

# First experience of salvage HDR brachytherapy after prostate cancer radiotherapy

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**Introduction.** Prostate cancer (PC) is the most common oncologic disease among men. The number of patients with recurrent PC after primary radiotherapy is increasing, unfortunately, criteria for the choice among different treatment methods for these patients have not been defined yet. Salvage treatment options include prostatectomy, brachytherapy (BT), cryotherapy, thermoablation, and high frequency ultrasound. The lack of long-term evaluation of the toxicity and influence on the survival of patients after salvage high-dose-rate (HDR) BT is an important problem when considering this treatment option. In this study we have analyzed the treatment results of twelve patients who were diagnosed with local recurrent prostate cancer after primary radiotherapy and then treated with HDR BT.

**Materials and methods.** Patients were treated with salvage HDR BT between January 2013 and February 2014 at the Institute of Oncology, Vilnius University

**Results.** Average age of the patients at the time of salvage treatment was 67.5 years (min 54 years, max 76 years). The PSA value at the salvage treatment was from 2.06 ng/ml to 9.20 ng/ml. The time from the initial diagnosis till the salvage treatment was from 33 months to 134 months. All 24 procedures were successful and without any early complications.

**Conclusions.** HDR BT is a presumable and safe treatment option for local prostate cancer recurrence after primary radiotherapy. Prospective clinical trial is initiated to evaluate survival, long-term toxicity and predictive value of different biomarkers.

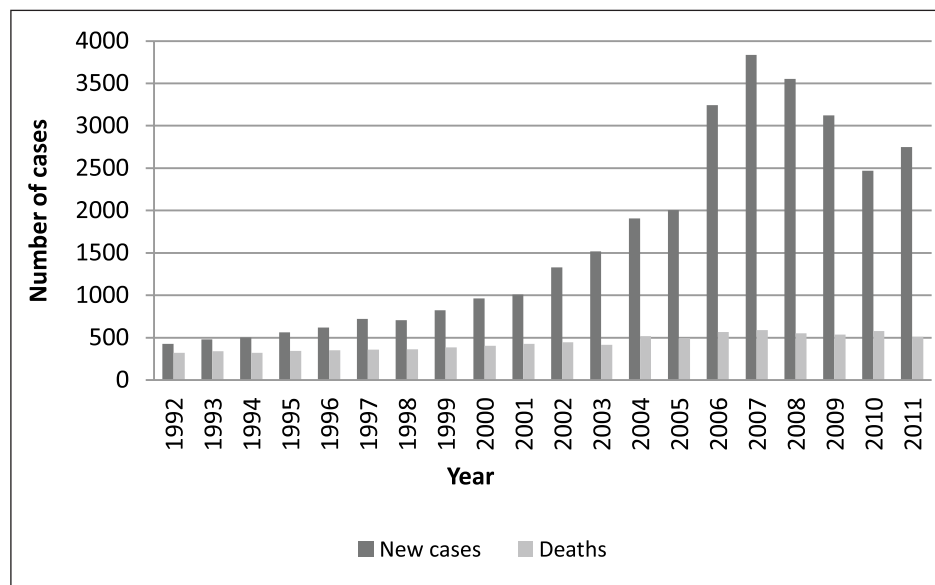
**Key words:** prostate cancer, salvage HDR brachytherapy, primary radiotherapy

## INTRODUCTION

Prostate cancer (PC) is the most common oncologic disease among men. In Lithuania nearly 3 000 men are newly diagnosed with prostate cancer and about 500 deaths occur from this disease annually (Figure).

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Radiotherapy is a standard treatment of local prostate cancer. Thirty percent of men with prostate cancer can be treated with radiotherapy. 500 men with prostate cancer are treated annually with radiotherapy at the Institute of Oncology, Vilnius University. In Lithuania the five-year survival rate among patients with PC is 90 percent (data from the Lithuanian Cancer Registry). The number of patients with recurrent PC after primary radiotherapy is increasing as well.



**Figure.** Number of new cases and deaths from prostate cancer in Lithuania (data from Lithuanian Cancer Registry)

Up to 30 percent of patients with the increased PSA level after radiotherapy will develop local recurrence if left untreated. Salvage treatment options include prostatectomy, low dose rate (LDR) brachytherapy, high dose rate (HDR) BT, cryotherapy, thermoablation, and high frequency ultrasound. It is still discussed which treatment modality is optimal for patients.

Our objective was to analyze the treatment results of the first patients who were diagnosed with local recurrent prostate cancer after primary radiotherapy and then treated with HDR BT at the Institute of Oncology, Vilnius University.

## MATERIALS AND METHODS

The analysis included twelve patients who underwent salvage HDR brachytherapy between January 2013 and February 2014. All patients were previously diagnosed with local prostate cancer and treated with external beam radiotherapy, the mean dose to prostate was 70.83 Gy (min 66 Gy, max 74 Gy) (Table 1). Nine patients were also treated with hormone deprivation therapy.

The T stage at the initial treatment was T1c in two patients, T2 in five patients and T3 in five patients. The PSA value at the initial treatment was from 4.72 ng/ml to 18.30 ng/ml.

Patients were treated with brachytherapy if biochemical recurrence (PSA value 2 ng/ml or

higher) occurred two years after initial treatment or later.

Local disease was confirmed by radiological (with magnetic resonance [MRT] or computer tomography [CT]) and histological (after transperineal prostate biopsy) methods. None of the patients had clinical or radiological evidence of distant metastases.

HDR BT was performed within two fractions delivering 11 Gy radiation dose (22 Gy in total) per fraction, separated with 7 days. One patient was treated with 9 Gy dose and 15 Gy dose after one week (24 Gy in total).

**Table 1.** Primary radiotherapy. Patients' characterization

Patients, n	12
T Stage, n: T1C	2
T2	5
T3	5
PSA, ng/ml	4.72–18.30
Dose, Gy	70.83 (66–74)

## RESULTS

The average age of patients at the time of salvage treatment was 67.5 years (min 54 years, max 76 years). Ten patients had cardiovascular disease

and two of them had diabetes. The PSA value at the salvage treatment was from 2.06 ng/ml to 9.20 ng/ml.

MRT (in eleven patients) and CT (in one patient) were used to diagnose local recurrence in prostate. All patients underwent transperineal prostate biopsy. The Gleason score at the moment of salvage treatment was 6 in four patients, 7 in five patients, 8 in two patients and 9 in one patient.

The average prostate volume before BT was 33.91 ml (min 12 ml, max 66 ml).

The time from the primary diagnosis till the salvage treatment was from 33 months to 134 months (Table 2). All 24 procedures were successful and without any early complications. The patients were able to leave hospital within one or two days after BT.

**Table 2.** Salvage treatment. Patients' characterization

Patients, n	12
Age, years	67.5 (54–6)
PSA, ng/ml	2.06–9.20
Prostate volume, ml	33.91 (12–66)
Time from primary diagnosis till salvage treatment, months	33–134

## DISCUSSION

Salvage treatment is indicated for patients who meet the following criteria: pathologically documented local failure, no clinical or radiographic evidence of distant metastases, life expectancy 5 to 10 years based on age and health, disease-free interval of >2 years, PSA <10 at time of salvage, long PSA doubling time (>9 months), Gleason score at salvage of 6 or less (3).

All twelve patients in our analysis underwent prostate biopsy and recurrence in prostate was confirmed. There was no evidence of distant metastases in any patient. The disease-free interval ranged from 33 till 134 months. The highest PSA level was 9.20 ng/ml. Only the Gleason score in eight patients exceeded the recommended value.

Patients who meet these criteria of salvage treatment can be treated with prostatectomy, cryoablation, thermoablation, BT or high frequency ultrasound.

The European Association of Urology recommends salvage prostatectomy only for patients who are well stratified (recurrence is local, PSA <10 ng/ml, PSA doubling time >12 months, Gleason score 7 or less) and patients must be informed about high risk of possible complications. Salvage prostatectomy must be performed only in medical centers with long experience of these surgeries.

Cryoablation can be used as an alternative for salvage surgery, but high frequency ultrasound is still an experimental procedure.

Salvage HDR BT is a safe and effective treatment option for recurrent prostate cancer (3–6). Lee et al. analyzed the results of 21 patients who were treated with salvage HDR BT because of recurrence in prostate after external beam radiotherapy. After pathologic confirmation of locally recurrent disease, all patients were treated with 36 Gy in six fractions using two transrectal ultrasound-guided HDR prostate implants, separated by 1 week. 18 patients reported Grade 1 to 2 genitourinary symptoms within 3 months after salvage treatment, three patients developed Grade 3 genitourinary toxicity. The maximum observed gastrointestinal toxicity was Grade 2. The 2-year biochemical control after recurrence was 89% (4).

Yo et al. described the clinical results of 11 patients who underwent salvage HDR BT cases of suspected local recurrence or of residual tumour after radiotherapy. A dose of 11.0 Gy radiation was delivered twice (22.0 Gy in total), separated by a 6-h interval. Follow-up after the completion of salvage HDR BT lasted for 18–41 months (mean 29 months). Of the 11 cases treated with salvage HDR BT, PSA levels remained low in seven cases and the incidence of complications was also low. This suggests that the salvage HDR BT is effective as an option for treatment of local prostate cancer recurrence after radiotherapy [5].

Burri et al. described long-term outcomes and toxicity after salvage BT for 37 men with local failure after initial prostate radiotherapy. With a median follow-up of 86 months, salvage prostate BT was associated with 10-year freedom from biochemical failure (FFbF) of 54% and cause-specific survival (CSS) of 96%. Improved FFbF was associated with a presalvage PSA <6 ng/mL. Toxicity was worse in patients who had undergone pelvic lymph node dissection before salvage BT. Careful

patient selection for salvage BT may result in improved outcomes and reduced toxicity (6).

Our analysis indicates that HDR brachytherapy is safe for patients with cancer recurrence in prostate.

This treatment method has several advantages: precise delivering of radiation to the prostate reducing side effects on the rectum, urethra and bladder, possibility to treat extra capsular tissues, possibility to calculate and control the radiation dose distribution before the treatment is given, radiobiological advantage.

High radiation dose delivery to prostate also has radiobiological basis. Prostate cancer, unlike most other types of cancer, is slow-growing. Because of that, cells mitotic activity is low and doubling time is long. These factors determine that alfa / beta ratio in prostate cancer is low. Wherefore prostate cancer cells are sensitive for high radiation doses delivered per fraction.

There are many facts suggesting that HDR brachytherapy is appropriate for treating local recurrences of prostate cancer. However, for the evaluation of long-term toxicity and survival impact prospective clinical trials are needed.

Prospective clinical trial to evaluate long-term toxicity and survival is initiated after the analysis presented. In the following study we are planning to investigate short-term and long-term toxicity, 3-year and 5-year survival and predictive value of different biomarkers for the patients treated with salvage HDR brachytherapy in case of local recurrence after primary prostate cancer radiotherapy.

## CONCLUSIONS

HDR brachytherapy is a presumable and safe treatment option for local prostate cancer recurrence

after initial radiotherapy. Prospective clinical trial is initiated to evaluate long-term toxicity, survival and predictive value of different biomarkers.

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## References

1. Zelefsky MJ, Chan H, Hunt M, Yamada Y, Shippy AM, Amols H. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urology*. 2006; 9: 1415–9.
2. Paparel P, Soulie M, Mongiat-Artus P, Cornud F, Borgogno C. Salvage radical prostatectomy after external radiotherapy for prostate cancer: indications, morbidity and results. Review from CCAFU prostate section. *Pro Urol*. 2010; 20(5): 317–26.
3. Song PY. Salvage high dose rate brachytherapy for recurrent prostate cancer after radiation therapy. *PCRI Insights*. 2008 Nov; 11.4: 2–9.
4. Lee B, Shinohara K, Weinberg V, Gottschalk AR, Pouliot J, Roach M, 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: 1106–12.
5. Jo Y, Fujii T, Hara R, Yokoyama T, Miyaji Y, Yoden E, et al. Salvage high-dose-rate brachytherapy for local prostate cancer recurrence after radiotherapy – preliminary results. *BJU*. 2012; 109: 835–9.
6. Burri RJ, Stone NN, Unger P, Stock RG. Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2010; 77: 1338–44.

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**PIRMOJI PATIRTIS TAIKANT ADG  
BRACHITERAPIJĄ KAIP GELBSTINTĮ METODĄ  
GYDANT PO SPINDULINĖS TERAPIJOS  
RECIDYVAVUSĮ PRIEŠINĖS LIAUKOS VĖŽĮ**

*Santrauka*

**Įžanga.** Priešinės liaukos vėžys (PLV) yra dažniausias vyrų onkologinis susirgimas. Pacientų, kurių liga recidyvuoja po taikyto pirminio spindulinio gydymo, skaičius didėja, tačiau nėra aiškių kriterijų, koks gydymo metodas šiems pacientams yra tinkamiausias. Kaip gelbstintis gydymas gali būti atliekama: prostatektomija, brachiterapija, krioterapija, termoabliacija, didelio intensyvumo fokusuoto ultragarso procedūra. Trūksta duomenų, kurie padėtų įvertinti aukštos dozės galios (ADG) brachiterapijos toksiškumą ilgą laiką ir šio gydymo metodo įtaką pacientų išgyvenamumui. Šiame tyrime išanalizavome pacientų, kuriems nustatytas lo-

kalus PLV recidyvas po taikytos pirminės spindulinės terapijos ir atlikta gelbstinčiosios ADG brachiterapijos procedūra, gydymo rezultatus.

**Medžiagos ir metodai.** Į analizę įtraukta 12 pacientų, kurie buvo gydyti gelbstinčiąja ADG brachiterapija Vilniaus universiteto Onkologijos Institute nuo 2013 m. sausio iki 2014 m. vasario mėnesio.

**Rezultatai.** Gelbstinčiojo gydymo metu vidutinis pacientų amžius siekė 67,5 metus (nuo 54 iki 76 m.); PSA vertė – 2,06–9,20 ng/ml; laikas tarp diagnozės nustatymo ir gelbstinčiojo gydymo svyravo 33–134 mėn. Visos 24 atliktos procedūros buvo sėkmingos ir be anks-tyvųjų komplikacijų.

**Išvados.** ADG brachiterapija yra tinkamas ir saugus metodas gydant po pirminio spindulinio gydymo lokaliai recidyvavusį priešinės liaukos vėžį. Planuojama atlikti prospektyvinį tyrimą siekiant įvertinti pacientų išgyvenamumą, ilgalaikį toksiškumą ir biožymenų predikcinę reikšmę taikant ADG brachiterapiją.

**Raktažodžiai:** priešinės liaukos vėžys, gelbstinčioji ADG brachiterapija, pirminė spindulinė terapija