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Impact of Prior Radical Prostatectomy on Response to 177 PSMA-Lutetium Therapy and Survival Outcomes in Metastatic Castration-Resistant Prostate Cancer

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Article

Keywords: Radical prostatectomy (PR), Lutetium PSMA (LuPSMA)

Posted Date: October 7th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11098188/v1

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Additional Declarations: There is **NO** conflict of interest to disclose.

Abstract

Background:

Radical prostatectomy (RP) remains a cornerstone treatment for patients with localized prostate cancer. Previous studies have suggested that prior RP may impact clonal evolution of metastatic disease and response to subsequent systemic therapies. In this study, we sought to investigate whether a history of prior RP is associated with treatment response and survival outcomes in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with ^{177}Lu-PSMA.

Methods:

In a single-institution retrospective study, we identified 260 patients who underwent 177Lu-PSMA for mCRPC. Patients were categorized based on the history of prior PR into two groups; Group A (n=147) included patients with prior PR, and Group B (n=113) included patients with intact prostate. The primary outcome was prostate-specific antigen (PSA) response, defined as a ≥50% decline from baseline (PSA50). Overall survival (OS) was evaluated as a secondary outcome. Univariable and multivariable regression analyses were performed to identify factors associated with PSA50 and OS.

Results: Among 260 patients, PSA50 was achieved in 55.1% of patients with prior RP compared with 34.5% of those with an intact prostate. On multivariable logistic regression, prior RP remained independently associated with greater odds of achieving PSA50 (OR 2.1, 95% CI 1.09–4.1; p=0.03), whereas de novo metastatic disease was not independently associated with PSA50 (OR 0.97, 95% CI 0.44–2.15; p=0.9). Prior RP was also associated with improved OS on multivariable Cox regression (HR 0.60, 95% CI 0.4–0.8; p=0.008).

Conclusion:

In our experience, Prior RP was independently associated with improved PSA response and OS among patients with mCRPC treated with ^{177}Lu-PSMA. These findings suggest that prior treatment of the primary tumor may be associated with subsequent response to PSMA-targeted radioligand therapy, although the underlying mechanisms and potential influence of treatment selection and disease biology warrant further investigation.

Introduction

Prostate cancer is one of the most prevalent diagnosed solid cancers in men worldwide and represents the second leading cause of cancer related deaths in this population (1). Treatment of localized prostate cancer with radical prostatectomy and or radiation therapy may provide curative benefits (2). However, a proportion of patients, particularly those with high-risk disease, experience disease recurrence and develop metastatic hormone-sensitive prostate cancer (HSPC), which can ultimately progress to metastatic castrate resistance prostate cancer (mCRPC) (1) (3). The treatment landscape for mCRPC has evolved substantially over the past decade and currently includes several life-prolonging therapies,

including chemotherapy, androgen deprivation therapy, poly (ADP ribose) polymerase (PARP) inhibitors, talazoparib, niraparib and radionuclide agents including Ra-223 and Lutetium-177 PSMA (4). This expanding treatment landscape allows for indivulaized treatment based on disease characteristics, prior therapies, molecular features, treatment-related toxicities, and patient tolerance (1). However, the optimal sequencing of these therapies to maximize survival while maintaining quality of life is under active investigation and continues to evolve (3, 5).

Lutetium-^{177} PSMA is PSMA dependent radioligand therapy; approved by the US Food and Drug Administration in March 2022, initially for patients with mCRPC in the setting of post-chemotherapy as well as 2nd Generation hormone therapy (6). ^{177}Lu-PSMA delivers beta-emitting radiation directly to PSMA-expressing tumor cells, enabling targeted cytotoxicity. Despite the growing use of ^{177}Lu-PSMA since its approval, factors that predict response and survival outcomes remain incompletely defined. Treatment response is likely influenced by multiple variables, including tumor burden, disease distribution, prior systemic therapies, molecular characteristics, and patient-related factors (7) (8). An emerging area of interest is the potential long-term biological impact of prior local treatment of the primary tumor on the response to subsequent therapies.

Emerging evidence suggests that local tumor control with radical prostatectomy and/or radiation therapy may influence disease progression and long-term outcomes in metastatic prostate cancer, by altering surrounding microenvironment, limiting the release of harmful factors, and hindering further tumor progression (9).

In addition to the well-established role of radical prostatectomy in localized prostate cancer, its potential utility in the metastatic setting has gained increasing interest in recent years. Contemporary data have suggested that removal of the primary tumor in the metastatic setting may influence long-term outcomes (9–11). The primary tumor has been hypothesized to serve as a source of continued metastatic seeding and tumor heterogeneity (12). Therefore, its removal at earlier stages of disease may alter the subsequent trajectory of metastatic disease and potentially modulate responsiveness to later-line systemic therapies. Additionally, in the context of radioligand therapy, the intact prostate gland, being a large PSMA-avid structure, may act as a "tumor sink," sequestering a share of the administered radioligand and thereby reducing delivery to metastatic sites. Indeed, the tumor sink effect has been shown to be present in patients receiving ^{177}Lu-PSMA therapy, with higher total lesional PSMA burden correlating with reduced uptake in other tissue. (13)

In this study, we sought to evaluate the association between prior radical prostatectomy and treatment response, as measured by prostate-specific antigen (PSA) decline, as well as overall survival in patients with mCRPC treated with ^{177}Lu-PSMA therapy.

Methods

2 – 1 Patient Population and Selection:

The study was approved by the Institutional Review Board. Using the Mayo Clinic advanced prostate cancer registry, we identified 260 patients with metastatic castration-resistant prostate cancer (mCRPC) who received ^{177}Lu-PSMA therapy between 2018 and 2025, comprising a total of 1,245 administered treatment cycles. Patients were excluded if PSMA PET/CT demonstrated local recurrence prior to PSMA-Lu therapy or if the pretreatment prostate-specific antigen (PSA) level was undetectable (< 0.1 ng/mL). Patients were categorized into two groups according to prior treatment of the primary tumor: patients who had previously undergone RP (Group A) and patients with an intact prostate (Group B). All patients had complete pretreatment laboratory panels, pre-treatment PSA, and post treatment PSA available. Castration-resistant prostate cancer was defined by disease progression in the setting of castrate testosterone levels (< 50 ng/dL). A favorable biochemical response to ^{177}Lu-PSMA was defined as a ≥ 50% decline in PSA from baseline (PSA50).

2–2 Study Objectives:

The Primary objective was to investigate the impact of prior radical prostatectomy on PSA response rate after ^{177}Lu-PSMA in patients with metastatic castrate resistant prostate cancer.

The secondary objective was to assess the impact of prior radical prostatectomy on overall survival (OS). Additionally, we aimed to identify clinical factors associated with PSA response (PSA50) and OS.

2–3 Statistical Analysis:

Categorical variables were summarized as frequencies and percentages, and continuous variables as median with interquartile range (IQR). Normality of continuous variables was assessed using the Shapiro Wilk and Anderson Darling tests. For non-normally distributed variables, group differences were assessed using the Wilcoxon rank-sum test or the Kruskal Wallis test. Categorical variables were compared using the Chi-square test.

Univariate and multivariate logistic regression analyses were conducted to identify predictors of PSA50 response. Logistic regression results are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI) and p-values.

Overall survival (OS) was defined as the interval from initiation of Lutetium therapy to death or last follow-up. Factor associated with OS survival were evaluated using univariable and multivariable Cox proportional hazards regression, with results expressed as hazard ratios (HRs) and 95% confidenece interval (CIs). Concurrently, OS was characterized by prior RP status using Kaplan-Meier estimates. And survival distributions were compared via log-rank testAll statistical analyses were performed using JMP Pro version 14.1.0 (SAS Institute, Cary, NC).

The results

3 – 1 Patients’ Baseline Characteristics:

A total of 260 patients treated with Lu-PSMA were included, of whom 147 (56.2%) had undergone prior RP and 113 (43.9%) had an intact prostate at the time of treatment.

Patients with prior RP were younger at initial prostate cancer diagnosis and had lower PSA levels at diagnosis compared with patients with an intact prostate. Differences were also observed in Gleason grade, prior prostate-directed radiation therapy, and presence of bone metastases before ^{177}Lu-PSMA therapy. In contrast, age at initiation of ^{177}Lu-PSMA, pretreatment PSA, presence of nodal metastases, and presence of visceral metastases were similar between groups (Table 1). Baseline laboratory parameters were generally comparable, although hemoglobin was higher among patients with prior RP (Table 2).

Table 1
summarizes baseline patient characteristics

Patients' characteristics (260)	**Group A "Prior radical prostatectomy" (n = 147)**	**Group B "Intact prostate" (n = 113)**	**P value**
Age Dx, median (IQR)	**59 (55–64)**	**68 (61.5–73)**	**< 0.0001**
PSA Dx, median (IQR)	**7.7 (4.6–14.5)**	**24 (9–98)**	**< 0.0001**
Gleason group			
Gleason Group ≤ 7	**72 (50.7%)**	**31 (31.6%)**	**0.003**
Gleason Group > 7	**70 (49.3%)**	**67 (67.7%)**	
Unknown	**5 (3.4%)**	**15 (13.3%)**	
Prior treatments(n)			
Radiation to prostate/prostate bed(fossa)	**119 (80.95%)**	**72 (63.72%)**	**0.002**
Chemotherapy			**0.67**
Chemotherapy cycles ≤ 6	**103 (71.03%)**	**83 (73.45%)**	
Chemotherapy cycles ≥ 7	**42 (28.97%)**	**30 (26.55%)**	
Age Tx median (IQR)	**74.6 (68 (67.95–80.76)**	**71.5 (67.66–77.01)**	**0.12**
Pre Lu PSA, median (IQR)	**15.1 (2.75–134.5)**	**9.8 (2.1–52.4)**	**0.08**
Disease distribution before Lu			
Nodal metastases	**88 (59.86%)**	**59(52.21%)**	**0.22**
Bone metastases	**123 (83.67%)**	**107 (94.69%)**	**0.004**
Visceral metastases	**30 (20.41%)**	**22 (19.47%)**	**0.9**
Lu Cycles, median (IQR)	**5** (3–6)	**6** (4–6)	**0.003**
PSA 50 (Yes)	**81 (55.1%)**	**39 (34.5%)**	**0.0009**
Interval between surgery-Lu, median (IQR) (months)	**130.4 (92.6-181.29)**	**--**	**--**

Table 2
summarizes Baseline laboratory parameters

Baseline laboratory parameters	Prior radical prostatectomy (146)	Intact prostate (114)	P value
Hemoglobin	12.5 (11-13.3)	11.9 (10.8–12.7)	0.02
Alkaline phosphates	94 (67-123.5)	99 (69.25-157.75)	0.3
Albumin	4.1 (4-4.3)	4.1 (3.8–4.3)	0.1

3 – 2 Impact of Prior Radical Prostatectomy on PSA Response (PSA 50 response):

In our study cohort, PSA50 was achieved in 81 of 147 patients (55.1%) with prior RP compared with 39 of 113 patients (34.5%) with an intact prostate (p = 0.0009). On univariable logistic regression, prior RP was associated with greater odds of achieving PSA50 (OR 2.3, 95% CI 1.4–4.9; p = 0.0009). Also, nodal metastases were associated with greater odds of PSA50 compared to other sites of metastatic disease (OR 1.79, 95% CI 1.09–2.96; p = 0.02). On the other hand, de novo metastatic disease (OR 0.50, 95% CI 0.27–0.91; p = 0.02) and the presence of bone metastases (OR 0.32, 95% CI 0.13–0.71; p = 0.005) were associated with lower odds of PSA50.

On multivariable analysis, prior RP remained independently associated with greater odds of achieving PSA50 (OR 2.1, 95% CI 1.09–4.1; p = 0.03). In contrast, de novo metastatic presentation was no longer associated with PSA50 after adjustment (OR 0.97, 95% CI 0.44–2.15; p = 0.9). Neither nodal nor bone metastases remained statistically significant in the multivariable model (Table 3).

3 – 2 Overall survival:

Kaplan–Meier survival analysis demonstrated improved OS among patients with prior RP compared with those with an intact prostate (Fig. 3).

Consistent with this finding, prior RP was associated with a lower hazard of death on univariable Cox regression (HR 0.54, 95% CI 0.4–0.7; p = 0.0001). In contrast, de novo metastatic presentation, higher Gleason grade, bone metastases, visceral metastases, and higher pretreatment PSA were associated with worse OS on univariable analysis.

After multivariable adjustment, prior RP remained independently associated with improved OS (HR 0.60, 95% CI 0.4–0.8; p = 0.003). On the other hand, bone metastases (HR 2.2, 95% CI 1.3–3.9; p = 0.002), visceral metastases (HR 1.7, 95% CI 1.6–2.4; p = 0.009), and higher pretreatment PSA were independently associated with worse OS. Of note, neither de novo metastatic presentation (HR 0.9, 95%

CI 0.6–1.5; p = 0.6) nor Gleason grade (HR 1.4, 95% CI 0.99–1.9; p = 0.08) were independently associated with impact on OS (Table 4).

Discussion

In this single-institution retrospective study of 260 patients with mCRPC treated with ^{177}Lu-PSMA, prior RP was independently associated with both improved PSA response and OS. Patients with prior RP had approximately twofold greater odds of achieving PSA50 compared with patients with an intact prostate. Additionally, prior RP was also independently associated with a 40% lower hazard of death. Importantly, although de novo metastatic presentation was associated with both PSA response and OS on univariable analyses, these associations were no longer significant after multivariable adjustment.

The biological relationship between the primary tumor and subsequent metastatic disease is complex. Traditionally, the primary treatment focus in patients with metastatic disease is on systemic therapy, due to theory that subsequent progression is predominantly driven by established metastatic clones (14). However, increasing evidence suggests that the primary tumor may remain biologically relevant even after metastatic dissemination. Tzelepi et al. demonstrated the persistence of biologically active and treatment-resistant tumor within the prostate despite prolonged androgen deprivation and docetaxel therapy (15). Furthermore, Heidenreich et al. demonstrated in a multicenter study the feasibility of cytoreductive radical prostatectomy (cRP) in selected patients with metastatic prostate cancer, with favorable biochemical progression-free, overall, and clinical relapse-free survival outcomes (16). Additionally, genomic studies have demonstrated complex evolutionary relationships between primary and metastatic prostate cancer, supporting the potential for continued clonal evolution and metastatic seeding (12). These observations provide a biological rationale by which removal of the primary tumor earlier in the disease course could potentially alter the subsequent evolutionary trajectory of metastatic disease. Given the promising findings of prior studies evaluating local treatment of the primary tumor in selected patients with metastatic prostate cancer, this concept continues to be evaluated in prospective fashion (9, 10) (11, 16–18)

Our findings extend the question beyond the role of RP as a cytoreductive intervention in patients with established metastatic disease, and examined whether a history of RP performed substantially earlier in the localized disease course could influence response to subsequent therapy with 177 Lu-PSMA in mCRPC. The median interval between RP and 177Lu-PSMA in our cohort exceeded 10 years, making a direct short-term treatment effect of surgery unlikely. Instead, the observed association may reflect longer-term differences in disease evolution after removal of the primary tumor. One hypothesis is that eliminating the primary tumor may reduce a potential reservoir of heterogeneous or treatment-resistant clones and thereby influence the phenotype of metastatic disease that emerges years later. Conversely, prior RP may simply identify a population with inherently different disease biology, treatment trajectories, or other favorable characteristics that are incompletely captured by available clinical variables. The present study cannot distinguish between these possibilities, but the persistence of the association after multivariable adjustment suggests that the observation warrants further investigation.

A second plausible explanation relates specifically to the pharmacokinetics of PSMA-targeted radioligand therapy. The “tumor sink” effect describes the relationship between PSMA-expressing tumor burden and radiopharmaceutical biodistribution, whereby extensive PSMA-avid disease can sequester circulating radioligand and alter its uptake in other tissues (13) (19, 20). Prior 177Lu-PSMA studies have demonstrated inverse relationships between total tumor burden and uptake or absorbed dose in normal organs, supporting changes in radioligand distribution according to PSMA-expressing disease burden. While the contribution of an intact primary prostate to this phenomenon is unknown, it raises the possibility that differences in total PSMA-expressing tissue between patients with and without prior RP could influence radioligand biodistribution and, potentially, treatment response.

Limited prior evidence has examined the relationship between previous prostatectomy and response to ^{177}Lu-PSMA. Kind et al. did not identify prior prostatectomy as a significant predictor of PSA response in patients receiving ^{177}Lu-PSMA (21). However, differences in cohort size, patient selection, disease characteristics, and treatment exposure may contribute to the discordant findings.

The association between RP and outcomes following ^{177}Lu-PSMA was not limited to PSA50, but also extended to OS. In our cohort, prior RP was associated with improved OS on both univariable and multivariable analyses, with a 40% lower adjusted hazard of death. While patients who underwent RP earlier in their disease course were likely selected for surgery and differed from patients with an intact prostate in several baseline characteristics, the association between prior RP and both PSA50 response and OS remained statistically significant after multivariable adjustment for measured differences, including de novo metastatic presentation.

Beyond prior RP, our survival findings were consistent with established features of advanced prostate cancer biology. Bone metastases, visceral metastases, and higher pretreatment PSA were independently associated with worse OS. The adverse prognostic significance of visceral disease among patients receiving ^{177}Lu-PSMA has been demonstrated previously in several studies, including systematic analyses and contemporary PSMA PET-based studies(22, 23). Similarly, greater osseous metastatic disease burden has been associated with inferior survival following PSMA-targeted radioligand therapy (24, 25). These observations reinforce the importance of metastatic distribution and overall disease burden in determining outcomes after ^{177}Lu-PSMA and provide clinical consistency with our survival findings.

The current study has several strengths. To our knowledge, this is one of the largest studies specifically evaluating the association between prior RP and subsequent outcomes following ^{177}Lu-PSMA therapy. The sample size (n = 260 patients) and long term follow up provided sufficient power to evaluate both biochemical response and survival outcomes and to perform multivariable analyses accounting for important clinical and disease characteristics. Importantly, de novo metastatic presentation was evaluated separately from prostatectomy status, allowing us to examine whether the observed association with prior RP persisted independently of metastatic presentation. The concordant

associations between prior RP and both PSA50 response and OS further strengthen the internal consistency of the observed findings.

Nevertheless, several limitations should be considered. The retrospective design introduces the potential for selection bias and residual confounding, which may influence the observed associations. Our findings should be interpreted cautiously as we did not evaluate quantitative PSMA uptake within the primary prostate, whole-body PSMA tumor volume, or tumor-specific dosimetry. Additionally, patients with PSMA PET-detected local recurrence before ^{177}Lu-PSMA were excluded. The observed association provides a rationale for future studies incorporating quantitative PSMA PET parameters and post-treatment dosimetry to determine whether prior local treatment is associated with measurable differences in ^{177}Lu-PSMA biodistribution. Such analyses may help distinguish a pharmacokinetic explanation from differences in underlying tumor biology. Additionally, the absence of toxicity and quality-of-life outcomes further limits the interpretation of the clinical impact of these findings. Despite these limitations, this study provides clinically relevant insights into treatment patterns and outcomes and may help inform future prospective investigations and individualized therapeutic strategies.

Conclusion

Our findings demonstrate that in those patients studied here with metastatic castration-resistant prostate cancer (mCRPC) who underwent prior radical prostatectomy (RP), better PSA response and survival outcomes following ^{177}Lu-PSMA therapy were exhibited as compared with those with an intact prostate. While our study does not evaluate the role of RP as a primary treatment in the metastatic setting, the observed associations raise the possibility that prior local tumor control may influence subsequent systemic treatment responsiveness, potentially through alterations in disease evolution or PSMA-targeted radioligand biodistribution. Alternatively, prior RP may represent a marker of distinct underlying disease biology rather than a direct mediator of improved treatment response. Collectively, these findings underscore the need to better understand how the primary tumor and its prior treatment may shape disease behavior and treatment response later in the disease course. Further prospective studies, larger retrospective cohorts, and biologic correlative studies incorporating quantitative PSMA PET imaging, dosimetry, and molecular profiling are warranted to validate these findings and elucidate their underlying mechanisms.

Declarations

Funding: No extramural funding

Financial Disclosures: None

Ethics approval and consent to participate: the study was approved by the institutional review board, and the requirement for informed consent was waived due to the retrospective nature of the study.

Consent for publication: Not applicable.

Availability of data and materials: Data is available from the corresponding author upon request.

Competing interests: the authors have no conflicts of interest to declare.

Funding: This research did not receive any specific funding.

Acknowledgements: Not applicable.

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Figures

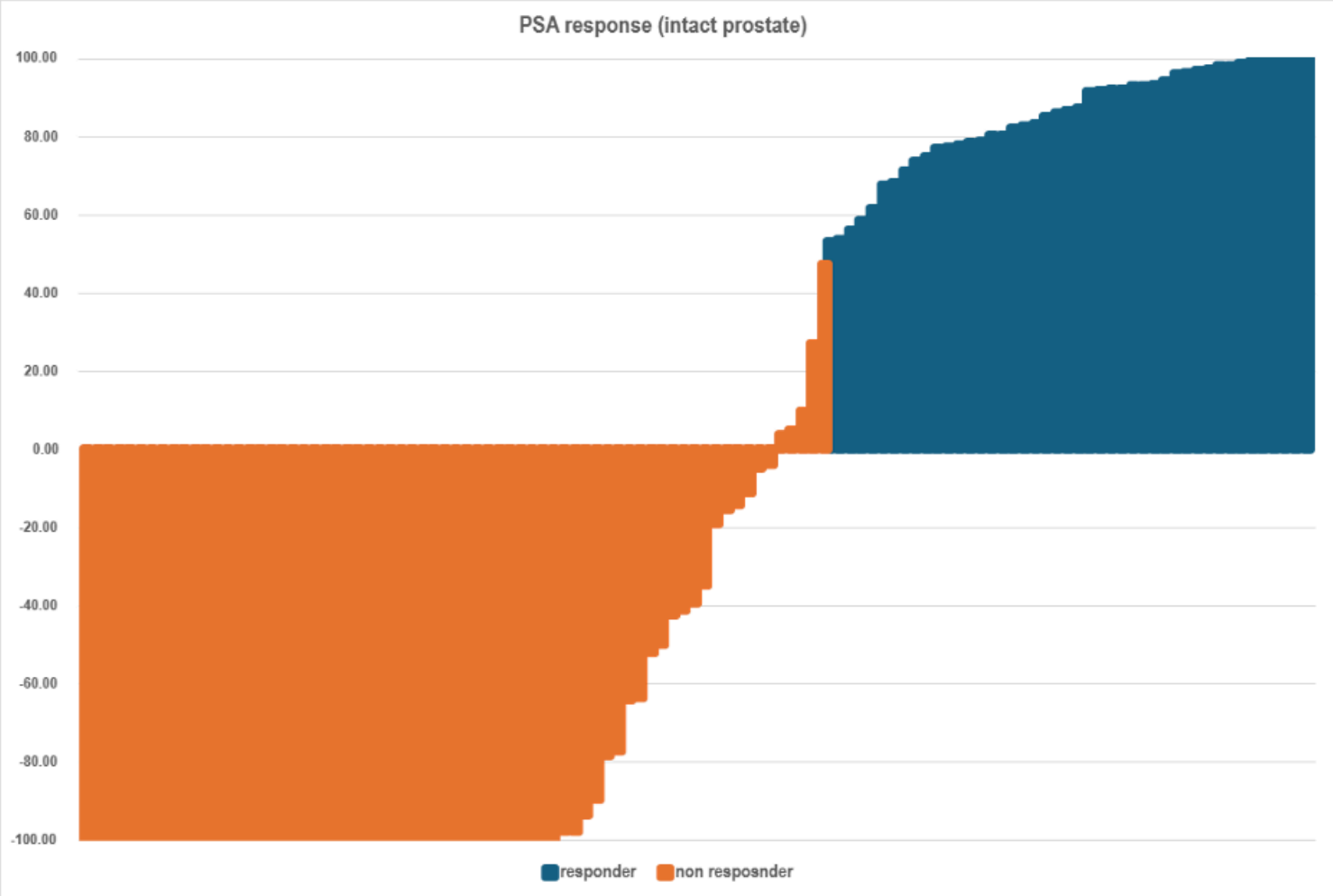

Figure 1

Waterfall plot illustrating PSA 50 responses in patients without prior radical prostatectomy (Group B)



Figure 2

Waterfall plot illustrating PSA 50 responses in patients with prior radical prostatectomy (Group A)

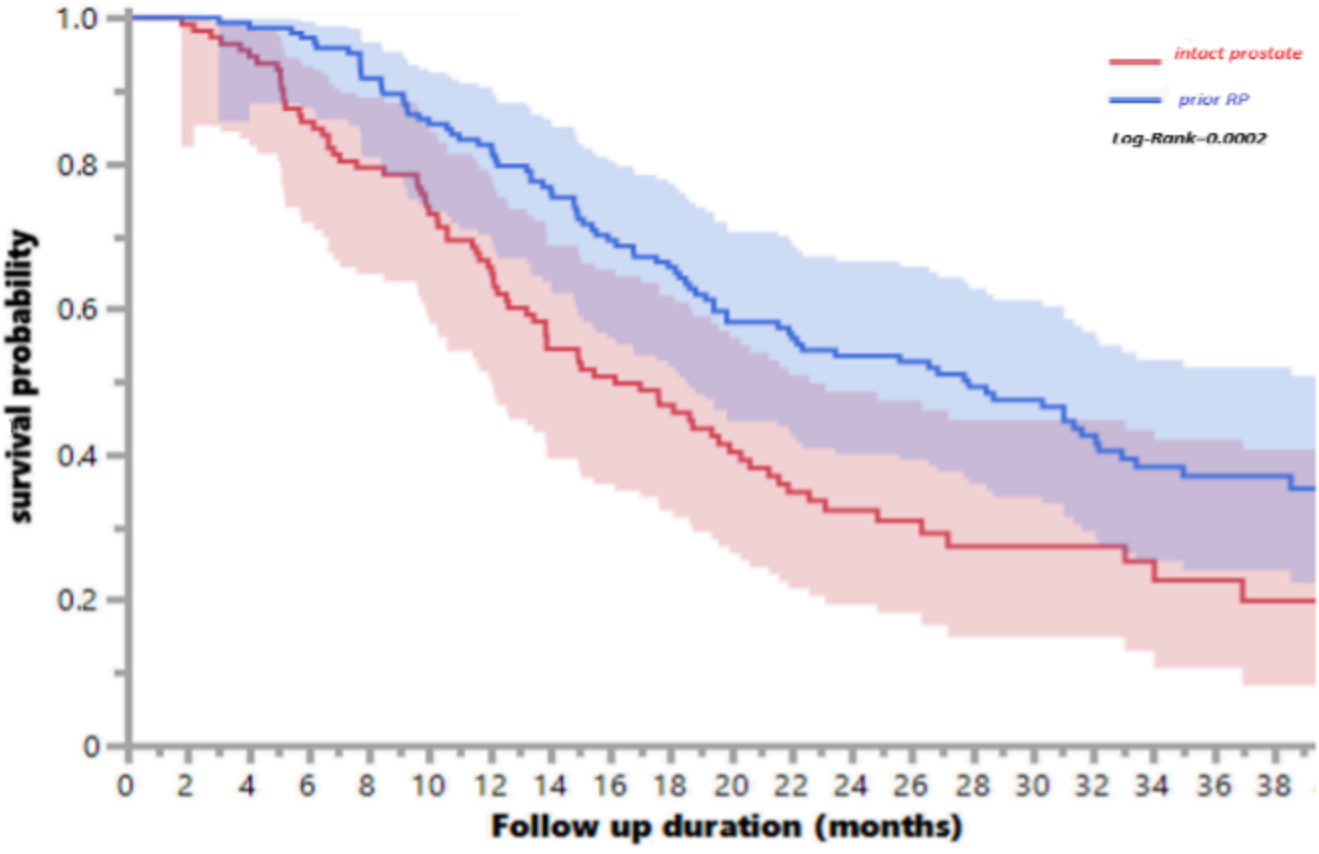

Figure 3

Kaplan–Meier curve for overall survival (OS) stratified by prior radical prostatectomy. Blue line: Group A, patients who underwent surgery; red line: Group B, patients with an intact prostate