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SALVAGE HIGH DOSE-RATE BRACHYTHERAPY IN PATIENTS WITH LOCAL RECURRENCE OF PROSTATE CANCER AFTER VARIOUS TYPES OF PRIMARY TREATMENT

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Background. Prostate cancer (PCa) is the second most common cancer worldwide. Current methods of definitive treatment of PCa provide good recurrence-free survival in patients with low and intermediate risk of progression, and yet about a third of men will face the local recurrence in the next 10 years of life. Today, there is a great need to find optimal technologies for treating local relapses of PCa.
Aim. To analyze the efficiency and toxicity of salvage high dose-rate (HDR) brachytherapy in the treatment of local recurrences of prostate cancer after various types of primary treatment.
Materials and methods. A total of 98 patients with local relapse of PCa after various types of radical treatment were included in the study. The age of the patients was on average 68 years (minimum 53 years, maximum 84 years) [95% CI = 66.9-69.7 years]. Recruitment of patients was carried out from January 2015 to December 2022 at the Federal State Budgetary Institution Russian Scientific Center for Radiology of the Ministry of Health of Russia. After a comprehensive examination, all patients underwent salvage HDR brachytherapy. The study included 34 patients after radical prostatectomy and 64 patients after radiation treatments (EBRT, brachytherapy).
Results. The median follow-up was 36 months (3–84 months). Depending on the previous treatment, the patients were divided into 2 groups. Group I (n=34) included patients after radical prostatectomy, while in group II (n=64) there were men after radiation treatment (EBRT, brachytherapy). The 5-year PSA-progression-free survival in group I was significantly higher than in group II and was 88.2 and 67.2%, respectively (p=0.023). The incidence of late genitourinary toxicity of grades 1, 2, 3 in both groups was 22.4, 10.2, and 4.1%, respectively, and late gastrointestinal toxicity of grades 1 and 2 were 10.2 and 1%, respectively. Severe complications of grades 2 and 3, both from the urinary system and from the rectum, were observed only in group II.
Conclusion. HDR brachytherapy is an effective salvage treatment option for local relapses of PCa after previous radiation and surgical treatment.

Key words: recurrence; prostate cancer; salvage brachytherapy; high dose brachytherapy; radical prostatectomy

The authors declare that they have no conflicts of interest. For citation: Solodkiy V.A., Pavlov A.Yu., Dzidzaria A.G., Tsybulsky A.D., Fedotova A.D., Gubanova V.I.Salvage high-dose brachytherapy in patients with local recurrence of prostate cancer after various types of primary treatment. Urologiia. 2025;1:22-28. Doi: https://dx.doi.org/10.18565/urology.2025.1.22-28

Introduction. Prostate cancer (PCa) is the second most common oncological disease worldwide [1, 2]. Existing methods of radical treatment for PCa provide good recurrence-free survival in patients with low- and intermediate-risk disease, however, about a third of patients will have a local PCa recurrence in the subsequent 10 years of life [3, 4]. Local recurrences after previous radiation therapy (RT) or radical prostatectomy (RP) are increasingly detected in those with biochemical recurrence. Brachytherapy for PCa is an effective and well-tolerated treatment option.

Aim. To analyze the efficiency and toxicity of salvage HDR-BT in the treatment of local PCa recurrences after various types of primary treatment.

Materials and methods. The study was carried out at the Russian Scientific Center for Radiology and Nuclear Medicine of the Ministry of Health of Russia since 2015 and included 98 patients with local recurrence of PCa after various types of primary treatment. The mean age of patients was 68 ± 7.01 years (from 53 to 84 years) (95% CI 66.9-69.7 years). Patients were recruited from January 2015 to December 2022. The cause for examination to detect recurrence after RP was an increase in prostate-specific antigen (PSA) levels above 0.2 ng/ml, and after RT it was an increase in PSA levels more than 2 ng/ml from the nadir or a gradual increase in PSA levels over several months (3 or more consecutive increases). All patients underwent multiparametric magnetic resonance imaging (MRI) of the pelvis to determine the local recurrence in the prostate bed.

To exclude regional and distant metastasis, all patients underwent positron emission tomography (PET-CT) with 18F or 68Ga + PSMA (prostate-specific membrane antigen). When analyzing the results of examination, it was found that PET-CT was a more accurate method, confirming the presence of a local recurrence in 86 out of 98 patients. Pelvic MRI had lower sensitivity and detected recurrence in only 72 (73.5%) patients. At the same time, in 21% of men, PET-CT had positive result, when MRI was negative, and conversely, in 7.1% of

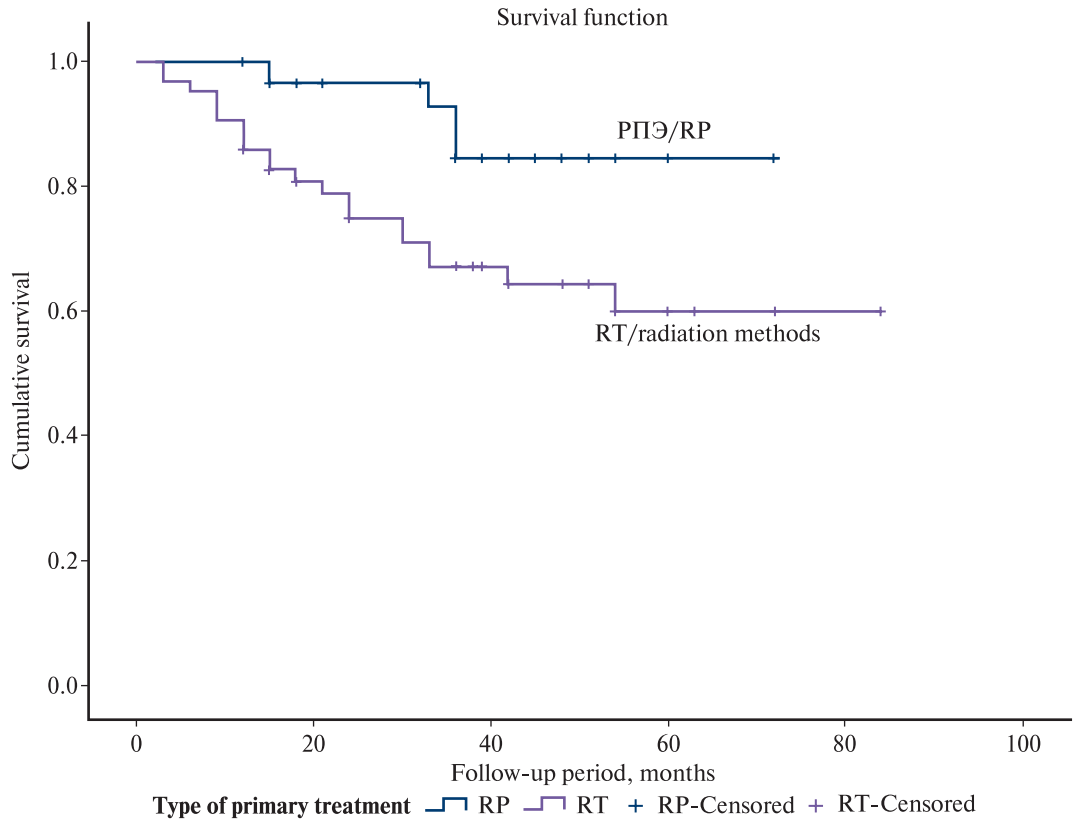


Fig. 1. Five-year PSA-specific survival (biochemical control) after salvage HDR-BT depending on the primary treatment (RP or RT)

cases, MRI revealed suspected lesion when PET-CT was a false negative. In 66.3% of patients, MRI and PET-CT simultaneously revealed a localization of recurrent tumor. It should be noted that in 5 (5.1%) patients, both imaging methods (MRI and PET-CT) gave a negative result, while in three out of five cases, the tumor lesion was determined by transrectal ultrasound. All patients included in the study underwent mandatory perineal biopsy of the prostate, seminal vesicles, or prostate bed, if RP was previously performed. Detailed characteristics are presented in the table.

Most patients received androgen deprivation therapy before salvage HDR-BT and for at least three months after brachytherapy. Four (4.1%) patients refused hormonal therapy. Three to six months after salvage HDR-BT, androgen deprivation therapy was discontinued.

Brachytherapy was performed on a Microselectron HDR device using a transrectal ultrasound probe 4-9 MHz, in two fractions of 15 Gy two weeks apart with a total dose of 30 Gy. Dosimetric planning was carried out on the PLATO-oncentra planning system (NUCLETRON). The total equivalent dose (EQD2) for two fractions was 141 Gy (with $\alpha/\beta=1.5$). After completing the salvage HDR-BT, all patients were under follow-up. In the first two years, examination was carried out every three months, while in subsequent years every six months. During follow-up, PSA and testosterone levels, complete blood count, and urinalysis were evaluated. Pelvic MRI with contrast was performed once every six months in the first year, then once a year. PET-CT with PSMA was performed if biochemical recurrence developed.

The primary endpoint of the study was PSA-specific survival, which was assessed based on the Phoenix criteria. An event was considered to be an increase in PSA levels by more than 2 ng/ml from the nadir in patients after RT and a PSA level of more than 0.2 ng/ml in patients after RP. The Kaplan-Meier method was used to evaluate survival. P values <0.05 were considered significant. P values <0.1 were included in the multivariate analysis.

Statistical analysis was performed using IBM SPSS Statistics 27. Assessment of early and late toxicity of brachytherapy was carried out according to the RTOG/EORTC classification.

Results. The median follow-up was 36 months (3-84 months). When analyzing the treatment results, we divided the patients into two groups according to the primary treatment method. Group I included 34 patients after RP, while in group II there were 64 patients after RT. The five-year PSA-specific survival in group I was significantly higher than in group II (88.2 versus 67.2%, respectively; $p=0.023$) (*Fig. 1*).

Such different survival rates in the groups are primarily due to the altered radiobiology of PCa after previous RT, which is characterized by the development of chronic tissue hypoxia, providing not only increased radioresistance of recurrent PCa but also contributing to the development of aggressive mutations, which in turn reduces the efficiency of treatment.

When analyzing the causes of PCa recurrence after salvage HDR-BT, it was found that significant predictors were the maximum PSA values at which recurrence was diagnosed after the primary treatment. In patients after RP with a PSA level of more than 4 ng/ml, recurrence

Table

Characteristics of patients included in the study

Parameter	Number	
	Abs.	%
Type of primary treatment		
External beam radiation therapy	21	21.4
LDR-BT	24	24.5
HDR-BT	5	5.1
RP	34	34.7
BT + external beam radiation therapy	14	14.3
T-stage after primary treatment		
cT1c	4	4.1
cT2a	8	8.1
cT2b	13	13.2
cT2c	17	17.5
cT3a	10	10.2
cT3b	13	13.2
pT2a	3	3.1
pT2b	4	4.1
pT2c	8	8.2
pT3a	11	11.2
pT3b	7	7.1
Gleason Score (G)		
G1: Gleason score 5–6	38	38.8
G2, 3: Gleason score 7 (3+4), (4+3)	38	38.8
G4: Gleason score 8 (4+4)	19	19.4
G5: Gleason score 9 (4+5) (5+4)	3	3
Maximum PSA level before primary treatment		
Less than 10 ng/ml	44	44.9
10 –20 ng/ml	26	26.5
More than 20 ng/ml	28	28.6
NCCN Risk Group		
Low risk	9	9.2
Intermediate risk	34	34.7
High risk	27	27.5
Very high risk	28	28.6
Maximum level PSA at recurrence after RP		
Менее 1 нг/мл	9	9.1
1–3 нг/мл	18	18.4.7
Более 3 нг/мл	7	7.1
Maximum PSA level in the diagnosis of recurrence after RT		
Less than 4 ng/ml	28	28.6
4-10 ng/ml	27	27.5
More than 10 ng/ml	9	9.1
Gleason score (G) based on repeat biopsy at time of recurrence		
G1: Gleason score 5–6	36	36.7
G2, 3: Gleason score 7 (3+4), (4+3)	28	28.6
G4: Gleason score 8 (4+4)	26	26.5
G5: Gleason score 9 (4+5) (5+4)	8	8.1

Note: EBRT, external beam radiation therapy; RT, radiotherapy; BT, brachytherapy; LDR-BT, low-dose brachytherapy; HDR-BT, high-dose brachytherapy; PSA, prostate-specific antigen; NCCN, National Comprehensive Cancer Network.; RP, radical prostatectomy.

was found significantly more commonly than in patients whose PSA level did not exceed 4 ng/ml (50% versus 93%, respectively; p=0.025) (*Fig. 2*). In the group after RT, this value was 10 ng/ml. In this group, the 5-year PSA-specific survival rate depending on the PSA level (less than 4 ng/ml, 4-10 ng/ml, and more than 10 ng/ml) was 77.4, 66.7, and 33.3%, respectively (p=0.008) (*Fig. 3*).

In addition, the analysis showed that in patients with local recurrence of PCa, significant predictors of treatment failure were very high risk of progression at the initial diagnosis (p=0.03), features of castration resistance before the start of salvage HDR-BT (p=0.13), development of biochemical recurrence within 24 months after the primary treatment (p=0.01).

Early and late toxicity were assessed according to the generally accepted RTOG/EORTC criteria (American Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer).

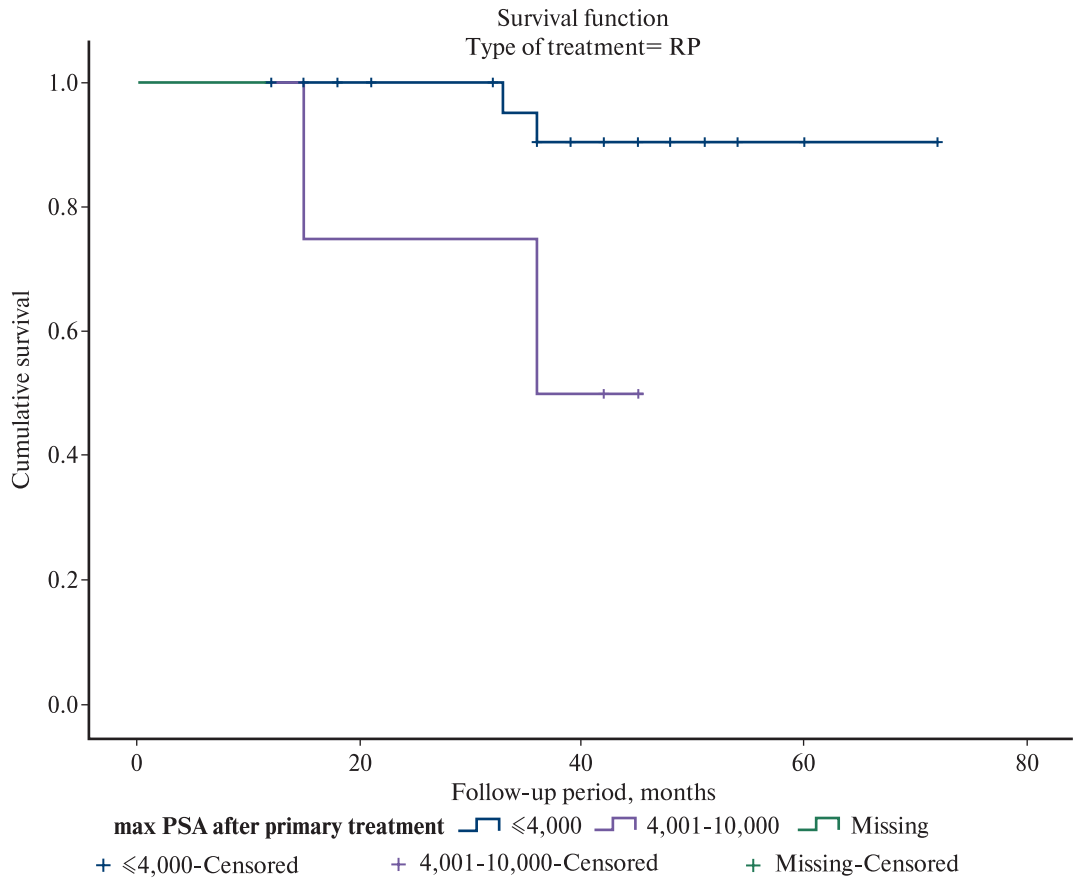


Fig. 2. Three-year PSA-specific survival (biochemical control) after salvage HDR-BT in patients with local recurrence of PCa after RP depending on the maximum PSA level at which tumor recurrence was diagnosed (less than 4 ng/ml and more than 4 ng/ml)

The frequency of early genitourinary toxicity of grades 1, 2, 3 in general was 43.9, 15.3, and 3%, respectively, while the rate of early gastrointestinal toxicity of grades 1 and 2 was 12.2 and 2%, respectively. The frequency of late genitourinary toxicity of grades 1, 2, 3 was 22.4, 10.2, and 4.1%, respectively, late gastrointestinal toxicity of grades 1 and 2 was 10.2 and 1%, respectively. At the same time, all severe reactions of grades 2 and 3, both from the urinary system and from the rectum, were observed only in group II. Such higher toxicity is explained by the fact that repeated RT in high total doses virtually leaves no reserve of surrounding healthy tissues, which in turn leads to a high frequency of complications. It should be noted that all cases of urinary retention (n=5), caused by the development of urethral stricture or bladder neck sclerosis, were seen in patients who had previously undergone one of the types of RT. Urinary incontinence after salvage HDR-BT was noted in 3 (8.8%) patients from group I. In two of them, urinary incontinence was determined even before salvage HDR-BT, but to a lesser extent. In group II, urinary incontinence was noted in 1 (1.5%) patient in the long-term period (after 48 months) after repeated attempts to incise the stricture of the membranous urethra.

Discussion. Treatment of locally recurrent PCa after previous RT remains a challenging task in medical practice. Due to the fact that primary treatment of PCa is quite aggressive, having a number of undesirable consequences, the vast majority of patients with suspected recurrence of PCa receive palliative androgen deprivation therapy. Repeated surgical treatment or external beam radiotherapy is often associated with high rate of complications [6]. Androgen deprivation therapy is also associated with risks of adverse events that affect not only the quality but also the duration of the patient's life [7-9]. A window of opportunity to reduce toxicity may be the options of salvage HDR-BT, which can not only affect the tumor focus but also significantly reduce toxicity, allowing to maintain the patient's quality of life at a high level. It is especially important that when carrying thorough examination, including perineal prostate biopsy, it is possible to conceptually change approaches to the treatment of patients in this category with the use of focal RT.

HDR-BT has several potential advantages that determine its prospect in the treatment of local recurrences of PCa both after RP and after various types of RT. Owing to the available systems of dosimetric planning of RT, there is an opportunity to optimize the position of the source and its exposure time at a given point, which allows delivering the maximum acceptable extremely high doses to a given area, taking into account the tolerance of organs at risk. The high gradient of dose reduction in HDR-BT allows to perform treatment even in case of intimate adherence of the tumor focus to critical organs of the small pelvis, which in turn ensures low radiation toxicity.

A number of studies devoted to salvage treatment methods for local recurrences after primary treatment

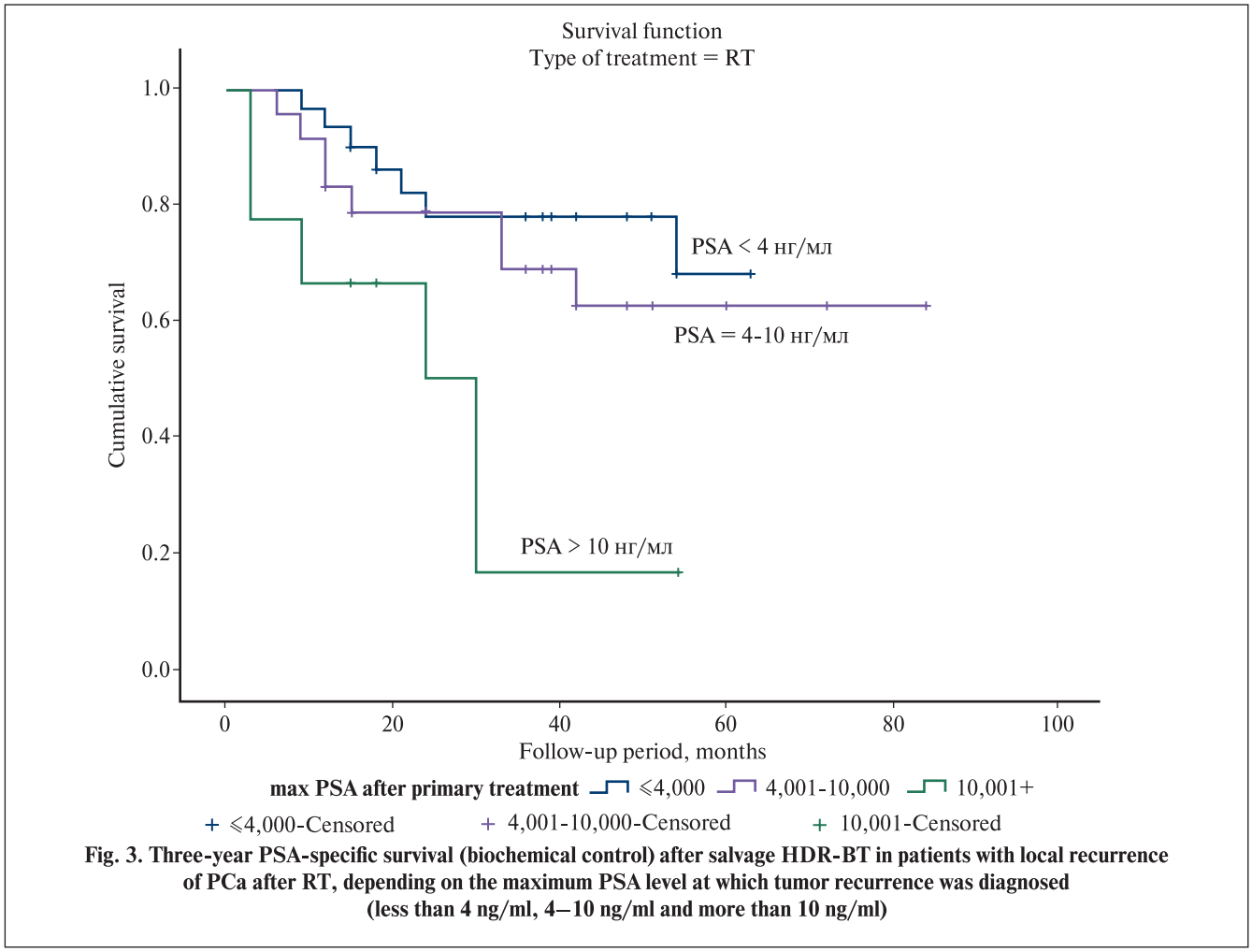


Fig. 3. Three-year PSA-specific survival (biochemical control) after salvage HDR-BT in patients with local recurrence of PCa after RT, depending on the maximum PSA level at which tumor recurrence was diagnosed (less than 4 ng/ml, 4–10 ng/ml and more than 10 ng/ml)

points to the high interest in the use of HDR-BT in this category of patients. In particular, a prospective study involving 30 patients who received salvage HDR-BT under MRI control demonstrated encouraging efficacy and safety when using standard doses as monotherapy with two fractions (13.5 Gy × 2) [10]. The three-year biochemical recurrence-free survival was 62%, and only one patient had grade 3 genitourinary toxicity, without pronounced gastrointestinal toxicity. On the other hand, a study of a single-fraction regimen for salvage HDR-BT showed not so encouraging results. The authors assumed that one fraction of HDR-BT would be more acceptable for the patient; however, it would significantly reduce toxicity for organs at risk [11]. Nevertheless, the three-year biochemical recurrence-free survival in this study, which included 175 patients, was only 43%, which indicates the low efficiency of one fraction. A number of other researchers analyzing the efficiency and toxicity of salvage HDR-BT in patients with local recurrences of PCa draw similar conclusions [12, 13].

The present study has limitations, essentially having a retrospective nature with a relatively short follow-up period for a number of patients. This circumstance may contribute to the fact that the frequency of delayed side effects in this study may increase, and a certain percentage of patients may have biochemical recurrence with longer-term follow-up.

Conclusion. HDR-BT is an effective option for salvage treatment of local recurrences of PCa after both radiation and surgical treatment. In addition to the brachytherapy technology itself, an important element of combined treatment is the diagnostic stage, the task of which is to accurately determine the localization of the recurrent tumor.

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Received 16.02.2024
Accepted 17.10.2024

Financing: The study was performed without external funding.

Informed consent: All patients gave written informed consent to participate in the study.

Compliance with patient rights and principles of bioethics: The study protocol was approved by the biomedical ethics committee of Russian Scientific Center of Roentgenradiology, Ministry of Health of Russia. Protocol №. 61/2014 dated 27.01.2014.

Authors' contributions: V. Solodkiy: development of research design. A. Pavlov: development of research design, scientific editing of manuscript text. A. Tsibulskiy: obtaining data for analysis, analyzing of results, statistical analysis of the data, writing the text of the manuscript. A. Dzidzaria: scientific editing of the manuscript text. A. Fedotova: analysis of results. V. Gubanova: analysis of results.

Gubanova V.I.Salvage high-dose brachytherapy in patients with local recurrence of prostate cancer after various types of primary treatment. Urologiia. 2025;1:22-28.

Doi: https://dx.doi.org/10.18565/urology.2025.1.22-28

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