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Review Paper

Techniques for adaptive prostate radiotherapy

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ABSTRACT

Variations in the position and shape of the prostate make accurate setup and treatment challenging. Adaptive radiation therapy (ART) techniques seek to alter the treatment plan, at one or more points throughout the treatment course, in response to changes in patient anatomy observed between planning and pre-treatment images. This article reviews existing and developing ART techniques for prostate cancer along with an overview of supporting in-room imaging technologies. Challenges to the clinical implementation of adaptive radiotherapy are also discussed.

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Introduction

Modern radiotherapy is tailored to maximize the therapeutic ratio for a specific patient setup as defined by a planning computed tomography (CT) scan. Due to the prostate's location, normal physiologic filling of the bladder and/or rectum results in random variations in its position, rotation and shape, making accurate setup and treatment difficult. To further complicate matters, the clinical target volume (CTV) often consists of the prostate, seminal vesicles and pelvic lymph nodes, which are known to move independently of one another [1]. To compensate for geometric variations associated with inconsistent inter-fraction patient setup, as well as inter- and intra-fraction internal organ motion,

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the ICRU recommends expanding CTVs by a pre-defined margin to create a planning target volume (PTV) [2]. The major pitfall of the CTV-to-PTV margin is increased dose delivered to nearby normal tissue such as the rectum and bladder.

Image-guided radiotherapy (IGRT) strategies have been introduced over the last two decades to address inter-fraction changes in patient setup and internal anatomy [7]. The current standard of care involves acquisition of on-board volumetric kV cone beam CTs (CBCT) to generate a 3D soft-tissue based registration with the planning CT [8]. Volumetric CBCTs enable visualization of the prostate and nearby organs at risk (OARs), including the rectum and bladder, with geometric accuracy of approximately 1 mm [9]. On-line setup verification using CBCTs and subsequent corrections partially reduce patient setup errors allowing safe reduction of planning margins [7,10]. Unfortunately, IGRT strategies cannot completely correct for patient setup errors and considerable CTV-to-PTV margins are still required due to large internal organ motion in prostate patients.

Adaptive radiation therapy (ART) techniques expand upon IGRT by altering the treatment plan, at any point(s) throughout treatment, based on variations in patient anatomy observed between the planning CT and in-treatment images. Clinical implementation of ART is the next step towards optimizing the therapeutic ratio for prostate therapy. This article aims to provide a broad overview of clinically-implemented off-line ART techniques as well as more technically demanding on-line approaches that are still in the development phase. A thorough survey of the literature was undertaken with the aim of summarizing recent technological advances towards ART for prostate cancer. A brief review of supporting in-room imaging technologies is also given followed by a discussion of current challenges to the clinical implementation of adaptive radiotherapy.

Rationale for adaptive radiation therapy in prostate cancer

The rationale for implementation of ART for prostate radiotherapy is that it should allow further reduction of CTV-to-PTV margins compared to treatments using IGRT alone, thereby improving the therapeutic ratio. Potential clinical benefits of reducing planning margins include reduced normal tissue toxicities due to smaller volumes of normal tissue in high dose regions and improved cure rates achieved by dose escalation to the reduced PTV. Currently, severe genitourinary (GU) or gastrointestinal (GI) toxicities limit dose escalation in prostate cancer patients, yet recent clinical trials have demonstrated that dose escalation improved outcomes [3–6]. Therefore, strategies to safely reduce CTV-to-PTV margins to enable dose escalation are in high demand for treatment of prostate cancer.

It is important to emphasize that even upon implementation of ART, appropriate planning margins will be needed to account for uncertainties associated with organ contouring, intra-fraction motion and linear accelerator mechanical performance. Successful implementation of ART will also depend on the robustness of the technologies required as well as proper patient preparation.

Current ART approaches

Off-line adaptation using PTV modification

Early ART strategies involved patient-specific modification of the PTV and off-line plan re-optimization partway through treatment. Generic CTV-to-PTV margins used for initial treatment planning are calculated to encompass systematic and random variations in patient setup across a large population [11,12]. Systematic errors represent the largest geometric component of these generic CTV-PTV margins [13] and patient-specific corrections enable safe margin reduction.

PTV modification based on patient setup errors

During the mid-1990s, the William Beaumont Hospital group first proposed an off-line adaptive strategy that used daily planar images from electronic portal imaging devices (EPIDs) to calculate daily setup errors for individual patients [13,14,16]. Each patient's PTV was then adjusted to eliminate the systematic error and to include a margin accounting for random errors only. PTV modification occurred after a few initial fractions and a new treatment plan was created to deliver the remaining dose to the adapted PTV. Initial studies showed that adaptive plan modifications enabled CTV-to-PTV margin reduction in a majority (70%) of patients. In patients with reduced margins, a higher dose could be delivered to the PTV without increasing dose to nearby OARs.

PTV modification based on patient setup errors and internal organ motion

In 2000, Yan et al. introduced the confidence-limited PTV concept [17]. Here, adaptive CTVs were calculated as the bounding volume containing the full geometric range of the CTV internal motion over 5 CT sets consisting of the planning CT plus 4 daily CTs. PTVs were then re-calculated as the bounding volume plus a patient-specific margin for random setup errors. Daily CTs were required over the first week of treatment to construct a confidence-limited PTV that compensates for patient-specific internal organ motion as well as systematic and random setup errors when using a conventional 3D conformal technique, whereas two weeks of daily CTs were needed for a more conformal intensity modulated radiation therapy (IMRT) approach. Clinical implementation of the confidence-limited PTV technique was accompanied by dose escalation, when possible, and resulted in improved biochemical control and survival at William Beaumont Hospital [12]. Follow-up studies found no significant correlation between dose escalation and acute GU or GI toxicities [12,18].

A similar ART strategy that uses multiple CT images to calculate average prostate and rectum volumes was developed at the Netherlands Cancer Institute [19]. Using repeat CT scans acquired throughout the course of treatment, Nuver et al. calculated average prostate and rectum volumes to be used for adaptive planning. When using average prostate volumes, CTV-to-PTV margins were reduced from 10 mm to 7 mm while maintaining acceptable dosimetric coverage of the prostate. Nuver et al. found that the reduced margins enabled lower doses to be delivered to the rectum and the use of the average rectum volume improved rectal dose estimation accuracy [12,19].

Cheung et al. [91] reported the clinical implementation of an adaptive PTV margin in 2005. During CT simulation, fluoroscopic imaging of fiducial markers in the prostate was performed to determine the extent of prostate motion due to respiration. The first phase of treatment delivered 42 Gy in 21 fractions to the CTV (prostate and seminal vesicles) plus a 1 cm uniform margin using 3D conformal radiotherapy. Orthogonal EPID images were acquired before and after the first 9 fractions to calculate intra-fraction prostate motion. The second phase delivered a hypo-fractionated 30 Gy in 10 fractions boost to the CTV plus a patient-specific margin using IMRT. Patient-specific margins were calculated to compensate for intra-fraction motion based on fluoroscopic and EPID data. Of the 33 patients reported, a mean margin of 3 mm in the lateral and superior-inferior directions and 4 mm in the antero-posterior direction was used in the boost phase. Acceptable acute GI and GU toxicities were reported.

Off-line adaptation using dose compensation

Margin reductions are possible if day-to-day variations in the dose delivered to the PTV could be detected and compensated for in subsequent fractions. Off-line plan adaptation occurs between