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Original research article

Reducing radiation-associated toxicity using online image guidance (IGRT) in prostate cancer patients undergoing dose-escalated radiation therapy

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ABSTRACT

Aim: To determine the influence of IGRT in terms of toxicities compared to non-IGRT patients undergoing definitive RT.

Background: Image-guided radiotherapy (IGRT) enables immediate correction of target movement by online imaging. For prostate cancer patients undergoing radiation therapy (RT), a geographical miss of the prostate may result in increased dose–volume effects in the rectum and bladder.

Methods: A total of 198 prostate cancer patients treated between 2003 and 2013 were recruited randomly for this evaluation. The rates of genitourinary (GU) and gastrointestinal (GI) toxicity for 96 non-IGRT patients (total dose: 72/73.8 Gy) were compared to those for 102 IGRT patients (total dose: 77.4 Gy) according to the Common Toxicity Criteria Version 3.0 (CTCAEv3.0). Follow-up information included treatment-related symptoms and PSA relapse.

Results: After a median follow-up of 55.4 months, a statistically significant difference was noted for acute GI toxicities ≥ 1 in favour of IGRT. Significantly more patients treated by IGRT were free of acute GI symptoms (43% vs. 19%, $p = 0.0012$). In the non-IGRT group, more patients experienced acute GU side effects (89% vs. 80%, $p = 0.07$). Late toxicity scores were comparable for both cohorts.

Conclusions: Based on the data, we demonstrated that despite dose escalation, IGRT enabled us to reduce the GI side effects of radiation. IGRT can therefore be considered to be the standard of care for dose-escalated RT of localized prostate cancer.

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1. Background

The efficacy of curative high-dose radiotherapy for localized prostate cancer has been proven in several randomized trials.[1–3] It has been shown that improvements of radiation treatment techniques could enhance biochemical relapse-free survival rates, but this has not been translated into better survival. Acute and chronic toxicities experienced by patients are dependent on the total radiation doses and the technique used for the treatment of prostate cancer. Pollack et al.[3] demonstrated that the biochemical control rate was improved by increasing the total dose (70–78 Gy), but this approach also increased toxicities to the organs at risk.

In the literature, acute (grade 2/3) genitourinary (GU) and gastrointestinal (GI) side effects have been reported in 30–50% of cases, and severe side effects, including chronic rectal bleeding ≥ grade 2, have been reported in 6–20% of patients.[4,5]

Several studies analyzed the inter-and intrafractional displacements of the prostate, which ranged from 0.2 to 21 mm[6] depending on rectal and bladder filling. Our prospective analysis of 66 prostate cancer patients demonstrated that standardized prostate immobilization using an endorectal balloon significantly reduced organ motion.[7] Furthermore, organ motion of the prostate can be reduced significantly by standardized bladder-filling.[8] Image-guided radiotherapy enables an immediate correction of target movement by online imaging.[6,9] A geographical miss of the prostate may result in increased dose–volume effects on the organs at risk. Higher mean doses to the rectum and bladder are more likely to increase treatment-related side effects, such as proctitis or cystitis. In addition, missing the target volume might result in higher rates of local failure.[7,9,10] In 2009, image guidance for dose-escalated irradiation of prostate cancer was implemented in our clinic as the standard of care.

2. Aim

In this retrospective analysis, the influence of IGRT versus non-IGRT in terms of treatment-related side-effects was determined for patients undergoing definitive radiotherapy with validated rectal and bladder filling protocols. For quality assurance, all patients underwent the same toxicity assessment and were treated uniformly based on standardized in-house protocols with the same planning constraints. Biochemical relapse rates for all patients were analyzed to demonstrate treatment efficacy.

3. Material and methods

A total of 207 prostate cancer patients treated in our department between 2003 and 2013 were randomly recruited for this retrospective evaluation. To exclude any selection bias we randomly chose a two years period before and a two years period after commencing the IGRT program for our study, during which we evaluated all patients with newly diagnosed prostate cancer that had undergone definitive radiotherapy.

Follow-up data were not complete for 9 patients and 198 patients were evaluable. In 60% of the patients androgen suppression was performed. 52 (25%) of the patients were diagnosed at stage T1, 111 (62.2%) were diagnosed at stage T2, 33 (17.9%) were diagnosed at stage T3, including 3 patients with lymph node metastasis, and 2 (1%) were diagnosed as stage T4, including 1 patient with lymph node metastasis.

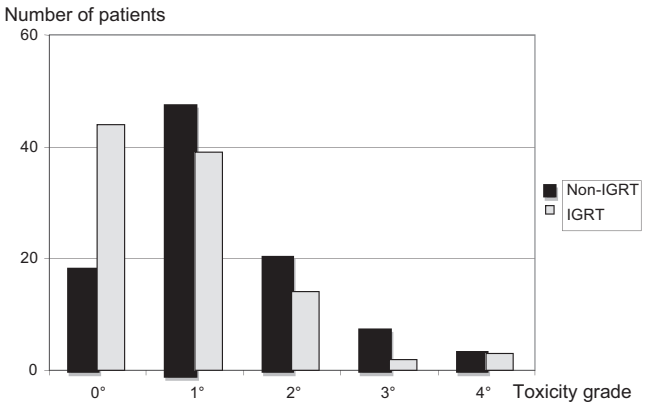

Fig. 1 – Comparison of acute gastrointestinal toxicity in IGRT vs. non-IGRT patients, $p < 0.05$.

85% of patients had either intermediate- or high-risk features defined by Gleason Score, PSA and T stage. Low-risk patients had a PSA ≤ 10 ng/ml combined with Gleason score 2–6 and stage cT1-2a. Intermediate risk was defined as PSA ≥ 10.0 ≤ 20.0 and/or Gleason = 7 and/or stage cT2b. High risk was defined as PSA ≥ 20.0 and/or Gleason 8–10 and/or cT2c-T3.[11]

Prior to the implementation of IGRT, 96 patients were irradiated with a total dose of 72.0 Gy (15 patients)/73.8 Gy (81 patients). After commencing the IGRT program, 102 patients were irradiated with a total dose of 77.4 Gy, 1.8 Gy fractions, 5 days/week.

All patients followed a standardized bladder-filling protocol. In addition, immobilization of the prostate was improved by using an endorectal balloon (filled with 40 ml of air), as reported previously.[7]

All patients underwent 3D CT virtual simulation (GE ADVSIM®) with knee and footstocks fitted onto an immobilization board, and CT was conducted at 2.5 mm spacing and 2.5 mm thickness. If possible, diagnostic MRI images and CT data sets were coregistered using the AW Server Fusion 2.0 (GE Healthcare). The prostate and seminal vesicles were contoured and the gtv, ctv and ptv were generated using the ADVSIM® system. For low-risk patients, the ctv included the prostate and the base of the seminal vesicles; for intermediate- and high-risk patients, the ctv encompassed the prostate and the entire seminal vesicles. For high-risk patients, the regional pelvic lymph nodes were involved. Margins for expansion were 10 mm in all directions, except posteriorly, which was set at 6 mm for the ptv1 (50.4 Gy). For boost contouring, the ctv2 included the prostate gland and any gross tumours observed outside of the prostate gland, and the expansion margins were 5 mm in all directions to generate the ptv2.

The bladder and femoral heads/bone were delineated consecutively, and the rectum was defined as an organ at risk beginning from 1 cm above the ptv1 to 1 cm below the ptv1.