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ORIGINAL ARTICLE

SHARP hypofractionated stereotactic radiotherapy for localized prostate cancer: a biochemical response to treatment

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Summary

Purpose: *The standard treatment for patients with early-stage prostate cancer are operation and radiotherapy. Stereotactic body radiation therapy (SBRT) is one of the new radiotherapy methods. The aim of the study was to analyze tumor control of prostate cancer patients treated with SBRT.*

Methods: *A prospective single-institution clinical study was conducted among previously untreated patients with histologically confirmed localized prostate cancer. Patients were treated with SBRT: 33.5 Gy in 5 fractions.*

Results: *A total of 68 men with clinical stage of prostate cancer T1c-T2cN0M0 were included in the study. The median combined Gleason score was 6, the median PSA level was 10ng/mL. The median follow-up period was 48 months. Five years after the end of radiotherapy, the median PSA levels were as follows: 0.29ng/mL for all patients, 0.39ng/mL for those who did not receive androgen deprivation therapy, 0.25ng/mL for patients who underwent 6 months and 0.31ng/mL for patients who underwent 2-3 years of hormone therapy. Median nadir PSA levels were 0.025ng/mL for all patients and 0.48ng/mL for patients without hormone therapy. Low PSA nadir (<0.5ng/ml) was noted in 50% of patients without hormone therapy and in 70% of all other patients. Only in 4 patients (out of those who did not receive hormone therapy) PSA failure was observed (nadir plus 2ng/mL). No cases of PSA failure were noted among patients who underwent 6 months or 2-3 years of androgen deprivation therapy.*

Conclusion: *A good biochemical control was observed in prostate cancer patients treated with SBRT at 5 years follow-up.*

Key words: *hypofractionated stereotactic radiotherapy, prostate cancer, PSA biochemical failure, SHARP*

Introduction

Prostate cancer remains one of the most common cancers in men worldwide, and in some countries, for example in the US, it is the most common cancer among men [1,2]. In Poland, prostate cancer is the second most frequent malignancy in men, with over 12000 newly diagnosed cases in 2013 alone [3]. The majority of prostate cancer patients are diagnosed in early stages of the disease. In case of clinically localized disease, the 5-year survival rate is nearly 100%. Radical prostatectomy or radiotherapy is the standard approach for patients with early-stage prostate cancer. The results of the surgical treatment and radiation therapy are comparable in patients with localized prostate cancer: the disease-specific 5-year survival rates are 97-98% for both methods [4-6]. Regarding the cancer patients with such good prognosis, the side effects and treatment-related toxicities should be minimized, and the quality of life (QoL) after treatment becomes the most discussed factor and the treat-

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ment decision should be based on different factors [6,7]. We have previously reported toxicity results and high QoL scores in this group of patients [8].

Conventionally fractionated external beam radiotherapy (1.8-2.0 Gy/fraction) is an established treatment modality for localized prostate cancer. Over the past decade, new conformal radiation techniques allowed for a safe administration of high doses (over 80 Gy), which increases the probability of cure. However, there are some disadvantages of standard fractionation, especially long treatment courses, i.e. 8-9 weeks. Some hypofractionated radiotherapy schedules are used in prostate cancer [9-11]. Stereotactic body radiation therapy (SBRT) takes advantage of a low α/β ratio of prostate cancer cells. Low α/β ratio allows to deliver a lower total dose in several high-dose fractions (6-7 Gy) in a short period of time with results in comparable clinical efficacy to higher total dose delivered in standard fractions.

Prostate-specific antigen (PSA) is a well-established biomarker for monitoring the response to treatment. PSA kinetics could reveal the biological effect of prostate cancer treatment and could be used as a marker of failure. Low PSA nadir (<0.5ng/ml) correlates with freedom from biochemical failure in the future [12-14]. PSA nadir seems to be correlated with improved clinical outcome. The stability of the PSA level is associated with cancer control [15,16]. PSA kinetics after treatment provides information about the biological effect of radiotherapy and could predict the clinical outcome, especially in patients without androgen deprivation therapy.

The objective of the study was to investigate the effectiveness of hypofractionated stereotactic radiation therapy for localized prostate cancer by analyzing PSA kinetics. Since the extremely hypofractionated radiotherapy (like in our protocol) was recently introduced into the clinic there are very few reports with longer follow-up published so far.

Methods

Ethics, consent and permissions

The study protocol was approved by the Ethics Committee of the University of Warmia and Mazury in Olsztyn, Poland (No 72010, March 25, 2010). Written informed consent was obtained from all participants.

A single-institution prospective clinical study was conducted among previously untreated patients with histologically confirmed localized prostate cancer. All patients were in low- and intermediate-risk groups (according to the NCCN). The patients received 33.5 Gy in 5 fractions (6.7 Gy per fraction), similarly to those enrolled in the SHARP trial [17]. The patients were treated twice weekly for a median of 15 days. This radiation regimen is equivalent to the conventional external beam radiotherapy of 78 Gy in 39 fractions. The SBRT technique, treatment planning and treatment delivery have been reported previously [8].

The patients were followed every 3 months and every 6 months after 3 years of observation. The PSA levels were obtained before the start of treatment and at each follow-up. Eventual biochemical failure was defined as the nadir plus 2ng/mL according to the Phoenix definition of PSA failure [18,19]. The PSA level was considered to be stable when the PSA value during follow-up did not increase over the nadir plus 0.5ng/mL.

Statistics

The median and mean of variables were estimated by descriptive statistics. Survival time without PSA progression was calculated with the Kaplan-Meier method. The log-rank test was used to establish the difference between survival curves. The differences between the subgroups were analyzed with Kruskal-Wallis test, *post hoc* Dunn's test, ANOVA Friedman test and *post hoc* Friedman test. The p value of <0.05 was considered as statistically significant. The analysis was conducted using STATISTICA (version 12.5) (StatSoft, Poland).

Table 1. Patient characteristics

Characteristics	*Number, n=68 n (%)*
Age, years	
55-83 (median 73, mean 72.5)	
≤65	10 (15)
>65	58 (85)
TNM	
T1cN0M0	6 (9)
T2aN0M0	15 (22)
T2bN0M0	19 (28)
T2cN0M0	28 (41)
Gleason score	
3-8 (median 6, mean 6)	
3	2 (3)
5	21 (31)
6	14 (20.5)
7	29 (42.5)
8	2 (3)
PSA, ng/mL	
4-20 (median 10, mean 10.9)	
≤10	35 (51)
>10	33 (49)
Risk group	
Low-risk	7 (10)
Intermediate-risk	61 (90)
Hormone therapy	
Without	16 (23.5)
6 months	31 (45.5)
2-3 years	21 (31)

Local ethics committee approved the study protocol. Written informed consent was obtained from all participants.

Results

A total of 68 men were include into the analysis (age 55-83 years; mean:72.5; median:73). The patients were treated between August 2011 and September 2013 at the Department of Radiation Oncology, Independent Public HealthCare Facility of the Ministry of the Interior with Warmia and Mazury Oncology Centre in Olsztyn, Poland. The clinical stage of prostate cancer was classified as T1c-T2cN0M0. The combined Gleason score was 3-8 (mean and median:6) according to the pathological reports. PSA level for all patients was 4-20ng/mL (mean:10.9ng/mL; median:10ng/mL), median pretreatment PSA level for patients who did not receive androgen deprivation therapy was 7.53ng/mL (mean:8.55ng/mL). Neoadjuvant androgen deprivation therapy beginning before radiotherapy was given to 52 patients (76.5%): hormonal therapy was stopped after 6 months for 31 patients (45.5% of all patients) or after 2-3 years for 21 patients (31% of all patients) (Table 1).

All patients completed the treatment. The follow-up duration was 9-75 months (average and median, 48 months). In the case of two patients (2.9%) the follow-up was stopped during the first year because of other illnesses (at 9 months for one patient and at 12 months for another patient). After 24 months 7 patients decided to continue the control closer to their place of residence. The follow-up for the remaining patients was minimum 36 months (median 48 months). No patients died during the observation period. Three patients (4.4%) developed second malignancy: sigmoid colon cancer, urinary bladder cancer and pleural mesothelioma after the end of radiotherapy for prostate cancer.

The median pretreatment PSA level of 10ng/mL declined to 0.08ng/mL for all patients and the median pretreatment PSA level of 7.53ng/mL declined to 2.8ng/mL for patients who did not receive androgen deprivation therapy at 3 months after radiotherapy completion. Five years after the end of radiotherapy, the median PSA levels were 0.29ng/mL for all patients, 0.39ng/mL for those who did not receive androgen deprivation therapy, 0.25ng/mL for patients who underwent 6 months of hormone therapy, and 0.31ng/mL for patients who underwent 2-3 years of hormone therapy (Table 2). Statistical differences were found between PSA levels in patients with and without hormone therapy at 12, 24 and 36 months after the end of radiotherapy ($p<0.05$), but not at 48, 60 and 72 months. This means that after 2 years from the end of any treatment (radiotherapy alone or radiotherapy plus

Table 2. PSA level in 12, 24, 36, 48, 60 and 72 months after end of radiotherapy

Time after the end of SBRT (months)	*Patients without hormone therapy (n=16)*			*Patients with 6 months hormone therapy (n=31)*			*Patients with 2-3 years hormone therapy (n=21)*			*All patients (n=68)*		
	PSA, ng/mL											
	median	*mean*	*SD*	*median*	*mean*	*SD*	*median*	*mean*	*SD*	*median*	*mean*	*SD*
12	0.77	0.95	0.73	0.04	0.16	0.22	0.03	0.09	0.20	0.05	0.32	0.53
24	0.89	0.99	0.77	0.18	0.24	0.21	0.02	0.12	0.24	0.17	0.39	0.56
36	0.78	0.92	0.88	0.21	0.28	0.22	0.08	0.18	0.41	0.19	0.37	0.54
48	0,39	0.94	1.01	0.34	0.38	0.29	0.14	0.22	0.27	0.29	0.45	0.57
60	0.39	1.16	1.43	0.25	0.46	0.50	0.31	0.45	0.52	0.29	0.59	0.79
72				0.21	0.40	0.52	0.30	0.31	0.35	0.22	0.40	0.46

Table 3. PSA increase during follow-up

PSA, ng/mL increase during follow-up	*Patients without hormone therapy (n=16)*		*Patients with 6 months hormone therapy (n=31)*		*Patients with 2-3 years hormone therapy (n=21)*		*All patients (n=68)*	
	n	%	*n*	%	*n*	%	*n*	%
0.0-0.5	8	50.0	23	74.2	13	61.9	44	64.7
>0.5-1.0	2	12.5	4	12.9	5	23.8	11	16.2
>1.0-2.0	2	12.5	4	12.9	3	14.3	9	13.2
>2.0	4	25.0	0	0.0	0	0.0	4	5.9

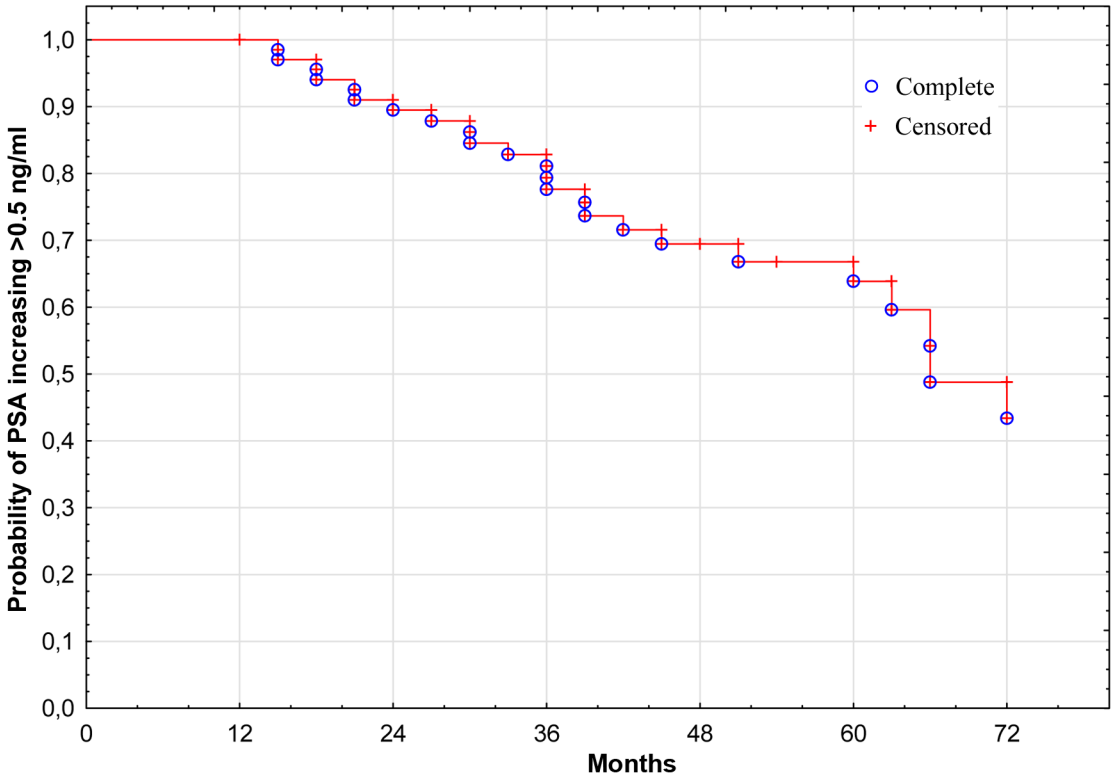

Figure 1. Survival without PSA level increase (nadir plus 0.5ng/mL) for all patients.

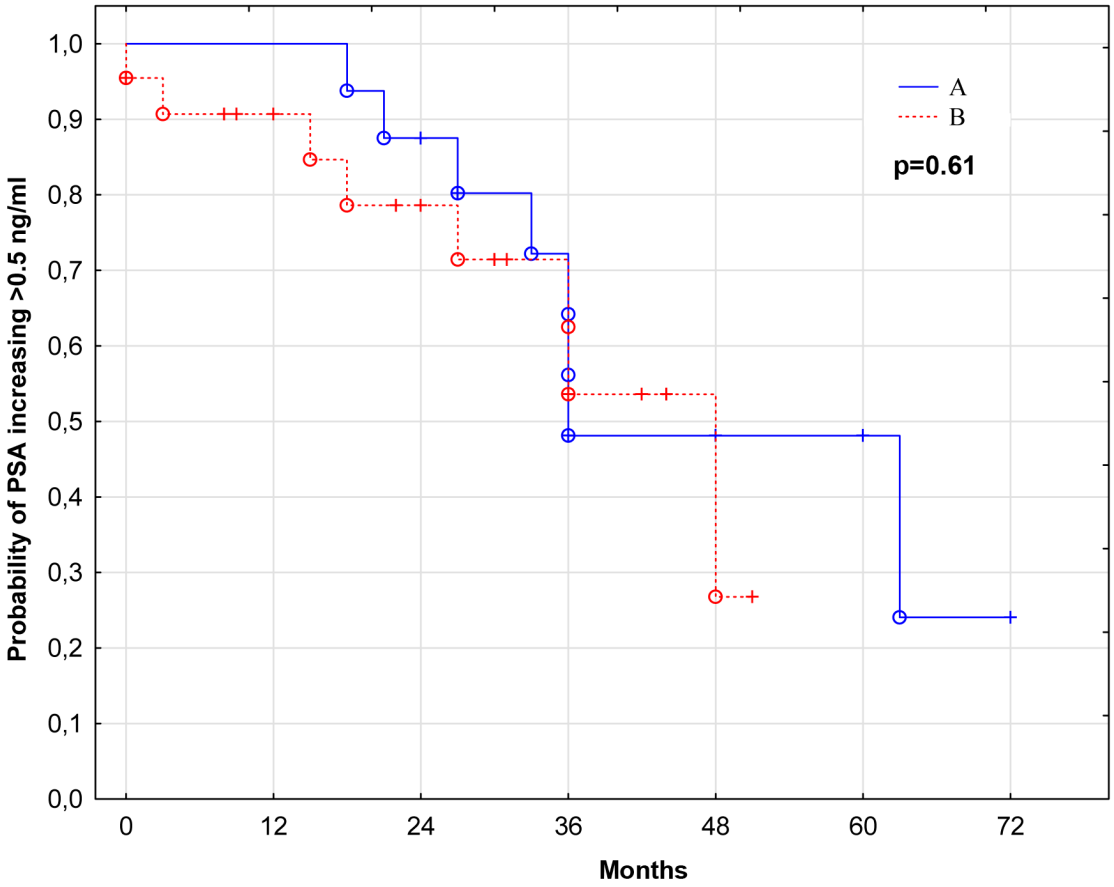

Figure 2. Survival without PSA level increase (nadir plus 0.5ng/mL) for patients without hormone therapy **(A)** and for patients with 2-3 years hormone therapy **(B)**, calculated from the end of any treatment (radiotherapy alone or radiotherapy plus hormone deprivation therapy).

hormone deprivation therapy) there were no differences in PSA-based outcome (p>0.05).

Median nadir PSA levels were 0.025ng/mL (mean, 0.18ng/mL) for all patients and 0.48ng/mL (mean 0.62ng/mL) for patients without hormone therapy. Low PSA nadir (<0.5ng/ml) was observed in 50% of the patients without androgen deprivation therapy and in all except one of the remaining (98%).

Seventy percent of all patients and 50% of patients who did not receive androgen deprivation therapy showed stable or decreased levels of PSA (not over the nadir plus 0.5ng/mL) (Table 3). PSA failure (nadir plus 2ng/mL) was observed only in 4 patients and only out of those who did not receive androgen deprivation therapy during observation (6% of all patients, 25% of patients without hormone therapy). In the case of 2 other patients who did not receive androgen deprivation therapy (12.5%), PSA level increased by more than 1ng/mL but less than 2ng/mL from nadir. At a median follow-up of 48 months, there were no patients with PSA failure among those who underwent 6 months or 2-3 years of hormone therapy. After 6 months of androgen deprivation, the PSA level of 4 patients (13%) increased by more than 1ng/mL from nadir and in another 4 patients (13%) increased by more than 0.5ng/mL during the observation period. Among patients after long hormone therapy, the PSA level increased by more than 1ng/mL in 3 subjects (14.3%) and by more than 0.5ng/mL in other 5 patients (23.8%) after the end of hormone therapy. Two years after the end of any treatment (radiotherapy alone or radiotherapy plus hormone deprivation therapy) in the similar proportion of patients in each treated group, PSA increase by more than 0,5 ng/mL from the PSA nadir was noted (2/16 patients without hormone therapy 12.5%; 4/31 patients with 6 months hormone therapy 12.9%; and 3/21 patients with 2-3 years hormone therapy 14%).

Time to PSA failure (nadir plus 2ng/mL) in 4 patients was 27, 30, 39 and 48 months, respectively. Median time to PSA level increase (nadir plus 0.5ng/mL) was 66 months for all patients and 36 months for patients without hormone therapy. There were no statistically significant differences between patients with and without androgen deprivation therapy (the median was not reached for patients with 6 months androgen deprivation therapy) (Figure 1). When we look at the probability of PSA level increasing (nadir plus 0.5ng/mL) from the end of any treatment (radiotherapy alone or radiotherapy plus 2-3 years hormone deprivation therapy) the lines almost overlap each other (p=0.61) (Figure 2).

Discussion

Hypofractionated stereotactic radiotherapy is a novel technique for the treatment of early-stage prostate cancer. Preliminary data have shown that this approach leads to successful tumor control, without significant complications [20-22]. There are also some reviews relating to this topic [23-26], but there are no randomized trials comparing SBRT with long-term radiotherapy.

Trials with dose escalation showed a lower PSA nadir with increased total dose [27], so it is rational to expect the SBRT regimen to result in lower PSA nadirs. The PSA nadirs in case of SBRT are lower than after standard radiotherapy regimens [28-30]. The post-radiation nadir PSA is the strongest predictor for the future patient clinical outcome. Zelefsky et al [31] showed that a nadir PSA value of ≤1.5ng/mL at 2 years after IMRT for prostate cancer is a predictive factor for distant metastases and cause-specific mortality. In the case of SBRT, some authors demonstrated low PSA nadirs. Median PSA nadir value was 0.65ng/mL in a study by Pham et al [32], 0.47ng/mL in a study by Siawasch et al [33], 0.3ng/mL in Freeman and King's report [34], 0.27ng/mL in a study by Kim et al [35], 0.23ng/mL in Lee et al series [36] and 0.12ng/mL in Park et al analysis [37]. In our study, median nadir PSA level was similar to the values reported by other authors: 0.48ng/mL for patients without hormone therapy.

It seems to be clinically significant that PSA level are kept at low level in follow-up. In a study by Kim et al [35], median PSA of 0.27ng/mL was achieved at 33 months. Katz et al [28] reported a low PSA level (0.25ng/mL) within 4-5 years. In our study, median PSA level for all prostate patients treated with SBRT was similar and stable during long term observation: 0.31ng/mL, 0.29ng/mL and 0.21ng/mL at 48, 60 and 72 months follow-up, respectively. In the paper of Lee et al [36] significantly lower PSA nadir was observed in SBRT group (nadir 0.23ng/mL) compared with standard radiotherapy group (nadir 0.37ng/mL), but the number of enrolled patients to the study were only 69 and there were no strict protocols for the clinical decision-making process.

According to the ASTRO (American Society for Radiation Oncology) definition, biochemical PSA failure as a surrogate endpoint for recurrence is defined as three consecutive increases in the PSA level after the posttreatment PSA nadir set at the mid-point between the nadir and the first increase [38]. The RTOG-Phoenix definition consists of a PSA level that increases by more than 2.0ng/mL above the nadir. As a potential surrogate end-

point in clinical trials, the Phoenix definition of PSA failure is a strong correlate of mortality and a predictor of metastatic disease; it is superior to the ASTRO definition [39]. The 2-year survival rate without PSA failure ranges from 90% to 100% [40].

In the SHARP study (67 patients with clinically localized low-risk prostate cancer, median follow-up 2.7 years), the 4-year PSA relapse-free survival (nadir plus 2ng/mL) was 94% [41]. Pham et al [32] demonstrated that the overall 5-year biochemical relapse-free survival rate was 93% for this cohort. Freeman and King [34], showed that also with a median follow-up of 5 years, the biochemical progression-free survival rate was identical (93%) in a cohort of 41 patients treated with 35 or 36.25 Gy in 5 fractions. In the group of 88 patients in Park et al study (35 to 37.5 Gy in 5 fractions) 5-year PSA progression-free survival was 94.7% [37]. There is only one study on SBRT for low-risk prostate cancer with 10-year observation (median follow up: 9 years) [42]. Ten-year biochemical disease free survival was 93%, the lowest PSA level was achieved at 48 months and had remained there. In our study, at a median follow-up of 48 months, 91% of the 47 patients with low- and intermediate-risk prostate cancer (without hormone therapy or after 6-month androgen deprivation treatment) after SBRT in the SHARP regimen had no PSA increase over nadir plus 2ng/mL. In general, at median of 48 months follow-up, two-thirds of all patients and half of the patients who did not receive hormone therapy showed stable levels of PSA (not over the nadir plus 0.5ng/mL). We noted that 2 years after the end of any treatment (radiotherapy alone or radiotherapy plus hormone deprivation therapy) there was similar proportion of patients in each treated with PSA increase by more than 0.5 ng/mL from the nadir. Probably, SBRT with high-dose level (40-50Gy in 5 fractions) is associated with higher PSA control [43,44], but it could result in increased side effects [23].

Some publications showed better treatment outcome in patients with biochemical response to neoadjuvant hormone therapy before conventional radiotherapy for prostate cancer [45]. The indications of androgen deprivation therapy for patients undergoing SBRT are unclear. In a multi-institutional data set there was no difference in 5-year PSA progression free survival between patients receiving hormone therapy and those not receiving [29]. Our observation showed that at 60 months after radiotherapy (2 years after the end of any treatment - radiotherapy alone or radiotherapy plus hormone deprivation therapy) there were no more statistical differences between PSA levels in patients with and without hormone therapy.

The literature offers more information about CyberKnife-based SBRT than LINAC-based SBRT in prostate cancer patients [46]. In our study, a linear accelerator was used, however our results of PSA increases (biochemical failure) are similar to those obtained in the CyberKnife series. An Italian phase II study [47] also showed that accelerated LINAC-based SBRT for low- and intermediate prostate cancer is feasible and well tolerated and the clinical outcome was similar as in our series (PSA nadir 0.33ng/mL for low- and 0.6ng/mL for intermediate group). LINAC-based SBRT could be a reasonable alternative to CyberKnife-based SBRT, with broader access for patients in Poland and other countries.

Our report demonstrates that SBRT can achieve good biochemical control rates, but further studies with more patients and longer follow-up are required.

Limitation of the study

We admit that the small group of patients and heterogeneity of hormonal treatment is an important limitation of our study. Relatively short observation time plus a reduction in the number of patients during observation (patients are old and not happy to come for future follow-ups) is also a limitation of the data presented.

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The preliminary data of this study with 39 months follow-up was presented as a poster at ECCO 2017 (Rucinska M, Osowiecka K, Nawrocki S. SHARP hypofractionated stereotactic radiotherapy is low and intermediate-risk prostate carcinoma patients - PSA outcome. EJC 2017; 72(Suppl 1):S193-S4).

Conflict of interests

The authors declare no conflict of interests.

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