

HDR brachytherapy as a solution in recurrences of locally advanced prostate cancer

Jarosław Łyczek, MD, PhD¹, Maria M. Kawczyńska, MSc², Darek Garmol, MSc², Anetta Kasprówicz, MD¹, Anna Kulik, MD, PhD¹, Mateusz Dąbkowski, MD¹, Beata Czyżew, MSc², Ewelina Gruszczyńska, MSc², Michał Bijok, MSc², Łukasz Kowalik, MSc²

¹Brachytherapy Department, ²Medical Physics Department, Cancer Centre – Institute, Warsaw

Abstract

Purpose: The object of this study was to analyze the outcome of salvage HDR brachytherapy treatment after local failure, for patients with prostate specific antigen (PSA) failure without distant metastasis, after external beam radiation and HDR brachytherapy treatment, or after radical prostatectomy, with or without hormonal therapy.

Material and methods: The group of 115 patients, without distant metastasis, after local failure and external beam radiation, followed by HDR brachytherapy treatment, or after radical prostatectomy, with hormonal therapy and without, have been enrolled to salvage HDR brachytherapy (SBR). All patients had minimum 3 months androgen deprivation therapy before salvage brachytherapy, which was continued until the next 9 months after SBR. Brachytherapy was administered in three 10 Gy fractions with 3 weeks gap between them. Each session of SBR was supported by trans-rectal USG real time pictures. The treatment planning was done on the base of Abacus system from Sauerwein® or with SWIFT system from Nucletron®. The following data were collected: Gleason score, clinical staging, the volume of the prostate, PSA before and after the initial treatment and periodically during the follow-up period. Also the time during which the PSA stays at the nadir level, patient's age and toxicity of treatments were taken into consideration.

Results: Doses from external radiotherapy or from HDR brachytherapy were recalculated to equivalent biological dose (EBD). The independence from biochemical progression in our group of patients after retreatment was 46% for patients with PSA ≤ 6 and 18% for patients with PSA > 6. Overall survival for patients with PSA ≤ 6 was 86% and 48% for patients with PSA > 6, respectively.

Conclusions: Salvage prostate brachytherapy (SBR) can be safely performed with acceptable biochemical control and toxicity.

J Contemp Brachyther 2009; 1, 2: 105-108

Key words: prostate cancer, recurrence, HDR, locally advanced.

Purpose

HDR brachytherapy is already a well established and safe treatment for localized prostate cancer [1]. It allows precise delivery of very high doses of radiation in a very short treatment time and is more conformal than LDR brachytherapy with seeds or IMRT. The accuracy offered by HDR brachytherapy is especially attractive for salvage therapy because it permits protection of healthy structures around the prostate with full dose of external beam radiotherapy already received during primary treatment [2-4]. Lee *et al.* have recently reported that patients with rising PSA after definitive treatment (approximately 26%) have a local recurrence, where 47% of cases developed distant metastases within five years [5]. However, after radiation therapy for clinically localized disease (stage T1, T2),

5-year biochemical failure rates have been reported as 25% to 50%, and 10-year local recurrence rates have been reported as 13% to 35% [6-8]. The aim of our study was to evaluate the suitability and safety of salvage high-dose-rate (HDR) brachytherapy (SBR) for local recurrence of prostate cancer after external beam radiotherapy, after HDR brachytherapy, or after radical prostatectomy.

Material and methods

One hundred and fifteen patients who underwent SBR for locally recurrent prostate cancer treated between December 1999 and August 2008 were retrospectively analyzed. Patients with prostate-specific antigen (PSA) failure, as the local failure, without distant metastasis, after external beam radiation, HDR brachytherapy treatment,

Address for correspondence: Jarosław Łyczek, MD, PhD, Brachytherapy Department, Cancer Centre – Institute, 5 Roentgen Street, Warsaw, Poland, phone +48 22 546 20 45, fax +48 22 546 31 51, e-mail: jaroslawlyczek@wp.pl

Received: 17.06.09

Accepted: 30.06.09

Published: 30.06.09

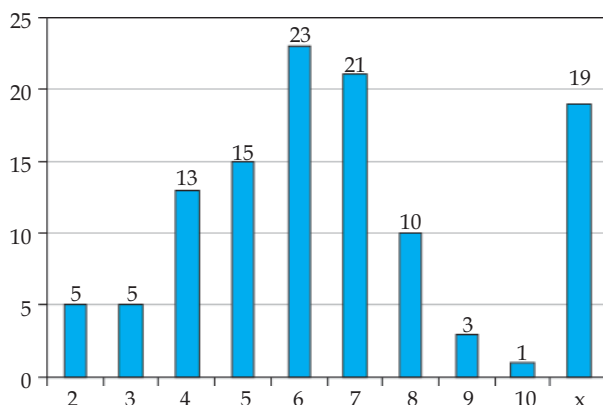


Fig. 1. Distribution of Gleason score for the group of 115 patients. Numbers over the columns indicate number of patients for the different Gleason score values (GS). The bar for patients with unknown GS is marked by x

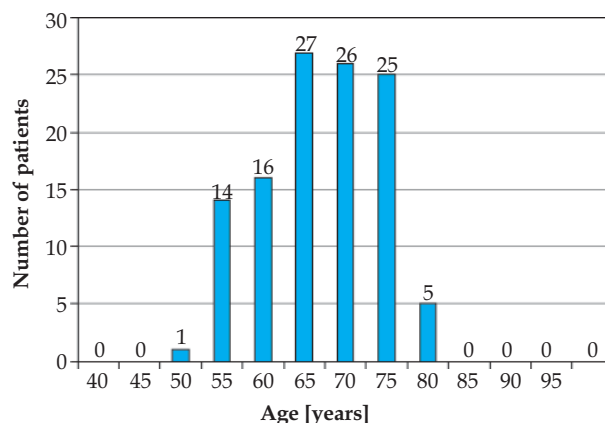


Fig. 2. The distribution of patients age at the time of primary treatment

Table 1. Clinical and pathological data of 115 patients

Characteristic	Value
Before treatment	
Age	
Median	65
Range	48-78
T stage at initial cancer diagnosis	
T1NxM0	7
T2NxM0	60
T3NxM0	38
TxNxMx	8
Malignancy	
G1	23
G2	67
G3	11
unknown	13
Initial PSA(ng/mL)	
Median	13
Range	2.34-64.5
≤ 10	40
10.1-19.9	28
≥ 20	33
unknown	14

after radical prostatectomy or combination of them, with or without hormonal therapy, have been enrolled to SBR. All patients were treated with 10 Gy per fraction using three HDR prostate applications guided by transrectal ultrasound. The fractions was separated by 3 week gaps. Files of 115 patients from Centre of Oncology were investigated as well as patients sent for salvage treatment from other hospitals in Poland. For this reason some of them didn't have the full set of clinical data, for instance in 19 patients the Gleason score was not defined. Among patients with Gleason score determined the distribution of the score values is presented in Fig. 1. The distribution of patients age at the time of primary treatment is presented in Fig. 2. Clinical and pathological data of 115 patients are summarized in Table 1. All patients before SBR treat-

Table 2. Data of the former treatment modalities

Characteristic	Value
Primary treatment	
RP	11
RTH	71
BR	26
S	7
Secondary treatment	
RTH (only patients after RP)	10
Time between RP and RTH (month)	
Median	12
Range	1-45
Courses of total treatment	
RTH + SBR	69
BR + SBR	26
RP + RTH + SBR	10
RTH + (SBR + HT)	2
S + SBR	6
S + (SBR + HT)	1
RP + SBR	1
Age at retreatment time (years)	
Median	70
Range	52-82
Time interval between primary treatment and SBR (month)	
Median	49.5
Range	20-220
Time interval to arise PSA after RTH	
Median month	33.5
Range	2-108

RP – radical prostatectomy, RTH – external radiotherapy, BR – HDR brachytherapy, S – sandwich radiotherapy, first fraction HDR brachytherapy + 15 fraction RTH each 2 Gy and directly after last fraction, second fraction HDR-BR, SBR – salvage HDR brachytherapy, HT – hyperthermia

ment were treated by surgery, external beam radiotherapy or brachytherapy. Data of the former treatment modalities are presented in Table 2. External beam radiotherapy has been performed in 88 patients. The radiation energy was 15 MV in 53 cases, 25 MV in 1 case, 9 MV in 3 patients, 6 MV in 3 cases, 4 MV in 10 cases and Co-60 in

14 patients. For 4 patients the photon energy was unknown. Total dose ranged from 30 to 76 Gy, median 52 Gy and fraction dose - 1.6 to 2.6 Gy. The median total treatment time was 33 days (range 22-66 days). Brachytherapy as the primary treatment was performed in 26 patients. Three of them received 27 Gy at 9 Gy fractions with 2 week gaps, 23 patients received 2 fractions with 3 weeks gap, each fraction of 15 Gy. Doses from external beam radiotherapy and brachytherapy were recalculated to equivalent biological dose (BED) using LQ model for α/β value equal 10 and 3 Gy, with total treatment time TD taking into account. According to Fowler and others suggestions, this is the duration of treatment considering the first fraction given on day 0 [9-12].

$$BED = nd [1+d/(\alpha/\beta)] - TD K$$

where: n - number of fractions, d - fraction dose, K - the loss of biological effectiveness per day as a result of proliferation depending not only on the rate of repopulation in tissue (doubling time) but also on its radiosensitivity (K has a unit Gy/day).

The calculated values of BED for the primary treatment for $\alpha/\beta = 10$ Gy ranged from 20 to 97.2 Gy with median 51.6 Gy, and for $\alpha/\beta = 3$ Gy ranged from 77.6 to 227.7 Gy with median 105.1 Gy. For SBR treatments for $\alpha/\beta = 10$ Gy, BED ranged from 20 to 51.7 Gy with median 34.2 Gy and for $\alpha/\beta = 3$ Gy BED range from 43.3 Gy to 171.7 Gy with median 125.7 Gy.

Patients follow up data concerning the toxicity of SBR was collected from the patients files. Post treatment PSA levels, occurrence of treatment related symptoms and complications were investigated in order to evaluate and possibly modify the SBR procedure. Evaluation of complication from SBR required careful revision and analysis of a patient's reports at follow-up visits in order to separate the toxic effects of the primary treatment from those of SBR.

Results

Taking into account the EORTC/RTOG scale of toxicity, acute urinary symptoms such as frequency, urgency, hesitancy and nocturia were common during the first

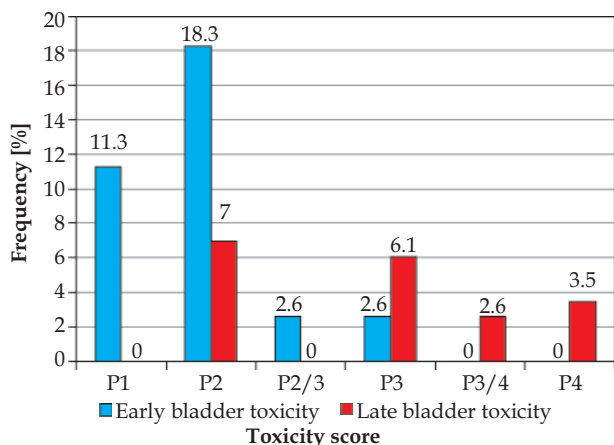


Fig. 3. Bladder toxicity

3 months after SBR. They were readily managed by prescribed alpha-blocker or cholinolytic treatment on a routine basis. In Figs. 3 and 4 the toxicity of SBR treatments for the bladder and rectum is presented respectively. Serious genitourinary complications such as uncontrolled hematuria were observed in 6 patients, urethral fistulas in 2, bladder outlet obstruction requiring permanent catheterization in 2, and complete urinary incontinence occurred in 4 patients. Effectiveness of SBR was assessed by PSA level after treatment. Follow-up examinations after SBR were performed during the first two years at 3 month intervals, during the next two years every 6 months, and every 6-12 months thereafter. In general, the first post SBR PSA level was measured after 3 months. Biochemical failure (BF) was defined as the nadir-plus 2 ng/mL or more than PSA nadir after SBR treatment. Figures 5 and 6 present the BF and survival data. Some of the patients were lost from observation during the first two years after treatment, mostly because they've lived in distant part of Poland and they considered the follow-up visits as complicated and costly. They were assumed as the BF. In Figure 5, according to Kaplan-Meier estimation, the PSA rising and stratified by PSA nadir (< 2 vs. ≥ 2 ng/mL) and Gleason score (2-6 vs. 7-10) are displayed. The independence from biochemical progression of our group of patients after retreatment was 46% of patients with PSA ≤ 6 and 18% of patients with PSA > 6. Overall survival for patients with PSA ≤ 6 is 86% and respectively 48% for patients with PSA > 6.

Discussion

Although salvage prostate brachytherapy demonstrated acceptable disease control without major complications, salvage brachytherapy should be limited only to patients with pathologically confirmed local recurrence. According to Allen and other authors, the base of selection of the future patients should be as follows: 1) clinical tumor status T1 or T2, 2) PSA ≤ 10 ng/ml, 3) Gleason score ≤ 6 , 4) pre-treatment PSA value of 2.0 ng/ml per year, 5) interval to PSA failure > 12 months, 6) PSA-DT (doubling time) > 12 months, 7) negative bone scan, 8) negative pelvic image studies, 9) positive re-biopsy [13, 14]. Additionally, younger patients with earlier-stage of a disease treated

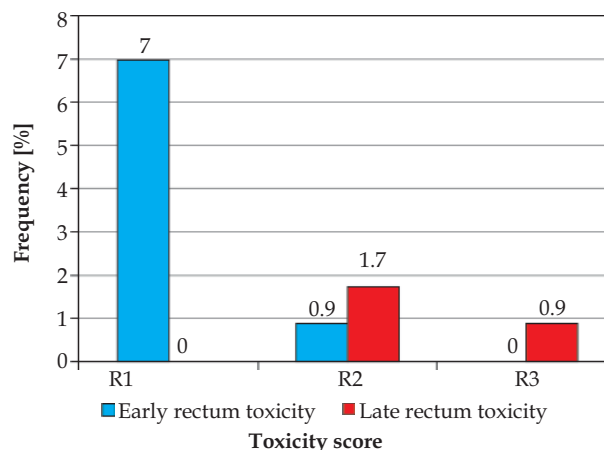


Fig. 4. Rectum toxicity

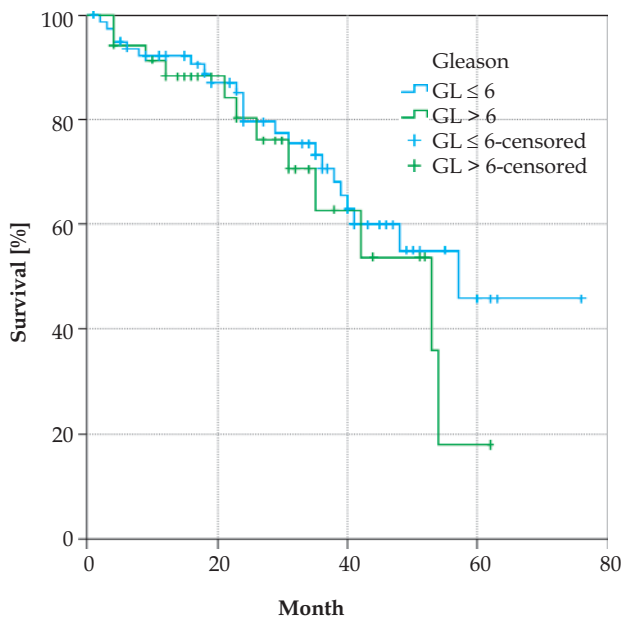


Fig. 5. Biochemical failure-free survival of all patients who underwent salvage brachytherapy

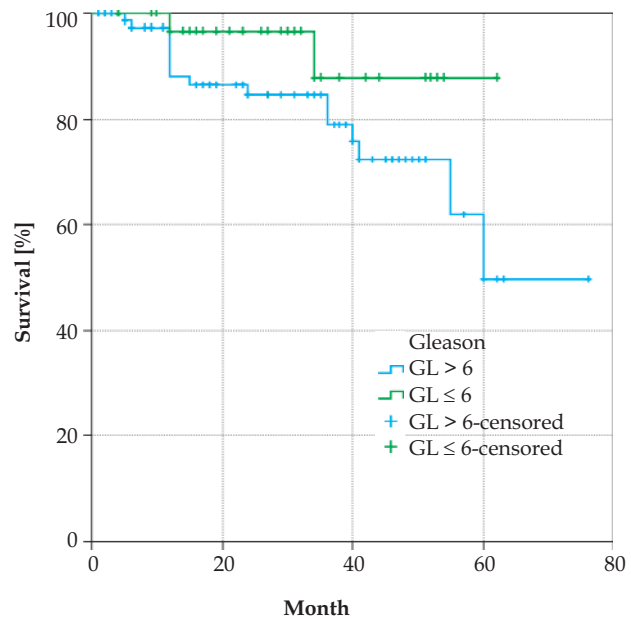


Fig. 6. Overall survivals of all patients who underwent salvage brachytherapy stratified by Gleason score

with radiation therapy are at higher risk for long-term biochemical failure compared to older patients [15]. A significant subset of these patients with recurrent disease will be candidates for curative salvage procedures [14]. Dose escalation with modern radiation therapy techniques based on 3D imaging shows the improvement of therapeutic ratio for patients with prostate cancer in recent years.

Conclusions

Salvage HDR prostate brachytherapy for biochemical failure after radiation therapy appears to be safe and well tolerated with promising results in carefully selected patients.

References

- Martinez A, Gonzalez, Spencer W et al. Conformal high dose rate brachytherapy improves biochemical control and causes specific survival in patients with prostate cancer and poor prognostic factors. *J Urol* 2003; 169: 974-980.
- Beyer DC. Brachytherapy for recurrent prostate cancer after radiation therapy. *Semin Radiat Oncol* 2003; 13: 158-165.
- Tharp M, Hardacre M, Bennett R et al. Prostate high-dose rate brachytherapy as salvage treatment of local failure after previous external or permanent seed irradiation for prostate cancer. *Brachytherapy* 2008; 7: 231-236.
- Niehoff P, Loch T, Nurnberg N et al. Feasibility and preliminary outcome of salvage combined HDR brachytherapy and external beam radiotherapy (EBRT) for local recurrences after radical prostatectomy. *Brachytherapy* 2005; 4: 141-145.
- Lee B, Shinohara K, Weinberg V et al. Feasibility of high-dose rate brachytherapy salvage for local prostate cancer recurrence after radiotherapy: the University of California-San Francisco experience. *Int J Radiat Oncol Biol Phys* 2007; 67: 1106-1112.
- Spiess PE, Lee AK, Leibovici D et al. Presalvage prostate-specific antigen (PSA) and PSA doubling time as predictors of biochemical failure of salvage cryotherapy in patients with locally recurrent prostate cancer after radiotherapy. *Cancer* 2006; 107: 275-280.
- Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997; 37: 1035-1041.
- Pollack A, Zagars GK, Antolak JA et al. Prostate biopsy status and PSA nadir level as early surrogates for treatment failure: Analysis of a prostate cancer randomized radiation dose escalation trial. *Int J Radiat Oncol Biol Phys* 2002; 54: 677-685.
- Fowler J, Chappell RC, Ritter MA. Is alpha/beta for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 2001; 50: 1021-1031.
- Williams SG, Taylor JM, Liu N et al. Use of individual fraction size data from 3,756 patients to directly determine the alpha/beta ratio of prostate cancer. *Int J Radiat Oncol Biol Phys* 2007; 68: 24-33.
- Dasu A. Is the α/β value for prostate tumors low enough to be safely used in clinical trials. *Clin Oncol* 2007; 19: 289-301.
- Chen BT, Wood DP Jr. Salvage prostatectomy in patients who have failed radiation therapy or cryotherapy as primary treatment for prostate cancer. *Urology* 2003; 62 Suppl 1: 69-78.
- Allen GW, Howard AR, Jarrard DF et al. Management of prostate cancer recurrences after radiation therapy-brachytherapy as a salvage option. *Cancer* 2007; 110: 1405-1416.
- Zelevsky MJ, Fuks Z, Hunt M et al. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys* 2002; 53: 1111-1116.