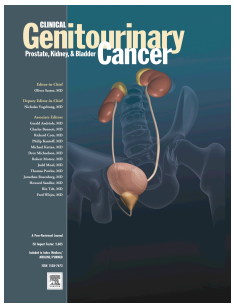

Primary Radical Prostatectomy or Ablative Radiotherapy (RP/EBRT) are Protective Factors in mCRPC Patients Treated With 223Radium-dichloride: An Italian Multicenter Study.

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PII: S1558-7673(19)30313-1

DOI: https://doi.org/10.1016/j.clgc.2019.10.009

Reference: CLGC 1371

To appear in: *Clinical Genitourinary Cancer*

Received Date: 5 August 2019

Revised Date: 2 October 2019

Accepted Date: 6 October 2019

Please cite this article as: Frantellizzi V, Costa R, Mascia M, Spanu A, Farcomeni A, Licari M, Cindolo L, Nuvoli S, Pontico M, De Vincentis G, Primary Radical Prostatectomy or Ablative Radiotherapy (RP/EBRT) are Protective Factors in mCRPC Patients Treated With 223Radium-dichloride: An Italian Multicenter Study., *Clinical Genitourinary Cancer* (2019), doi: https://doi.org/10.1016/j.clgc.2019.10.009.

Microabstract

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Primary Radical Prostatectomy or Ablative Radiotherapy (RP/EBRT) are Protective Factors in mCRPC Patients Treated With 223Radium-dichloride: An Italian Multicenter Study.

Short title: Protective Factors in mCRPC 223Radium Patients

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

This article does not contain any studies with animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Funding statements

No funding has been received for this paper

Microabstract

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Abstract

Background. We provide an analysis aiming to investigate, in a real-life setting, the prognostic relevance of previous primary treatment (radical prostatectomy (RP) or external beam radiotherapy (EBRT)) in terms of overall survival, in mCRPC patients treated with 223-Ra.

Materials and methods In this multicenter retrospective study we enrolled 275 consecutive patients. Demographics and clinical data, as well as mCRPC characteristics, have been obtained and evaluated at baseline and the end of the treatment or progression. 223-Ra has been administered according to the current label authorization until disease progression or unacceptable toxicity. We divided the whole cohort into 2 groups: men previously treated with primary radical prostatectomy or ablative radiotherapy (RP/EBRT) and patient with no prior primary treatment available (NO).

Results 128 out of 275 patients (46.5%) are alive and currently on follow-up; 103 patients (37.4%) dropped treatment out for disease progression or onset of comorbidities, and 147 patients died during the follow-up (53.5%). 93 patients underwent RP, 76 patients performed ablative EBRT. 132 patients enrolled in the RP/EBRT group (48%), 143 patients in the NO group (52%).

Data showed a clear advantage for patients subjected to RP or EBRT in respect of those without primary treatment performed, with an estimated median survival of 18 months and 11 respectively ($p<0.001$). The multivariate analysis corroborated this trending results, returning in an HR of 0.7 (p-value= 0.0443), confirming the best outcome of the RP/EBRT group.

Conclusions Previous radical treatment plays a protective role in mCRPC patients who underwent 223-Ra treatment.

Keywords

223-Ra; mCRPC; prostatectomy; radiotherapy; overall survival

Introduction

Prostate cancer (PCa) is the most prevalent malignancy in Western countries and the second leading cause of cancer-related mortality in men[1]. In Italy, PCa accounts for approximately 30% of complete diagnoses of cancer and 10-year overall survival of men with PCa is near 90% in our country[2]. PCa management could vary from monitoring policy, such as active surveillance or watchful waiting approach, waiting for an appropriate definitive treatment that includes radical prostatectomy (RP), external beam radiation therapy (EBRT), androgen deprivation therapy (ADT), or any combination of these. Most recent guidelines provide treatment recommendations based on the PCa risk stratification[3-5] but, considering that multiple treatment options could be suggested for any risk group and the relative heterogeneity of risk groups, currently there is no unequivocal consensus regarding the superiority of treatment with other options within the risk groups.

Since its FDA approval and clinical introduction, lots of studies have been carried out concerning the clinical outcomes of 223-Radium dichloride (223-Ra) treatment in patients with metastatic castration-resistant prostate cancer (mCRPC)[6-12]. Despite this, to our knowledge, at present, it has never been reported the significance and pre-therapeutic prognostic value of previous primary radical treatment in patients treated with 223-Ra therapy. To address this gap in knowledge, we provided a large multicenter retrospective analysis aiming to investigate, in a real-life setting, the prognostic relevance of previous RP or ablative radiotherapy (EBRT), in terms of overall survival (OS), in patients receiving 223-Ra treatment for mCRPC.

Materials and methods

This is a multicenter, retrospective study, conducted in 4 Italian Nuclear Medicine Units. All consecutive patients treated with 223-Ra affected by mCRPC, from 2013 to 2018, were included in

this study. All patients had an histological confirmation of prostatic adenocarcinoma, at least two symptomatic bone secondary lesions detected by 99m-Tc HDP bone scintigraphy and no known visceral metastases at contrast enhanced CT scan, except for malignant lymphadenopathy with less than 3 cm in the short-axis diameter, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-2 and adequate hematological, hepatic and renal function[13]. The decision to perform RP or EBRT for prostate cancer primary treatment was based mainly on the stage of the disease at the time of diagnosis, and/or on the multidisciplinary team discretion and/or on patients' preference. All patients received the radiometabolic treatment, consisting of six intravenous injections of the 223-Ra (standard dose of 55 kBq/kg) at four-week intervals, until disease progression or unacceptable toxicity. Anti-androgenic therapy was continued during the treatment, by contrast, it was not permitted 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 has been administered according to the Italian current label authorization[14]. At least one cycle of radionuclide therapy with 223-Ra was required for the enrollment. Clinical data of all patients were collected, including patients characteristics (age, ECOG PS, complete blood count, baseline total alkaline phosphatase (tALP), prostate-specific antigen (PSA) and pain score by Numeric Rating Scale) and mCRPC details (Gleason score (GS), number of bone metastases), as well as additional clinical data about previous and current treatments (cycles of 223-Ra, prior use of docetaxel and concomitant use of bisphosphonates or denosumab). Furthermore, a survey of each patient's medical history was collected to obtain data about the presence of comorbidities and their respective relevance in the general clinical context of each patient. Clinical data have been evaluated at baseline, before treatment with 223-Ra and whenever applicable, at the end of the treatment and/or at progression. We divided the whole cohort into two groups: patients previously treated with primary radical prostatectomy or ablative radiotherapy (RP/EBRT) and patients with no previous primary treatment (NO). In addition, it has been performed a subgroup OS analysis between the group of patients treated with RP versus those submitted to EBRT. This retrospective multicenter study was approved by the local Ethics Committee, following the ethical standards of the institutional and national research committee and with the Declaration of Helsinki (1975) and its later amendments or comparable ethical standards. Written informed consent was obtained from each participant included in the study.

For the statistical assessment of our cohort’s outcomes, in terms of OS, it has been considered a timeframe starting from the date of the I cycle of 223-Ra treatment, as a baseline, to the time of analysis.

Statistical analysis

Data are expressed as means ± standard deviation, differences between groups were evaluated with the independent samples T-test, chi-square test. Univariate and multivariable Cox regression models were used to assess (adjusted) hazard ratios. Incidence of events was estimated through Kaplan-Meier curves. Proportionality of hazards was checked using residual analysis. The significance threshold was set as 5% before data collection. All analyses were conducted with R software version 3.5.1.

Results

275 men affected by mCRPC were enrolled. Patients baseline characteristics are illustrated in Table 1. At the time of analysis, 129 out of 275 patients (46.5%) are alive and for them, clinical follow-up is currently ongoing, 146 patients died during the observational follow-up. The mean age was 73.2, ranging from 50 to 90 years. The GS median value, as reported at first clinical evaluation, was 8. The mCRPC secondary bone involvement has proved to be between 6 and 20 metastatic lesions in 174 patients (63.2%), over 20 bone localizations in 63 patients and within 6 in 38 cases. At the time of diagnosis secondary bone lesions were found in 119 patients (43.3%). Among the overall pool of 275 patients, 143 patients did not perform any previous primary RP neither EBRT, 93 of them underwent RP and 76 patients performed EBRT in their clinical course. For 39 of the latter 76 subjects, the EBRT treatment was applied as a single primary treatment, whereas the other subjects received both RP and EBRT at different times during the disease course. 123 patients received no medical treatment for the bone involvement; 87 out of 152 patients left was treated with zoledronate, 53 with denosumab and 12 with a combination of these. Prior to the 223-Ra treatment, a large majority of patients (218 pts, 79%) have undergone some antiandrogenic or chemotherapeutic agents, after the castration resistance onset: mostly of them (100 pts, 45.9%) were subjected to chemotherapeutic first-line only, whereas 58 patients received second-line treatment, 39 patients third-line, 18 fourth-line and even up to fifth-line treatment in one case. Antiandrogenic and chemotherapeutic agents adopted during disease were distributed with a wide variability depending on the stage at the time of diagnosis and the disease progression over time. The most common agents applied were bicalutamide (201 pts), leuprolide (158 pts), abiraterone (158 pts), docetaxel (136 pts), triptorelin (112 pts), enzalutamide (68 pts). 170 out of 275 enrolled patients (62%) completed all of the six cycles planned for 223-Ra treatment. The mean number of cycles received by our cohort was 5. Thirty-one men received five cycles of 223-Ra, 23 patients four

cycles, 15 three cycles, 21 two cycles, and 15 patients only one cycle. The mean follow-up period from the first cycle of radiometabolic treatment until the time of the analysis or the time of death was 11.3 months, with some patients experiencing even up to 38 months. 103 patients (37.4%) dropped out of the treatment for death, disease progression or because of the onset of comorbidities, mining the safety of the treatment, particularly fractures, consumption and bone marrow failure.

132 patients were enrolled in the RP/EBRT Group (48%), 143 patients in the NO group (52%). A comparison between the patients' characteristics of RP/EBRT and NO groups has shown in Table 2. Our data showed an estimated median survival of 18 months and 11 months ($p < 0.001$) for patients in RP/EBRT Group compared with NO Group, with an advantage of prostate primary ablative treatment (Figure 1).

The multivariate analysis corroborated these results, returning in an HR of 0.7 (p-value = 0.0443) and confirming the overall best outcome of RP/EBRT Group as compared to NO Group (See Table 3).

In both these groups (RP/EBRT Group), the previous radical treatment proved to play a protective role in mCRPC patients who underwent 223-Ra therapy.

Two further subgroups were examined: RP group (93 patients) and EBRT group (39 patients).

Some differences in the characteristics of the subgroups emerged: RP subgroup showed a longer median time from diagnosis (10.3 vs 9.4 years) and a slight difference in the number of previous systemic treatments in comparison with EBRT subgroup (1.6 vs 1.49). Data obtained from subgroups analysis, in terms of OS, showed no clear difference between RP and EBRT in respect of the group who sustained no radical treatment (NO), having both an HR of 0.66, with a p-value respectively of 0.023 for RP and 0.052 for EBRT.

Discussion

Despite most of the PCa patients reaches an estimated 5-year survival rate of about 98%, it is still the most prevalent malignancy in Western countries and the second leading cause of cancer-related mortality in men. CRPC applies to a group of patients rather heterogeneous, both from a clinical and biological point of view, mainly affected by locally advanced or metastatic disease, which is in progression after the first-line treatment with ADT, as long as an optimal condition of gonadic suppression is present (Testosterone level ≤ 0.5 ng/ml)[15]. The risk of developing the metastatic disease during long-term follow-up, turning into mCRPC, range from 26% to 38% after RP or other curative approaches, and about 4% of the patients are initially diagnosed with metastatic disease[16].

Management of mCRPC

The purpose of medical treatment for mCRPC is to slow down the disease progression. In this regard, traditional therapeutic approaches have consisted of hormonal therapy, chemotherapy, bisphosphonates, and best supportive care[17-19]. The large number of studies accomplished to evaluate the oncological outcomes among PCa patients treated with RP or EBRT have brought conflicting results[20-22]. Many evidences obtained from retrospective cohorts have suggested that patients with locally advanced disease could take advantage of active treatment and those subjected to RP should have reduced risk of secondary involvement[23, 24]. Moreover, a high number of reports have recently underlined that specific mortality rates were improved in those patients who underwent RP as compared with EBRT or watchful waiting[25, 26]. As evidenced by several reports on the use of 223-Ra in the real world populations, accurate and careful selection of candidates for 223-Ra therapy has revealed to be as complex as strongly relevant[27]. Previous retrospective studies identified various prognostic variables associated with overall survival outcomes[28], but the presence of validated therapy predictive factors is still lacking until now. In this context, there is a strong rationale to collect multicenter real-world data about patients treated with 223-Ra in clinical practice to assess the best modalities of application of this radiopharmaceutical agent and to test its tolerability and long-term outcomes in a selected range of mCRPC patients. The management of PCa is still controversial because it could vary from monitoring interventions such as active surveillance or watchful waiting approach expecting to definitive treatment including RP, EBRT, brachytherapy, ADT, or any combination of these[29, 30].

RP vs EBRT: a challenging choice.

Currently, the choice of which treatment could be the most appropriate at each stage of the disease is best accomplished within a "Prostate Unit", in which different specialists discuss patient and disease history leading to the decision best suited for each case, taking into account the tumor features, Gleason score, the local and distant extent of the disease, the severity of symptoms, the response to previous treatments if any, PSA levels, comorbidity, life expectancy, and, not least, the patients' preference. RP and EBRT, with or without ADT, are both considered recommended treatment options. Guidelines provided by the most recognized international associations (European Association of Urology, American Urological Association, National Comprehensive Cancer Network) have brought treatment recommendations based on the PCa risk groups[3-5, 31]. However, there are multiple treatment options for any risk group and no unequivocal consensus regarding the superiority of one approach over others within the risk groups. Nowadays, RP is a therapeutic

option that can be proposed to selected patients, if strongly motivated to face an invasive treatment that often requires complementary approaches, as EBRT and ADT, and with an adequate life expectancy, in the absence of important comorbidities and contraindications to surgical procedure. The efficacy of surgical treatment has been demonstrated both by observational studies and by prospective comparative studies in respect of watchful waiting[24, 32], has proved an advantage in terms of OS, cancer-specific mortality and reduction of risk of local progression and distant spread. Besides, the RP allows obtaining an objective pathological staging of the disease, which means to know more accurately the factors influencing the patient's prognosis so that choice of potential adjuvant strategies could be ruled out in a less empirical and more personalized way[29]. Moreover, in the case of localized PCa, the oncologic follow-up is strongly favored by serum PSA dosage, that after RP must be undetectable in the absence of disease relapse[3]. On the other hand, EBRT is a therapeutic option with a radical purpose for localized PCa treatment commonly reserved for older patients, or for patients with comorbidities that contraindicate a major surgical procedure, or in those that prefer to avoid the most frequent side effects caused by surgery, as urinary incontinence and erectile dysfunction[21]. Recent clinical trials[20] have suggested that RP and EBRT produce comparable results in terms of overall survival to 10 years in low and intermediate-risk patients. Conversely, in advanced stages, EBRT alone appears to be insufficient and therefore patients will need multimodal therapy in a multidisciplinary framework[29]. About 90% of PCa patients are diagnosed with localized disease and therefore subjected to primary curative treatment, either RP or EBRT[1]. RP represents the most commonly performed therapeutic procedure: the CaPSURE trial and National Cancer Data Base data showed that about 50% of all patients diagnosed with PCa received an RP[33]. Age plays a crucial role in the treatment choice: RP is the most common treatment modality in patients aged <65 years, by contrast, in patients aged >65 years, EBRT is the most frequently adopted treatment modality. The utilization of RP decreases as the risk strata increases, whereas the use of EBRT was lowest in low-risk patients and highest in high-risk patients. A factor that may increase EBRT application over RP in this population is the increased morbidity associated with RP in older men[34].

Heterogeneity of mCRPC patients population and its consequence

What has been discussed above explains how this considerable heterogeneity and uncertainty in the choice of PCa treatment strategy during the disease will inevitably cause some issues of patient selection bias when analyzing such a large population. Furthermore, this heterogeneity makes the comparison between various treatment outcomes even more difficult, avoiding any further statistical evaluation of potentially significant differences between the RP and EBRT Group in terms of

survival outcomes. The clinical characteristics of the patients enrolled for treatment with 223-Ra in our centers have led to reaching a high number of missed primitive therapies for radical purposes, as evidenced by the greater number of the NO Group in respect of RP/EBRT Group.

A secondary underlying endpoint of this study involved the comparison, in terms of OS, between the RP group and the EBRT group. The latter consists of patients who underwent ablative EBRT on the prostatic loggia only, in the absence of previous radical prostatectomy surgery. The EBRT group is numerically significantly lower than the RP group. This discrepancy depended both on the characteristics of the primary prostatic neoplasm, as well as on the clinical conditions of the subject that most commonly undergoes treatment with 223Ra.

It is important to underline that in this group only patients who performed EBRT in primitive treatment with radical intent are included; subjects with a positive anamnesis were therefore excluded for EBRT cycles performed, after RP intervention, or only for palliative purposes, which represents a not-insignificant percentage of subjects.

The interaction between these two fundamental factors in the choice of primary treatment after a PCa diagnosis leads the multispeciality team to prefer the execution of radical surgery in a large percentage of cases. This intervention, as is known, represents the most frequently performed intervention in patients with PCa. Unfortunately, the small number of patients of EBRT Group, compared to the RP group, makes them poorly comparable from a statistical point of view, risking to generate a selection bias.

OS outcomes of primary ablative treatments (RP/EBRT)

Data derived from this study showed a better median survival for patients subjected respectively to radical ablative treatment (RP/EBRT), regardless of surgical or by means of radiotherapy, in respect of those without primary ablative treatment (NO), underlining the clear oncological benefit in receiving a prostate primary ablative treatment in this kind of PCa patients. Data obtained from subgroups analysis in terms of OS showed no significant differences, as we should be expect taking into account recent data in literature[22]. Furthermore, any possible differences between the two subgroups, RP and EBRT, regarding time from diagnosis, number of systemic treatments and time of follow-up, did not express any statistical significance. The multivariate analysis has led to confirm that the variable RP/EBRT (primary ablative treatment), also if considered as independent, has got the statistical significance previously obtained in the univariate analysis. In our opinion, this outcome appears to have a remarkable and relevant impact on mCRPC clinical management. Moreover, as well known from the recent literature[35], the multivariate analysis showed a strong

statistical significance of the other independent values examined, as Hb, neutrophils count, ECOG PS, PSA and tALP (Table 3).

Aiming to achieve a more balanced assessment, it was advisable to consider the clinical relevance of any further treatment administered to our patients after the one with 223Ra. Taking into due consideration its current indications, consisting of a therapeutic option applied for palliative purposes and mostly as a second or third-line treatment, we estimated that only about 3% of patients enrolled in this study actually underwent further treatments after the end of the radiometabolic treatment, as we expected[4]. Moreover, any eventual further treatment is proposed mainly for a pain relief palliative purpose. This small percentage is therefore too low to influence significantly the large cohort of patients object of discussion.

Role of primary tumor cytoreduction in mCRPC

Cytoreductive surgery in PCa has not traditionally been considered and current practice guidelines do not recommend RP or EBRT on the primary tumor for patients with metastatic PCa[36]. In general, for mCRPC patients, ADT with or without chemotherapy was recommended by EAU guidelines. Along with the successful application of cytoreductive surgery for other metastatic cancers, particularly in breast and kidney cancer, and the progress achieved in surgical and radiotherapeutic techniques, the role of cytoreductive prostatectomy approach for mCRPC has gained a great of interest[37]. Several studies suggested an interaction between 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 may prevent the development of new metastasis[38]. The crucial interaction via a complex connecting network between the primary PCa, its host, and its distant metastases may justify how primary tumor ablation could lead to preventing 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 remain enigmatic, Kaplan et al. described a “premetastatic niche” theory according to which the primary tumor is the predominant source of metastasis through circulating tumor cells[39]. Nowadays, no unifying theory is chorally established, but several hypotheses are supporting the concept that the primary tumor ablation may provide benefit in the management of the systemic disease.

Even if the biological mechanisms underlying this hypothesis are not yet known in detail, most of the evidences obtained in the literature confirm that the treatments for ablative purpose of the primitive tumor, aiming to reduce the local load of disease, are able to positively influence the biological behavior of secondary locations and their response to adjuvant therapies[40], resulting in an

overall improvement of the OS, as well as quality of life. With particular regard to the radiometabolic treatment with 223Ra, it is known that this acts directly on the microenvironment surrounding the bone metastases[41]; in our opinion it is reasonable to think that the mentioned microenvironment is, in a complex way, favored by the presence of the primary site of disease and that consequently its ablation would be decisive for a better control of systemic disease[42].

Proposed mechanisms of potential benefit include the elimination of the immunosuppressive effect of the primary tumor, the removal of the leading source of malignant clone reseeding and systemic release, and the avoidance of local progression morbidity. Whether these theories apply to all or only specific solid tumors remain still to be determined. As pointed out by the results of our study, cytoreductive prostatectomy could have the potential to enhance mCRPC disease control[43, 44], but the lack of randomized controlled trials and the low level of evidence in the current literature preclude any firms conclusion on the benefit of cytoreductive strategy in mCRPC and to clearly identify the patients who would most benefit from their primary PCa ablation. Further, ongoing phase II and future phase III studies are mandatory to gain better insight in this regard. Although this is a multicenter study with a high number of patients analyzed, a possible limitation may be its retrospective nature and it would be useful to perform a larger scale prospective trial to better validate these surprising 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 which received RP or EBRT as primary treatment compared to patients with no previous ablative treatment, with an estimated median survival of 18 months versus 11 respectively ($p<0.001$). In both these cases, the previous radical treatment proved to play a protective role in mCRPC patients who underwent 223-Ra therapy, as opposed to those who missed previous ablative treatments, carrying confirmation about the positive impact of the cytoreductive approach on the oncological outcomes of this PCa population.

Even if a relatively solid biological rationale does support the idea that removing the primary tumor does have a positive impact on oncologic outcomes, so that cytoreductive prostatectomy could have the potential to enhance mCRPC disease control, further in-depth studies and randomized controlled trials are necessary aiming to a more clear definition of cytoreductive prostatectomy benefits in mCRPC patients. Finally, this achievement leads to a relevant step forward to further knowledge about the significance of clinical prognostic factors in 223-Ra treatment.

Clinical Practice Points

• At present, it has never been reported the significance and pre-therapeutic prognostic value of previous primary radical treatment in patients treated with 223-Ra therapy

• Our data showed an estimated median survival of 18 months and 11 months ($p < 0.001$) for patients previously treated with Radical Prostatectomy and/or Ablative Radiotherapy Group compared with no prior primary treatment Group, with an advantage of prostate primary ablative treatment

• Cytoreductive prostatectomy could have the potential to enhance mCRPC disease control, further in-depth studies and randomized controlled trials are necessary to a more clear definition of cytoreductive prostatectomy benefits in mCRPC patients submitted to Ra-223 therapy.

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Table 1. Baseline patients' characteristics.

Patients Characteristics	Population (*n*=275)	%
Age (years)		
Mean (range)	73.2 (50-90)	
Gleason Score		
Mean (range)	7.8 (5-10)	
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 (range)	183,3 (0.08-3000)	
ECOG Performance Status		
Mean (range)	0.95 (0-3)	
0	88	32
1	118	43
≥ 2	69	25
Skeletal burden		
0-6 mets	37	13
6-20 mets	174	64
≥20 mets	63	23
Brief Pain Inventory Pain Score		
Low (0-3)	79	29
Intermediate (4-7)	142	51
Severe (8-10)	54	20

N of previous systemic treatments		
0	58	21
1	100	36
2	58	21
≥3	59	22

PSA = Prostate-Specific Antigen; ECOG = Eastern Cooperative Oncology Group

Table 2. RP/EBRT and NO Groups baseline characteristics.

	RP/EBRT Group (n=132)	NO Group (n=143)	P-value
Age (years)			
Mean (range)	73.8 (51-90)	72.3 (50-90)	0.089
Gleason Score			
Mean (range)	7.2 (6-10)	7.8 (5-10)	0.998
Baseline PSA			
Mean (range)	159.7 (0.08-3000)	205.7 (0.8-1711)	0.001
Skeletal burden			0.4294
0-6 mets	16 (12%)	22 (15%)	
6-20 mets	89 (68%)	85 (60%)	
≥20 mets	27 (20%)	36 (25%)	
N of previous systemic treatments			
Mean	1.54	1.47	0.62
0	28 (21%)	28 (20%)	
1	43 (33%)	57 (39%)	
2	31 (23%)	27 (19%)	
≥3	30 (23%)	31 (22%)	

RP: radical prostatectomy; EBRT = external beam radiotherapy; NO = patient with no prior primary treatment available; PSA= Prostate-Specific Antigen

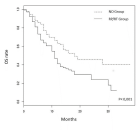
Table 3. Univariate and multivariate analysis analysis of OS in relation to baseline variables.

Clinical Covariates	Univariate Models			Multivariate Models		
	HR	**C.I. (95%)**	**p-value**	**HR**	**C.I. (95%)**	**p-value**
RP/EBRT	0.7	0.49 - 0.99	0.0443	0.562	0.40 - 0.78	0.0007
PSA (ng/dl)	1	1 - 1.001	0.0361	1.001	1.001 - 1.001	0
tALP (U/I)	1.001	1 - 1.001	0.0007	1.001	1.001 - 1.002	0
Hemoglobin (g/dl)	0.771	0.69 - 0.86	0	0.706	0.63 - 0.78	0
Neutrophils count	1.117	1.02 - 1.22	0.0168	1.118	1.02 - 1.22	0.0125
ECOG PS	1.454	1.17 - 1.80	0.0007	1.664	1.35 - 2.04	0

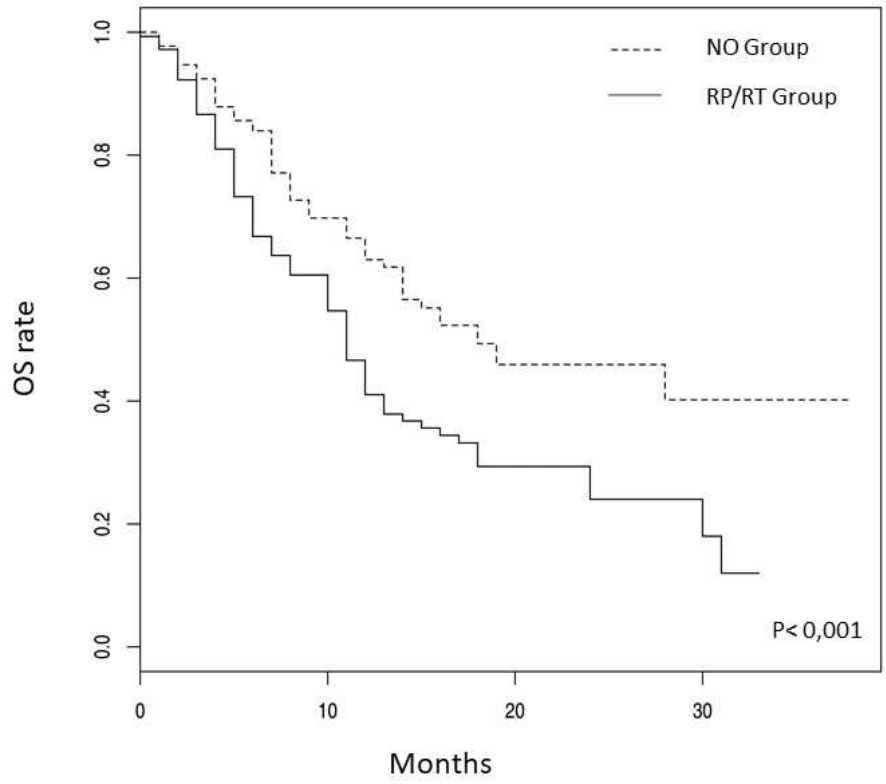
RP: radical prostatectomy; EBRT = external beam radiotherapy; PSA= Prostate-Specific Antigen; tALP = total alkaline phosphatase; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; CI: Confidence interval

Figure legends

Fig 1. Kaplan-Meyer Analysis shown the RP/EBRT and the NO Groups. The curve underlines the clear advantage in the overall survival of the RP/EBRT Group against the NO Group.



Kaplan-Meyer Analysis shown the RP/RT and the NO Groups. The curve underlines the clear advantage in the overall survival of the RP/RT Group against the NO Group.



Number at risk

NO GROUP

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
0	142	1	0.993	0.00702	0.9793	1.000
1	141	3	0.972	0.01388	0.9450	0.999
2	138	7	0.923	0.02243	0.8796	0.968
3	131	8	0.866	0.02857	0.8120	0.924
4	123	8	0.810	0.03293	0.7478	0.877

5	115	11	0.732	0.03715	0.6631	0.809
6	102	9	0.668	0.03963	0.5944	0.750
7	86	4	0.637	0.04072	0.5617	0.722
8	80	4	0.605	0.04168	0.5285	0.692
10	73	7	0.547	0.04306	0.4687	0.638
11	61	9	0.466	0.04432	0.3869	0.562
12	50	6	0.410	0.04450	0.3317	0.507
13	39	3	0.379	0.04465	0.3006	0.477
14	34	1	0.368	0.04470	0.2896	0.466
15	32	1	0.356	0.04476	0.2783	0.456
16	30	1	0.344	0.04481	0.2667	0.444
17	28	1	0.332	0.04487	0.2547	0.433
18	26	3	0.294	0.04481	0.2177	0.396
24	11	2	0.240	0.05010	0.1596	0.362
30	4	1	0.180	0.06416	0.0896	0.362
31	3	1	0.120	0.06507	0.0415	0.347

RP/RT GROUP

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
1	132	3	0.977	0.0130	0.952	1.000
2	129	4	0.947	0.0195	0.910	0.986
3	125	3	0.924	0.0230	0.880	0.971
4	122	6	0.879	0.0284	0.825	0.936
5	116	3	0.856	0.0306	0.798	0.918
6	104	2	0.840	0.0321	0.779	0.905

7	98	8	0.771	0.0375	0.701	0.848
8	87	5	0.727	0.0403	0.652	0.810
9	75	3	0.698	0.0420	0.620	0.785
11	64	3	0.665	0.0441	0.584	0.757
12	57	3	0.630	0.0462	0.546	0.727
13	52	1	0.618	0.0468	0.533	0.717
14	47	4	0.565	0.0497	0.476	0.672
15	41	1	0.551	0.0503	0.461	0.660
16	39	2	0.523	0.0516	0.431	0.635
18	35	2	0.493	0.0528	0.400	0.608
19	29	2	0.459	0.0544	0.364	0.579
28	8	1	0.402	0.0717	0.283	0.570

Clinical Practice Points

• At present, it has never been reported the significance and pre-therapeutic prognostic value of previous primary radical treatment in patients treated with 223-Ra therapy

• Our data showed an estimated median survival of 18 months and 11 months ($p < 0.001$) for patients previously treated with Radical Prostatectomy and/or Ablative Radiotherapy Group compared with no prior primary treatment Group, with an advantage of prostate primary ablative treatment

• Cytoreductive prostatectomy could have the potential to enhance mCRPC disease control, further in-depth studies and randomized controlled trials are necessary to a more clear definition of cytoreductive prostatectomy benefits in mCRPC patients submitted to Ra-223 therapy.