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van Mossel, S., van der Velden, K. J. M., Kleiburg, F., Bosch, D., van der Hulle, T., Koffijberg, H., Kuppen, M. C. P., van Oort, I. M., de Geus-Oei, L. F., & More Authors (2026). Laying the groundwork for future health economic evaluation of [18F]PSMA PET/CT in guiding treatment decisions for metastatic castration-resistant prostate cancer patients. *European Journal of Radiology*, 205, Article 113213. <https://doi.org/10.1016/j.ejrad.2026.113213>

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Laying the groundwork for future health economic evaluation of [¹⁸F]PSMA PET/CT in guiding treatment decisions for metastatic castration-resistant prostate cancer patients

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ARTICLE INFO

Keywords:

Metastatic castration-resistant prostate cancer
PSMA PET/CT
Health economic implications
Prostate-specific membrane antigen
Prostate-specific antigen
Hormone therapy
Chemotherapy

ABSTRACT

Introduction: Recent study results of our group demonstrated that [¹⁸F]PSMA-1007 (PSMA) PET/CT outperforms PSA response in predicting overall survival in metastatic castration-resistant prostate cancer (mCRPC) patients. However, its health economic implications for guiding treatment decisions remained unclear. This post-hoc analysis explores the potential impact of PSMA PET/CT on treatment decisions and patient-level costs, highlighting its relevance for future health economic evaluations.

Methods: Time from therapy initiation to therapy discontinuation and the reasons for discontinuation were studied. A swimmer plot visualised individual patient timelines and censored events. Hospital-perspective cost estimates were determined per patient.

Results: Among 60 patients, 53 discontinued therapy: 28 due to disease progression, 7 due to toxicity, and 18 after completing chemotherapy cycles. Seven patients remained on-treatment at the time of analysis. Costs varied by treatment duration and medication: monthly hospital costs were €1,826 for abiraterone, €3,652 for enzalutamide and €3,190 for chemotherapy. The cost of PSMA PET/CT was estimated at €1,286 and requires contextual evaluation within rapidly changing treatment pathways.

Discussion: PSMA PET/CT helps inform treatment decisions, but its cost is considerable relative to the cost of conventional therapy. Whether the use of PSMA PET/CT translates into avoidance of ineffective therapy or in therapy-related cost savings should be studied in formal cost-effectiveness analysis. Cost savings are less evident where conventional treatment costs are low compared with novel (but costly) targeted therapy options. Standardised imaging protocols, multicentre data and population registries are essential to strengthen the evidence base and enable future health economic evaluation.

1. Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is characterised by disease progression despite androgen deprivation therapy. mCRPC treatment consists of life-prolonging drugs, including taxane-

based chemotherapy, mainly docetaxel [1,2] and cabazitaxel [3,4], androgen receptor pathway inhibitors (ARPIs), mainly enzalutamide [5,6] and abiraterone [7,8], and novel targeted radionuclide therapies including radium-223 [9] and [177Lu]Lu-PSMA-617 [10–13]. These therapies have proven to delay disease progression, increase quality-of-

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life (QoL) and prolong overall survival (OS) in both a trial setting and a national Dutch population [14]. In the real-world setting, serum prostate-specific antigen (PSA) responses vary hugely due to the heterogeneity of disease and tumour de-differentiation [15]. Recent study results of our group at Leiden University Medical Centre (LUMC) demonstrated that using [^{18}F]PSMA-1007 (PSMA) PET/CT for therapy response monitoring at pre-defined timepoints is superior to PSA response to predict OS in mCRPC patients [16]. However, it remained unclear whether PSMA PET/CT is also a cost-effective strategy for guiding treatment decisions.

Table 1 provides information on the median time on-treatment, time to PSA progression, radiological progression-free survival (based on a combinational use of bone scintigraphy and contrast-enhanced CT), and OS as published in prominent phase 3 studies, evaluating ARPIs and docetaxel in both mCRPC treatment naïve and previously treated mCRPC patients. The median time on treatment ranged widely from 7.4 to 28.0 months, while the median time to PSA progression and the median radiological progression-free survival ranged between 8.3 to 11.2 months and 5.6 to 16.5 months, respectively. Novel use of PSMA PET/CT has a superior diagnostic sensitivity and specificity to detect pelvic nodal or distant metastases than contrast-enhanced CT [17,18], and to detect previously unknown visceral metastases [19]. Therefore, consensus exists that PSMA PET/CT may support early discontinuation of therapy and timely switching to alternative more likely effective treatment options [20,21]. This may reduce unnecessary therapy-related toxicities and costs, while also allowing for earlier initiation of alternative (targeted) therapies that might be more effective.

This short communication aims (i) to explore the potential impact of using PSMA PET/CT at predefined timepoints on treatment decisions, and (ii) to provide a descriptive overview of individual patient care pathway costs. We discuss how this information provides a necessary basis for future health economic evaluations of PSMA PET/CT in the mCRPC setting. This paper should be read as a post-hoc analysis of our original work [16]. It should, therefore, not be read as a formal cost-effectiveness analysis, but it provides valuable guidance and relevant parameters for future health economic evaluation efforts.

2. Methods

Retrospectively gathered individual patient data of 60 mCRPC patients, who underwent PSMA PET/CT at baseline and for response assessment, and treated at LUMC, The Netherlands, from December 2019 to December 2023, were included for this analysis. A detailed description of the patient population and PSMA PET/CT scan procedures is published in our previous work [16]. In summary, therapy with ARPI was provided in 31 patients and 29 patients received taxane-based chemotherapy. The median time between baseline PSMA PET/CT and therapy initiation was 11 days (interquartile range (IQR) 8–20 days). By study protocol, PSMA PET/CT for response assessment was performed either after three months of ARPI therapy (median 95 days, IQR 82–110 days), or three weeks (median 21 days, IQR 16–31 days) after completion of 3–8 (median 6) cycles of chemotherapy. At the time of analysis, 38 out of 60 patients were deceased and median OS was 16.5 months. Median follow-up was 26 months. PSMA PET/CT consensus statements on response assessment criteria in prostate cancer [22] were used to evaluate tumour responses and to categorise patients as progressive or non-progressive.

In this post-hoc analysis of our original work [16], the time to discontinuation of therapy starting from therapy initiation and reasons for discontinuation were studied (disease progression, major toxicity or maximum therapy cycles reached). A time-to-event analysis reflects how quickly patients discontinue therapy and allows inclusion of patients who have not yet discontinued therapy at the time of analysis (censored events). Disease progression was defined based on a composite assessment incorporating PSMA PET/CT findings, PSA test results, clinical deterioration and physician judgements. PSMA PET/CT could inform discontinuation decisions or confirm decisions if clinical deterioration or PSA progression prompted an earlier-than-scheduled scan. Discontinuation decisions should, therefore, not always be attributed solely to the PSMA PET/CT findings. Major therapy-related toxicities were described in our original work [16].

A swimmer plot tracks individual patients and visualises time to therapy discontinuation and censored events. For each patient, a cost estimation is provided from the hospital perspective. Table 2 presents the unit costs of standard therapies and diagnostic testing. The costs of

Table 1

Information on time on-treatment, time to PSA progression, rPFS and OS in prominent phase 3 studies. Studies differ in study population and reported time-to-event outcomes. Time-to-event data are provided in months. *Abbreviations:* CI, confidence interval. mCRPC, metastatic castration-resistant prostate cancer. PSA, prostate-specific antigen. OS, overall survival. rPFS, radiological progression-free survival.

Phase 3 trial	Study population	Median time on treatment	Median time to PSA progression (95 %-CI)	Median rPFS (95 %-CI)	Median OS (95 %-CI)
PREVAIL study ^a [6]	mCRPC treatment naïve patients (n = 872) receiving <i>enzalutamide</i> at a dose of 160 mg once daily	28.0	11.2 (not reported)	Not reached	32.4 (not reported)
AFFIRM study ^b [5]	mCRPC patients (n = 800) receiving <i>enzalutamide</i> at a dose of 160 mg once daily and previously being treated with one or two chemotherapy regimens	8.3	8.3 (5.8–8.3)	8.3 (8.2–9.4)	18.4 (17.3–not reached)
COU-AA-301 study ^c [7]	mCRPC patients (n = 797) receiving <i>abiraterone acetate</i> at a dose of 1000 mg once daily plus prednisone (5 mg twice daily) and previously being treated with one or two chemotherapy regimens	7.4	8.5 (8.3–11.1)	5.6 (5.6–6.5)	15.8 (14.8–17.0)
COU-AA-302 study ^d [8]	mCRPC treatment naïve patients (n = 546) receiving <i>abiraterone acetate</i> at a dose of 1000 mg once daily plus prednisone (5 mg twice daily)	25.2	11.1 (not reported)	16.5 (not reported)	Not reached
SWOG-99-16 study [1]	mCRPC patients (n = 770) receiving <i>docetaxel</i> and <i>estramustine</i> every three weeks (60 mg/m ²) with at most one prior systemic therapy permitted	Not reported	Not reported	6.3 (not reported)	17.5 (not reported)
TAX-327 study [2]	mCRPC patients (n = 1006) receiving 75 mg of <i>docetaxel</i> /m ² every three weeks, or 30 mg of <i>docetaxel</i> /m ² weekly for five of every six weeks	Not reported	Docetaxel every three weeks: 7.7 (7.1–8.6) Weekly docetaxel: 8.2 (6.3–11.5)	Not reported	Docetaxel every three weeks: 18.9 (17.0–21.2) Weekly docetaxel: 17.4 (15.7–19.0)

^a The study was stopped after a planned interim analysis at the time of 540 deaths (time to interim analysis was not reported).

^b The study was stopped after a planned interim analysis at the time of 520 deaths (time to interim analysis was not reported).

^c The study was unblinded before crossover from placebo to *abiraterone acetate* (after 775 of the prespecified 797 death events).

^d The study was unblinded before crossover from placebo to *abiraterone acetate* (after 333 of the prespecified 773 death events).

Table 2

Unit cost of various diagnostic testing, therapy with abiraterone, enzalutamide, docetaxel and cabazitaxel. All costs were based on Euro 2024 cost data. If needed, costs were adjusted to 2024 prices using the consumer price index from Statistics Netherlands.

Resource use	Reference price	Source
Abiraterone (500 mg tablet)	€ 30,00	[24]
Enzalutamide (40 mg tablet)	€ 30,00	[24]
Docetaxel (20 mg/ml FL 1 ml)	€ 70,00	[24]
Cabazitaxel (10 mg/ml FL 5 ml)	€ 2.500,00	[24]
[¹⁸ F]PSMA-1007 PET/CT (per procedure)	€ 1.286,00	[23]
Contrast-enhanced CT (per procedure)	€ 261,00	[23]
Bone scintigraphy (per procedure)	€ 307,00	[23]
Biochemical testing (per request) ^a	€22,91	[23]

^a This includes the testing of serum PSA level, alkaline phosphatase and hematologic evaluation

diagnostic testing were valued using tariffs issued by the Dutch Healthcare Authority [23]. Costs of medication were retrieved from the Dutch drug database [24]. Medication costs were based on the recommended dose as issued by the Dutch National Healthcare Institute [25]. All costs were based on Euro 2024 cost data. Costs were adjusted to 2024 prices using consumer price index from Statistics Netherlands [26]. All analyses were performed in R Statistical Software (version 4.5.0) [27].

3. Results

Fig. 1 records the time to discontinuation and the reason to discontinue therapy for each individual patient in the study cohort (n = 60). Reasons for treatment discontinuation were disease progression (28 out of 53 patients), therapy-related toxicities (7 out of 53 patients) and the maximum number of chemotherapy cycles reached (18 out of 53 patients). Notably, 7 patients remained on-treatment at the time of analysis and were censored.

In treatment-naïve mCRPC patients receiving enzalutamide or abiraterone (n = 27), the median time to treatment discontinuation was 11.8 months. In the group of patients who before received first-line mCRPC therapy with docetaxel (n = 4), it was only 5.0 months. Therapy was discontinued in 18 patients based on disease progression. Therapy was discontinued due to major toxicities in 6 patients.

In treatment-naïve mCRPC patients undergoing chemotherapy (n = 10), the median time to treatment discontinuation was 3.5 months. In the group of patients who before received first-line mCRPC therapy with abiraterone or enzalutamide (n = 19), it was 3.4 months. By study protocol [16], PSMA PET/CT was scheduled three weeks after completion of 6–8 chemotherapy cycles. However, in 10 patients, PSMA PET/CT was performed early (3–5 cycles) due to either PSA progression (n = 7) or clinical deterioration (n = 3), and chemotherapy was discontinued after confirming PSMA PET/CT results in all these patients.

For each individual patient, a cost estimation was provided from the hospital perspective. Costs varied substantially depending on type of

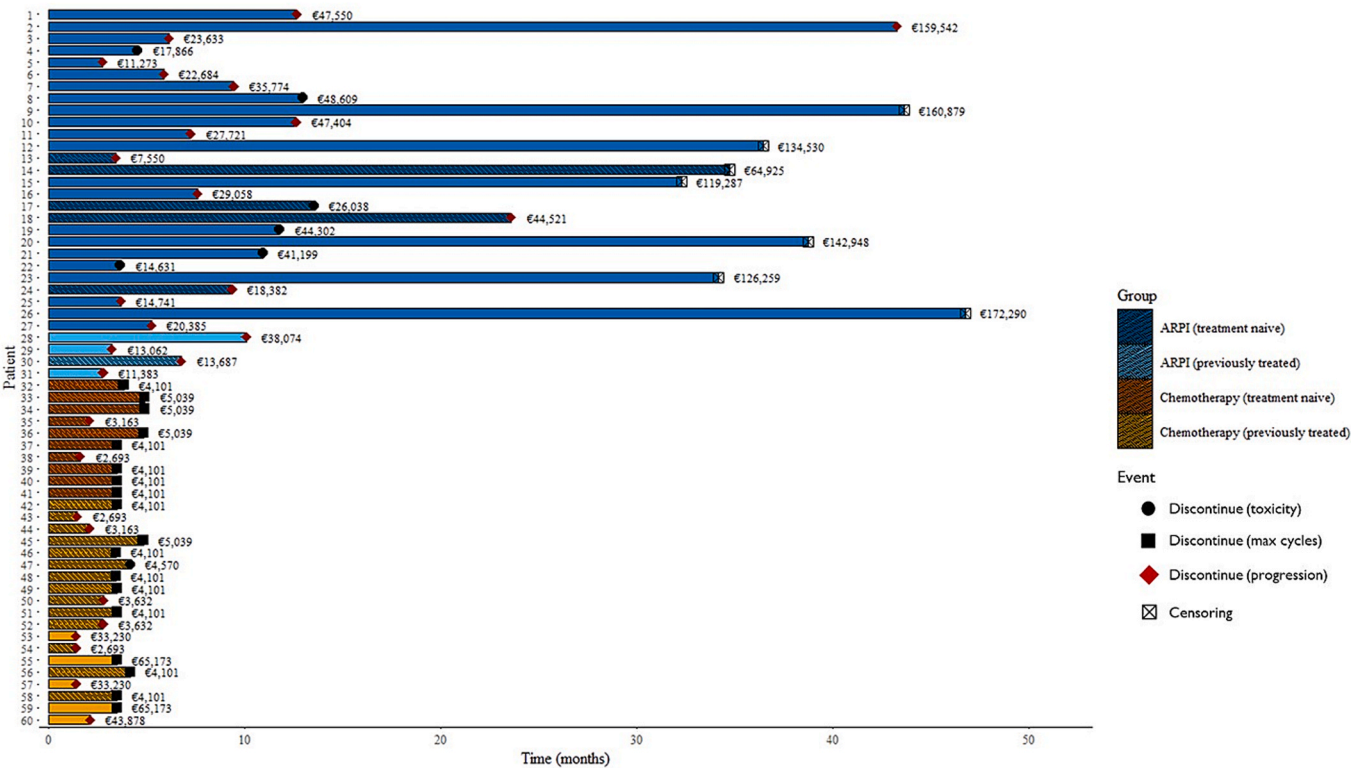


Fig. 1. Swimmer plot to track all individual patients in the single-centre study cohort. The swimmer plot represents a total study cohort of 60 mCRPC patients. The dark/light blue swimmer lanes represent mCRPC patients treated with ARPIs (n = 31). More specifically, the dark blue swimmer lanes represent first-line mCRPC therapy (n = 27), while the light blue swimmer lanes represent second-line mCRPC therapy (n = 4). Also, note that the striped dark/light blue swimmer lanes represent mCRPC patients treated with abiraterone (n = 6), while the solid dark/light blue swimmer lanes represent mCRPC patients treated with enzalutamide (n = 25). The red/orange swimmer lanes represent mCRPC patients treated with taxane-based chemotherapy (n = 29). More specifically, the red swimmer lanes represent first-line mCRPC therapy (n = 10), while the orange swimmer lanes represent second-line mCRPC therapy (n = 19). Also, notice that the striped red/orange swimmer lanes represent mCRPC patients treated with docetaxel (n = 24), while the solid red/orange swimmer lanes represent mCRPC patients treated with cabazitaxel (n = 5). Furthermore, all events are marked. Red diamonds for therapy discontinuation due to disease progression (n = 28). Black circles for therapy discontinuation due to therapy-related toxicities (n = 7). Black squares for therapy discontinuation after the maximum number of chemotherapy cycles reached (n = 18). Crosses for censoring (n = 7). Time-to-event data is depicted in months. **Abbreviations:** ARPI, androgen receptor pathway inhibitor. mCRPC, metastatic castration-resistant prostate cancer.

medication and time on-treatment. The expected monthly hospital medication costs per patient were €1,826 for abiraterone, €3,652 for enzalutamide and €3,190 for chemotherapy. In comparison, the cost of a PSMA PET/CT scan with Dutch reference tariff of €1,286 represents an expense that must be weighed within the rapidly changing treatment landscape.

4. Discussion

4.1. Main findings

This post-hoc analysis shows that PSMA PET/CT findings help guide or confirm therapy discontinuation decisions. PSA progression or clinical deterioration could occur and prompt imaging requests, meaning discontinuation was influenced by multiple clinical factors rather than PSMA PET/CT findings alone. In patients who were treated with abiraterone or enzalutamide and not censored, disease progression accounted for therapy stops in 18 out of 24 patients (i.e., the remaining 6 patients had major therapy-related toxicities). Similar observations were made in patients who were treated with taxane-based chemotherapies. Where early PSMA PET/CT was used at request to early PSA progression or clinical deterioration, PSMA PET/CT findings confirmed disease progression in all these patients. Our findings suggest that PSMA PET/CT frequently contributes to decisions on treatment discontinuation in mCRPC patients, alongside other clinically relevant factors and physician judgements.

4.2. Clinical and economic implications

From a health economic point of view, the value of PSMA PET/CT lies in its ability to potentially help improve treatment planning, avoid ineffective therapy and reduce downstream costs associated with disease progression and toxicities. Currently, the cost of PSMA PET/CT (Dutch tariff €1,286) is less than the monthly cost of pharmacotherapy with abiraterone, enzalutamide or docetaxel. However, in these rather low-cost conventional therapies, PSMA PET/CT still represents a considerable proportion of the monthly expenses. Within novel and high-cost therapies, such as the targeted radionuclide therapies radium-223 and [177Lu]Lu-PSMA-617, the cost of PSMA PET/CT is comparatively small. For these novel therapies, which are most commonly administered as a third-line therapy, the main consideration is whether PSMA PET/CT can meaningfully inform decisions at late disease stage. This reasoning includes evaluating whether alternative and potentially more effective therapy is still available and relevant. Therefore, consequences of using PSMA PET/CT should not be assessed based solely on its standalone costs, but rather in relation to its capacity to help improve treatment decisions and optimise resource allocation across costly and rapidly evolving therapeutic care pathways.

It is important to acknowledge that the economic profile of imaging with PSMA PET/CT is affected by the choice of radiopharmaceutical. Evidence comparing the tariffs of PSMA tracers remains [28,29], but available data suggest similar diagnostic performance for [¹⁸F]DCFPyL and [⁶⁸Ga]PSMA-11, while [¹⁸F]PSMA-1007 is associated with a slightly higher rate of equivocal findings. Additionally, pricing and reimbursement of PSMA tracers vary between countries. In the Netherlands, available data indicate comparable tariffs for [¹⁸F]PSMA-1007 and [⁶⁸Ga]PSMA-11, whereas cost structures may differ in other healthcare systems.

4.3. Study limitations

Certain limitations of this study should be considered when interpreting the findings. The relatively small sample size ($n = 60$) and single-centre study design limit external validity and generalisability of our findings. Cohort heterogeneity is introduced because of the inclusion of different systemic therapy strategies (both ARPIs and taxane-based

chemotherapies). They act through fundamentally different biological mechanisms, potentially affecting disease progression and clinical outcomes independently of imaging findings. Furthermore, this study provides a descriptive cost analysis. It does not include a comparative or formal cost-effectiveness analysis. As such, no conclusions can be drawn regarding the cost-effectiveness of PSMA PET/CT compared with conventional imaging in the mCRPC setting.

4.4. Future research and clinical practice

This post-hoc analysis was not designed to provide conclusive evidence on the cost-effectiveness of PSMA PET/CT in the mCRPC setting, but rather to offer preliminary descriptive data that can inform future formal analysis. Particularly, our findings highlight certain methodological considerations that should be addressed before a full health economic evaluation can be performed. It includes (i) a need for standardised imaging protocols, (ii) structured registry documentation, and (iii) multicentre data collection. The latter, we will explore these methodological considerations in more depth.

The therapeutic care pathway for mCRPC is rapidly changing, with increasing use of targeted therapies, including radium-223 [9] and [177Lu]Lu-PSMA-617 [10–13], and ongoing phase 2 and 3 trials (e.g., see [ClinicalTrials.gov](https://clinicaltrials.gov) studies NCT05204927, NCT04647526, NCT04343885, NCT03574571, NCT02194842), exploring novel sequencing and post-ARPI combination strategies. Moreover, several therapy options are increasingly being introduced earlier in the disease course as a treatment option for metastatic castration-sensitive prostate cancer patients [30], but upfront treatment decisions add complexity to interpreting the specific role and value of PSMA PET/CT in subsequent mCRPC management.

Clinical trials can benefit from multicentre study designs which consider variability in imaging practices and treatment procedures [31]. Further, incorporating standardised PET/CT protocols –consistent and transparent in radiopharmaceutical selection, scan timing and response assessment criteria– improve comparability across centres. Additionally, reporting the clinical rationale for imaging (i.e., reasons to scan) in a structured way enhances interpretability of imaging-guided treatment decisions. Reporting the decisions to continue or discontinue treatment can be complemented with the underlying clinical reasoning and, if relevant, a detailed description of therapy-related toxicity [32]. Improved reporting would contribute to a more in-depth understanding of treatment dynamics and the role of PSMA PET/CT therein. Stratifying patients by disease characteristics and treatment history further clarify the specific contribution of PSMA PET/CT, helping to distinguish its impact from other diagnostic testing procedures and physician judgements that also guide therapeutic choices.

Simultaneously, real-world evidence is essential to complement trial data [33]. Population registries, such as the Dutch mCRPC registry (CAPRI with registry no. NTR9372) that combines automated data extraction with manual data validation, can play a major complementary role by providing larger and more diverse datasets that reflect everyday practice [34]. An advantage of registry-based research is its capacity to include heterogeneity of a real-world mCRPC population, rather than selected patients enrolled in trials. This allows for more representative insights into treatment effectiveness, tolerability and evolving care pathways. In addition, registry systems commonly offer longer follow-up periods, information on treatment adherence and sequencing, and more detailed data on healthcare resource use. These features make registries uniquely positioned to complement clinical trial data, to support cost-effectiveness analysis, and to identify practice variations that inform guideline development [35].

However, data completeness remains very challenging in population registries [36]. A main limitation is that, once a registry has been established, it is difficult to introduce new variables without disrupting existing data structures or compromising longitudinal consistency. It is particularly difficult in rapidly evolving fields, where novel imaging

modalities or treatment strategies require additional variables to be collected. Further, registries rely heavily on structured and standardised fields to allow automated data extraction. However, much clinically relevant information is documented in the electronic patient record in unstructured narrative form, making automated extraction problematic. Currently, such data require manual review, which is labour-intensive and introduces variability. Consequently, important information on imaging features (e.g., tracer type, scan purpose, timing) and treatment dynamics (e.g., reasons for therapy discontinuation, therapy-related toxicities) are often incomplete or inconsistently recorded [37,38]. Incorporating structured and standardised fields for these variables would not only improve data completeness, but also enables robust longitudinal analysis and good health economic evaluation practices. This need is particularly evident for PSMA PET/CT, where precise documentation of scan timing, imaging findings and their impact on treatment decisions are essential to understand *how* imaging help inform treatment adjustments or discontinuation [39]. As the therapeutic landscape continues to expand with increasingly complex treatment sequencing and combination strategies, registry designs must remain adaptable while ensuring structured and high-quality data capture.

5. Conclusion

This post-hoc analysis provides a descriptive overview of healthcare resource use and cost of PSMA PET/CT in the mCRPC setting. PSMA PET/CT helps inform treatment decisions. Whether this translates into avoidance of ineffective therapy or in therapy-related cost savings should be explored in health economic evaluations. Our findings serve as the groundwork for near-future formal cost-effectiveness analyses, required to determine whether PSMA PET/CT can be seen as a cost-effective alternative to conventional imaging. While PSMA PET/CT has the potential to offer clinical and economic benefits by guiding treatment decisions, its cost remains high relative to the costs of conventional therapies. Also, cost savings are less evident where conventional therapy costs are low compared to novel (but costly) targeted therapy costs. It is important to establish standardised imaging protocols, collect multicentre data and further improve registry documentation. These efforts strengthen the evidence base that is necessary to evaluate the clinical and economic value that PSMA PET/CT brings to decision-making and resource allocation in the rapidly changing mCRPC setting.

CRediT authorship contribution statement

S. van Mossel: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **K.J.M. van der Velden:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **F. Kleiburg:** Writing – review & editing, Validation, Resources, Project administration, Investigation, Data curation, Conceptualization. **D. Bosch:** Writing – review & editing, Resources, Project administration, Data curation. **T. van der Hulle:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **H. Koffijberg:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **M.C.P. Kuppen:** . **I.M. van Oort:** Writing – review & editing, Supervision, Resources, Data curation. **S. Saing:** Writing – review & editing, Validation, Supervision, Software, Methodology, Investigation, Conceptualization. **L.F. de Geus-Oei:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **L. Heijmen:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Data curation, Conceptualization.

Ethics approval

Ethical approval was obtained from the local medical ethical committee. Informed consent was waived for the retrospective data gathering.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data statement

The datasets generated and/or analysed during the current study, and on which the conclusions of our paper rely, are available upon reasonable substantiated request.

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.

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