

Salvage brachytherapy for local recurrences of prostate cancer treated previously with radiotherapy

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Abstract

Purpose: The aim of the study was to analyze early effects and toxicity of salvage high dose rate brachytherapy for local recurrences of adenocarcinoma of the prostate after external beam radiotherapy (EBRT).

Material and methods: In MCS Memorial Institute of Oncology in Gliwice a research programme on salvage HDR brachytherapy for local recurrences of prostate cancer treated previously with EBRT has been ongoing since February 2008. The treatment consisted of 3 fractions of 10 Gy each given every 14 days. Maximal urethral doses were constrained to be $\leq 120\%$ of the prescribed dose. Maximal bladder and rectum doses were constrained to be $\leq 70\%$ of the prescribed dose.

Results: Fifteen eligible patients were treated and analyzed from February 2008. All patients completed the treatment without major complications. The most common early complications were: macroscopic haematuria, pain in lower part of the abdomen, and transient dysuria. During the first week after the procedure a transient increase in IPSS score was noticed. The Foley catheter was removed on day 2 to 5. No complications after spinal anaesthesia were observed. Acute toxicity according to EORTC/RTOG was low. For bladder EORTC/RTOG score ranged from 0 to 2. Only in two patients grade 1 toxicity for rectum was observed. The follow-up ranged from 3 to 9 months. In one patient grade 2 rectal toxicity was observed, and one had urethral stricture. Other patients did not have any other significant late toxicity of the treatment. Two patients developed bone metastases.

Conclusions: Salvage brachytherapy for localized prostate cancer (3×10 Gy every 14 days) seems to be a safe and well tolerated procedure. A significant decline in prostate-specific antigen (PSA) level is seen in patients with hormone-responsive cancer. Long-term efficiency and toxicity of the procedure are yet to be established.

J Contemp Brachyther 2009; 1, 4: 211-215

Key words: prostate cancer, radiotherapy, recurrences, salvage brachytherapy.

Purpose

Carcinoma of the prostate is one of the most common health problems among men [1]. In Poland the prostate cancer incidence rate is 28.3/100 000 [2] and it is the second leading cause of cancer-related deaths after lung carcinoma [3]. Radiation therapy for localized prostate cancer is a standard option of treatment. The risk of local recurrences depends on the initial stage, Gleason score and PSA level. Usually recurrences have ominous prognosis. The standard treatment is androgen deprivation therapy. Local recurrences after EBRT are a difficult clinical problem [4]. Increasing PSA in patients after radical therapy may occur as a signal of local failure after initial local therapy or as

a sign of dissemination [5]. The response to hormone therapy lasts about 2 years and then the disease progresses. Patients who do not have distant metastases potentially may be cured with a salvage local therapy [5, 6]. There is no standard treatment for locally relapsed prostate cancer after EBRT. Radical prostatectomy, brachytherapy (BT), cryotherapy and high-intensity focused ultrasound are currently used as local salvage treatments [5, 7].

Depending on initial prognostic factors, it is estimated that about 10-70% of patients who undergo definitive radiotherapy for prostate cancer may experience a biochemical recurrence [4, 8]. Post-radiotherapy increasing PSA level can predict tumour recurrence. It is estimated

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Received: 04.12.09

Accepted: 29.12.09

Published: 07.01.10

that 75% of patients will have clinically detectable recurrent prostatic cancer 5 years after a PSA elevation [9]. Patients with local-only recurrence after EBRT can be treated with a salvage therapy, and salvage HDR-BT is one of the most promising options. Prostatectomy and cryotherapy have very serious side effects and only some patients are eligible for the treatment [10]. High-intensity focused ultrasound is still an experimental method [11]. In MCS Memorial Institute of Oncology in Gliwice a research programme on salvage HDR-BT for local recurrences of prostate cancer treated previously with radiotherapy was started in February 2008. The aim of the study was to analyze early effects and toxicity of salvage high dose rate brachytherapy for local recurrences of prostate cancer after EBRT.

Material and methods

Eligibility criteria: confirmed local recurrence after radiotherapy for localized prostate cancer (transrectal ultrasound or MRI of the prostate, bone scan for occult metastases, biopsy of the prostate for histopathological confirmation of the recurrences). Time interval from radiotherapy had to be at least 2 years. Exclusion criteria were the same as for any HDR brachytherapy of the prostate: metastatic disease, volume > 60 cm³, TURP (transurethral resection of the prostate) within 6 months, infiltration of the external sphincter of the bladder neck, significant urinary obstructive symptoms, pubic arch interference, lithotomic position or anaesthesia not possible.

According to these criteria from February 2008 to October 2009 fifteen patients were enrolled, treated and analyzed in the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch.

It was an inhomogeneous group in terms of initial stage and treatment. The mean age was 67 years (range 62-81 yrs). According to NCCN 2008 before primary treatment five patients had low risk cancer, two intermediate risk, seven high risk and one with cancer of unknown risk. All patients were treated with EBRT: six patients had conventional EBRT (73-76 Gy), eight EBRT with HDR-BT boost (EBRT:

54 Gy plus 10 Gy Ir 192), one patient underwent hypofractionated EBRT (52 Gy, dose per fraction 2.6 Gy). 10/15 patients had whole pelvis irradiation (45-46 Gy) and 4/15 received adjuvant hormone therapy after the primary treatment. Mean time of follow-up after prior radiotherapy to salvage treatment was 4.5 years (range 2-9). PSA nadir range: 0.03-5.72 ng/ml (mean 1.42 ng/ml, median 0.24). PSA before salvage HDR-BT range 1.04-11.57 ng/ml (median 4.01 ng/ml; mean 5.07). All recurrences were confirmed by biopsy. Gleason score of recurrence ranged from 6 to 8 (in 6 patients only foci adenocarcinoma was noted). Three patients had perineural invasion. Four patients had hormone-resistant cancer. Eight were on androgen deprivation therapy before BT salvage (two on the second line).

HDR brachytherapy was delivered using an iridium-192 stepping source (MicroSelectron®, Nucletron NV). Treatment planning was performed intra-operatively based on real time rectal ultrasonography (Oncentra Prostate 3.0 by Nucletron BV®). Needle applications were performed during spinal anaesthesia. The treatment consisted of 3 fractions of 10 Gy each given every 14 days. The dose was calculated on the prostate capsule or 2-3 mm from it (depending on clinical case). Generally homogeneous needle distributions were applied, with a hot-spot planned in the case of a visible tumour. Maximal urethral doses (calculated at the centre of the urethral outline each 3 mm) were constrained to be 120% of the prescribed dose. Maximal bladder and rectum doses were constrained to be 70% of the prescribed dose. Mean V 100% of prostate was 95% of prescribe and mean D10 in urethra from all applications was 118.5% (Fig. 1). The mean follow-up period is 9 months (range: 3-15 months).

Acute and late radiation toxicity were evaluated according to the EORTC/RTOG scale [6]. Change in IPSS (International Prostate Symptoms Score) and in PSA level was analyzed. A statistical analysis of results was carried out using Statistica 7.0 software. Student's t-test was used for statistical analysis.

Results

All patients completed the treatment without major complications. The most common early complications were: macroscopic haematuria, pain in lower part of the abdomen or transient dysuria. During the first week after the procedure a transient increase in IPSS score was noticed (Fig. 2). The Foley catheter was removed on day 2 to 5. No complications after spinal anaesthesia were observed.

Acute toxicity according to EORTC/RTOG was low. For the bladder EORTC/RTOG score ranged from 0 to 2. Only in two patients grade 1 toxicity for the rectum was observed.

One patient had developed late rectum toxicity grade 2 after 12 months post salvage HDR-BT. One patient had urethral stricture 9 months post salvage BT and two patients developed bone metastases (one after a major surgical procedure, orthopaedic surgery, performed one month after salvage BT, the second after TURP for urethral stricture that developed 9 months after salvage HDR-BT) (Fig. 3).

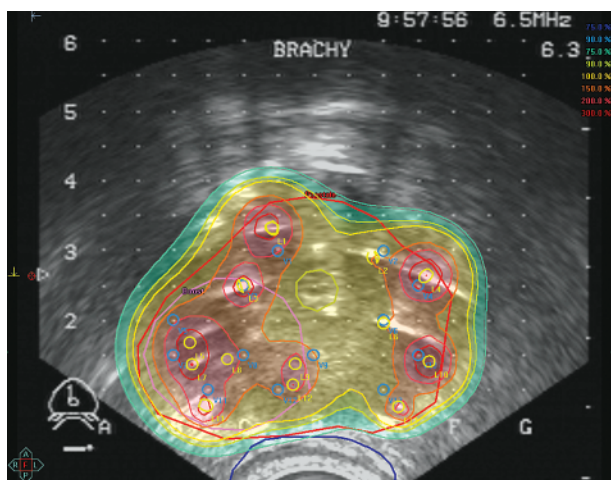


Fig. 1. Transverse scan of the treatment plan for salvage brachytherapy of prostate

PSA levels at 3, 6 and 9 months after salvage HDR-BT were examined. A decrease in PSA level between PSA before the treatment and after the treatment (except two cases where dissemination was observed; in those two patients a rapid increase of PSA level was observed just after dissemination). Mean PSA level after 3 months in all patients was 10.7 ng/ml (median 1.3 ng/ml), and after 9 months median was 1.8 ng/ml (Fig. 4). In the group of 13 patients without distant metastasis there was observed a statistically significant decrease in PSA level. Mean PSA level after 3 months in that group was 2.53 ng/ml (median 1.02 ng/ml), and after 9 months median was 0.9 ng/ml (Fig. 5). In a group of 11 patients with the best prognostic factors, without distant metastasis, with hormone-responsive tumour the PSA level decrease was the most striking. Mean PSA level after 3 months in that group was 3.35 ng/ml (median 1.9 ng/ml), and after 9 months median was 0.2 ng/ml (Fig. 6). The PSA level before and after salvage HDR-BT was summarised in Table 1.

Discussion

The first salvage brachytherapy was performed 40 years ago. But only now HDR units for brachytherapy

for prostate cancer are more extensively available. Brachytherapy shows advantages over external beam radiotherapy in terms of re-irradiation mainly by the chance to spare organs at risk [12, 13]. Experience in salvage brachytherapy is limited, in the literature about 370 cases have been reported [13, 14] and the biggest

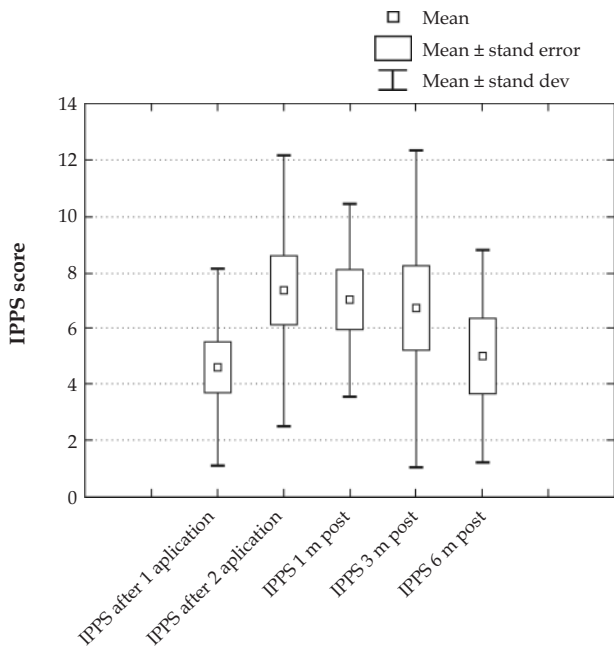


Fig. 2. International Prostate Score during and 1, 3 and 6 months after the treatment

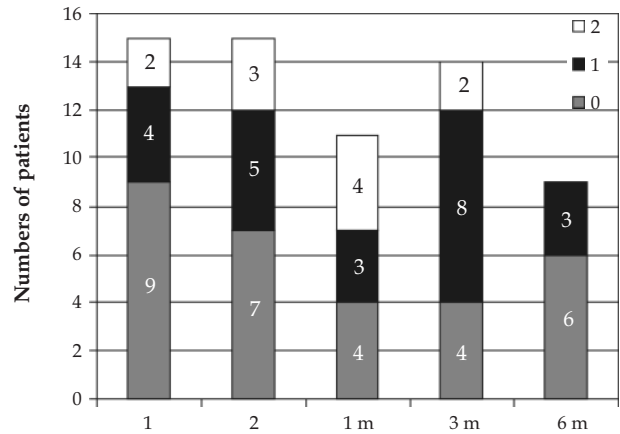


Fig. 3. Acute bladder toxicity during and after treatment according to RTOG

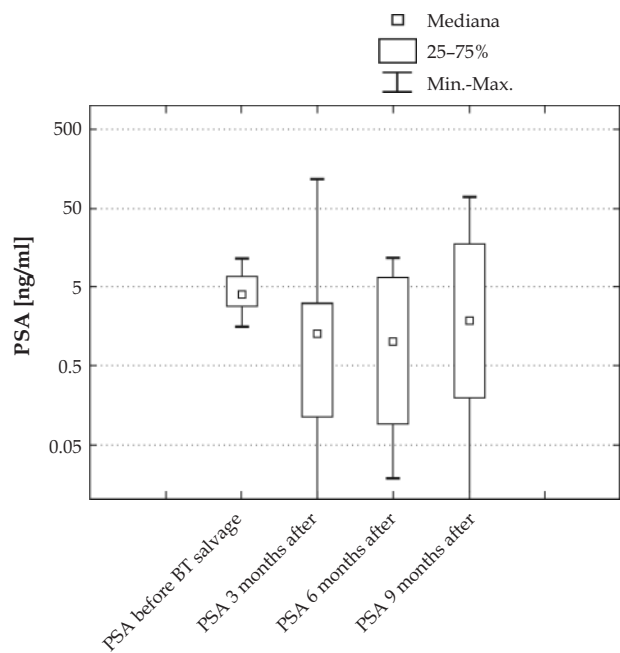


Fig. 4. PSA value before and after treatment in all patients

Table 1. PSA level before and after salvage HDR-BT

PSA ng/ml	Before sBT		3 months after sBT		6 months after sBT		9 months after sBT	
	mean	median	mean	median	mean	median	mean	median
All patients	5.07	4.01	10.7	1.3	3.76	1.01	18.3	1.80
All patients	5.07	4.01	10.7	1.3	3.76	1.01	18.3	1.80
Patients without metastasis	4.94	3.97	2.53	1.02	3.76	1.01	4.9	0.9
Patients without metastasis and hormonal resistance	4.11	3.35	1.904	0.3	2.22	0.25	0.66	0.2

sBT – salvage HDR brachytherapy

group was described by Łyczek *et al.* [14]. Unresolved questions concern: the maximal dose for rectum, urethra and bladder neck after previous irradiation, the optimal dose and scheme of fractionation, and optimal qualification (who really benefits from the procedures). The presented early results are encouraging. The treatment was generally well tolerated and the toxicity

was acceptable, which is consistent with data from other authors [7, 13-15].

Our inclusion criteria are among the widest. We assume that low toxicity of the treatment allowed the procedure to be used even in patients with general poor prognosis, mainly as an attempt at palliative treatment (which still may give a chance to prolong life for patients who have failed hormonal manipulation). The small numbers of analyzed patients prevent us from drawing any hard conclusions, but there is a clear trend for PSA level to fall after the treatment. Among the 15 patients only 4 with hormone-responsive cancer had endocrine treatment, so the observed drop in PSA should be attributed to brachytherapy. The two patients who suffered from dissemination did not have any significant risk for dissemination before the procedure. What is striking is the fact that dissemination was observed soon (4 and 6 weeks) after surgical procedures. Another interesting observation is the development of grade 2 late rectum toxicity in patients who had pronounced acute and late toxicity during and after previous irradiation.

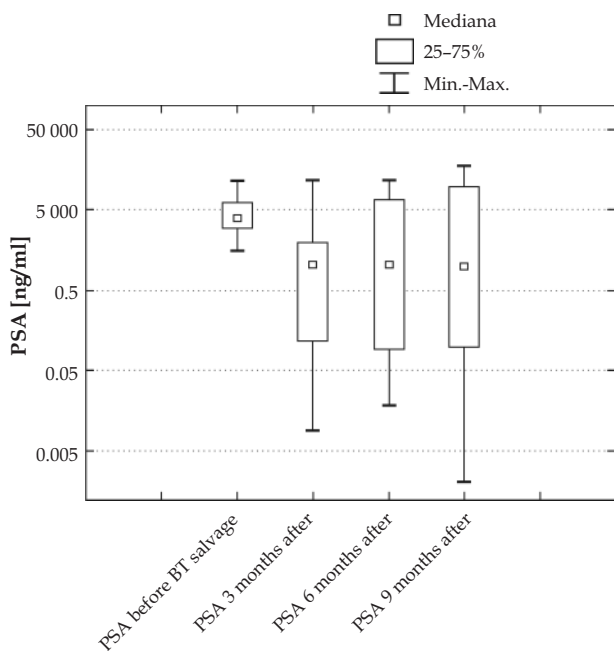


Fig. 5. PSA value before and after treatment in patients without disseminations

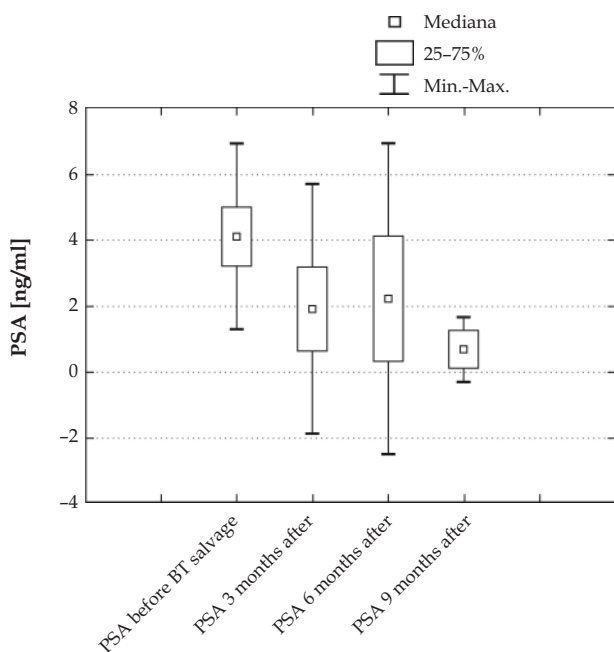


Fig. 6. PSA value before and after treatment in patients without disseminations and hormone resistance

Conclusions

Salvage brachytherapy for localized prostate cancer (3×10 Gy every 14 days) seems to be a safe and well tolerated procedure. A significant decline in PSA level is seen in patients with hormone-responsive cancer. Long-term efficiency and toxicity of the procedure are yet to be established.

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