doi:10.4149/218_150807N435

# CyberKnife stereotactic radiosurgery and stereotactic ablative radiation therapy of patients with prostate cancer bone metastases.

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**Received August 7, 2015 / Accepted October 5, 2015**

The aim of the study was to evaluate the effectiveness and toxicity of CyberKnife (CK) stereotactic radiosurgery (SRS) and stereotactic ablative radiation therapy (SABR) of patients with prostate cancer bone metastases. Analysis of prognostic and predictive factors was also performed.

Material consisted of 51 patients with 71 bone oligometastases treated using CK SRS/SABR. In half of the patients single lesion was treated, in half 2-5 lesions. Median PSA concentration at the time of metastasis detection was 5.75 ng/ml. Total dose of 6-45Gy (median 20) was delivered with 1-5 fractions of 6-15 Gy (median 9). Biologic equivalent dose (BED) ($\alpha/\beta$=1.6) over 100 Gy was delivered to 45 lesions (63%) in 38 patients (75%).

In statistical analysis Kaplan-Meier method, log-rank test and the Cox proportional hazard model were used.

One-, two- and three-year overall survival (OS) was 90%, 76% and 70%, respectively. All patients having PSA concentration lower that 1 ng/ml at last control lived at least three years. One-, two- and three- year local control (LC) was 97%, 70% and 30%. Patients with PSA below 20 ng/ml at the time of metastasis detection had better local control of lesions and lower PSA at the last control. Median of PSA concentration after CK based SRS/SABR remains stable during first 12 months of follow-up, dropped during the next months and at last control was comparable to initial level. Median PSA at last control in patients without disease progression was 1.67ng/ml and 20 patients had PSA below 1.0ng/ml. At the last control 59% of patients had no other metastases. Rapid pain decrease was observed in analysed group and during each control about 90% of patients had pain relief. No major toxicity was observed, 3 patients suffered from fracture of irradiated bone.

SRS/SABR of prostate cancer bone oligometastases provides good LC of lesions, excellent pain control without additional toxicity. Patients with PSA concentration below 20ng/ml at the time of metastasis detection have better LC and PSA concentration response.

*Key words: stereotactic radiosurgery, stereotactic ablative radiation therapy, stereotactic radiotherapy, CyberKnife, prostate cancer bone metastases, prognostic factors*

Cancer metastases are the major cause of death of cancer patients. As they are homogenously distributed throughout the body, they are very difficult to treat using any therapeutic modality [1]. Malignant tumours show an organ-specific pattern of metastasis and the most frequent prostate cancer metastatic site are bones (over 90%) with a predominant presence in the lumbar spine [2]. Prognosis of prostate cancer patients is mainly determined by the presence or absence of metastases [2]. Hormonal therapy (HT), chemotherapy (CT) and palliative radiotherapy (RT) are commonly used in the treatment of prostate cancer patients with metastatic disease [2, 3].

In 1995 Hellman S and Weichselbaum RR proposed to introduce the term "oligometastases" as metastases concentrated in single or limited number of organs [4]. They suggested that the likelihood of the oligometastatic state can correlate with the biology of tumour progression. Tumours which are early in the chain of progression may have not fully developed the facility for metastatic growth [3, 4]. The consequence of the oligometastatic disease is that some patients fit the curative therapeutic strategy [3, 4, 5]. Surgery or radiation ablation have been used for some time in case of small number of pulmonary, brain or hepatic metastases [4, 5].

New term "oligo-recurrence" was proposed by Niibe Y et al. in 2006 [6]. He proposed the following conditions of the oligo-recurrence: one to several distant metastases, controlled primary site of the cancer and no presence of other distant metastases [6].

With the development of new imaging modalities as CT, MRI, bone scintigraphy or PET-CT it is more likely to detect a single or limited number or metastases at lower PSA concentration level [7, 8]. PET-CT (18F-Choline-, 11C-Choline-, 11C-Octane-, 18F-NaF-, $^{18}$F-DCFBC-PET-CT) showed to be more sensitive than bone scintigraphy, MRI or CT in case of bone metastases detection especially in patients with PSA concentration over 3 ng/ml but there is still no one "gold standard" imaging technique to delineate metastasized prostate cancer [7, 8, 9].

According to current knowledge, the criteria for performing ablative treatment of patients with metastases are: oligo-recurrence, good performance status, five or less metastases located preferably in bone (although the current guidelines do not include the possibility of ablative treatment for metastatic prostate cancer as standard treatment) [10]. In the majority of stereotactic radiosurgery (SRS)/ stereotactic ablative radiotherapy (SABR) studied schemes used for treating prostate cancer oligometastases average total dose varies from 8 to 50 Gy [10 – 18]. Tree et al. in review concerning ablative radiotherapy in the management of oligometastases suggested that biologically effective dose (BED) delivered should be higher than 100 Gy [19].

Since yet no consensus about adding HT to stereotactic body radiation therapy (SBRT) for patients with prostate cancer bone oligometastases has been established. Recent European Association of Urology (EAU) recommendations suggested that HT delays clinical progression and prolongs survival in patients with asymptomatic prostate cancer and because of that HT is usually prescribed for most of the patients undergoing SBRT [20].

The main aim of this study was an effectiveness and toxicity evaluation of the CyberKnife based radiosurgery (SRS) and stereotactic ablative body radiotherapy (SABR) for prostate cancer patients suffering from oligometastases or oligorecurrence.

The second aim was an assessment of prognostic and predictive factors for aforementioned patients.

## Patients and methods

At the Radiotherapy Department of Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice branch, we irradiated and followed 51 prostate cancer patients with 71 bone oligometastases or oligo-recurrences. All of them received CyberKnife (CK) SRS or SABR between January 2011 and February 2015. Information about patients and treatment characteristics was collected retrospectively from patient`s folders and from treatment planning system files.

**Patients and primary treatment characteristics.** A total of 51 prostate cancer patients with 71 bone metastases were treated with CK SRS/SABR during the study period. The age of patients at the time of the diagnosis of metastases ranged from 51 to 84 years (mean 68, median 66). Almost all of them (94%) were in good performance status. 59% were primary diagnosed with the advanced stage of disease (III or IV), 65% with Gleason score equal or over 7 and 43% with PSA concentration over 20ng/ml. Over 90% of patients received hormonotherapy during primary treatment (78% of them received total androgen blockade, 9% – Luteinizing Hormone-Releasing Hormone (LHRH) analogs only, 13% anti-androgens only). Radiotherapy was a part of the primary treatment in 75% of patients. Patients detailed characteristics are presented in Table 1.

**Diagnosis of metastases.** The diagnosis of the oligometastasis or oligo-recurrence was based on biochemical (PSA concentration) progression and/or local relapse evaluation (imaging). Median PSA concentration at the time of metastasis detection was 5.75 ng/ml. Among all the patients 25 (49%) was diagnosed with single metastasis and 26 (51%) with more than one metastasis (range 2-5). Despite that metastases were found in more than one location the number of them did not exceed five. Median time from detection of the metastases to the onset of SRS/ SABR was 3 months. No other local therapy

**Table 1. Clinical features of irradiated patients (n=51 patients).**

| Characteristics | Number (%) |
|---|---|
| **TNM primary stage** | |
| I | 1 (2%) |
| IIA | 11 (21%) |
| IIB | 9 (18%) |
| III | 13 (26%) |
| IV | 17 (33%) |
| **ECOG performance status** | |
| 0 | 23 (45%) |
| 1 | 25 (49%) |
| 2 | 2 (4%) |
| Non available | 1 (2%) |
| **Gleason score** | |
| <7 | 14 (27%) |
| 7 | 18 (35%) |
| >7 | 15 (30%) |
| Non available | 4 (8%) |
| **PSA – range (mean; median) (ng/ml)** | |
| at the time of prostate cancer diagnosis (n=49) | 0.02 – 991.20 (73.44; 13.92) |
| PSA >20 (ng/ml) | 21 (43%) |
| **Primary treatment** | |
| Hormonotherapy | 46 (90%) |
| Surgery [radical] | 16 [7] (31%) |
| Radiotherapy | 38 (75%) |
| Total dose – range (mean; median) (Gy) | |
| Prostate/prostate bed (38 cases) | 20 – 76 (67; 76) |
| Lymph nodes (22 cases) | 30 – 50 (42; 44)* |

* in 3 cases boost to 66Gy on enlarged lymph nodes

**Table 2. Characteristics of factors related to metastases.**

| Characteristics | Number (%) |
|---|---|
| **Number of metastases treated (n=51)** | |
| 1 | 39 (76%) |
| 2 | 7 (14%) |
| 3 | 3 (6%) |
| 4 | 1 (2%) |
| 5 | 1 (2%) |
| **Imaging modalities (n=51)** | |
| Computed tomography | 26 (51%) |
| Scintigraphy | 34 (67%) |
| $^{18}$Choline PET-CT | 29 (57%) |
| **Location of metastases (n=71)** | |
| Cranium | 6 (9%) |
| Spine | 42 (59%) |
| Pelvis | 15 (21%) |
| Ribs | 8 (11%) |
| **Size of metastases (n=71)** | |
| Range (mean; median) (mm) | 7-55 (27; 25) |
| **Time from diagnosis of metastases to the beginning of SRS/SABR (n=51)** | |
| Range (mean; median) (months) | 0.7 – 78.5 (9.2; 3.0) |
| **PSA – range (mean; median) (ng/ml)** | |
| at the time of metastases diagnosis (n=48) | 0.02 – 454.69 (35.05; 5.75) |
| at the time of PET-CT (n=28) | 0.08 – 83.00 (9.90; 2.83) |

before was delivered. Detailed data of metastases are presented in Table 2.

**CK based SRS/ SABR.** All patients signed informed consent. PSA concentration at the beginning of the treatment ranged from <0.00 to 387.18 ng/ml (median 2.16, mean 29.71). For 21 patients (41%) CT was used for contouring, fusion of CT and MRI for 19 patients (37%), fusion of PET and CT for 4 patients (8%), and fusion of CT, MRI and PET for 7 (14%) of patients.

The treatment planning was performed using MultiPlan system. The target volumes consisted of gross tumor volume (GTV) which was defined as a lesion itself and planning target volume (PTV) which provided margins in order to correct inaccuracies in the delivery system (set-up margin) or/and interfracion and intrafraction organ motion. PTV margins ranged from 0 to 5 mm (median 5.0) and in all cases of spinal lesions PTV never overlapped spinal cord. In all cases organs at risk (spinal cord, rectum, urinary bladder, small bowels etc.) dependently on the metastases site were contoured in order to reduce the delivered dose. In cases in which metastases were located close to or in previously irradiated areas, previous plans were reviewed to check the dose delivered.

Doses delivered in CK based SRS/SABR in cases of particular patients and lesions are presented in Table 3. Reference isodose (covering whole lesion and corresponding to planned and delivered dose) ranged from 73 to 90% (mean 83%, median 83%). Metastases (n=71) were irradiated with fraction doses (fd) of 6 to 15 Gy (mean 9.4, median 9.0, SD ±2.1) to the total dose (TD) within the range of 6 to 45 Gy (mean 21.5, median 20.0, SD±9.1) delivered in 1 (14 lesions – 20%), 2 (24 lesions – 34%), 3 (32 lesions – 45%) or in 5 fractions (1 lesion – 1%). The overall treatment time (OTT) ranged from 1 to 15 days.

Because of non-uniform SRS/SABR schedules, a biological equivalent dose (BED) was calculated for all patients (and le-

**Table 3. Total and fraction doses delivered in the SRS/ SABR treatment of particular lesions (n=71) and patients (n=51).**

| Number of patients | Number of lesions | Fraction dose (Gy) | Number of fractions | Total dose (Gy) | Biological equivalent dose – BED (Gy) |
|---|---|---|---|---|---|
| **1*** | 1 | 6 | 1 | 6 | 29 |
| **6*,**** | 9 | 8 | 1 | 8 | 48 |
| **1*** | 1 | 10 | 1 | 10 | 73 |
| **1**** | 1 | 12 | 1 | 12 | 102 |
| **2**** | 2 | 15 | 1 | 15 | 156 |
| **7***** | 12 | 8 | 2 | 16 | 96 |
| **1***** | 1 | 9 | 2 | 18 | 119 |
| **4** | 4 | 6 | 3 | 18 | 86 |
| **6** | 6 | 10 | 2 | 20 | 145 |
| **1** | 1 | 7 | 3 | 21 | 113 |
| **3** | 3 | 11 | 2 | 22 | 173 |
| **3** | 4 | 8 | 3 | 24 | 144 |
| **1** | 2 | 12 | 2 | 24 | 204 |
| **4** | 5 | 9 | 3 | 27 | 179 |
| **1** | 1 | 5 | 5 | 30 | 143 |
| **10** | 11 | 10 | 3 | 30 | 218 |
| **3** | 5 | 12 | 3 | 36 | 306 |
| **2** | 2 | 15 | 3 | 45 | 467 |

* one patient had one lesion treated with 1 fraction of 6 Gy, three lesions treated with 1 fraction of 8 Gy and one lesion treated with 1 fraction of 10 Gy;
** one patient had one lesion treated with 1 fraction of 8 Gy, one lesion treated with 1 fraction of 12 Gy and one lesion treated with 1 fraction of 15 Gy.
*** one patient had two lesions treated with 2 fractions of 8 Gy to the total dose of 16 Gy and one lesion treated with 2 fractions of 9 Gy to the total dose of 18 Gy

sions) treated using following formula: BED = (TD) / [1+fd/(α/β)], where TD = total dose, fd = dose per fraction, and α/β = 1.6 (according to Phoenix) [21]. BED over 100 Gy was delivered to 45 lesions (63%) in 38 patients (75%) and BED over 200 Gy was prescribed in 21 cases (33%) in 17 patients (29%).

During the treatment, all patients were immobilized using vacuum system. Depending on location of metastasis, different types of the tracking software was used: Xsight Spine – for lesions located in spine and part of the lesions located in pelvis, 6D Skull Tracking – for lesions located in skull and Fiducials Tracking – for metastases located in ribs and part of the lesions within the pelvis (it requires the implantation of markers to enable tracking during the irradiation).

**Follow-up.** Patients were followed one month after the irradiation and next every three or six months to the end of follow-up. Size of metastatic lesion, presence of other metastases, PSA concentration, pain level and need for additional treatment were evaluated. Size of the lesion was evaluated based on images taken before the treatment. Local control was defined as a lack of "in-field" (irradiated volume) progression. In all cases an evaluation of acute and late toxicity using Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria was performed [22].

**Statistical analysis.** In statistical analysis overall survival (OS) was evaluated using Kaplan-Meier method and log-rank test. To verify the significance of variables influencing the OS in the univariate analysis, the Cox proportional hazard model was employed. P-values of less than 0.05 were considered to indicate statistical significance. OS was measured from the end of the treatment to the date of last contact or death. Local control (LC) was measured from the end of CK SRS/SABR to the date of progression of lesion size or last control/ death. In

**Table 4. Univariate analysis of factors influencing overall survival, presence of other metastases and local control.**

| Characteristics | Long rank p value |
|---|---|
| **Overall survival from CK SABR (n=51)** | |
| Radiotherapy (primary treatment) | 0.315 |
| **Total dose > 70 Gy (primary treatment)** | **0.023** |
| Single vs. multiple (2-5) metastases | 0.652 |
| ECOG performance status (0 vs.1) (n=48) | 0.133 |
| ECOG performance status (n=50) | 0.051 |
| PSA > 20ng/ml at the time of metastasis detection | 0.599 |
| Spine location of metastases vs. other | 0.090 |
| Gleason score ≥7 | 0.536 |
| **Size of the metastasis > 20mm** | **0.020** |
| Size of the metastasis > 30mm | 0.126 |
| BED >100 Gy | 0.220 |
| BED >200 Gy | 0.987 |
| **PSA >20 ng/ml at last control** | **0.006** |
| **PSA <1ng/ml at last control** | **0.006** |
| Presence of other metastases at last control | 0.062 |
| **Number of metastases** | **0.003** |
| Local control at last control (stable/regression vs. progression) | 0.787 |
| **OS from metastases detection (n=51)** | |
| Total dose > 70 Gy (primary treatment) | 0.338 |
| Size of the metastasis > 20mm | 0.122 |
| Gleason score ≥7 | 0.905 |
| **Spine location of metastases vs. other** | **0.043** |
| **Presence of other metastases at last control** | **0.033** |
| **PSA >20 ng/ml at last control** | **0.017** |
| **PSA <1ng/ml at last control** | **0.028** |
| Number of metastases | 0.207 |
| ECOG performance status | 0.153 |
| **Presence of other metastases (n=51)** | |
| **Gleason ≥7** | **0.050** |
| **PSA <10 ng/ml at the time of diagnosis of prostate cancer** | **0.006** |
| **PSA >20 ng/ml at the time of diagnosis of prostate cancer** | **0.018** |
| **Surgery (primary treatment)** | **0.004** |
| **No lymph node irradiation (primary treatment)** | **0.013** |
| **PSA >20ng/ml at last control** | **0.034** |
| **Local control of lesion (regression vs. stabilization vs. progression)** | **0.022** |

| Characteristics | Long rank p value |
|---|---|
| **PSA >20ng/ml at last control** | |
| **Irradiation to TD>70Gy in primary treatment** | **0.022** |
| **PSA >20ng/ml at metastasis detection** | **0.018** |
| **BED >100Gy** | **0.022** |
| **Presence of other metastases at last control** | **<0.001** |
| **ECOG performance status** | **0.012** |
| Gleason score ≥7 | 0.096 |
| Location of metastasis | 0.082 |
| **PSA <1 ng/ml at last control** | |
| **PSA >20ng/ml at metastasis detection** | **0.034** |
| **PET in diagnostic** | **<0.001** |
| **BED >100Gy** | **0.002** |
| **BED >200Gy** | **0.003** |
| **Local control of lesion (regression or stabilization vs. progression)** | **<0.001** **0.002** |
| **Presence of other metastases at last control** | **0.047** |
| **ECOG performance status** | 0.609 |
| Gleason score ≥7 | |
| **Local control (n=62)** | |
| TNM stage IV | 0.054 |
| **Surgery in primary treatment** | **0.018** |
| **Radiotherapy in primary treatment** | **0.002** |
| **Single vs. multiple (2-5) metastases** | **0.011** |
| **PSA >20ng/ml at the time of metastasis detection** | **<0.001** |
| Use of PET-CT in diagnosis | 0.082 |
| **BED >100Gy** | **0.038** |
| BED >200Gy | 0.862 |
| Gleason score ≥7 | 0.254 |
| **Presence of other metastases at last control** | **0.007** |
| **PSA >20ng/ml at last control** | **0.001** |
| **PSA <1ng/ml at last control** | **0.001** |

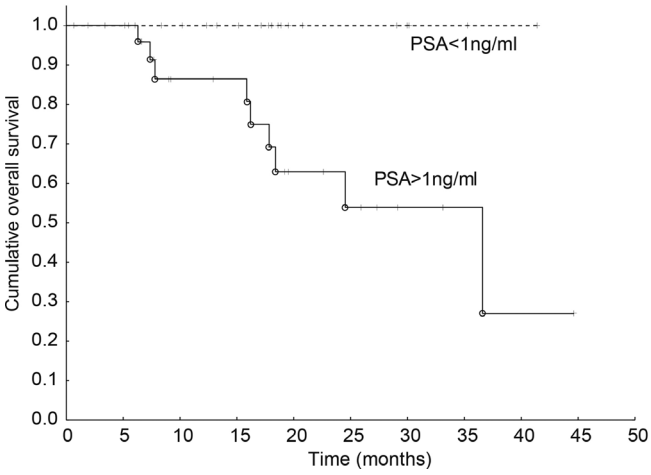


**Figure 1. Overall survival according to PSA concentration level at last control (below or over 1 ng/ml).**

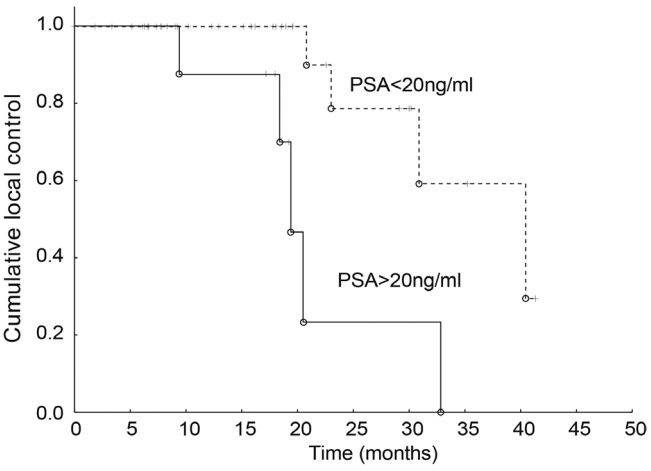


**Figure 2. Local control of the lesions according to PSA concentration level at the time of metastasis detection (below or over 20 ng/ml).**

all cases also metastases-overall survival (m-OS) was calculated from the date of diagnosis of the metastases to the date of last contact or death.

## Results

**Overall survival.** Follow-up ranged from 1.2 to 105.9 months (median 50.0) after diagnosis of the metastases and from 0 to 44.6 months (median 36.6) after CK based SRS/SABR. During that time 10 patients (19.6%) died. One-, two- and three-years long OS had 90%, 76% and 70% of patients respectively. Factors which had influence on OS are presented in Table 3 and 4. All patients having PSA concentration lower that 1 ng/ml at last control lived at least three years, comparing to 77%, 59% and 47% for patients with PSA over 1 ng/ml at last control, who lived one, two and three years respectively (Fig. 1). Factors having an impact on m-OS and presence of other metastases at last control are presented in Table 4 and 5.

**Table 5. Multivariate analysis of factors influencing overall survival, presence of other metastases and local control.**

| Characteristics | P value |
|---|---|
| **Overall survival from CK SABR (n=51)** | |
| PSA >20ng/ml at last control | 0.030 |
| **OS from metastases detection (n=51)** | |
| None of the factors was found to have statistical significance | n/a |
| **Presence of other metastases (n=51)** | |
| Surgery in primary treatment | 0.014 |
| Lymph node irradiation in primary treatment | 0.003 |
| PSA >20ng/ml at last control | 0.026 |
| **PSA >20ng/ml at last control** | |
| PSA >20ng/ml at the time of metastasis detection | 0.019 |
| **Local control (n=62)** | |
| PSA >20ng/ml at the time of metastasis detection | 0.032 |

**Local control.** During the follow-up in 47 patients local control (LC) of irradiated metastases was evaluated. In 10 patients (15 lesions) local progression occurred after median time of 31 months. One-, two- and three- year LC was 97%, 70% and 30%. Patients who had PSA concentration below 20 ng/ml at the time of metastases detection had better LC of the lesions at one, two and three years compared to those with PSA over 20 ng/ml – 100%, 83% and 62% compared to 87%, 62% and 0%, respectively (Fig. 2). Factors which influenced LC are presented in Table 3 and 4. Progression of the disease was evaluated based on CT in 19%, scintigraphy in 50%, PET-CT in 12%, MRI in 12% and based on CT, MRI and PET-CT in **7%.**

**PSA concentration.** Median of PSA concentration after CK based SRS/SABR remains stable during first 12 months of follow-up, dropped during the next months and at last control was comparable to initial level. Median PSA at last control in patients without disease progression was 1.67ng/ml and 20 patients had PSA below 1.0ng/ml (39%). Among 51 assessed patients 35 patients had PSA concentration below 20 ng/ml at the time of metastasis detection and among them 46% of them had PSA concentration below 1 ng/ml during the last control compared to only 8% of patients who had PSA concentration above 20 ng/ml at the time of metastasis detection. In 3 patients value of PSA concentration at the time of metastasis detection were not available, and among them in 2 PSA concentration during the last control was above 1 ng/ml and in one patient value of PSA concentration was not available.

Factors having impact on PSA concentration at last control are presented in Table 4 and 5. PSA concentrations during the follow-up are presented in Table 6.

**Pain intensity.** In the analysed group, we observed rapid pain decrease and during each control about 90% of patients

**Table 6. PSA concentration level during follow-up.**

| Time | Number of patients assessed | PSA concentration (ng/ml) – range | PSA concentration (ng/ml) – median | PSA concentration (ng/ml) – mean |
|---|---|---|---|---|
| Metastasis detection | 48/51 | <0.02 – 454.69 | 5.75 | 35.05 |
| Beginning of CK SABR | 48/51 | <0.01 – 387.18 | 2.16 | 28.71 |
| 1 month after CK SABR | 16/51 | <0.00 – 47.00 | 4.07 | 8.42 |
| 3 months after CK SABR | 27/51 | <0.00 – 3617.16 | 2.53 | 154.02 |
| 6 months after CK SABR | 36/51 | <0.00 – 14676.00 | 2.93 | 433.00 |
| 9 months after CK SABR | 21/51 | <0.00 – 2489.68 | 3.37 | 117.67 |
| 12 months after CK SABR | 19/51 | <0.00 – 755.02 | 0.04 | 58.55 |
| 15 months after CK SABR | 15/51 | <0.00 – 301.21 | 0.04 | 26.25 |
| 18 months after CK SABR | 13/51 | <0.00 – 47.22 | 0.08 | 9.14 |
| 24 months after CK SABR | 11/51 | <0.00 – 577.27 | 1.14 | 86.64 |
| 30 months after CK SABR | 8/51 | <0.00 – 182.17 | 0.01 | 23.29 |
| Last control | 50/51 | <0.00 – 15489.00 | 3.67 | 727.10 |

had pain relief. This effect remained stable through the follow-up and at last control, only 8% of patients suffered from bone pain. Analgesic effect during the follow-up is presented in Table 7.

**Presence of other metastases.** At the last control 59% of patients had no other metastases. Higher PSA concentration (>20ng/ml) at the time of prostate cancer diagnosis and during last control correlated with presence of other metastases. Other factors related to presence of other metastases at last control are presented in Tables 4 and 5.

**Additional treatment.** During the follow-up period 8 patients (16%) received chemotherapy as part of disseminated disease therapy due to progression. For 2 patients 90Sr therapy was used. All patients received hormonal therapy after the CK based SRS/SABR. In 35 patients hormonal treatment did not change during follow-up, in 11 cases HT modifications were made after CK SRS/SABR (after median time of 6 months since the end of the radiotherapy), in 2 cases HT was employed with the start of CK SRS/SABR and in 2 cases HT was started during the follow-up. During the follow-up, 12 patients needed additional RT due to progression of the disease and local pain, but only in 2 cases reirradiation of lesion which was treated with CK SRS/SABR was performed. One patient was treated with lower-half body irradiation.

**Treatment toxicity.** No acute toxicity was observed, but one patient had irradiated bone fracture one month after CK SRS/SABR (BED 179Gy). Two other patients had also fracture of irradiated bone (BED in that cases was: 144Gy and 467Gy). No other adverse events were observed during the follow-up.

## Discussion

Prognosis for patients with metastatic prostate cancer is poor. Sinhg D. et al. reported 1-, 2-, and 3- year OS from the date of metastasis detection of 65%, 60% and 40%, respectively for patients with prostate cancer metastases [3]. He found that patients with less than 5 metastatic lesions had significantly better OS and suggested implementation of more aggressive local treatment in such cases [3]. Reports concerning SRS/SABR of patients with oligometastatic prostate cancer showed better OS compared to standard treatment results. Muacevic A et al. reported OS of 80% after median time of follow-up of 10.2 months [13]. Decaestecker K et al. treated 50 patients with oligometastatic prostate cancer (44% bone metastases)

**Table 7. Pain level during the follow-up (n=51)**

| Time Pain level | Number of patients assessed | No pain (%) | Partial pain relief (%) | Pain (%) |
|---|---|---|---|---|
| 1 month after CK SABR | 20/51 | 14 (70%) | 6 (30%) | - |
| 3 months after CK SABR | 28/51 | 22 (79%) | 5 (18%) | 1 (3%) |
| 6 months after CK SABR | 39/51 | 27 (69%) | 11 (28%) | 1 (3%) |
| 9 months after CK SABR | 30/51 | 21 (70%) | 7 (23%) | 2 (7%) |
| 12 months after CK SABR | 28/51 | 20 (71%) | 5 (18%) | 3 (11%) |
| 15 months after CK SABR | 20/51 | 13 (65%) | 5 (25%) | 2 (10%) |
| 18 months after CK SABR | 17/51 | 9 (53%) | 6 (35%) | 2 (12%) |
| 24 months after CK SABR | 13/51 | 10 (77%) | 2 (15%) | 1 (8%) |
| 30 months after CK SABR | 8/51 | 7 (88%) | 1 (12%) | - |
| Last control | 51/51 | 32 (63%) | 15 (29%) | 4 (8%) |

and reported 2-year OS of 96% [14]. Also in our group OS was better than reported by Singh D. et al. which suggest that use of SRS/SABR can result in prolongation of patients life despite other treatment options used [3]. Ost P et al. reported that number of metastases correlates with OS and patients with only 1 lesion had 5-year OS of 90% (compared to 35% for patients with more than one lesion) but this correlation was of statistical significance in our group only in univariate analysis [15].

Published reports concerning local control of lesions after SRS/SABR are very promising. Ahmed KA et al. reported excellent outcome and LC of 100% after median follow-up of 6 months [11]. Greco C et al. reported LC of 86% after median time of 18 months for patients irradiated due to bone metastases of prostate cancer. In their group (42/124 patients with prostate cancer) they found that irradiation to the single dose of 23-24Gy resulted in better local control of the lesions (2-year LC of 82% in whole group) although no correlation between the dose and LC was observed in prostate cancer group [12]. Very good results were also published by Muacevic et al. (2-year LC of 95%), Decaestecker K et al. (LC of 100% after median time of follow-up of 2 years) and Berkovic P et al. (LC of 100% during the follow-up) [13, 14, 16]. Results obtained in our group are comparable to those reported in literature. Correlation between PSA concentration at the time of metastasis detection and response of irradiated lesion might suggest that patients with PSA concentration below 20ng/ml at the time of metastasis detection are more suitable candidates for SRS/SABR although this correlation was observed only in our group. Further studies are needed to determine which patients might benefit the most from SRS/SABR treatment.

Median PSA concentration after CK SRS/SABR remains stable during the first 12 months of follow-up, dropped during the next months and at last control was comparable to initial level. Also other researchers observed a decrease in PSA concentration during follow-up [11, 13, 14, 17]. PSA concentration at last control was lower in patients with PSA below 20 ng/ml at the time of metastasis detection and based on data of other researchers similar observations can be made [11]. Use of PET-CT in diagnosis of metastases had statistically significant impact on PSA concentration at last control but this could be cause by more precise diagnosis of metastases at the time of diagnosis. Higher BED (>100Gy) resulted in better local control of lesions which is in accordance with data presented by Tree et al. [19]. Among patients with PSA concentration below 1ng/ml 16 (73%) had no changes in HT after CK SRS/SABR, 4 (18%) had HT started with SRS/SABR and only 2 had switched to another HT drugs. Better local control of the lesion with SRS/SABR resulted in lower PSA concentration and better control of the disease.

Approximately 50 to 70% of patients with bone metastases responds with pain decrease after conventional radiotherapy compared to 85 to 100% patients treated with radiosurgery or stereotactic body radiotherapy [23]. High level of pain control was also observed in our group with analgesic effect seen in over 90% of patients. Although cost of this treatment is much more higher than conventional palliative radiotherapy, SRS/SABR of bone metastases could be particularly indicated for patients with spine lesions located in previously irradiated fields.

At the last control 59% of our patients had no other metastases detected. Patients who undergo surgery during primary treatment and those who did not received lymph node irradiation had better control of the disease. This could be related with more aggressive treatment employed in high-risk group of patients (not suitable for surgery) and higher probability of metastasis detection from the beginning of the treatment. Correlation with higher Gleason score and PSA level at the time of prostate cancer diagnosis supports this conclusion. Similar observation were made by Decaestecker K et al. which reported 52% of patients progression-free at last follow-up [14]. In his group HT was commenced if more than 3 metastases were detected during the follow-up and SRS/SABR delayed start of HT for a median time of 25 months [14].

The current treatment guidelines for patients with prostate cancer metastases recommend to use HT when asymptomatic metastases are detected to delay progression to symptomatic stages [20]. According to this guidelines all patients in our group received HT during follow-up after CK SRS/SABR. Although recent observations suggest that survival and response to HT varies as a function of the number of metastases (i.e. oligometastases) and some authors have hypothesized that local treatment of limited metastases with surgery or radiotherapy might delay the start of potentially toxic systemic treatments [3, 24]. Furuya Y et al. reported that patients with an initial low-volume metastatic disease were more likely to progress locally during ADT instead of distantly, which might support delayed implementation of HT in patients with oligometastatic prostate cancer treated with SABR [24, 25]. Also studies of Berkovic et al. and Decaestecker K et al. showed that HT can be delayed until progression of the disease and part of the patients had not received HT for 3 years without PSA concentration increase [14, 16]. There are currently two phase II study concerning HT and stereotactic body radiation therapy (SBRT) of patients with oligometastic prostate cancer: one led by Conde et al and focused on association between HT and SBRT and another from the University of Florida which explore the efficacy and safety of SBRT in patients with metastatic prostate cancer, either with or without an active primary tumour in two subgroups: castration-resistant and hormone-receptive patients [26, 27].

Conventional radiotherapy is the one of the main treatment methods of patients with painful bone metastases of prostate cancer. Gerszten PC et al. in their systematic literature review concerning radiotherapy and radiosurgery of spinal metastases (which were the most common treatment target in our study) suggested that radiosurgery should be considered over conventional fractionated radiotherapy in case of oligometastatic disease [23]. Chow E et al. reported that partial pain relief was seen in 50% of patients and 23-24% of patients achieved com-

plete pain relief after conventional treatment [28]. Hamouda WE et al. assessed the duration of pain relief after conventional radiotherapy of painful bone metastases and median duration of analgesic effect was 12-14 weeks which is much less than results obtained in our study (more than 90% had pain relief or decrease after 30 months of observation) [29]. Westhoff PG et al. reported the results of 1157 patients which were treated with radiation therapy for painful bone metastases. In theirs study after maximum follow-up time of 35 months 74% patients died (compared to 3-year overall survival of 70% seen in investigated group) [30]. Results obtained in our group and in cited studies supports the conclusion made by Gerszten PC et al. that stereotactic radiotherapy could prolongs patients life and provide better local control of the pain and disease compared to conventional radiotherapy [23].

## Conclusions

SRS/SABR of prostate cancer bone oligometastases provides good local control of lesions, excellent pain control without additional toxicity and have a potential to prolongs patients life compared to standard palliative treatment. Patients PSA concentration below 20ng/ml at the time of metastasis detection have better local control and PSA concentration response. Patients with PSA concentration over 20 ng/ml at last control have worse OS compared to those with lower PSA level.

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