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Original Article

Prostate Dose-painting Radiotherapy and Radiobiological Guided Optimisation Enhances the Therapeutic Ratio

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Abstract

Aims: To describe the treatment of 11 patients with radiobiologically guided dose-painting radiotherapy and report on toxicity.
Materials and methods: Boost volumes were identified with functional magnetic resonance imaging scans in 11 patients with high-risk prostate cancer. Patients were treated using a dose-painting approach; the boost dose was limited to 86 Gy in 37 fractions, while keeping the rectal normal tissue complication probability to 5–6%. Rotational intensity-modulated radiotherapy was used with daily image guidance and fiducial markers.
Results: The median dose to the prostate (outside the boost volume) and urethra was 75.4 Gy/37 fractions (range 75.1–75.8 Gy), whereas the median boost dose was 83.4 Gy (range 79.0–87.4 Gy). The tumour control probability (TCP) (Marsden model) increased from 71% for the standard plans to 83.6% [76.6–86.8%] for the dose-painting boost plans. The mean (Lyman-Kutcher-Burman) normal tissue complication probability for rectal bleeding was 5.2% (range 3.3–6.2%) and 5.2% for faecal incontinence (range 3.6–7.8%). All patients tolerated the treatment well, with a low acute toxicity profile. At a median follow-up of 36 months (range 24–50) there was no grade 3 late toxicity. Two patients had grade 2 late urinary toxicity (urethral stricture, urinary frequency and urgency), one patient had grade 1 and one grade 2 late rectal toxicity. The mean prostate-specific antigen at follow-up was 0.81 ng/ml after stopping hormone therapy; one patient relapsed biochemically at 32 months (2.70 ng/ml).
Conclusions: The toxicity for this radiobiological guided dose-painting protocol was low, but we have only treated a small cohort with limited follow-up time. The advantages of this treatment approach should be established in a clinical trial.

Key words: Dose-painting; prostate cancer; radiobiological modelling; toxicity

Introduction

Prostate patients with low-risk tumours have satisfactory outcomes when treated with conventional doses of 74 Gy in 2 Gy fractions [1]. However, poorly differentiated and bulky tumours may need doses over 80 Gy to achieve local control; severely hypoxic tumours may require even higher doses [2–5]. Delivering such high doses to the whole prostate gland would cause an undesirable increase in complications. If tumour nodules or dominant intra-prostatic lesions (DIL) can be identified with functional magnetic resonance imaging (MRI) [6], boosting subvolumes to a higher dose can be an effective strategy to improve local control without increasing complication rates [7–12]. A dose-painting approach requires an accurate localisation of the DIL(s) on the planning computed tomography scan and the minimisation of intra- and inter-fractionation shifts [13,14].

Here we describe how we planned and treated 11 patients with a dose-painting protocol using radiobiological objectives [7,15] in the framework of a feasibility study. We also report on toxicity and biochemical status after a mean follow-up of 36 months.

Materials and Methods

Patients and Follow-up

Patients with localised high-risk prostate carcinoma, i.e. at least two risk factors prostate-specific antigen (PSA) ≥

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20 ng/ml, dominant Gleason 4 to 5, stage T3a or T4 on MRI or a single risk factor plus a bulky tumour (diameter >5 mm) [4] were invited to take part in a feasibility study, prior to a randomised trial. Eleven patients were recruited after obtaining informed consent (see Table 1 for patient characteristics). Patients had neoadjuvant hormone therapy starting 3 months before radiotherapy; the duration was 6 months or 3 years at the clinician's discretion. All patients were treated with a dose-painting plan (see below). Acute and late toxicity were graded prospectively according to the Radiation Therapy Oncology Group (RTOG) and the Common Toxicity Criteria version 4 toxicity scales. Patients were followed up 3 monthly until month 6 and 6 monthly thereafter, with a toxicity assessment and a PSA test at each visit.

Imaging and Contouring

Patients underwent a functional MRI scan before a diagnostic sextant biopsy, according to the European Society of Uroradiology (ESUR) guidelines [6]. At least one DIL volume was identified in all patients; these were outlined and graded by a radiologist. The presence, location and pathology were confirmed by targeted biopsies or template biopsies if the MRI DIL grading was 1–3 according to the ESUR definition [16].

Planning computed tomography and MRI were acquired and registered with the use of fiducial markers and an indwelling 12G soft Foley urethral catheter. Patients emptied their bowels with a mini enema and drank 300 ml of water 20 min before scanning. Planning scans were taken supine with knee and ankle support from the bottom of the sacro-iliac joints to below the anal margin. Registration with both fiducial markers and catheter was found to be more accurate than using fiducial markers alone. DIL contours were manually transferred to the planning dataset by the clinician. This procedure produced more appropriate boost volumes than a rigid co-registration of diagnostic MRI and planning MRI. The clinical target volume (CTV1) included the prostate and seminal vesicles; the planning target volume (PTV1) was formed by the addition of a 9 mm margin. CTV2 included the prostate and base of the seminal vesicles; PTV2 was formed by the addition of a 5 mm margin; the margin was reduced to 2 mm posterior when overlapping with the rectum [17]. The gross tumour volume (GTV3) included the DIL(s) to which 3 mm were added to form CTV3 without extending beyond CTV2 or overlapping rectum, bladder and urethra. PTV3 was generated by the addition of 2 mm to CTV3 (Figure 1). Because of the uncertainty of boost-volume definition, we used a 5 mm margin from GTV3 to PTV3 [18].

Table 1
Patient characteristics

	Mean	Range
Age (years)	68	49–77
PSA at diagnosis (ng/ml)	15.9	6.8–51
T2N0M0 stage (MRI)	6	
T3a or T4N0M0 (MRI)	5	
Gleason score 7	6	
Gleason score 8 or 9	5	
DIL volume (cm^3)	5.3	1.9–11.1
Length of follow-up (months)	36	24–50
PSA at follow-up (ng/ml)*	0.81	0.1–2.7
Genitourinary toxicity† grade 1/2	2/2	
Gastrointestinal toxicity† grade 1/2	1/1	

PSA, prostate-specific antigen; MRI, magnetic resonance imaging; DIL, dominant intra-prostatic lesion.

* Results for eight patients post-hormone therapy and with normal testosterone levels.

† Incidence of any late toxicity >3 months after starting radiotherapy.

Treatment Planning

Three treatment plans were created per patient with dose prescriptions of 74 Gy to PTV2 and 64 Gy to PTV1. The first (reference) plan was a 37-fraction, five-beam inverse-optimised intensity-modulated radiotherapy plan without boost. The plan set-up and optimisation goals were adapted from the 74 Gy arm of the CHHIP trial [19–23]. From the resulting dose distribution we calculated the normal tissue complication probability (NTCP) (Lyman-Kutcher-Burman model [24]) to be used as toxicity limits for the subsequent plans, and tumour control probability (TCP) (Marsden model) for comparison [24] – for the parameters used, see next section. The second plan was an experimental 11-coplanar beam plan generated on a research treatment planning system (TPS; Philips Research Pinnacle, Madison, USA). The large number of beams was used to give the research TPS comparable degrees of freedom to the clinical TPS used for the final plan. This research plan was inverse-optimised with a combination of custom radiobiological and standard dose/volume objectives to achieve as high a DIL TCP as possible while not exceeding the NTCP limits from the reference plan. The clinical treatment plan was created on a clinical TPS (Varian Eclipse, Palo Alto, USA) using a rotational intensity-modulated radiotherapy delivery technique; dose–volume histogram (DVH) objectives were derived directly from the research plan dose distribution. Daily image guidance and weekly cone beam

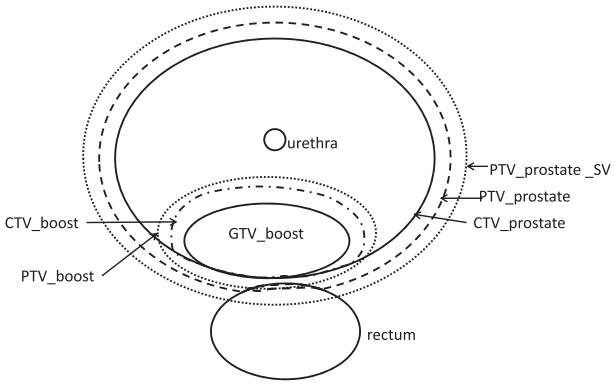

Fig 1. Planning target volumes.

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