Radiotherapy and Oncology xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

High-dose-rate brachytherapy alone given as two or one fraction to patients for locally advanced prostate cancer: Acute toxicity

Peter Hoskin, Ana Rojas *, Peter Ostler, Robert Hughes, Roberto Alonzi, Gerry Lowe, Linda Bryant

Cancer Centre, Mount Vernon Hospital, Middlesex, UK

ARTICLE INFO

Article history:
Received 20 February 2013
Received in revised form 11 August 2013
Accepted 7 September 2013
Available online xxxx

Keywords:
High-dose-rate brachytherapy
Monotherapy
Prostate cancer
Single dose
Large dose per fraction
Early adverse events

ABSTRACT

Background: To evaluate early urinary (GU) and gastrointestinal (GI) adverse events (AEs) after two or one fraction of high-dose rate brachytherapy (HDR-BT) in advanced prostate cancer.

Patients and methods: 165 patients were treated with 2 × 13 Gy (n = 115), or a single dose of 19 Gy (n = 24) or 20 Gy (n = 26) HDR-BT. Early AEs were assessed using the RTOG scoring system and the International Prostate Symptom Score (IPSS).

Results: Week-2 prevalence of severe IPSS symptoms was higher after 20 Gy than after 26 or 19 Gy but by 12 weeks all groups were at pre-treatment levels or less. Grade-3 GU toxicity was observed ⩽9% of patients. No Grade 4 GU and no Grade 3 or 4 GI complications were observed. However, there was a significant increase in catheter use in the first 12 weeks after implant after 19 and 20 Gy compared with 2 × 13 Gy.

Conclusion: Single dose HDR-BT is feasible with acceptable levels of acute complications; tolerance may have been reached with the single 19 Gy schedule.

A variety of radiotherapy modalities are available for the radical treatment of locally advanced prostate cancer, all achieving similar rates of biochemical control although with differing degrees and types of genito-urinary and rectal morbidities.

High-dose-rate brachytherapy (HDR-BT) monotherapy was first proposed by Yoshioka et al., almost 2 decades ago [1]. Radiobiological considerations, which assume a low α/β for prostate cancer, predict a significant advantage for HDR-BT alone delivered in a small number of very large fractions in terms of total biologically effective dose (BED) over external beam radiotherapy (EBRT) and low-dose rate brachytherapy (LDR-BT). HDR-BT also offers other advantages over EBRT and LDR-BT relating to dosimetry and radioprotection [1]. An increasing literature on this subject supports many of these claims [2–7].

There are however disadvantages for the patient when compared to LDR brachytherapy [1]. The "convenience factor" is considered one of, if not the main, drawback primarily related to using multifraction schedules. In an effort to improve this recent work we attempted to reduce the number of fractions. Previous schedules in use at our Centre have included 4 × 8.5, 4 × 9 and 3 × 10.5 Gy [2,4]. Subsequently further cohorts have been treated with two fractions of 13 Gy or a single dose of 19 or 20 Gy. Early outcome data from these three cohorts are presented here.

Patients and methods

Between July 2008 and August 2012, 165 patients, with histologically proven prostate adenocarcinoma were sequentially enrolled into this study, which received ethical approval through the UK Integrated Research Application System. Written informed consent was mandatory. Patients with localised T_1–T_{3b} tumours, based on digital rectal examination and pelvic magnetic resonance imaging (MRI) were included. Exclusion criteria were evidence of metastases on isotope bone scan or pelvic MRI, a previous TURP and those unfit for a general or spinal anaesthetic. Stopping-rules were defined: if excess severe morbidity (RTOG toxicity ⩾3) was encountered in 1 out of the first 3 or 2 out of the first 6 patients then that dose level would be terminated.

Treatment schedule

The technique of HDR iridium (^{192}Ir) after-loading used has been previously described [2]. Briefly, after implantation computed tomography imaging (CTI) and MRI were obtained for all patients and the clinical target volume (CTV) was defined by the prostate capsule and extended to cover extra-capsular and seminal vesicle disease. The planning target volume (PTV) was a 3 mm volumetric expansion from the CTV, constrained to the anterior rectal wall as defined in the GEC ESTRO guidelines [8]. On the day of implant, patients received either a single dose of 19 or 20 Gy, or the first fraction of the 2 × 13 Gy-schedule. The dose was prescribed to the PTV as a minimum peripheral dose. In the two-fraction cohort a CT scan

* Corresponding author. Address: Cancer Centre, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, UK.
E-mail addresses: arc03@btconnect.com, arc@macunlimited.net (A. Rojas).

0167-8140/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2013.09.025

Table 1
Urethral and anterior rectal wall dosimetry constraints and achieved doses.

Organ	2 × 13 Gy	19 Gy	20 Gy
Urethra			
$D_{30\%}$ (Gy)	13.8–14.8	20.5–20.9	20.5–21.1
[Constraint (Gy)]	*14.25	<20.8	<20.8
$D_{10\%}$ (Gy)	Not defined	20.9–21.8	20.7–21.9
[Constraint (Gy)]	Not defined	<22	<22
Volume (cc)	0–0.06	0	0
	*($V_{15\ Gy}$)	($V_{28.5\ Gy}$)	($V_{30\ Gy}$)
Rectum			
D_{2cc} (Gy)	5.8–10.3	7.92–15	11.1–15.7
[Constraint (Gy)]	*10	15	15
Volume (cc)	0–0.25	0–0.04	0–0.1
	*($V_{12.5\ Gy}$)	($V_{19\ Gy}$)	($V_{20\ Gy}$)

* Per fraction.

was obtained before the second fraction, and appropriate adjustments made to dwell positions to optimise dose distribution compensating for any changes in implant dosimetry [9]. Table 1 shows the rectal and urethral planning constraints and the range of urethral and anterior rectal wall dosimetry parameters achieved for each schedule.

Endpoints and statistical analysis

Early adverse events were evaluated using the RTOG scoring system for genito-urinary and gastro-intestinal morbidity and the International Prostate Symptom Score (IPSS). Assessments were scheduled at 2, 4 and 12 weeks after the first fraction. Not all patients were seen precisely at these intervals therefore the follow-up times were grouped in 3 "bin categories" comprising follow-ups on weeks 1.5–3, 3.5–6 and 9–16 weeks. For convenience, intervals as "intended" are used as labels in Figs. 1 and 2 and Table 3.

Differences in the prevalence of demographic features, genito-urinary, gastro-intestinal and IPSS symptoms were compared using χ^2 and Kruskal–Wallis tests for categorical and continuous variables and differences in catheter use compared using a χ^2 test. Where appropriate, the level of significance was adjusted using Bonferroni's correction method to compensate for multiple comparisons.

Results

One hundred and fifteen patients were treated with 26 Gy in two fractions, 24 received 19 Gy and 26 received 20 Gy. Table 2 summarises demographics and risk categories. Differences in the distribution of co-variates between groups were not significant.

Fig. 1 shows prevalence of moderate and severe IPSS symptoms for each schedule prior to implant and during the first 12 weeks after treatment. On weeks 2 and 4 moderate and/or severe IPSS symptoms increased relative to pre-treatment levels, particularly after 20 Gy for patients with IPSS ⩾20, however differences were not significant. Nonetheless by week 12 the percentage of patients with moderate or severe symptoms was at or below baseline pre-treatment levels.

Prevalence of RTOG early urinary and bowel adverse events is summarised in Table 3. There is no evidence of a difference between dose groups. No Grade 4 urinary and no Grade 3 or 4

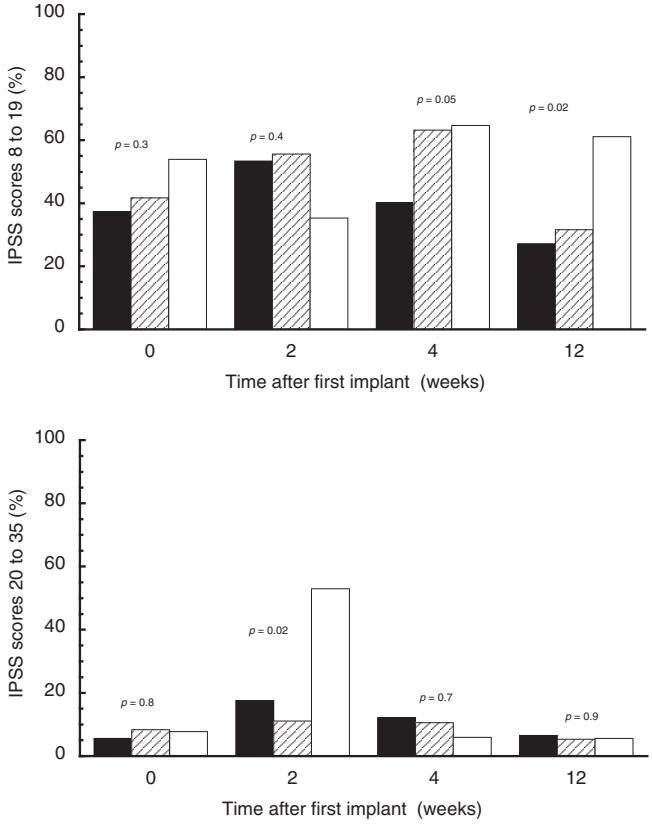
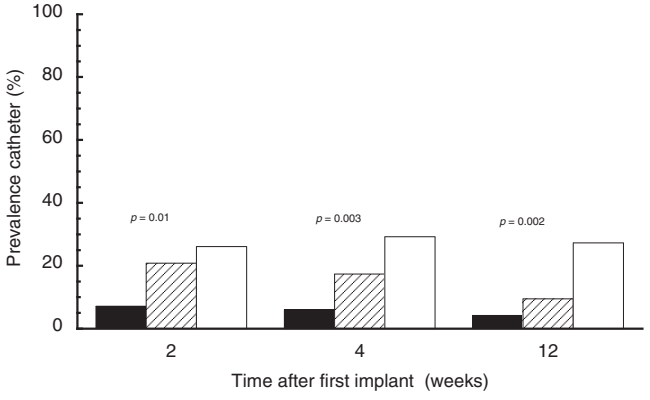


Fig. 1. Prevalence of moderate (top panel; scores 8–19) or severe (bottom panel; scores 20–35) IPSS symptoms before and after 2 × 13 Gy (solid bar), 19 Gy (hatched bar) or 2 × 13 Gy (empty bar) high-dose-rate brachytherapy alone at the indicated follow-up times ($p < 0.006$ considered significant).



Dose	Catheter present on 1 FU	Catheter present on 2 FUs	Catheter present on 3 FUs
26 Gy (n = 109)	2 1.8%	3 2.8%	4 3.7%
19 Gy (n = 24)	1 4.2%	2 8.3%	2 8.3%
20 Gy (n = 23)	0	2 8.7%	5 21.7%
All patients (n = 156)	3 1.9%	7 4.5%	11 7.1%

Fig. 2. Top: Prevalence of catheter bearing (top panel) during the first 12 weeks after 2 × 13 Gy (solid bar), 19 Gy (hatched bar) or 20 Gy (empty bar) high-dose-rate brachytherapy alone at the indicated follow-up times ($p < 0.006$ considered significant). Bottom panel: Table illustrating the number and percent of patients who had a catheter on one, two or three of the 3 planned follow-up events.

Please cite this article in press as: Hoskin P et al. High-dose-rate brachytherapy alone given as two or one fraction to patients for locally advanced prostate cancer: Acute toxicity. Radiother Oncol (2013), http://dx.doi.org/10.1016/j.radonc.2013.09.025