EJNMMI Reports

ORIGINAL ARTICLE

Open Access

Real world experience with [^{99m}Tc]Tc-HYNIC-iPSMA SPECT prostate cancer detection: interim results from the global NOBLE registry

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Abstract

Purpose [^{99m}Tc]Tc-HYNIC-iPSMA is a novel technetium-99m-labelled small molecule inhibitor of the prostate-specific membrane antigen (PSMA) for detecting prostate cancer (PC). The objective of this registry was to collect and evaluate [^{99m}Tc]Tc-HYNIC-iPSMA patient data and images to establish the safety and tolerability, and clinical utility of this agent in imaging at different stages of PC.

Methods Patients 18 to 80 years old with primary staging and metastatic PC were eligible. Patients unable to perform prescribed examinations, undergo a [^{99m}Tc]Tc-HYNIC-iPSMA planar and SPECT or SPECT/CT (when available), or sign a patient informed consent form were excluded from the registry. All eligible patients underwent a screening and baseline visit before imaging with [^{99m}Tc]Tc-HYNIC-iPSMA. The primary safety endpoint was assessed by collecting and grading all treatment-related adverse events using the Common Terminology Criteria for Adverse Events. Patients were followed until disease progression, death, serious or intolerable adverse events, registry termination by the sponsor, patient withdrawal, or lost to follow-up. Analysis was planned for when data was available from 40 enrolled patients.

Results 40 patients enrolled in 6 countries and received [^{99m}Tc]Tc-HYNIC-iPSMA tracer administration followed by planar and SPECT imaging. Of the 40 patients included, investigators reported a change in management due to the [^{99m}Tc]Tc-HYNIC-iPSMA imaging in 17/40 of patients (42.5%). No adverse events were reported.

Conclusions [^{99m}Tc]Tc-HYNIC-iPSMA is a promising option to identify PSMA-positive prostate cancer on SPECT and could improve patient access to PSMA imaging worldwide.

Keywords 99mTc-HYNIC-iPSMA, SPECT, Tc-99m-iPSMA, PET/CT, Prostate cancer, PSMA

Introduction

Prostate cancer (PC) is the most common malignancy among older men (Jemal et al. 2010; Crawford 2003). Approximately two million men globally are diagnosed with PC each year, with 10 million men living with the disease and 700,000 living with metastatic

disease (Global 2018; Sung et al. 2021; Siegel et al. 2022). In patients with localized PC, the five-year survival rate approaches 100%; however, in patients with metastases, the five-year survival rate drops to 31% (Wei et al. 2007). A precise diagnosis of the metastatic site and disease stage will influence the treatment decision and therapeutic outcome. Therefore, developing accurate diagnostic methods to stratify patients for the most appropriate treatment strategy is essential.

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein overexpressed in more than 90% of PC cells, and levels directly correlate with androgen independence, metastasis, and PC progression (Santoni et al. 2014; Afshar-Oromieh et al. 2013). PSMA-targeting compounds (e.g., PSMA-11, PSMA I&T, PSMA-617, PSMA-1007, DCFPyL, rhPSMA7.3) can be coupled with positron emitting radionuclides such as Gallium-68 [^{68}Ga], Fluorine-18 [^{18}F] or Copper-64[^{64}Cu] to form a positron emission tomography (PET) radiotracer (Cardillo et al. 2004; Hillier et al. 2009). The PET radiotracer biodistribution can be imaged using PET/computed tomography (CT) or PET/magnetic resonance imaging (MRI) generated whole-body mapping of PSMA expression (Cardillo et al. 2004; Hillier et al. 2009). Compared to CT or MRI alone, radionuclide-based imaging (PET and single-photon emission CT [SPECT]) provides richer pathological insights at the molecular level. PET generally provides higher spatial resolution and sensitivity over SPECT; therefore, most of the commercial PSMA-inhibiting diagnostic radiopharmaceuticals have been labelled with positron-emitting radionuclides. Importantly, access to PET-based PSMA imaging can be limited based on socio-economic factors, geographic factors, or health care structure and funding models.

In the past decade, data has emerged to show ^{68}Ga-labelled PSMA imaging with combined PET and CT ([^{68}Ga]Ga-PSMA PET/CT) as a safe, efficacious, and an overall superior alternative to conventional imaging approaches in PC (Afshar-Oromieh et al. 2014; Giesel et al. 2015; Maurer et al. 2016). Furthermore, meta-analyses show PSMA PET/CT has excellent diagnostic performance for primary and secondary staging due to its ability to detect lesions even at low PSA serum levels (Perera et al. 2016; Eyben et al. 2018; Duncan et al. 2023). Given the broad availability of SPECT devices and inherently lower radionuclide costs, SPECT systems have immense potential for application to improve PSMA imaging capacity, particularly on an international level where SPECT cameras out-number PET worldwide by >4:1 (Li et al. 2022a, b; Hirschfeld et al. 2021). Accordingly, the [^{99m}Tc] radionuclide widely continues to play an important role in diagnostic nuclear medicine, accounting for 75–80% of nuclear medicine studies globally (Brunello et al. 2022). Moreover, [^{99m}Tc] may be a cost-effective option in SPECT imaging, given its well-established global supply chain and comparable ease of manufacturing (OECD/NEA 2019; Albalooshi et al. 2020). Implementing [^{99m}Tc] as a PSMA-targeted imaging tracer with SPECT would significantly increase patient access and fulfil an unmet need for millions of patients who do not have access to PET imaging (Robu et al. 2017).

Recently, a novel ^{99m}Tc-labelled PSMA inhibitor (iPSMA) containing hydrazinonicotinamide (HYNIC) has been synthesised ([^{99m}Tc]Tc-HYNIC-iPSMA) (Xu et al. 2017; Zhang et al. 2020). Adding HYNIC as a chemical group improves the molecule's lipophilicity and enhances coupling to PSMA hydrophobic sites, allowing specific accumulation in PSMA-positive tumours to match the sensitivity of PET imaging (Santos-Cuevas et al. 2018). The HYNIC ligand incorporates the Lys(Nal)-urea-Glu inhibitor motif to

facilitate the indirect labelling procedure necessary to complete the technetium coordination sphere (Duatti 2021). The prepared [^{99m}Tc]Tc-HYNIC-iPSMA freeze kit formulation has a high radiochemical yield (>99%) without post-labelling purification, making it a straightforward and cost-effective option to consumers, and is ideal for routine clinical applications in PC patients (Duatti 2021; Li et al. 2022a, b; Ferro-Flores et al. 2017). The kit-based reconstitution process is an advantage to clinical sites without an on-site radiopharmacist over other ^{99m}Tc-based PSMA probes that require more complex synthesis and purification.

In vitro studies have shown specific receptor binding and internalisation of [^{99m}Tc]Tc-HYNIC-iPSMA in LNCaP cells (Duatti 2021). Preclinical studies in xenografts revealed a high and stable PSMA-dependent tumour uptake (9.84±2.63% ID/g at 3 h after infusion) with little accumulation in other non-target organs (<2% ID/g at 1 h after infusion) (Ferro-Flores et al. 2017). In healthy human volunteers, [^{99m}Tc]Tc-HYNIC-iPSMA exhibited renal and hepatic excretion with significant uptake in parathyroid, salivary and lacrimal glands; SPECT imaging of two patients with PC demonstrated clear PSMA overexpression in prostate tumours and metastases (Santos-Cuevas et al. 2018; Ferro-Flores et al. 2017). These results were mirrored in a registry evaluating the clinical safety of [^{99m}Tc]Tc-HYNIC-iPSMA in PC patients, where the compound was excreted mainly through the urinary system and non-target organ absorption (including the brain and heart) was low (Zhang et al. 2021). Currently, [^{99m}Tc]Tc-HYNIC has been evaluated for breast tumour targeting ([^{99m}Tc]Tc-HYNIC-FROP), neuroendocrine tumour diagnosis ([^{99m}Tc]Tc-HYNIC-TOC), and pulmonary fibrosis imaging ([^{99m}Tc]Tc-HYNIC-VNTANST) (Ahmadpour et al. 2018; Liepe and Becker 2018; Rezaeianpour et al. 2023). In PC clinical studies, [^{99m}Tc]Tc-HYNIC-iPSMA SPECT imaging has demonstrated high detection rates for biochemically recurrent PC patients after radical prostatectomy (overall detection rate of 80.3%; 118/147) (Li et al. 2022a, b).

[^{99m}Tc]Tc-HYNIC-iPSMA has significant potential for widespread clinical application on an international level where PET is less readily available or accessible (Eiber et al. 2015). The primary aim of this prospective registry was to assess the safety and efficacy/tolerability of [^{99m}Tc]Tc-HYNIC-iPSMA SPECT imaging in the detection/diagnosis of PC as reported in the published interim findings.

Materials and methods

Participants

Forty patients (40% of target enrollment) with confirmed PC have been enrolled in this prospective, observational, multicentre, multi-national registry (100 patients total intended to be enrolled) with PC. The primary objective is to assess the safety and tolerability of [^{99m}Tc]Tc-HYNIC-iPSMA administration by collection of all treatment-related (serious) adverse events ([S]AE). The secondary objective is to determine the clinical relevance of [^{99m}Tc]Tc-HYNIC-iPSMA SPECT imaging in detecting disease at different stages of PC. Patients aged 18 to 80 years old diagnosed with PC are eligible for participation. Patients who have psychiatric disease or are unable to perform the prescribed examinations; do not having sufficient background preventing a thorough evaluation of the diagnostic applicability of a [^{99m}Tc]Tc-HYNIC-iPSMA SPECT scan; or are unable to understand (or unwilling to sign) a written patient informed consent are excluded from this registry.

Registry design

Eligibility of patients is being ascertained through screening of medical records at participating institutions in this prospective study. This study was approved by Institutional Review Boards at each participating site. All procedures performed in studies involving human patients were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all patients included in the study.

To evaluate the safety endpoint, all treatment-related adverse events were collected and graded using the Common Terminology Criteria for Adverse Events. Patients were monitored until disease progression, death, serious or intolerable adverse events, registry termination by the sponsor, patient withdrawal, or loss to follow-up. An analysis was scheduled when data were available from 40 enrolled patients. Patients participated in a screening visit where demographic information, medical history, and physical exam findings were recorded. In a subsequent visit, [^{99m}Tc]Tc-HYNIC-iPSMA imaging was performed 2 to 4 h after intravenous administration of 555 to 740 MBq (15 to 20 mCi) and 50 μg of HYNIC-iPSMA. Patients were followed, and data were collected from post-imaging records.

Synthesis and preparation of [99mTc]Tc-HYNIC-iPSMA

Synthesis of [^{99m}Tc]Tc-HYNIC-iPSMA has been previously described (Ferro-Flores et al. 2017). Each kit of [^{99m}Tc]Tc-HYNIC-iPSMA was prepared according to the manufacturer's instructions. Briefly, 10 mg of HYNIC-Glu-Urea-A, 0.5 mL of EDDA (20 mg/mL in 0.1MNaOH), 0.5 ml Tricine solution (40 mg/mL in 0.2MPBS, pH=6.0), 25 ml of SnCl2 solution (1 mg/mL in 0.1MHCl) was reconstituted with 1110 to 2220 MBq of Na^{99m}TcO4. Reconstitution involved addition of 1.0 mL of 0.2 M phosphate buffer solution (pH 7.0) followed by the addition of 1.0 mL of a sterile, bacterial endotoxin-free solution of sodium pertechnetate and incubation for 15 min in a block heater at 95° C or in boiling water. Post reconstitution, an aqueous, transparent solution of [^{99m}Tc]Tc-HYNIC-iPSMA, with a pH of 6.5–7.5, was ready for intravenous administration. The radiochemical purity was not less than 95%, as determined by radio-TLC or high-performance liquid chromatography (HPLC).

Imaging and data analysis

Planar whole-body (WB) images and SPECT data acquisition were performed using dual-head gamma camera and hybrid SPECT/CT cameras when available (Table 1).

Following planar image acquisition, SPECT or SPECT/CT of the thoracic, abdominal and pelvic regions were performed for each patient. Planar, SPECT and low-dose CT scan (when available) were performed per site standard of care practises. Nuclear

Table 1 Nuclear Medicine scanners and sites where utilised

Site Name	Scanner
Egypt	GE Tandem 830
South Africa	Mediso SPECT/CT
Mexico	Philips Brightview
Australia	GE Infinia Hawkeye
Indonesia	Philips Brightview
Azerbaijan	Siemens Intevo 6

medicine camera calibrations and quality control procedures were performed per manufacturer recommendations.

SPECT, and if available, CT, and fused imaging of [^{99m}Tc]Tc-HYNIC-iPSMA scans were analysed at local centres by an experienced nuclear medicine physician, and a determination made of whether the [^{99m}Tc]Tc-HYNIC-iPSMA scan resulted in a change in the patient's management. Positive lesions were identified if the [^{99m}Tc]Tc-HYNIC-iPSMA uptake in the lesion was higher than the surrounding normal tissues and not associated with physiological uptake. In this registry, all lesions suggesting recurrence of PC were categorised into local recurrence, lymph node metastases, bone metastases, and visceral metastases (e.g., lung, liver) via visual assessment. We report changes in planned or current treatment based on [^{99m}Tc]Tc-HYNIC-iPSMA imaging results.

Results

Demographic and baseline characteristics

Data from 40 patients were included in the analysis. The average age at imaging was 68 ± 7.2 years. At diagnosis, 8 patients had a reported Gleason score (median score 7.5 (Siegel et al. 2022; Wei et al. 2007; Santoni et al. 2014; Afshar-Oromieh et al. 2013; Cardillo et al. 2004)). The mean prostate specific antigen (PSA) was 66 ng/mL; 6 (15%), 6 (15%), and 28 (70%) patients had PSA values between 0 to ≤2, >2 to ≤10, and >10 ng/mL, respectively. Most patients enrolled were Caucasian (n=27 [67.5%]) and from the Australia clinical site (37.5%), followed by Azerbaijan (17.5%), Mexico and Indonesia (both 15.0%), Egypt (12.5%), and South Africa (2.5%). Clinical staging was the most common reason for [^{99m}Tc]Tc-HYNIC-iPSMA imaging (n=21 [52.5%]), followed by restaging of the disease (n=11 [27.5%]), therapy response assessment (n=6 [15.0%]), and biochemical recurrence (n=2 [5.0%]). Seven patients had radical treatment therapy (radical prostatectomy, n=4 [10.0%]; exposure and response prevention therapy, n=3 [7.5%]). The most common treatment was androgen deprivation therapy (ADT) (n=19 [47.5%]), followed by surgery (n=11 [27.5%]), radiotherapy (n=3 [7.5%]), chemotherapy (n=2 [5.0%]) or other (including surveillance, clinical trials, high intensity focused ultrasound, tadalafil, and palliative care; n=7 [17.5%]). Five patients (12.5%) had an unknown treatment history. Patient baseline characteristics are summarised in Table 2.

Safety and biodistribution

No adverse reactions or events were observed regarding the use of the radiotracer. Normal physiologic biodistribution of [^{99m}Tc]Tc-HYNIC-iPSMA on SPECT scans was observed with high activity background in the liver, spleen, kidneys, lacrimal and salivary glands, oral and nasal mucosa, bowels, and urinary bladder (see Fig. 1). Compared to other organs, the kidneys displayed the highest uptake of [^{99m}Tc]Tc-HYNIC-iPSMA throughout the test while the spleen and heart had relatively low levels of uptake, consistent with previous reports.

[^{99m}Tc]Tc-HYNIC-iPSMA clinical utility & prior imaging

It was found that 30 patients (75%) had one or more prior imaging: bone scan (only) was the most common (n=9 [22.5%]); followed by MRI (n=6 [15.0%]); ^{68}Ga-PSMA PET (n=5 [12.5%]); CT (n=3 [7.5%]); CT and bone scan (n=3 [7.5%]); [^{68}Ga]Ga-PSMA PET, MRI and bone scan (n=1 [2.5%]); [^{68}Ga]Ga-PSMA PET and CT (n=1 [2.5%]); chest

Table 2 Demographic & baseline characteristics of patients at initial screening

Characteristic	Initial screening (n = 40)
Age at scanning, mean (SD), yrs	68 ± (7.2)
Gleason score, n	8
Median (range)	7.5 (5–9)
≤7, n (%)	4 (50.0%)
≥8, n (%)	4 (50.0%)
PSA range (ng/mL), mean (range)	66 (0–428)
0–2, n (%)	6 (15%)
2–10, n (%)	6 (15%)
>10, n (%)	28 (70%)
Race	
Caucasian, n (%)	27 (67.5%)
Asian, n (%)	6 (15.0%)
Hispanic or Latino, n (%)	4 (10.0%)
Black or African American, n (%)	2 (5.0%)
American Indian, n (%)	1 (2.5%)
Clinical sites, n (%)	
Egypt	5 (12.5%)
South Africa	1 (2.5%)
Mexico	6 (15.0%)
Australia	15 (37.5%)
Indonesia	6 (15.0%)
Azerbaijan	7 (17.5%)
Indications, n (%)	
Initial clinical staging	21 (52.5%)
Restaging of disease	11 (27.5%)
Therapy response assessment	6 (15.0%)
Biochemical recurrence	2 (5.0%)
Radical treatment count, n (%)	
None	33 (82.5%)
Radical prostatectomy	4 (10.0%)
EBRT	3 (7.5%)
Treatment, n (%)	
ADT	19 (47.5%)
Surgery	12 (30.0)
Radiotherapy	3 (7.5%)
Chemotherapy	2 (5.0%)
Other[b]	7 (17.5%)
Unknown	5 (12.5%)

[a]One or more imaging types possible

[b]Including surveillance, clinical trials, high-intensity focused ultrasound, tadalafil, and palliative care

ADT, Androgen Deprivation Therapy; **CT**, Computed Tomography; **EBRT**, External Beam Radiation Therapy; **LN**, Lymph Node; **MRI**, Magnetic Resonance Imaging; **PET**, Positron Emission Tomography; **PSMA**, Prostate-Specific Membrane Antigen; **SD**, Standard Deviation

X-ray and ultrasound ($n=1$ [2.5%]); and MRI and bone scan ($n=1$ [2.5%]). In 10 patients with previous imaging, metastases were detected, in the bones ($n=5$ [12.5%]), locoregional lymph nodes ($n=2$ [5.0%]), or both ($n=1$ [2.5%]), including the prostate bed and distant lymph nodes ($n=2$ [5.0%]).

At least one PSMA-positive lesion was detected in 77.5% (31/40) of patients with [^{99m}Tc]Tc-HYNIC-iPSMA SPECT imaging. The detection rate of [^{99m}Tc]Tc-HYNIC-iPSMA tracer was 16.6% (1/6), 83.3% (5/6), and 89.2% (25/28) at PSA levels of 0–2 ng/mL, >2–10 ng/mL, and >10 ng/mL, respectively. Furthermore, the detection rate of

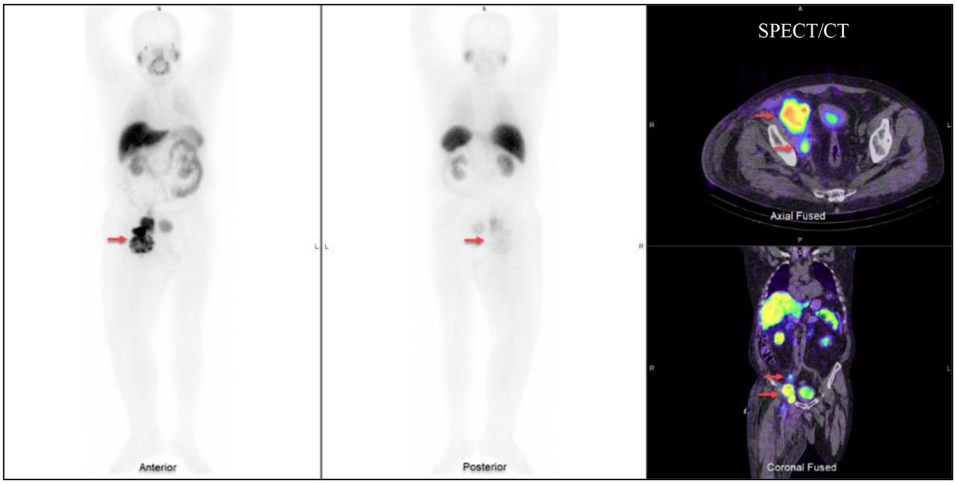

Fig. 1 Biodistribution of [^{99m}Tc]Tc-HYNIC-iPSMA. Planar images (left and middle pane) show normal biodistribution in the liver, spleen, kidneys, lacrimal and salivary glands, oral and nasal mucosa, bowels, and urinary bladder. Red arrows show enlarged pelvic and inguinal lymph nodes with increased [^{99m}Tc]Tc-HYNIC-iPSMA uptake, in the planar images, and the axial (top right) and coronal (bottom right) fused SPECT/CT images

patients treated with ADT was higher than those without (85.0% versus 70.0%, respectively). 75% of patients had at least one prior imaging assessment reported (30/40), with bone scan (only) being the most frequent at 22,5% (9/40), followed by MRI, [^{68}Ga]Ga-PSMA PET alone, CT alone and CT plus bone scan at 15% (6/40), 12.5% 5/40), 7.5% (3/40) and 7.55% (3/40), respectively. One patient (2.5%) had [^{68}Ga]Ga-PSMA PET, MRI and bone scan imaging, one patient had [^{68}Ga]Ga-PSMA PET plus diagnostic CT (2.5%) and one other patient (2.5%) had both a chest x-ray and abdominal ultrasound imaging done previously. These results are described in Table 3.

Lesion locations and clinical impact

Among the 31 patients who were positive for PC lesions after [^{99m}Tc]Tc-HYNIC-iPSMA imaging, 15 patients (48.3%) had lesions identified in the prostate or prostate bed, 10 patients (32.2%) had lesions in the bones, 1 (3.2%) patient had lesions present in the local, regional lymph nodes, and 6 (16.1%) had lesions identified in all these locations. These lesions largely agreed with the 30% (12/40) of patients who had positive findings on prior imaging, including 8 (66.7%) patients with bone lesions, 5 (41.6%) patients with lesions present in the local or regional lymph nodes, and 2 (16.6%) patients with lesions in the prostate or prostate bed. [^{99m}Tc]Tc-HYNIC-iPSMA imaging changed the treatment for 17 patients (42.5%) (Table 3).

Discussion

An increasing body of evidence suggests that progression to metastasis or recurrence of PC remains a significant cause of death, responsible for >375,000 deaths worldwide in 2020 (Sung et al. 2021; Guldvik et al. 2021). PSMA is overexpressed predominantly in 90–100% of PC lesions, so it has gained increasing attention as an attractive target for lesion imaging. The rich literature available substantiating [^{68}Ga]-and [^{18}F]-labelled PSMA PET/CT imaging as an accurate modality for detecting PC has established its use in the current standard of care. Nonetheless, PET imaging equipment may not always be accessible (Sachpekidis et al. 2018). In Australia, PSMA PET/CT is rebatable

Table 3 Summary of [^{99m}Tc]Tc-HYNIC-iPSMA imaging results, PSA levels at imaging, adverse events, treatment, and treatment response

Patient	PSA (ng/mL) at Imaging	PSMA Scan	Disease Location (PSMA Scan)	Prior Imaging	Disease Location (from Prior Imaging)	Treatment	[^{99m}Tc] Tc- HYNIC-iPSMA change treatment?	Treatment change reason
1	100.0	(+) for suspected PC lesions	Other (Prostate, nodes, and bones)	No	N/A	ADT	Yes	Metastatic disease
2	74.0	(+) for suspected PC lesions	Other (Prostate, nodes and bones)	^{68}Ga-PSMA PET	Prostate or prostate bed, Loco-regional lymph nodes, Distant lymph nodes, Bones	ADT	No	N/A
3	0.1	(+) for suspected PC lesions	Bones	^{68}Ga-PSMA PET	Prostate or prostate bed, Loco-regional lymph nodes, Distant lymph nodes, Bones	ADT	Yes	Confirm good response to therapy
4	200.0	(+) for suspected PC lesions	Other (Prostate, nodes and bones)	Bone Scan	Bones	ADT	No	N/A
5	20.0	(-)	N/A	No	N/A	Radiotherapy, ADT	Yes	No metastases
6	155.0	(+) for suspected PC lesions	Other (Prostate, nodes and bones)	No	N/A	ADT	No	N/A
7	100.0	(+) for suspected PC lesions	Bones	No	N/A	ADT, palliative	Yes	Metastatic disease

Table 3 (continued)

Patient	PSA (ng/mL) at Imaging	PSMA Scan	Disease Location (PSMA Scan)	Prior Imaging	Disease Location (from Prior Imaging)	Treatment	[^{99m}Tc] Tc- HYNIC-iPSMA change treatment?	Treatment change reason
8	27.0	(+) for suspected PC lesions	Prostate or Prostate Bed	MRI	N/A	HIFU	Yes	No metastases
9	1.5	(-)	N/A	SPECT Bone Scan	N/A	Tadalafil	No	N/A
10	0.0	(-)	N/A	MRI	N/A	Other (unknown)	No	No metastases
11	364.0	(+) for suspected PC lesions	Bones	CT	Bones	ADT	Yes	Follow up
12	0.0	(-)	N/A	^{99m}Tc-HYNIC-iPSMA	N/A	ADT	No	N/A
13	5.9	(+) for suspected PC lesions	Prostate or Prostate Bed	No	N/A	Surgery	Yes	No LN disease
14	40.0	(+) for suspected PC lesions	Prostate or Prostate Bed	Bone Scan	N/A	ADT	No	N/A
15	9.4	(+) for suspected PC lesions	Prostate or Prostate Bed	MRI	N/A	Surgery, ADT	No	N/A
16	45.0	(+) for suspected PC lesions	Prostate or Prostate Bed	Bone Scan	N/A	Surgery	No	N/A
17	6.9	(-)	N/A	MRI	N/A	Other (watchful waiting)	No	N/A
18	110.0	(+) for suspected PC lesions	Other (prostate bed, nodes and bones)	Bone Scan	Bones	Chemoradiation	No	N/A

Table 3 (continued)

Patient	PSA (ng/mL) at Imaging	PSMA Scan	Disease Location (PSMA Scan)	Prior Imaging	Disease Location (from Prior Imaging)	Treatment	[^{99m}Tc] Tc- HYNIC-iPSMA change treatment?	Treatment change reason
19	58.0	(+) for suspected PC lesions	Bones	No	N/A	Chemotherapy	No	N/A
20	24.0	(+) for suspected PC lesions	Prostate or Prostate Bed	CT	N/A	Surgery	No	N/A
21	0.2	(-)	N/A	CT, Bone Scan	N/A	Surveillance	No	N/A
22	14.0	(+) for suspected PC lesions	Prostate or Prostate Bed	CT, Bone Scan	Suspicious lesions not proven	Surgery, radiotherapy, chemotherapy	Yes	Confirmation of PSMA-avid lesions
23	6.0	(+) for suspected PC lesions	Prostate or Prostate Bed	CT	N/A	Surgery	Yes	No metastases
24	16.0	(-)	N/A	No	N/A	Surgery	No	N/A
25	6.4	(+) for suspected PC lesions	Prostate or Prostate Bed	Bone Scan	Locoregional LNs	Other (unknown)	No	N/A
26	58.0	(+) for suspected PC lesions	Prostate or Prostate Bed	CT, Bone Scan	N/A	Other (not yet seen by CA specialist)	Yes	Expedited referral
27	22.0	(+) for suspected PC lesions	Prostate or Prostate Bed	Bone Scan	N/A	Other (not yet seen by CA specialist)	Yes	Expedited referral
28	48.9	(+) for suspected PC lesions	Prostate or Prostate Bed	Bone Scan	N/A	Surgery	No	N/A

Table 3 (continued)

Patient	PSA (ng/mL) at Imaging	PSMA Scan	Disease Location (PSMA Scan)	Prior Imaging	Disease Location (from Prior Imaging)	Treatment	[^{99m}Tc] Tc- HYNIC-iPSMA change treatment?	Treatment change reason
29	1.6	(-)	N/A	Bone Scan	Bones	Other (not specific for Ca)	Yes	Neg scan decision to perform biopsy
30	23.7	(-)	N/A	MRI, Bone Scan	Unknown	Other (anti - androgen)	Yes	Neg biopsy and PSMA scan
31	428.2	(+) for suspected PC lesions	Prostate or Prostate Bed	MRI	Locoregional LNs	Surgery	No	N/A
32	5.6	(+) for suspected PC lesions	Prostate or Prostate Bed	^{68}Ga-PSMA PET, MRI, Bone scan	N/A	Surgery	No	N/A
33	23.5	(+) for suspected PC lesions	Bones	^{68}Ga-PSMA PET	Locoregional LNs and bone	ADT	No	N/A
34	96.0	(+) for suspected PC lesions	Bones	CXR, Abd US	N/A	ADT	No	N/A
35	234.1	(+) for suspected PC lesions	Bones	CT, ^{68}Ga-PSMA PET	N/A	ADT	No	N/A
36	135.5	(+) for suspected PC lesions	Loco-regional lymph nodes	MRI	N/A	ADT	Yes	Underestimated metastatic LNs
37	14.1	(+) for suspected PC lesions	Bones	^{68}Ga PSMA PET	Bones	ADT, clinical trial	Yes	Bone and LN metastases

Table 3 (continued)

Patient	PSA (ng/mL) at Imaging	PSMA Scan	Disease Location (PSMA Scan)	Prior Imaging	Disease Location (from Prior Imaging)	Treatment	[^{99m}Tc] Tc- HYNIC-iPSMA change treatment?	Treatment change reason
38	147.9	(+) for suspected PC lesions	Bones	No	N/A	ADT, clinical trial	Yes	Bone and LN metastases
39	12.5	(+) for suspected PC lesions	Bones	^{68}Ga-PSMA PET	N/A	Surgery, ADT	No	N/A
40	12.1	(+) for suspected PC lesions	Prostate or Prostate Bed	MRI	N/A	Surgery, Radiotherapy, ADT	Yes	Treatment management

Abd US, Abdominal Ultrasound; **ADT**, Androgen Deprivation Therapy; **CA**, Cancer; **CT**, Computed Tomography; **CXR**, Chest X-Ray; **HIFU**, High-Intensity Focused Ultrasound; **HYNIC**, Hydrazinonicotinamide; **LN**, Lymph Node; **MRI**, Magnetic Resonance Imaging; **N/A**, Not Applicable; **PC**, Prostate Cancer; **PET**, Positron Emission Tomography; **PSA**, Prostate-Specific Antigen; **PSMA**, Prostate-Specific Membrane Antigen; **SPECT**, Single Photon Emission Computed Tomography; **99mTc**, Technetium-99 m

Table 4 Summary of PC detection with ^{99m}Tc-labelled PSMA-targeted tracers stratified by PSA levels[a]

Imaging modality	Study Design	DR	PSA stratified DR (ng/ml)		Reference
[^{99m}Tc]Tc-PSMA-T4	Prospective	21/36 (58%)	NR		Sergieva et al. (2021)
[^{99m}Tc]Tc-PSMA-I&S	Retrospective	87/152 (57%)	≤ 1	8/41 (20%)	Werner P, aet al (2020)
			> 1–4	32/58 (55%)	
			> 4–10	29/35 (83%)	
			> 10	18/18 (100%)	
[^{99m}Tc]Tc-MIP-1404	Retrospective	25/50 (50%)	> 0.2–0.5	11/25 (44%)	Schmidkonz et al. (2019)
			> 0.5-1	14/25 (56%)	
	Retrospective	174/225 (77%)	≤ 1	25/43 (58%)	Schmidkonz C, aet al (2018)
			> 1–3	38/61 (62%)	
			> 3–5	28/33 (85%)	
			> 5–10	33/37 (89%)	
			> 10–20	29/29 (100%)	
			> 20	21/22 (96%)	
	Retrospective	42/60 (70%)	≤ 1	4/11 (36%)	Reinfelder J, aet al (2017)
			> 1–2	6/14 (43%)	
			> 2–5	13/15 (87%)	
			> 5–10	6/6 (100%)	
			> 10–20	5/5 (100%)	
			> 20	8/9 (89%)	
[^{99m}Tc]Tc-HYNIC-PSMA	Retrospective	39/50 (78%)	≤ 1	3/10 (30%)	Su HC, aet al (2017)
			> 1–4	8/10 (80%)	
			> 4–10	5/5 (100%)	
			> 10	23/23 (100%)	
	Retrospective	151/208 (73%)	> 0.2-1	28/55 (51%)	Liu et al. (2018)
			> 1–2	14/23 (61%)	
			> 2–5	44/53 (83%)	
			> 5–10	39/45 (87%)	
			> 10	26/32 (81%)	

Table 4 (continued)

Imaging modality	Study Design	DR	PSA stratified DR (ng/ml)		Reference
	Retrospective	118/147 (80%)	> 0.2-2	17/35 (49%)	Li B, aet al (2022a)
			> 2–5	40/47 (85%)	
			> 5–10	35/38 (92%)	
			> 10	26/27 (96%)	
[^{99m}Tc]Tc-HYNIC-iPSMA	Prospective	31/40 (77.5%)	0–2	1/6 (17%)	*Present study*
			2–10	5/6 (83.3%)	
			> 10	25/28 (89%)	

[a]This table was adapted from Li B, aet al (2022b)[27]

99mTc, Technetium-99 m; DR, Detection Rate; HYNIC, Hydrazinonicotinamide; NR, Not Reported; PC, Prostate Cancer; PSA, Prostate-Specific Antigen; PSMA, Prostate-Specific Membrane Antigen

by Government health funding; however, due to a geographically dispersed population, many communities lack access to PET/CT imaging, particularly those already disadvantaged in health (Lynch et al. 2021; Song et al. 2022). In South Africa, where the cost of services may be prohibitive and fewer PET scanners reduce availability, an affordable imaging technique that effectively detects prostate cancer lesions is urgently needed (Boppart and Richards-Kortum 2014). The utilization of a cost-effective, easily accessible imaging option, such as SPECT imaging, could be an effective alternative in constrained settings (Wall 2014; Hicks and Hofman 2012).

Radiolabelled compound carries inherent risks, such as potential radiation exposure to non-target tissues, allergic reactions, or unforeseen adverse events; thus it is critical to minimise safety risks to patients. Demonstrating a favourable safety and tolerability profile may mitigate these risks and provide confidence in its application in clinical settings, and can facilitate the broader acceptance of the technique by the medical community and patients. With a clear understanding of the safety implications, subsequent studies, regulatory approvals, and clinical applications can be improved. Thus, a rigorous assessment of safety and tolerability is a procedural necessity and a cornerstone in advancing medical science and patient care (Meisenhelder and Semba 2006).

Results of this interim analysis support the favourable safety and tolerability profile of [^{99m}Tc]Tc-HYNIC-iPSMA. No adverse events were reported in any of the 40 patients. The biodistribution characteristics and safety profile of [^{99m}Tc]Tc-HYNIC-iPSMA in this registry are consistent with other ^{99m}Tc-labelled PSMA-targeted tracers, including [^{99m}Tc]Tc-MIP-1404, [^{99m}Tc]Tc-MIP-1405, [^{99m}Tc]Tc-PSMA-I&S, and [^{99m}Tc]Tc-EDDA/HYNIC-iPSMA (Li et al. 2022a, b; Schmidkonz et al. 2018; Vallabhajosula et al. 2014) (Table 4). The lack of adverse events highlights [^{99m}Tc]Tc-HYNIC-iPSMA's favourable safety and tolerability profile and lends credibility to the agent's suitability for widespread clinical use, offering patients a promising avenue for accurate and safe PC assessment.

Nuclear medicine imaging is established as a versatile and highly accessible diagnostic tool with an important role for cancer assessment globally. While PSMA PET is widely used for PC imaging, SPECT imaging may be a feasible alternative in regions where PET resources may be limited or cost-prohibitive. The ubiquity of SPECT instrumentation and radiopharmaceuticals contributes to enhanced accessibility, Furthermore, clinical sites without PET/CT may lack the personnel and infrastructure for complex radiopharmaceutical synthesis. [^{99m}Tc]Tc-HYNIC-iPSMA is kit-based with simple reconstitution and is a key advantage supporting its clinical implementation.

This multi-national registry demonstrating successful utilised [^{99m}Tc]Tc-HYNIC-iPSMA for PC across multiple centres using different SPECT imaging equipment which underscores its robust versatility and potential for widespread clinical application. [^{99m}Tc]Tc-HYNIC-iPSMA SPECT imaging may provide access to communities where PSMA PET imaging is not accessible, which may have important impacts on patient outcomes. The adaptability of [^{99m}Tc]Tc-HYNIC-iPSMA to varying technological environments, suggests that it could seamlessly integrate into diverse healthcare settings while maintaining consistent and reliable imaging results. It also, speaking to the agent's reproducibility and reliability - key attributes for any imaging tool.

The registry contributes to the larger body of evidence demonstrating this imaging agent as clinically beneficial to PC in all stages, including initial staging, restaging, treatment evaluation, and metastasis evaluation. Other studies investigating ^{99m}Tc-labelled

PSMA-targeted tracers for PC lesion identification have demonstrated similar detection rates, although these studies are limited in number (Li et al. 2022a, b; Schmidkonz et al. 2018, 2020; Werner et al. 2020; Reinfelder et al. 2017; Su et al. 2017). In this analysis, the average detection rates of 77.5% are consistent with more extensive retrospective studies investigating [^{99m}Tc]Tc-HYNIC-iPSMA in PC, including one by Li and colleagues, who report an 80.4% detection rate from 147 patients (Li et al. 2022a, b).

The similarity of our detection findings with previous studies using [^{99m}Tc]Tc-HYNIC-iPSMA and other ^{99m}Tc-labelled PSMA-targeted tracers in PC lesion detection suggests robust reproducibility of the imaging agent's performance. This consistency in detection rates further substantiates [^{99m}Tc]Tc-HYNIC-iPSMA clinical utility and positions it as a potentially reliable alternative (or complement) to existing imaging modalities, enhancing diagnostic accuracy and patient care in PC management. Importantly, patient management was changed based on the [^{99m}Tc]Tc-HYNIC-iPSMA findings in 42.5% of patients.

Our study has limitations. First, the study's sample size of 40 patients, predominantly Caucasian and from specific regions, may not adequately represent the broader population affected by PC, potentially limiting the generalizability of the findings. A larger, more diverse cohort would enhance the study's external validity. Second, the interpretation of SPECT images by nuclear medicine physicians at local centers introduces the potential for observer bias, where subjective judgments could influence diagnostic ouTcomes. This risk could be mitigated through blinded analysis or multiple independent assessments. Last, while no immediate adverse events were reported, the absence of long-term safety data for [^{99m}Tc]Tc-HYNIC-iPSMA may leave unanswered questions about potential delayed or long-term side effects, particularly important topics given the tracer's radioactive nature. Comprehensive long-term follow-up is essential to fully understand the tracer's safety profile and its implications for clinical use.

Conclusion

The high prevalence of PC and variable accessibility of PET/CT emphasises the need to develop a novel, cost-effective, and easily accessed ^{99m}Tc-labelled PSMA ligand. Furthermore, clinical sites with PET/CT may need more personnel and infrastructure for complex radiopharmaceutical synthesis. The reconstitution process of [^{99m}Tc]Tc-HYNIC-iPSMA, which is straightforward and kit-based, offers a significant advantage due to its simplicity compared to the more complex synthesis processes of other similar agents. In this prospective, multicentre registry, 40 PC patients enrolled and received [^{99m}Tc]Tc-HYNIC-iPSMA tracer followed by planar and SPECT imaging. Results found [^{99m}Tc]Tc-HYNIC-iPSMA to be a reliable and suitable tracer for PSMA-targeted SPECT imaging across varied centres and imaging equipment. Detection rates were high (77.5%) among the patients studied and consistent with previously reported results. Patient management was changed based on [^{99m}Tc]Tc-HYNIC-iPSMA findings in 42.5% of cases. No adverse events were reported. In conclusion, [^{99m}Tc]Tc-HYNIC-iPSMA is a promising option to identify PSMA-positive PC on SPECT imaging with the potential for improving patient access to imaging worldwide across various indications, patient PSA levels, and scanner types.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41824-024-00226-4.

Supplementary Material 1

Acknowledgements

The authors would like to thank Darren Lynn, MD of Omni Tech Medical for medical writing assistance. All authors read and approved the final manuscript.

Author contributions

M. M. T., N. M. N. and M. M. E. conceived the study and was involved in the design and coordination of the study. M. M. T., N. M. N., A. S., H. M. H., R. M. R., O. A., S. H., and M. M. E. were involved in practical part. M. M. T., N. M. N. and M. M. E. were involved in data analysis, manuscript drafting, and editing. All authors read and approved the final manuscript.

Funding

The sites are sponsoring the registry through the Principal Investigator/s, who are responsible for initiating and conducting the Registry. Telix Pharmaceuticals is providing IP and, along with the Oncidium Foundation, clinical and operational support.

Data availability

The datasets used and/or analyzed during the current study were provided within the manuscript and supplementary information files.

Declarations

Ethics approval

This study was approved by IRBs/REBs at each participating site. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate

Written informed consent was obtained from all patients included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of the images in Fig. 1.

Competing interests

The authors declare no competing interests.

Received: 14 May 2024 / Accepted: 24 September 2024

Published online: 30 December 2024

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