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Salvage prostate HDR brachytherapy combined with interstitial hyperthermia for local recurrence after radiation therapy failure

The two main treatment methods for primary prostate cancer are surgery and radiation therapy, with or without androgen deprivation therapy. Radiotherapy, thanks to technological progress giving opportunities to reduce doses in critical organs, is becoming an increasingly popular option for men who wish to avoid invasive surgery. However, some patients experience a biochemical recurrence [1, 2, 3]. The most commonly used definition of biochemical failure after definitive RT is the Phoenix definition [prostate-specific antigen (PSA) increase of >2 ng/ml above the nadir reached after RT] [4]. The sole local recurrence (without distant progression) is found in about one-fourth of the patients with biochemical failure meeting the Phoenix criteria. The majority of local recurrences occur at the same site as the dominant primary tumor [5].

At present, there is no consensus with respect to the optimal treatment for this group of patients. The recommended curative treatment options for patients with favorable risk factors (initial T1–2 stage, life expectancy >10 years, PSA at salvage <10 ng/ml) are radical prostatectomy, cryosurgery or brachytherapy [6]; however, most patients receive only androgen deprivation therapy as a palliative treatment [7]. Aggressive salvage treatment options should be offered with great care, because reported failure rates as well as toxicity rates can be significant, regardless of salvage technique [8].

Most centers perform only one method of salvage therapy, which is reflected in the literature—typically there is a series of patients treated with one method at a single center. Brachytherapy, including HDR (high-dose rate), LDR (low-dose rate), and PDR (pulsed-dose rate), is becoming a common salvage treatment for prostate cancer failure after radiotherapy.

Hyperthermia enhances the effect of radiation without a significant increase in adverse events, as demonstrated by studies in both prostate cancer cell lines in vitro [9, 10], as well as in non-randomized clinical trials [11, 12, 13]. The combination of interstitial hyperthermia (IHT) with HDR brachytherapy (HDRBT) is feasible during spinal anesthesia—both methods use the same catheters and there is no need for additional traumatization of patients [14].

The treatment program combining interstitial hyperthermia with HDR brachytherapy for recurrent prostate cancer started in the Centre of Oncology in Krakow in 2008. In this paper we present the results of the retrospective analysis of early toxicity and clinical outcomes of this combined treatment.

Material and methods

Patients' characteristics

Between 14 March 2007 and 04 March 2013, at the Institute of Oncology in Krakow, 34 patients diagnosed with local recurrence of prostate cancer after previous definitive external beam radiation therapy (EBRT) were treated with salvage HDR prostate brachytherapy (sHDRBT). In 25 patients, interstitial hyperthermia (IHT) was a part of the treatment. IHT was offered to patients as an additional treatment option. Patients gave informed consent to the proposed treatment. The patients' characteristics are presented in **Tab. 1**.

Eligibility criteria

During follow-up after EBRT, rising PSA levels were detected in the analyzed patients of whom 16 met the Phoenix definition for biochemical relapse. Imaging was performed to locate the site of recurrence, and if suspected lesions were found, regardless of the Phoenix criterion, a core biopsy was performed. The eligibility criteria for the sHDRBT were the following: histological confirmation of the local recurrence of prostate cancer, exclusion of nodal or distal metastases by imaging (pelvic ± abdominal CT or MRI and a bone scan) and met the technical criteria for brachytherapy [prostate volume of <60 cc, no pubic arch interference, the distance between the rear edge of the prostate and the rectum at least 5 mm, transurethral resection of the prostrate (TURP) ≥6 months before qualification]. No patients had contraindications to spinal anesthesia.

Tab. 1 Patient characteristics

	At initial treatment	At salvage
Median age [years] (range)	65 (53–76)	71 (62–83)
Median PSA [ng/ml] (range)	16.3 (6.37–64)	2.8 (1.044–25.346)
Gleason score		
≤6	15	5
7	7	10
≥8	1	5
Unknown	2	5
T stage		
T1a	1	0
T1b	1	1
T1c	7	6
T2a	3	11
T2b	0	2
T2c	8	3
T3a	4	2
T3b	1	0
Risk group (according to D'Amico)		
Low	1	n.a.
Intermediate	12	n.a.
High	12	n.a.
Hormonal treatment		
No	0	15
Orchiectomy	1	1
ADT Median duration (range)	24 16 (4–40)	9 n.a.
PSADT [months] Median (range)	n.a.	10.1 (2.44–28.85)
PSA velocity [ng/ml/year] Median (range)	n.a.	2.28 (0.42–7.29)
Time to biochemical relapse [months]	n.a.	43 (17–122)[a]
Time to histological confirmation [months]	n.a.	68 (19–139)

ADT androgen deprivation therapy, *PSADT* prostate-specific antigen doubling time.[a]16 patients.

Tab. 2 Dose–volume histrogram parameters of primary external beam radiation therapy

Prostate [Gy] Median (range)			Rectum [Gy] Median (range)		Bladder [Gy] Median (range)	
Dmin	**Dmean**	**Dmax**	**Dmax**	**Dmean**	**Dmax**	**Dmean**
71.7 (3–73.5)	73.9 (61–75)	76.4 (71.9–77.5)	75.6 (68.8–78.248)	50 (24–58.8)	75.465 (70.1–77.484)	53 (23.6–70.6)

Primary treatment characteristics

EBRT

All patients received their initial treatment at the Institute of Oncology in Krakow. They received EBRT, and 23 of the patients received 74, 1–72, 1–70 Gy (fraction dose was 2 Gy). The target volume included prostate and seminal vesicles in 19 patients and in 6 patients it also included regional lymph nodes (irradiated to a dose of 50 Gy). It was not possible to extract D2 cc parameters for the bladder and rectum. In 4 patients the dose–volume histograms were not created because of 2D planning. The detailed parameters of 21 treatment plans for prostate and rectum, and 20 for bladder are summarized in **Tab. 2**.

Androgen deprivation therapy

As part of their initial treatment, 24 patients received hormone therapy. One patient underwent orchiectomy. Most of the patients were referred to our center by their urologists after initiation of ADT (androgen deprivation therapy). This treatment consisted of neoadjuvant, concomitant, and adjuvant LHRH (luteinizing hormone-releasing hormone) agonist and antiandrogen (usually flutamide). The median duration of hormonal therapy was 16 months (range 4–40 months).

Salvage brachytherapy combined with interstitial hyperthermia

The procedure was previously described by our group [14], but can be briefly summarized as follows: the aim of hyperthermia treatment was to heat the peripheral zone of the prostate to 41–43°C for 60 min immediately before each fraction of brachytherapy. For this purpose, plastic needles were inserted into the prostate under transrectal ultrasound control (TRUS). These catheters served as guides for antennas and thermistor probes of the hyperthermia system (BSD500, BSD Medical Corporation, Salt Lake City, UT, USA), followed by a HDR brachytherapy source (Ir192). Based on TRUS images, a radiation oncologist (AMK, TD or TW) delineated the contours of the prostate, urethra, rectum and, optionally, the bladder. Then a physicist performed a treatment plan using SWIFT software or ONCENTRA Prostate™ (Nucletron BV, The Netherlands).

It was acceptable to shorten the time or withdraw from the hyperthermia procedure in the cases of an early recovery from anesthesia, saddle block, excessive mobility, or request of the patient. Hyperthermia was performed according to the RTOG guidelines [15]. All patients received the planned dose of 30 Gy in three fractions at intervals of 3 weeks. The dose was specified on prostate capsule. The equivalent doses in 2-Gy fractions (EQD2) for our treatment schedules using α/β ratios of 1 and 3 were 110 and 78 Gy, respectively. The aim was to achieve the prescribed dose in at least 95% of PTV (planning target volume, D90>95%) and not exceeding 80 and 120% of the prescribed dose in the rectum and urethra, respectively.

Antihormonal therapy was not routinely implemented, although 6 patients (24%) received antiandrogen ± LHRH agonist because of biochemical relapse, and 3 (12%) were treated with ADT concomitantly with sHDRBT. This treatment was discontinued thereafter.

Statistical analysis

The analysis included only patients who received at least one session of hyperthermia and all scheduled brachytherapy fractions. For statistical analyses we used Statistica software (version 9.0, StatSoft, Inc. Tulsa, OK, USA). The main endpoint of the analysis was to measure biochemical disease-free survival (bDFS) and toxicity. Biochemical disease-free survival was

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Salvage prostate HDR brachytherapy combined with interstitial hyperthermia for local recurrence after radiation therapy failure

Abstract

Purpose. The aim of the present retrospective study is to evaluate toxicity and early clinical outcomes of interstitial hyperthermia (IHT) combined with high-dose rate (HDR) brachytherapy as a salvage treatment in patients with biopsy-confirmed local recurrence of prostate cancer after previous external beam radiotherapy.

Patients and methods. Between September 2008 and March 2013, 25 patients with local recurrence of previously irradiated prostate cancer were treated. The main eligibility criteria for salvage prostate HDR brachytherapy combined with interstitial hyperthermia were biopsy confirmed local recurrence and absence of nodal and distant metastases. All patients were treated with a dose of 30 Gy in 3 fractions at 21-day intervals. We performed 62 hyperthermia procedures out of 75 planned (83%). The aim of the hyperthermia treatment was to heat the prostate to 41–43°C for 60 min. Toxicity for the organs of the genitourinary system and rectum was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, v. 4.03). Determination of subsequent biochemical failure was based on the Phoenix definition (nadir +2 ng/ml).

Results. The median age was 71 years (range 62–83 years), the median initial PSA level was 16.3 ng/ml (range 6.37–64 ng/ml), and the median salvage PSA level was 2.8 ng/ml (1.044–25.346 ng/ml). The median follow-up was 13 months (range 4–48 months). The combination of HDR brachytherapy and IHT was well tolerated. The most frequent complications were nocturia, weak urine stream, urinary frequency, hematuria, and urgency. Grade 2 rectal hemorrhage was observed in 1 patient. No grade 3 or higher complications were observed. The 2-year Kaplan–Meier estimate of biochemical control after salvage treatment was 74%. The PSA in 20 patients decreased below the presalvage level, while 11 patients achieved a PSA nadir <0.5 ng/ml. All patients are still alive. Of the 7 patients who experienced biochemical failure, bone metastases were found in 2 patients.

Conclusion. IHT in combination with salvage HDR brachytherapy is a well tolerated and effective treatment.

Keywords

Prostate neoplasms · Salvage therapy · Side effects · Treatment outcome · Neoplasm recurrence, local

Salvage-HDR-Brachytherapie in Kombination mit interstitieller Hyperthermie bei Lokalrezidiv eines Prostatakarzinoms nach erfolgloser Strahlentherapie

Zusammenfassung

Ziel. Die vorliegende retrospektive Studie bewertet die Toxizität und die frühen klinischen Ergebnisse der interstitiellen Hyperthermie (IHT) in Kombination mit HDR-Brachytherapie (Brachytherapie mit hoher Dosisrate, „high-dose rate") als Salvage-Verfahren bei Patienten mit histologisch gesichertem Lokalrezidiv eines Prostatakarzinoms nach früherer externer Strahlentherapie.

Patienten und Methoden. Zwischen September 2008 und März 2013 wurden 25 Patienten mit Lokalrezidiv eines zuvor perkutan bestrahlten Prostatakarzinoms behandelt. Die Hauptselektionskriterien für das kombinierte Salvage-Verfahren einer HDR-Brachytherapie in Verbindung mit interstitieller Hyperthermie waren: histologische Sicherung eines Lokalrezidivs durch Biopsie und Abwesenheit von Lymphknoten- bzw. Fernmetastasen. Alle Patienten wurden mit der Dosis von 30 Gy in 3 Fraktionen in Abständen von 21 Tagen behandelt. Von den geplanten 75 wurden 62 Hyperthermieverfahren (83%) durchgeführt. Das Ziel der Hyperthermiebehandlung war die Erwärmung der Prostata auf 41–43°C für die Dauer von 60 min. Die Toxizität für die Organe des Harn- und Geschlechtssystems sowie des Mastdarms wurde anhand der Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03 bewertet. Die Bestimmung der nachfolgenden biochemischen Tumorkontrolle basierte auf der Phoenix-Definition (Nadir +2 ng/ml).

Ergebnisse. Das Alter betrug im Median 71 Jahre (62–83 Jahre), der mediane prätherapeutische PSA-Wert 16,3 ng/ml (6,37–64 ng/ml) und der mediane PSA- Wert zum Zeitpunkt der Salvage-Behandlung 2,8 ng/ml (1,044–25,346 ng/ml). Die mediane Nachbeobachtungszeit lag bei 11 Monaten (4–48 Monate). Die Kombination der HDR-Brachytherapie mit IHT wurde gut vertragen. Die häufigsten Komplikationen waren: Nykturie, schwacher Harnstrahl, häufiges Wasserlassen, Hämaturie und Harndrang. Bei einem Patienten wurde eine rektale Grad-2-Blutung beobachtet. Es traten keine Komplikationen 3. Grades oder höher auf. Die Kaplan-Meier-2-Jahres-Schätzung der biochemischen Kontrolle nach der Salvage-Therapie betrug 74%. Bei 20 Patienten fiel der PSA unter die Werte vor Salvage-Behandlung, 11 Patienten erreichten einen PSA-Nadir von 0,5 ng/ml. Alle Patienten überlebten. Einen biochemischen Rückfall erlitten 7 Patienten – bei 2 von ihnen wurden Knochenmetastasen gefunden.

Schlussfolgerung. Die Kombination aus IHT und Salvage-HDR-Brachytherapie ist eine gut verträgliche und effektive Therapieform.

Schlüsselwörter

Prostataneoplasien · Salvage-Therapie · Nebenwirkungen · Behandlungsergebnis · Lokalrezidiv

measured from the date when treatment was completed to the date of biochemical relapse. The Kaplan–Meier method was used to calculate survival rates.

Toxicity assessment

Toxicity for the genitourinary organs and the rectum was assessed according to the Common Terminology Criteria for Adverse Events version 4.03 [16] on the basis of the data extracted from medical records and I-PSS questionnaires (International Prostate Symptom Score). We documented the following symptoms: frequent urination, urgency to urinate, urinary tract infection, urinary retention, urinary incontinence, nocturia, narrowing of the urinary stream, urinary tract

Tab. 3 Dose–volume histogram parameters of salvage high-dose rate brachytherapy (sHDRBT)

	Prostate (PTV)					Rectum		Urethra	
	Dmin	D90	V100	V150	V200	Dmax	D2cc	Dmax	D0.1cc
[%] Median ± SD	64.2±5.2	99.4±4.7	89.6±2.3	30.9±3.4	9.4±1.6	79.4±2.6	56.1±6	116.9±3.7	113.3±3.7
[Gy] Median ± SD	19.26±1.6	29.86±1.4	26.88±0.7	9.27±1	2.82±0.5	23.82±0.8	16.8±1.8	35±1.1	34±1.1

Tab. 4 Adverse events of interstitial hyperthermia (IHT) + high-dose radiation (HDR) evaluated according to CTCAE version 4.03

	Acute (0–3 months)				Late (>3 months)			
	G1	G2	G3	G4	G1	G2	G3	G4
Genitourinary								
Nocturia	16 (64%)	8 (32%)	0	0	7 (32%)	2 (9%)	0	0
Frequency	11 (44%)	6 (24%)	0	0	4 (18%)	1 (4.5%)	0	0
Obstruction	13 (52%)	7 (28%)	0	0	5 (22.7%)	1 (4.5%)	0	0
Noninfective cystitis	10 (40%)	0	0	0	0	0	0	0
Retention	5 (20%)	3 (12%)	0	0	2 (9%)	0	0	0
Urgency	11 (44%)	1 (4%)	0	0	1 (4.5%)	0	0	0
Hematuria	14 (56%)	2 (8%)	0	0	0	0	0	0
Incontinence	3 (12%)	1 (4%)	0	0	1 (4.5%)	0	0	0
Perineal, hypogastric, or penile pain	5 (20%)	0	0	0	0	0	0	0
Gastrointestinal								
Rectal hemorrhage	2 (8%)	1 (4%)	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0
Proctitis	0	0	0	0	0	0	0	0

bleeding, pain, rectal bleeding, diarrhea, and inflammation of the rectum. Erectile dysfunction was not monitored. The acute symptoms are assumed to be revealed within 3 months after treatment.

Follow-up

The follow-up visits for patients treated with brachytherapy consisted of at least a history, digital rectal examination, and PSA measurement. Visits at our institute were scheduled 1, 6 and 12 weeks after treatment and at 3-month intervals thereafter. The follow-up time was measured from the completion of brachytherapy up to the date of the last recorded follow-up visit or the death of the patient (overall survival, OS).

Results

Brachytherapy

A total of 75 fractions of sHDRBT were performed. The median total treatment time was 42 days (range 40–72 days). The median D90 was 99.5±3%. The median maximum dose in the urethra and rectum amounted to 116.9±3.6% and 79.4±2.6%, respectively. Other DVH parameters are presented in **Tab. 3**.

Hyperthermia

We performed 62 sessions of hyperthermia (out of 75 planned). There were 17 patients who underwent 3 sessions of hyperthermia, 3 patients—2 sessions, and 5 patients—1 session. The reasons for a smaller amount of IHT sessions than planned were equipment failure (4 patients—6 sessions), the saddle block (2 patients—2 sessions), excessive mobility of patients (3 patients—3 sessions), and patient's request (1 patient—2 sessions). The median hyperthermia session time was 50 min (range 30–60 min). The average temperature measured in the prostate was in median 41.2°C (range 38.4–42.9°C); the maximum temperature measured in the prostate was 42°C (range 40.4–43.4°C), while the average rectal temperature was 38.5°C (range 36.8–42.0°C)—data from 28 measurements. The temperature distribution in the heated area was inhomogeneous.

Toxicity

Side effects associated with IHT combined with sHDRBT are summarized in **Tab. 4**. There were no grade 3 or higher toxicities.

Acute side effects were evaluated in all patients (25); however, in 22 patients late complications were reported (with the follow-up longer than 6 months). In 6 patients we prospectively observed changes in IPSS. The median score before treatment was 6 points (range 2–19), and 6 weeks after treatment, it was 14 points (range 13–30). Acute complications of the urinary tract are very common (occur in almost all patients), but their intensity does not normally require chronic medication or medical intervention. The most common are nocturia, narrowing of urinary stream/obstruction, frequency and transient hematuria. Late urinary toxicities are mild and occur in up to 40% (grade 1 and 2 nocturia).

We did not register late complications of the gastrointestinal tract. Acute complications occurred in 3 patients who reported bleeding from the rectum. One patient required medical treatment (G2), which delayed application of the third brachytherapy fraction. Apart from complications that occurred due to radiation, we also recorded two mild complications associated with anesthesia and patient positioning. One patient experienced a post-lumbar puncture headache, the other one, a sacral decubitus.

Outcomes

The median follow-up was 13 months (range 4–48 months). During the last follow-up, all patients were alive. The 2-year estimated biochemical failure free survival (Kaplan–Meier method) was 74%. During the follow-up visits, 20 patients achieved a decreased PSA; for 11 of them, the level dropped below 0.5 ng/ml. In 2 patients, PSA levels remained stable (variation

Tab. 5 Interstitial hyperthermia (IHT) + salvage high-dose rate brachytherapy (sHDRBT) effects

Treatment time [days] Median (range)	42 (40–72)
PSA at last follow-up [ng/ml] Median (range)	0.71 (0.004–91.534)
Time to biochemical failure [months] Median (range)	13 (0–22)
Biochemical failure [proportion of patients]	7/25
Local relapse [proportion of patients]	1/25
Nodal relapse [proportion of patients]	0/25
Distant metastases [proportion of patients]	2/25

<1 ng/ml). Seven patients (28%) met the Phoenix definition criteria of biochemical failure. The median time from the end of the salvage to biochemical failure was 13 months (range 0–22 months).

In 1 patient, local recurrence was diagnosed 13 months after salvage treatment. It was localized in the frontal part of the prostate, behind the pubic symphysis (this tumor was not seen on the multiparametric MRI taken prior to treatment). One patient underwent HIFU 26 months after sHDRBT due to rising levels of PSA (actually with no effect on PSA). One patient experienced a PSA bounce (the maximum value of 2.169 ng/ml, a duration of 11 months, nadir reached 1.365 ng/ml). In 2 patients, bone metastases developed (4 and 6 months after salvage HDR). Clinical outcomes are summarized in **Tab. 5**.

Discussion

As mentioned above, due to the lack of prospective studies, there is no consensus regarding salvage therapy in patients with local only recurrence after irradiation. The 5-year bDFS after radical prostatectomy ranges from 50 to 70%. The results after cryosurgery are somewhat inferior and differ substantially (2-year bDFS 19–75%) [8]. For brachytherapy, both the temporary (HDR or PDR implants using Ir192) and permanent LDR 'seeds' implants (I125, Pd103) are used for the treatment of both primary and recurrent prostate cancer after EBRT failure. There are only a few available publications on salvage HDR prostate brachytherapy [17, 18, 19, 20, 21, 22, 23]. Some of them were published only as abstracts (congress reports). Most of them are retrospective analyses of small groups of patients.

Lee et al. [17] reported a retrospective study that included 21 patients with locally recurrent prostate cancer after prior definitive radiotherapy. The patients were treated with 36 Gy in 6 fractions (two implants separated by 1 week, each implant consisted of three fractions). With a median follow-up of 19 months, the 2-year estimated biochemical disease-free survival (bDFS) was 89%. In 2013 the report was updated in a paper by Chen et al. [18], who analyzed 52 patients, with a median follow-up of 59.6 months; the 5-year estimated bDFS was 51%, and the 5-year estimate of OS was 92%. Grade 3 urinary acute and late adverse events were infrequent (2%/2%). No rectal toxicities higher than grade 2 were reported.

Jo et al. [19] reported 11 patients with local recurrence of prostate cancer after previous EBRT or proton RT. Salvage HDR brachytherapy consisted of 22 Gy in 2 fractions separated by 6 h delivered during one implant. The median follow-up was 29 months. There were 7 patients (63%) who showed biochemical nonevidence of disease. No toxicities higher than grade 2 were observed.

Tharp et al. [20] reported retrospectively on a group of 7 patients with local recurrence of prostate cancer after EBRT or seed irradiation. The dose for salvage treatment was not constant, and in 3 cases was combined with EBRT. All patients received neoadjuvant androgen deprivation therapy. With the median follow-up of 58 months, the crude rate of DFS was 71%. Two patients (28.5%) developed grade 3 urethral necrosis, and other 2, grade 3 perineal pain.

Łyczek et al. [21] described a heterogeneous group of 115 patients with biochemical relapse after primary treatment of prostate cancer. There were 71 patients who received definitive EBRT, 26 HDR brachytherapy, 7 combined EBRT with HDR brachytherapy, and 11 underwent prostatectomy with salvage EBRT. There was no information about histological confirmation of local recurrence. All patients received 30 Gy in 3 fractions separated by 3 weeks (the same scheme as in our series) and neoadjuvant and adjuvant androgen deprivation therapy. The bDFS estimated using the Kaplan–Meyer method was 46% in patients with PSA <6 and only 18% in those with PSA >6. There was no information about the median or mean follow-up. Acute and late grade 3 and 4 urinary toxicities were 5.2 and 12.2% respectively (uncontrolled hematuria, fistulas, incontinence, or urethral stricture). Grade 3 rectal toxicity was reported in only 0.9% of patients.

Gawkowska-Suwińska et al. [22] reported 15 patients treated with salvage HDR brachytherapy to a total dose of 30 Gy in 3 fractions performed every 2 weeks. During a mean follow-up of 9 months, the authors reported mild acute toxicities (maximium grade 2 haematuria, dysuria and lower abdominal pain). One patient developed late grade 3 urethral stricture 9 months after salvage treatment.

Recently Lahmer et al. [23] presented early results and toxicity of salvage PDR brachytherapy. There were 18 patients (including 6 post-prostatectomy patients) who achieved 3 year bPFS of 57.1% with a median follow-up of 21 months. There were no gastrointestinal toxicities reported, and only 11% of patients developed grade 2, and 17% grade 3, genitourinary side effects.

Salvage HDR or PDR brachytherapy is, therefore, a good option for patients with locally recurrent prostate cancer after external beam irradiation. Treatment results are encouraging, and toxicity is on an acceptable level.

In the treatment of prostate cancer regional or interstitial hyperthermia is used in various treatment regimens. It is usually combined with external beam radiation therapy or, rarely, with brachytherapy. We previously reported [14] low acute toxicity in a group of 72 patients treated with IHT + HDRBT, both as the initial and salvage treatment. In the literature we found only one full-text article [24] about combining IHT and HDRBT. The conclusion of this publication was that the combination of these methods is feasible and well tolerated.

To avoid harm to the patient, the key is the proper qualification of patients to a lo-

cal salvage therapy. A histological confirmation of recurrence in the prostate and ruling out distant and nodal metastases is also essential. Moreover, it is important to identify patients that are most likely to have only local disease. Factors that are associated with better biochemical control included postradiation PSA nadir of <0.5 ng/ml, presalvage PSA <10, PSADT (PSA doubling time) >6–9 months, Gleason score at salvage <7–8, low-risk initial tumor, no extraprostatic extension at salvage, and a disease-free interval >24 months [8, 25, 26]. However, in a prospective UCSF study, none of these factors reached statistical significance [18].

As we found in the literature, the group presented is the largest one combining IHT and HDRBT. Nevertheless, our report has many limitations: a small sample size, retrospective design, wide selection criteria, and short follow-up. There are no ongoing prospective trials regarding this kind of treatment.

Our results were slightly inferior to those reported above. This can be explained by the fact that about half (48%) of our patients were initially from a high-risk group. Many of recurrent prostate cancer patients are hormone resistant. Only 36% of patients in our series were given hormonal treatment, which can influence the PSA level but is associated with significant toxicity. Strict patient selection for salvage combination of brachytherapy and hyperthermia should improve the outcome. Tolerance of IHT and sHDRBT is good and similar to that mentioned in other reports; nevertheless, the follow-up is still short.

Conclusion

Interstitial hyperthermia in combination with HDR brachytherapy, as a treatment for local recurrence of prostate cancer after EBRT failure, has acceptable toxicity and is effective. In the analyzed group of patients, no complications higher than grade 2 were observed. The most common adverse events were mild urinary frequency, nocturia and temporary weakening of the urinary stream. Treatment results are comparable to sHDRBT alone; however, the retrospective nature of our analysis and the fact that a large proportion of our patients had unfavorable prognostic factors should be considered. The prospective clinical trial should be conducted to properly evaluate the effectiveness and toxicity of IHT + sHDRBT.

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Compliance with ethical guidelines

Conflict of interest. A.M. Kukiełka, M. Hetnał, T. Dąbrowski, T. Walasek, P. Brandys, D. Nahajowski, R. Kudzia, D. Dybek, and M. Reinfuss state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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