Mini-review

Magnetic Resonance Imaging Guidance in High-Dose Rate Prostate Brachytherapy: Will Radiation Dose Delivery Be More Accurate?

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Abstract

High-dose rate (HDR) brachytherapy has been established as an effective treatment modality for localized prostate cancer in any risk category. Magnetic resonance imaging (MRI) is increasingly used in HDR brachytherapy procedures of image-guided prostate biopsy, treatment target delineation, catheter insertion, and treatment planning. MRI is superior in soft-tissue contrast than other imaging modalities thus enables easy identification of the prostate gland and the treatment target. Highly conformal treatment plan can be achieved with MRI guidance for the whole prostate gland or focal boost HDR brachytherapy. The application of MRI in HDR prostate brachytherapy has demonstrated reasonable potentials; however, attention should be paid to catheter displacement and anatomy changes that may cause adverse dosimetric impacts during treatment delivery.

Keywords: prostate cancer, high-dose rate brachytherapy, magnetic resonance imaging

Introduction

Prostate cancer is the most common malignancy in man and the second leading cause of cancer-related deaths among men in the United States [1]. Standard local treatments for prostate cancer include radical prostatectomy, external beam radiotherapy (EBRT), and brachytherapy. Radical prostatectomy is associated with decreased overall mortality in patients with intermediate risk, and the role of EBRT has been established for patients with high-risk or locally advanced disease [2]. Brachytherapy, radiation dose delivery at a short distance with sealed radioactive sources, is an important treatment option for appropriately selected men with non-metastatic prostate cancer. Brachytherapy is used as monotherapy or in combination with EBRT [3-5]. In men with intermediate and high-risk prostate cancer, brachytherapy may serve as a dose escalation tool to achieve radiobiological advantages. Studies have demonstrated that compared with EBRT alone, combined EBRT and brachytherapy improved biochemical control outcomes [6].

One advantage of brachytherapy over external beam radiotherapy is that the prescribed radiation dose is localized to the target volume, beyond which the radiation dose decreases rapidly. This characteristic allows for highly conformal target dose distribution as well as normal tissue sparing. Brachytherapy made remarkable progress in the
past few decades. In the recent years, high-dose rate (HDR) brachytherapy that delivers radiation dose at a rate of >12 Gy/hr with $^{192}$Iridium source has been proven to be effective for localized prostate cancer treatment [7]. The American Brachytherapy Society consensus guidelines for HDR prostate brachytherapy consider this modality an excellent option for the definitive treatment of localized prostate cancer in any risk category, with only a few contraindications [8]. HDR prostate brachytherapy has a variety of fractionation schedules, ranging from 12 Gy × 2 to 6 Gy × 9 for monotherapy and from 15 Gy × 1 to 6 Gy × 4 for boost after EBRT [8]. An HDR prostate brachytherapy procedure can be completed within a single day, or up to five days [9].

Compared with EBRT and low-dose rate (LDR) brachytherapy, HDR prostate brachytherapy has its strength as well as limitations. Brachytherapy is a complex procedure and demands physician's proficient skills which can only be obtained through specialized training and upkeep. Both HDR and LDR prostate brachytherapy procedures are invasive and require either spinal anesthesia or general anesthesia. HDR patients may have to stay in the hospital overnight. In contrast, EBRT is an outpatient procedure. In LDR prostate brachytherapy, the implanted seeds produce low levels of radiation outside of patient for weeks, but HDR does not have this issue. Also, HDR does not have the concern of radioactive seed migration. Based on the alpha/beta ratio for prostate cancer reported so far [10,11], alpha/beta is around 1.4 to 1.8. This indicates that prostate cancer is more sensitive to high dose per treatment fraction, which in turn favors HDR to LDR. HDR plans have more flexibility to achieve optimized dose distribution than LDR [12].

Contemporary brachytherapy has incorporated morphologic imaging modalities into its workflow [13]. These modalities include computed tomography (CT) as well as ultrasound and magnetic resonance imaging (MRI). A number of MRI techniques are available for prostate imaging [14]. High-resolution T2-weighted imaging allows detection, localization, and staging of prostate cancer. It can be combined with functional sequences such as diffusion-weighted imaging, dynamic contrast-enhanced MRI, and MR spectroscopic imaging [15]. MRI is increasingly used in image-guided biopsy, treatment target delineation, catheter insertion, and treatment planning for prostate cancer treatment.

The nature of brachytherapy requires highly spatially accurate dose delivery. Studies have shown that applicator instability and organ variations are among the major clinical uncertainties in brachytherapy. For prostate malignancies, brachytherapy source positioning relative to the target and organs-at-risk (OAR’s) is considered the main source of dosimetry uncertainty besides contouring uncertainties [16]. In this manuscript, we briefly review the application of MRI guidance in the prostate HDR brachytherapy workflow, and the factors that may potentially cause adverse dosimetric consequences.

**MRI in HDR Prostate Brachytherapy**

In a series of 40 patients with intermediate- or high-risk prostate cancer, Murgic et al. performed MRI guided HDR brachytherapy [17]. This prospective clinical trial showed that MRI-only HDR brachytherapy workflow was feasible for prostate boost combined with EBRT. Among these patients, 14 were found to have a higher stage of disease than based on digitorectal examination or transrectal ultrasound (TRUS). The authors reported that the median duration of the interventional procedure was 100 minutes, and the median overall anesthesia time was 4 hours.

In a study to evaluate the long-term outcomes of MRI-guided HDR brachytherapy boost, 20 patients with intermediate-risk prostate cancer underwent multiparametric MRI and MR spectroscopy with which the dominant intraprostatic lesions (DIL’s) were identified [18]. After 40 Gy of EBRT treatment, these patients received a single fraction HDR brachytherapy boost of 15 Gy to the whole prostate gland and the DIL defined on the multiparametric
MRI findings was boosted to 18 Gy. This study showed that HDR brachytherapy boost to the DIL was feasible and good long-term outcomes in terms of tumor control and toxicity could be achieved [18]. A prospective multi-institutional trial, RTOG 0321, also showed the feasibility of CT-based HDR brachytherapy and external beam radiotherapy. In this trial, patients from 14 institutions were treated with 45 Gy in 25 fractions using external beam radiotherapy and HDR implant of 19 Gy in two fractions. The preliminary results of this trial demonstrated an acceptable level of adverse events [19].

Diffusion-weighted imaging can provide high image contrast between normal and malignant prostate tissue [20]. In a prospective phase II clinical trial, DIL’s were segmented in multiparametric MRI. These lesions received dose escalation of 18.75 Gy, while the rest of the prostate was treated to 15 Gy with HDR brachytherapy followed by EBRT to a dose of 37.5 Gy [20].

**Target Identification and Treatment Planning**

Favorable outcome of prostate HDR brachytherapy depends on accurate staging and tumor delineation. Conventional staging strategies include digital rectal examination, prostate-specific antigen, random systematic biopsies, CT and bone scan. These approaches are known to underestimate the disease burden and location in 20%-30% of patients [21]. TRUS-guided biopsy was considered gold standard for prostate cancer detection. However, this approach suffers low sensitivity (39%-52%) although the specificity is high [22].

Multiparametric MRI of the prostate is able to overcome some limitations of the conventional approaches. For example, seminal vesicles are readily visible in T2-weighted MRI sequences and their evaluations for tumor invasion are nearly 100% sensitivity and specificity [23]. Prostate cancer has a variety of appearances on multiparametric MRI depending on lesion location, size, and aggressiveness [14]. MRI allows for better visualization of prostate cancer, and studies show higher overall detection with MRI-guided biopsy than ultrasound-guided biopsy [24]. A number of MRI-guided biopsy systems have been developed for the prostate [25]. The MRI-guided prostate biopsy is usually performed on a different image dataset from the diagnostic MRI. This causes longer procedure time and additional expenses.

Alternatively, the fusion of MR and TRUS images is utilized in prostate biopsy for brachytherapy planning. The MRI-ultrasound fusion technique does not require interventional procedures in MR imaging room, thus saves costs and allows for quicker turnover [26]. Several devices have been approved by the United States Food and Drug Administration for the purpose of MRI-ultrasound fusion guided prostate biopsy [26]. These devices use rigid or elastic image fusion mechanisms. Prostate is segmented in the MRI, and real-time ultrasound generates 3D ultrasound model of the prostate. Systematic and targeted prostate biopsies are obtained with the fused images being used to determine the location of biopsy cores. In a retrospective analysis of 649 patients who had a median prostate specific antigen of 6.65 ng/ml, MR-ultrasound fusion biopsy was shown to have a higher prostate cancer detection rate than that of TRUS-guided biopsy in the literature [27].

TRUS has been used to guide needle insertion and treatment planning [28], and now it is considered the standard care for image-guided HDR prostate brachytherapy planning [29]. Even though, uncertainties remain at the anterior gland because the inserted catheters create echogenic artifacts. Digitization of catheters, especially catheter tips, becomes more challenging in ultrasound than in CT image. Zheng and Todor developed a method to identify needle tip position on the TRUS images based on the physical measurements of the residual needle length. This method could achieve an average needle tip detection accuracy of 0.7 mm, compared with 1.6 mm of the conventional method [30]. In MRI guided HDR prostate brachytherapy planning, uncertainties still exist in the digitization of catheters. In a clinical series, 296 of 313 catheter tips defined in MRI by an independent observer were reported to be
within 1.5 mm of the initial intraoperative catheter reconstruction. However, more than 2.5 mm differences were observed for 6 catheters [31].

MRI-guided HDR brachytherapy was shown to be a feasible monotherapy for intraprostatic lesions [32]. In this trial, the prostate and intraprostatic lesion were contoured in multiparametric MRI, which was deformably registered with post catheter insertion planning MRI. Dose escalation could be achieved for MRI-defined target volumes while the OAR dose constraints were maintained [32].

During the HDR prostate brachytherapy treatment planning process, it should be noted that MRI may underestimate the histologically determined tumor boundaries. Le Nobin et al. observed in 33 patients that MRI underestimated tumor size with 2 mm average maximum discrepancy between imaging and histological boundaries [33]. Thus a 9 mm treatment margin was needed to achieve complete histological tumor destruction in all of those patients. Anwar et al. reported similar results in 16 patients and they recommended a 5 mm non-capsular margin to achieve adequate tumor coverage [34].

### Catheter Displacement

In HDR prostate brachytherapy, catheters remain in the target volume throughout the procedures and their displacement is a major concern. Needle displacement has been a persisting issue since the early implementation of HDR prostate brachytherapy. In a series of 96 patients, measurements with radiographic films showed that mean overall needle displacement was over 1.3 cm during a course of 4-fraction treatment, with a maximum of 4.7 cm [35]. Mullokandov and Gejerman found in 50 patients that, the template-catheter unit moved by increasing distances in caudal direction between HDR fractions, although they did not observe interfraction catheter movement relative to the template [36]. Other investigators also reported similar observation [37]. However, it was noted in a study that a few catheters displaced by different distances [35].

A Netherlands group reported the use of plastic irradiation catheters with a foldable umbrella in HDR prostate brachytherapy procedure [31]. The foldable umbrella functions as an anchoring mechanism so that the catheters could be fixed within the prostate tissue to limit unintended catheter displacements [38]. These catheters were inserted into the prostate guided by ultrasound fused with diagnostic MRI. In patients treated with a single fraction of 19 Gy, post-treatment MRI revealed that the average caudal displacements of 241 umbrella catheters was 0.9 mm with a few catheters having >4 mm overall displacements [31].

Because of the steep dose falloff outside the target volume, displacements of needles or catheters may result in unacceptable dosimetric consequences. Tiong et al. performed a dosimetric study using simulated interstitial catheter displacements of 3, 6, 9, and 12 mm in 20 patients. The results showed that catheter displacements in HDR prostate brachytherapy significantly compromised the tumor control probability. They recommended a tolerance of ≤3 mm for catheter displacements [39]. In a study of 15 patients, mean interfraction catheter displacement of 5.1 mm was observed with the comparison between planning CT and interfraction cone-beam CT. The mean prostate V100 decreased from 93.8% to 76.2% due to catheter displacement, which also caused other adverse impacts such as unacceptable OAR dose [40]. In another series of 22 patients, implanted flexible catheters had a mean displacement of 12.6 mm in the caudal direction over a course of 20 hours, with a range of 0.6 mm to 24.5 mm [41]. It was proposed that tissue swelling due to hemorrhage and edema caused these displacement [42].

The consequences of catheter displacement should be corrected by re-optimization [40], catheter re-implantation, or image guided catheter re-adjustment. In 20 patients who received single-fraction prostate HDR brachytherapy, Holly et al. observed mean catheter displacement of 11 mm between the treatment planning CT and pre-treatment cone-beam CT, which was subsequently adjusted under image guidance [37]. Kovalchuk et al.
performed needle adjustment between two fractions by -1.4 to 1.3 cm with CT guidance. They found that without replanning for the subsequent fractions, even needle displacements less than 3 mm or prostate volume changes less than 3 cc would result in suboptimal dose distribution [43]. In a recent study, Buss et al. measured needle migration in 24 high-risk prostate cancer patients treated with 2 × 8.5 Gy HDR boost using planning, pre-treatment, and post-treatment MRI. They observed an average needle migration of 2.2 ± 1.8 mm between planning and pre-treatment MRI, and 5.0 ± 3.0 mm between planning and post-treatment MRI. Based on dosimetric impact of needle migration, a 3-mm threshold of needle migration was proposed, but 2 mm was suggested for dose levels ≥ 15 Gy [44].

Prostate Swelling

Prostate swelling is a well-known fact in permanent prostate seed implant that may result in target dose coverage reduction. Although prostate volume changes are often considered irrelevant in HDR brachytherapy procedures [45], prostate swelling after catheter insertion may cause radial catheter displacement relative to the prostate contour. These changes have been observed by clinicians, but systematic dosimetry studies based on MRI are relatively sparse. The Netherlands group reported average radial catheter displacements of 0.6 mm and 0.5 mm in x- and y-directions in single-fraction HDR brachytherapy [31]. Another group reported an average increase of 8.9% in prostate volume measured by MRI over an interval of 135 min during 16 HDR brachytherapy procedures [46]. In addition to an average caudal displacement of 1 mm, the catheters were pushed centrifugally from the axis of the urethra. This increase in distance between the catheters was in consistent with the observed dosimetric impacts. Specifically, there was reduction in dose coverage for both prostate and planning volume, and a decrease in $D_{0.5cc}$ for bladder [46].

Conclusion

In HDR prostate brachytherapy procedures, MRI is useful in tumor delineation and helps monitor catheter insertion. The geometric distortion in MRI is a common issue and particularly crucial in HDR. To optimize the MRI guidance in HDR, a preparation study about the sequences to balance the geometry fidelity and signal-to-noise ratio should be performed. Another issue is the artifacts from the catheters. Even the MRI compatible HDR catheters cause susceptibility artifacts. This also needs to be addressed before put MRI guidance in clinical HDR treatment. MRI can be used in combination with CT, ultrasound or by itself. If available, MRI-only workflow does not require separate diagnostic MRI acquisition and eliminates image registration errors. If MRI scanner is installed inside the HDR suite, it will further reduce the errors from tissue swelling and catheter movement; provide the possibility to monitor dose delivery, thus may result in the best possible treatment to patients.

There is increasing use of MRI in prostate HDR brachytherapy for guidance and treatment planning; however, no consensus has been established in this regard [47]. MRI-guided prostate HDR brachytherapy procedures demand more resources and manpower than CT- or ultrasound-guided procedures. Workflow-related burden and limited access to MRI will continue to limit broader acceptance of MRI-only HDR workflow [17]. The use of MRI may be justified by its superior prostate and treatment target visualization, which enables highly conformal target dose distribution and possibly lower doses to normal tissues. Because of a variety of uncertainties during the treatment courses, caution must be exercised in order to take into account these factors and ensure that tumor dose coverage is not compromised.

References


