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Original article

Hypofractionated radiation therapy for prostate cancer: The McGill University Health Center experience

Radiothérapie hypofractionnée pour le cancer de la prostate : expérience du centre universitaire de santé McGill

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ABSTRACT

Purpose. – In 2002, at the McGill University Health Centre, we began a program of hypofractionated radiotherapy for patients with low risk prostate cancer as an alternative to conventionally fractionated radiotherapy.
Material and methods. – Our initial hypofractionation regimen was 66 Gy given in 22 fractions, prescribed to the isocenter, delivered with 3D-conformal radiotherapy plan. The clinical target volume was the prostate gland and the planning target volume consisted of the clinical target volume plus a 7-mm margin in all directions. Hormonal therapy was not given to any patient.
Results. – The long-term results for this group of patients confirmed the feasibility, good tolerance and excellent disease control of the regimen with the extra-benefit of being convenient to both patients and the health system by shortening treatment duration. The outcomes of this approach stimulated us to use hypofractionation in patients with intermediate-risk. Analysis of 100 intermediate-risk patients receiving our hypofractionated radiotherapy regimen (no hormones) shows, at median follow-up of 75 months, 8-year biochemical recurrence free and cancer specific survival rates of 90% and 95%, respectively, with acceptable toxicity.
Discussion. – Our technique changed from 3D to intensity modulated radiotherapy with the dose adjusted to 60 Gy in 20 fractions. Lastly, we have expanded the program to high-risk patients where IMRT treatments are given to the pelvic nodes (44 Gy in 20 fractions) with a simultaneous integrated boost delivery to the prostate (60 Gy in the same 20 fractions). Our long-term results have shown that moderate hypofractionated radiotherapy for prostate cancer is safe and provides good tumor control comparable to high-dose conventionally fractionated radiotherapy. This hypofractionated regimen has been routinely used in our institution.

Mots clés :
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Toxicité

RÉSUMÉ

Objectifs. – En 2002, au centre de santé de l'université McGill, nous avons débuté un programme de radiothérapie hypofractionnée comme alternative au fractionnement classique pour les cancers de prostate à bas risque.
Matériels et méthodes. – Initialement, une dose de 66 Gy en 22 fractions, prescrite à l'isocentre, était délivrée via une technique conformationnelle tridimensionnelle. Le volume cible prévisionnel était constitué du volume cible anatomoclinique (glande prostatique), plus une marge uniforme de 7 mm. Aucune hormonothérapie n'a été prescrite. L'analyse des résultats à long terme, pour ce groupe de patients, a confirmé la faisabilité, une tolérance acceptable et l'excellent contrôle tumoral de ce régime, qui est de plus, par réduction du temps global de traitement, bénéfique pour le patient et le système de santé. Les résultats favorables obtenus ont aussi stimulé l'utilisation de l'hypofractionnement chez les patients atteints de cancer de risque intermédiaire. Nous avons analysé les résultats sur 100 patients et, après un suivi

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médian de 75 mois, les taux de survie sans récidive biochimique et de survie spécifique à 8 ans étaient respectivement de 90 % et 95 %, avec une toxicité acceptable.
Discussion. – En 2010, la technique tridimensionnelle a été délaissée pour la radiothérapie conformationnelle avec modulation d'intensité (RCMI), avec ajustement subséquent de la dose à 60 Gy en 20 fractions. Finalement, en 2011 l'hypofractionnement a été utilisé pour les cancers de prostate à haut risque. Ceux-ci ont reçu, par RCMI, une dose de 44 Gy en 20 fractions dans le pelvis avec *boost* intégré simultané dans la prostate de 60 Gy. À l'heure actuelle, l'analyse de nos résultats a montré que la radiothérapie hypofractionnée était sûre et procurait un taux de contrôle tumoral comparable à celui de la radiothérapie classique de haute dose, ce qui justifie ainsi son utilisation en routine dans notre département.

1. Introduction

In the early 2000s, most radiation oncology departments in Quebec, Canada, were faced with long waiting times for patients to start treatment. Due to the typically slow growing pattern of the disease, prostate cancer patients had the last priority to start radiotherapy [1].

At that time, analysis of clinical studies in prostate cancer suggested that the alpha/beta ratio for prostate cancer was lower than previously anticipated and probably lower than that estimated alpha/beta ratio for the rectal mucosa. This radiobiological finding lead to the hypothesis that therapeutic gain could be obtained by delivering hypofractionated radiotherapy [2–4].

These two factors stimulated us to start a program with hypofractionated radiotherapy for favorable prostate cancer at McGill University Health Center (MUHC) in Montreal, Quebec. With hypofractionated radiotherapy, fewer, larger daily fractions using an equivalent biologically effective dose (BED) to conventionally fractionated radiation therapy should have the potential to improve the therapeutic ratio with the extra-benefit of shortening the overall treatment duration, decreasing the waiting time to start radiation treatments and, consequently, allowing more patients to be treated within a reasonable time.

2. Material and methods

We began our program of hypofractionated radiotherapy in prostate cancer in November 2002, using 3-dimensional (3D) conformal radiation therapy as an alternative treatment for patients with favorable-risk prostate cancer, as previously reported in detail [5]. Briefly, eligible patients had histologically proven prostate adenocarcinoma, did not receive hormonal therapy (before, during, or after radiotherapy), and were at low or favorable intermediate-risk, defined as T1–2c, prostate specific antigen (PSA) $\leq$ 20 ng/mL, and Gleason score $\leq$ 7.

The experience with escalated dose hypofractionated radiotherapy was limited and the MUHC genitourinary radiation oncologists and medical physicists conjointly defined several treatment parameters. Patients underwent CT scan simulation in the supine treatment position with a comfortably full bladder. An urethrogram was routinely performed to help define the prostatic apex. The clinical target volume (CTV) was the prostate gland only for low risk disease and the proximal 1 cm of seminal vesicles could be included in the CTV at the discretion of the treating radiation oncologist in patients with intermediate-risk disease. The PTV consisted of the CTV plus a uniform 7-mm margin in all directions. The seminal vesicles, whole bladder, femoral heads, penile bulb, and the whole rectum (from anus to the sigmoid) were contoured in all patients. There were no specifically defined normal tissue constraints for the organs at risk. Daily pretreatment localization of the prostate gland was performed initially using ultrasound (BAT system; Nomos Corporation, Sewickley, PA) [6].

Soon after we began our hypofractionated program, intensity modulated radiation therapy (IMRT) became available in our department. Its beginning was laborious, cumbersome and time-consuming. Thus, after studies carried out in our institution did not show much of a dosimetric difference between 3D-conformal radiation therapy and IMRT, it was decided to continue the hypofractionated treatments using 3D-conformal radiation therapy [7] (Fig. 1). Patients were treated with a 3D-conformal radiation therapy plan consisting of five 18-MV photon beams prescribed to the isocenter, five treatments per week. After some calculations using the linear quadratic formula it was decided to give 66 Gy in 22 daily fractions of 3 Gy, which was believed to be biologically equivalent to 79 Gy in 44 fractions or 78 Gy in 39 fractions. The coverage of the planning target volume (PTV) was between 95% and 107%, as per the International Commission for Radiation Units and Measurements Report 50.

The major concern with any hypofractionated radiotherapy regimen, particularly using a high BED, is the potential for increased late effects. With that in mind, gastrointestinal and genitourinary toxicity was prospectively assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3, in every patient at each follow-up visit.

3. Results

From November 2002 to December 2005, we had 129 patients who entered in our program of 66 Gy in 22 fractions as described above. At a median follow-up time of 90 months, the biochemical recurrence free rates at 5- and 8-year were 97 and 92%, respectively. The 8-year cancer specific and overall survival rates were 98 and 88%, respectively [8] (Fig. 2).

The majority of patients tolerated the treatment well, with 57% of patients not experiencing any acute gastrointestinal or genitourinary toxicity. Up to 90 days after radiotherapy (acute toxicity), 83% of patients had no gastrointestinal symptoms, 13% had grade 1, 4% grade 2, and no patient had grade 3 or greater gastrointestinal toxicity. Concerning acute genitourinary toxicity, 66% had grade 0, 25% grade 1, 8% grade 2, and 1% had grade 3. For late toxicity, the worst grade $\geq$ 2 rate for gastrointestinal and genitourinary toxicity was 27% and 33%, respectively. There was no toxicity grade 3 or higher. At last follow-up, the rate of grade 2 or higher for both gastrointestinal and genitourinary toxicity was only 1.5%. No patient ever experienced grade 4 or 5 gastrointestinal or genitourinary toxicity.

4. Discussion

The start of hypofractionated radiotherapy for prostate cancer (66 Gy in 22 fractions) in our department was carefully planned and began with patients harboring low risk disease. As outcomes for