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Long-term outcome for prostate cancer using pseudo pulse–dosed rate brachytherapy, external beam radiotherapy, and hormones

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ABSTRACT

PURPOSE: We report the long-term outcomes of pulse-dose rate (PDR) brachytherapy used in a nonstandard style (pseudo-PDR) with an high-dose rate brachytherapy technique in conjunction with external beam radiotherapy (EBRT) and hormonal manipulation on prostate cancer (PC).

METHODS AND MATERIALS: We treated 253 patients with Stage T1–T3 N0M0 PC, between December 1999 and March 2006. All patients received neoadjuvant androgen deprivation for a median 6 months. Treatment consisted of three pulses of pseudo-PDR brachytherapy to a median dose of 18 Gy with 50.4 Gy in 28 fractions of EBRT.

RESULTS: At a median 6 years followup, (range, 1–11 years), 5-year overall survival was 92%, and PC-specific survival was 96%. The 5-year biochemical control (biochemical no evidence of disease) by the Phoenix definition for low-, intermediate-, and high-risk groups was 95%, 90%, and 71%, respectively ($p < 0.00001$). At 6 years, the incidence of Radiotherapy Oncology Group Grade 2 and 3 genitourinary toxicity was 1% and 6%; Radiotherapy Oncology Group Grade 2 and 3 gastrointestinal toxicity was 4% and 0%. Erectile preservation at 3 years was 58%. The Phoenix definition best predicted clinical failure with a high specificity (94%).

CONCLUSIONS: Pseudo-PDR brachytherapy plus EBRT with limited neoadjuvant hormonal manipulation is an effective treatment option in localized PC, with minimal and tolerable morbidity and provides excellent control. This technique of a modified PDR-delivery technique appears as effective as high-dose rate therapy.

Keywords: Prostatic neoplasm; Brachytherapy; Pulsed dose rate; PDR; High dose rate; HDR

Introduction

The rationale for brachytherapy is to increase the local dose delivery and synchronously use the inverse-square law effect to minimize toxicity to surrounding normal tissue, including rectum, bladder, and urethra. Despite the newer volumetric modulated arc therapy and intensity-modulated radiotherapy (IMRT) techniques of dose-delivery, brachytherapy is able to deliver a large dose to a smaller volume with a lower integral dose (1). Pulse-dose rate (PDR) brachytherapy is one method of delivery. It has advantages in a lesser source strength and subsequently lower requirements for surrounding shielding and has a strong, albeit mostly theoretical, argument that PDR brachytherapy will provide equivalent cancericidal effects and simultaneously minimize normal tissue damage (2, 3). Only recently has clinical evidence arisen to support this argument (4–6). Simultaneously, the use of high-dose rate (HDR) brachytherapy now has regular utilization and acceptance in the United States and worldwide (7). In this article, we endeavor to show that PDR-brachytherapy

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equipment can be used in an HDR technique of delivering dose in three large fractions rather than multiple small fractions. We believe that this can be done with similar therapeutic efficacy to an HDR program. This article aims to provide more mature followup data of our previously published PDR equipment-based treatment program and assess long-term control and morbidity.

Methods and materials

Study population and rationale

Between December 1999 and March 2006, we treated 253 patients with localized prostate cancer (PC) at The Mater Hospital in Sydney, Australia. This is a community-based private hospital with staff links to the local university. The program was offered as an alternative to radical prostatectomy or external beam radiotherapy (EBRT) alone, with institutional approval granted at the start of the program and all patients giving written consent after appropriate discussion of choices. This treatment was designed to mimic the HDR programs then in use but also used resources available in the department. At the time of inception, external beam dose delivery was limited to 60–70 Gy, a dose that was increasingly being recognized as suboptimal. Tissue tolerances were kept to the same as for HDR brachytherapy then in use and are described in detail in our original article (6). Staging was performed using the American Joint Committee on Cancer staging systems, initially 5th edition, but retrospectively corrected to the 6th edition when it was published in 2002 (8). Staging incorporated contemporary computerized tomography and bone scans in the majority of cases.

Treatment

Details of the treatment are in our initial article (6). The program entailed a median of 6 months hormonal manipulation using a luteinizing hormone releasing hormone agonist (LHRHa) with an anti-androgen briefly (to minimize flare) to maximize gland size reduction followed by a temporary brachytherapy implant and subsequent EBRT. Nearly all patients (>95%) received 6 months of hormones, none received more than 12 months, if their gland had not reduced to a transverse width of under 5 cm by that time; they were deemed to large for brachytherapy and were switched to EBRT alone. Brachytherapy was delivered before EBRT in most cases.

Although the brachytherapy system (Nucletron MicroSelectron PDR Nucletron; Elekta AB [an Elekta company], Stockholm, Sweden) was designed to deliver PDR, we did not use it in its designed fashion, that is, hourly pulses over many hours. Rather, we delivered doses from 15 to 22 Gy (median 18 Gy) in three equal and separate fractions over 26 hours, with a minimum 6 hours between the start of each fraction. This could be considered as HDR brachytherapy delivery with low source strength. The first 45 patients were treated with three fractions of 5.5 Gy to a total of 16.5 Gy, but this was increased to 18 Gy when minimal short-term morbidity was demonstrated. Prescribed doses occasionally varied from 15 to 22 Gy, varying to cover the prostate volume and keep urethral doses down. The dose was prescribed to the planning target volume (PTV) in the fashion of Kiel, that is, the prostate plus a margin as described in detail in the original article (6). Dose constraints to the urethra or rectum were those used for HDR brachytherapy; urethral dose was kept such that <10% of urethra received >125% and <5% received >130% of the prescribed dose. Similarly, we aimed to keep the rectal dose low with a V80 < 30%. There was no 100% dose on pubic arch. Brachytherapy was planned using the Plato planning system (Plato BPS, v13.7-14.2.5, Nucletron; Elekta AB [an Elekta company]) and delivered with a 1Ci ^{192}Ir source. Each pulse took between 20 and 40 minutes to deliver. EBRT was 50.4 Gy in 28 fractions via a four-field conformal approach. Clinical target volume was the prostate and immediately proximate seminal vesicle. Dose was delivered to PTV, created by expanding the clinical target volume with a 10-mm uniform margin, commencing within 2 weeks of the implant, and dosed to the isocenter using the International Commission on Radiation Units and Measurements 62 criteria. This was delivered with 6 MV photons from a Varian C-series Linear Accelerator (Varian Medical Systems Inc, Palo Alto, CA).

Followup

Routine followup was shared between the radiation oncologist and the urologist. At the time of treatment, all patients consented to share their longer term outcome. Only one patient of the cohort declined providing information of his progress. The start of the time of followup was from the date of the start of radiation treatment.

Post-treatment assessment was carried out using serial prostate-specific antigen (PSA) readings to assess progression (bNED [biochemical no evidence of disease]). PSA was measured five times in the first year (1, 3, 6, 9, 12 months), 6 monthly to 5 years, and at least yearly subsequently. PSA was measured using standard clinical measurement (e.g., Architect CI16200; Abbot Diagnostics, Abbott Laboratories, Abbott Park, IL) to two decimal places, with the lowest reading recorded as less than 0.01 ng/mL (<0.01 ng/mL). Assessment of bowel and bladder toxicity was according to the Radiotherapy Oncology Group–European Organization for Research and Treatment of Cancer Late Effects of Normal Tissue, Subjective, Objective, Management scoring system (RTOG, EORTC LENT-SOMA) (9), and erectile function was discussed at each visit. No formal scoring system was used for assessing erectile function: it was regarded as functional if the man was comfortable that it was adequate for intercourse with or without phosphodiesterase type 5 inhibition.

Risk grouping was defined according to the National Comprehensive Cancer Network recommendation with