Primary Radical Prostatectomy or Ablative Radiotherapy as Protective Factors for Patients With mCRPC Treated With Radium-223 Dichloride: An Italian Multicenter Study

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Abstract

The present study investigated the effects on overall survival of previous radical primary treatment for patients with metastatic castration-resistant prostate cancer who had received radium-223. In our multicenter retrospective study, we enrolled 275 consecutive patients. The results showed a clear advantage for patients who had undergone radical primary treatment compared with those who had not, with an estimated median survival of 18 versus 11 months, respectively.

Background: We investigated, in a real-life setting, the prognostic relevance of previous primary treatment (radical prostatectomy [RP] or external beam radiotherapy [EBRT]) on overall survival for patients with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223 (^{223}Ra). **Materials and Methods:** In the present multicenter retrospective study, we enrolled 275 consecutive patients. The demographic and clinical data and mCRPC characteristics were recorded and evaluated at baseline and at the end of treatment or progression. ^{223}Ra was administered according to the current label authorization until disease progression or unacceptable toxicity. We divided the whole cohort into 2 groups: those who had undergone primary radical prostatectomy or ablative radiotherapy (RP/EBRT) and those who had not received previous primary treatment (NO). **Results:** Of the 275 patients, 128 (46.5%) were alive and undergoing monitoring at the last follow-up examination, 103 (37.4%) had stopped treatment because of disease progression or the onset of comorbidities, and 147 (53.5%) had died during the study period. Of the 275 patients, 132 were in the RP/EBRT group (48%), of whom 93 had undergone RP and 76 had undergone ablative EBRT, and 143 patients were in the NO group (52%). The data showed a clear advantage for the patients in the RP/EBRT group compared with those in the NO group, with an estimated median survival of 18 versus 11 months, respectively ($P < .001$). The results from the multivariate analysis corroborated this trend, with a hazard ratio of 0.7 ($P = .0443$), confirming the better outcome for the RP/EBRT group. **Conclusions:** Previous radical treatment provides a protective role for patients with mCRPC undergoing ^{223}Ra treatment.

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Introduction

Prostate cancer (PCa) is the most prevalent malignancy and the second leading cause of cancer-related mortality in men in Western countries.[1] In Italy, PCa has accounted for ~30% of all diagnoses of cancer, and the 10-year overall survival (OS) for men with PCa has been close to 90%.[2] PCa management can vary from a monitoring protocol, such as active surveillance or a watchful waiting approach, to appropriate definitive treatment, such as radical prostatectomy (RP), external beam radiotherapy (EBRT), and androgen deprivation therapy (ADT), or any combination of these. Most of the recent guidelines have provided treatment recommendations based on the PCa risk stratification.[3-5] However, considering that multiple treatment options can be suggested for any risk group and the relative heterogeneity of risk groups, no unequivocal consensus has been reached regarding the superiority of treatment compared with active surveillance or watchful waiting within the risk groups.

Since the Food and Drug Administration approval and clinical introduction of radium-223 (^{223}Ra), a number of studies have been performed concerning the clinical outcomes of ^{223}Ra therapy for patients with metastatic castration-resistant prostate cancer (mCRPC).[6-12] However, to the best of our knowledge, the significance and pretherapeutic prognostic value of previous primary radical treatment for patients undergoing ^{223}Ra has not been reported. To address this gap in knowledge, we performed a large, multicenter, retrospective analysis to investigate, in a real-life setting, the prognostic relevance of previous RP or ablative radiotherapy (EBRT), in terms of OS, for patients undergoing ^{223}Ra treatment for mCRPC.

Materials and Methods

The present study was a multicenter, retrospective study conducted at 4 Italian nuclear medicine units. All consecutive patients who had received ^{223}Ra to treat mCRPC from 2013 to 2018 were included in the present study. All the patients had had histologic confirmation of PCa, $\geq$ 2 symptomatic bone secondary lesions detected using 99m-technetium hydroxydiphosphonate bone scintigraphy, and no known visceral metastases found on contrast-enhanced computed tomography scan, except for malignant lymphadenopathy with $<$ 3 cm in the short-axis diameter. In addition, the patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 to 2 and adequate hematologic, hepatic, and renal function.[13] The decision to perform RP or EBRT as primary treatment of prostate cancer will be determined mainly by the disease stage at diagnosis, multidisciplinary team discretion, and/or patient preference. All the included patients had undergone radiometabolic treatment, consisting of 6 intravenous injections of ^{223}Ra (standard dose, 55 kBq/kg) at 4-week intervals, until disease progression or unacceptable toxicity had developed. ADT was continued during ^{223}Ra treatment. However, ADT was not permitted as concomitant treatment with abiraterone and enzalutamide. Conventional analgesics and glucocorticoids were administered to control pain, as prescribed by the best standard of care. ^{223}Ra was administered according to the Italian current label authorization.[14] At least 1 cycle of radionuclide therapy with ^{223}Ra was required for enrollment in the present study. The clinical data from all included patients were collected, including the patient characteristics (eg, age, ECOG PS, complete blood count, baseline total alkaline phosphatase, prostate-specific antigen [PSA], and pain score using the numeric rating scale), mCRPC details (eg, Gleason score, number of bone metastases), and additional clinical data regarding the previous and current treatments (eg, cycles of ^{223}Ra, previous use of docetaxel, concomitant use of bisphosphonates or denosumab). Furthermore, a survey of each patient's medical history was collected to obtain data regarding the presence of comorbidities and their respective relevance in the general clinical context of each patient. The clinical data were evaluated at baseline, before treatment with ^{223}Ra, and at the end of treatment and/or at progression, as applicable. We divided the whole cohort into 2 groups: those who had undergone previous treatment with primary RP/EBRT and those who had not received previous primary treatment (NO). In addition, we performed a subgroup OS analysis between the patients treated with RP and who had undergone EBRT. The local ethics committee, in accordance with the ethical standards of the institutional and national research committee and the Declaration of Helsinki (1975) and its later amendments or comparable ethical standards, approved the present study. All the participants included in the present study had provided written informed consent before inclusion.

Statistical Analysis

For the statistical assessment of our cohort's outcomes, in terms of OS, the study period was the interval from the start date of the first cycle of ^{223}Ra treatment, as the baseline, to the time of analysis. Data are presented as the mean $\pm$ standard deviation, and differences between the 2 groups were evaluated using the independent samples t test or χ^2 test. Univariate and multivariable Cox regression models were used to assess the adjusted hazard ratios (HRs). The incidence of events was estimated using Kaplan-Meier curves. The proportionality of hazards was checked using residual analysis. The significance threshold was set at 5% before data collection. All analyses were conducted using R software, version 3.5.1.

Results

A total of 275 men affected by mCRPC were enrolled in the present study. The patients' baseline characteristics are listed in Table 1. At the final analysis, 129 of the 275 patients (46.5%) were alive and have continued clinical follow-up. The remaining 146 patients had died during the study period. The mean patient age was 73.2 years (range, 50-90 years). The median Gleason score, as reported at the first clinical evaluation, was 8. The mCRPC secondary bone involvement was 6 to 20 metastatic lesions in 174 patients (63.2%), $>$ 20 bone localizations in 63 patients, and $\geq$ 6 in 38 patients. At the diagnosis, secondary bone lesions were found in 119 patients (43.3%). Of the overall pool of 275 patients, 143 had not undergone any previous primary RP or EBRT, and 93 had undergone RP, and 76 had undergone EBRT during their clinical course. For 39 of the latter 76 subjects, EBRT had been given as a single primary treatment, and 37 had undergone both RP and EBRT at different points during their disease course. Of the remaining 275 patients, 123 had not received medical treatment for the bone involvement and 152 patients had received medical treatment. Of these 152 patients, 87 had been treated with zoledronate, 53 with

Table 1 Baseline Patient Characteristics (n = 275)

Characteristic	Value
Age, y	
Mean	73.2
Range	50-90
Gleason score overall	
Mean	7.8
Range	5-10
Gleason score	
5	2 (0.7)
6	14 (5)
7	64 (23.2)
8	73 (26.5)
9	65 (23.6)
10	3 (1)
Unknown	54 (19.6)
Baseline PSA, ng/mL	
Mean	183.3
Range	0.08-3000
ECOG PS overall	
Mean	0.95
Range	0-3
ECOG PS	
0	88 (32)
1	118 (43)
≥2	69 (25)
Skeletal burden of metastases	
0-6	37 (13)
6-20	174 (64)
≥20	63 (23)
Brief pain inventory pain score	
Low (0-3)	79 (29)
Intermediate (4-7)	142 (51)
Severe (8-10)	54 (20)
Previous systemic treatment, n	
0	58 (21)
1	100 (36)
2	58 (21)
≥3	59 (22)

Data presented as n (%), unless noted otherwise.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status; PSA = prostate-specific antigen.

denosumab, and 12 with a combination of these. Before ^{223}Ra treatment, a large majority of patients (n = 218; 79%) had received some ADT or chemotherapy agents, after the onset of castration resistance onset. Most (n = 100; 45.9%) had received first-line chemotherapy only, 58 had received second-line treatment, 39 had received third-line, 18 fourth-line, and 1 patient had even received fifth-line treatment. The antiandrogenic and chemotherapy agents used were widely distributed with wide variability, depending on the stage at diagnosis and disease progression over time. The most common agents were bicalutamide (201 patients), leuprolide (158 patients), abiraterone (158 patients), docetaxel (136 patients), triptorelin (112 patients), and enzalutamide (68 patients). Of the 275 enrolled patients, 170 (62%) had completed all 6 cycles planned for ^{223}Ra. The mean number of cycles received by our cohort was 5. Of the 105 men who had received fewer cycles, 31 had received 5 cycles of ^{223}Ra, 23 had received 4 cycles, 15 had received 3 cycles, 21 had received 2 cycles, and 15 patients had received only 1 cycle. The mean follow-up period from the first cycle of radiometabolic treatment until analysis or death was 11.3 months, with some patients having ≤ 38 months of follow-up. A total of 103 patients (37.4%) had been withdrawn from ^{223}Ra treatment because of death, disease progression, or the onset of comorbidities, in particular, fractures, consumption, and bone marrow failure.

A total of 132 patients were enrolled in the RP/EBRT group (48%) and 143 in the NO group (52%). The results from a comparison of the patient characteristics between the RP/EBRT and NO groups are presented in Table 2. Our data showed an estimated median survival of 18 months and 11 months for the RP/EBRT and NO groups ($P < .001$), with an advantage provided by primary RP/EBRT (Figure 1) See Kaplan-Meier number-at-risk in Supplemental Material section. The multivariate analysis corroborated these results, returning an HR of 0.7 ($P = .0443$), confirming the overall best outcome for the RP/EBRT group compared with the NO group (Table 3). In this group (RP/EBRT group), the previous radical treatment was shown to have played a protective role in patients with mCRPC undergoing ^{223}Ra therapy.

Two further subgroups were examined, the RP group (93 patients) and the EBRT group (39 patients). Some differences in the characteristics of the subgroups emerged. The RP subgroup had had a longer median interval from diagnosis (10.3 vs. 9.4 years) and a slight difference in the number of previous systemic treatments (1.6 vs. 1.49) compared with the EBRT subgroup. The data from the subgroup analysis, in terms of OS, showed no clear differences between the RP and EBRT group compared with the NO group (HR, 0.66 for both; $P = .023$ for RP and $P = .052$ for EBRT).

Discussion

Although most patients with PCa will have an estimated 5-year survival rate of ~98%, PCa remains the most prevalent malignancy in Western countries and the second leading cause of cancer-related mortality in men. The characteristics of patients with CRPC are rather heterogeneous, both clinically and biologically. These patients will be mainly affected by locally advanced or metastatic disease, which has progressed after first-line ADT, though an optimal condition of gonadic suppression is present (testosterone, ≤ 0.5 ng/mL).[15] The risk of metastatic disease developing during long-term follow-up, and progression to mCRPC, has ranged from 26% to 38% after RP or other curative approaches.[16] In addition, ~4% of the patients will have metastatic disease at the initial diagnosis.[16]

Management of mCRPC

The purpose of medical treatment of mCRPC has been to slow the progression of the disease. The traditional therapeutic approaches have consisted of hormonal therapy, chemotherapy, bisphosphonates, and best supportive care.[17-19] The large number of studies performed to evaluate the oncologic outcomes among patients with PCa who had undergone RP or EBRT have reported conflicting results.[20-22] The data obtained from many retrospective

Table 2 Baseline Characteristics Stratified by Treatment Group

Characteristic	RP/EBRT Group (n = 132)	NO Group (n = 14)	*P* Value
Age, y			.089
Mean	73.8	72.3	
Range	51-90	50-90	
Gleason score			.998
Mean	7.2	7.8	
Range	6-10	5-10	
Baseline PSA, ng/mL			.001
Mean	159.7	205.7	
Range	0.08-3000	0.8-1711	
Skeletal burden			.4294
0-6	16 (12)	22 (15)	
6-20	89 (68)	85 (60)	
≥20	27 (20)	36 (25)	
Previous systemic treatment, n			.62
Mean	1.54	1.47	
0	28 (21)	28 (20)	
1	43 (33)	57 (39)	
2	31 (23)	27 (19)	
≥3	30 (23)	31 (22)	

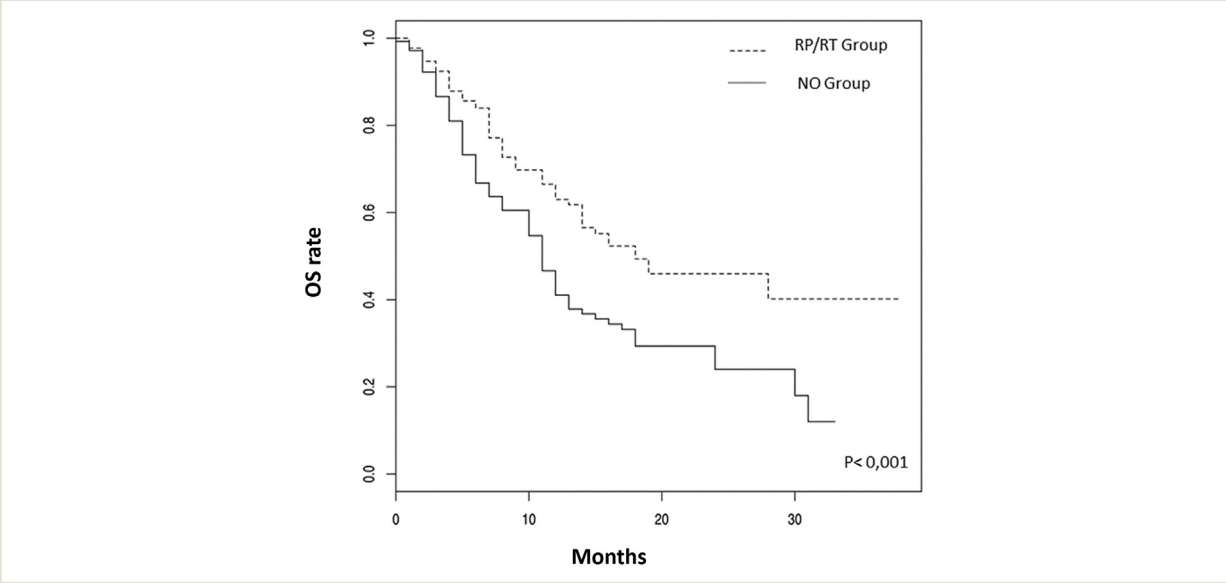
Data presented as n (%), unless otherwise noted.
Abbreviations: EBRT = external beam radiotherapy; NO = no previous primary treatment; PSA = prostate-specific antigen; RP = radical prostatectomy.

cohort studies have suggested that patients with locally advanced disease should undergo active treatment and that those who have undergone RP should have a reduced risk of secondary involvement.[23,24] Moreover, a high number of studies have recently reported that the specific mortality rates were improved in those patients who had undergone RP compared with those who had undergone EBRT or a watchful waiting approach.[25,26] Several studies reporting on the use of ^{223}Ra in real-world populations have shown that the accurate and careful selection of candidates for ^{223}Ra therapy is as complex as it is strongly relevant.[27] Previous retrospective studies have identified various prognostic variables associated with OS outcomes[28]; however, validated therapy predictive factors have been lacking. Thus, a strong rationale exists to collect multicenter real-world data from patients treated with ^{223}Ra in clinical practice to assess the best modalities of the application of this radiopharmaceutical agent and test its tolerability and long-term outcomes for a selected range of patients with mCRPC. The management of PCa has remained controversial because it can vary from monitoring interventions such as active surveillance or watchful waiting to definitive treatment, including RP, EBRT, brachytherapy, ADT, or any combination of these.[29,30]

RP Versus EBRT: A Challenging Choice

Currently, the choice of which treatment would be the most appropriate at each disease stage can best be accomplished within a multidisciplinary team meeting, in which different specialists discuss the patient's case and disease history. Such multidisciplinary team meetings can lead to the decision best suited for each patient, after consideration of the tumor features, Gleason score, local and distant disease extent, symptom severity, the response to previous treatments if any, PSA levels, comorbidity, life expectancy, and, not least, patient preference. RP and EBRT, with or without ADT, have both been considered the recommended treatment options. The guidelines from the most recognized international associations, including the European Association of Urology, American Urological Association, and National Comprehensive Cancer Network, have provided treatment recommendations for each PCa risk group.[3-5,31] However, multiple treatment options are available for each risk group, and no unequivocal consensus has been reached regarding the superiority of 1 approach compared with the others within the risk groups. At present, RP is a therapeutic option that can be proposed to selected patients who are strongly motivated to undergo an invasive treatment that often requires complementary therapies, such as EBRT and ADT, with an adequate life expectancy and the absence of important comorbidities and contraindications to the surgical procedure. The efficacy of surgical treatment has been demonstrated in both observational studies and prospective studies compared with watchful waiting.[24,32] Surgical therapy has proven advantages in terms of OS, cancer-specific mortality, and a reduction in the risk of local progression and distant spread. In addition, RP allows for objective pathologic staging of the disease, resulting in more accurate knowledge of the factors influencing the patient's prognosis. Thus, the choice of the potential adjuvant strategies can be determined using a less empirical and more personalized method.[29] Moreover, in the case of localized PCa, the oncologic follow-up protocol will be strongly influenced by the serum PSA level, which, after RP, must remain undetectable in the absence of disease relapse.[3] In contrast, EBRT is a therapeutic radical option for localized PCa treatment commonly reserved for older patients, patients with comorbidities that contraindicate a major surgical procedure, and those who prefer to avoid the most frequent side effects caused by surgery, such as urinary incontinence and erectile dysfunction.[21] Recent clinical trials have suggested that RP and EBRT will produce comparable results in terms of OS to 10 years for low- and intermediate-risk patients. In contrast, in advanced disease stages, EBRT alone has appeared to be insufficient; therefore, patients will require multimodal therapy within a multidisciplinary framework.[29] Approximately 90% of patients with PCa will have localized disease at diagnosis and will, therefore, receive primary curative treatment, either RP or EBRT.[1] RP represents the most commonly performed therapeutic procedure. The CaPSURE (cancer of the prostate strategic urologic research endeavor) trial and National Cancer Data Base data showed that ~50% of all patients with a diagnosis of PCa had undergone RP.[33] Patient age plays a crucial role in the treatment choice. RP has been the most common treatment modality for patients aged < 65 years. However, for patients aged > 65 years, EBRT has been the most frequently adopted modality. The use of RP will decrease as the risk strata increases. In contrast, the use of EBRT was lowest for the low-risk patients and highest for the high-risk patients. A factor that might increase the use of EBRT compared with RP in this population would be the increased morbidity associated with RP in older men.[34]

Figure 1 Kaplan-Meier Curves Highlighting the Clear Advantage in Overall Survival (OS) for the Radical Prostatectomy/External Beam Radiotherapy (RP/RT) Group Compared With the No Treatment (NO) Group



Heterogeneity of mCRPC Population and the Consequences

The previous discussion has explained how the considerable heterogeneity of the patient population and the uncertainty in the choice of the PCa treatment strategy during the disease course will inevitably cause some issues with patient selection bias when analyzing such a large population. Furthermore, the heterogeneity has made comparisons among the various treatment outcomes even more difficult, contraindicating any further statistical evaluation of the potentially significant differences between the RP and EBRT groups in terms of the survival outcomes. The clinical characteristics of the patients enrolled for treatment with ^{223}Ra in our centers led to a high number of patients not undergoing primary radical therapy, as evidenced by the greater number of patients in the NO group than in the RP/EBRT group.

A secondary underlying endpoint of the present study was the comparison of OS between the RP and EBRT groups. The latter group consisted of patients who had undergone ablative EBRT to the prostate bed only, in the absence of previous RP. The number of patients in the EBRT group was significantly lower than in the number of patients in the RP group. This discrepancy resulted from both the characteristics of the primary PCa and the clinical conditions of the patients who most commonly receive treatment with ^{223}Ra.

It is important to underline that in our study, only the patients who had undergone EBRT as primary treatment with radical intent were included. Those patients with a positive anamnesis of EBRT performed after RP intervention or only for palliative purposes were, therefore, excluded, which was a not insignificant percentage of subjects.

The interaction between these 2 fundamental factors in the choice of primary treatment after the diagnosis of PCa has led our multispeciality team to prefer radical surgery for a large percentage of patients. This intervention has represented the most frequently performed intervention for patients with PCa. However, the small number of patients in the EBRT group, compared with the RP group, made the 2 groups poorly comparable statistically, risking the presence of a selection bias.

Table 3 Results From Univariate and Multivariate Analyses of OS in Relation to Baseline Variables

Clinical Covariates	Univariate Models			Multivariate Models		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
RP/EBRT	0.7	0.49 - 0.99	.0443	0.562	0.40-0.78	.0007
PSA, ng/mL	1	1-1.001	.0361	1.001	1.001-1.001	.0000
tALP, IU/L	1.001	1-1.001	.0007	1.001	1.001-1.002	.0000
Hemoglobin, g/dL	0.771	0.69-0.86	.0000	0.706	0.63-0.78	.0000
Neutrophil count	1.117	1.02-1.22	.0168	1.118	1.02-1.22	.0125
ECOG PS	1.454	1.17-1.80	.0007	1.664	1.35-2.04	.0000

Abbreviations: CI = confidence interval; EBRT = external beam radiotherapy; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PS = performance status; PSA = prostate-specific antigen; RP = radical prostatectomy; tALP = total alkaline phosphatase.

OS Outcomes After Primary Ablative Treatment (RP/EBRT)

The data derived from the present study showed better median survival for patients who had undergone radical ablative treatment (RP/EBRT), regardless of the surgical approach or RT method, compared with those without primary ablative treatment (NO). This finding highlights the clear oncologic benefit of primary ablative treatment for these patients with PCa. The data obtained from the subgroup analysis in terms of OS showed no significant differences, as expected considering the recently reported data.[22] Furthermore, any possible differences between the 2 subgroups of RP and EBRT in the interval from diagnosis, number of systemic treatments, and duration of follow-up did not show any statistical significance. The multivariate analysis results have confirmed that the differences in the outcomes after RP and EBRT as primary ablative treatment, and if considered independently, reached the statistical significance previously obtained on univariate analysis. This outcome appears to have a remarkable and relevant effect on mCRPC clinical management. Moreover, as is well known from recent reports,[35] the multivariate analysis results showed strong statistical significance for the other independent values examined, including hemoglobin, neutrophil count, ECOG PS, PSA level, and total alkaline phosphatase (Table 3).

To achieve a more balanced assessment, we decided to consider the clinical relevance of any further treatment administered to our patients after the ^{223}Ra therapy. With consideration of its current indications of palliative therapy and as second- or third-line treatment, we estimated that only ~3% of patients enrolled in the present study had actually undergone further treatment after radiometabolic treatment, as we had expected.[4] Moreover, any eventual further treatment will usually be proposed mainly for pain relief and palliative purposes. This small percentage was, therefore, too low to influence significantly data from our large cohort of patients.

Role of Primary Tumor Cytoreduction in Patients with mCRPC

Cytoreductive surgery for patients with PCa has not traditionally been considered, and the current practice guidelines have not recommended RP or EBRT for the primary tumor for patients with metastatic PCa.[36] In general, for patients with mCRPC, ADT, with or without chemotherapy, has been recommended by the European Association of Urology guidelines. With the successful application of cytoreductive surgery for other metastatic cancers, in particular, breast and kidney cancer, and the progress achieved in surgical and RT techniques, the role of cytoreductive prostatectomy for mCRPC has increased in interest.[37] Several studies have suggested an interaction among solid tumors, their circulating and disseminated tumor cells, and the development and maintenance of secondary lesions. In mouse models, it has been shown that the removal of the primary tumor can prevent the development of new metastases.[38] The crucial interactions via a complex connecting network between the primary PCa, its host, and distant metastases might justify how primary tumor ablation could lead to the prevention of the development of new metastases and, by analogy with other types of cancer, a regression of metastases or their disappearance. However, the mechanisms underlying the survival benefit of cytoreductive prostatectomy in the metastatic setting have remained enigmatic. Kaplan et al[39] described a "premetastatic niche" theory, according to which the primary tumor is the predominant source of metastasis via circulating tumor cells.[39] At present, no unifying theory has been established. However, several hypotheses have supported the concept that primary tumor ablation can provide benefit in the management of the systemic disease.

The biologic mechanisms underlying this hypothesis are not yet known in detail. However, most of the reported evidence has confirmed that ablative treatment of the primary tumor to reduce the local disease burden can positively influence the biologic behavior of metastases and their response to adjuvant therapies,[40] resulting in an overall improvement in OS and quality of life. Radiometabolic treatment with ^{223}Ra is known to act directly on the microenvironment surrounding bone metastases.[41] Thus, it is reasonable to believe that the tumor microenvironment will be favored by the presence of the primary disease site. Thus, ablation of the primary tumor would be decisive for better control of the systemic disease.[42]

The proposed mechanisms of potential benefit include the elimination of the immunosuppressive effect of the primary tumor, removal of the leading source of malignant clone reseeding and systemic release, and avoidance of morbidity from local progression. Whether these theories apply to all, or only specific, solid tumors remain remains to be determined. As highlighted by the results from our study, cytoreductive prostatectomy could have the potential to enhance mCRPC disease control.[43,44] However, the lack of randomized controlled trials and the low level of evidence from reported current have precluded any firm conclusions regarding the benefit of a cytoreductive strategy for mCRPC or the ability to clearly identify those patients who would most benefit from primary PCa ablation. Furthermore, ongoing phase II and future phase III studies are mandatory for a better insight in this regard. Although ours was a multicenter study with a high number of included patients, one possible limitation was its retrospective nature. Thus, it would be useful to perform a larger scale prospective trial to validate our results.

Conclusions

Our multicenter retrospective analysis showed, in a real-life clinical setting of ^{223}Ra treatment, a clear advantage in terms of OS for patients who had received RP or EBRT as primary treatment compared with patients with no previous ablative treatment. The estimated median survival was 18 months for the RP/EBRT group compared with 11 months for the NO group ($P < .001$). For both treatment modalities, the previous radical treatment played a protective role for patients with mCRPC receiving ^{223}Ra therapy compared with those who had not undergone previous ablative treatment. This finding has confirmed the positive effect of the cytoreductive approach on oncologic outcomes in this PCa population.

A relatively solid biologic rationale supports the positive effect of removal of the primary tumor on the oncologic outcomes, such that cytoreductive prostatectomy could have the potential to enhance mCRPC disease control. However, further in-depth studies and randomized controlled trials are necessary to achieve a clearer definition of the cytoreductive prostatectomy benefits for patients with mCRPC. Finally, our findings have resulted in a relevant step

forward regarding the significance of the clinical prognostic factors in ^{223}Ra treatment.

Clinical Practice Points

- The significance and pretherapeutic prognostic value of previous primary radical treatment for patients receiving ^{223}Ra therapy has not, to the best of our knowledge, been previously reported.
- Our data revealed an estimated median survival of 18 months and 11 months ($P < .001$) for patients who had previously undergone RP and/or ablative RT compared with no previous primary treatment, with an advantage in OS shown for primary ablative treatment.
- Cytoreductive prostatectomy could have the potential to enhance mCRPC disease control.
- However, further in-depth studies and randomized controlled trials are necessary for a clearer definition of the benefits of cytoreductive prostatectomy for patients with mCRPC receiving ^{223}Ra therapy.

Disclosure

The authors declare that they have no competing interests.

Supplemental Data

Supplemental material accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2019.10.009.

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