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Stereotactic body radiation therapy to postpone systemic therapy escalation for castration-resistant prostate cancer: A multicenter retrospective analysis

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ABSTRACT

Purpose: To evaluate the oncological outcome after stereotactic body radiation therapy (SBRT) for oligoprogressive metastatic castration-resistant prostate cancer (omCRPC) patients.
Materials-Methods: In this retrospective, observational, multi-institutional study, omCRPC patients (≤5 metastases) underwent SBRT. Primary endpoint was systemic therapy escalation-free survival (STE-FS) after SBRT. Local relapse (LR), distant (DP) and isolated biochemical (iBP) progressions were reported with progression-free survival (PFS) and overall survival (OS). Prognostic factors for STE-FS were investigated. Toxicity was reported.
Results: From 01/07 to 09/19, 50 pts with omCRPC underwent SBRT. With a MFU of 23 months [3—100], median STE-FS was 13.1 months (95 %CI 10.8 – 36.4). Median OS was not reached and PFS was 13 months (CI95% 10.1 – 20.8). Post-SBRT PSA remained stable or decreased in 19 pts (38 %). Progression events (LR, DP, iBP) were observed in 34 pts (68 %), among whom 6 relapsed in the irradiated area (local control rate: 88 %). DP and iBP were observed in 28 pts (56 %) and 4 pts (8 %) respectively. In multivariate analysis, post-SBRT biochemical response was an independent prognostic factor for STE-FS. Grade ≥ 3 toxicity occurred in 2 pts.
Conclusion: With excellent local control and tolerance, SBRT for omCRPC patients represents an acceptable approach to defer systemic therapeutic escalation and prevent its side effects. Accurate patient selection for SBRT requires more data with longer follow-up and higher numbers of patients pending the results of upcoming randomized trials.

Introduction

With 1.41 million cases and a mortality of more than 375,000 patients in 2020, prostate cancer is one of world's leading causes of death in men [1]. Moreover, the rate of metastatic patients, whether synchronous or metachronous, is growing rapidly, with projections for 2025 of +42 % in the United States, mainly due to more accurate detection techniques [2]. At the metastatic stage, patients' life expectancy plummets to 4.3 years and 5.3 years for high and low-burden metastatic disease respectively [3]. Improving the management of

Abbreviations: #, number (of); 95%CI, 95% confidence interval; ADT, androgen deprivation therapy (first generation); age_{diag}, patient age at the time of prostate cancer diagnosis; age_{SBRT}, patient age at the time of SBRT; a-LHRH, luteinizing hormone-releasing hormone analogs; BED, biologically effective dose; CTCAE, common terminology criteria for adverse events; DP, distant metastatic progression; EBRT, external beam radio-therapy; EPLN, extra-pelvic lymph node metastasis; EQD2, equivalent dose in 2Gy fraction; HIFU, high intensity focused ultrasounds; LR, local relapse; iBP, isolated biochemical progression; mCRPC, castration-resistant metastatic prostate cancer; MFU, median follow-up; mHSPC, hormone-sensitive metastatic prostate cancer; NA, not applicable; NHT, novel hormone therapy (second generation androgen deprivation therapy); omHSPC, oligometastatic hormone-sensitive prostate cancer; OS, overall survival; PFS, progression free survival; PLN, pelvic lymph node metastasis; PLND, pelvic lymph node dissection; PSA, prostate specific antigen; PSA_{+1}, first prostate specific antigen blood test after SBRT; PSA_{diag}, PSA at the time of prostate cancer diagnosis; PSA_{DT}, PSA doubling time; PSA_{SBRT}, PSA at the time of SBRT; $PSA_{Velocity}$, PSA velocity; Pts, patients; RECIST, response evaluation criteria in solid tumors; RP, radical prostatectomy; SBRT, stereotactic body radiation therapy; SM, synchronous metastasis; ST, systemic therapies; STE, systemic therapy escalation.

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these metastatic patients is therefore a public health issue.

Since the middle of the 20th century [4], androgen deprivation therapy (ADT) based on Luteinizing hormone-releasing hormone analogs (aLHRH), has been the treatment of choice for metastatic patients [5]. However, a hormone-sensitive metastatic prostate cancer (mHSPC) patient undergoing ADT has a median time of about 30 months before becoming castration-resistant (mCRPC) [6].

Against this backdrop of castration resistance, certain systemic therapies have shown improvements in progression-free survival (PFS) and/or overall survival (OS), such as docetaxel- or cabazitaxel-based chemotherapies, and novel hormone therapies (NHT) like Abiraterone acetate and Enzalutamide [7–10]. New therapies are also emerging, such as radionuclide treatments ([^{177}Lu] Lu-PSMA-617 and ^{223}Radium dichloride) and PARP inhibitors.

These treatments may be accompanied by grade ≥ 3 adverse effects: 39 % of (febrile-) neutropenia with Docetaxel [11], about 10 % of fractures or cardiac events with Enzalutamide [12], hypertension or liver disorders for Abiraterone acetate [13].

Nevertheless, the effectiveness of systemic therapies remains limited in time and the median OS for castration-resistant metastatic prostate cancer (mCRPC) is about 27 months [9].

Faced with the limited number of systemic medications available, their respective side effects and their reduced duration of efficacy, systemic therapy escalation (STE) is a significant milestone in mCRPC progression.

MCRPC patients presenting new localizations, or morphological or metabolic progression of known lesions, up to 5 sites, define oligo-progressive metastatic castration-resistant prostate cancer (omCRPC). In this case, according to European guidelines, recommendations are to change therapeutic lines, corresponding to systemic treatment escalation (STE).

By locally controlling a small number of metastases, SBRT could temporarily avoid STE, and preserve the systemic treatments available while reducing the occurrence of side effects. This study analyzed the oncological outcome after SBRT for omCRPC patients.

Material and methods

As previously described for oligometastatic prostate cancer patients [14], this is a retrospective, observational, multi-institutional study (Nice, Lille, Monaco), collecting databases of patients with omCRPC who underwent SBRT. Consent of each patient was obtained prior to analysis, after providing clear and fair information on the use of the data. In accordance with current legislation, data collection was registered at the National Health Data Hub under the number N° F20210402112942.

Patient features

Selection criteria were omCRPC patients treated with ablative SBRT on at least one of the metastatic sites (bone, pelvic (PLN - below the promontory) or extra-pelvic lymph node (EPLN), or viscera / brain). Castration resistant prostate cancer was defined according to the PCWG-1 criteria: “Prostate cancers progressing despite castrate levels of testosterone” [15]. Oligoprogression was defined as the appearance of metastatic lesions or the morphological or metabolic progression of known lesions in ≤ 5 sites. The imaging workup was left to the discretion of participating centers. After SBRT, patients were followed according to the usual modalities of each center (clinical examination, blood test and/or imaging). Patients could receive ADT, NHT and/or chemotherapy (CT) before or during SBRT.

Initial prostate cancer characteristics, patient epidemiological data, prostate specific antigen (PSA) kinetics and specific therapies before first SBRT were reported. Patients could have a history of synchronous (metastatic disease discovered within 3 months after PC diagnosis) or metachronous metastatic disease.

SBRT technique

SBRT had to be performed using a device allowing delivery of a high dose in a small volume, with a strong dose gradient, with a maximum of 10 fractions. Methods of delineation, delivery and performance of the irradiation were to be in accordance with good clinical practice. All SBRT regimens were considered. Data related to total dose, fractionation, total treatment time, and irradiation site were collected.

Patient follow-up

Primary endpoint was systemic therapy escalation-free survival (STE-FS), corresponding to the time interval between SBRT first course and the next introduction or modification of a systemic treatment. Systemic therapies could be NHT (Abiraterone acetate + Prednisolone, Enzalutamide, Apalutamide or Darolutamide), or chemotherapy (Docetaxel or Cabazitaxel). Nuclear medical therapies (Radium^{223} / [^{177}Lu] Lu-PSMA-617) were also considered. The initiation or modification of systemic therapy was left to the discretion of the physicians at each center, who followed the EAU guidelines available at the time of management.

Secondary endpoints were overall-survival (OS) defined by the time interval between SBRT and death (from any cause), progression free-survival (PFS) corresponding to the time interval between SBRT and any prostate cancer progression events. Oncological progression events after SBRT were considered: local relapse (LR; i.e. in the SBRT field), distant metastatic progression (DP), or isolated biochemical progression (iBP). LR and DP were defined as the appearance of new lesions or progression of known lesions (RECIST analysis) combined with a rising PSA ($\geq$25 % over the last 12 months). Patients presenting a rising PSA without imaging relapse in the 6 following months were considered iBP. The first three PSA blood tests after irradiation were collected. Based on the comparison between PSA at the time of SBRT (PSA_{SBRT}) and first PSA after SBRT (PSA_{+1}), three different biochemical situations were observed: PSA response (PSA_{SBRT}-$PSA_{+1} > 0.2 +/- 0.1$ ng/mL), PSA stable (PSA_{SBRT}-$PSA_{+1} = 0 +/- 0.1$ ng/mL) and PSA progression (PSA_{SBRT}-$PSA_{+1} < -0.2 +/- 0.1$ ng/mL).

Prognostic factors of STE-FS were analyzed. Toxicity (acute and late) was assessed (CTCAE v5.0).

Statistical analysis

Results for primary and secondary endpoints were presented with a 95 % confidence interval (95 %CI, Rothman for survival data). Qualitative data were presented as absolute frequency, relative frequency, 95 % confidence interval, percentage of missing data. These data were compared using the Chi2 test or Fisher’s test in case of non-compliance with the Chi2 conditions.

Quantitative data were presented as a histogram, median, extreme and standard deviation. The normality of these parameters was evaluated using frequency histograms and Shapiro’s test. Simple mathematical transformations were used to normalize non-normal data. Quantitative data were compared using Student’s T test or Mann-Withney test in case of non-compliance with the conditions of application of Student’s test.

Censored data were defined between the date of inclusion and the date of occurrence of the event, patients lost to follow-up were censored at the date of last news. These data were presented graphically as Kaplan Meier curves; survival rates at various times, median survival and 95 % CI of the study population were shown. The survival curves were compared by the Log-Rank test. All statistical analyses were performed using R.3.0.2 software for Windows.

Results

Patient and treatment features

From January 2007 to September 2019, 50 pts (61 metastatic lesions) with oligoprogressive metastatic castration-resistant prostate cancer underwent SBRT. At the time of primary prostate cancer diagnosis, 41 pts (82 %) were localized while 9 pts (9 %) also had synchronous metastatic disease. Among the 41 pts with localized prostate cancer, 20 pts (40 %) and 18 pts (36 %) underwent primary surgical procedure or external beam radio-therapy (EBRT) respectively. Six pts underwent salvage radiation therapy for biochemical relapse after radical prostatectomy (***e-Table1, Supplementary data***).

At the time of SBRT, median age was 73.9 years [52.6–85.5] (Table 1). Bone metastases represented the majority of the treated lesions (56 %). The median number of radiologically visible metastases was 1 [1 –5] with a median number of irradiated metastases of 1 [1–3]. Over 95 % of patients were treated at all oligoprogressive metastatic sites (Table 1). Two patients received SBRT on bone sites, while the other oligoprogressive sites were lymph node sites managed by surveillance. Thirty patients (60 %) were omCRPC at the time of SBRT without ever having received NHT and/or CT.

Regarding irradiation procedures, the Nice and Lille Centers used Cyberknife® linac (Accuray® Sunnyvale, California, US) and the Monaco institute used Novalis® TrueBeam STx® linac (Varian® Palo Alto, California, US). Different irradiation regimens were used (total dose and fractionation). Forty-five patients (90 %) were treated with a total dose ranging between 24 and 36 Gy in a 3 to 6 fraction protocol (Table 1; ***e-Table 2, Supplementary Data***). Calculating with an alpha/beta ratio of 1.3 Gy for prostate cancer, as in the PROFIT trial [16], the median Biologically Effective Dose (BED) of the irradiation protocols was 214 Gy, and the median Equivalent Dose in 2 Gy fraction (EQD2) was 84 Gy.

Table 1
Patient and treatment descriptions at the time of SBRT (# pts = 50).

Item	Data	%/[min - max]
Median age$_{SBRT}$ (year)	73.9	[52.6–85.5]
Total number of irradiated metastases	61	
Number of irradiated metastasis/number of metastasis (# pts)		
1/1	39	78
2/2	8	16
3/3	1	2
1/5	1	2
2/4	1	2
Metastatic disease irradiated sites (# pts)		
Bone	28	56
PLN	11	22
EPLN	7	14
Brain	4	8
Previous systemic treatments		
Without history of NHT / CT	30	60
With history of NHT / CT	20	40
Median PSA		
PSA$_{SBRT}$ (ng/ml)	3.2	[0.03–130]
PSA$_{DT}$ (months)	3.6	[1.1–21.3]
PSA$_{Velocity}$ (ng/ml/y)	4.8	[0.2–28.8]
SBRT regimens		
35 Gy / 5f	12	24
27 Gy / 3f	11	22
36 Gy / 6f	9	18
Others	18	36
Median overall SBRT time (d)	8	[1–22]

MFU (months): Median follow-up; PSA$_{SBRT}$: Prostate specific antigen at the time of SBRT; PSA$_{DT}$: Prostate specific antigen doubling time; PSA$_{Velocity}$: Prostate specific antigen velocity; PC: Prostate cancer; PLN: Pelvic lymph node metastasis; EPLN: Extra-pelvic lymph node metastasis; # pts: number of patient; # metastases: number of metastases; age$_{SBRT}$: patient age at the time of SBRT; NHT: Novel hormone therapy; CT: Chemotherapy; SBRT: Stereotactic body radiation therapy.

Oncological outcome

With a median follow-up (MFU) of 23 months [3–100], 16 pts (32 %) were free of prostate cancer progression. Regarding the primary endpoint, STE occurred in 19 pts (38 %) leading to a median STE-FS of 13.1 months (95 %CI [10.8–36.4]) (Fig. 1). The introduction (first or reintroduction) of NHT was the most frequent STE event (12 pts) before chemotherapy (10 pts) (Table 2).

Thirty-four patients (68 %) experienced progression and median PFS was 13 months (CI95% [10.1–20.8]) (Table 2 **and** Fig. 1). Local control rate was 88 % with 6 pts who underwent a local relapse in the SBRT field, of which 4 pts had synchronous distant progression. Local relapse irradiated sites were bone (4 pts), PLN (1pt) and EPLN (1pt). For these 6 pts, the delivered doses were 27 Gy/3f (3 pts), 35 Gy/5f (2pt) and 25 Gy/5f (1pt). Distant metastatic progression occurred in 28 pts. Four isolated biochemical progressions have been observed (Table 2). PSA progression, stable and response were observed for 12pts (24 %), 3 pts (6 %) and 16 pts (32 %) respectively (missing data: 38 %). Median OS was not reached (Fig. 1). Among the 9 deaths (18 %), 8 were related to prostate cancer.

In univariate and multivariate analysis, only the post-SBRT biochemical response was a prognostic factor for STE-FS (12 vs. 31 months for PSA progression vs. PSA stable/response; HR 0.26, 95 %CI [0.10–0.68]; $p < 0.006$). STE-FS was not correlated with previous systemic treatments history (NHT and/or CT), synchronous/metachronous metastatic status, metastasis number, metastatic sites, PSA$_{SBRT}$, PSA$_{Velocity}$ and PSA$_{DT}$ (e-Table 3, e-Fig. 1).

Oncological outcome was investigated in a subgroup analysis according to the history of previous treatments: with (20 pts) or without (30 pts) NHT and/or CT history (Fig. 2). Previous systemic treatments were not associated with STE-FS (10.1 vs. 15.3 months; HR 1.9, 95 %CI [0.87–4.2]; $p = 0.104$), and OS (medians not reached; HR 2.6, 95 %CI [0.43–15]; $p = 0.302$). PFS was not significantly associated, with an improving trend for patients without history of previous treatments (15.2 vs 9 months; HR 1.5, 95 %CI [0.62–3.7]; $p = 0.358$) (Fig. 2).

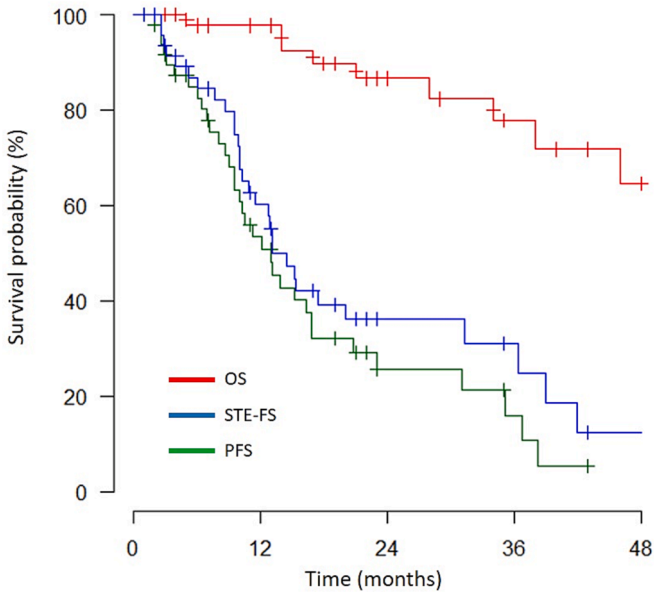

Fig. 1. Kaplan-Meier survival curves after SBRT on metastasis for oligoprogressive metastatic prostate cancer patients (50 pts): OS (overall survival: red line); STE-FS (systemic therapy escalation-free survival: blue line) and PFS (progression free survival: green line).

Table 2
Oncological outcome analysis after SBRT.

Items	Data	%/[min - max]/CI95%
MFU (months)	23	[3–100]
Post-SBRT oncological outcome (# pts)		
Non-progressive disease	16	32
Progressive disease	34	68
LR alone	2	
LR + DP	4	
DP	24	
iBP	4	
Median progression-free survival (months)	13	[10.1–20.8]
Post-SBRT biochemical response (# pts)		
Response	16	32
Stable	3	6
Progression	12	24
Missing data	19	38
Median STE-free survival (months)	13.1	[10.8–36.4]
Post-SBRT STE (# pts)		
No STE	19	38
STE	31	62
NHT	19	
Chemotherapy	10	
[^{177}Lu] Lu-PSMA-617	1	
^{223}Radium dichloride	1	

pts: number of patients; MFU: Median follow-up; SBRT: Stereotactic body radiation therapy; PSA_{+1}: First prostate specific antigen after SBRT; PSA_{SBRT}: Prostate specific antigen at the time of SBRT; PSA + 1: first prostate specific antigen blood test after SBRT; NHT: novel hormonal therapy; STE: systemic therapy escalation; LR: local relapse in the irradiated field; DP: distant metastatic progression; iBP: isolated biochemical progression.
Post-SBRT biochemical response: Response represents $PSA_{+1} < PSA_{SBRT}$; Stable represents $PSA_{+1} = PSA_{SBRT} +/- 0.1$ ng/mL; Progression represents $PSA_{+1} > PSA_{SBRT}$.

Toxicity profile

Only 2 pts (4 %) experienced grade ≥ 3 acute toxicities, while no late toxicity was observed. Radiation induced pneumonitis (1pt) was observed after costal irradiation, with favorable evolution under corticosteroid therapy delivered in the course of hospitalization. One patient with cerebral irradiation presented an intracranial hypertension requiring an emergency ventricular shunt.

Asymptomatic radio-induced fractures (grade 2) in the irradiated field occurred in 1pt after vertebral irradiation, without requiring surgery.

Discussion

Although systemic therapy represents the standard strategy for oligoprogressive metastatic prostate cancer, its escalation reduces future therapeutic options, uses up the period of treatment effectiveness and exposes to risks of toxicities with deleterious impact on patient quality of life. This retrospective study on SBRT in omCRPC patients highlights the feasibility and safety of this treatment, as well as the benefit of delaying systemic therapy. SBRT is presented as a therapeutic modality that makes it possible to defer this escalation by controlling metastatic disease progression, with an acceptable risk of toxicity.

To our knowledge, this study is the first reporting STE-FS after SBRT in mCRPC patients with a median STE-FS of 13.1 months leading to the suggested inclusion of SBRT as part of the therapeutic arsenal.

In our study, the median PFS for the entire cohort was 13.1 months, and median OS was not reached. Zhang et al. [17] published the results of a prospective phase I/II trial investigating SBRT in mCRPC patients. In this study, the 23 patients included had a median OS of 29.3 months and 40 % of patients were free of biochemical progression at 12 months (21 % at 24 months). Moreover, 84 % of patients were free of local recurrence at 12 months (75 % at 24 months). In this field, other studies have included mHSPC patients in their cohort, which could be considered a major limitation (***e-Table 3, Supplementary data***). Our results are therefore consistent with the current literature.

In our study, for the subgroup of patients without history of NHT and/or CT (30 pts), the STE-FS and PFS were 15.3 and 15.2 months respectively. In mCRPC patients who had never received chemotherapy, Ryan et al. [9] underline that cytotoxic chemotherapy was delayed by 8.4 months for patients treated with Abiraterone acetate and prednisolone compared with prednisolone alone. For this same category of patients, the article by Beer et al. [10] describes a radiographic PFS of around 13 months with the use of Enzalutamide. The phase 3 ACIS study by Saad et al. [18] found a radiographic PFS of 22.6 months for the same category of patients when treated with Apalutamide.

On the other hand, for patients with a history of NHT and/or CT (20 pts), our data show a PFS of 9 months. There are few robust data on this category of patients. Of interest are the studies by Matsubara et al. [19] and Khalaf et al. [20] which examined PFS during progression on Enzalutamide or Apalutamide, with switching from one to the other NHT. They found a PFS of 2.9 months (Matsubara et al.) and 1.7 months (Khalaf et al.) with the switch to Enzalutamide, and a PFS of 3.4 months (Matsubara et al.) and 2.7 months (Khalaf et al.) with the switch to Apalutamide. This reinforces the feasibility of SBRT without loss of opportunity for the patient.

In our cohort, with a MFU of 23 months, local control was 88 %, comparable to the current results reported in literature[17,21–23],***e-***

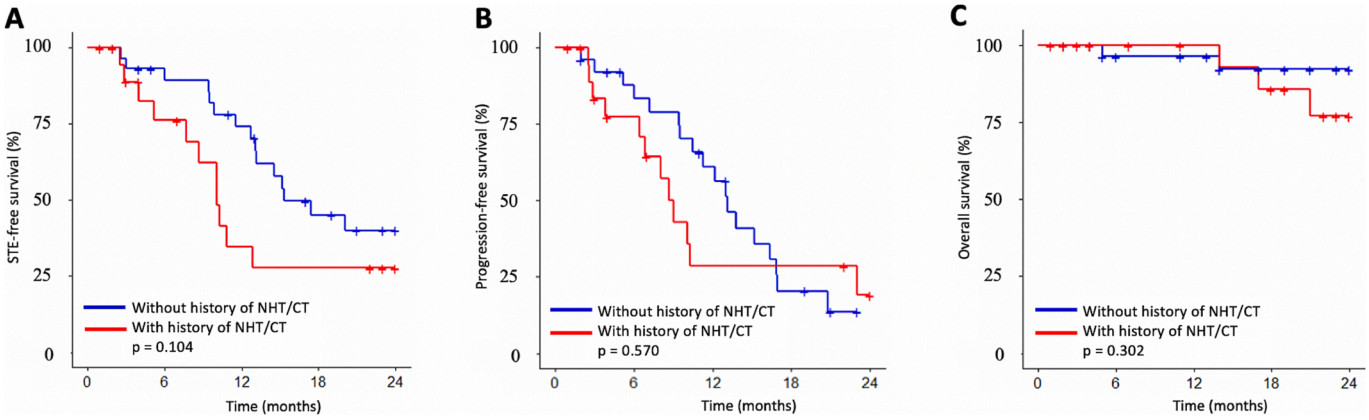

Fig. 2. Kaplan-Meier STE-free survival (A), PFS (B) and OS (C) curves after SBRT on metastasis for oligoprogressive metastatic castration-resistant prostate cancer patients with or without history of NHT and/or Chemotherapy at the time of SBRT for 20 pts (red lines) and 30 pts (blue lines) respectively (STE-FS: systemic therapy escalation-free survival; PFS: progression-free survival; OS: overall survival; NR: not reached; NHT: novel hormone therapy; CT: chemotherapy: pts: patients).

Table 3, Supplementary data).

Post-SBRT biochemical response was the only prognostic factor for STE-FS in our study. This is in line with data from the TAX327 [24] and AFFIRM [7] studies, which used Docetaxel and Enzalutamide respectively in mCRPC patients and showed that a PSA drop $>$ 30 % was predictive of progression-free survival. Interestingly, Francolini G et al. recently reported the results of the ARTO phase 2 randomized prospective trial comparing, for omCRPC pts, Abiraterone acetate + prednisolone with or without SBRT [25]. The authors showed that SBRT yielded a significant PFS improvement (HR 0.35 (95 % CI, [0.21–0.57]; $p < 0.001$).

Regarding SBRT safety for omCRPC, as already reported in literature, SBRT was associated with less than 5 % of G $\geq$ 3 acute toxicities with no late observable side-effects (*e-Table 3, Supplementary data*).

The main limitations of this study, in addition to its retrospective nature, are the heterogeneity of the different patient groups and their small number. Furthermore, the 12-year collection period represents another issue due to major changes in omCRPC patient management including imaging modalities, systemic treatments as well as the current use of SBRT in daily practice. Various imaging modalities have been used to define oligoprogressive metastasis status: CT scan, bone scan, PSMA-PET, Choline-PET, Fluciclovine-PET. No robust data are available to assess the impact of staging imaging on the primary endpoint.

Conclusion

The management of omCRPC patients is undergoing an evolution rather than a revolution. In this setting, SBRT is becoming an interesting therapeutic tool by not only providing excellent local control of metastatic disease but also substantially delaying the introduction or modification of systemic therapy, without significant deleterious impact on OS. Furthermore, SBRT for omCRPC provides excellent safety and could have a positive impact on patient quality of life and possibly on health reimbursement systems. Patient selection for SBRT remains a crucial point to be defined. More consistent data with longer follow-up and higher numbers of patients are needed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100710.

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