



# Three-year outcomes of 324 prostate carcinoma patients treated with combination high-dose-rate brachytherapy and intensity modulated radiation therapy

Jekwon Yeh, Brandon Lechrich, Albert Mesa, Carolyn Tran, Lucy Barnes, Christopher Long, Jeffrey Yoshida, Robert Torrey, Michael Gazzaniga, Shlomi Albert, Alan Weinberg, Ali Alavi, Ruben Baghdassarian, Stuart Chalfin, John Ravera, Kenneth Tokita

Cancer Center of Irvine, Irvine, CA 92618, USA

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*Correspondence to:* Jekwon Yeh, MD. Cancer Center of Irvine, 16100 Sand Canyon #130, Irvine, CA 92618, USA. Email: jekwon.md22@yahoo.com.

**Background:** To report 3-year outcomes of patients treated with combination high-dose-rate (HDR) brachytherapy with intensity modulated radiation therapy (IMRT) for prostate carcinoma.

**Methods:** Between 2002 and 2014, 324 prostate carcinoma patients received combination HDR brachytherapy [Iridium-192 (Ir-192)] and external beam IMRT. A total of 16 Gray (Gy) over 4 fractions was administered with HDR brachytherapy followed by 59.4 Gy over 33 fractions of external beam IMRT. Rates of biochemical control and distant metastasis were recorded along with incidence of late genitourinary (GU) and gastrointestinal (GI) toxicities.

**Results:** Three-year prostate specific antigen (PSA) biochemical control rates for low, intermediate, and high risk patients were 95%, 99%, and 83%, respectively. Three-year incidence of distant metastases for low, intermediate, and high risk patients were 0%, 0%, and 7%, respectively. Three-year incidence of late grade 1, 2, and 3 GU toxicities were 9.0%, 3.0%, and 1.5%, respectively, and the 3-year incidence of grade 1, 2, and 3 GI toxicities were 6%, 2.2% and 0.4%, respectively. Multivariate analysis showed that age (>65), PSA (>10), and Gleason scores ( $\geq 8$ ) were predictive of decreased biochemical control.

**Conclusions:** Combination HDR/IMRT for the treatment of clinically localized prostate cancer yields excellent clinical outcomes. High rates of PSA control and low incidence of late GI and GU toxicities are achievable with combination HDR/IMRT treatment for prostate cancer.

**Keywords:** Brachytherapy; cancer; adenocarcinoma; radiation; intensity modulated radiation therapy (IMRT); prostate; high-dose-rate (HDR)

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## Introduction

There are various radiation treatment options for men with prostate cancer. Treatment options include: conventionally fractionated radiation [intensity modulated radiation therapy (IMRT)], stereotactic ablative radiotherapy, and interstitial implantation [high-dose-rate (HDR), low dose rate (LDR)]. Numerous reports have shown a combination

of HDR and IMRT confers excellent prostate specific antigen (PSA) control rates (1-3). Some reports have shown improved biochemical control rates for patients treated with combination radiation as compared with patients treated with external beam radiation alone (1,4-10). In this study we report clinical outcomes from combination HDR and IMRT.

## Methods

This was a single center study performed at the Cancer Center of Irvine (Irvine, CA). Study candidates included non-metastatic patients with T2–T3b tumors and prostate glands less than 60 cc. We did not classify patients in the cT1 “clinical T1” category as the T1 staging does not accurately quantify the amount of tumor in the prostate. All patients were classified into T2–T3b categories based on biopsy, physical exam, and imaging studies. There were no stage T4 patients. All Gleason and PSA levels were included. Patients were stratified into risk groups according to NCCN Guidelines v1.2011. Gleason 3+4 [7] patients were treated without androgen deprivation therapy (ADT) unless PSA >10. Gleason scores 4+3 [7] and 4+4 [8] were treated with 6 months of ADT. Gleason 9 and 10 received 12 months of ADT. 158 patients (49%) received an absorbable polyethylene glycol (PEG) rectal spacer to help reduce rectal toxicity. All patients consented to having their full clinical data included in our research study.

### *HDR brachytherapy*

Two HDR implants were performed 1 week apart. During each implant procedure, the patient was positioned in the dorsal lithotomy position with either spinal or general anesthesia administered. A Foley catheter was placed into the bladder and expanded with 5 mL of contrast media. A 6.5-megahertz (MHz) endorectal ultrasound probe was inserted to provide ultrasound image guidance, and an interstitial template was secured against the perineum to position and secure the implant needles. Needles were implanted and placed strategically to provide optimal dose conformity. In a typical implant 13 to 15 needles were implanted. Dose was delivered twice daily, once in the morning and once again in the afternoon. Most patients received 4 Gray (Gy) per fraction for a total 8 Gy for each implant, 16 Gy for the two HDR implants combined. The average HDR dose was 17.7 Gy [standard deviation (SD) =3.3 Gy].

HDR plans were generated using the Brachyvision treatment planning program (varian medical systems). The prostate gland was contoured as both the clinical target volume (CTV) and planning target volume (PTV) for treatment planning. The brachytherapy dose was prescribed to the 100% isodose line. Treatment planning goals were as follows: prescribed dose to at least 90% of the CTV (V100 >90), nor more than 40% of the CTV to receive greater than 150% of prescribed dose (V150 <40%), maximum

urethral dose under 120%, and no more than 2 cc of either the rectum or bladder to receive greater than 75% of prescribed dose. For 158 patients (49%), a PEG spacer was injected during the second implant to aid in reducing the radiation dose the rectal area. The spacer material resorbs within 6 weeks of implantation.

### *IMRT*

IMRT treatment commenced approximately 1 week after the second HDR implant. A total dose of 59.4 Gy in 33 daily fractions was delivered with IMRT. The mean total IMRT dose was 57.1 Gy (SD =5.4 Gy).

IMRT treatment plans were generated using the Eclipse treatment planning system (varian medical systems). MRI fusion was utilized to better delineate target, normal structures and if applicable, the spacer material. An initial CTV was treated for the first 25 fractions followed by a modified CTV for the final eight fractions. The initial CTV was defined in one of two ways depending on the risk of pelvic lymph node involvement. If the risk of pelvic lymph node involvement was 15% or lower, the initial CTV was defined as the prostate gland and inferomedial 10 mm of the seminal vesicles (11). If the risk of pelvic lymph node involvement was greater than 15%, the initial CTV included the pelvic lymph nodes as defined by Hsu *et al.* (12). After the first 25 treatments, the CTV was defined as the prostate and inferomedial 10 mm of the seminal vesicles. For both the initial and modified CTV, the CTV was expanded 5–10 mm to produce a PTV. The bladder was contoured as seen on CT, while the rectum was contoured from the ischial tuberosities to the rectosigmoid intersection.

Treatment planning objectives were as follows: prescribed dose to at least 95% of the PTV (V100 >95%), maximum dose less than 110% of prescribed dose (PTVmax <110%). Rectal dose limits were kept within the Radiation Therapy Oncology Group protocol 0415 for IMRT for localized prostate cancer with no more than 15%, 20%, 25%, 35%, and 50% of the rectal volume receiving 60.4, 56.3, 52.3, 48.3, and 40.3 Gy, respectively.

### *Image-guided radiation therapy*

All patients had five gold fiducial markers inserted into the prostate. The fiducial markers were used for daily image guided radiation therapy. Cone beam computed tomography (CBCT) images were obtained prior to every

treatment. Using the original treatment planning CT as a reference, the gold fiducials were aligned precisely in three dimensions. This process was repeated prior to every treatment thus ensuring a high level of treatment accuracy.

### **PEG spacer use**

One hundred and fifty eight patients (49%) were treated in combination with a perirectal spacer made from PEG gel. This procedure has been detailed in previous reports (13), but here will be described briefly. A needle is placed under ultrasound guidance into the anterior perirectal space. 10 cc of the spacer material is injected to create an approximately 1.5 cm separation between the rectum and prostate. The spacer material resorbs and is excreted through the kidneys in roughly 6 weeks.

### **Biochemical control/overall survival**

PSA control was evaluated according to the Phoenix definition of biochemical failure (2 ng/mL over absolute nadir) (14). Biochemical control and overall survival were calculated according to the Kaplan-Meier method. The statistical significant threshold was 0.05.

### **Gastrointestinal (GI)/genitourinary (GU) toxicity**

Patients were evaluated at baseline, weekly during the external beam radiation, and every 3 months for the first year. If PSA results were stable the first year, patients were then evaluated every 4–6 months thereafter. Acute toxicity was defined as toxicity occurring during radiation and within 90 days after finishing radiation treatment.

Late toxicity was defined as all adverse events occurring 90 days after finishing treatment. All GI/GU adverse events from radiation treatment were recorded and graded by a board of physicians. GI and genito-urinary symptoms were graded during radiation treatments according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 grading scheme.

## **Results**

### **Biochemical control/overall survival/distant metastasis**

Of the 324 patients treated: 35 were low risk, 201 were intermediate risk, and 87 were high risk. Patient

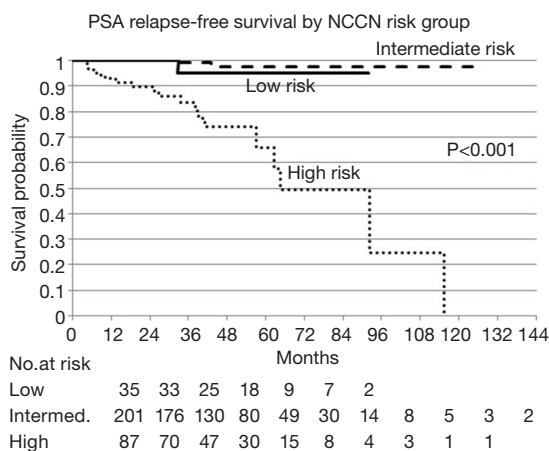
**Table 1** Patient characteristics

Patient characteristics	N	%
Age		
≤65	78	24.1
66–75	167	51.5
>75	79	24.4
Gleason total		
6 (3+3)	104	32.1
7 (3+4)	91	28.1
7 (4+3)	56	17.3
8 (4+4)	52	16.0
9 (4+5)	17	5.2
9 (5+4)	3	0.9
10 (5+5)	1	0.3
Stage		
T2a	91	28.2
T2b	68	21.0
T2c	160	49.4
T3a	3	0.2
T3b	2	0.6
NCCN risk group		
Low	35	10.9
Intermediate	202	62.2
High	87	26.9
Initial PSA		
≤10	255	78.6
10.1–20	48	14.9
>20	21	6.5

PSA, prostate specific antigen.

characteristics are presented in *Table 1*. The average age at diagnosis was 70 years old (SD: ±7). The 3-year PSA relapse free survival rates were 95% [95% confidence interval (CI), 70.7–99.3%], 99% (95% CI, 92.9–99.9%), and 83.4% (95% CI, 71.2–90.7%) for low, intermediate, and high risk patients respectively. PSA relapse free survival by NCCN risk group is presented in *Figure 1*. Median follow-up for the whole group was 31 months.

There were no distant metastasis developments in the low or intermediate risk groups. There were five distant



**Figure 1** PSA relapse-free survival by NCCN risk group.

metastasis observed in the high risk group. The mean time to development of metastasis was 48 months with a range of 5–128 months.

Five-year overall survival for the whole cohort was 94% (95% CI, 88.0–97.0%). Multivariate analysis showed that age (>65), PSA (>10), and Gleason scores ( $\geq 8$ ) were predictive of decreased biochemical control.

#### Acute GU toxicity

Acute grade 1, 2, and 3 GU toxicities were 36%, 0.4%, and 0%. Most grade 1 toxicities consisted of increase in urinary frequency which on average resolved in 7 months.

#### Late GU toxicity

Late grade 1, 2, and 3 GU toxicities were 9.0%, 3.0%, and 1.5%. GU toxicities included urethral strictures, urinary retention, hematuria, urinary tract pain, and urinary urgency. Four patients developed grade 3 GU toxicity which consisted of: (I) bladder neck stricture; (II) urethral stricture; (III) hematuria; and (IV) urinary tract pain. Average time to development of grade 3 late toxicity was 26 months (range, 18–33 months). Three of the 4 patients with grade 3 late GU toxicity had a history of previous transurethral resection of prostate (TURP).

#### Acute GI toxicity

Twenty three percent of patients experience grade 1 toxicity during the radiation treatment which consisted mainly

of mild diarrhea. Three patients (1%) developed grade 2 toxicity which represented moderate diarrhea. Average time to resolution of acute GI symptoms was 6 months. No patients developed an acute grade 3 or 4 reaction.

#### Late GI toxicity

The 3 years incidence of late grade 1, 2 and 3 rectal toxicities were 6%, 2.2%, and 0.4%. All late grade 1 and 2 reactions eventually resolved symptomatically within 1 year after treatment. The patient with a late grade 3 reaction developed severe proctitis 17 months after finishing radiation. The patient developed a mixture of severe fecal obstruction, explosive diarrhea, and fecal incontinence. He was treated with a combination of laxatives, stool softeners, and hydrocortisone suppositories. His symptoms resolved after 9 months and did not require any surgical procedures.

#### Discussion

Several studies have highlighted the importance of dose escalation in the treatment of intermediate and high risk prostate cancer (2-3,15). With dose escalation, however it is predicted that men will experience more acute and chronic toxicities. Our data shows that with our HDR brachytherapy/IMRT combination, PSA control rates are extremely high with very low early and late side effects. Despite limited 3-year of follow-up, our results are consistent with data reported by other institutions that practice combined modality radiation for the treatment of prostate cancer (1,5,15). Three-year biochemical control rates were excellent for the low and intermediate risk patients at 95% and 97% respectively. It is interesting to note that biochemical control was higher for the intermediate risk patients than the low risk patients. We attribute this to statistical variation resulting from the low number of patients in the low risk arm. There were no biochemical failures in patients with Gleason 3+4 [7] prostate cancer, showing that ADT is not critical in their treatment management. The clinical outcomes of our patients receiving combined modality radiation therapy for prostate cancer are consistent with other comparison studies (1) which have shown improved PSA relapse free survival with the addition of HDR brachytherapy to external beam radiation. Deutsch (1) showed improved 5-year actuarial PSA relapse-free survival (PRFS) for combination therapy (HDR/IMRT) *vs.* ultra-high-dose IMRT: 100% *vs.* 98% ( $P=0.71$ ), 98% *vs.* 84% ( $P<0.001$ ),

and 93% *vs.* 71% ( $P=0.23$ ), for NCCN low, intermediate, and high-risk groups, respectively.

Almost half (49%) of patients received a PEG spacer along with radiation. The spacer does not appear to have an appreciable effect on the biochemical control rates of our patients, as our control rates are very similar to other published series (1-5). GI toxicity was very low with only one grade 3 rectal complication that resolved without surgical intervention.

Overall our treatment fractionation has much lower rates of acute and late GU and GI side effects as compared with other published series (16). This is likely because our HDR fractionation consists of smaller more frequent doses. Since the doses per fraction we use are lower than other centers, it makes radiobiological sense that the toxicity profile is much lower. Despite the protracted HDR fractionation, biochemical control does not appear to be compromised but leads to a decrease in acute and late GI/GU toxicities.

Another limitation of this study was that most high risk patients only received 12 months of hormonal therapy instead of 2–3 years of hormonal blockade as recommended by NCCN guidelines. A longer course of hormonal therapy could possibly lead to improved biochemical control in high risk patients.

## Conclusions

We continue to show that the combination HDR/IMRT therapy results in high PSA control rates with minimal GI and GU toxicities.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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