Pattern of relapse and dose received by the recurrent intraprostatic nodule in low- to intermediate-risk prostate cancer treated with single fraction 19 Gy high dose-rate brachytherapy

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ABSTRACT

**PURPOSE:** The purposes of this study were to investigate the pattern of relapse in patients with low- or intermediate-risk prostate cancer treated with 19-Gy high-dose-rate brachytherapy (HDR-BT) and to calculate the dose received by the area of recurrence.

**METHODS AND MATERIALS:** Patients included in this analysis were treated under a Phase II randomized trial that evaluated the role of 19-Gy HDR-BT monotherapy in low- and intermediate-risk prostate cancers. Multiparametric prostate MRI and prostate biopsy were performed in patients with suspicious local recurrence. The site of local relapse was compared with the initial site of disease. The dose received by the site of recurrence was investigated through registration of the post-treatment multiparametric prostate MRI with the HDR-BT treatment plan.

**RESULTS:** Eight of 87 treated patients were found to have local recurrence after 19-Gy HDR-BT. Seven of the eight recurrences were at the site of initial bulk disease. Seven patients were found to have a more aggressive histology in the posttreatment biopsy. The mean volume of prostate that had received 100% of prescription dose was 97%. Mean dose to area of recurrence was 29.1 Gy, whereas dose to 98% and dose to 90% of the recurrence were 21.6 Gy and 23.2 Gy, respectively.

**CONCLUSIONS:** The relapse pattern after a single 19-Gy HDR-BT is predominantly associated with the site of initial disease. This lends some rationale to future strategies of further focused dose escalation to initial site of disease, notwithstanding the fact that the calculated biologically equivalent dose using linear–quadratic assumptions is already very high.

Keywords: HDR brachytherapy; Prostate cancer; Intraprostatic recurrence; Linear–quadratic model

Introduction

Increasing evidence supports the use of high-dose-rate brachytherapy (HDR-BT) as monotherapy for the treatment of localized prostate cancer. It has been shown to be a safe and effective treatment for many men with low- and intermediate-risk disease, with results comparable to those following permanent seed low-dose-rate brachytherapy (LDR-BT). These mature favorable results have used fractionated treatment regimens, most commonly using four, six, or as many as nine fractions (1–3). However, multifraction regimens are resource intensive, logistically demanding, and more expensive than LDR-BT (4) as patients require either inpatient admission for the duration of treatment or multiple catheter insertions.

Recently, authors have evaluated more hypofractionated regimens using three, two, or even single fractions (5–8). Prostate cancers are thought to have a lower alpha/beta ratio than late-responding tissues suggesting that hypofractionation may be advantageous, providing the necessary biological dose to control the cancer without exceeding normal tissue tolerances. Nevertheless, the linear–quadratic (LQ) model used to calculate bioequivalent doses has a questionable accuracy for doses over 10 Gy per fraction (9) and fails to take into account the dose heterogeneity inherent to brachytherapy treatments.

A randomized Phase II clinical trial (8) evaluated the role of two dose-fractionation regimens using...
monotherapy HDR-BT in patients with low- or intermediate-risk prostate cancer. Based on the LQ model and assuming a prostate cancer alpha/beta ratio of 1.5, treatment doses (19 Gy in a single fraction and 27 Gy in two fractions) were estimated to be biologically equivalent to previous studies reporting good outcomes with multifractionated treatments (1–3). Nevertheless, after a median followup time over 30 months, a higher than expected rate of local failure has been seen in those patients randomized to the single-fraction 19-Gy arm.

The purposes of this study were to determine the pattern of relapse within the prostate with reference to the initial site of disease in patients randomized to the single-fraction 19-Gy arm and to determine dose delivered to these areas of recurrence to inform future strategies of focused dose escalation.

Methods and materials

Eligible patients had locally recurrent prostate cancer after 19-Gy HDR monotherapy. These patients were treated under an ongoing Phase II randomized clinical trial held at Sunnybrook Health Sciences Centre that included patients with histologically proven prostate adenocarcinoma, clinical Stage T1c or T2a, Gleason score 6 or 7, and serum prostate-specific antigen (PSA) < 20 ng/mL. All patients had biopsy confirmation of recurrent prostate cancer showing no radiation effect.

The HDR-BT technique used in this trial has been previously reported (8). In summary, implant was performed under general anesthesia and with transrectal ultrasound guidance (TRUS). Flexible 24-cm plastic ProGuide needles (Elekta, Stockholm) were inserted into the prostate through the perineum. Tungsten obturators were removed after insertion. Then, TRUS images were acquired and sent to Oncentra Prostate planning station v.4.2.2 (Elekta, Stockholm), where volumes of interest were contoured, catheters were reconstructed, and a plan was generated. The planning target volume consisted of the prostate with a 0- to 2-mm margin, and the urethra and rectum were contoured as organs at risk. The goal was to deliver 19 Gy to at least 95% of the planning target volume. HDR-BT treatment was delivered with the patient still under general anesthesia and without removing the ultrasound probe or changing the patient position. Patients were discharged home once recovered from anesthesia.

Patients were followed every 3 months for the first year and every 6 months thereafter with symptom assessment, digital rectal examination (DRE), and PSA. Patients presenting with rising PSA after 2 years of followup and/or abnormal DRE were restaged with bone scan and CT of the thorax, abdomen, and pelvis. Patients also underwent multiparametric MRI (mpMRI) of the prostate. This study was performed in a 3-T Philips Ingenia MR system (Philips Health Care, Netherlands), and the protocol included T2-weighted images (T2W), diffusion-weighted images, and dynamic contrast-enhanced series. Magnetic resonance images were evaluated by an experienced radiologist in prostate tumors, and the suspicious lesion was graded by using the Prostate Imaging Reporting and Data System score system.

Patients with no evidence of systemic disease in the restaging investigation and with suspicious findings on DRE or prostate mpMRI were assessed with prostate biopsy. The biopsy usually targeted a suspicious nodule seen in the MRI and was guided by TRUS with cognitive MRI fusion. In addition, some patients were also investigated with a random prostate biopsy in conjunction with the targeted investigation.

Pattern of relapse and prostate biopsies

The pattern of recurrence within the prostate was characterized in sextants by taking into consideration the pretreatment and posttreatment MRI and biopsy results. This was achieved by correlating the sites of initial positive biopsy to the posttreatment MRI and biopsy. When available, a pretreatment prostate MRI was also used in this comparative analysis.

MRI contouring and registration

The recurrent intraprostatic nodule was contoured on an MIMvista (MIM software, Inc., Cleveland, OH) image processing station with the use of posttreatment T2W, diffusion-weighted images, and dynamic contrast-enhanced MRI data sets. Contours were generated by consensus of two physicians. After contouring, the TRUS-based treatment plan that had been used for treatment was exported from Oncentra Prostate (Nucletron, Veenendaal, Netherlands) and coregistered to the posttreatment magnetic resonance data sets. An in-house contour-based deformable registration algorithm was used to register the prostate delineated on the TRUS images to the prostate delineated on the T2W magnetic resonance images. The contoured nodule on the magnetic resonance data set was then transferred to the TRUS data set and the dosimetry extracted for the nodule (Fig. 1).

The metrics prostate $V_{100}$ (prostatic volume receiving 100% of the dose) and recurrent nodule mean dose, $D_{90}$ and $D_{98}$ (dose received by 90% and 98% of the nodule, respectively), were collected after image registration. The first parameter assesses dose delivered to the entire prostate volume, whereas the other metrics reflect the dose received by the site where the disease recurred.

Statistics

A descriptive analysis of the pattern of relapse was performed. Prostate and nodule metrics were reported with appropriate measures of central tendency and dispersion.
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