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# Costs of radium-223 and the pharmacy preparation $^{177}$Lu-PSMA-I&T for metastatic castration-resistant prostate cancer in Dutch hospitals

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## ABSTRACT

**Objective:** The radiopharmaceuticals radium-223 and the pharmacy preparation $^{177}$Lu-PSMA-I&T are reimbursed in the Netherlands for metastatic castration-resistant prostate cancer (mCRPC) treatment. Although shown to be life-prolonging in patients with mCRPC, the treatment procedures associated with these radiopharmaceuticals can be challenging for both patients and hospitals. This study investigates the costs of mCRPC treatment in Dutch hospitals for currently reimbursed radiopharmaceuticals with a demonstrated overall survival benefit.

**Methods:** A cost model that calculated the direct medical per-patient costs of radium-223 and $^{177}$Lu-PSMA-I&T was developed, following clinical trial regimens. The model considered six 4-weekly administrations (i.e. ALSYMPCA regimen) of radium-223. Regarding $^{177}$Lu-PSMA-I&T, the model used both the VISION regimen (i.e. five 6-weekly administrations) and the SPLASH regimen (i.e. four 8-weekly administrations). Based on health insurance claims, we also estimated the coverage a hospital would receive for providing treatment. No fitting health insurance claim for $^{177}$Lu-PSMA-I&T is currently available; therefore, we calculated a break-even value for a potential health insurance claim that would exactly counterbalance the per-patient costs and coverage.

**Results:** Radium-223 administration is associated with per-patient costs of €30,905, and these costs are fully covered by the coverage a hospital receives. The per-patient costs of $^{177}$Lu-PSMA-I&T range between €35,866 and €47,546 per administration period, depending on the regimen. Current healthcare insurance claims do not fully cover the costs of providing $^{177}$Lu-PSMA-I&T: hospitals must pay €4,414–€4,922 for each patient out of their own budget. The break-even value for the potential insurance claim covering $^{177}$Lu-PSMA-I&T administration with a VISION (SPLASH) regimen is €1,073 (€1,215).

**Conclusion:** This study shows that, without consideration of the treatment effect, radium-223 treatment for mCRPC leads to lower per-patient costs than treatment with $^{177}$Lu-PSMA-I&T. The detailed overview of the costs associated with radiopharmaceutical treatment provided by this study is relevant for both hospitals and healthcare insurers.

## PLAIN LANGUAGE SUMMARY

Prostate cancer is the most common form of cancer among men in the Netherlands, and its treatment is increasingly expensive. Given the limited hospital budget, it is important to consider costs in the treatment of prostate cancer. Radiopharmaceuticals are one of the multiple treatment options for metastatic prostate cancer. The current study looked at the costs of two radiopharmaceuticals, radium-223 and 177Lu-PSMA-I&T, while using multiple treatment regimens.

The cost of radium-223 treatment is €30,905 per patient and is fully covered by insurance. The cost of 177Lu-PSMA-I&T treatment ranges from €35,866 to €47,546 per patient and is partially paid from the budget of the hospitals considering current reimbursement amounts. The study shows that, without consideration of the treatment effects, radium-223 treatment for prostate cancer leads to lower per-patient costs than treatment with 177Lu-PSMA-I&T. The detailed overview of the costs associated with radiopharmaceutical treatment provided by this study is relevant for both hospitals and healthcare insurers to manage prostate cancer treatment costs.

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## Introduction

Prostate cancer is the most prevalent cancer among males in the Netherlands, with over 12,000 cases diagnosed every year.[1] Some of these patients will have metastatic castration-resistant prostate cancer (mCRPC), an advanced form of prostate cancer that no longer responds to castration treatments (surgical or chemical [induced by hormones]).[2,3] Despite several available treatment options, mCRPC has a poor prognosis – patients have an estimated overall survival of 14.0 months.[3] Moreover, skeletal-related events and severe pain associated with bone metastases impact a patient's physical well-being and ability to perform the basic activities of daily life, which significantly reduces their quality-of-life.[4,5] The economic impact of prostate cancer is also substantial – in 2019, the total healthcare expenses for prostate cancer in the Netherlands were estimated at 350 million euros. Hospital care and medicine use comprised 80% and 11% of these costs, respectively.[6]

Life-prolonging drugs in mCRPC include chemotherapy, androgen receptor pathway inhibitors, poly(adenosine diphosphate-ribose) polymerase inhibitors, Sipuleucel-T, and radiopharmaceuticals.[7,8] Although many options are available, not all treatments are effective in all patients. The selection of treatment for mCRPC is multifactorial and generally depends on previous treatments, quality of response, resistance, and patient characteristics.[8] Therefore, appropriate treatment management is critical. Several radiopharmaceuticals are used for the treatment of metastatic bone pain in mCRPC.[9–12] However, currently, only two with a demonstrated overall survival benefit are reimbursed for the treatment of mCRPC in the Netherlands: radium-223 and the pharmacy preparation $^{177}$Lu-PSMA-I&T.[9,13]

Radium-223 is a radiopharmaceutical that emits alpha radiation and targets bone metastases that has been on the Dutch market since 2013[9,14,15]. $^{177}$Lu-PSMA-I&T is a pharmacy preparation with an almost similar mechanism of action to the commercial $^{177}$Lu-PSMA-617.[16] These $^{177}$Lu-PSMA therapies target cancer cells by binding to prostate-specific membrane antigen (PSMA) receptors (present in over 80% of mCRPC patients) and emitting beta radiation.[17] The commercial[16] $^{177}$Lu-PSMA-617 has recently received approval from the European Commission for the treatment of progressive PSMA-positive mCRPC; however, the time frame in which $^{177}$Lu-PSMA-617 will receive reimbursement in the Netherlands is uncertain as the Dutch reimbursement process for hospital drugs varies in duration (median duration is 420 days).[18,19] The SPLASH trial is currently studying the efficacy of $^{177}$Lu-PSMA-I&T compared with abiraterone or enzalutamide in chemo-naïve patients with mCRPC.[20] Although the European Medicines Agency (EMA) is yet to approve $^{177}$Lu-PSMA-I&T, the pharmacy preparation already received reimbursement in the Netherlands in 2021. Reimbursement is restricted to the treatment of mCRPC in adult men that are PSMA positive in the absence of a more suitable therapeutical.[12]

The economic impact of metastatic prostate cancer is substantial and is escalating.[21] Although both radium-223 and $^{177}$Lu-PSMA-I&T are effective in the treatment of mCRPC, radiopharmaceuticals are also accompanied by additional treatment procedures (e.g. diagnostic scans and observation) that impact resource use and costs.[16,22] As the introduction of new radiopharmaceuticals in metastatic prostate cancer continues (e.g. actinium-225-PSMA)[23] and the use of radiopharmaceuticals is expected to increase, the (economic) impact of radiopharmaceuticals on clinical practice in the Netherlands is still unclear. Radiopharmaceutical treatment is subsidized by the hospital budget and given the budget cap of hospitals and high mCRPC expenses,[6] it is important to consider the treatment procedures and associated cost impact in the use of radiopharmaceuticals. This study contributes to insight into the cost aspects of radiopharmaceutical treatment by investigating the integral per-patient costs of mCRPC treatment in Dutch hospitals for currently reimbursed radiopharmaceuticals with demonstrated overall survival benefit.

## Methods

### Model characteristics

A cost model was developed in Microsoft Excel 2016 (Redmond, WA) to calculate the per-patient costs of radium-223 and the pharmacy preparation $^{177}$Lu-PSMA-I&T in Dutch hospitals with a bottom-up approach following the Consolidated Health Economic Evaluation Reporting Standards 2022 (Supplementary Appendix 1).[24] In addition, to assess the impact of radiopharmaceutical treatment on the economic burden, the model estimated the difference between the per-patient costs and the coverage a hospital receives for the treatment based on the average claim to healthcare insurers. This insight into the per-patient costs and coverage which is of value for hospitals and healthcare insurance companies given the limited yearly hospital budget. Besides the average outcomes, we performed a scenario and breakeven analysis in which the impact of different treatment patterns and reimbursement values was determined.

The course of radium-223 treatment was based on its Summary of Product Characteristics (SmPC) and the ALSYMPCA trial.[9,14] The course of $^{177}$Lu-PSMA-I&T treatment was based on the VISION and SPLASH trials.[16,20] In the ALSYMPCA trial, radium-223 significantly improved median overall survival by 3.6 months (hazard ratio for death = 0.70 [0.58–0.83, $p < 0.001$]) compared with a placebo.[14] In the VISION trial, $^{177}$Lu-PSMA-617 was shown to significantly improve median overall survival by 4.0 months (hazard ratio for death = 0.62 [0.52–0.74, $p < 0.001$]) compared with standard care.[16] Although the overall survival benefits seem comparable,[14,16,25] no (in)direct treatment comparisons have been performed, and there are some differences in their targeted patient population. Radium-223 is approved as monotherapy or in combination with a luteinizing hormone-releasing hormone (LHRH) analogue in the treatment of adult mCRPC patients with symptomatic bone metastases and no known visceral metastases, who progressed after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues) or who are not eligible for available systemic mCRPC treatment.[9] $^{177}$Lu-PSMA-I&T is indicated for

PSMA-positive mCRPC patients as last resort treatment.[9,16] Our analysis focused on the treatment costs for hospitals and healthcare insurers and did not encompass the treatment effect and patient characteristics reported in the clinical trials. The model structure and inputs were validated by two Dutch clinical experts.

### Time horizon and perspective

Because our study focused on treatment costs that are relevant for hospitals and healthcare insurers, we used a Dutch healthcare payer's perspective, which includes all direct medical costs related to mCRPC treatment with radiopharmaceuticals.[26] Only variable cost parameters were considered, and these consisted of medication, administration, clinic visits, imaging, hospital admission, and supportive care. The time horizon was equal to the administration period of radiopharmaceuticals because it covered all costs relevant to Dutch healthcare payers. Due to the short time horizon, no discount rate was used.[27]

### Healthcare utilization during radiopharmaceutical treatment

Our model based the number of injections, dosage, and regimen on clinical trial data (Table 1). The base case treatment regimen of radium-223 was based on the median number of injections in the ALSYMPCA trial.[14] The treatment regimen of $^{177}$Lu-PSMA-I&T in the base case was based on the median number of injections used in the VISION trial and the number of injections in the SPLASH trial.[16,20] As of this writing, the efficacy of $^{177}$Lu-PSMA-617 was established in the VISION regimen,[16] but the efficacy of $^{177}$LU-PSMA-I&T in the SPLASH regimen was yet to be determined.[20] Our analysis included both regimens to reflect the Dutch clinical practice as closely as possible.

Other healthcare utilization input was based on literature, hospital websites, and expert opinion. Prior to radium-223 treatment, the presence of bone metastases was recognized by a bone scan, the presence of visceral metastases was ruled out by a CT scan,[9] and an alkaline phosphatase assessment was performed before radium-223 administration.[9,14] After each $^{177}$Lu-PSMA-I&T administration, an observation period of 6 hours was incorporated because of the beta radiation exposure.[28] Prior to $^{177}$Lu-PMSA-I&T treatment, the presence of PSMA receptors on the tumor cells was established using $^{68}$Ga-PSMA-PET/CT scans following Dutch clinical practice.[22]

Patients can be admitted to a hospital in between or during their radiopharmaceutical injections. Diagnosis treatment combination (*diagnose-behandelcombinatie* [DBC]) registration data from 2020 suggest that approximately 12% of patients experience a hospital admission during or between radiopharmaceutical administrations.[29] The hospital admission was assumed to last 1 day, based on expert opinion. The use of bone health agents such as bisphosphonates or denosumab was considered during radium-223 treatment.[9] During $^{177}$Lu-PSMA treatment, the use of both bone health agents and anti-emetics was assumed.[16]

### Costs

Table 2 summarizes all costs that were incorporated into the model. All costs were inflated to 2021 prices in euros using the published consumer price index from the Dutch Central Bureau of Statistics.[30] Treatment costs incorporated medication costs, administration costs, and outpatient visits for every injection.[31,32] Medication costs were based on list prices retrieved from data on file, excluding value-added tax. For $^{177}$Lu-PSMA-I&T, the list price reflects the cost price of hospital preparation (i.e. raw materials, devices, and labor).[13,33] Imaging, biomarker assessments, observation time, hospital admission, and supportive care costs were also incorporated (Table 1). Imaging costs were estimated on the average of the published rates of two Dutch hospitals.[34,35] Biomarker assessment costs were based on the rates published by the Dutch Healthcare Authority.[36] Costs of observation and hospital admissions were determined following the Dutch cost manual.[32] The costs of bone health agents were calculated by using the average list prices of denosumab and the available bisphosphonates in the Netherlands (Supplementary Appendix 2). The costs of anti-emetics were based on an average of the list prices of dexamethasone.

### Difference in per-patient costs and coverage

After establishing the per-patient costs of treating mCRPC with radiopharmaceuticals, the model calculated the

**Table 1.** The healthcare utilization of radium-223 and $^{177}$Lu-PSMA-I&T.

| Treatment | Trial (regimen) | Imaging | Biomarker assessment | Treatment schedule[a] | Observation time | Supportive care | Source |
|---|---|---|---|---|---|---|---|
| Radium-233 | ALSYMPCA | CT and bone scan | Hematologic, PSA, and alkaline phosphatase | Six injections of 55 kBq/kg body weight every 4 weeks | N/A | - Bone health agents | ALSYMPCA[14]<br>SmPC radium-223[9] |
| $^{177}$Lu-PSMA-I&T | VISION | $^{68}$Ga-PSMA PET/CT scan | Hematologic and PSA assessment | Five injections of 7.4 GBq every 6 weeks | Six hours per administration | - Bone health agents<br>- Anti-emetics | VISION[16]<br>Expert opinion<br>Guideline[28] |
| $^{177}$Lu-PSMA-I&T | SPLASH | $^{68}$Ga-PSMA PET/CT scan | Hematologic and PSA assessment | Four injections of 6.8 GBq every 8 weeks | Six hours per administration | - Bone health agents<br>- Anti-emetics | SPLASH[20]<br>Expert opinion<br>Guideline[28] |

Note. 12% of patients were admitted for 1 day during administration.
Abbreviations. Bq, becquerel; CT, computed tomography; Ga, gallium; $^{177}$Lu-PSMA-I&T, lutetium-177-labeled prostate-specific membrane antigen imaging and treatment; N/A, not applicable; PET, positron emission tomography; PSA, prostate specific antigen; SmPC, summary of product characteristics.

**Table 2.** Overview of included cost inputs.

| Cost input | Costs per quantity | Cost year | Source |
|---|---|---|---|
| Treatment costs | | | |
| Medication costs $^{177}$Lu-PSMA-I&T[a,b] | 7.4 Gbq: €8,436<br>6.8 Gbq: €7,752 | 2021 | Z-index 16995740[13] |
| Medication costs radium-223[b] | €4,460 | 2021 | Z-index 16225643[15] |
| Administration costs intravitreal injection | €260 | 2017 | Peters et al.[31] |
| Outpatient visit | €102 | 2014 | Dutch costs manual[26] |
| Imaging costs | | | |
| 68Ga PSMA PET/CT scan | €1,286 | 2021 | Netherlands Cancer Institute (Antoni van Leeuwenhoek) and Erasmus Medical Center [Average][34,35] |
| 18-F FDG PET/CT scan | €1,209 | 2021 | Netherlands Cancer Institute (Antoni van Leeuwenhoek) and Erasmus Medical Center [Average][34,35] |
| CT-scan | €416 | 2014 | National Health Authority[33]<br>Reimbursement code: 87042 and 85042 |
| Bone scan | €106 | 2014 | National Health Authority (NZA)[33]<br>Reimbursement: 29399003 |
| Biomarker assessment | | | |
| Hematologic evaluation (Hemoglobin and LDH) | €4.08 | 2014 | National Health Authority[33]<br>Reimbursement code: 70702 hemoglobin; 74892 LDH |
| PSA | €10.14 | 2014 | National Health Authority[33]<br>Reimbursement code: 72621 |
| Alkaline phosphatase | €2.17 | 2014 | National Health Authority[33]<br>Reimbursement code: 74896 |
| Observation time (per hour) | €22.25 | 2014 | Dutch costs manual[26] |
| Hospital admission | €534 | 2104 | Dutch costs manual[26] |
| Supportive care[b,c] | | | |
| Bone health agents (denosumab and available bisphosphonates) | During $^{177}$Lu-PMSA-I&T administration: €1,157<br>during Radium-223 administration: €926 | 2021 | Z-index (Supplementary Appendix 1) [Average][d] |
| Anti-mimetics (ondansetron) | During $^{177}$Lu-PMSA-I&T administration: €47.59 | 2021 | Z-index [Average][c,d] |

[a]The medication price for pharmacy preparations is based on the use of raw materials, labor, and devices. This information is provided by hospitals to health insurance companies but is not publicly available.[29][a]The medication price for pharmacy preparations is based on the use of raw materials, labor, and devices. This information is provided by hospitals to health insurance companies but is not publicly available.[29]
[b]The Z-indexes are retrieved from the internal data that is accessible for hospitals and health insurance companies.
[c]The costs of supportive care are dependent on the treatment duration.
[d]Z-indexes included: 15933911 16760220 15933938 16742966 16305078 16305027 16801229 15213536 15213552.

difference between the per-patient costs and the coverage that a hospital receives. In the Netherlands, a hospital covers healthcare expenses with claims to healthcare insurers. This coverage is retrieved via DBC codes for healthcare utilization and add-on codes for expensive medicines (i.e. >€1,000 per patient per year). DBC codes are standardized sets of care activities that are combined into one product.[29] When a care activity is performed, a healthcare provider can reimburse the costs for this activity by invoicing the corresponding DBC code at a health insurance company. In theory, DBC codes should cover all hospital expenses; however, the coverage may be below or above the actual expenses because expenses and coverage are based on the average patient and are hospital dependent.

The impact on the hospital budget was calculated by subtracting the calculated hospital expenses from the average coverage a hospital receives from health insurance claims in the form of DBC codes. The average DBC code values were obtained from OpenDIS (Table 3).[29] Currently, there is a dedicated DBC code for radium-223 administration, but no DBC code for $^{177}$Lu-PSMA-I&T administration. This dedicated DBC code for radium-223 is restricted to radium-233 administration; that is, hospitals cannot use the DBC code for radium-223 administration for $^{177}$Lu-PSMA-I&T.[29] Therefore, hospitals commonly use a more general, less restrictive DBC code for supportive care in prostate cancer to cover $^{177}$Lu-PSMA-I&T administration. The selection of the supportive care DBC codes was based on expert opinion.

### Break-even price

As no dedicated DBC code is currently available for $^{177}$Lu-PSMA-I&T, a break-even value for a future DBC code for $^{177}$Lu-PSMA-I&T administration was calculated – defined as the DBC value that would exactly counterbalance the per-patient costs and the coverage. Instead of the implementation frequency of 120 days of the current DBC code for supportive care, the calculation assumed an implementation before every administration.[37]

### Univariate sensitivity and scenario analysis

To assess the impact of input parameters on the per-patient costs of radiopharmaceutical treatment, a univariate sensitivity analysis was performed. In the univariate sensitivity analysis, parameters were varied within a 25% interval.[27] Because no SmPC or guideline regarding $^{177}$Lu-PSMA-I&T treatment is available, the specific treatment protocols in

Table 3. DBC codes used to calculate the coverage of hospitals for radiopharmaceutical administration.

| Treatment | DBC codes | DBC code description | DBC code implementation frequency | DBC code value |
|---|---|---|---|---|
| Radium-223[29] | DBC 1:020109026<br>DBC 2:020109027 | DBC 1: Administration of radiopharmaceuticals (i.e. radium-223) in mCRPC (12%)[b]<br>DBC 2: Administration of radiopharmaceuticals (i.e. radium-223) in mCRPC during hospitalization (88%)[b] | Before every administration[c] | DBC 1: €920<br>DBC 2: €4,128 |
| $^{177}$Lu-PSMA-I&T[29] | DBC 1: 20109080<br>DBC 2: 20109086 | DBC 1: Supportive/relieving care with 1–2-day treatment or more than 2 outpatient visits (20%)[a]<br>DBC 2: Supportive/relieving care with one to two outpatient visits (80%)[a] | Every 120 days | DBC 1: €800<br>DBC 2: €340 |

Abbreviations. DBC, diagnosis treatment combination; $^{177}$Lu-PSMA-I&T, lutetium-177-labeled prostate-specific membrane antigen imaging and treatment.
[a]The division of supportive care DBC code for $^{177}$Lu-PSMA-I&T administration was based on expert opinion.
[b]The percentage of patients that were hospitalized during administration was based on OpenDIS data.
[c]Generally, DBC codes can be closed once every 120 days. As radium-223 administration is more frequent, an exception is made and the DBC code for administration can be closed before every administration.

hospitals differ, and several assumptions had to be made (Supplementary Appendix 3). A scenario analysis was performed to account for those differences. First, in the base case, our analysis based the regimens of radiopharmaceuticals on clinical trial regimens. However, the $^{177}$Lu-PSMA-I&T regimens in Dutch hospitals are ambiguous and may differ from those clinical trials.[22,38,39] Therefore, the scenario analysis estimated the per-patient costs of three $^{177}$Lu-PSMA-I&T administrations. The three administrations were based on expert opinion and given in a modified SPLASH trial regimen (i.e. 8-week intervals and a dosage of 6.8 GBq), the effectiveness of which has not yet been studied. Second, some hospitals use a CT whole body scan or 18 F-FDG PET/CT scan before and during 177Lu-PSMA-I&T treatment besides the diagnostic PET/CT scan at the start of treatment.[39] Therefore, the impact of including these scans was explored in the scenario analysis. Third, the duration of observation varies between hospitals; consequently, the effect of an observation period of 24 hours was explored.[22,39]

## Results

### Base case outcomes

Table 4 shows the per-patient costs and coverage costs over the administration periods of radium-223 and $^{177}$Lu-PSMA-I&T. Radium-223 is associated with the lowest per-patient costs (€30,905). The coverage a hospital receives with radium-223 treatment (€34,806) is sufficient to cover the expenses made. With five 6-weekly injections of 7.4 GBq (VISION regimen), the per-patient costs of $^{177}$Lu-PSMA-I&T are €47,546, and the coverage costs are €42,624, resulting in a difference of −€4,922. With four 8-weekly injections of 6.8 GBq (SPLASH regimen), the per-patient costs of $^{177}$Lu-PSMA-I&T are €35,866, and the coverage costs are €31,452, resulting in a difference of −€4,414. For both treatments, regardless of the regimen, medication costs account for the largest part of the costs (i.e. 85–88% of the total costs).

### Break-even analysis

The break-even analysis was performed to establish the tariff for a potential DBC code of $^{177}$Lu-PSMA-I&T that would exactly counterbalance the per-patient costs and the coverage (Figure 1). When the VISION regimen was followed (i.e. five 6-weekly injections of 7.4 GBq), the break-even value per injection for the DBC code covering $^{177}$Lu-PSMA-I&T administration was €1,073. When a hospital followed the SPLASH regimen (i.e. four 8-weekly injections of 6.8 GBq), the break-even value per injection of the DBC code covering $^{177}$Lu-PSMA-I&T administration was €1,215.

Table 4. Per-patient costs and coverage in the administration period of radiopharmaceuticals.

| | Radium-223 | $^{177}$Lu-PSMA-I&T | |
|---|---|---|---|
| | ALSYMPCA regimen | VISION regimen | SPLASH regimen |
| Medication | €26,796 | €42,546 | €31,008 |
| Administration | €1,559 | €1,299 | €1,039 |
| Hospital admission | €393 | €327 | €262 |
| Observation | N/A | €667 | €534 |
| Supportive care | €926 | €1,205 | €1,237 |
| Monitoring | €612 | €510 | €408 |
| Imaging | €619 | €1,357 | €1,342 |
| Total costs | €30,905 | €47,546 | €35,866 |
| Total coverage | €34,806 | €42,624 | €31,452 |
| Difference | €3,901 | −€4,922 | −€4,414 |

Abbreviations. $^{177}$Lu-PSMA-I&T, lutetium-177-labeled-prostate-specific membrane antigen imaging and treatment.

### Univariate sensitivity analysis

For both radium-223 and $^{177}$Lu-PSMA-I&T, the parameters with the most impact were the number of injections and medication costs (Figure 2). Administration and supportive care expenditures had a substantial influence on the per-patient costs of radium-223. For $^{177}$Lu-PSMA-I&T in the VISION regimen, the costs of both the administration and frequency of PET/CT scans were also important contributors to the total expenses. In the SPLASH regimen, costs and frequency of PET/CT scans and costs of supportive care were important contributors to the per-patient costs.

### Scenario analysis

The scenario analysis estimated the impact of a modified SPLASH regimen with three $^{177}$Lu-PSMA-I&T administrations (Scenario 1). Figure 3 and Table 5 show that three administrations for $^{177}$Lu-PSMA-I&T led to lower per-patient costs than the per-patient costs of radium-223: $^{177}$Lu-PSMA-I&T incurred per-patient costs of €27,221 with a dosage of 6.8

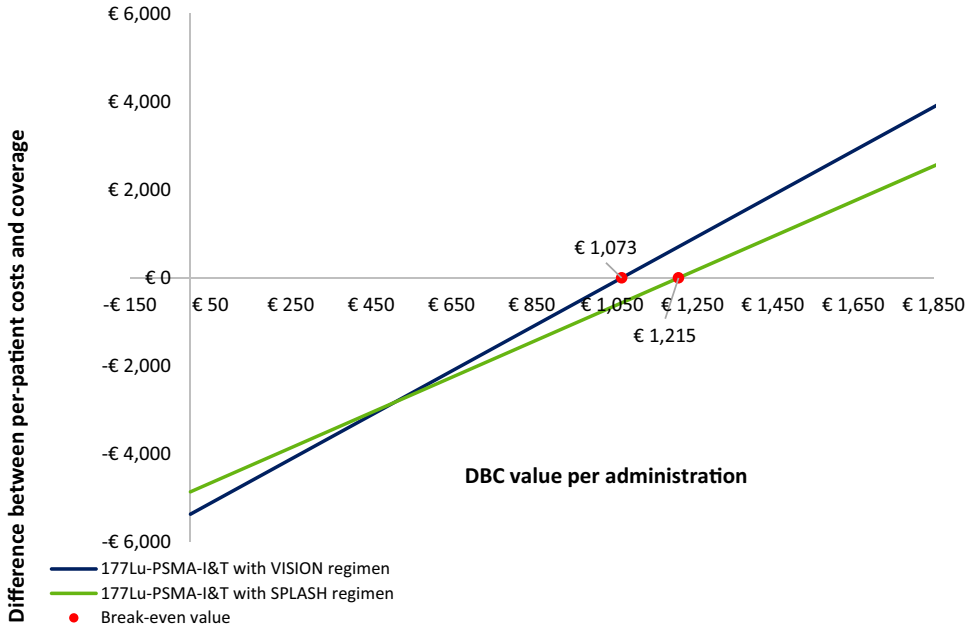


**Figure 1.** Difference between per-patient costs and coverage calculated per DBC value and break-even value for each regimen included in the model. Abbreviations. DBC, diagnosis treatment combination; $^{177}$Lu-PSMA-I&T, lutetium-177-labeled-prostate-specific membrane antigen imaging and treatment.

GBq and 8-weekly administrations, and radium-223 incurred per-patient costs of €30,905 (Figure 3). The coverage does not fully cover the costs of providing $^{177}$Lu-PSMA-I&T, but the difference is smaller than in the base case: hospitals have to pay €3,521 for each patient out of their budget. The break-even value per injection of the DBC code covering $^{177}$Lu-PSMA-I&T was €1,322 when three injections were used (Supplementary Appendix 4).

Both the 24-hour observation period after $^{177}$Lu-PSMA-I&T administration (Scenario 2) and the inclusion of extra PET/CT and 18-FDG PET/CT scans (Scenario 3) increased the per-patient costs of $^{177}$Lu-PSMA-I&T (Table 5). The 24-hour observation period after $^{177}$Lu-PSMA-I&T administration led to per-patient costs of €49,548 in the VISION regimen and €37,468 in the SPLASH regimen. The addition of more scans led to per-patient costs of €50,117 in the VISION regimen and €38,437 in the SPLASH regimen.

## Discussion

The insights into the per-patient costs and coverage per administration period of radiopharmaceutical therapies that our study provides can help guide hospitals in the appropriate use of these treatments for mCRPC and contribute to the management of the escalating costs.[21] Our research shows that, among the radiopharmaceuticals currently reimbursed for the treatment of mCRPC patients, radium-223 treatment incurs lower per-patient costs (€30,905) than treatment with $^{177}$Lu-PSMA-I&T (VISION regimen: €47,546; SPLASH regimen: €35,866) when following clinical trial regimens. While the claims of the health insurance companies cover all expenses of radium-223 administration, hospitals pay €4,414–€4,922 out of their own budget per patient treated with $^{177}$Lu-PSMA-I&T.

Currently, there is no fitting DBC code for $^{177}$Lu-PSMA-I&T administration available, which forces hospitals to invoice DBCs that do not cover all costs. It is expected that a DBC code for $^{177}$Lu-PSMA-I&T will become available in the coming years;[37] therefore, our study calculated the break-even value that would be needed to reach equal per-patient costs and coverage for this DBC code. Our study indicates that the break-even value of this DBC code will be dependent on the regimen used (i.e. €1,073 in the VISION regimen and €1,215 in the SPLASH regimen).

Our study includes the radiopharmaceuticals that are reimbursed in the Netherlands for the treatment of mCRPC. Although $^{177}$Lu-PSMA-617 has recently received European Commission approval,[18] it is not yet reimbursed in the Netherlands and therefore not included in our analysis. It is expected that $^{177}$Lu-PSMA-617 will have a comparable regimen and treatment protocol to $^{177}$Lu-PSMA-I&T, but higher medication costs will result in higher per-patient costs.[40,41] However, an update of this study after reimbursement is needed to confirm these expectations.

As of this writing, the efficacy of $^{177}$Lu-PSMA was determined in the VISION trial using five injections,[16] but the efficacy based on four injections, studied in the SPLASH trial, had not yet been established.[20] Although costs should be considered only when the treatment (regimen) has proven to be effective, we chose to include both regimens to reflect Dutch clinical practice as closely as possible; regimens differ between hospitals and every hospital negotiates its budget with healthcare insurers. Nevertheless, not all hospitals use the four to five cycles that are protocol in the VISION and SPLASH trial.[16,20] Therefore, based on expert opinion, the scenario analysis further assessed the uncertainty in the $^{177}$Lu-PSMA-I&T treatment regimen. The costs of a modified SPLASH regimen (i.e. three 8-weekly $^{177}$Lu-PSMA-I&T injections of 6.8 GBq) were established, although the efficacy of

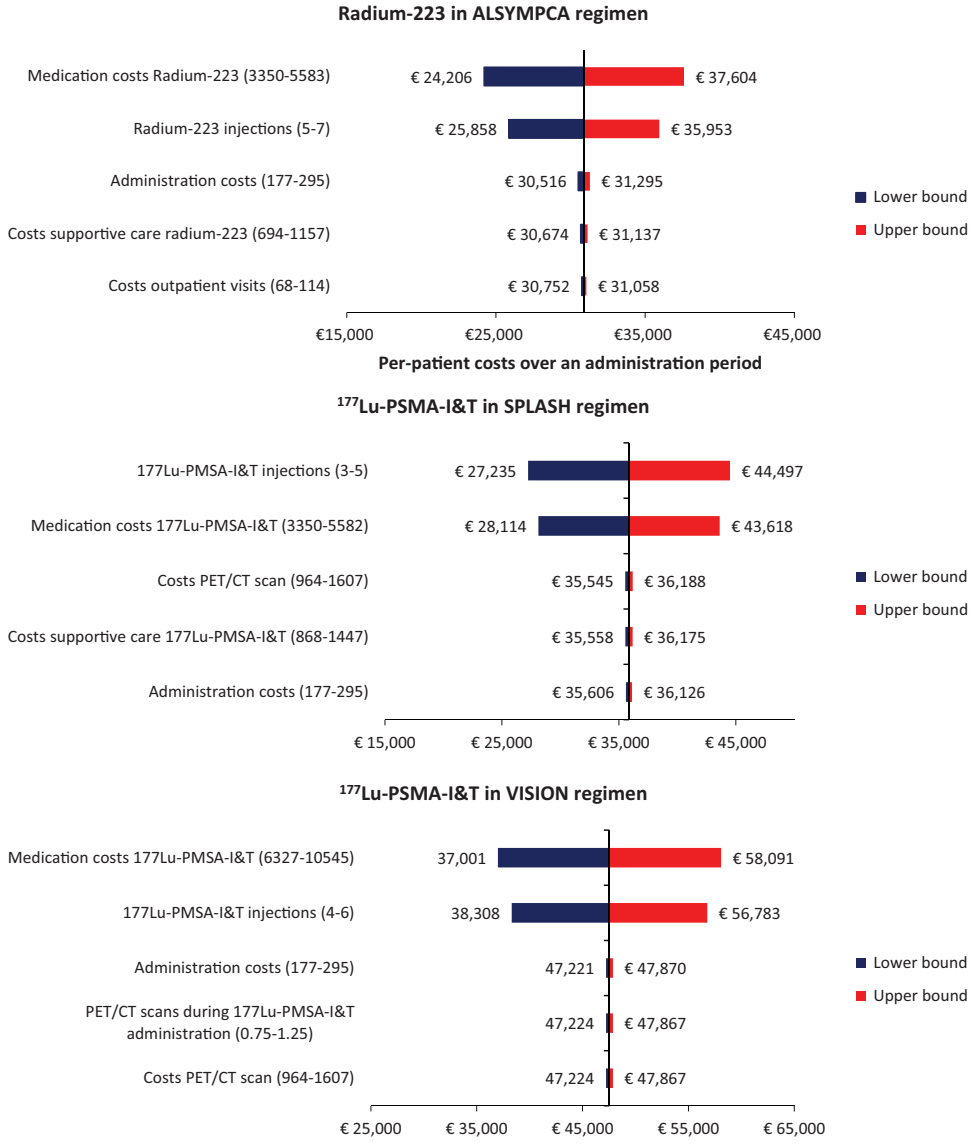


**Figure 2.** Tornado diagrams presenting the five most influential parameters on the per-patient costs of radium-223 in the ALSYMPCA regimen, and the per-patient costs of $^{177}$Lu-PSMA-I&T in the VISION and SPLASH regimens. Abbreviations. CT, computed tomography; $^{177}$Lu-PSMA-I&T, lutetium-177-labeled-prostate-specific membrane antigen imaging and treatment.

this regimen has not yet been studied. This scenario resulted in lower per-patient costs than radium-223 per administration period (i.e. €27,221 for $^{177}$Lu-PSMA-I&T and €30,905 for radium-223).

It is important to relate clinical trial data to real-world evidence. Currently, several real-world data projects in prostate cancer are being conducted, which might help homogenize treatment patterns for patients with mCRPC.[42] Older Dutch real-world data suggest that the patient characteristics of mCRPC in $\geq$ third-line treatment slightly deviate from the clinical trial data (i.e. similar age but higher ECOG).[14,16,43] However, patient characteristics and treatment effects do not necessarily affect the treatment course and therefore, in our case, the study outcomes. To account for the possibility that subsets of patients receive different numbers of injections, we provided a detailed overview of the different cost parameters to make the results translatable to different clinical practices.

The treatment patterns assumed for radium-223 were based on clinical trial data and SmPC description. Moreover, the input for the resource use is in line with earlier Dutch health economic models focusing on the costs of radium-223.[31] However, the lack of SmPC or guidelines regarding $^{177}$Lu-PSMA-I&T treatment means hospitals differ in specific treatment protocols and thus assumptions were required for the model, resulting in uncertainty in the outcomes. Therefore, several scenarios were performed in which the impact of different treatment patterns was explored. First, the use of scans before and during $^{177}$Lu-PMSA-I&T treatment differs between hospitals.[22,39] The base case scenario only considers the use of a diagnostic PET/CT scan. However, some hospitals use an additional PET/CT after the first administration and/or use a (diagnostic) F18-FDG PET/CT scan.[39] The scenario analysis showed that the inclusion of those scans increased costs by €2,571 for each patient per administration period. Second, the observation period differs

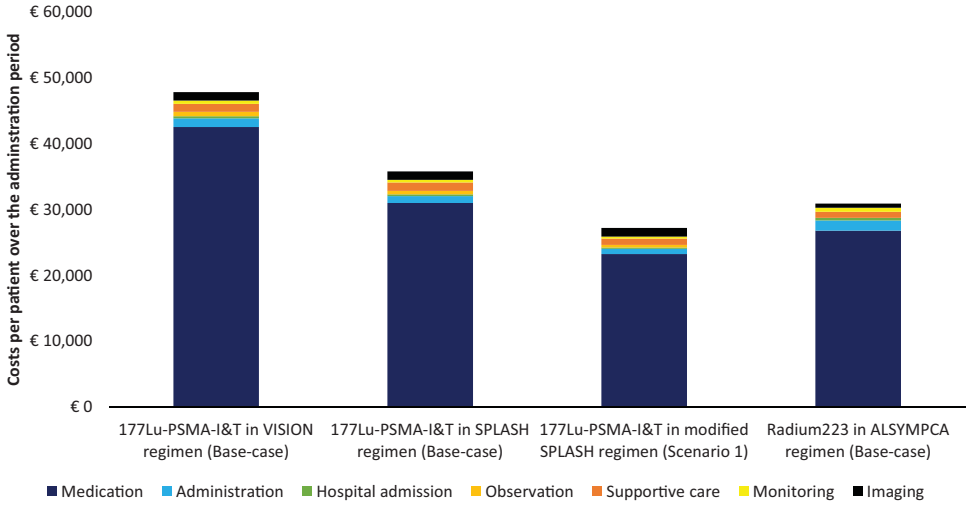


**Figure 3.** Per-patient costs for $^{177}$Lu-PSMA-I&T and radium-223 per administration period. Note, the modified SPLASH regimen consisted of three 8-weekly injections of 6.8 GBq. Abbreviations. $^{177}$Lu-PSMA-I&T, lutetium-177-labeled-prostate-specific membrane antigen imaging and treatment.

**Table 5.** The impact on and the difference between per-patient costs and coverage in the scenario analyses.

| | | Radium-223 | $^{177}$Lu-PSMA-I&T | |
|---|---|---|---|---|
| | | ALSYMPCA regimen | VISION regimen | SPLASH regimen |
| Base case | Costs | €30,905 | €47,546 | €35,866 |
| | Coverage | €34,806 | €42,624 | €31,452 |
| | Difference | €3,901 | −€4,922 | −€4,314 |
| Scenario 1 | Costs | €30,905 | N/A | €27,221 |
| Three $^{177}$Lu-PSMA-I&T administrations in modified SPLASH regimen[a] | Coverage | €34,806 | N/A | €23,256 |
| | Difference | €3,901 | N/A | −€3,521 |
| Scenario 2 | Costs | €30,905 | €49,548 | €37,468 |
| 24-hour observation period after $^{177}$Lu-PSMA-I&T administration | Coverage | €34,806 | €42,624 | €31,452 |
| | Difference | €3,901 | −€6,924 | −€6,016 |
| Scenario 3 | Costs | €30,905 | €50,117 | €38,437 |
| Inclusion of an extra PET/CT and 18 FDG PET/CT scan | Coverage | €34,806 | €42,624 | €31,452 |
| | Difference | €3,901 | −€7,493 | −€6,986 |

Abbreviations. CT, computed tomography; FDG, F-fluorodeoxyglucose; $^{177}$Lu-PSMA-I&T, lutetium-177-labeled-prostate-specific membrane antigen imaging and treatment; PET, Positron emission tomography.
[a]The modified SPLASH regimen consisted of three 8-weekly injections of 6.8 GBq.

between hospitals. The scenario analysis showed that an observation period of 24 hours increased the total per-patient costs by €2,002 in the VISION regimen and €1,602 in the SPLASH regimen.

Pharmacy preparation requires raw materials, labor, and devices. The list price of $^{177}$Lu-PSMA-I&T is estimated to be a reliable indicator of its total preparation and medication costs and, to further explain uncertainties in the list price, we account for variations in the univariate sensitivity analysis.[33] However, the list price does not consider investment and hospital capacity as it already requires facilities, equipment, and labor. In addition, hospitals need access to dedicated rooms and a sufficient workforce for the observation of patients who have been administered radiopharmaceuticals that emit beta radiation.[22,44] It is a limitation of our study that it does not consider the investment costs of facilities or the impact on the capacity of a hospital, and that it is restricted to direct medical per-patient costs. Therefore, in a future study, it is important to also consider the impact of radiopharmaceutical treatment on hospital capacity.

Although our study includes the costs of radiopharmaceutical therapies, our analysis does not consider patient characteristics and treatment effectiveness. Selecting the most appropriate therapy for a patient should not be led by costs but rather by patient characteristics and patient preferences. In this respect, it is important to consider the suitability of radiopharmaceuticals by, for example, taking patient characteristics and preferences into account. Although both $^{177}$LU-PSMA-I&T and radium-223 are used to treat mCRPC, the exact indications do not correspond. Differences in the indications include the type of metastases (i.e. radium-223 solely targets bone metastases) and PSMA status (i.e. $^{177}$Lu-PSMA-I&T only targets PSMA-positive cells).[14,20] Current research and experience in daily practice are needed to determine which treatment is most appropriate for each patient.[42] To improve the clinical interpretability of our analysis, an update should be performed as soon as this long-term real-world data on treatment effect is available.

Given the limited hospital budget and capabilities combined with the high mCRPC expenses, it is important to consider the treatment procedures and associated economic impact in the use of radiopharmaceuticals. Therefore, the detailed overview of the costs and coverage associated with the radiopharmaceutical treatment of mCRPC produced by this study is highly relevant information that can be of use to Dutch hospitals and healthcare insurers to improve the

treatment management of mCRPC patients. The findings inform stakeholders about the impact of different cost parameters of radiopharmaceutical treatment on the hospital budget and can be used in price negotiations.

Our study shows that, without consideration of the treatment effect, the per-patient costs of treating mCRPC are lower for radium-223 compared with $^{177}$Lu–PSMA-I&T when following clinical trial regimens. Furthermore, our study demonstrates that the current lack of a fitting DBC code results in insurance company claims that do not cover the expenses incurred during $^{177}$ Lu-PSMA-I&T administration. The results of this study can contribute important data for improving healthcare allocation in radiopharmaceutical treatments for mCRPC.

## Transparency

### Declaration of funding

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### Declaration of financial/other relationships

SWQ, JHP, DNJW, and RDF have no relationships to be declared in relation to the subject. JN has disclosures in the form of Research Grants, Consulting, Teaching, and Invited Talks for AAA/Novartis, ABX, Bayer AG, CURIUM, NRG, Pfizer, and POINT biopharma.

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All authors are accountable for all aspects of the work

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### Data availability statement

Most data are included in the manuscript and its supporting information files. The analyses were largely conducted based on publicly available information which is presented and referenced in the article and supplementary information files.

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