considerations for the treatment of prostate cancer. Med Dosim 2005;30:155–61.
[9] Nederveen AJ, van der Heide UA, Dehnad H, van Moorselaar RJ, Hofman P, Lagendijk JJ. Measurements and clinical consequences of prostate motion during a radiotherapy fraction. Int J Radiat Oncol Biol Phys 2002;53:206–14.
[10] Aubry JF, Beaulieu L, Girouard LM, Aubin S, Tremblay D, Laverdiere J, et al. Measurements of intrafraction motion and interfraction and intrafraction rotation of prostate by three-dimensional analysis of daily portal imaging with radiopaque markers. Int J Radiat Oncol Biol Phys 2004;60:30–9.
[11] Letourneau D, Martinez AA, Lockman D, Yan D, Vargas C, Ivaldi G, et al. Assessment of residual error for online cone-beam CT-guided treatment of prostate cancer patients. Int J Radiat Oncol Biol Phys 2005;62:1239–46.
[12] Huang E, Dong L, Chandra A, Kuban DA, Rosen II, Evans A, et al. Intrafraction prostate motion during IMRT for prostate cancer. Int J Radiat Oncol Biol Phys 2002;53:261–8.
[13] Schallenkamp JM, Herman MG, Kruse JJ, Pisansky TM. Prostate position relative to pelvic bony anatomy based on intraprostatic gold markers and electronic portal imaging. Int J Radiat Oncol Biol Phys 2005;63:800–11.
[14] Kitamura K, Shirato H, Shimizu S, Shinohara N, Harabayashi T, Shimizu T, et al. Registration accuracy and possible migration of internal fiducial gold

marker implanted in prostate and liver treated with real-time tumor-tracking radiation therapy (RTRT). Radiother Oncol 2002;62:275–81.
[15] Kotte AN, Hofman P, Lagendijk JJ, van Vulpen M, van der Heide UA. Intrafraction motion of the prostate during external-beam radiation therapy: analysis of 427 patients with implanted fiducial markers. Int J Radiat Oncol Biol Phys 2007;69:419–25.
[16] Butler WM, Merrick GS, Reed JL, Murray BC, Kurko BS. Intrafraction displacement of prone versus supine prostate positioning monitored by real-time electromagnetic tracking. J Appl Clin Med Phys 2013;14:4141.
[17] Tanyi JA, He T, Summers PA, Mburu RG, Kato CM, Rhodes SM, et al. Assessment of planning target volume margins for intensity-modulated radiotherapy of the prostate gland: role of daily inter- and intrafraction motion. Int J Radiat Oncol Biol Phys 2010;78:1579–85.
[18] 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.
[19] Tong X, Chen X, Li J, Xu Q, Lin MH, Chen L, et al. Intrafractional prostate motion during external beam radiotherapy monitored by a real-time target localization system. J Appl Clin Med Phys 2015;16:5013.
[20] Shimizu S, Osaka Y, Shinohara N, Sazawa A, Nishioka K, Suzuki R, et al. Use of implanted markers and interportal adjustment with real-time tracking radiotherapy system to reduce intrafraction prostate motion. Int J Radiat Oncol Biol Phys 2011;81:e393–9.
[21] Ng JA, Booth JT, Poulsen PR, Fledelius W, Worm ES, Eade T, et al. Kilovoltage intrafraction monitoring for prostate intensity modulated arc therapy: first clinical results. Int J Radiat Oncol Biol Phys 2012;84:e655–61.
[22] Polat B, Guenther I, Wilbert J, Goebel J, Sweeney RA, Flentje M, et al. Intrafractional uncertainties in image-guided intensity-modulated radiotherapy (IMRT) of prostate cancer. Strahlenther Onkol 2008;184:668–73.
[23] Xie Y, Djajaputra D, King CR, Hossain S, Ma L, Xing L. Intrafractional motion of the prostate during hypofractionated radiotherapy. Int J Radiat Oncol Biol Phys 2008;72:236–46.
[24] Adamson J, Wu Q. Prostate intrafraction motion assessed by simultaneous kV fluoroscopy at MV delivery II: adaptive strategies. Int J Radiat Oncol Biol Phys 2010;78:1323–30.
[25] Ballhausen H, Li M, Hegemann NS, Ganswindt U, Belka C. Intra-fraction motion of the prostate is a random walk. Phys Med Biol 2015;60:549–63.
[26] Kron T, Thomas J, Fox C, Thompson A, Owen R, Herschtal A, et al. Intra-fraction prostate displacement in radiotherapy estimated from pre- and post-treatment imaging of patients with implanted fiducial markers. Radiother Oncol 2010;95:191–7.
[27] Mutanga TF, de Boer HC, Rajan V, Dirkx ML, Incrocci L, Heijmen BJ. Day-to-day reproducibility of prostate intrafraction motion assessed by multiple kV and MV imaging of implanted markers during treatment. Int J Radiat Oncol Biol Phys 2012;83:400–7.
[28] Quon H, Loblaw DA, Cheung PC, Holden L, Tang C, Pang G, et al. Intra-fraction motion during extreme hypofractionated radiotherapy of the prostate using pre- and post-treatment imaging. Clin Oncol 2012;24:640–5.
[29] Lin Y, Liu T, Yang W, Yang X, Khan MK. The non-Gaussian nature of prostate motion based on real-time intrafraction tracking. Int J Radiat Oncol Biol Phys 2013;87:363–9.
[30] Zelefsky MJ, Crean D, Mageras GS, Lyass O, Happersett L, Ling CC, et al. Quantification and predictors of prostate position variability in 50 patients evaluated with multiple CT scans during conformal radiotherapy. Radiother Oncol 1999;50:225–34.
[31] Stroom JC, Koper PC, Korevaar GA, van Os M, Janssen M, de Boer HC, et al. Internal organ motion in prostate cancer patients treated in prone and supine treatment position. Radiother Oncol 1999;51:237–48.
[32] Hoogeman MS, van Herk M, de Bois J, Lebesque JV. Strategies to reduce the systematic error due to tumor and rectum motion in radiotherapy of prostate cancer. Radiother Oncol 2005;74:177–85.
[33] de Boer HC, van Os MJ, Jansen PP, Heijmen BJ. Application of the No Action Level (NAL) protocol to correct for prostate motion based on electronic portal imaging of implanted markers. Int J Radiat Oncol Biol Phys 2005;61:969–83.
[34] Litzenberg DW, Balter JM, Hadley SW, Sandler HM, Willoughby TR, Kupelian PA, et al. Influence of intrafraction motion on margins for prostate radiotherapy. Int J Radiat Oncol Biol Phys 2006;65:548–53.
[35] Van den Heuvel F, Fugazzi J, Seppi E, Forman JD. Clinical application of a repositioning scheme, using gold markers and electronic portal imaging. Radiother Oncol 2006;79:94–100.
[36] O'Daniel JC, Dong L, Zhang L, de Crevoisier R, Wang H, Lee AK, et al. Dosimetric comparison of four target alignment methods for prostate cancer radiotherapy. Int J Radiat Oncol Biol Phys 2006;66:883–91.
[37] Soete G, De Cock M, Verellen D, Michielsen D, Keuppens F, Storme G. X-ray–assisted positioning of patients treated by conformal arc radiotherapy for prostate cancer: comparison of setup accuracy using implanted markers versus bony structures. Int J Radiat Oncol Biol Phys 2007;67:823–7.
[38] van der Heide UA, Kotte AN, Dehnad H, Hofman P, Lagenijk JJ, van Vulpen M. Analysis of fiducial marker-based position verification in the external beam radiotherapy of patients with prostate cancer. Radiother Oncol 2007;82:38–45.
[39] McNair HA, Hansen VN, Parker CC, Evans PM, Norman A, Miles E, et al. A comparison of the use of bony anatomy and internal markers for offline verification and an evaluation of the potential benefit of online and offline verification protocols for prostate radiotherapy. Int J Radiat Oncol Biol Phys 2008;71:41–50.
[40] Beltran C, Herman MG, Davis BJ. Planning target margin calculations for prostate radiotherapy based on intrafraction and interfraction motion using four localization methods. Int J Radiat Oncol Biol Phys 2008;70:289–95.
[41] Fiorino C, Di Muzio N, Broggi S, Cozzarini C, Maggiulli E, Alongi F, et al. Evidence of limited motion of the prostate by carefully emptying the rectum as assessed by daily MVCT image guidance with helical tomotherapy. Int J Radiat Oncol Biol Phys 2008;71:611–7.
[42] Bylund KC, Bayouth JE, Smith MC, Hass AC, Bhatia SK, Buatti JM. Analysis of interfraction prostate motion using megavoltage cone beam computed tomography. Int J Radiat Oncol Biol Phys 2008;72:949–56.
[43] Frank SJ, Dong L, Kudchadker RJ, De Crevoisier R, Lee AK, Cheung R, et al. Quantification of prostate and seminal vesicle interfraction variation during IMRT. Int J Radiat Oncol Biol Phys 2008;71:813–20.
[44] Mutanga TF, de Boer HC, van der Wielen GJ, Wentzler D, Barnhoorn J, Incrocci L, et al. Stereographic targeting in prostate radiotherapy: speed and precision by daily automatic positioning corrections using kilovoltage/megavoltage image pairs. Int J Radiat Oncol Biol Phys 2008;71:1074–83.
[45] Nijkamp J, Pos FJ, Nuver TT, de Jong R, Remeijer P, Sonke JJ, et al. Adaptive radiotherapy for prostate cancer using kilovoltage cone-beam computed tomography: first clinical results. Int J Radiat Oncol Biol Phys 2008;70:75–82.
[46] Su Z, Zhang L, Murphy M, Williamson J. Analysis of prostate patient setup and tracking data: potential intervention strategies. Int J Radiat Oncol Biol Phys 2011;81:880–7.
[47] Mayyas E, Chetty IJ, Chetvertkov M, Wen N, Neicu T, Nurushev T, et al. Evaluation of multiple image-based modalities for image-guided radiation therapy (IGRT) of prostate carcinoma: a prospective study. Med Phys 2013;40 041707.
[48] Oh YK, Baek JG, Kim OB, Kim JH. Assessment of setup uncertainties for various tumor sites when using daily CBCT for more than 2200 VMAT treatments. J Appl Clin Med Phys 2014;15 4418.
[49] Oehler C, Lang S, Dimmerling P, Bolesch C, Kloeck S, Tini A, et al. PTV margin definition in hypofractionated IGRT of localized prostate cancer using cone beam CT and orthogonal image pairs with fiducial markers. Radiat Oncol 2014;9:229.
[50] Li JS, Lin MH, Buyyounouski MK, Horwitz EM, Ma CM. Reduction of prostate intrafractional motion from shortening the treatment time. Phys Med Biol 2013;58:4921–32.
[51] Choi Y, Kwak DW, Lee HS, Hur WJ, Cho WY, Sung GT, et al. Effect of rectal enema on intrafraction prostate movement during image-guided radiotherapy. J Med Imaging Radiat Oncol 2015;59:236–42.
[52] Li JS, Jin L, Pollack A, Horwitz EM, Buyyounouski MK, Price Jr RA, et al. Gains from real-time tracking of prostate motion during external beam radiation therapy. Int J Radiat Oncol Biol Phys 2009;75:1613–20.
[53] Badakhshi H, Wust P, Budach V, Graf R. Image-guided radiotherapy with implanted markers and kilovoltage imaging and 6-dimensional position corrections for intrafractional motion of the prostate. Anticancer Res 2013;33:4117–21.
[54] 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.
[55] Mah D, Freedman G, Milestone B, Hanlon A, Palacio E, Richardson T, et al. Measurement of intrafractional prostate motion using magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2002;54:568–75.
[56] Villeirs GM, De Meerleer GO, Verstraete KL, De Neve WJ. Magnetic resonance assessment of prostate localization variability in intensity-modulated radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2004;60:1611–21.
[57] 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.
[58] Nichol AM, Brock KK, Lockwood GA, Moseley DJ, Rosewall T, Warde PR, et al. A magnetic resonance imaging study of prostate deformation relative to implanted gold fiducial markers. Int J Radiat Oncol Biol Phys 2007;67:48–56.
[59] Kerkhof EM, van der Put RW, Raaymakers BW, van der Heide UA, van Vulpen M, Lagendijk JJ. Variation in target and rectum dose due to prostate deformation: an assessment by repeated MR imaging and treatment planning. Phys Med Biol 2008;53:5623–34.
[60] Heijmink SW, Scheenen TW, van Lin EN, Visser AG, Kiemeney LA, Witjes JA, et al. Changes in prostate shape and volume and their implications for radiotherapy after introduction of endorectal balloon as determined by MRI at 3T. Int J Radiat Oncol Biol Phys 2009;73:1446–53.
[61] Vargas C, Saito AI, Hsi WC, Indelicato D, Falchook A, Zengm Q, et al. Cine-magnetic resonance imaging assessment of intrafraction motion for prostate cancer patients supine or prone with and without a rectal balloon. Am J Clin Oncol 2010;33:11–6.
[62] Dinkel J, Thieke C, Plathow C, Zamecnik P, Prum H, Huber PE, et al. Respiratory-induced prostate motion: characterization and quantification in dynamic MRI. Strahlenther Onkol 2011;187:426–32.
[63] Ogino I, Kaneko T, Suzuki R, Matsui T, Takebayashi S, Inoue T, et al. Rectal content and intrafractional prostate gland motion assessed by magnetic resonance imaging. J Radiat Res 2011;52:199–207.
[64] Terashima K, Nakamura K, Shioyama Y, Sasaki T, Ohga S, Nonoshita T, et al. Can a belly board reduce respiratory-induced prostate motion in the prone position?–assessed by cine-magnetic resonance imaging. Technol Cancer Res Treat 2013;12:447–53.
[65] 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.

[66] Shelton J, Rossi PJ, Chen H, Liu Y, Master VA, Jani AB. Observations on prostate intrafraction motion and the effect of reduced treatment time using volumetric modulated arc therapy. Pract Radiat Oncol 2011;1:243–50.
[67] Cramer AK, Haile AG, Ognjenovic S, Doshi TS, Reilly WM, Rubinstein KE, et al. Real-time prostate motion assessment: image-guidance and the temporal dependence of intra-fraction motion. BMC Med Phys 2013;13:4.
[68] Mansson Haska T, Honore H, Muren LP, Hoyer M, Poulsen PR. Intrafraction changes of prostate position and geometrical errors studied by continuous electronic portal imaging. Acta Oncol 2008;47:1351–7.
[69] Reggiori G, Mancosu P, Tozzi A, Cantone MC, Castiglioni S, Lattuada P, et al. Cone beam CT pre- and post-daily treatment for assessing geometrical and dosimetric intrafraction variability during radiotherapy of prostate cancer. J Appl Clin Med Phys 2011;12:3371.
[70] Curtis W, Khan M, Magnelli A, Stephans K, Tendulkar R, Xia P. Relationship of imaging frequency and planning margin to account for intrafraction prostate motion: analysis based on real-time monitoring data. Int J Radiat Oncol Biol Phys 2013;85:700–6.
[71] Steiner E, Georg D, Goldner G, Stock M. Prostate and patient intrafraction motion: impact on treatment time-dependent planning margins for patients with endorectal balloon. Int J Radiat Oncol Biol Phys 2013;86:755–61.
[72] van de Water S, Valli L, Aluwini S, Lanconelli N, Heijmen B, Hoogeman M. Intrafraction prostate translations and rotations during hypofractionated robotic radiation surgery: dosimetric impact of correction strategies and margins. Int J Radiat Oncol Biol Phys 2014;88:1154–60.
[73] Deurloo KE, Steenbakkers RJ, Zijp LJ, de Bois JA, Nowak PJ, Rasch CR, et al. Quantification of shape variation of prostate and seminal vesicles during external beam radiotherapy. Int J Radiat Oncol Biol Phys 2005;61:228–38.
[74] van der Wielen GJ, Mutanga TF, Incrocci L, Kirkels WJ, Vasquez Osorio EM, Hoogeman MS, et al. Deformation of prostate and seminal vesicles relative to intraprostatic fiducial markers. Int J Radiat Oncol Biol Phys 2008;72:e3.
[75] Mayyas E, Kim J, Kumar S, Liu C, Wen N, Movsas B, et al. A novel approach for evaluation of prostate deformation and associated dosimetric implications in IGRT of the prostate. Med Phys 2014;41 091709.
[76] Khoo VS, Bedford JL, Padhani AR, Leach M, Husband JE, Dearnaley D. Prostate and rectal deformation assessed using cine magnetic resonance imaging (MRI) during a course of radical prostate radiotherapy. Radiother Oncol 2002;64:S285.
[77] Frank SJ, Kudchadker RJ, Kuban DA, De Crevoisier R, Lee AK, Cheung RM, et al. A volumetric trend analysis of the prostate and seminal vesicles during a course of intensity-modulated radiation therapy. Am J Clin Oncol 2010;33:173–5.
[78] Roeske JC, Forman JD, Mesina CF, He T, Pelizzari CA, Fontenla E, et al. Evaluation of changes in the size and location of the prostate, seminal vesicles, bladder, and rectum during a course of external beam radiation therapy. Int J Radiat Oncol Biol Phys 1995;33:1321–9.
[79] Tinger A, Michalski JM, Cheng A, Low DA, Zhu R, Bosch WR, et al. A critical evaluation of the planning target volume for 3-D conformal radiotherapy of prostate cancer. Int J Radiat Oncol Biol Phys 1998;42:213–21.
[80] Kasaova L, Sirak I, Jansa J, Paluska P, Petera J. Daily prostate volume and position monitoring using implanted gold markers and on-board imaging during radiotherapy. Acta Medica 2011;54:149–52.
[81] Boda-Heggemann J, Kohler F, Wertz H, Welzel G, Riesenacker N, Schafer J, et al. Fiducial-based quantification of prostate tilt using cone beam computer tomography (CBCT). Radiother Oncol 2007;85:247–50.
[82] Huang CY, Tehrani JN, Ng JA, Booth J, Keall P. Six degrees-of-freedom prostate and lung tumor motion measurements using kilovoltage intrafraction monitoring. Int J Radiat Oncol Biol Phys 2015;91:368–75.
[83] Amro H, Hamstra DA, McShan DL, Sandler H, Vineberg K, Hadley S, et al. The dosimetric impact of prostate rotations during electromagnetically guided external-beam radiation therapy. Int J Radiat Oncol Biol Phys 2013;85:230–6.
[84] Dehnad H, Nederveen AJ, van der Heide UA, van Moorselaar RJ, Hofman P, Lagendijk JJ. Clinical feasibility study for the use of implanted gold seeds in the prostate as reliable positioning markers during megavoltage irradiation. Radiother Oncol 2003;67:295–302.
[85] Mutanga TF, de Boer HC, van der Wielen GJ, Hoogeman MS, Incrocci L, Heijmen BJ. Margin evaluation in the presence of deformation, rotation, and translation in prostate and entire seminal vesicle irradiation with daily marker-based setup corrections. Int J Radiat Oncol Biol Phys 2011;81:1160–7.
[86] Graf R, Boehmer D, Budach V, Wust P. Interfraction rotation of the prostate as evaluated by kilovoltage X-ray fiducial marker imaging in intensity-modulated radiotherapy of localized prostate cancer. Med Dosim 2012;37:396–400.
[87] Smeenk RJ, Louwe RJ, Langen KM, Shah AP, Kupelian PA, van Lin EN, et al. An endorectal balloon reduces intrafraction prostate motion during radiotherapy. Int J Radiat Oncol Biol Phys 2012;83:661–9.
[88] Eifler JB, Feng Z, Lin BM, Partin MT, Humphreys EB, Han M, et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. BJU Int 2013;111:22–9.
[89] Kestin L, Goldstein N, Vicini F, Yan D, Korman H, Martinez A. Treatment of prostate cancer with radiotherapy: should the entire seminal vesicles be included in the clinical target volume? Int J Radiat Oncol Biol Phys 2002;54:686–97.
[90] Stenmark MH, Vineberg K, Ten Haken RK, Hamstra DA, Feng M. Dosimetric implications of residual seminal vesicle motion in fiducial-guided intensity-modulated radiotherapy for prostate cancer. Med Dosim 2012;37:240–4.
[91] Mak D, Gill S, Paul R, Stillie A, Haworth A, Kron T, et al. Seminal vesicle interfraction displacement and margins in image guided radiotherapy for prostate cancer. Radiat Oncol 2012;7:139.
[92] Fleshner NE, O'Sullivan M, Premdass C, Fair WR. Clinical significance of small (less than 0.2 cm3) hypoechoic lesions in men with normal digital rectal examinations and prostate-specific antigen levels less than 10 ng/mL. Urology 1999;53:356–8.
[93] Dawson LA, Mah K, Franssen E, Morton G. Target position variability throughout prostate radiotherapy. Int J Radiat Oncol Biol Phys 1998;42:1155–61.
[94] Liang J, Wu Q, Yan D. The role of seminal vesicle motion in target margin assessment for online image-guided radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2009;73:935–43.
[95] van der Burgt M, Bergsma L, de Vries J, Pos FJ, Kalisvaart R, Heemsbergen W, et al. Impact of tumour invasion on seminal vesicles mobility in radiotherapy of prostate cancer. Radiother Oncol 2015.
[96] Ten Haken RK, Forman JD, Heimburger DK, Gerhardsson A, McShan DL, Perez-Tamayo C, et al. Treatment planning issues related to prostate movement in response to differential filling of the rectum and bladder. Int J Radiat Oncol Biol Phys 1991;20:1317–24.
[97] Schild SE, Casale HE, Bellefontaine LP. Movements of the prostate due to rectal and bladder distension: implications for radiotherapy. Med Dosim 1993;18:13–5.
[98] Crook JM, Raymond Y, Salhani D, Yang H, Esche B. Prostate motion during standard radiotherapy as assessed by fiducial markers. Radiother Oncol 1995;37:35–42.
[99] van Herk M, Bruce A, Kroes AP, Shouman T, Touw A, Lebesque JV. Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration. Int J Radiat Oncol Biol Phys 1995;33:1311–20.
[100] Adamson J, Wu Q. Inferences about prostate intrafraction motion from pre- and posttreatment volumetric imaging. Int J Radiat Oncol Biol Phys 2009;75:260–7.
[101] Pinkawa M, Siluschek J, Gagel B, Demirel C, Asadpour B, Holy R, et al. Influence of the initial rectal distension on posterior margins in primary and postoperative radiotherapy for prostate cancer. Radiother Oncol 2006;81:284–90.
[102] Oates R, Gill S, Foroudi F, Joon ML, Schneider M, Bressel M, et al. What benefit could be derived from on-line adaptive prostate radiotherapy using rectal diameter as a predictor of motion? J Med Phys 2015;40:18–23.
[103] Engels B, Tournel K, Soete G, Storme G. Assessment of rectal distention in radiotherapy of prostate cancer using daily megavoltage CT image guidance. Radiother Oncol 2009;90:377–81.
[104] de Crevoisier R, Tucker SL, Dong L, Mohan R, Cheung R, Cox JD, et al. Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy. Int J Radiat Oncol Biol Phys 2005;62:965–73.
[105] Heemsbergen WD, Hoogeman MS, Witte MG, Peeters ST, Incrocci L, Lebesque JV. Increased risk of biochemical and clinical failure for prostate patients with a large rectum at radiotherapy planning: results from the Dutch trial of 68 GY versus 78 Gy. Int J Radiat Oncol Biol Phys 2007;67:1418–24.
[106] McNair HA, Wedlake L, Lips IM, Andreyev J, Van Vulpen M, Dearnaley D. A systematic review: effectiveness of rectal emptying preparation in prostate cancer patients. Pract Radiat Oncol 2014;4:437–47.
[107] Melian E, Mageras GS, Fuks Z, Leibel SA, Niehaus A, Lorant H, et al. Variation in prostate position quantitation and implications for three-dimensional conformal treatment planning. Int J Radiat Oncol Biol Phys 1997;38:73–81.
[108] Pinkawa M, Asadpour B, Gagel B, Piroth MD, Holy R, Eble MJ. Prostate position variability and dose-volume histograms in radiotherapy for prostate cancer with full and empty bladder. Int J Radiat Oncol Biol Phys 2006;64:856–61.
[109] Beard CJ, Kijewski P, Bussiere M, Gelman R, Gladstone D, Shaffer K, et al. Analysis of prostate and seminal vesicle motion: implications for treatment planning. Int J Radiat Oncol Biol Phys 1996;34:451–8.
[110] Antolak JA, Rosen II, Childress CH, Zagars GK, Pollack A. Prostate target volume variations during a course of radiotherapy. Int J Radiat Oncol Biol Phys 1998;42:661–72.
[111] Moiseenko V, Liu M, Kristensen S, Gelowitz G, Berthelet E. Effect of bladder filling on doses to prostate and organs at risk: a treatment planning study. J Appl Clin Med Phys 2007;8:2007.
[112] Fiorino C, Reni M, Bolognesi A, Cattaneo GM, Calandrino R. Intra- and inter-observer variability in contouring prostate and seminal vesicles: implications for conformal treatment planning. Radiother Oncol 1998;47:285–92.
[113] Cazzaniga LF, Marinoni MA, Bossi A, Bianchi E, Cagna E, Cosentino D, et al. Interphysician variability in defining the planning target volume in the irradiation of prostate and seminal vesicles. Radiother Oncol 1998;47:293–6.
[114] Gao Z, Wilkins D, Eapen L, Morash C, Wassef Y, Gerig L. A study of prostate delineation referenced against a gold standard created from the visible human data. Radiother Oncol 2007;85:239–46.
[115] Rasch C, Barillot I, Remeijer P, Touw A, van Herk M, Lebesque JV. Definition of the prostate in CT and MRI: a multi-observer study. Int J Radiat Oncol Biol Phys 1999;43:57–66.
[116] Hentschel B, Oehler W, Strauss D, Ulrich A, Malich A. Definition of the CTV prostate in CT and MRI by using CT-MRI image fusion in IMRT planning for prostate cancer. Strahlenther Onkol 2011;187:183–90.
[117] Tanaka H, Hayashi S, Ohtakara K, Hoshi H, Iida T. Usefulness of CT-MRI fusion in radiotherapy planning for localized prostate cancer. J Radiat Res 2011;52:782–8.

[118] Debois M, Oyen R, Maes F, Verswijvel G, Gatti G, Bosmans H, et al. The contribution of magnetic resonance imaging to the three-dimensional treatment planning of localized prostate cancer. Int J Radiat Oncol Biol Phys 1999;45:857–65.
[119] Sannazzari GL, Ragona R, Ruo Redda MG, Giglioli FR, Isolato G, Guarneri A. CT-MRI image fusion for delineation of volumes in three-dimensional conformal radiation therapy in the treatment of localized prostate cancer. Br J Radiol 2002;75:603–7.
[120] Jackson AS, Reinsberg SA, Sohaib SA, Charles-Edwards EM, Mangar SA, South CP, et al. Distortion-corrected T2 weighted MRI: a novel approach to prostate radiotherapy planning. Br J Radiol 2007;80:926–33.
[121] Parker CC, Damyanovich A, Haycocks T, Haider M, Bayley A, Catton CN. Magnetic resonance imaging in the radiation treatment planning of localized prostate cancer using intra-prostatic fiducial markers for computed tomography co-registration. Radiother Oncol 2003;66:217–24.
[122] Khoo EL, Schick K, Plank AW, Poulsen M, Wong WW, Middleton M, et al. Prostate contouring variation: can it be fixed? Int J Radiat Oncol Biol Phys 2012;82:1923–9.
[123] Rosewall T, Kong V, Vesprini D, Catton C, Chung P, Menard C, et al. Prostate delineation using CT and MRI for radiotherapy patients with bilateral hip prostheses. Radiother Oncol 2009;90:325–30.
[124] Sosna J, Rofsky NM, Gaston SM, DeWolf WC, Lenkinski RE. Determinations of prostate volume at 3-tesla using an external phased array coil: comparison to pathologic specimens1. Acad Radiol 2003;10:846–53.
[125] Jeong CW, Park HK, Hong SK, Byun SS, Lee HJ, Lee SE. Comparison of prostate volume measured by transrectal ultrasonography and MRI with the actual prostate volume measured after radical prostatectomy. Urol Int 2008;81:179–85.
[126] Barentsz JO, Weinreb JC, Verma S, Thoeny HC, Tempany CM, Shtern F, et al. Synopsis of the PI-RADS v2 guidelines for multiparametric prostate magnetic resonance imaging and recommendations for use. Eur Urol 2016;69:41–9.
[127] Groenendaal G, Borren A, Moman MR, Monninkhof E, van Diest PJ, Philippens ME, et al. Pathologic validation of a model based on diffusion-weighted imaging and dynamic contrast-enhanced magnetic resonance imaging for tumor delineation in the prostate peripheral zone. Int J Radiat Oncol Biol Phys 2012;82:e537–44.
[128] Cellini N, Morganti AG, Mattiucci GC, Valentini V, Leone M, Luzi S, et al. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: implications for conformal therapy planning. Int J Radiat Oncol Biol Phys 2002;53:595–9.
[129] Lips IM, van der Heide UA, Haustermans K, van Lin EN, Pos F, Franken SP, et al. Single blind randomized phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial. Trials 2011;12:255.
[130] Steenbergen P, Haustermans K, Lerut E, Oyen R, De Wever L, Van den Bergh L, et al. Prostate tumor delineation using multiparametric magnetic resonance imaging: Inter-observer variability and pathology validation. Radiother Oncol 2015;115:186–90.
[131] de Boer J, Wolf AL, Szeto YZ, van Herk M, Sonke JJ. Dynamic collimator angle adjustments during volumetric modulated arc therapy to account for prostate rotations. Int J Radiat Oncol Biol Phys 2015;91:1009–16.
[132] Yan D, Lockman D, Martinez A, Wong J, Brabbins D, Vicini F, et al. Computed tomography guided management of interfractional patient variation. Semin Radiat Oncol 2005;15:168–79.
[133] Li XA. Adaptive radiation therapy. CRC Press; 2011.
[134] Yan D, Lockman D, Brabbins D, Tyburski L, Martinez A. An off-line strategy for constructing a patient-specific planning target volume in adaptive treatment process for prostate cancer. Int J Radiat Oncol Biol Phys 2000;48:289–302.
[135] Birkner M, Yan D, Alber M, Liang J, Nusslin F. Adapting inverse planning to patient and organ geometrical variation: algorithm and implementation. Med Phys 2003;30:2822–31.
[136] Court LE, Dong L, Lee AK, Cheung R, Bonnen MD, O'Daniel J, et al. An automatic CT-guided adaptive radiation therapy technique by online modification of multileaf collimator leaf positions for prostate cancer. Int J Radiat Oncol Biol Phys 2005;62:154–63.
[137] Mohan R, Zhang X, Wang H, Kang Y, Wang X, Liu H, et al. Use of deformed intensity distributions for on-line modification of image-guided IMRT to account for interfractional anatomic changes. Int J Radiat Oncol Biol Phys 2005;61:1258–66.
[138] Ahunbay EE, Peng C, Chen GP, Narayanan S, Yu C, Lawton C, et al. An on-line replanning scheme for interfractional variations. Med Phys 2008;35:3607–15.
[139] Ludlum E, Mu G, Weinberg V, Roach 3rd M, Verhey LJ, Xia P. An algorithm for shifting MLC shapes to adjust for daily prostate movement during concurrent treatment with pelvic lymph nodes. Med Phys 2007;34:4750–6.
[140] Ahunbay EE, Peng C, Holmes S, Godley A, Lawton C, Li XA. Online adaptive replanning method for prostate radiotherapy. Int J Radiat Oncol Biol Phys 2010;77:1561–72.
[141] Qin A, Sun Y, Liang J, Yan D. Evaluation of online/offline image guidance/adaptation approaches for prostate cancer radiation therapy. Int J Radiat Oncol Biol Phys 2015;91:1026–33.
[142] Stanley K, Eade T, Kneebone A, Booth JT. Investigation of an adaptive treatment regime for prostate radiation therapy. Pract Radiat Oncol 2015;5:e23–9.
[143] Li X, Quan EM, Li Y, Pan X, Zhou Y, Wang X, et al. A fully automated method for CT-on-rails-guided online adaptive planning for prostate cancer intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 2013;86:835–41.
[144] Park SS, Yan D, McGrath S, Dilworth JT, Liang J, Ye H, et al. Adaptive image-guided radiotherapy (IGRT) eliminates the risk of biochemical failure caused by the bias of rectal distension in prostate cancer treatment planning: clinical evidence. Int J Radiat Oncol Biol Phys 2012;83:947–52.
[145] Ghilezan M, Yan D, Martinez A. Adaptive radiation therapy for prostate cancer. Semin Radiat Oncol 2010;20:130–7.
[146] Li XA, Wu Q, Orton CG. Point/Counterpoint. Online adaptive planning for prostate cancer radiotherapy is necessary and ready now. Med Phys 2014;41:080601.
[147] Engels B, Soete G, Verellen D, Storme G. Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted markers. Int J Radiat Oncol Biol Phys 2009;74:388–91.
[148] Mutic S, Dempsey JF. The ViewRay system: magnetic resonance-guided and controlled radiotherapy. Semin Radiat Oncol 2014;24:196–9.
[149] Lagendijk JJ, Raaymakers BW, van Vulpen M. The magnetic resonance imaging-linac system. Semin Radiat Oncol 2014;24:207–9.
[150] Morrow NV, Lawton CA, Qi XS, Li XA. Impact of computed tomography image quality on image-guided radiation therapy based on soft tissue registration. Int J Radiat Oncol Biol Phys 2012;82:e733–8.