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Review Article

Future Direction of Image-Guided Radiotherapy for Localized Prostate Cancer for more Precise and Conformal Treatment Delivery

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Abstract

Recent technological developments in External Body Radiation Therapy (EBRT), such as intensity-modulated radiation therapy and Image-Guided Radiation Therapy (IGRT), have confirmed the advantages of delivering high doses to achieve optimal tumor-control outcomes and a significant reduction of digestive and urinary toxicities in localized prostate cancer patients. The use of fiducial markers is a reliable and accurate method to localize and register the prostate gland during EBRT. However, a number of publications have pointed out the limitations of using fiducial marker registration in IGRT for the Seminal Vesicles (SVs) when they are included in the target volumes. The SVs may become deformed and move to some extent relative to the prostate gland. In this review, several recent publications dealing with technical advances in IGRT that appear to further improve the quality of position verification methods in EBRT for localized prostate cancer are discussed. The importance of investigating the possible advantage of integrating novel systemic technologies for the improvement of outcomes of locally advanced prostate cancer patients is also examined.

INTRODUCTION

Several recent studies have confirmed the advantages of delivering high doses of External Beam Radiotherapy (EBRT) to achieve optimal tumor-control outcomes in patients with localized prostate cancer [1,2]. In addition, a higher EBRT dose requires greater accuracy and precision. Thus, various position verification methods, including Image-Guided Radiotherapy (IGRT), have been developed, and their effectiveness has been reported [3,4]. The use of fiducial markers is one of the reliable and accurate methods to localize and register the prostate gland during EBRT [4-6].

However, a number of publications have pointed out the limitations of using fiducial marker registration in IGRT for the seminal vesicles (SVs) when they are part of the target volumes. The SVs may become deformed and move to a certain extent relative to the prostate gland [7-9]. De Boer et al reported that fiducial markers are a good surrogate for the prostate gland during EBRT, but they provided little information on the position and orientation of the SVs [10]. The main reason is that the SVs move with respect to the prostate gland, and that motion is not captured by the fiducial markers [8-10].

The aim of the current review was to discuss several recent papers on IGRT for further improving the quality of EBRT for localized prostate cancer. The issues of methodologies, including repositioning techniques, are also examined for future directions.

DISCUSSION AND CONCLUSION

Studies of prostate gland and SV displacement and margins

Suitable evaluation of prostate gland and SV motion is important. Several recent investigators reported motion and deformation of the prostate gland and SVs in EBRT.

Deurloo et al reported that, for contour delineation-based correction strategies, residual deformation of the SVs is small compared to inter-fraction displacement and that the prostate gland and SVs could be irradiated as a rigid body [7]. Thus, the authors suggested that this is a valid approximation in IGRT of prostate cancer, in first order, to correct only for setup errors and organ motion. They also noted that deformation of the prostate gland and SVs can be considered as a second-order effect.

According to Frank et al, the rectal and bladder volume changes during treatment correlated with the anterior and superior displacement of the prostate gland and SVs, and the variability in SV displacement appeared larger than the variability in prostate gland displacement with respect to pelvic bony anatomy [11]. The dominant prostate and SV variations occurred in the Anteroposterior (AP) and superoinferior directions. Even an AP margin of 1 cm for the SVs might be inadequate in some cases. However, they used the center of volume, which does not fully account for the potential effect of the 3-dimensional (3D) shape variation, which might require an even larger margin. The systematic prostate gland and SV variations between the treatment planning Computed Tomography (CT) and daily therapy due to the rectal and bladder volume changes emphasize the need for daily directed target localization and/or immobilization techniques.

Van der Wielen et al analyzed the deformation of the prostate gland and SVs relative to intra-prostatic fiducial markers to quantify the residual geometric uncertainties after on-line corrections [8]. According to them, the largest clinical target volume deformations were observed at the anterior and posterior sides of the SVs (population average standard deviation ≤3 mm). Prostate gland deformation was small (standard deviation ≤1 mm). Although prostate gland deformation with respect to implanted fiducial markers was small, the corresponding deformation of the SVs was considerable. They concluded that adding marker-based rotational corrections to on-line translation corrections provided a limited reduction in the estimated planning margins.

Smitsmans et al quantified residual inter-fraction displacement of SVs and investigated the efficacy of rotation correction on SV displacement in marker-based prostate IGRT [9]. They also determined the effect of marker registration on the measured SVs displacement and its impact on margin design. They found that considerable residual SV displacement was present in marker-based IGRT. Rotation correction barely reduced SV displacement, but a larger SV displacement was shown relative to the prostate gland that was not captured by the marker position. Marker registration error partly explains SV displacement when correcting for rotations. Correcting for rotations, therefore, is not advisable when the SVs are part of the target volume. Margin design for SVs should take these uncertainties into account.

Mutanga et al accounted for all measured displacements during treatment of 21 prostate cancer patients treated with stereographic targeting marker-based online translation corrections and dose distributions with varying margins and gradients [12]. By developing a system for margin validation in the presence of deformations in their population, a 5-mm margin provided sufficient dosimetric coverage for the prostate gland. In contrast, an 8-mm SV margin was still insufficient owing to deformations. Addition of 3D rotation corrections had a minor effect.

Stenmark et al reported that the SVs move differentially from the prostate gland and show greater variation with increasing distance from the prostate gland [13]. For plans targeting just the prostate gland and proximal (1 cm) SVs, 5-mm Planning Target Volume (PTV) expansions are adequate. However, despite daily localization of the prostate gland, larger PTV margins are required for cases where the intent is to completely cover the full SVs.

De Boer et al analyzed the differential rotation between the prostate gland and SVs and compared the required SV margins for the following three correction strategies [10]. The first two strategies were to localize the prostate gland by Cone-Beam Computed Tomography (CBCT)-to-planning-CT alignment of the fiducial markers, allowing both translations and rotations. In the third strategy, using the marker registration as a starting point, the SVs were registered based on gray values, allowing only rotations around the lateral axis. Daily marker-based corrections required an SV margin of 11.4 mm (translations only) and 11.6 mm (translations + rotations) in the first two strategies. Rotation corrections of the SVs reduced the required margin to 8.2 mm in the third strategy. They found substantial differences between the orientation of the prostate gland and SVs.

Thörnqvist et al presented a statistical deformable motion model for multiple targets and applied it to margin evaluations for locally advanced prostate cancer [14]. Their research revealed large individual differences in accumulated dose mainly for Clinical Target Volume (CTV) of the SVs, demanding the largest margins, compared to those required for CTV of the prostate gland and CTV of the pelvic lymph nodes.

Future directions of new radiotherapy approaches

A large margin at the SVs leads to more rectum volume

irradiated, increasing gastrointestinal toxicity [10,15]. Safe reduction of the margin of the SVs is permitted by more accurate Radiotherapy (RT). De Boer et al proposed a hybrid registration technique for the localization of the prostate gland and SVs [10]. Their rotation corrections of the SVs reduced the required margin to 8.2 mm in the third phase of the procedure. They stated that, alternatively, rotational correction can be performed by a more straightforward adaptive technique, such as re-planning or daily plan selections. However, the whole procedure seems to consume time to a certain extent and lead to intra-fractional setup errors caused by bowel peristalsis. For that purpose, further investigation of IGRT using protocols with hypo-fractionation appears to be essential.

According to National Comprehensive Cancer Network guidelines version 4.2013, the accuracy of treatment should be improved by attention to daily prostate localization, with IGRT using CT, ultrasound, implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects [16-19]. Placement of an endorectal balloon during RT may help reduce prostate gland and SV motion. Moreover, Gez et al reported the safety and efficacy of an implantable and biodegradable balloon specifically designed to protect rectal tissue during RT by increasing the interspace between the prostate gland and rectum [20].

Future RT should strive to improve dose conformity by adaptive RT to take into account individual motion patterns throughout the RT course, with real-time imaging and RT alteration [14,21]. Both target and relevant normal tissues as organs at risk become recognized to present complicated motions and/or deformation during the RT course in both intra- and inter-fraction. Therefore, we need to more rigorously develop faster and more accurate calculation algorithms for deformable image registration and dose accumulation for effective adaptive RT. Muren and colleagues stated that current challenges in this area include image quality aspects of online imaging such as CBCT, the performance of auto-segmentation algorithms, plan generation strategies, and quality assurance procedures [21]. Real-time motion management, including studies to take account of intra-fractional motion of the target and normal tissues at risk in planning and delivery, is important [21,22]. Not only the prostate gland and SVs, but also most targets in the abdomen and pelvis, are affected by geometrical changes due to bladder/bowel shape and mobility. This research will connect the four-dimensional (4D) imaging technologies (e.g., CT, positron emission tomography, CBCT), on-line and with real-time target confirmation, as well as technology to regulate RT delivery in real-time [21,23,24].

RT planning should be performed in a patient-individualized fashion, and multiple plans might be prepared to select an optimal plan [25]. Thörnqvist et al proposed that daily treatment plan selection from a plan library is a major adaptive RT strategy to account for individual internal anatomy variations [26]. RT planning will depend increasingly and heavily on 4D imaging data throughout the RT course and adaptive RT plans to provide changed anatomical and functional status [25]. Furthermore, 4D medical imaging will be used to adaptively adjust the plan both for inter-fraction motion and intra-fractional motion. The fractionally accumulated delivered RT dose will be computed to form the basis for adaptation.

Predict-ahead techniques will be required to overcome system latency between making a measurement of patient motion and correcting for it [25,28,29]. Smitsmans et al reported an automatic 3D gray-value registration method for fast prostate localization that could be used during online or offline IGRT [30]. Similar technology is being developed currently with respect to autonomous cars. This novel technology requires immediate, accurate, and automatic judgments, along with procedures for the next movement, a vast number of times repeatedly. Preparing a certain number of patterned processes in advance is necessary for the whole series of procedures.

In conclusion, further investigation is essential to deal with the issues previously described, including unpredictable intra-fractional prostate gland and SV motion and deformation, using more precise RT delivery systems and reducing the burden of patients and medical staff.

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