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Original Article

A Comparison of Treatment Planning Techniques Used in Two Randomised UK External Beam Radiotherapy Trials for Localised Prostate Cancer

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ABSTRACT:
Aims: **To compare the radiotherapy planning techniques from two multicentre randomised external beam radiotherapy trials in the UK of conformal radiotherapy vs intensity-modulated radiotherapy (IMRT).**
Materials and methods: **Sixteen sequential patients with histologically confirmed localised prostate cancer treated in the conventional or hypofractionated IMRT trial (CHHiP) were planned using both the CHHiP and Medical Research Council RT-01 planning protocols to 74 Gy in 37 daily fractions. The CHHiP plan used a single phase simple forward planned three-field IMRT plan for easy multicentre adoption. The RT-01 plan used two phases: three-field conformal radiotherapy plan to 64 Gy followed by a six-field boost of 10 Gy. After coverage of the planning target volumes according to the respective trial protocols, the dose to the rectum and bladder was assessed for the two planning techniques.**
Results: **There was acceptable planning target volume coverage by both the CHHiP and RT-01 plans. All CHHiP plans produced lower mean irradiated rectal volumes at all measured dose levels compared with the RT-01 plans, particularly for irradiated rectal volumes at 50 and 70 Gy ($P < 0.05$). In the cases when a CHHiP plan failed to meet its own trial dose constraints, the volumes of irradiated rectum were less than if an RT-01 planning technique had been used. The CHHiP plans gave lower mean irradiated bladder volumes at both 50 and 60 Gy, but higher volumes at 74 Gy. These differences in irradiated bladder volumes were significant at the 60 and 74 Gy dose levels ($P < 0.05$) in favour of the CHHiP and RT-01 plans, respectively.**
Conclusion: **The forward planned CHHiP IMRT planning solution gives more favourable rectal sparing than the RT-01 plan. This is important to limit any potential increase in late rectal toxicity for prostate cancer patients treated with high-dose conventional or hypofractionated schedules. South, C. P. *et al*. (2008). *Clinical Oncology* 20, 15—21**

Key words: Conformal radiotherapy, hypofractionation, intensity-modulated radiotherapy, prostate cancer

Introduction

Radiotherapy is a recognised curative treatment option for localised prostate cancer [1]. Advances in radiation treatment planning and technique have led to the development of conformal radiotherapy (CFRT) and intensity-modulated radiotherapy (IMRT) methods, which have permitted better matching of the high dose distributions to the planning target volume (PTV). The added benefit of improved dose distributions is 'conformal avoidance' of unnecessary dose to the surrounding normal structures and tissues such as the rectum and the penile bulb in prostate radiotherapy. It is anticipated that both CFRT and IMRT can improve the therapeutic ratio in radical prostate radiotherapy and this will translate into opportunities for safer dose escalation and improved local control in prostate cancer as well as reduced radiotherapy-related morbidity.

Institutional experiences and results from phase I/II radiotherapy studies suggest that both these goals may be achievable [2—4]. These reports suggest that in prostate radiotherapy a dose—response relationship exists for tumour control with a dose—volume complication relationship for the development of late normal tissue damage. The benefit of conformal shaping of treatment fields in prostate cancer has been reported in a randomised trial that compared unshaped fields (conventional radiotherapy) and shaped fields (CFRT) at a dose of 64 Gy [5]. This trial showed that the use of CFRT provided a significant reduction in clinically relevant proctitis levels, which remains the dose-limiting late side-effect of prostate radiotherapy. The

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potential benefit of dose escalation in prostate cancer was first reported in a prospective trial from MD Anderson Cancer Center that randomised patients to either 70 or 78 Gy using a combination of conventional and CFRT techniques in both treatment arms [6]. This study reported a 6% improvement in biochemical prostate-specific antigen (bPSA) failure-free survival for men receiving the 78 Gy dose arm compared with the 70 Gy dose arm, with the greatest benefit for the subgroup of men with pre-treatment PSA of greater than 10 ng/ml. The benefits in bPSA rates, in fact, have been larger (up to 10–18%) in the other randomised trials [7–10]. Additionally, the Medical Research Council (MRC) RT-01 trial and the Massachusetts General Hospital/Loma Linda University Medical Center trial have shown benefits in all risk groups (low to high) [9,10], whereas the MD Anderson Cancer Center and the Netherlands trials did not show benefit in low-risk patients [6,8].

More importantly, the effect of dose escalation in these reported randomised trials has been up to a two-fold increase in late rectal toxicity [6–10]. In the MRC RT-01 trial, dose escalation to 74 Gy compared with 64 Gy caused a small but measurable and clinically significant increase in bowel side-effects. The change was statistically significant using both physician-based and patient-completed quality-of-life instruments. For example, the hazard ratio for $\geq$ grade 2 Radiation Therapy Oncology Group late toxicity was 1.47 ($P = 0.005$) for the dose-escalated group and using the University of California Los Angeles prostate cancer index the hazard ratio for modest or greater late bowel symptoms was 1.28 ($P = 0.02$) for patients treated with 74 Gy. We therefore consider it of considerable importance to ensure that radiotherapy techniques used in future trials of high-dose treatments produce more favourable dose distributions that would probably moderate this potential increase in treatment-related side-effects.

Recently, radiobiology reviews of prostate radiotherapy have suggested that the alpha/beta ratio of prostate cancer cells may be much lower that that of other tumours [11–13]. If correct, this hypothesis suggests that shorter courses of radiotherapy giving a higher dose per fraction (i.e. $>$ 2 Gy per fraction) at each treatment (hypofractionated radiotherapy) may give improved local control for the same or reduced level of radiation-related side-effects [14,15]. The use of hypofractionation has additional implications for patient convenience and radiotherapy resource allocation. In order to test this hypothesis, a three-arm randomised trial was developed to compare the use of 74 Gy using 2 Gy per fraction over 7.5 weeks with 57 and 60 Gy using 3 Gy per fraction over 4 weeks. The Conventional or Hypofractionated High-dose Intensity-modulated Radiotherapy for Prostate Cancer (CHHiP) trial uses forward or inverse planned IMRT techniques. In order to minimise treatment-related side-effects while delivering a high dose to the prostate, three different clinical target volumes (CTV) are defined based on the individual's clinical risk profile for sub-clinical involvement of their seminal vesicles [16], with a different dose prescribed to each corresponding PTV. The aim of this planning study was to compare the dose to normal tissues and dose-limiting structures, such as the rectum, when delivering prescriptions using the forward planned IMRT technique in the CHHiP trial compared with the technique used to treat the prostate to 74 Gy using the MRC RT-01 trial protocol [17].

Materials and Methods

The initial 16 patients sequentially enrolled into the CHHiP trial were used in this planning study. All patients had histologically confirmed and clinically staged localised prostate cancer. All patients were treated radically within the CHHiP trial. This patient cohort had a mean age at diagnosis of 68 years (range 54–78), a median Gleason score of 6 (range 5–7) and a mean PSA at presentation of 12.7 ng/ml (range 0.91–33.4).

Treatment plans were produced and analysed using the ADAC Pinnacle3 v6.2b treatment planning system (Philips Medical Systems, Milpitas, CA, USA), with doses calculated over an isotropic dose grid with 2 mm spacing using a collapsed-cone convolution algorithm. Plans were produced for treatment on Elekta SL-series (Elekta Oncology Systems, Crawley, UK) linear accelerators at a beam energy of 10 MV. Field shaping was achieved in all cases using multileaf collimators with a leaf width of 1 cm at the isocentre. For each patient, treatment plans were created according to each of the two trial protocols. The definitions of gross tumour volume, CTV and PTV for each target within the RT-01 and CHHiP trials are outlined in Table 1. The aim of this planning exercise was to obtain dosimetric coverage of the nominated PTV as designated by the respective trial protocol and its dose constraints while evaluating the dose

Table 1 – Definition of target volumes used in the RT-01 and CHHiP trials

	Low risk	Moderate risk
RT-01 trial		
CTV1	Prostate + base of seminal vesicles	Prostate + seminal vesicles
PTV1	GTV1 + 1 cm	GTV1 + 1 cm
CTV2	Prostate	Prostate
PTV2	Prostate	Prostate
CHHiP trial		
GTV1	Prostate	Prostate
CTV1	Prostate + base of seminal vesicles + 0.5 cm	Prostate + seminal vesicles + 0.5 cm
PTV1	CTV1 + 0.5 cm	CTV1 + 0.5 cm
GTV2	Prostate	Prostate
CTV2	Prostate + 0.5 cm	Prostate + 0.5 cm
PTV2	CTV2 + 0.5 cm/0.0 cm*	CTV2 + 0.5 cm/0.0 cm*
GTV3	Prostate	Prostate
CTV3	Prostate	Prostate
PTV3	CTV3 + 0.5 cm/0.0 cm†	CTV3 + 0.5 cm/0.0 cm†

CTV, clinical target volume; PTV, planning target volume; GTV, gross tumour volume. *0.0 cm posteriorly except for computed tomography slices in which the rectum seems large and distended. †0.0 cm posteriorly.