Radiotherapy and Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review

MRI-guided prostate adaptive radiotherapy – A systematic review

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ARTICLE INFO

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

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.

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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

Please cite this article in press as: McPartlin AJ et al. MRI-guided prostate adaptive radiotherapy – A systematic review. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.04.014