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Original Article

Moderate Hypofractionation with Simultaneous Integrated Boost in Prostate Cancer: Long-term Results of a Phase I–II Study

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Abstract

Aims: To report 5 year outcome and late toxicity in prostate cancer patients treated with image-guided tomotherapy with a moderate hypofractionated simultaneous integrated boost approach.

Materials and methods: In total, 211 prostate cancer patients, 78 low risk, 53 intermediate risk and 80 high risk were treated between 2005 and 2011. Intermediate- and high-risk patients received 51.8 Gy to pelvic lymph nodes and concomitant simultaneous integrated boost to prostate up to 74.2 Gy/28 fractions, whereas low-risk patients were treated to the prostate only with 71.4 Gy/28 fractions. Daily megavoltage computed tomography (MVCT) image guidance was applied. Androgen deprivation was prescribed for a median duration of 6 months for low-risk patients (for downsizing), 12 months for intermediate-risk and 36 months for high-risk patients. The 5 year biochemical relapse-free survival (bRFS), cancer-specific survival (CSS), overall survival and late gastrointestinal and genitourinary CTCAE.v3 toxicity were assessed. The effect of several clinical variables on both outcome and gastrointestinal/genitourinary toxicity was tested by uni- and multivariate Cox regression analyses.

Results: After a median follow-up of 5 years, the late toxicity actuarial incidence was: genitourinary ≥ grade 2: 20.2%; genitourinary ≥ grade 3: 5.9%; gastrointestinal ≥ grade 2: 17%; gastrointestinal ≥ grade 3: 6.3% with lower prevalence at the last follow-up visit (≥ grade 3: genitourinary: 1.9%; gastrointestinal: 1.9%). Major predictors of ≥ grade 3 genitourinary and gastrointestinal late toxicity were genitourinary acute toxicity ≥ grade 2 (hazard ratio: 4.9) and previous surgery (hazard ratio: 3.4). The overall 5 year bRFS was 93.7% (low risk: 94.6%; intermediate risk: 96.2%; high risk: 91.1%), overall survival and CSS were 88.6% (low risk: 90.5%; intermediate risk: 87.4%; high risk: 87%) and 97.5% (low risk: 98.7%; intermediate risk: 95%; high risk: 94.3%), respectively. Risk classes and androgen deprivation were not significantly correlated with either bRFS, overall survival or CSS. Twelve patients experienced a biochemical relapse but none experienced clinically proven local and/or pelvic recurrence.

Conclusion: A satisfactory 5 year outcome with an acceptable toxicity profile was observed. The combination of image-guided radiotherapy–intensity-modulated radiotherapy, high equivalent 2 Gy dose (EQD2) with a moderate hypofractionated approach and extensive prophylactic lymph node irradiation also leads to very good outcome in high-risk patients.

Key words: Moderate hypofractionation; prostate cancer; simultaneous integrated boost; tomotherapy

Introduction

Randomised clinical trials showed that dose-escalated radiotherapy improves prostate cancer control [1–3]. Hypofractionated prostate radiotherapy has the potential to deliver a higher biologically effective dose over a shorter time when compared with conventional fractionation. The α/β ratio for prostate cancer has been suggested to be low, indicating that prostate cancer treatments may benefit from hypofractionation, although some publications have suggested higher α/β values, especially for high-risk patients [4–8]. Moderately hypofractionated (e.g. 2.5–3.5 Gy/fraction) radiotherapy to treat prostate cancer is not a novel

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approach, having been the standard in the UK, Canada and Australia for years [9–11]. Delivering fractions higher than 2 Gy may not only be radiobiologically and therapeutically advantageous, but also logistically convenient, both for patients and busy radiation oncology departments [12]. Hypofractionated radiotherapy can be safely implemented thanks to the development of both image-guided (IGRT) and intensity-modulated radiotherapy (IMRT). IMRT is now a widely accepted and efficient technique for dose escalation in localised prostate cancer, in order to better limit high doses to normal tissues, especially in the case of whole-pelvis irradiation (WPRT).

Although combining WPRT with a hypofractionated prostate boost (simultaneous integrated boost; SIB) has been shown to be feasible and efficient, few published data are thus far available, and this approach remains investigational.

The sharp dose gradient created with intensity-modulated helical tomotherapy can efficiently conform the high-dose region to the planning target volume (PTV) and limit the dose to the bladder, rectal wall, bowel and femoral heads while concomitantly delivering different dose levels to different PTVs. In 2005, a phase I–II study based on a SIB approach delivering 71.4–74.2Gy to the prostate in 28 fractions with image-guided helical tomotherapy was started.

Here we report the 5 year update of the outcome and late toxicity results referring to 211 patients.

Materials and Methods

Study Design, Doses and Volumes

Between November 2005 and May 2011, 211 patients were enrolled in a single-institution, phase I–II, open-label prospective clinical trial at the Radiation Therapy Department of San Raffaele Scientific Institute. Before enrolment, all patients signed an informed consent form. Details of the study can be found elsewhere [13]. In accordance with the National Comprehensive Cancer Network (NCCN v.2.2005), three patient risk groups were identified: low risk (clinical stage T1–T2, Gleason score $\leq$ 6, prostate-specific antigen [PSA] $\leq$ 10); intermediate risk (clinical stage T1–T2, Gleason score $\leq$ 6, PSA $>$ 10; clinical stage T1–T2, Gleason $>$ 6, PSA $\leq$ 10; or clinical stage T3, Gleason score $<$ 6, PSA $<$ 10); and high risk (clinical stage T1–T3, Gleason score $\geq$ 7, PSA $>$ 10). Patients were treated in 28 fractions with different doses to different volumes. In summary, low-risk patients received 71.4 Gy(2.55 Gy/fraction) to the prostate, whereas intermediate- and high-risk patients were treated to 74.2 Gy (2.65 Gy/fraction). All intermediate- and high-risk patients (NCCN 2.2005) received prophylactic lymph node irradiation (51.8 Gy) on common iliac (under L5–S1 space), external iliac, internal iliac, presacral and obturator lymph nodes, taking into account the results of the randomised trial Radiation Therapy Oncology Group (RTOG) 9413, showing a benefit to long-term androgen deprivation and radiotherapy using WPRT in these patients [14,15]. Seminal vesicles were split into 1/3 proximal and 2/3 distal and always treated to different doses, according to the class risk (Table 1). The overlap between rectum and prostate PTV was constrained to 65.5 Gy.

Androgen deprivation primarily consisted of an oral anti-androgen or gonadotropin-releasing hormone agonist. Androgen deprivation prescription was 12 months for intermediate-risk patients and 36 months for high-risk patients. Neoadjuvant androgen deprivation of 3–6 months was prescribed for low-risk patients with high prostate volume and urinary symptoms, in order to obtain a volume decrease, a better dosimetry and thus a lower probability of urinary side-effects. Patients who had treatment modification in the sense of a decrease or an increase in the duration of the prescription, according to the decision of their urologist or oncologist, were not excluded from the study.

Planning, Image Guidance and Delivery

Details have been reported in other publications [13,16,17]. In short, patients' legs were immobilised in the supine position. An empty rectum and a comfortably full bladder were required. Axial images were obtained at 3–5 mm intervals through the pelvis. PTVs referring to prostate and seminal vesicles were defined as clinical target volume (CTV) +8 mm margin (except those in the cranial-caudal direction 10 mm); for pelvic lymph nodes PTVs margins of 7–10 mm in all directions were used.

Patients were optimised with the tomotherapy planning system following previously described strategies [16,18]: the parameters typically used were 2.5 cm, 0.25–0.30, 2.5–3.5 for field width, pitch and modulation factor, respectively. For all patients, the dose was prescribed as the median dose to the prostate PTV (corresponding to the prostate).

Daily MVCT image guidance was applied for all patients using the system integrated in the tomotherapy machine. A two-step matching strategy was followed: a fully automatic registration based on bony anatomy followed by 'fine' manual adjustment matching the prostate [17].

Patient Population

Patient characteristics are shown in Table 2.

One hundred and forty-eight (70%) patients underwent androgen deprivation as follows: neoadjuvant/concomitant androgen deprivation in 147 (70%) for a median of 4 months (1–146 months); adjuvant androgen deprivation only in 119 (56%) patients for a median period of 18 months (1–54 months). According to the NCCN risk group classification, the median treatment period was 12 months (2–32 months) for the intermediate-risk group and 34 months (5–54 months) for the high-risk group. In one-third of low-risk patients, androgen deprivation was prescribed for downsizing: the median treatment period was 6 months (1–28 months); one patient continued the treatment for up to 28 months on the prescription of the family doctor.

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