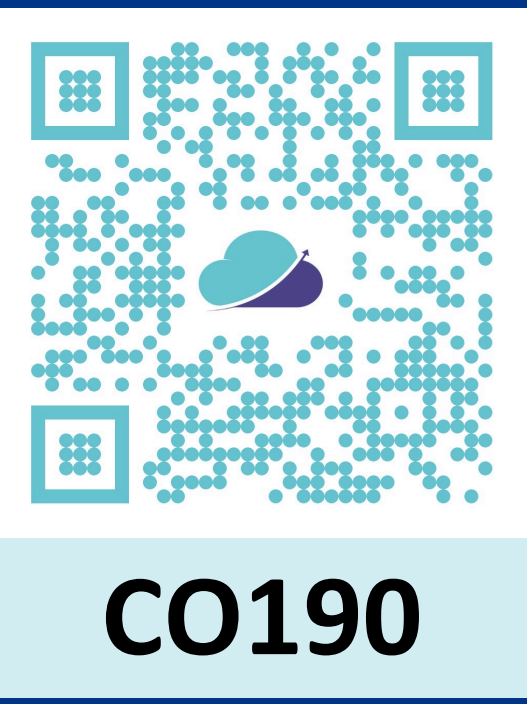


Prognostic Accuracy and Clinical Effectiveness of ⁶⁸Ga-PSMA-11 PET/CT (ILLUCCIX®) Imaging Followed by ¹⁷⁷Lu-PSMA-617 Therapy in Metastatic Castration-Resistant Prostate Cancer: A Systematic Literature Review

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INTRODUCTION

- Accurate patient selection and early response assessment are critical to optimize health outcomes and reduce unnecessary toxicity in metastatic castration-resistant prostate cancer (**mCRPC**)¹
- ⁶⁸Ga prostate-specific membrane antigen positron emission tomography/computed tomography (**⁶⁸Ga-PSMA-11 PET/CT**) detects PSMA expression and enables a theranostic approach to identify patients suitable for **¹⁷⁷Lu-PSMA-617** therapy
- While the ¹⁷⁷Lu-PSMA-617 therapy is associated with higher costs than cabazitaxel or best supportive care (BSC), the therapy offers significant QALY gains²⁻³
- This systematic literature review (SLR) evaluates the prognostic accuracy of ⁶⁸Ga-PSMA-11 PET/CT imaging for treatment response assessment and its clinical effectiveness compared to no PSMA PET/CT imaging in patients with mCRPC who are potential candidates for PSMA-targeted radioligand therapy

METHOD

Search Strategy: A systematic search was conducted in Embase, Medline, and the Cochrane Library (inception to July 2023) to identify randomized controlled trials (RCTs), single-arm studies, and observational studies

Study selection:

- Studies were included if they evaluated the prognostic accuracy of ⁶⁸Ga-PSMA-11 PET/CT imaging for treatment response assessment
- Studies were also included if they compared the clinical effectiveness of ⁶⁸Ga-PSMA-11 PET/CT imaging followed by ¹⁷⁷Lu-PSMA-617 therapy* vs no PSMA PET/CT imaging followed by cabazitaxel or BSC in mCRPC patients (**Table 1**)

*as a proxy for PSMA radioligand therapy

Table 1. Eligibility Criteria

Component	Description
Population	Patients with progressive or symptomatic mCRPC
Intervention	<ul style="list-style-type: none">Diagnostic test: ⁶⁸Ga-PSMA-11 PET/CT imagingTherapeutic intervention: ¹⁷⁷Lu-PSMA-617 (as proxy for PSMA-targeted therapy)
Comparator	<ul style="list-style-type: none">Diagnostic test: No ⁶⁸Ga-PSMA-11 PET/CT imagingTherapeutic intervention: Cabazitaxel or best supportive care (BSC)
Outcomes	<p>Treatment Response Assessment: <i>Response evaluation:</i> Assessment of therapy response using tumour markers (e.g., PSA) and imaging-based criteria (RECIST, PERCIST)</p> <p>Clinical Effectiveness: <i>Efficacy outcomes:</i> Overall survival (OS), progression-free survival (PFS), and mortality (including cancer-specific mortality)</p> <p><i>Safety outcomes:</i> Radiation exposure (patients, carers, staff) and adverse effects of therapy (haematologic, renal, xerostomia, etc.)</p>
Study design	<ul style="list-style-type: none">Randomized controlled trials (RCTs), single-arm studies, observational studiesSLR and meta-analysis (for bibliographic searching only)

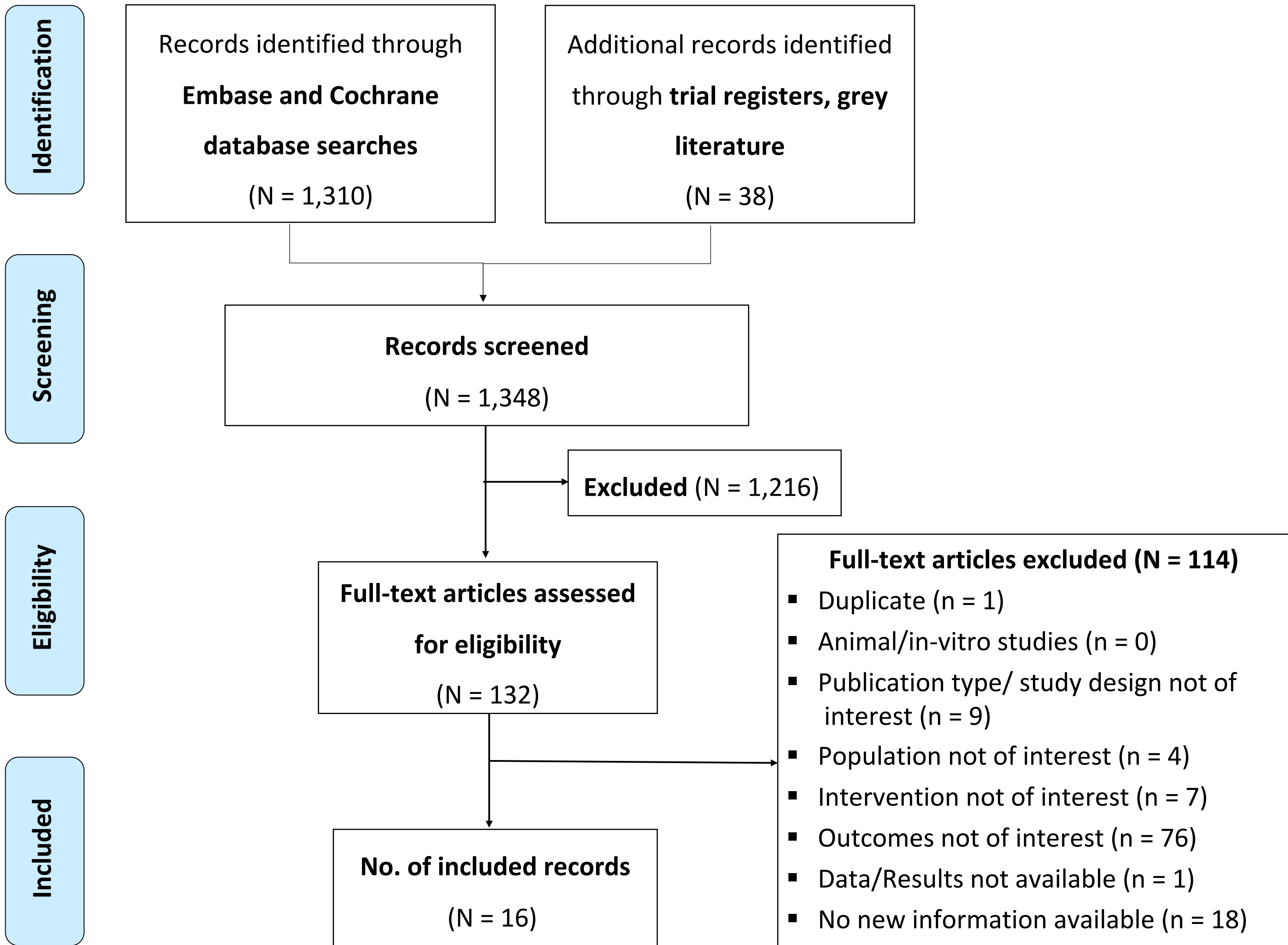
Abbreviations: BSC, Best supportive care, mCRPC, Metastatic castration-resistant prostate cancer; OS, Overall survival; PERCIST, Positron emission tomography response criteria in solid tumours; PET/CT, Positron emission tomography; PFS, Progression-free survival; PSA, Prostate-specific antigen; PSMA, Prostate specific membrane antigen; RCTs, Randomized controlled trials; RECIST, Response evaluation criteria in solid tumours; SLR, Systematic literature review.

RESULTS

Study Characteristics

- Sixteen publications reporting fifteen studies (two RCTs, three single-arm phase II trials, and 10 observational studies) were included in the SLR (**Figure 1** and **Table 2**)

Figure 1. PRISMA Flow Diagram Depicting Study Selection and Inclusion Process



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Table 2. Characteristic of the Included Studies

Study (Year)	N	Design	Treatment	Imaging	Response Assessment	Outcomes
Hofman et al., 2021 (TheraP) ⁴	200	Phase II RCT	¹⁷⁷ Lu-PSMA-617	⁶⁸ Ga-PSMA-11 PET/CT	RECIST, EORTC	OS, PFS, PSA response
Sartor et al., 2021 (VISION) ⁵	831	Phase III RCT	¹⁷⁷ Lu-PSMA-617	⁶⁸ Ga-PSMA-11 PET/CT	RECIST	OS, PFS, PSA response
Hofman et al., 2018 ⁶	30	Single-arm Phase II	¹⁷⁷ Lu-PSMA-617	⁶⁸ Ga-PSMA-11 PET/CT	RECIST, SUVmax	OS, PFS, PSA response
Violet et al., 2020 ⁷	50	Single-arm Phase II	¹⁷⁷ Lu-PSMA-617	⁶⁸ Ga-PSMA-11 PET/CT + ¹⁸ F-FDG	RECIST, EORTC	OS, PFS, PSA response
Yadav et al., 2020 ⁸	90	Single-arm Phase II	¹⁷⁷ Lu-PSMA-617	⁶⁸ Ga-PSMA-HBED-CC	RECIST, SUVpeak	OS, PFS, PSA response
Ahmadzadehfar et al., 2016 ⁹	20	Retrospective observational	¹⁷⁷ Lu-PSMA-617	⁶⁸ Ga-PSMA-11 PET/CT	RECIST	PSA response
Baum et al., 2016 ¹⁰	56	Retrospective observational	¹⁷⁷ Lu-PSMA RLT	⁶⁸ Ga-PSMA-11 PET/CT	RECIST, SUVmax	OS, PFS, PSA response
Heinzel et al., 2018 ¹¹	45	Retrospective observational	¹⁷⁷ Lu-PSMA-617	⁶⁸ Ga-PSMA-11 PET/CT	PERCIST	PSA response
Grubmüller et al., 2019 ¹²	38	Retrospective observational	¹⁷⁷ Lu-PSMA-617	⁶⁸ Ga-PSMA-HBED-CC	RECIST, PERCIST	OS, PSA response
McBean et al., 2019 ¹³	50	Prospective observational	¹⁷⁷ Lu-PSMA	⁶⁸ Ga-PSMA-11 PET/CT	–	PSA response
Zang et al., 2019 ¹⁴	9	Retrospective observational	¹⁷⁷ Lu-EB-PSMA-617	⁶⁸ Ga-PSMA-617 PET/CT	ΔSUVmax	PSA response
Kesavan et al., 2021 ¹⁵	100	Retrospective observational	¹⁷⁷ Lu-PSMA I&T	⁶⁸ Ga-PSMA-11 PET/CT	PERCIST	OS, PFS
Khreish et al., 2021 ¹⁶	51	Retrospective observational	¹⁷⁷ Lu-PSMA-617	⁶⁸ Ga-PSMA-11 PET/CT	PERCIST, SUVpeak	OS, PFS
Erdogan et al., 2022 ¹⁷	23	Retrospective observational	¹⁷⁷ Lu-PSMA I&T	⁶⁸ Ga-PSMA-11 PET/CT	PERCIST, SUVmax	PSA response
Rosar et al., 2022 ¹⁸	66	Retrospective observational	¹⁷⁷ Lu-PSMA-617	⁶⁸ Ga-PSMA-11 PET/CT	PERCIST, PCWG3	OS, PSA response

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; FDG, Fluorodeoxyglucose; I&T, Imaging and therapy; OS, Overall survival; PCWG3, Prostate Cancer Working Group 3; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumours; PET/CT, Positron emission tomography/computed tomography; PFS, Progression-free survival; PSA, Prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours; RLT, Radioligand therapy; SUV, Standardized uptake value.

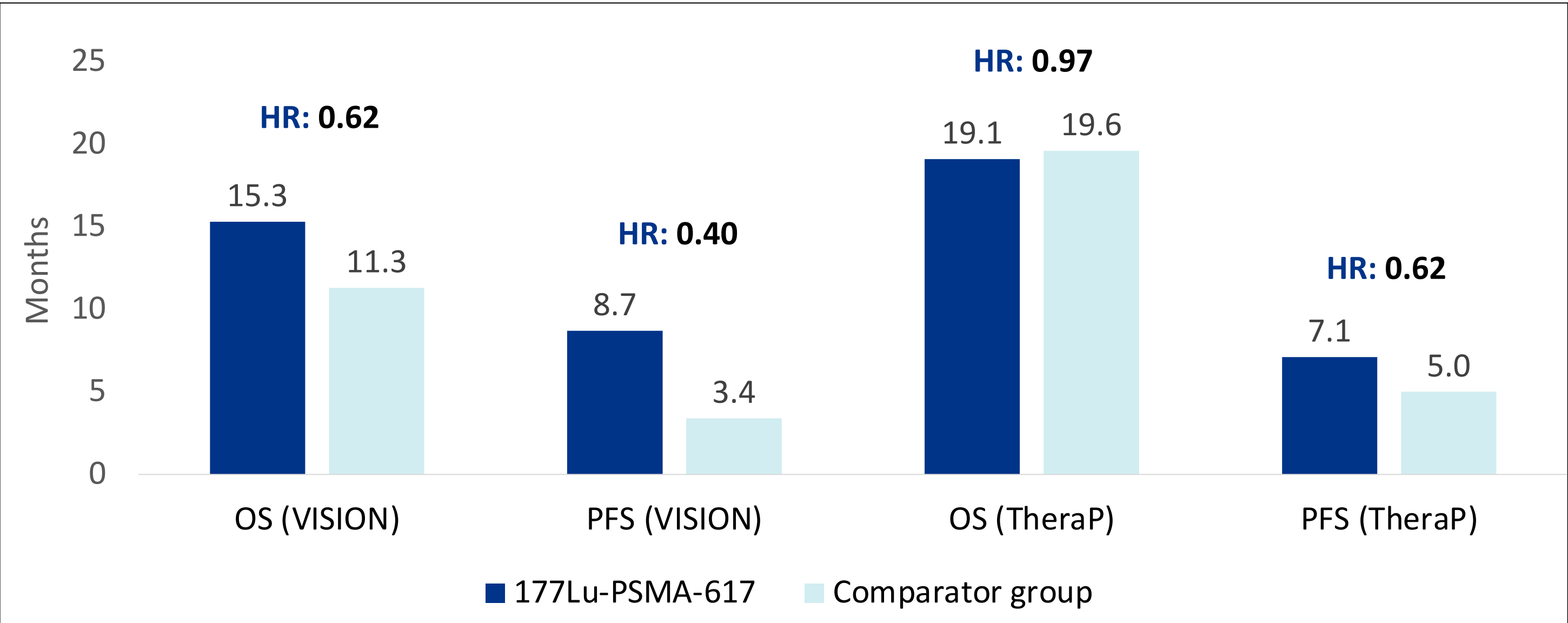
Treatment Response Assessment

- In the TheraP trial⁴, a ≥50% prostate-specific antigen (PSA) decline was achieved in 66% of patients treated with ¹⁷⁷Lu-PSMA-617 compared with 37% receiving cabazitaxel
- Similarly, Hofman et al., 2018⁶ reported a ≥50% PSA decline in 57% of patients, while Yadav et al., 2020⁸ showed ≥50% PSA declines in 32–45% of patients
- Favorable radiographic and molecular responses were observed: 56% and 42% in Violet et al., 2020⁷, and 77% and 71% in Yadav et al., 2020⁸, respectively

Clinical Effectiveness

- None of the studies directly evaluated the impact of ⁶⁸Ga-PSMA-11 PET/CT imaging on patient health outcomes; however, evidence from two RCTs⁴⁻⁵ showed improved outcomes with ¹⁷⁷Lu-PSMA-617 in patients selected using ⁶⁸Ga-PSMA-11 PET/CT
- In the **TheraP trial**⁴ (n=200; median follow-up of 36 months), ¹⁷⁷Lu-PSMA-617 demonstrated improved progression-free survival (PFS) (HR 0.62, p=0.0028) compared with cabazitaxel, while overall survival (OS) was comparable between arms (19.1 vs 19.6 months; HR 0.97, p=0.99) (**Figure 2**)
- In the **VISION trial**⁵ (n=831; median follow-up of 20.9 months), ¹⁷⁷Lu-PSMA-617 significantly improved PFS (8.7 vs 3.4 months; HR 0.40, p<0.001) and OS (15.3 vs 11.3 months; HR 0.62, p<0.001) compared with BSC (**Figure 2**)
- Across both trials, ¹⁷⁷Lu-PSMA-617 was associated with more hematologic but fewer chemotherapy-related toxicities, showing an overall manageable safety profile

Figure 2. Clinical Effectiveness Outcomes



Abbreviations: HR, Hazard ratio; OS, Overall survival; PFS, Progression-free survival; PSMA, Prostate-specific membrane antigen

CONCLUSIONS

- This review supports the theranostic approach of using ⁶⁸Ga-PSMA-11 PET/CT imaging to identify suitable candidates for PSMA-targeted radioligand therapy and to enable accurate assessment of treatment response
- While direct evidence of imaging-related health outcomes is lacking, downstream improvements in clinical outcomes with ¹⁷⁷Lu-PSMA-617 validate the utility of this imaging-guided treatment strategy in mCRPC

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