Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: March 31, 2024

Citation: Vorster M, Mallum A, et al., 2024. Considering the Costs of Targeted Radionuclide Therapies in Prostate Cancer, Medical Research Archives, [online] 12(3). https://doi.org/10.18103/mra.v12i3.5043

DOI
https://doi.org/10.18103/mra.v12i3.5043

ISSN: 2375-1924

RESEARCH ARTICLE

Considering the Costs of Targeted Radionuclide Therapies in Prostate Cancer

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The authors have no conflicts of interest to declare and no funding was received.

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ABSTRACT

There is no denying the importance of prostate cancer as a leading cause of mortality and morbidity in men. As such, it represents an important driver of healthcare costs and there is a (mostly unmet) need to provide evidence that assists decision-makers in prioritizing one management strategy over another in budget planning.

Theranostics in prostate cancer represents a non-invasive out-patient strategy for patient management, which consists of imaging with a PSMA-based agent, followed by targeted radionuclide therapy with either a beta emitter (such as Lutetium-177) or an alpha emitter (such as Actinium-225). Evidence for these management approaches is mounting with FDA approval of imaging and therapy agents following landmark trials like the ProPSMA study, the VISION- and the TheraP trial.

Despite the explosion in publications on the use of targeted radionuclide therapies in prostate cancer, studies that compare the cost-effectiveness of available nuclear medicine imaging and treatment strategies remain hard to find. The aim of this mini review was to summarize the most important current evidence related to cost-effectiveness strategies that evaluate imaging and targeted radionuclide therapies for PSMA-based PET theranostics.

We found a paucity of literature that deals with healthcare costs, with an obvious need for more cost-effectiveness studies to demonstrate the positive impact of nuclear medicine in the management of oncology (and other) patients. These studies need to be based on well-conducted clinical trials and meta-analyses, with appropriate model simulations and decision analysis and should ideally be reported according to the CHEERS 2022 guidelines to improve uniformity and robustness.

Keywords: Cost-effectiveness, Prostate cancer, targeted radionuclide therapy, Lu-177-PSMA, PRRT, CER, ICER, ACER, QALY

Introduction

Prostate cancer is the most common cancer in men and the second most common cancer affecting men's mortality globally. GLOBOCAN recently reported that approximately 1.41 million new prostate cancer (PCa) cases were registered globally in 2020.[1] The corresponding socio-economic burden is enormous, and according to some reports the costs of treating prostate cancer are increasing more rapidly than those of any other cancer.[2] There is no denying the importance of prostate cancer as a leading cause of mortality and morbidity globally. As such, it represents an important driver of healthcare costs and the need to provide evidence that assists decision-makers in prioritizing one management strategy over another during budget planning.

At the turn of the last century, Gambhir and Schwimmer[3] had conducted a methodological review of the economic evaluation studies in nuclear medicine between 1985 and 1999. They identified only 45 studies over nearly 15 years, of which only 29 was deemed suitable for further evaluation (having at least adhered to basic requirements). This selection included a mixture of cost-effectiveness analyses, cost utility analyses- and cost analyses studies. Non-uniformity represents a major theme in their findings, with only 38% of papers clearly stating the perspective that was adopted for the evaluation. Just over half of these studies included long-term costs and discounting was applied in only 28%. Ultimately only six studies met all ten criteria that was deemed essential when evaluating cost effectiveness. Eighty-three percent included true outcome measures (stated in terms of the patients' clinical condition). Incremental costs were cited in just over half of the studies included- this of course allows decision-makers to make informed decisions when considering trade-offs in budget allocations. Three integral components that were highlighted, include the cost-effectiveness ratio (CER), which represents a summary measurement of both the costs and the effect on health outcomes, the importance of sensitivity analysis and the use of decision tree-based models. In summary, the authors discovered an important gap in the literature both with regards to both quantity and quality.[3]

Today, nearly 25 years later, the situation remains very similar, despite the explosion in publications on the use of targeted radionuclide therapies in prostate cancer. Economists (and policymakers/ funders!) are often accused of "knowing the price of everything, but the cost of nothing." It is up to us as clinicians to advocate for our patients also with regards to how money should best be spent. Arguments should be based on a good understanding of the basic concepts used in health economics and on the best available evidence that compares new interventions to the current best standard of care.

The costs of managing prostate cancer

In the United States (US), prostate cancer deaths accounted for more than 25% of cancer-related deaths, whilst in Europe, it accounts for almost 21.8% of all newly diagnosed cancer patients and about 10% of cancer-related deaths. Moreover, prostate cancer is the leading type of malignancy in 28 European countries.[4]

In the US in 2010, the direct medical cost of prostate cancer was estimated to be the fifth largest cancer-related economic burden at $US 11.9 billion. Projections for 2020 and beyond estimated increases in cost of care, to be the third largest, at $US16.3 billion. This is largely due to expected increases in survival and in the expansion of an aging population. Studies have shown that healthcare resource utilization (HCRU) and costs increase (up to 4 times) with progressive and metastatic prostate cancer (making the prevention and early treatment of these stages a priority).[2]

When considering the management of prostate cancer, it is important to define and differentiate various concepts, such as cost, price, and value. Whilst the direct costs are often relatively easy to calculate (i.e., transactions that involved transfer of money), it is often difficult to calculate value.

Basic concepts in health economics

In 2022, Husreau et al compiled the **CHEERS guidelines**[5] (which replaced the 2013 version) which consists of 28 checklist items grouped under title, abstract, introduction, methods, results, discussion, and other relevant information. This is intended to guide standardisation and transparency in reporting.

Let's first consider the types of studies that are most frequently used. A **cost-effectiveness analysis** (CEA) allows for a comparison between interventions intended to achieve similar outcomes. It provides the ratio of costs incurred to effectiveness achieved (as measured by a particular health outcome).[6-8]

A **cost-utility analysis** (CUA) represents a "sub-type" of cost-effectiveness analysis, where outcomes are expressed as Quality Adjusted Life Years (QALYs). This reflects both morbidity and mortality and considers patients' preferences (e.g.,

a short life of good quality vs a prolonged survival of a poor quality). It is typically reported as the cost per unit of health, typically in US dollars/ Quality Adjusted Life Year saved ($/QALY). This allows for direct comparisons of health-related outcomes for different types of health interventions.

This brings us to the **incremental cost-effectiveness ratio (ICER)** as an outcome measurement, which represents comparative cost-effectiveness in a single value. It is the ratio of differences in costs to differences in effectiveness and represents the cost of a single additional successful outcome.

A **Cost Benefit Analysis** (CBA) is used to compare interventions that have different outcomes. Both benefits and harms are considered and converted to dollars.

Costs represent the money that is paid for a particular product or service, whilst **value** represents the worth of such a product to the customer or client. This is often dependent on a patient's situation and specific needs, thereby including an important subjective component.

Average cost-effectiveness ratio (ACER) represents the average cost for one successfully treated patient, whereas **ICER** provides a comparator to answer the question: "how much do we have to spend to obtain an additional successful outcome?" (used to compare two different treatment strategies). This links well to the concept of Number Needed to Treat (NNT) which is the number of patients that we need to treat (with a new/ alternative treatment strategy) to achieve **one additional** successful outcome. In these terms ICER can also be expressed as the cost difference (between treatment A and B) x NNT. (Number needed to treat is the inverse of the absolute risk reduction).

This leads to consideration of the **opportunity costs**, which is important in settings where there is scarcity of resources (i.e everywhere!). With a fixed budget allocation, if funds are spent on Product X, we must forego Product Y, **together with its associated benefits**.

Costs include direct- and indirect costs, collectively representing the amount of money paid for a treatment or scan (direct costs) and all other costs incurred, such as medical resources used to treat side effects, travel, loss of income, resources required during the remainder of a patients' life and any money "saved" when an effective form of therapy negates the need for other services.

Willingness to pay (WTP) represents the maximum amount that the funder is willing to pay for a product or service. Factors that may affect the willingness-to-pay include geographical location, demographics, income, education levels, urgency, availability, and the capacity to tolerate risk.

Clearly stating the **perspective** from which an economic analysis has been conducted, allows the reader to determine its usefulness in the context needed from the outset. The most comprehensive analysis is provided from the societal perspective as it includes all costs incurred from all relevant viewpoints (i.e., policy makers, funders, health professionals, patients, and the broader public).[6-8]

The natural course of prostate cancer

The prognosis of prostate cancer is generally good, with a 5-year survival rate of over 98% when localised. (It therefore makes sense to compare long-term costs over at least a period of 60 months).[9] The prognosis obviously varies with the stage of tumour, and worsens significantly with metastatic involvement. Complications include pain requiring irradiation, pathologic fractures, and spinal cord compression. The most appropriate course of treatment is directed by accurate imaging staging which could reveal localised-, oligometastatic- or widespread metastatic disease. Further tailoring of treatment is determined by whether the patient is symptomatic or not and whether the disease is hormone sensitive or castrate-resistant.

Imaging of prostate cancer

Prostate cancer imaging has the potential to avert 3.2% (2.46 million) of all cancer deaths caused, based on cancers modelled between 2020-2030. This would lead to a significant cost savings of 54.92 million life years. Considering a full income approach that is based on the same model, and combining imaging and treatment with quality of care, would result in a potential net benefit of $2.66 trillion, and a net return of $12.43 per $1 invested.[10]

National Comprehensive Cancer Network (NCCN) Guidelines

Current National Comprehensive Cancer Network (NCCN) guidelines (2023)[11] classify Prostate Specific Membrane Antigen Positon Emission Tomography (PSMA PET) as a first-line staging tool for those with unfavourable intermediate- or high-risk disease due to its greater sensitivity and specificity than conventional imaging (i.e. CT or abdominal/pelvic MRI and bone scan). Featured updates to the 2023 NCCN guidelines for prostate

cancer now also includes Lu-177-PSMA-617 as a category 1 consideration for patients with PSMA-positive lesions and/or metastatic disease that is predominately PSMA-positive and with no dominant PSMA-negative metastatic lesions who have been treated previously with androgen receptor–directed therapy and a taxane-based chemotherapy.

Advanced Prostate Cancer consensus conference (**APCCC) 2022**

The Advanced Prostate Cancer consensus conference (APCCC) of 2022[12] published the results of their findings in European Urology earlier this year (2023). An international panel consisting of 117 prostate cancer experts used a modified Delphi process to develop 198 multiple choice questions (MCQs). Experts in the management of prostate cancer were then surveyed (using the afore-mentioned developed MCQs) on complex clinical scenarios encountered when treating prostate cancer patients. They defined consensus as 75% agreement, and strong consensus as 90% agreement. In the majority of clinical scenarios, experts now agree that PSMA-based imaging is the investigation of choice, given its high sensitivity and specificity and based on the results of the ProPSMA trial, which included a significant impact on patient management and lower radiation exposure.[12]

Pivotal Clinical trial(s)

IMAGING OF PROSTATE CANCER: PROPSMA STUDY

Michael Hofman and colleagues were the first to demonstrate the superiority of PSMA-based PET/CT over conventional imaging (consisting of CT and bone scintigraphy) in their 2020 Lancet publication.[13] They included just over 300 men with high risk localised prostate cancer in their two-arm, multicentre clinical trial, and randomised patients to either conventional imaging or PSMA PET/CT. Ninety-eight percent of the 295 men who completed follow up, 30%) had pelvic nodal or distant metastatic disease.

PSMA PET/CT demonstrated an accuracy of 92% compared to 65% accuracy of conventional imaging. It also outperformed conventional imaging in terms of sensitivity (85% vs 38%) and specificity (91% vs 85%) Subgroup analyses confirmed the superiority of PSMA PET-CT with an area under the curve of the receiver operating characteristic curve of 91% compared to 59%. Conventional imaging resulted in more equivocal findings, higher radiation exposure (19.2 vs 8.4 mSv) and effected fewer management changes relative to PSMA-based PET imaging. The authors concluded that PSMA PET with its clearly superior accuracy is a suitable replacement for conventional imaging consisting of CT and bone scintigraphy.[13]

Subsequently several meta-analyses have been published assessing outcomes following imaging with PSMA-based PET, comparing various tracer options (e.g. ^{18}F-Choline-PSMA, ^{68}Ga-PSMA) with conventional imaging such as CT and MRI in different settings and evaluating impact on outcomes.[14] A recent meta-analysis featured in Nature, considered the impact of PSMA PET on the treatment and outcomes of prostate cancer patients with biochemical recurrence. The 34 studies that were included in this analysis (total of 3680 prostate cancer patients) demonstrated positive findings in over two thirds of patients with resultant management changes in more than 50%.[15]

Summary of cost-effectiveness trials in nuclear medicine imaging of prostate cancer

Rovera and colleagues recently shared a mini review (based on four studies) on the use of PSMA PET in striving towards more cost-effective management of prostate cancer. Their literature review revealed only preliminary evidence that was relevant to the pre-surgical setting and in the setting of biochemical recurrence. The authors concluded that PSMA-based PET has the potential to decrease time and expenditure from both a patient and a health-care perspective, likely resulting in a more personalised approach that is guided by appropriate imaging.[16]

They also included a study which compared the cost-effectiveness of PSMA PET as compared to extended pelvic lymph node dissection (ePLND) for patients with intermediate to high risk prostate cancer. This study found that despite a significant savings of 3047 Euro, PSMA provided decreased QALYs compared to ePLND.[17]

The cost-effectiveness study by De Feria Cardet[18], that was based on the ProPSMA trial, identified imaging with ^{68}Ga-PSMA PET/CT as the preferred strategy from an Australian societal perspective. The authors reported savings of AU$ 959 and AU$ 1412 per additional accurate detection of nodal and distant metastases respectively. This resulted in an overall cost saving of more than AU$ 428 per additional accurate diagnosis. Further downstream cost-savings were predicted considering the higher accuracy and significant impact on patient management.

In a very comprehensive Australian study by Song et al, published in 2022[19], the researchers conducted a detailed cost-utility evaluation of PSMA PET/CT in the primary staging of prostate cancer, compared to conventional imaging. The Markov model and decision tree on which calculation were based included a reflection of the percentage of patients with localised vs metastatic disease. They included the following seven health states in their comprehensive model: (1) locoregional Androgen Deprivation Therapy (ADT), (2) locoregional no active treatment; (3) locoregional no active treatment following ADT; (4) Biochemical recurrence (BCR); (5) metastatic disease; (6) died from other causes; and (7) died from prostate cancer.

Their results indicated that an estimated ICER for PSMA PET/CT at $21,147/quality- adjusted life-year gained versus CT+WBBS, and A$36,231/quality-adjusted life-year gained versus CT alone. Sensitivity analyses highlighted the impact of the time horizon and the initial treatments received by metastatic cancer patients. The probability of PSMA PET/CT being cost effective was estimated to be 91% versus CT+WBBS and 89% versus CT alone, using a threshold of AU$50,000/quality-adjusted life-year gained. Despite these findings in this particular Australian setting, the authors still concluded that PSMA PET/CT is likely to be more cost effective compared with conventional imaging.[19]

In 2022, Van der Sar et al[20], evaluated the cost-effectiveness of ^{68}Ga-PSMA-11 when used as part of initial staging as part of treatment planning, and they made use of data obtained from the Dutch healthcare system. Comparison was made to extended pelvic lymph node dissection (e-PLND) and skeletal scintigraphy, which resulted in findings that are comparable to the study by Scholte et al. Their results indicated a cost saving (674 Euro) that was a result of better detection of metastatic involvement, together with a small loss in quality of Life (QoL). The small QoL loss (0,011 QALY/patient was due to the potential false positive findings on PSMA PET, which could wrongly direct a patient to receive palliative therapy rather than curative therapy). All findings were subjected to sensitivity analyses, which indicated that a small reduction (0.8%) in false positives on PSMA PET, or including more information on the side effects of ePLND, would likely change findings to indicate PSMA PET as the dominant, most cost-effective strategy.[20]

A more recent (2023) short communication by Holzgreve et al[21], aimed to evaluate the cost-effectiveness of PSMA outside of the Australian setting in Europe and the USA. They included Belgium, Germany, Italy and the Netherlands in their evaluation and found that PSMA-based PET was more costly in the selected centres. The average cost of a PSMA PET/CT study varied significantly amongst the included centres within wide price ranges provided. This was more significant for PSMA PET than for the conventional imaging modalities, and the cost of PSMA PET is clearly a major contributor to the findings. The scan duration had a significant impact on cost-effectiveness analysis as the patients' hourly wages was also taken into account. Despite these findings, the authors highlight that early PSMA PET imaging direct patient management more accurately (e.g. metastases detection leads to an appropriate referral for systemic therapy rather than first attempting futile local strategies). It is in light of the latter, that the authors suggest that from a health economics perspective, PSMA PET may still be the preferred option, considering the consequences of inappropriate treatment strategies in the absence thereof.[21]

Complicating matters further, are the studies comparing the cost-effectiveness of different PET tracers (e.g. ^{18}F-Choline, ^{18}F-PSMA) and functional magnetic resonance imaging (f-MRI) to conventional imaging approaches.[22] This will not be discussed in depth and suffice to say that cyclotron-produced tracers allow for mass production at presumably lower costs (at the cost of more indeterminate findings) and that MRI is often less accessible than PET.

Following this review of the published evidence, we would like to highlight the following aspects:

- Ga-68-based PSMA PET scans become more cost-effective when in-house generators are available at reasonable cost and when at least two patients can be imaged from the same elution.
- In the setting of biochemical recurrence (BCR), early detection of metastatic disease allows for appropriate escalation of systemic therapy upfront as well as avoidance of futile local therapies such as surgery and external beam radiation. This is likely to result in significant downstream health-related savings.
- There is now sufficient evidence to recommend PSMA PET/CT as a first line imaging investigation to accurately stage and guide appropriate management of prostate cancer patients. Evidence regarding the most cost-effective therapy for prostate cancer patients continue to evolve and should also include consideration of the various targeted

radionuclide therapies offered by nuclear medicine.

Therapy-related costs

Costs that must be considered when comparing different treatment strategies, are more complex, when compared to the imaging possibilities. Costs should not only include that of the drug or therapy administered, but also any costs related to hospitalization needed and treatment costs related to the management of adverse effects.

A requirement for frequent hospitalization results in added costs to the patient such as transport and loss of income. Treatment costs for the duration of a patients' life, as well as the post-treatment costs needed, should all be considered.

When comparing new forms of targeted radionuclide therapies to existing, conventional forms of treatment, outcomes should be compared in terms of progression free survival (PFS), overall survival (OS) and quality of life (QoL). It should ideally be corrected for its chronological place in the treatment landscape, considering the likely outcomes if introduced earlier in the disease, rather than as a last resort.

When considering funding targeted radionuclide therapy, it would be imperative to consider the evidence provided by two recent landmark trials, namely the VISION trial[23] and the TheraP trial.[24]

Pivotal Clinical trial(s) on targeted radionuclide therapy for prostate cancer

VISION TRIAL

This phase 3 trial represents the largest well-designed trial evaluating the use of the theranostic pair consisting of ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA in managing prostate cancer patients. Hofman and colleagues randomized patients (in a ratio of 2:1) to receive either 177-Lu-PSMA-617 in combination with standard of care or best supportive care; or to receive standard of care or best supportive care only. Included patients all had progressive metastatic castrate-resistant prostate cancer that had been heavily pre-treated. All patients had PSMA positive disease on PET/CT. Endpoints included PFS, OS, Quality of life assessments, biochemical- and imaging responses. Results from this trial indicate that all key secondary endpoints significantly favoured the Lu-177-PSMA group. This treatment group demonstrated a median PFS of 8.7 vs. 3.4 months; hazard ratio for progression or death of 0.40; with a 99.2% confidence interval [CI], 0.29 to 0.57; P<0.001) and overall survival (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; P<0.001). Importantly, their quality of life remained unaffected, despite a higher incidence (52.7% vs. 38.0%) of grade 3 adverse events.[23]

TheraP trial

In another landmark trial, TheraP, Hofman and colleagues included 11 Australian centres in an open-labelled, randomised trial to compare ^{177}Lu-PSMA-617 to cabazitaxel. They included 200 patients with metastatic castration-resistant prostate cancer that progressed after docetaxel and all patients were imaged with [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET prior to randomisation. Ninety-nine patients were randomised to the PRRT and 101 patients received cabazitaxel, and no difference in overall survival could be demonstrated. The researchers proposed [^{177}Lu]Lu-PSMA-617 as an alternative form of treatment for patients with metastatic castrate-resistant prostate cancer that progress after docetaxel.[24]

Considering the treatment costs in prostate cancer

There is an obvious gap in the published literature on targeted radionuclide therapy for prostate cancer, with hardly a handful of papers reporting on the costs of targeted radionuclide therapies offered by nuclear medicine physicians (amongst the targeted alpha therapies, only the cost of Radium-225 has been reported on[25]). Probably the most important paper in this domain, is the one by Mehrens and colleagues published in the JNCCN in January 2023.[26]

These authors based their cost-effectiveness evaluation on the findings provided by the VISION trial, for which a partitioned survival model was developed based on decision analysis software. (Hofman et al in the afore-mentioned trial demonstrated both increased progression-free and overall survival for prostate cancer patients treated with ^{177}Lu-PSMA-617 compared to standard of care alone). The costs of treatment were extrapolated from that of ^{177}Lu-DOTATATE and adverse effects and health state utilities, were obtained from public databases and publications.[26]

They adopted the perspective of the US healthcare system over a lifetime period of 60 months (based on time duration to 99% death rate), a treatment cycle length of one month and willingness to pay thresholds of 50 000, 100 00 and 200 000 USD per Quality Adjusted Life Year (QALY). Incremental cost effectiveness ratio (ICER) and cost-effectiveness ratios were reported. Probabilistic sensitivity

analysis was performed based on 10 000 iterations with a Markov model, which included three states (progression free, disease progression and death as the only absorptive state). The authors reported their findings in accordance with the 2022 CHEERS guideline for health economic analysis. Costs were discounted at three percent per annum and all costs were adjusted to USD according to the 2021 Consumer Price Index.[26]

The base case analysis demonstrated an increased effectiveness of 0.42 QALY at an increase in cost of 83 712 USD, which resulted in an ICER of $200,708 per QALY. Sensitivity analysis demonstrated no significant impact when variations in time horizon, discount rate, adverse events, posttrial treatment, costs for best supportive care, and end-of-life costs were considered.[26]

The authors concluded that therapy with Lu-177-PSMA provides significant clinical benefit (prolonged PFS and OS with minimal side effects), which would be a cost-effective strategy under certain clinical scenarios (37% of Monte Carlo simulations). This recommendation is based on the significantly higher cost of targeted radionuclide therapy with Lu-177-PSMA (approximately 169 100 USD vs 85 300 USD, which results in a cost-effectiveness ratio of just over 200 000 USD/QALY and 0.42 gained QALYs in the Lu-177-treatment group.[26]

Notably, this applies to a willingness-to pay threshold of over 200 000 USD/QALY (an unrealistic expectation in lower- to middle income countries). Since analysis was based on the VISION trial data, it follows that these findings hold true for those patients with widespread metastatic castrate-resistant cancer. However, future data may indicate the importance of initiating therapy with Lu-177-PSMA at an earlier stage- potentially improving PFS and OS further with a significant increase in QALYs.

Other limitations include the lack of data on certain aspects of standard treatment regimes, adverse events and assumptions made by the authors, despite the high quality of this publication. Hospitalisation costs were not considered, which may lead to increased cost-effectiveness for the outpatient-based Lu-177-PSMA therapy. Importantly, it is the significantly higher cost of Lu-177-PSMA-617 (compared to conventional forms of therapy) that seriously impacts on the cost-effectiveness of the former. Studies from a societal perspective, should further highlight the costs of hospitalisation with its resultant loss of income (in favour of targeted radionuclide therapy).

Conclusion

We found a paucity of literature that deals with healthcare costs, with an obvious need for more cost-effectiveness studies to demonstrate the positive impact of nuclear medicine in the management of oncology (and other) patients. These studies need to be based on well-conducted clinical trials and meta-analyses, with appropriate model simulations and decision analysis and should ideally be reported according to the CHEERS 2022 guidelines to improve uniformity and robustness.

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