RESEARCH ARTICLE

Cyberknife Radioablation of Prostate Cancer – Preliminary Results for 400 Patients

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Abstract

Objectives: To evaluate the tolerance and effectiveness of stereotactic ablative radiotherapy (SABR) applied in the treatment of low and intermediate risk (LR & IR) prostate cancer patients (PCP) and provide an evaluation of the level of risk group impact on treatment results. In addition, androgen deprivation therapy (ADT) usage and prostatic specific antigen (PSA) decline after SABR were assessed. **Material and Methods:** A total of 400 PCP (213 LR and 187 IR, including T2c) were irradiated with a CyberKnife using fd 7.25 Gy to TD 36.25 Gy. At the start of treatment, 60.3% of patients were undergoing ADT and this gradually decreased to 0% after 38 months. Follow-up was for a median of 15.0 months. Patients were monitored on SABR completion and 1, 4, 8 months later and then subsequently every 6 months. GI (Gastro-Intestinal) and GU (Genito-Urinary) acute and late adverse effects, PSA and ADT usage were evaluated. **Results:** Failure was noted in 9 patients (2.25%) (5 in LR and 4 in IR groups) - 4 relapses and 5 nodal metastases. No G3/4 late adverse effects (EORTC/RTOG) were observed. Some 0.5% of G3 GU and 0.3% of G3 GI acute reactions were noted respectively on the SABR completion day and one month later. The median of PSA declined 1.5 ng/ml during the first month and 0.6 ng/ml during the next three months. No impact of risk groups on treatment results was found. An impact of ADT on PSA decline was only confirmed for time point interactions. **Conclusions:** SABR for LR and IR PCP is a safe and effective treatment. The inclusion of T2c patients and the low percentage of IR patient failure permit us the assumption that this procedure could be utilized in the treatment of more advanced cases. The results do not allow clear definition of the impact of ADT on radioablation results in LR and IR+ T2c cases.

Keywords: SABR- SBRT- CyberKnife- prostate cancer radioablation- prostate radiotherapy

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Introduction

The high incidence of prostate cancer (PC) in developed countries justifies the increasing interest in new radiotherapy technologies. There is consensus that radical treatment of PCP can be based on surgery or radiotherapy. The radiation treatment can be performed as brachy or radiotherapy (RT). Brachytherapy, irresepective of its form, is a relatively short treatment, but the vast majority of radiotherapy schedules are based on a lengthy treatment plan (8-9 weeks); often unacceptable for patients. Hence numerous attempts at hypofractionation introduction (Incrocci et al., 2016; Lee et al., 2016). There is an additional radiobiological argument for this; the α/β ratio for PC is considered low – 1.5 Gy, making it sensitive to large fractions (Fowler, 2005; Fowler et al., 2013). However, one major problem persists: the risk of late effects. There is also a connection with the irradiated volume and margins used. Due to prostate mobility with bladder and rectum filling, and in order to hit the target, we must enlarge the margins or track the prostate. The latter option is used in the CyberKnife system, enabling margin shrinkage while decreasing the likelihood of severe adverse effects.

Objectives

The main aim of this study was to evaluate the tolerance and effectiveness of SABR on PCP.

The secondary aims were to provide an evaluation of the level of risk group impact on the treatment results and an assessment of ADT usage on PSA decline after SABR.

Materials and Methods

Material

213 LR and 187 IR (including T2c) consecutive PCP, age range 53-83 (mean and median 69) treated between June 2011 and November 2015 according to

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routine clinical protocol in one RT center. The LR group included T2a or lower stage patients with PSA ≤ 10 ng/ml and Gleason score ≤ 6. The IR group comprised T2b-2 cpatients with PSA≤ 20 ng/ml and Gleason score 7 (3+4 only). Maximum prostate dimension 50 mm.

Prior to SABR, patients were informed of their options by urologists and given an informed choice.

Detailed data concerning PSA concentration, Gleason score, T stage, risk group and ADT usage of irradiated patients are presented in Table 1. Diagnosis was formed on the basis of the core biopsy performed transrectally (eight cores - four from each lobe). From one core, six slices were examined. In ambiguous cases AMCR and P63 expressions were checked. PC was identified if AMCR was positive and P63 negative. As we could not verify some cores from remote urological ambulatories; in 31 cases the Gleason score was below 5.

The TNM stage was evaluated based on MRI (if contraindicated, CT was performed), abdomen USG, chest X-ray and bone scintigraphy. If scintigraphy was unclear, a fluorocholine or sodium fluoride PET was undertaken.

Means of prostate dimensions (X-Y-Z) - 42.9 x 37.3 x 40.6 mm.

117 patients were comorbidities-free. 254 suffered from cardiovascular diseases, 45 diabetes, 24 pulmonary diseases, 22 arthritis, 9 GI diseases, 8 other neoplasms, 4 renal failure, 2 anemia, 2 Parkinson's disease, 1 hyperthyroidism and 1 syringomielia.

122 patients had no urinary symptoms. 229 nycturia, 110 polyuria, 54 difficult urination, 14 dysuria, 2 rectal bleeding and 1 hematuria.

According to our protocols, ADT is not a standard treatment for LR and IR PCP, although urologists use it. Thus, at SABR initiation 60.3% of patients took ADT and PSA varying from 0.008 to 20.4 ng/ml (median 2.3). 159 patients used a combination of LHRH analogs and flutamide, 42 LHRH analogs alone, 18 flutamide, 1 bicalutamide and in 12 cases no information concerning ADT was available. ADT duration before SABR ranged from 0.5 to 48 months (median 2.3). During FU we tried to convince urologists to cease ADT.

FU varied from 1 to 53.9 months (mean 16.9, median 15.0) (time after failure was not included in the FU).

The last update was completed 12th May 2016.

Method

Patients were irradiated using the CyberKnife system, comprising a 6MV linear accelerator installed on a robotic arm with six degrees of freedom. The system is connected to a robotic couch (six degrees of freedom) and a tracking system allowing correction of the patient position and beams inlet. For this purpose, three markers (Gold Anchors, 2-cm-long golden wires, 0.3 mm in diameter, incised every 2 mm) were implanted transrectally, under USG control, in a triangular-like configuration. During implantation it bends itself to prevent migration. From one week after implantation, treatment planning procedures were initiated. An individual vacuum system was prepared followed by CT and MRI scans.

The treatment plan was prepared on the basis of CT-MRI fusion using the Multiplan system. 180 to 250 non-isocentric beams were used and the time of fraction delivery varied from 40 to 65 min.

The prostate position was checked every 5 to 150 seconds (depending on stability).

Patients were irradiated on alternate days (9 days) with fd of 7.25 Gy to the TD 36.25 Gy delivered to the Planning Target Volume (PTV) comprising Clinical Target Volume (CTV) (prostate + proximal 1 cm of seminal vesicles) and 3 mm of margin in posterior and 5 mm in other directions. The organs at risk were: the rectum, bladder, penile bulb and femoral heads.

Patients were monitored on the day of SABR completion and subsequently 1, 4, 8 months thereafter and then every 6 months. GI and GU acute (till the 4th month) and thenceforth, late adverse effects using the EORTC/RTOG grading system were evaluated. Moreover, additional urological symptoms, PSA and ADT usage were monitored. If a treatment failure occurred, a salvage treatment was undertaken.

Biochemical failures (BF) were evaluated using the Phoenix criterion.

Statistical analysis

Cox analysis was performed to check the impact of various factors on nodal dissemination as well as relapse risk.

Dependencies between symptoms and potentially influencing factors were analyzed using logistic hierarchical regression.

Linear hierarchical regression was utilized to evaluate the impact of treatment-dependent factors for the intensity of adverse effects and PSA.

A random effects ANOVA was applied to estimate the effects of the risk groups and ADT in time points on the PSA concentration.

All analyses took place within 26 months of FU; subsequent data were too limited to obtain reliable results.

Results

Detailed results concerning ADT usage, adverse effects and PSA are presented in Table 2.

During FU 9 patients (2.25%) failed: 4 relapses and 5 nodal dissemination, as specified:

Relapses

- Patient 1 – BF after 18 months; the biopsy, relapse confirmation and salvage BT. Now disease-free (DF).
- Patient 2 – BF after 32 months; urologist started ADT, patient lost from FU.
- Patient 3 – BF after 32 months, a biopsy proposed, patient disagreement (poor PS). ADT introduced.
- Patient 4 - BF after 14 months; urologist started ADT, patient lost from FU.

Nodal disseminations

- Patient 5 – BF after 26 months, choline-PET performed - solitary node (illiac) metastasis. ADT was initiated by the brachytherapist and CK based SABR was undertaken. Now DF.
- Patient 6 - BF after 26 months; metastasis in illiac

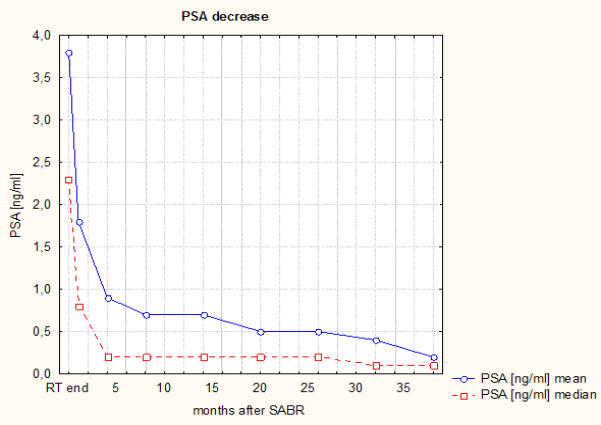

Figure 1. The Course of PSA Concentration During Follow-Up

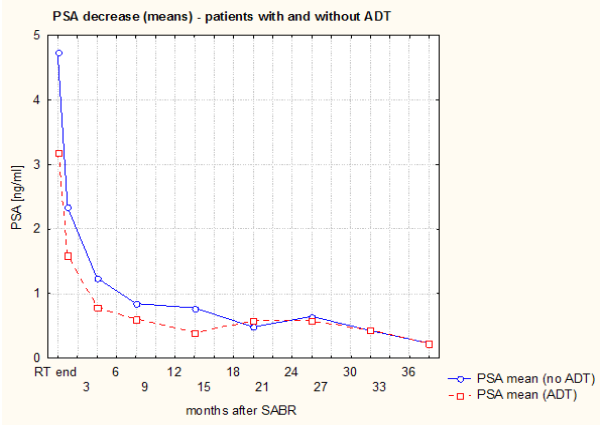

Figure 2. The Course of PSA Means During Follow-Up (Patients with and without ADT)

node found (choline-PET) and CK based SABR was undertaken. Now DF.

- Patient 7 – BF after 14 months; metastasis in illiac node found (choline-PET). Urologist started ADT, patient lost from FU.

- Patient 8 – BF after 14 months, metastasis in illiac node found (choline-PET). Next, CK based SABR was done. Now DF.

- Patient 9 – BF after 14 months; illiac node metastasis found (choline-PET). Next, CK based SABR was done; now DF.

Among the patients with failures, five were LR and four IR. The median of the Gleason score was 6.0; the median of PSA 8.6. Seven patients had T1c, one T2a and one T2b stage. Three had ADT at the SABR start (two nodal disseminations and one local relapse).

Acute and late GI and GU adverse effects were low and their percentages during FU are presented in Table 2.

The PSA decline in the whole group of patients is shown in Figure 1. It was most rapid during the first month (median of fall 1.5 ng/ml). During the next three months, PSA decline was 0.6 ng/ml (median). PSA decreased at a slower pace – 0.1 ng/ml (median) in the following 28 months. The courses of means and medians of PSA in subgroups of patients with and without ADT (at the SABR start) are presented on Figures 2 and 3. The PSA decline is faster (equally for the mean as the median) in the subgroup without ADT (patients using ADT had lower PSA at the beginning) and from the 20th month of FU values in both subgroups are highly similar. Courses of PSA during FU for LR and IR patients with and without ADT are shown in Figure 4. Furthermore, we can notice the impact of ADT (mainly in IR patients group) until the 20th month of FU only.

Statistical analysis - results

The Cox analysis showed that the risk of nodal dissemination and relapse is reduced in patients using ADT (p=0.018 and p=0.046 respectively). Moreover, this analysis revealed risk reduction failure in correlation with the patient's age (p=0.029); each additional year resulted in a 10% risk decrease; if the difference was ten years, then the risk decreased over (1-0.910)*100%=65%.

Positive dependencies between the presence of nycturia and the patient's age (p=0.0055) and tumor stage (TNM) (p=0.0281) and between the presence of dysuria and TNM (p=0.0089) and ADT usage (p=0.0008) were clearly identified (logistic regression). This analysis showed inverse dependency between the presence of both the aforementioned symptoms and FU (p=0.000).

Linear regression showed an impact of diabetes on GI reaction (p=0.0411) – it increased GI acute and late adverse effects. Inverse dependencies between the acute GU reaction and Gleason score (p<0.026) and ADT usage

Table 1. Patient's Characteristics

PSA concentration	PSA ≤ 10 ng/ml			10 ng/ml> PSA <20 ng/ml		
	302			98		
Gleason score	2	3	4	5	6	7
	4	2	25	84	223	62
TNM stage	T_{1c}		T_{2a}	T_{2b}		T_{2c}
	218		107	49		26
Risk group	LR			LR		
ADT	(-)		(+)	(-)		(+)
(before SABR)	95		119	72		114

PSA, Prostate Specific Antigen; TNM, Tumor, Nodes, Metastases; ADT, Androgen Deprivation Therapy; SABR, Stereotactic Ablative Radiotherapy

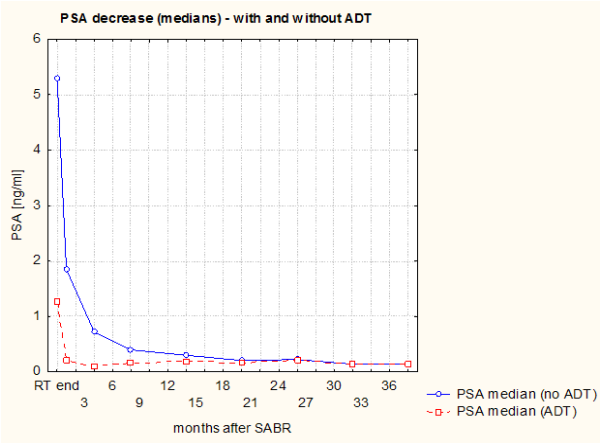

Figure 3. The Course of PSA Medians During Follow-Up (Patients with and without ADT)

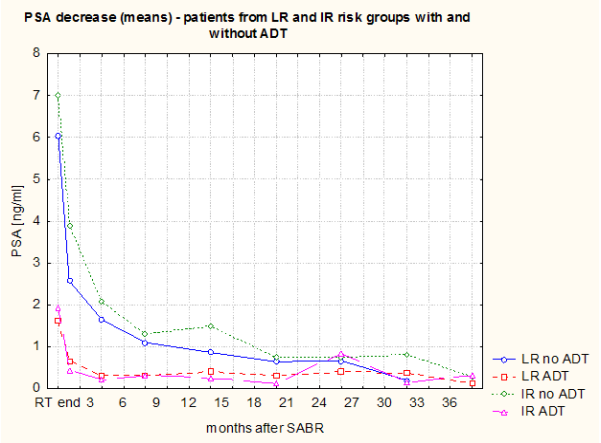

Figure 4. The Course of PSA Means During Follow-Up (LR and IR Patients with and without ADT)

(p=0.008) were identified.

Linear regression revealed an inverse dependency between PSA and FU, age, ADT usage and the presence of comorbidities (p=0.0000, p=0.0.0014, p=0.0000 and p=0.0064 respectively). A positive dependency was found for PSA and TNM (p=0.045).

A random effects ANOVA presented a difference in means of the PSA between the time points (p<0.001), however, no statistical difference was observed between the risk groups and the risk groups and time points interaction. No difference was found for ADT usage but statistical difference was registered for groups with and without ADT and time points interaction (p<0.001).The same results were observed for ADT impact evaluated separately in both risk groups (p<0.001 for both).

Ten patients developed second malignancies during FU: 2 bladder, 2 colon, 2 lung and one stomach cancer, lymphoma, multiple myeloma and brain tumor.

Discussion

Failures

The failure ratio is unexpectedly low (2.25%) and not connected with TNM (none of the failures in T2c subgroup) nor with the risk group (5 failures in LR and 4 in IR group). It suggests that there is no relevant impact of the risk group (taking into account LR, IR and T2c) on SABR treatment results. Additionally, we did not find statistical impact of the risk group on PSA values, even with time interaction. The low failure ratio is probably connected to a short FU (median 15 months). It could be supported by our previous results based on 200 patients with shorter FU (only 0.5% of failures) (Miszczyk et al., 2015). Other authors reported a larger failure ratio during longer FU: 9.8% (FU median 36 months) (Fan et al., 2015), 6.1% (FU median 30 months) (Jeong et al., 2015), 10.3% (FU median 63 months) (Lee et al., 2014), 4.4% and 10.4% for low and intermediate risk patients respectively (FU median 72 months) (Katz et al., 2014) and 4.5% (FU median 36 months) (King et al., 2013). An interpretation of these reports is difficult because of the low patient number i.e. Fan (2015), Jeong (2015) and Lee (2014) reported 31, 39 and 45 patients respectively; Katz (2014) and King (2013) had larger groups – 477 and 1100 (a multicentric study). Large groups were also analyzed by Freeman (2014) - a multi-institutional study comprising

Table 2. The Percentage of Evaluated Patients without ADT, GI and GU Adverse Effects and PSA Concentration of Evaluated Patients During FU

	RT end	1 month	4 months	8 months	14 months	20 months	26 months	32 months	38 months
N of observed patients	400	250	343	303	242	143	87	40	14
No ADT [%]	41.8	61.5	56.3	75.7	82.2	86.1	97.7	95	100
GI 0 [%]	90.7	89.6	94.4	95	97.5	93.7	96.5	100	92.9
GI 1 [%]	8.8	8.4	4.7	4.3	2.1	5.6	2.3	-	7.1
GI 2 [%]	0.5	1.6	0.6	0.7	0.4	0.7	1.2	-	-
GI 3 [%]	-	0.4	0.3	-	-	-	-	-	-
GU 0 [%]	77.5	70.1	90.1	95.7	91.3	96.5	95.3	92.5	100
GU 1 [%]	16	25.5	7	3.6	7.1	2.1	2.3	5	-
GU 2 [%]	6	4	2.9	0.7	1.6	1.4	2.4	2.5	-
GU 3 [%]	0.5	0.4	-	-	-	-	-	-	-
PSA mean	3.8	1.8	0.9	0.7	0.7	0.5	0.5	0.4	0.2
PSA median	2.3	0.8	0.2	0.2	0.2	0.2	0.2	0.1	0.1

ADT , Androgen Deprivation Therapy; GI , Gastro-Intestinal; GU , Genito-Urinary; PSA , Prostate Specific Antigen; FU , Follow-Up

45 radiotherapy centers and 2000 men (8% of failures at 2 years FU), by Bernetich (2014) – 0%, 8.3%, 4.8%, 10% and 13.3% of failures (5-years actuarial analysis) for very low, low, intermediate, high and very high risk patients respectively (142 men) and by Tan (2014) (a review of 14 CK studies – 1472 patients) – the failures rate varied from 0 to 19%. An exception is the Kim (2016) study, illustrating a lack of failures (33 patients). In all cited studies, the fractionation was the same (5 fractions) and the TD were highly similar: 35 Gy (Bernetich et al., 2014; Katz et al., 2014; Tan et al., 2014), 36 Gy (Lee et al., 2014), 36.25 Gy (the vast majority of patients) (King et al., 2013; Bernetich et al., 2014; Katz et al., 2014; Tan et al., 2014; Miszczyk et al., 2015; Kim et al., 2016) and 37.5 Gy (Fan et al., 2015; Jeong et al., 2015).

One possible explanation for failure disproportion in risk groups: 5 in LR vs 4 in IR could be the inconsistency in patient numbers [213 LR and 187 IR]). A similar phenomenon is described by Bernetich (2014) - 8.3% vs 4.8% of failures in LR and IR group respectively. On the other hand, Katz (2014) reported a larger failure number in IR than in LR group (14 vs 11) (LR group was more numerous – 324 vs 153).

Adverse effects

The intensity and frequency of acute as well as late GI and GU adverse effects were low. None of the patients had rectal bleeding. Admittedly, Joh (2014) reported 1.5% of rectal bleeding (269 men) during a 2-year observation, but the percentage was minimal. Also, Davis (2015) described low toxicity in the group of 437 patients. No grade 3 GI or GU acute and late toxicity was reported (in our material no G3 late toxicity was found, but we noted 0.4% of G3 acute GI and 0.5% of G3 acute GU toxicity). These authors (Davis et al., 2015) reported 3% G1 and 2% G2 late proctitis in comparison to 5.6% and 1.2% observed by us. Similar results were reported (515 patients) by Katz (2014) – no G3 and 4 acute toxicity and 1.7% of G3 GU late toxicity; acute G2 GI and GU adverse effects were observed in less than 5% of patients and G2 late GI and GU toxicity in 4% and 9.1% respectively. Good SABR tolerance and a low percentage (1.5%) of late urinary retention needing catheterization or TURP was also described by Arscott (2014) (269 men). Janowski (2014) described 3.5% of late GU G3 toxicity (no GI G3) in the group of 57 men with a large prostate (>50 ccm). More frequent and intense adverse GU effects were reported by Woo (2015). All aforementioned results regarded similar fractionation (35-36.25 Gy in 5 fractions), but even, after more intense SABR (38 Gy in 4 fractions) (Pontoriero et al., 2016) no G3 toxicity was reported.

Urinary incontinence after SABR, described by Chen (2014) - 5.7% leaking, more than once daily, was not observed in our material.

PSA decline

The decline of PSA concentration observed was similar to other reports. We can divide FU into three periods: the first month – rapid PSA fall, the next three months, slower but still intense PSA decrease and the rest of FU – with a slow PSA decline. Similar observations were reported by Kim (2015) – a rapid initial PSA decline followed by a slow decrease and Park (2015) – rapid decline during the first month and a slow decline within the next 2 years. Despite very fast PSA decline in first 4 months after the radioablation, Lee (2016) revealed that this decline is slower than after conventional irradiation (0.43 vs 0.53 ng/ml/month during the first year after RT). On the other hand Kim (2016) reported even larger PSA decline in the group of intermediate and high risk patients after combination of whole pelvis irradiation and SABR boost (0.61 ng/ml/month during the first year after RT).

Figures 2 and 3 illustrate that ADT has no real effect in terms of the velocity of PSA decline (in the subgroup with ADT, PSA decline is even slower) and from the 20th month PSA in both subgroups is similar. A random effects ANOVA revealed lack of significant differences between PSA during FU in subgroups with and without ADT, but significant difference for ADT and time interaction. The same results for ADT usage was found in LR and IR subgroups. In analyzing this, we should consider that the percentage of patients using ADT decreases over time.

The most unexpected result is the lack of a clear risk group impact on PSA decline.

Statistical analysis - results discussion

The observed dependency between failure risk and ADT usage and patient age seems obvious. Taking into account the character of SABR, we can compare it to brachytherapy. In some studies, the lack of ADT impact on biochemical outcome in LR and IR risk groups was reported (Merrick et al., 2005); in another, ADT deteriorated treatment results (among men of African descent) (Kovtun et al., 2016). Age impact is unsurprising as prostate cancer among younger patients is usually more aggressive (Ruska et al., 1999; Kanto et al., 2002).

The positive dependency between nycturia and the patient age and TNM is also clear; the probability of this symptom increases with age and tumor stage. A similar justification works for dysuria and TNM and ADT usage; the risk of dysuria is higher for larger T stage and, on the other hand, T stage is strictly interlinked with the probability of ADT usage. All patients were treated due to PC, therefore during FU the frequency of both symptoms decreased.

An impact of diabetes on adverse acute GI effects was previously described by us on the basis of a smaller study (Glowacki et al., 2015). We cannot find an explanation for acute GU decline with Gleason increase and its dependency on ADT usage.

A clear explanation for inverse dependencies among PSA, FU and ADT usage is as follows: longer FU after the treatment leads to better results, and PSA decline; the impact of ADT is commonly known. In contrast, the explanation for PSA and comorbidities connection is less obvious. The positive diabetes impact on PSA decline could be explained by metformin use. Such an effect is widely described in the literature (Gillessen et al., 2016; Jayalath et al., 2016). Unfortunately, we do not have data on metformin use at present.

Study limitations

Reading this text, we should be aware of four limitations of this study. Two of them concern patient recruitment, one treatment and one Follow-Up.

The first two limitations consider patient enrollment. Choline and/or PSMA-PET was not an obligatory examination before the SABR. Due to financial reasons, we undergo this examination for HR patients only; but this could, potentially, exclude patients with solitary, early metastases.

On the other hand, the 50 mm limit of maximal prostate dimension could impact the final results contrarily – there is some possibility that the cancer mass in a larger prostatic gland is bigger, which could influence indirectly treatment results (this 50 mm limit could improve them).

One of the weaknesses is connected to the treatment itself – not meeting ADT usage criteria (an additional issue was the different kinds of anti-hormonal drugs used). As aforementioned, we as radiation oncologists have a clear protocol of ADT usage and we had a limited impact on this phenomenon, but such a situation could lead to a change in the treatment results. On the other hand, it permitted ADT impact analysis.

The main weak-point is the short Follow-Up (mean 16.9, median 15.0 months). As mentioned in the first part of the Discussion, it probably resulted in a very low failure percentage, enabling sustained analysis of their causes.

The results obtained and the performed discussion enable us to conclude that stereotactic ablative radiotherapy of low and intermediate risk prostate cancer patients is a safe, well-tolerated and effective treatment modality (2.25% of failures).

The inclusion of T2c patients to the treatment group and the low percentage of failures in the intermediate risk group, as well as a lack of risk group impact on PSA decline, allow us to form the assumption that such a treatment could even be used in more advanced cases.

The results do not enable us to define clearly the impact of ADT on radioablation results of LR and IR+ T2c prostate cancer patients.

Conflict of interest statement

The main author has lectured on this topic during Accuray meetings.

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