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Cyclotron vs generator-produced 68Ga PSMA: a single-institution, prospective clinical trial

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ABSTRACT

The clinical utility of gallium 68 (^{68}Ga)-PSMA PET for the diagnosis and management of prostate cancer is driven in part by radioisotope availability and production costs. This study evaluates the equivalence between the two manufacturing processes for ^{68}Ga-PSMA: ^{68}Ga-PSMA-cyclotron (from a solid target) and ^{68}Ga-PSMA-generator. A prospective, single-arm, single-institution non-randomized study was conducted where 16 patients with prostate adenocarcinoma underwent PET/CTs consecutively within 12 to 48 hours with each type of manufactured ^{68}Ga-PSMA between December 2020 and June 2021. The intraclass correlation coefficients suggested acceptable reliability in all lesion parameters (ICC > 0.70). Bland-Altman analysis demonstrated acceptable bias levels for all lesion parameters. Thereby ^{68}Ga-cyclotron (solid target) and ^{68}Ga-generator production methods tagged to the same PSMA ligand resulted in scans which were deemed to be equivalent in detecting PSMA+ lesions in our study. As cyclotron-produced, solid- target ^{68}Ga can be made in large (Ci) quantities, it is a promising tool for future application in ^{68}Ga-PSMA PET scans with the potential to decrease radiotracer production costs and increase isotope availability.

Introduction

Prostate cancer (PCa) is the second most common cancer and second leading cause of cancer death among American men following skin cancer and lung cancer respectively. The American Cancer Society (ACS) estimated that in 2022, there will be approximately 268,490 new cases and 34,500 deaths from PCa[1]. The treatment and prognosis of PCa are determined by the extent of the disease and vary from active surveillance to invasive treatments depending on whether the patient has organ-confined disease, locally advanced disease, or metastases. For this purpose, a sensitive and specific imaging modality that can identify and localize pathologic lesions is crucial for optimizing patient care.

Prostate specific membrane antigen (PSMA) positron emission tomography (PET) has been studied for several years as an imaging target for PCa. The PSMA transmembrane protein functions as a zinc metalloenzyme carboxypeptidase and is highly expressed in both primary and metastatic PCa lesions[2]. It binds to a ligand that initiates the hydrolysis of glutamate from the C terminus of peptides. The extracellular portion of PSMA can be targeted by urea-based small molecule inhibitors such as the small molecule inhibitor Glu-NH-CO-NH-Lys (Ahx)-HBED-CC labeled with gallium-68 (^{68}Ga -HBED-CC-PSMA), which is the mainstay of our study.

^{68}Ga-HBED-CC PSMA PET has shown superiority in staging and restaging PCa patients compared to conventional imaging[3–6]. In December 2020, the Food & Drug Administration (FDA) granted limited approval for the use of ^{68}Ga-HBED-CC PSMA PET, opening the door to a new era in the diagnosis and management of prostate cancer. However, production of ^{68}Ga-HBED-CC PSMA has limitations consequential to radioisotope availability and production costs. ^{68}Ga is usually obtained from a generator, which can at most supply 2.7 gigabecquerels (GBq) ^{68}Ga per day. Radioactive waste disposed from generator production is expensive, especially when considering the cost of the generator itself.

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As such, logistical considerations impact production output and expenses associated with generator-produced ^{68}Ga, making it a poor candidate for optimizing large-scale production. Conversely, utilizing a solid target-based medical cyclotron can produce up to 194 GBq of ^{68}Ga radioactivity[7].

Because of the high incidence and prevalence of prostate cancer, there is an enormous clinical need for ^{68}Ga for PCa imaging. Proving equivalence in clinical imaging between the generator-produced and solid target cyclotron-produced gallium may remedy excess production costs and improve isotope availability. Previous studies have demonstrated the practicality of the different ^{68}Ga production methods; however, these methods have not definitely been established in animal or clinical models[8–11]. To our knowledge, this is the first study comparing consecutively performed PET/CT scans utilizing the ^{68}Ga-PSMA-cyclotron (solid target) and ^{68}Ga -PSMA-generator radioisotopes in patients with metastatic PCa.

The aim of this study was to evaluate equivalence between the two manufacturing methods for ^{68}Ga-PSMA in patients diagnosed with metastatic PCa: ^{68}Ga-PSMA-cyclotron (from a solid target) and ^{68}Ga-PSMA-generator.

Objective

The primary objective was to evaluate detection rate and radiotracer uptake between the cyclotron- and generator-produced radioisotope to prove equivalence between the generator-produced gallium and solid target cyclotron-produced gallium, presented as single score intraclass correlation coefficient (ICC) in a population of prostate cancer patients.

Methods

Study design

This was a prospective, single-arm, non-randomized study done at Weill Cornell Medicine (WCM)/NewYork-Presbyterian (New York, NY). Patients were enrolled after being referred by their primary oncologist, radiation oncologist, or urologist, after undergoing standard-of-care imaging for staging (magnetic resonance imaging (MRI), computed tomography (CT), and/or technetium-99m (Tc99m) bone scan) with confirmed metastatic PCa. ^{68}Ga-PSMA-cyclotron and ^{68}Ga-PSMA-generator scans of the same patient were obtained within 12 to 48 hours of each other. SUV values, for both production methods, were acquired via Siemens “MI Whole Body Analysis Suite” prototype. The Analysis Suite calculates both total and regional metabolic tumor volume, as well as radiomics features for each lesion and organ on fused whole-body PET/CT images. Through various processes, statistical data was collected and analyzed for each lesion, system, and normal uptake organs. Each dataset was then compared to the opposing production method to establish uptake, efficacy, and homogeneity.

^{68}Ga -HBED-CC-PSMA production

I Generator production: [^{68}Ga]-gallium chloride was generated from an IGG100 Eckert and Ziegler closed system ^{68}Ga-generator consisting of a borosilicate glass column containing a titanium dioxide bed on which ^{68}Ge was absorbed and fully shielded, per the specifications of investigational new drug (IND) 124495. Both the HBED-PSMA non-radioactive precursor and the ^{68}Ga radionuclide were obtained from the Citigroup Biomedical Imaging Center (CBIC) core and accompanied by a certificate of analysis as described in the Chemistry, Manufacturing, and Controls (CMC) section of the IND. A single dose of the final product was delivered to the imaging scanner with a two-hour dose expiration time.

II Cyclotron production: Gallium-68 was produced by NCM USA LLC, a New York City (NYC)-based advanced PET radiopharmaceutical manufacturing and distribution company (461 Park Avenue South, New York, NY 10016) with whom we have an academic-industrial partnership, National Institutes of Health (NIH) grant to investigate manufacturing of this nuclide based on an IND held by the company. Simply put, the NCM cyclotron used an enriched (>99% purity) zinc-68 target. The target was first dissolved in a 10-12N HCl solution. It was then passed on an AG-50W-X8 resin which separated the Zn-68 and eluted the gallium-68 s [^{68}Ga]-GaCl3 in 3N HCl. The cyclotron produced ^{68}Ga that was released by NCM for labeling and formulation of the ^{68}Ga-HBED-PSMA product. The radiochemical purity of the in-house product was required to match and be equivalent to the specifications of the ^{68}Ga-HBED-PSMA generator-produced radiopharmaceutical.

Purity of cyclotron-produced ^{68}Ga high performance liquid chromatography (HPLC) was measured using an ORTEC GEM series high-purity germanium (HPGe) coaxial detector system (model GEM20-70-SMP, CFG-SV-70). The purified sample of ^{68}Ga showed only two peaks at 511 keV and 1077 keV. Several experiments were performed in mice to determine repeatability of the cyclotron-produced ^{68}Ga-HBED-CC, which are published in *Molecular Imaging and Biology*[12].

^{68}Ga-HBED-CC-PSMA PET/CT acquisition

Patient scans were performed with a standard technique on a Siemens Biograph mCT^{TM} PET/CT scanners with a preference for the same instrument on all scans. Individual patients preferably utilized the same PET/CT scanner for both imaging scans. Prior to imaging, pre-scan vital signs were taken. An intravenous catheter (Hep-Lock) was placed for radiopharmaceutical administration. A single dose of 185 $\pm$ 74 MBq (5$\pm$2 mCi) of ^{68}Ga-PSMA-HBED-CC was injected, and the waiting time post-injection was 60-90 minutes. The patient was encouraged to drink water during the first 30 minutes post-injection and was instructed to use the bathroom before the scan. Imaging was acquired over 5 beds, with 3 minutes over each non-pelvic bed and 4 minutes over the pelvis for a combined scan time ranging between 25-35 minutes.

Quality assurance images from each system were acquired at the beginning of the protocol on all mCT scanners using a ^{68}Ga-filled 20-cm-diameter cylindrical water phantom with average SUVs in the range of 1.0 +/- 0.5 g/ml with no artifacts on visual inspection.

Setting

This study was part of an open-label, single-center, Health Insurance Portability and Accountability Act (HIPAA)-compliant prospective clinical trial which enrolled patients from December 2020 to June 2021 at the NewYork Presbyterian - WCM campus. Informed consent was obtained from all enrolled patients as required by federal regulations and approved by the WCM institutional review board (IRB) (protocol # 19-11021092).

Participants

Patients were recruited through outpatient referrals from the Weill Cornell Medicine Department of Radiation Oncology and Genitourinary Medicine. Patients were initially screened for eligibility by research staff through the electronic medical records. The referring physician would query the patient first regarding interest. If favorably recommended by the referring physician, the investigator and/or research staff discussed the study protocol and obtained consent from each patient for further enrollment.

The inclusion criteria were as follows:

(1) Adult males who were above the age of 21 years
(2) Had histologically proven metastatic prostate cancer
(3) Staging imaging exam confirming metastatic disease, e.g., total body MRI, or CT chest/abdomen/pelvis, 99mTc bone scan, NaF PET
(4) Willing to sign informed consent

The exclusion criteria were as follows:

(1) Laboratory values:
- Serum creatinine >2.5 mg/dL
- AST (SGOT) >2.5x ULN
- Bilirubin (total) >1.5x ULN
- Serum calcium >11 mg/dL

(2) Presence of any other co-existing condition which, in the judgment of the investigator, might increase the risk to the subject
(3) Inability to lay on the scanner table for the required period of time, e.g., due to bone pain or claustrophobia

Variables

The main variable was the binary characterization of lesion positivity on each PET scan, as well as the total number of lesions identified. Serum PSA levels were collected prior to the initial PET scan for further analysis.

Data sources/measurement

SUV values, for both production methods, were acquired via Siemens "MI Whole Body Analysis Suite" prototype. The Analysis Suite calculates both total and regional metabolic tumor volume, as well as radiomics features for each lesion and organ on fused whole-body PET/CT images. Study data were collected and managed using the REDCap (Research Electronic Data Capture) server hosted at WCM. REDCap is a secure, web-based software platform designed to support data capture for research studies[13,14].

Bias

To prevent biased interpretation, the ^{68}Ga-PSMA-cyclotron and ^{68}Ga-PSMA-generator scans were independently read and dictated.

Study size

A total of 16 patients were enrolled. A sample size calculation to evaluate odds ratio (equality test) determined that an optimal sample size of 22 was needed at a power of 18.47% and an alpha (type 1 error) level of 5%. Due to a delay in generator-based radioisotope production, there was a three-month halt in patient recruitment, allowing for only 16 patients to be enrolled in the study during the time frame permitted by the IRB. Considering that the median statistical power of studies in the neurosciences ranged from ~8 to ~31%, this sample size and associated power level were deemed to be sufficient.

Quantitative variables

PSMA positivity was defined as having a SUV value above that of the reference blood pool, liver, and/or salivary glands when evaluating lesions as described using the PROMISE criteria[15]. Quantitative analysis reviewed the SUV_{max} and SUV_{mean} of the parotid gland, liver, and aortic arch (blood pool), as well as the SUVmax and SUVmean of suspected metastatic lesions. The same ROIs were evaluated on both scans for each respective patient.

Statistical methods

Repeatability was evaluated by calculating the variance among group means of the SUV_{mean} and SUV_{max} of each reference and lesion over the sum of the group-level and data-level (residual) variance. The intraclass correlation coefficient (ICC), based on a one-way random effects model (i.e., assumes subjects are randomly selected from the larger population), was used to assess reliability between generator and cyclotron scanning methods. Bland-Altman analysis evaluated the agreement between the two scanning methods. Confidence levels of 95% were estimated to assess precision of the obtained estimates. All analyses were performed in R Version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient demographics

A total of 16 patients were enrolled in this study. Population characteristics are shown in Table 1. There were no adverse effects in any of the patients following radiotracer injection. All patients (100%) were self-identified as non-Hispanic, and 14 patients (87.5%) were self-identified as White. The average age of the participants was 73.3 years, and the average PSA level at the time of the scans was 258.2 ng/mL. Thirteen patients had treatment with androgen deprivation therapy before the scans.

Reliability between generator and cyclotron scans

Single score intraclass correlation coefficient (ICC) was calculated as an index for reliability between generator and cyclotron scans. The ICC values suggested acceptable reliability in all lesion parameters (ICC > 0.70) except for the SUV_{max} aorta (Table 2). The highest level of reliability was demonstrated when looking at the top five lesions with the highest SUVmax values (ICC $\geq$ 0.97). When comparing the different types of lesions, the average SUV_{max} for bone lesions (ICC: 0.96 [95% CI:0.88 - 0.99]) demonstrated the highest level of reliability, followed by lymph nodes (ICC: 0.86 [95% CI: 0.62 - 0.95]), salivary glands and parotids (ICC: 0.70 [95% CI: 0.34 - 0.88]), and the spleen (ICC: 0.82 [95% CI: 0.57 - 0.93]).

Bias levels and agreement

Bland-Altman analysis demonstrated acceptable bias levels for all lesion parameters, including the SUV_{max} aorta (Fig. 1). In fact, SUV_{max} aorta revealed the lowest amount of bias compared to the other parameters (bias: -1.39×10^{-17} [95% CI: -0.156 - 0.156]). 15 out of the 19 selected parameters had negative estimated bias values, suggesting that generator scans produced slightly higher values compared to cyclotron scans. However, bias for all parameters were estimated to be close to zero, thus indicating high agreement between the two scanning

Table 1
Demographic and clinic-pathological characteristics.

Total Number of Patients	16
Age (years)	73.3125
Ethnicity/Race	
Non-Hispanic/Latino	16
AA/Black	2
White	14
Asian	0
Other	0
Hispanic/Latino	0
PSA at Initial Diagnosis (ng/mL)	
Mean	232.82
Median	11
Last PSA levels (ng/mL) before PET	
Mean	258.2844
Median	20.96
Prior RP	9
Prior RT	13
Prior ADT	13
Prior Chemotherapy	14
Prior TRT	7

PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radiation therapy; ADT: androgen deprivation therapy; TRT: targeted radionuclide therapy.

Table 2
Intraclass correlation coefficients for selected parameters of interest.

Intraclass correlation coefficient (ICC) Parameter	ICC estimate	95% CI
Lesion 1	0.98	(0.94 - 0.99)
Lesion 2	0.98	(0.95 - 0.99)
Lesion 3	0.99	(0.96 - 1)
Lesion 4	0.99	(0.96 - 1)
Lesion 5	0.97	(0.91 - 0.99)
Average SUV Max - Bone Lesions	0.96	(0.88 - 0.99)
Average SUV Max - Lymph Nodes	0.86	(0.62 - 0.95)
Average SUV Max - Salivary Glands and Parotids	0.70	(0.34 - 0.88)
Average SUV Max - Spleen	0.82	(0.57 - 0.93)
Max SUV - Aorta	0.59	(0.17 - 0.84)
Max SUV - Liver	0.91	(0.76 - 0.97)
Max SUV - Parotid	0.78	(0.48 - 0.92)
Total Lesion Average Coefficient Variation	0.97	(0.92 - 0.99)
Total Lesion Average Standard Deviation	0.94	(0.85 - 0.98)
Total Lesion Average SUV_{Max}	0.97	(0.91 - 0.99)
Total Lesion Average SUV_{mean}	0.71	(0.36 - 0.89)

methods.

The scatter plots of the SUV_{mean} aorta and the SUV_{mean} liver demonstrates a linear relationship between the two methods (Fig. 2) showing, again, a high agreement between the two methods.

Image quality

There are no differences in the image quality between the scans acquired using ^{68}Ga-PSMA-cyclotron (from a solid target) and ^{68}Ga-PSMA-generator (Fig. 3).

Discussion

Our study demonstrated a high level of reliability and agreement between the two manufacturing processes for ^{68}Ga-PSMA: ^{68}Ga-PSMA-cyclotron (from a solid target) and ^{68}Ga-PSMA-generator. All lesion parameters aside from the SUV_{max} of the aorta demonstrated acceptable reliability with ICC values greater than 0.70, with the greatest level of reliability noted in osseous lesions and lymph nodes, concordant with the expected presentation of PCa metastatic disease. All lesions also demonstrated acceptable bias levels and inter-reader agreement, including the SUV_{max} of the aorta. The small sample size which resulted from recruitment and logistical challenges was a limiting factor in the analytical interpretation.

Rodnick et al. evaluated radiochemical purity and manufacturing logistics when producing ^{68}Ga-PSMA -cyclotron (from a liquid target) and ^{68}Ga-PSMA -generator[16]. The authors found that limited overall production from the ^{68}Ga-PSMA -generator impaired practical application when scheduling patients, concluding that cyclotron produced

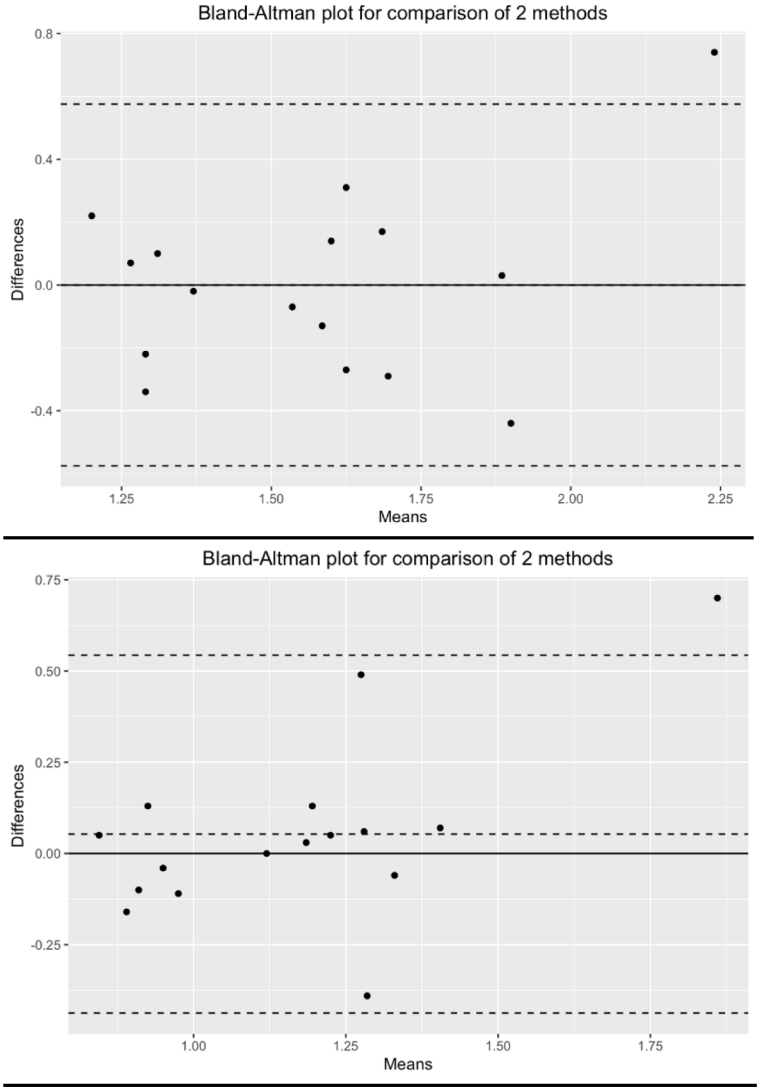

Fig. 1. Bland-Altman analysis for the SUVmax and the SUVmean of the Aorta.

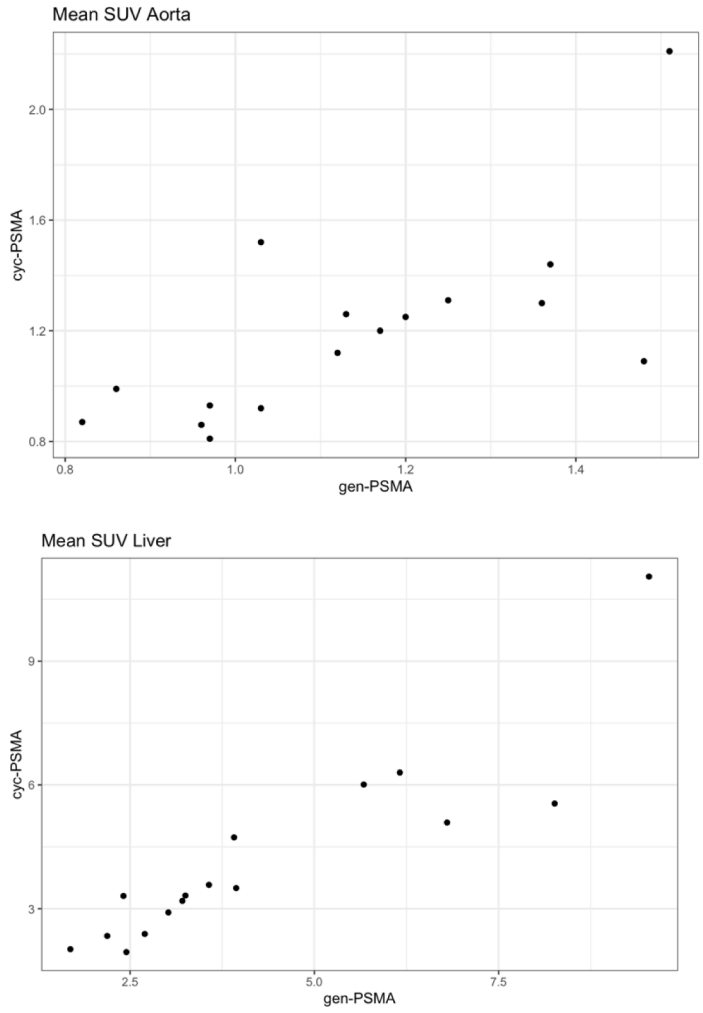

Fig. 2. Scatter plot for the SUVmean Aorta and the SUVmean Liver showing a linear relationship.

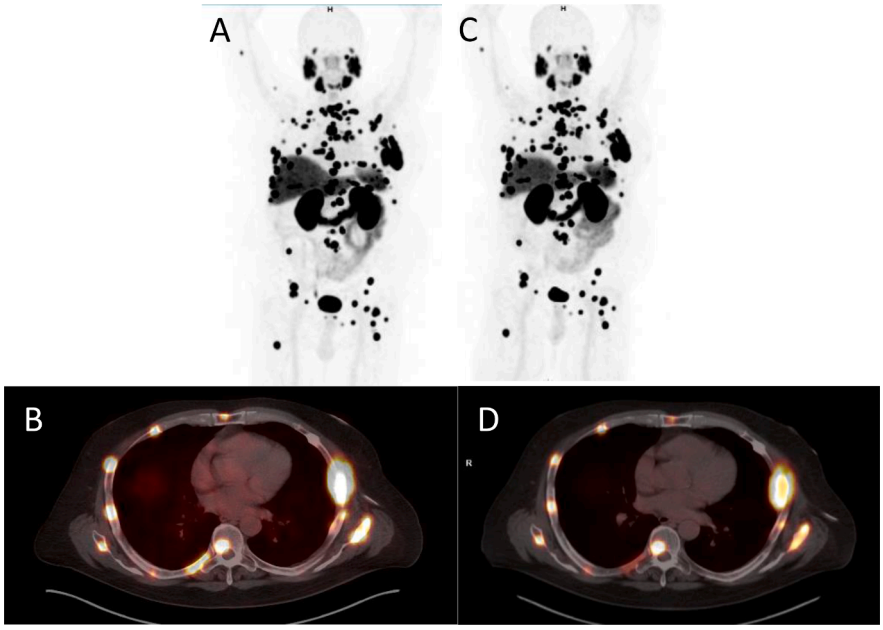

Fig. 3. Biochemical recurrence in a 70- year-old patient with a PSA of 27.52ng/mL at the time of the scans. Maximum intensity projection (MIP) (**A**) and fused PET/MR (**B**) images show the ^{68}Ga-PSMA-cyclotron scan uptake, and the (MIP) (**C**) and fused PET/MR (**D**) images show the ^{68}Ga-PSMA-generator scan uptake.

68Ga is not inferior in radiochemical purity and may be logistically superior. Because the majority of prior literature has demonstrated the clinical utility of 68Ga-PSMA-HBED-CC that was produced from a generator, our study focused on evaluating and successfully demonstrating the clinical equivalence of both ^{68}Ga-PSMA -generator and ^{68}Ga-PSMA -cyclotron methods by performing both scans in each patient.

Recently, ^{18}F bound PSMA agents became commercially available in the United States (US). Osborne et al.[17] noted that the biodistribution and imaging interpretation of ^{18}F-PSMA and ^{68}Ga-PSMA PET/CT scans were overall similar. However, ^{18}F based tracers are not locally producible and the dependency on external distribution can be a major limiting factor, especially when multiple institutions are requesting for doses from the same production house. Future studies should evaluate the cost-benefit analysis of ^{68}Ga based radioisotopes with ^{18}F based radioisotopes in the context of PSMA availability, taking into consideration local manufacturing of each agent or the need for shipment.

In addition, high-volume production of ^{68}Ga may aid in the imaging of other organ studies. For instance, the FDA-approved ^{68}Ga-DOTATATE PET/CT and ^{68}Ga-DOTATOC PET/CT are the preferred imaging modalities for initial diagnosis, disease extent evaluation, and selection of patients for peptide receptor radionuclide therapy (PRRT), in patients with neuroendocrine tumors (NETs)[18–20]. ^{68}Ga ventilation and perfusion PET/CT imaging is an upcoming study for pre-operative and radiotherapy planning in patients with lung cancer [21,22]. Thus, if ^{68}Ga produced by cyclotron is indeed cost-effective and accessible for most US institutions, then access to PET imaging for a variety of indications will improve.

Conclusion

^{68}Ga-cyclotron (solid target) and ^{68}Ga-generator production methods tagged to the same PSMA ligand resulted in scans that were determined to be equivalent in detecting abnormal PSMA positive lesions in our study. Moreover, both methods demonstrated the same imaging quality. However, the cyclotron produced, solid target ^{68}Ga, can be made in Ci quantities which will increase the isotope availability nationally and it can significantly decrease costs of tracer production to currently available generator systems. As such, it is a promising tool for future application in ^{68}Ga-PSMA PET scans.

CRediT authorship contribution statement

Juana Martinez: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Kritika Subramanian:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Sandra Huicochea Castellanos:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Charlene Thomas:** Formal analysis, Writing – review & editing. **Arindam Roy Choudhury:** Formal analysis, Writing – review & editing. **Brett Muench:** Writing – review & editing. **Scott T. Tagawa:** Conceptualization, Writing – review & editing. **Naga Vara Kishore Pillarsetty:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Joseph R. Osborne:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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