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Pelvic bone anatomy vs implanted gold seed marker registration for image-guided intensity modulated radiotherapy for prostate carcinoma: Comparative analysis of inter-fraction motion and toxicities

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ABSTRACT

Objectives: We compared the prostate motion variability and toxicities between patients treated with gold marker registration based IG-IMRT (IG-IMRT-M) and bony landmark registration based IG-IMRT (IG-IMRT-B).

Methods: T1c-T3b (node negative), intermediate and high risk (non-metastatic) adenocarcinoma of prostate, age ≥18 years, Karnofsky Performance Status of ≥70 were included in this retrospective study. The prostate motion variability, acute and late radiation toxicities between the two treatment arms (IG-IMRT-M versus IG-IMRT-B) were compared.

Results: Total of 35 patients (17 for IG-IMRT-M and 18 for IG-IMRT-B) were treated with a median radiotherapy dose of 76 Gray. The prostate variability observed with and without markers in millimeter was 4.1 ± 2.3 vs 3.7 ± 2.1 [Antero-Posterior (A-P); p = 0.001], 2.3 ± 1.5 vs 2.1 ± 1.2 [Superior-Inferior (S-I); p = 0.095] and 1.1 ± 1.7 vs 0.4 ± 1.4 [Left-Right (L-R); p = 0.003]. There was higher acute toxicity in IG-IMRT-B arm compared to IG-IMRT-M arm in terms of grade ≥2 diarrhea [50% vs 11% OR = 7.5 (1.3–42.7); p = 0.02] and grade ≥2 proctitis [38% vs 5.8%, OR = 10.1 (1.09–94.1); p = 0.04]. At a median follow up of 36 months, the late genitourinary toxicities grade ≥2 [27% vs 0%; p = 0.04] were higher in the IG-IMRT-B arm compared to IG-IMRT-M arm.

Conclusions: IG-IMRT-M detects higher prostate motion variability as compared to IG-IMRT-B, inferring a significant prostate motion inside fixed pelvic bony cavity. The addition of marker based image guidance results in higher precision of prostate localization and lesser acute and late toxicities.

Introduction

Radiotherapy (RT) is an integral component of the management of prostate cancer and can be delivered in several ways which include external beam radiotherapy (EBRT) with or without brachytherapy [1]. EBRT for prostate carcinoma has undergone spectral changes over the last two decades. Traditionally, conventional doses of 66–70 Gray have been used. Recently there has been a paradigm shift with the introduction of conformal and intensity modulated radiotherapy which has facilitated dose escalation ranging from 72 to 86 Gray. Dose escalation has been associated with better biochemical progression free survival (B-PFS), overall survival (OS), and this has been demonstrated in various large randomized clinical trials [2–6]. However, this comes at the possible added risk of acute as well as late toxicities, specifically gastrointestinal (GI) and genitourinary (GU) toxicities. The grade ≥ 2 chronic GI toxicities were 5–20% in conventional doses versus 13–30% in dose escalated arm [7,8], and it was statistically significant. Similarly, 8–25% grade ≥ 2 chronic GU toxicities are reported with conventional doses which are reported to increase to 11–40% with escalated doses. The acute grade 2 or worse GI

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and/or GU toxicity is approximately 10% with conventional doses as against 15.1% (p = 0.042) with escalated dose [7].

Intra and inter-fraction organ motion has posed a challenge for precise dose delivery to the target volume and sparing of organ at risk (OAR). The addition of image guidance to RT has facilitated dose escalation with acceptable toxicity and reduction of set up margins. Zelefsky et al. [9] demonstrated 3 year likelihood of grade ≥2 late urinary toxicities as 10.4% with image guidance compared to 20% without image guidance (p = 0.02). Acute GI grade ≥2 toxicity was 60% vs 34%, and GU grade ≥2 toxicity was 58% vs 53% in 3 dimensional conformal RT compared to image guided RT and was statistically significant [10]. Intensity modulated radiotherapy (IMRT) with image guidance yields lower acute grade ≥ 2 rectal (13% vs. 80%, p = 0.004) and bladder toxicities (13% vs. 60%; p = 0.014) as compared with those treated without image guidance [11].

Electronic portal imaging device (EPID) or cone beam computed tomography (CBCT) using bony landmark as reference has been used to reduce the random errors prior to delivery of radiotherapy. However, it fails to account for the prostatic movement inside rigid bony pelvic cavity attributable to differential filling of bladder and rectum along with peristaltic and respiratory movements. The prostate movement is usually restricted in left-right direction, but is more pronounced in craniocaudal and antero-posterior direction. Studies show 0.5–0.9 mm, 2.7–9 mm, and 1.7–8.9 mm in left–right, antero-posterior and supero-inferior directions, respectively [12,13]. Fiducial markers like implantable gold seeds and CBCT together provide an affective mean to evaluate and accommodate the interfraction prostate motion [14].

We treat patients of localized prostate carcinoma with gold marker based IG-IMRT. However, few patients fail to comply with this protocol due to financial constraints. Those patients are treated with bony landmark based IG-IMRT. We retrospectively analyzed and compared the prostate motion variability among patients treated with gold marker registration based image guided-intensity modulated radiotherapy (IG-IMRT-M) vs bony landmark based image guided intensity modulated radiotherapy (IG-IMRT-B) arm. Further, we also analyzed and compared the acute and late GI and GU toxicities of both the arms.

Patients and methods

This was a single institutional, retrospective study. Patients with histopathologically proven adenocarcinoma of prostate, age ≥ 18 years, Karnofsky Performance Status of ≥70, non-metastatic and with no prior history of chemotherapy or radiotherapy were included in the study. Pretreatment work up included history, clinical examination, complete blood count, serum biochemistry including serum prostate specific antigen (PSA) levels, contrast enhanced magnetic resonance imaging (CEMRI) pelvis and technetium 99 methylene diphosphonate (Tc-99 m MDP) bone scan. Patients were staged according to American Joint Committee on Cancer (AJCC)recommendations [15]. Risk groups were determined by the National Comprehensive Cancer Network (NCCN) guidelines [16], and stratified into high, intermediate, and low risk categories. T1c-T3b (node negative), intermediate and high-risk cases of adenocarcinoma prostate were included in the study. All patients signed an informed consent form prior to initiation of the treatment as part of routine institutional protocol. All patients underwent bilateral orchidectomy followed by neoadjuvant and adjuvant androgen deprivation therapy (ADT) with bicalutamide 50 mg once a day. ADT was continued for a total of 6 months in intermediate risk patients and for 2 years in high risk patients.

Patients in IG-IMRT-M arm fulfilling the protocol conditions were planned for insertion of fiducial gold markers 2 weeks before RT planning. Pre-insertion urine sample was checked for signs of infection and three gold markers measuring 1 × 5 mm (Cyber Mark™ Fiducial Marker Kit; CIVCO Medical Solutions, Kalona) were inserted into the prostate under the guidance of trans-rectal ultrasound. The intended positions of the seeds were 3 non-coplanar positions as left superior lobe, left apex and right mid-gland. Ultrasound images were acquired and a 5-day course of antibiotics was given to reduce the risk of infection.

Computed tomography (CT) simulation was performed about 7 days post seed insertion in IG-IMRT-M group and at the earliest in IG-IMRT-B group. Patients were advised to void bladder followed by drinking 500 ml of water, 30 min prior to simulation. The planning CT was acquired with 3 mm slices and injection of 70–100 ml of non-ionic contrast on multi-slice CT simulator (Somatom sensation; Siemens Medical Solution, Germany). Target volume and OAR delineation was done as per International Commission on Radiation Units and Measurements (ICRU) Reports [17–19] No. 50, 62 and 83. The structures contoured included the prostate, proximal and distal seminal vesicle and the pelvic lymph node group that included bilateral internal and external iliac lymph nodes along with bilateral obturator and presacral group of lymph nodes. In intermediate risk cancer patients, prostate along with proximal seminal vesicle were included in high risk clinical target volume (HR-CTV); whereas in high risk patients, in addition to the above, gross extra capsular extension was also included in HR-CTV. Low Risk CTV (LR-CTV) included distal seminal vesicle and pelvic lymph nodes. A uniform planning target volume (PTV) expansion of 7 mm, except posteriorly (6 mm), was used to obtain the respective HR-PTV and LR-PTV. Among OARs, rectum (up to sigmoid colon), bladder, bowel bag, bilateral femoral heads were contoured. Rectum was contoured inferiorly from the anal verge till recto-sigmoid flexure. Bowel bag was contoured inferiorly from the most inferior small or large bowel loop to 2 cm superior to PTV. Additionally, in group B, the three markers were contoured.

Patients with high risk were planned for RT to both primary diseases (prostate + seminal vesicle) along with prophylactic lymph node irradiation to bilateral pelvic lymph nodes, whereas intermediate risk patients received RT only to primary disease. A total dose of 74–78 Gray in 37–39 fractions at 2 Gray per fraction over 8 weeks was delivered in 2 phases. In 1st phase 46 Gray was delivered in 23 fractions to both HR and LR-PTV, followed by boost of 28–32 Gray in 14–16 fractions to HR PTV. The dose constraints prescribed and achieved for OARs in the two groups are listed in Table 1. Volumetric modulated arc therapy (VMAT) planning was performed using CMS Monaco (Version 5.0). All treatment plans were evaluated and implemented only after meeting the stringent quality assurance parameters. Treatment was delivered on ELEKTA Infinity (Crawley, UK) linear accelerator with dynamic multileaf collimation (40-pair MLC), leaf width of 1 cm at the isocenter.

The CT simulation images with target volume outlines were transferred to X-ray Volume Imaging (XVI) (version 4.5.1) console. Pretreatment kV-CBCT images of target volume were acquired on XVI using Volume View (Imaging technique) and Dual Registration (Click box registration facility). In patients of IG-IMRT-M group, daily CBCT with online correction was performed. Acquired CBCT images were auto registered with reference CT simulation images using seed matching module to determine translational errors [Fig. 1a]. Online correction was done in the anterior–posterior (AP), superior–inferior (SI), and left–right (LR) dimensions after data acquisition. In patients of IG-IMRT-B group, daily CBCT was performed and online corrections were applied according to bony anatomy based registration [Fig. 1b].

Patients were evaluated weekly for acute toxicities and were graded as per Common Terminology Criteria for Adverse Events [20] (CTCAE version4.03]. Late toxicities were graded as per Radiation Therapy Oncology Group (RTOG) late morbidity criteria

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