ELSEVIER

Brachytherapy ■ (2016) ■

BRACHYTHERAPY

Dose escalation with external beam radiation therapy and high-dose-rate brachytherapy combined with long-term androgen deprivation therapy in high and very high risk prostate cancer: Comparison of two consecutive high-dose-rate schemes

Alicia Olarte[1], Mauricio Cambeiro[1], Marta Moreno-Jiménez[1,4], Leire Arbea[1], José Luis Pérez-Gracia[2], Ignacio Gil-Bazo[2], Ignacio Pascual[3], Javier Aristu[1], Rafael Martínez-Monge[1,*]

[1]*Department of Radiation Oncology, Clínica Universitaria de Navarra, University of Navarra, Pamplona, Navarre, Spain*
[2]*Department of Medical Oncology, Clínica Universitaria de Navarra, University of Navarra, Pamplona, Navarre, Spain*
[3]*Department of Urology, Clínica Universitaria de Navarra, University of Navarra, Pamplona, Navarre, Spain*
[4]*Instituto de Investigación Biosanitaria de Navarra (IdiSNA), Pamplona, Navarre, Spain*

ABSTRACT

PURPOSE: To compare rectal toxicity, urinary toxicity, and nadir+2 PSA relapse-free survival (bRFS) in two consecutive Phase II protocols of high-dose-rate (HDR) brachytherapy used at the authors institution from 2001 to 2012.

METHODS AND MATERIALS: Patients with National Comprehensive Cancer Network high risk and very high risk prostate cancer enrolled in studies HDR4 (2001−2007, $n = 183$) and HDR2 (2007−2012, $n = 56$) were analyzed. Patients received minipelvis external beam radiation therapy/intensity-modulated external radiotherapy to 54 Gy and 2 years of androgen blockade along with HDR brachytherapy. HDR4 protocol consisted of four 4.75 Gy fractions delivered in 48 hours; the HDR2 protocol delivered two 9.5 Gy fractions in 24 hours. Average 2-Gy equivalent dose ($\alpha/\beta = 1.2$) prostate D_{90} doses for the HDR4 and HDR2 groups were 89.8 Gy and 110.5 Gy, respectively ($p = 0.0001$). Both groups were well balanced regarding risk factors. Prior transurethral resection of the prostate was more frequent in the HDR2 group ($p = 0.001$).

RESULTS: After a median followup of 7.4 years (range, 2−11.2), there was no difference in adverse grade ≥ 2 rectal events (HDR4 = 10.4% vs. HDR2 = 12.5%; p = ns) or grade ≥3 (HDR4 = 2.2% vs. HDR2 = 3.6%; p = ns). No differences in urinary grade ≥2 adverse events (HDR4 = 23% vs. HDR2 = 26.8%; p = ns) or grade ≥3 (HDR4 = 7.7% vs. HDR2 = 8.9%; p = ns) were detected. The 7-year bRFS for HDR4 and HDR2 protocols was 88.7% and 87.8%, respectively (p = ns).

CONCLUSIONS: HDR4 and HDR2 protocols produce similar results in terms of toxicity and bRFS at the intermediate time point of 7 years.

Keywords: Prostate cancer; High risk; Androgen deprivation therapy; 3DCRT; HDR brachytherapy

Introduction

The National Comprehensive Cancer Network (NCCN) recommends that most patients with NCCN criteria high risk prostate cancer (HRPC) or very high risk prostate cancer (VHRPC) be treated with standard-dose external beam radiation therapy (EBRT) combined with long-term (2−3 years) androgen deprivation therapy (ADT) (1, 2). Although combined modality therapy compares favorably with EBRT alone at a variety of end points, including freedom from biochemical failure (2), local control (1, 2), distant metastases-free survival (2), disease-free survival (1, 2), cause-specific survival (2), and overall survival (1), about 50% of the patients will still develop biochemical failure (3).

Received 5 November 2015; received in revised form 14 December 2015; accepted 15 December 2015.

Conflict of interest: The authors declare no conflict of interest.

* Corresponding author. Department of Oncology, Clínica Universitaria de Navarra, University of Navarre, Avda Pío XII s/n, Pamplona, Navarre, Spain. Tel.: +34-948-255400; fax: +34-948-255500.

E-mail address: rmartinezm@unav.es (R. Martínez-Monge).

1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2015.12.008

Radiation dose escalation without ADT is a completely different strategy designed to improve treatment results in HRPC and VHRPC. There is a large body of evidence showing improved biochemical control rates (4–7) and more efficient postirradiation biopsy status with higher radiation dosages.

Because both dose escalation and combined ADT have shown improved treatment results in HRPC and VHRPC, we started the high-dose-rate (HDR4) Phase II trial in January 2001 to investigate the feasibility of combined long-term ADT and dose escalation with HDR brachytherapy. The reports on feasibility and intermediate-term results of the HDR4 trial can be found elsewhere. The HDR4 trial closed to accrual in 2007 and was replaced by the HDR2 trial. In the HDR2 trial, a further dose intensification was attempted by reducing the number of fractions from four to two while keeping the total physical dose of 19 Gy. The present study compares the rates of rectal toxicity, urinary toxicity, and nadir+2 PSA relapse-free survival achieved by protocols HDR4 and HDR2.

Methods and materials

Eligibility criteria

Patients with NCCN criteria HRPC and VHRPC were prospectively enrolled in two consecutive Phase II protocols of dose escalation with HDR brachytherapy. Protocol HDR4 was open to accrual from January 2001 to October 2007 and protocol HDR2 from November 2007 to July 2012. Moving toward a shorter HDR protocol was based on a growth in information between 2001 and 2007 showing that larger doses per fraction in HDR brachytherapy were both safe and efficacious, a desire to improve patient comfort and compliance with department logistics, and decreased uncertainty regarding the motion or deformation of the target relative to the applicator.

Patients with a single high-risk factor or two intermediate-risk factors were classified as HRPC, and patients with a single very high-risk factor, two high-risk factors, or two intermediate-risk factors and a single high-risk factor were classified as VHRPC. The median ages at diagnosis of the patients treated under the HDR4 and HDR2 protocols were 70 years (range, 48–82) and 67 years (range, 45–80), respectively. The median pretreatment PSAs of the patients treated under HDR4 and HDR2 protocols were 14.4 ng/mL (range, 4.0–98.2) and 11.5 (2.2–73.1), respectively.

The treatment protocol was approved by the Institutional Review Board, and patients gave informed consent before protocol entry. All patients enrolled had a life expectancy of at least 5 years and pretreatment PSA levels of less than 100 ng/mL. All patients were staged according to the sixth edition criteria of the American Joint Committee on Cancer (Table 1). Pretreatment evaluation included a complete history and physical examination, baseline PSA, complete blood count, renal and liver function tests, chest x-ray, CT or MRI of the abdomen and pelvis, and bone scan.

Table 1
Patient and tumor factors

	HDR4 (n = 183)		HDR2 (n = 56)		p[a]
Age					
<70	83	45.4	35	62.5	0.025
≥70	100	54.6	21	37.5	
Prior TURP	5	2.7	8	14.3	0.001
Gleason					
Gleason 2–6	51	27.9	14	25	ns
Gleason 7	75	41	21	37.5	
Gleason 8–10	57	31.1	21	37.5	
Pretreatment PSA					
<10.0 ng/mL	48	26.2	23	41.1	ns
10.0–19.9 ng/mL	70	38.3	20	35.7	
≥20.0 ng/mL	65	35.5	13	23.2	
AJCC stage[b]					
T1b–T2a	36	19.7	11	19.6	0.03
T2b–T2c	104	56.8	18	32.1	
T3a	25	13.7	16	28.6	
T3b–T4	18	9.8	11	19.6	
NCCN risk category					
Single factor[c]					
Intermediate risk	65	35.5	13	23.2	ns
High risk	100	54.6	32	57.1	
Very high risk	18	9.8	11	19.6	
Combined factors[d]					
High risk	117	63.9	29	51.8	ns
Very high risk	66	36.1	27	48.2	

HDR = high dose rate; TURP = transurethral resection of the prostate; PSA = prostate-specific antigen; NCCN = National Comprehensive Cancer Center; ns = not significant.

[a] Comparison of variables was performed with the χ^2 test.

[b] American Joint Committee on Cancer 2.2014 guide.

[c] Multiple same-risk factors do not promote into the next risk group.

[d] Multiple same-risk factors promote into the next risk group.

External radiation

The details of the treatment program have been described previously (8). Target definition was done according to the recommendations of the International Commision on Radiological Units and Measurements reports 50 and 62. The PTV_1 received 45 Gy in 25 daily treatments and included the lymph nodes of the external iliac, internal iliac, and presacral node chains bilaterally (clinical target volume $[CTV]_1$) (9), the seminal vesicles (CTV_2), and the prostate (CTV_3) with 2.0-cm margins. The PTV_2 received 54 Gy in 30 daily treatments and included the CTV_2 and CTV_3 with 2.0 cm margins in all directions, except 1.5-cm margins posteriorly. A four-field technique with 15 MV photons was used in most patients treated under the HDR4 and HDR2 protocols. The later 26 patients included in the HDR2 protocol were treated with intensity-modulated external radiotherapy (IMRT). IMRT target delineation of CTV_1, CTV_2, and CTV_3 followed the same principles outlined above. IMRT was delivered with the step-and-shoot technique with seven gantry angles and a median of 51 segments (range, 28–78) to deliver a median dose of 53.3 Gy (41.5–54.7) in a median of 25 (range, 15–27) fractions.