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TOPIC PAPER

^{68}Ga-PSMA PET/CT-based metastasis-directed radiotherapy for oligometastatic prostate cancer recurrence after radical prostatectomy

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Abstract

Purpose The aim of this communication was to assess the efficacy of directed oligometastatic radiotherapy (RT) based on ^{68}Ga-PSMA PET/CT in patients with prostate cancer (PCa) biochemical relapse (BCR) after primary treatment with curative intent.

Methods This is a retrospective analysis of a monocentric cohort of PCa patients diagnosed with oligometastatic disease on ^{68}Ga-PSMA PET/CT and treated with metastasis-directed RT. Inclusion criteria were: histologically proven PCa, BCR after primary treatment with curative intent, oligometastatic disease defined as ≤ 3 metastatic lesions. To evaluate the efficacy of the therapy, biochemical response defined as a decrease of $> 50\%$ of PSA (PSA_{50}) was measured at 1 and 4 months. Patients were followed up until progression and start of androgen deprivation therapy (ADT). BCR-free survival and ADT-free survival were calculated.

Results 20 patients met the inclusion criteria. Median PSA value: 1.4 ng/ml (IQR, 0.3–2.3 ng/ml). A total of 30 PSMA-positive lesions were treated: 18 lymph nodes (60%), nine bone (30%) and three visceral lesions (10%). Median follow-up was 15 months (range 4–33 months). Biochemical response at 1 and 4 months was found in 3/20 patients (15%) and 14/20 (70%), respectively. BCR-free survival rate at 1 year was 79% and 53% at 2 years. ADT-free survival at 2 years was 74%.

Conclusion This retrospective study suggests that metastasis-directed RT based on ^{68}Ga-PSMA PET/CT may be a valuable treatment in patients with PCa oligometastatic disease, providing promising BCR-free survival rates and potentially postponing ADT for at least 2 years in 74% of the patients. Response assessment should not be measured before 4 months after treatment.

Keywords PSMA · Oligometastatic · Prostate cancer · Radiotherapy · Metastasis-directed therapy

Introduction

Prostate cancer (PCa) is the most common cancer in male worldwide and a major public health problem in developed countries [1]. After initial treatment with curative intent, including surgery and radiotherapy (RT), about 21% of patients will develop biochemical recurrence (BCR) with an increase of prostate-specific antigen (PSA) [2]. However, PSA cannot localize the recurrence and imaging techniques are less sensible than PSA, struggling in detecting recurrent sites, notably at low PSA levels. Conventional imaging techniques (CIT) including bone scan (BS), computed tomography (CT) or magnetic resonance image (MRI) have limited accuracy in this field, with a sensitivity of only 11% [3], resulting in an enormous number of negative or

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inconclusive investigations performed in this setting of often anxious patients. It is crucial to distinguish between limited vs extended metastatic disease as prognosis differs completely as well as consequent therapeutic strategy. While extensive metastatic disease will need systemic therapies starting with androgen deprivation therapy (ADT), oligometastatic disease defined as the presence of up to three metastatic sites can be treated locally as it is considered to be an intermediate state of tumor spread with limited metastatic capacity and less aggressive behavior [4–6]. Treating oligometastatic disease with metastasis directed therapy aims to control limited cancer spread while avoiding or delaying the toxicity associated with the use of systemic therapies [7]. This approach has been shown to be an effective treatment improving survival and disease progression-free survival in different cancers [8, 9].

During the last decade, one of the most accurate imaging modalities available for PCa recurrence detection was PET–CT with F18-of C11-labeled choline which has been widely investigated. Detection rates can vary widely as it is dependent on PSA values and kinetics, being recommended if patients present with a PSA doubling time < 6 months and a PSA value of > 1.5 ng/ml [10]. New molecular imaging tracers have recently been developed showing higher efficacy in the diagnosis of recurrent PCa as compared with choline-PET.

Prostate-specific membrane antigen (PSMA) is a transmembrane type II glycoprotein, also called folate hydrolase I or glutamate carboxypeptidase II, with a large extracellular domain and which is over-expressed on prostate cancer cells surface in both local and metastatic lesions [11]. ^{68}Ga-PSMA-HBED-CC, also called ^{68}Ga-PSMA-11, is a recently developed imaging technique for PCa using small molecular weight molecules (PSMA-ligands or inhibitors) binding to the active site of the extracellular domain of PSMA [12]. Those ligands become a radiotracer when labeled with the positron-emitter isotope gallium-68. Whole-body PET/CT images of PSMA expression can be obtained after intravenous injection of this tracer [13]. During the last years, there has been an exponential increase in the publications using this tracer in PCa in different scenarios, showing promising results at BCR with detection rates and tumor to background ratios higher than choline-PET, even at low PSA levels [14]. More specifically, for PSA ≤ 2 ng/ml, the detection rate of choline-PET ranges from 20 to 43%, whereas PSMA-PET ranges from 42 to 76% [15, 16]. This makes this technique an ideal exam to early detect sites responsible for biochemical recurrence, increasing the probability of finding limited number of lesions (oligometastatic disease) that could be treated with directed-RT. Treating those lesions could increase progression-free survival and delay the start of ADT which can have a detrimental effect in the quality of life.

Many studies analyzing metastasis directed therapy in oligometastatic PCa recurrence have been performed using choline-PET showing local control in 98% of patients, a median PFS of 22.5 months and a median ADT-free survival of 32.8 months. Even if encouraging results, those studies were retrospective analysis not allowing extrapolation to standard of care and needed validation [17]. A prospective randomized phase II trial was recently published [18] demonstrating an increase in ADT-free survival for patients treated with metastasis-directed therapy (21 months) compared to those with surveillance alone (13 months) at a median follow-up of 3 years. It can be hypothesized that repeating those experiences but using a better imaging technique could result in better outcomes.

Our center implemented the use of ^{68}Ga-PSMA PET/CT for the first time in Belgium in 2014 replacing choline-PET. As well as choline-PET was previously used for metastasis-directed RT in PCa, PSMA-PET has been the imaging technique used to guide RT treatment in selected patients always after discussion in the multidisciplinary uro-oncology committee. The aim of the present study was to retrospectively assess the efficacy of oligometastatic directed RT based on ^{68}Ga-PSMA PET/CT in patients with BCR after primary treatment with curative intent.

Materials and methods

Patients

This is a retrospective analysis of a monocentric cohort of 20 PCa patients diagnosed with oligometastatic disease based on ^{68}Ga-PSMA PET/CT findings and treated with metastasis-directed RT between January 2015 and September 2017. Inclusion criteria were: (1) histologically proven prostate cancer adenocarcinoma; (2) BCR after primary treatment with curative intent (surgery ± radiotherapy) and (3) oligometastatic disease defined as three or less metastatic lesions on ^{68}Ga-PSMA PET/CT. Decision for metastasis-directed RT was made after discussion at the multidisciplinary uro-oncologic tumor board and consent from the patient. This retrospective study complied with the regulations of the local institutional review board and the principles of the Declaration of Helsinki.

Radiotracer preparation

^{68}Ga-PSMA was produced at room temperature, using a cold kit containing lyophilized PSMA-11 (ANMI S.A., Belgium) and ^{68}Ga elution from a ^{68}Ge/^{68}Ga radionuclide generator (IGG100; Eckert and Ziegler, Germany). It was subsequently purified over a C18 reverse-phase cartridge (Sep-Pak C18,

Waters) and formulated in saline with 2.5% EtOH. Radiochemical purity was > 98% [19].

Imaging procedure

Images were acquired at Jules Bordet Institute on a General Electric (GE) Discovery 690 time of flight (TOF) PET system, 60 min after injection (range 60–70 min) of 2 MBq/kg of ^{68}Ga-PSMA-11. No diuretics were administered and patients were asked to void their urinary bladder immediately prior to the scan. No fasting, special diet or pause of ADT was required. Patients were scanned from top of the skull to mid-thigh in caudo-cranial orientation with raised arms. All PET scans were acquired in three-dimensional mode with an acquisition time of 2 min per bed position with an overlap of 23.4%. PET images were reconstructed with the built-in GE VUE Point Fx algorithm, a sharper resolution recovery algorithm, an ordered subset expectation maximization algorithm with three iterations and 18 subsets, and were post-filtered with a 6.8-mm full-width at half-maximum (FWHM) Gaussian function. The images were corrected for attenuation and for scatter using the CT data. CT was performed with a 64-slice helical scanner (VCT; GE Medical Systems, Chicago, IL, USA). The tension was 120 kV, and the current was modulated by the Auto-mA software with a noise index of 30 (range 30–200 mA) and ASIR. The other CT acquisition parameters were 0.5 s/CT rotation and a pitch of 0.98. The CT images were reconstructed with the ASIR algorithm set at 40%, with a matrix of 512 × 512 (0.97 × 0.97 mm pixel size) and a slice thickness of 2.5 mm. The PET matrix was 192 × 192 pixels of 2.73 9 2.73 mm with a slice thickness of 3.27 mm.

Image analysis

Reading of PSMA PET–CT images was done by two experienced nuclear medicine physicians (C.A., P.F.) on a dedicated workstation (Advantage Workstation; GE Healthcare, Chicago, IL, USA) using the commercial PET VCAR software AW Server 3.2; with access to clinical data and previous imaging exams. Images were interpreted visually with any focal uptake of ^{68}Ga-PSMA-11 higher than surrounding background and not associated with physiological uptake considered as suggestive for malignancy. Description of the number and localization of lesions were noted in the final report as it is done in clinical routine practice.

In the absence of a histologic gold standard, best valuable comparator was used [20]. Validation criteria to consider a lesion as positive (pathologic) included: the confirmation by other imaging techniques (bone scan, MRI or CT), clinical follow-up with PSA values, and imaging evolution after a watchful waiting period. Finally, a multidisciplinary consensus meeting decided on the treatment to be adopted.

Radiotherapy treatment

All PSMA PET/CT-positive lesions had to be anatomically correlated with either a CT scan or an MRI in order to perform radiotherapy planning and dose painting. Previous radiotherapy treatment volumes and administered doses were also taken into account for the treatment planning. A scheme of 3 times 10 Gy was used for isolated lymph node or bone PSMA-PET-positive lesions based on the STOMP trial [18]. In case of concomitant radiotherapy of the pelvis (5 patients), 66 Gy were delivered with a boost to the PSMA-PET-positive lesion. Some variations in doses could occur to comply with the limiting doses to organs at risk.

Patients follow-up

In order to evaluate the efficacy of the therapy, PSA was measured defining biochemical response as a decrease of > 50% of PSA (PSA_{50}). A first evaluation was done 1 month after the end of directed-RT and a second evaluation at 4 months after directed-RT. Patients had follow-up visits with PSA measure every 3 months until progression and until start of androgen deprivation therapy. Two consecutive increases of PSA at least 1 month apart was considered as a biochemical progression. At that point, a PSMA-PET/CT was performed in all patients. ADT was started in case of PSA recurrence with appearance of new metastatic lesions not considered for another MDT or in case of progression of the lesions treated with MDT.

Data analysis

Statistical analyses were performed using the GraphPad 7.04 software (Prism®). Waterfall plots were performed by calculating the percentage of PSA level changes at 1 and 4 months after metastasis-directed RT. Kaplan–Meier product limit method was used to estimate biochemical relapse (BCR)-free survival and androgen deprivation therapy (ADT)-free survival. Time to event was defined as the time between the last day of RT treatment to the day of biochemical progression (for BCR-free survival) or to the day of start of ADT (for ADT-free survival). Last contact was considered as date of censoring.

Results

Patient characteristics are summarized in Table 1. Patient mean age was 69 years (range 56–82). All patients presented high-risk disease according to D'Amico classification, with 60% of Gleason Score 7. Radical prostatectomy (RP) was the primary treatment with curative intent for all patients. 13/20 patients had local disease control with salvage or adjuvant

Table 1 Patient characteristics

Patient	Age	Gleason	TNM	Primary treatment	Local RT	Adjuvant ADT	PSA before PET	Recurrent site	Number
1	75	7	Unknown	RP	Yes	Yes	1.7	Lung	3
2	71	7 (4+3)	pT3Nx	RP	Yes	No	0.4	Pelvic LN	1
3	64	7	pT2cN0	RP	Yes	Yes	1.8	Pelvic LN	1
4	56	8 (3+5)	pT3aNx	RP	Yes	Yes	0.2	Pelvic LN + bone	2
5	71	7 (4+3)	pT3N0	RP	Yes	No	2.5	Pelvic LN	1
6	72	7 (4+3)	pT2bN0	RP	Yes	No	1.5	Pelvic LN	1
7	74	–	–	RP	Yes	No	0.9	Bone	1
8	62	7 (3+4)	pT3bNx	RP	Yes	Yes	4.4	RetroP LN + bone	3
9	60	7 (3+4)	pT3bNx	RP	Yes	No	4.6	Pelvic LN	2
10	67	6 (3+3)	pT2cNx	RP	Yes	No	0.4	Pelvic LN	1
11	75	8 (3+5)	pT2N0	RP	Yes	Yes	0.3	Bone	1
12	69	8 (4+4)	pT3aN0	RP	Yes	No	0.3	Bone	1
13	72	7 (4+3)	pT3bN0	RP	Yes	No	1.6	Bone	1
14	82	7 (3+4)	pT3Nx	RP	No	No	3.2	Pelvic LN	1
15	80	8 (4+4)	pT3N0	RP	No	No	0.3	Bone	1
16	75	8 (4+4)	pT2cN1	RP	No	No	1.4	Pelvic LN + bone	2
17	69	8 (4+4)	pT3aN0	RP	No	No	0.6	Pelvic LN	3
18	67	7	pT2cNx	RP	No	No	0.3	Bone	1
19	63	7	pT2cN0	RP	No	No	2.2	Pelvic LN	1
20	65	7 (4+3)	pT3aN1	RP	No	No	15.0	Pelvic LN	2

radiotherapy before PSMA PET/CT, while 7/20 patients had not received RT before PSMA-PET. Patients were not under androgen deprivation therapy although 5/20 patients had previously received ADT as an adjuvant therapy. Mean time from last treatment (surgery or RT) to PSMA-PET recurrence was 4 years (range 1–11 years). The median PSA value at the time of PSMA-PET/CT was 1.4 ng/mL (IQR, 0.3–2.3 ng/ml).

A total of 30 lesions were defined as positive (pathologic) based on ^{68}Ga-PSMA-11 PET/CT results and selectively treated with directed-RT: 18 lymph nodes (60%), nine bone lesions (30%) and three visceral lesions (10%). No recurrent lesion was found in the prostatic bed on PSMA PET/CT. ^{68}Ga-PSMA PET/CT detected only one metastatic site in 13 patients, two lesions in four and three lesions in three patients. 10 patients presented only lymph node disease, six only bone, three mixed bone and LN and one with visceral metastasis (lung). A median dose of 35 Gy (range 24–66 Gy) was delivered. There was no grade 2 or more toxicity according to CTCAR v4.0.

During follow-up period, biochemical response was evaluated at two different time-points: early evaluation at a median follow-up of 27 days (IQR, 25–31 days), considered as 1-month follow-up; and a second evaluation at a median follow-up of 121 days (IQR, 110–137) considered as 4 months follow-up. Early biochemical response at 1 month after directed-RT was found in only 3/20 patients (15%), while 14/20 (70%) patients presented biochemical response at 4 months (Fig. 1).

The median follow-up was 15 months (range 4–33 months). 4 patients were lost of follow-up before progression with a mean follow-up of 17 months. 7 patients presented biochemical progression during follow-up with two consecutive increases of PSA and a subsequent PSMA-PET/CT. Of them, three patients presented no response to treatment with increase in PSA and appearance of new lesions on PSMA-PET/CT already at 4 months of follow-up, starting ADT. 2 patients presented again oligometastatic disease on PSMA-PET/CT and were re-treated with directed-RT to the new lesions postponing ADT. One patient presented slow increase of PSA and no lesion on PSMA-PET and it was decided to postpone ADT and put him under surveillance. Finally, one patient progressed 15 months after directed-RT with PSMA-PET showing two new pelvic lymph nodes. In this case, a second directed-RT treatment was excluded due to dosimetry limitations and patient started ADT.

BCR-free survival rate at 1-year follow-up was 79% and 2-year BCR-free survival was 53% (Fig. 2a). Only 4/20 patients started ADT at the end of this analysis, as shown in the Kaplan–Meier curve, with 85% ADT-free survival at 1 year and 74% at 2-year follow-up (Fig. 2b).

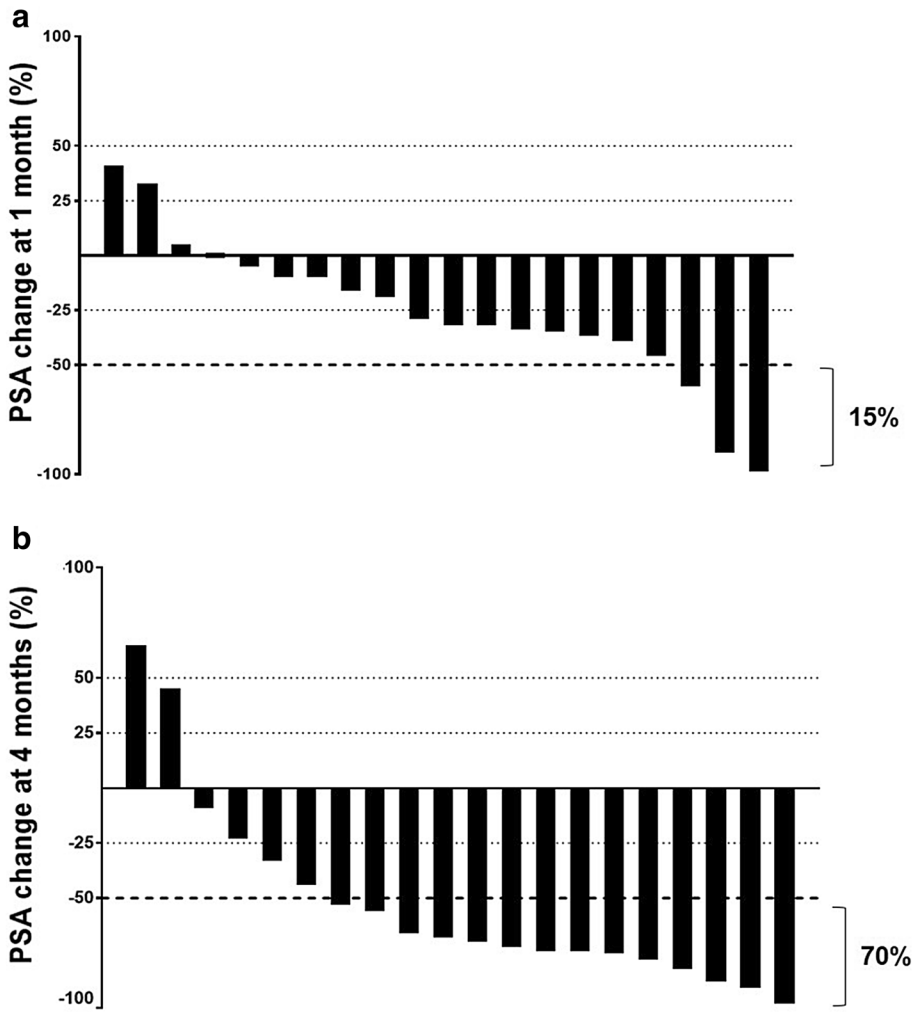

Fig. 1 Waterfall plot showing PSA percentage changes at 1 month (**a**) and 4 months (**b**) after directed-RT. 15% of patients present biochemical response early at 1 month increasing to 70% of patients at 4 months after directed-RT

Discussion

After primary treatment for PCa, BCR can occur in over one-third of the patients [2], with most of these men then developing clinical metastases within 5–8 years. An accurate diagnostic tool, capable of detecting the exact site responsible for the recurrence is of crucial importance to guide the correct therapeutic strategy for a single patient [21]. Conventional imaging techniques, widely available and used in most clinical trials, include bone scintigraphy, CTscan and pelvic MRI. Unfortunately, those imaging examinations are frequently unable to identify the lesion responsible for the PSA recurrence at an early stage with low PSA levels, being recommended for PSA > 10 ng/ml [22]. Those patients are frequently treated by systemic ADT, with heavy metabolic consequences, reduced quality of life, and possibly increased cardiovascular mortality [23]. In the current study, ^{68}Ga-PSMA-11 PET/CT was used as the routine imaging technique for PCa patients with BCR after treatment with radical intent and low PSA levels. In our cohort, median PSA was 1.4 ng/ml (IQR, 0.3–2.3 ng/ml).

^{68}Ga-PSMA PET/CT is a novel molecular imaging technique for PCa, based on the use of small molecular weight ligands binding to the extracellular domain of PSMA. PSMA is expressed in nearly all prostate cancers and its expression is further increased in poorly differentiated, metastatic and hormone-refractory carcinomas [24, 25]. Upon ligand binding, PSMA is internalized via clathrin-coated pits and subsequent endocytosis resulting in an effective transportation of the bound molecule into the cells. PSMA restricted expression to the prostate, it's up-regulation in PCa, its location on the cell surface and the fact that it is not shed into the circulation, all these aspects, make PSMA a very attractive target for detection, management and treatment of PCa. Physiologic PSMA extra-prostatic expression has been reported with lower levels in kidney proximal tubules, intestinal brush border membranes, liver and salivary glands. Endothelial expression of PSMA in the neovasculature of a variety of non-prostatic solid malignancies (e.g., kidney, colorectal, lung, bladder, pancreatic, breast, thyroid, melanoma) has also been described [26]. Moreover, benign conditions with increased neovasculature like bone Paget disease or vertebral

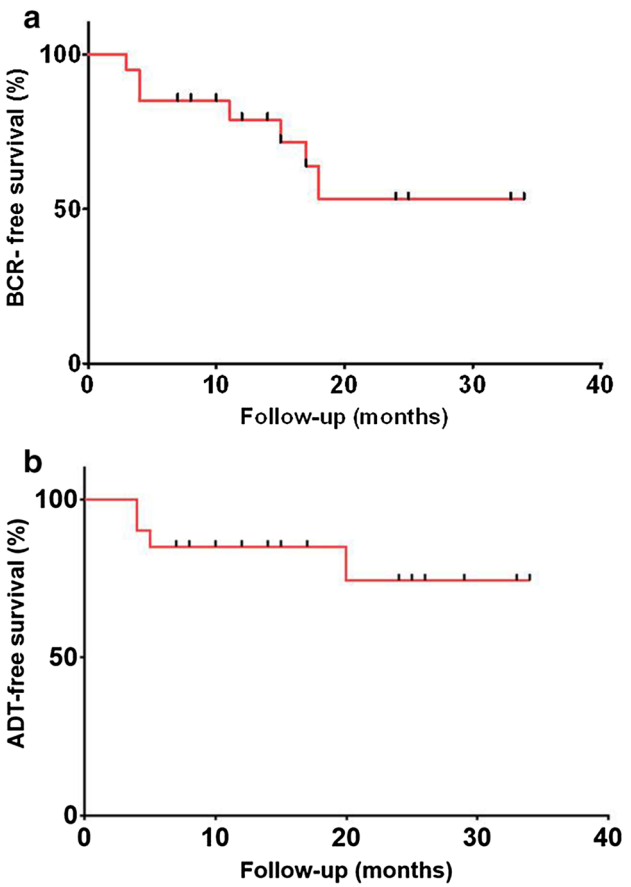

Fig. 2 BCR-free survival curve (**a**) and ADT-free survival curve (**b**). 1-year BCR-free survival was 79% and 2-year BCR-free survival 53%. After a median follow-up of 15 months, only three patients had started ADT

hemangiomas can present with an increased PSMA expression [27, 28].

^{68}Ga-PSMA-11 detection rates in patients with BCR have significantly increased as compared with previous imaging techniques like choline-PET [14]. This increased sensitivity can lead to an increase in the number of lesions detected and what's more important, in detecting them earlier, even at very low PSA levels (PSA < 1 ng/ml), where it is clinically relevant [16]. Recent publications have shown an impact in the clinical management of up to 75% of the patients after ^{68}Ga-PSMA PET/CT results [29], considering an impact as either the change from one treatment strategy to another (e.g., appearance of distant metastases in patients selected for pelvis RT) or the modification of the same strategy (e.g., enlargement of the RT field). Calais et al. [30] studied the impact of PSMA-PET findings previous RT-planning in BCR after radical prostatectomy. They found a major impact in 16% of patients with planned RT field covering prostate and pelvis, and 37% when planned RT field covered only prostate and seminal vesicles. ^{68}Ga-PSMA PET can alter the decision of referring physicians or multidisciplinary oncology committees in approximately half of the patients as shown in a recent metanalysis [31].

Using SBRT to treat limited metastatic disease (oligometastatic) has shown to increase ADT-free survival [32] as compared to surveillance alone (21 vs 13 months) in a prospective randomized phase II trial [18]. However, this trial used choline-PET for BCR staging as PSMA-PET was still not available at recruitment. In our cohort, of the seven patients presenting biochemical progression during follow-up, only four patients started ADT: three patients did not respond to directed-RT, with PSA increasing already at 4 months after treatment, and one patient progressed 15 months after directed-RT. 2 patients presented oligometastatic recurrence on PSMA-PET at progression and were re-treated with directed-RT and are nowadays on biochemical response. One patient showed no lesion on PSMA-PET at progression with slow increasing PSA and is under surveillance postponing ADT. In fact, one of the arguments against of the oligometastatic treatment approach is that it is based on a static image showing the metastatic spread in a very single moment, missing information on the kinetics of the progression. Some patients can present slow-growing metastatic deposits while others may present rapidly progressive disease, already unknown multimetastatic at the moment of RT treatment. This means that we need more biomarkers to better select patients, excluding those not likely to benefit from MDT [33].

Other series have used ^{68}Ga-PSMA PET/CT to select patients for metastasis-directed RT [34]. Populations are quite heterogeneous with patients already under ADT in some cases and others including local treatment a part from metastasis. Guler et al. [35] selected a population of patients under ADT dividing them into castrate sensitive ($n = 13$) vs castrate resistant ($n = 10$). Statistically significant difference was found in terms of PFS between castrate sensitive (1-year PFS 67%) and castrate resistant (1-year PFS 0%), probably reflecting the less aggressive behavior of oligometastatic hormone-sensitive disease. This should be taken into account when selecting patients for metastasis-directed RT. In patients without ADT one of the largest series ($n = 45$) showed PSA remission in 89% of patients after a median follow-up of 20 months [36]. When splitting this population into biochemical recurrence vs biochemical persistence, the percentage of patients with PSA < 0.2 ng/ml is 94% vs 82%, respectively. However, pelvic and prostatic bed radiotherapy was delivered, introducing a possible bias in the evaluation of efficacy of metastasis only directed-RT. Emmet et al. [37] showed similar results with PSA responses in 83% of patients when disease was confined to prostate vs 63% when there was nodal involvement. Our patients were all previously treated with radical prostatectomy as primary treatment with curative intent and none of them

was under ADT so that there was no influence of hormonal treatment. 13 patients had already had salvage RT treatment to the prostatic bed, so that they had theoretically, local disease control. This allowed to exclude PSA changes due to local disease and to attribute PSA response exclusively to metastasis-directed RT. There were seven patients without local disease control of which five received prostatic bed RT at the same time as metastasis-directed RT, and two patients were treated with directed-RT only to the metastatic site. Those two patients are still on remission after a follow-up of 10 months. Even if there are very few patients, this raises the question of which is the right sequence of treatment, and if prostatic bed salvage radiotherapy should still be done in patients with prostate-negative PSMA-PET. The same type of question could be raised for lymph node dissection in patients with negative PSMA-PET [38]. These are questions that will need prospective randomized trials to be answered.

To our knowledge, this is the first study using ^{68}Ga-PSMA PET/CT for guided RT and assessing efficacy in two different time-points: early at 1 month and at 4 months after treatment. PSA measure at 1 month shows few responses (15%), increasing to 70% of responders at 4 months. This information can have important implications in daily clinical practice in the moment of decision-making and as an argument for postponing decisions in front of an anxious patient.

Our present study is not exempt of limitations. The study is retrospective in nature, thus its results must be interpreted with caution as selection bias cannot be excluded. There are a limited number of patients included in this study. Moreover, all our patients presented high-risk disease meaning that results should not be applicable to intermediate or low-risk disease. Even if we didn't find any grade 2 or more toxicity after treatment, reporting of minor complications can be underestimated in a retrospective trial. Finally, short follow-up period is also a limitation in our study. Adapting our therapeutic decisions according to a more sensitive and specific imaging technique seems the right step for a better personalized therapeutic approach. It has to be taken into account that the results of this study cannot be extrapolated to other studies if those did not use PSMA PET/CT. Our study has no control group. If treating oligometastatic disease leads to a benefit in terms of PFS and overall survival is something that has still to be answered. In this scenario, time to castrate resistance has been proposed as a surrogate endpoint of overall survival [39]. For this purpose, prospective randomized clinical trials using PSMA PET/CT are needed.

Conclusion

This retrospective study suggests metastasis-directed RT based on ^{68}Ga-PSMA PET/CT may be a valuable treatment in patients with PCa oligometastatic disease, potentially delaying ADT for at least 2 years in 74% of the patients and providing promising BCR-free survival rates of 72% at a median follow-up of 15 months. Response to treatment based on PSA changes should not be measured before 4 months after the end of metastasis directed RT. Further larger, randomized and prospective studies are necessary to confirm our present findings.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this retrospective study formal consent is not required.

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