Radiotherapy and Oncology 107 (2013) 140–146

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate morbidity

Late toxicity and biochemical control in 554 prostate cancer patients treated with and without dose escalated image guided radiotherapy

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ARTICLE INFO

Article history:
Received 1 August 2012
Received in revised form 4 April 2013
Accepted 5 April 2013
Available online 14 May 2013

Keywords:
Prostate cancer
IGRT
Fiducial markers
Late toxicity
Dose escalation

ABSTRACT

Background and purpose: To compare rates of late gastrointestinal toxicity, late genitourinary toxicity and biochemical failure between patients treated for prostate cancer with implanted fiducial marker image guided radiotherapy (FMIGRT), and those treated without FMIGRT.

Methods and materials: We performed a single institution retrospective study comparing all 311 patients who received 74 Gy without fiducial markers in 2006 versus all 243 patients who received our updated regimen of 78 Gy with FMIGRT in 2008. Patient records were reviewed 27 months after completing radiotherapy. Biochemical failure was defined using the Phoenix definition. Details of late gastrointestinal and genitourinary toxicities were graded according to CTCAEv4. Moderate/severe toxicity was defined as a grade 2 or higher toxicity. Cumulative incidence and prevalence curves for moderate/severe toxicity were constructed and compared using multistate modeling while biochemical failure free survival was compared using the log rank test. A Cox regression model was developed to correct for confounding factors.

Results: Median follow-up time for both groups was 22 months. The hazard ratio for moderate/severe late gastrointestinal toxicity in the non-FMIGRT group was 3.66 [95% CI (1.63–8.23), $p = 0.003$] compared to patients in the FMIGRT group. There was no difference in the hazard ratio of moderate/severe late genitourinary toxicity between the two groups (0.44 [95% CI (0.19–1.00)]), but patients treated with FMIGRT did have a quicker recovery from their genitourinary toxicities HR = 0.24 [95% CI (0.10–0.59)]. We were unable to detect any differences in biochemical failure free survival between the cohorts HR = 0.60 [95% CI (0.30–1.20), $p = 0.143$].

Conclusion: Despite dose escalation, the use of FMIGRT in radical radiotherapy for prostate cancer significantly reduces the incidence of gastrointestinal toxicity and the duration of late genitourinary toxicity when compared to conventional non-FMIGRT techniques.

External beam radiation therapy (EBRT) is a well-established treatment option for localized prostate cancer [1–3]. A number of phase III trials have demonstrated that dose escalation results in improved biochemical control following EBRT [4–6]. However, the ability to deliver these escalated doses has been limited by the resulting toxicity to adjacent normal tissues [7].

Doses of 68–70 Gy to the prostate delivered using standard EBRT techniques (without fiducial markers, daily imaging or online corrections) result in 3–10 percent of patients experiencing moderate to severe late effects, but dose escalation $\geqslant$74 Gy increases the proportion to approximately 20 percent [5,8,9].

Image guided radiotherapy (IGRT) is a technique whereby daily in-treatment-room imaging is used to correct for setup and physiological changes encountered during the treatment course. Fiducial marker based IGRT (FMIGRT) specifically utilizes implanted fiducial markers to localize the prostate immediately prior to treatment [10–12]. Multiple dosimetric and geometric studies have described that, in theory, FMIGRT should significantly reduce dose delivered to adjacent tissues by more accurately targeting the prostate [13–15] and potentially reducing CTV and PTV margins [16]. This should therefore translate into reduced post-radiotherapy side effects, circumventing the issues of normal tissue toxicity that normally accompany dose escalation.

It is thus believed that escalated dose FMIGRT should result in better biochemical control compared to conventional EBRT, with a similar or lower incidence of toxicity. However, clinical data to support this is still limited. The purpose of this study is to directly

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http://dx.doi.org/10.1016/j.radonc.2013.04.007

compare late toxicity as well as biochemical control between patients treated with dose escalated FMIGRT versus conventional dose non-FMIGRT who have otherwise been treated with similar radiotherapy planning techniques and equipment.

Methods and materials

Study design and patient selection

We performed a retrospective study of patients with localized prostate cancer at our institution, comparing all those who received 74 Gy without fiducial markers in 2006 (our standard regimen at this time) versus all those who received our updated regimen of 78 Gy with FMIGRT in 2008. Patients who were treated in 2007 were not considered for this study due to it being a changeover year during which our new FMIGRT regimen was phased in. Patients were excluded from the analysis if they had nodal disease, did not complete the planned course of radiotherapy, or if there were no follow up data available.

The medical records of all qualifying patients were reviewed 27 months after the completion of radiotherapy. Ensuring equal follow up time in both arms was considered important as otherwise non-FMIGRT patients would consistently have had 2 years additional follow up over the FMIGRT group that could have biased results. 27 months was chosen as it was the duration between the FMIGRT close-out date, 31st Dec 2008, and the commencement of this study, April 2011. Any follow up information after 27 months was censored. Data were collected on the end dates of radiotherapy, age, TNM staging, Gleason scores, pre- and post-treatment PSA levels and rectal examination findings. Dates of any imaging tests showing metastatic or local recurrence were documented. Patients who died during follow up had the date and cause of death documented where available.

Details of late gastrointestinal and genitourinary toxicities experienced were audited from each review appointment within the 27 month time frame and graded according to common terminology criteria for adverse events (CTCAE)v4 [17]. Information on factors potentially affecting late toxicity was also collected including any history of transurethral resection of the prostate (TURP), diabetes, myocardial infarct, prosthetic hip replacement, connective tissue disorder, and use of anti-androgen medication.

Radiotherapy simulation and planning

Patients treated in both the FMIGRT and non-FMIGRT groups had identical simulation and planning procedures that have been previously described [18]. All patients followed a bowel emptying and bladder filling protocol prior to simulation and each treatment fraction. FMIGRT patients had three gold fiducial markers measuring 1 mm by 5 mm inserted into the base, apex and contra-lateral mid-prostate one week before the simulation CT scan. Patients were simulated supine with a bolster under knees and foot-stocks fitted onto an immobilization board (Combifix-Sinmed, Civco, Kalona, IA). The CT was conducted at 3 mm spacing and prostate, rectum and femoral heads were delineated from this. The CTV was defined as the prostate unless there were high-risk features present (T3, Gleason $\geqslant$ 8, PSA $\geqslant$ 20), in which case the seminal vesicles were also included. Intermediate risk patients had the base of the seminal vesicles included. Elective pelvic nodal irradiation was not used in these patients. CTV to PTV expansion margins were 10 mm cranio-caudal, laterally and anterior, and 7 mm posteriorly. Rectal volumes were contoured on axial slices 12 mm above and below the PTV. Planning constraints were such that 50% of the rectal volume received <50 Gy; 30% of the volume received <60 Gy; and 25% of the volume received <70 Gy. No bladder dose–volume constraints were used. Radiotherapy was planned conformally, unless rectal constraints were not met, in which case intensity modulated radiotherapy (IMRT) was used.

Image guidance procedure

All patients were treated on Varian linear accelerators (Varian Medical Systems, Palo Alto, USA). Our protocol for non-FMIGRT patients was to conduct pre-treatment orthogonal electronic portal imaging (EPI) in the first week of radiotherapy, and bony anatomy registration was compared to the digitally reconstructed radiographs (DRRs) from the planning CT scan. The average bony anatomy displacement was calculated and if greater than 3 mm on average in the first week then an isocentre move was made for the remainder of the treatment. After the first week pre-treatment orthogonal EPI was conducted weekly.

For FMIGRT patients, pretreatment orthogonal imaging was conducted daily using kV equipped linear accelerators. Fiducial marker position was matched with the planning DRRs and patient position was corrected if any discrepancy was noted in the three cardinal directions (pitch, yaw and roll were not adjusted for). In cases where kV imaging was unavailable patients were imaged using EPI with a 3 mm threshold.

Analysis

Descriptive statistics were produced to provide an overview of the study cohorts. Demographic information of men treated both with and without FMIGRT was compared using chi-square test or Fisher's exact test.

Late toxicity was defined as any toxicity experienced three months after the completion of radiotherapy treatment. The grade of toxicity was grouped as moderate/severe (grade 2 or more) or minimal/none (grade 0 or 1). Cumulative incidence curves and prevalence curves for moderate/severe toxicity were obtained and compared for FMIGRT and non-FMIGRT groups using multistate modeling allowing for patient recovery. Death was a censoring event. Differential use of IMRT in the cohorts was identified a priori as a potential confounding factor and so its potential effect was accounted for using multivariate modeling and by performing a subgroup analysis of only those patients who did not receive IMRT.

The Phoenix definition of biochemical failure was used (increase in PSA $\geqslant$2 ng/ml from nadir [19]). Biochemical failure free survival (BFFS) was measured from the date of the end of radiotherapy to the date of the biochemical failure or death without preceding biochemical failure. Patients who had more than 6 months of adjuvant androgen deprivation were censored from the biochemical control analysis. Kaplan Meier curves of BFFS were produced for FMIGRT and non-FMIGRT groups and compared using the log-rank test. A Cox regression model was developed to correct for confounding factors. Subgroup analyses comparing FMIGRT patients to non-FMIGRT patients for high, intermediate and low risk prostate cancer groups were performed.

Results

Patient characteristics

324 patients were identified who received 74 Gy without FMIGRT in 2006. Twelve patients were excluded due to having no follow up data and a further one patient excluded due to incomplete disease details making a total cohort of 311 patients in the non-FMIGRT group. In 2008, there were 251 patients who received 78 Gy with FMIGRT. Six of these were excluded due to no follow up and two patients had incomplete data resulting in a total of 243 patients in the FMIGRT cohort.