Clinical Oncology xxx (2015) 1–8

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Accelerated Hypofractioned Postoperative Radiotherapy for Prostate Cancer: A Prospective Phase I/II Study

A. Gladwish *, A. Loblaw *†, P. Cheung *, G. Morton *, H. Chung *, A. Deabreu ‡, G. Pang *, A. Mamedov ‡

* Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada
† Institute for Health Policy, Measurement and Evaluation, University of Toronto, Toronto, Canada
‡ Clinical Trials, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Canada

Received 12 April 2014; received in revised form 10 October 2014; accepted 10 December 2014

Abstract

Aims: To present the initial findings of a single institution, phase I/II study investigating hypofractionated radiotherapy in patients undergoing post-prostatectomy treatment.

Materials and methods: Patients requiring postoperative radiotherapy were prospectively enrolled. Dose was prescribed to the prostate bed with 51 Gy in 17 daily fractions. Androgen deprivation was optional. Acute and late gastrointestinal/genitourinary toxicity were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 and quality of life was assessed using the Expanded Prostate Cancer Index Composite evaluation tool. Prostate-specific antigen (PSA) was evaluated at every follow-up.

Results: Thirty patients were enrolled between 2009 and 2011. The median age was 65 years and most had Gleason 7 disease (86%) with pT2c or pT3a (82%). Positive margins were documented in 67% of the patients. The median pre-treatment PSA was 0.12 ng/ml. The median follow-up was 24 months. Overall toxicity was low, with >80% of patients having ≤ grade 1 acute toxicity in both genitourinary and gastrointestinal realms. Similarly, only two patients (6%) experienced grade 2/3 late gastrointestinal/genitourinary toxicity. Quality of life scores were also indicative of a well-tolerated treatment. PSA failure was seen in five patients (17%).

Conclusions: We present a hypofractionated schedule of postoperative prostate radiotherapy that is both well tolerated in terms of both toxicity and quality of life measures. Initial PSA control is encouraging. Further evaluation with a longer follow-up and a larger cohort is warranted.

Key words: Prostate cancer; quality of life; salvage therapy

Introduction

Prostate cancer is the most commonly diagnosed cancer among Canadian men, with about 26 000 new diagnoses in 2011 [1]. Radical prostatectomy represents the primary treatment in about 25% of these patients. Of these, about one-third will develop biochemical recurrence after definitive surgery [2]. This risk is greater among men with adverse surgical pathology, including positive margins, seminal vesicle invasion, extraprostatic extension and higher Gleason scores. The results of three randomised controlled trials have shown a benefit of postoperative radiotherapy in these patients in terms of biochemical-free survival [3–5]. The SWOG 8794 study, in particular, showed a benefit in terms of local recurrence, distant recurrence and overall survival [6]. These studies also showed acceptable rates of acute and late gastrointestinal and genitourinary toxicity, <5% and <10%, respectively. These data prompted the development of two clinical practice guidelines recommending adjuvant radiotherapy to all patients with adverse pathological findings at prostatectomy [7,8].

The use of hypofractionation in the context of *in situ* prostate cancer has been the subject of numerous studies, with the rationale of exploiting the likely late-responding nature of prostate tumours. In recent years, a number of

Author for correspondence: A. Loblaw, Rm T2-103, 2075 Bayview Avenue, Sunnybrook Health Sciences Center, Toronto, Ontario, M4N 3M5, Canada. Tel: +1-416-480-4806; Fax: +1-416-480-6002.
E-mail address: andrew.loblaw@sunnybrook.ca (A. Loblaw).

http://dx.doi.org/10.1016/j.clon.2014.12.003
0936-6555/

reports have suggested that prostate tumours may have a low α/β value (<3 Gy), suggesting that the use of hypofractionation could result in increased tumour cell kill and the theoretical widening of the therapeutic window with respect to the surrounding, early responding, tissue [9–14]. In addition, hypofractionation is more convenient for patients and more cost-effective than conventional fractionation because the number of radiotherapy fractions is decreased. This can be particularly advantageous for radiotherapy centres with limited resources and/or long waiting lists.

A natural extension to hypofractionation in the definitive setting is to investigate its utility in the postoperative setting. In 2011, Kruser and colleagues [15] provided a retrospective analysis of their experience of treating postoperative, biochemically recurrent patients with 65 Gy in 2.5 Gy daily fractions. Their data suggested that hypofractionation was indeed safe with similar biochemical control rates as standard fractionation schemes. It should be noted that over half of these patients were treated with helical tomotherapy. A similar prospective, single-centre, phase II trial reported similar results, using solely standard fixed-beam intensity-modulated radiotherapy (IMRT) [16] and yet another phase I/II trial reported on their experience, but with four-field treatment to the pelvis and a prostatic boost [17]. We present here our institution's phase I/II study investigating the role of post-prostatectomy, hypofractionated radiotherapy.

Patients and Methods

This was designed as a prospective phase I/II clinical trial of hypofractionated postoperative radiotherapy and it was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre. The primary end point was to measure acute gastrointestinal and genitourinary toxicities during radiotherapy. The secondary end points were to measure prostate-specific antigen (PSA) biochemical disease-free survival 5 years after radiotherapy, quality of life (QOL), sexual function and late (after 3–6 months after the start of treatment) gastrointestinal and genitourinary toxicities.

Eligibility

Patients were considered eligible if they were >18 years of age and had histologically confirmed adenocarcinoma of the prostate, pathological stage T3 NX-0 M0, positive surgical margins and/or a rising PSA post-radical prostatectomy (two consecutive rises in PSA, at least 4 weeks apart). Patients were excluded if they met any of the following criteria: (i) pathological T4 disease; (ii) positive surgical margin within the seminal vesicle; (iii) pathologic nodal involvement; (iv) previous pelvic radiation; (v) genetic syndromes of hyper-radiosensitivity or inflammatory bowel disease. Baseline investigations included a postoperative PSA obtained at least 1 month after radical prostatectomy. Postoperative diagnostic imaging was left to the discretion of the attending radiation oncologist, although in practise diagnostic imaging was not carried out in any of the patients in this study. Based on this institution's unpublished experience, and that of previous published reports, the utility of either transrectal ultrasound or magnetic resonance imaging has limited utility with PSA < 2.0 ng/ml, well above the pre-treatment PSA in this work [18].

Planning and Treatment

We have developed three prospective, phase II primary image-guided radiotherapy protocols and have generated a large experience with gold seed fiducial marker implantation and daily image guidance [19,20]. A critical issue with this proposal is the absence of a prostate in which to implant the fiducial markers. Our institution developed an in-house protocol for inserting three gold seed fiducial markers (1×3 mm) in the post-prostatectomy setting (one at the bladder neck, one near the anastomosis and one at the urogenital diaphragm). This was accomplished under local anaesthetic using transrectal ultrasound guidance. An unpublished feasibility study of this process provided confidence that this method was feasible and safe. Of note, a separate manuscript will be dedicated to evaluating the data regarding the intrafraction prostatic bed motion measured in this study.

One week after the insertion of the fiducial markers, a planning computed tomography scan was carried out with the patient supine and a custom vacuum lock bag for immobilisation (Vac-Lock, MED-TEC Inc., Orange City, Iowa, USA). Patients were simulated with a comfortably full bladder and were asked to empty their rectum prior to simulation and each treatment. No specific medications or diet were given to empty the rectum before simulation or treatment.

The clinical target volume was defined as the prostate bed, which was contoured based on our institutional guideline, which mirrors the now widely accepted Radiation Therapy Oncology Group consensus guidelines [21].The planning target volume (PTV) was created by adding a 4 mm symmetrical margin around the contoured clinical target volume to take into account potential motion of the prostate bed during treatment. The rectum and bladder were contoured as organs at risk, the rectum specifically was established from the bottom of the ischium to the sigmoid flexure. A dose of 51 Gy in 17 daily (5 days per week) fractions was prescribed with the 95% isodose covering at least 99% of the PTV. This dose was chosen as an equivalent target biologically effective dose (BED) as the standard post-prostatectomy prescription of 66 Gy/33 fractions (assuming a tumour $\alpha/\beta = 1.5$ Gy). An inverse planned, IMRT technique was used and the Pinnacle v. 9.0 (Philips Radiation Oncology Systems, Fitchburg, Wisconsin, USA) software was used for treatment planning. IMRT planning constraints were calculated by converting our institution's common dose–volume histogram limits using 2 Gy/day to equivalent 3 Gy/day doses using the linear-quadratic equation (using α/β of 3 for rectum and bladder) [22]. These included: V48 bladder < 40%, V42 rectum < 40%

Please cite this article in press as: Gladwish A, et al., Accelerated Hypofractioned Postoperative Radiotherapy for Prostate Cancer: A Prospective Phase I/II Study, Clinical Oncology (2015), http://dx.doi.org/10.1016/j.clon.2014.12.003