Evaluation of an Automated Module Synthesis and a Sterile Cold Kit-Based Preparation of 68Ga-PSMA-11 in Patients with Prostate Cancer.

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Evaluation of an automated module synthesis and a sterile cold kit-based preparation of ^{68}Ga-PSMA-11 in patients with Prostate Cancer

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Keywords

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ABSTRACT

Introduction

^{68}Ga-labeled urea-based inhibitors of the prostate-specific membrane antigen (PSMA), such as ^{68}Ga-PSMA-11, are promising small molecules for targeting prostate cancer (PCa). Although this radiopharmaceutical was mostly produced by the means of manual synthesis and automated synthesis modules, a sterile cold kit was recently introduced. The aim of our study was to evaluate the image quality of ^{68}Ga-PSMA-11 PET/CT (PSMA-PET) in a population of PCa patients following the injection of comparable activities of ^{68}Ga-PSMA-11 obtained with the two different synthetic procedures. A secondary aim was to identify secondary factors which may have an impact on image quality and thus final interpretation.

Material and Methods

Two different groups of 100 consecutive PCa patients who underwent PSMA-PET were included in the study. The first group of patients was imaged with ^{68}Ga-PSMA-11 obtained by employing synthesis modules while the second group's tracer activity was synthesized using a ANMI sterile cold kit. All PET images were independently reviewed by two experienced nuclear medicine diagnosticians with at least 2 years of experience in PSMA-based imaging and unaware of the patients' clinical history. The 2 reviewers independently rated the quality of each PSMA-PET scan using a 3-point Likert-type scale. In case of discordance the operators reviewed the images and reached a consensus. Performance was evaluated on the basis of the expected bio distribution, lesion detection rate and expected physiologic background uptake.

Results

Overall, 104/200 (52%) PSMA-PET resulted positive in terms of PCa-related findings. No significant differences in image quality between cold kits and synthesis modules were found (p=0.13) although a higher proportion of images were rated as "excellent" by the observers among kit examinations when compared to modules (45% vs. 34%). Furthermore, according to multivariate regression analysis, after the dichotomization of image quality as “excellent” and “not excellent”, increases in patient age (+5 years: OR=1.40; CI 95%=1.12-1.75), patient weight (+5 kg: OR=1.89; CI 95%=1.53-2.32) ^{68}Ga-PSMA-11 uptake times (+10 minutes: OR=1.45; CI 95%=1.08-1.96) and reduction of injected activity (-10 MBq: OR=1.28; 95%CI 1.07-1.52) were significantly associated with a "not excellent" image quality.

Conclusions

No significant differences were identified between the 2 groups of patients undergoing PSMA-PET, therefore we were not able to ascertain any significant influences of tracer production methodology on final scan quality. However, patient age, patient weight, reduced injected activity and ^{68}Ga-PSMA-11 uptake times were significantly associated with an overall poorer image quality.

TEXT

Introduction

Prostate cancer (PCa) is the second cancer for incidence and is the fifth cause of cancer-related death among males(*1*). Accurate identification of PCa represents a major challenge among the urologic community at all different disease stages, namely primary staging, biochemical recurrence and castration-resistance. Conventional imaging modalities for the detection of PCa include magnetic resonance imaging (MRI), bone scintigraphy (BS), computed tomography (CT) and positron-emission tomography (PET). In recent years the introduction of a new class of small-molecule prostate-specific membrane antigen (PSMA) inhibitor radiotracers, shows promising results for imaging of PCa. PSMA is a glutamate carboxypeptidase II, a membrane bound metallo-peptidase present at high levels on PCa cells(*2*). Despite the name, PSMA is not specific to the prostate gland and is expressed in several normal (e.g. duodenal mucosa, salivary glands, renal tubular cells) and neoplastic (renal cell carcinoma, tumoral neo-vasculature) tissues. PSMA-ligand PET/CT images the expression of PSMA and detects prostate cancer metastases with superior accuracy when compared to conventional imaging(*3*). Among all the other imaging techniques PSMA-ligand PET/CT has an improved detection rate for smaller lesions and may be able to identify nodal or distant metastatic disease in earlier stages, in the lower range of PSA than other PET radiotracers(4). Several molecular PSMA-targeted tracers have been investigated in both PET and SPECT imaging and for PET imaging, a variety of PSMA ligands has been introduced into clinical practice, bound with different radioisotopes as shown in Table 1. Much data is present in literature, especially for PSMA-11, and some for PSMA-I&T, labelled with Gallium-68(5–8). Recently Fluorine-18-labeled compounds have been proposed for PSMA-imaging, such as ^{18}F-DCFBC, ^{18}F-DCFPyL and PSMA-1007 for their potentially easier production and distribution logistics(9–11). To date, ^{68}Ga-labelled PSMA inhibitor Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (^{68}Ga-PSMA-11) is the most employed radioligand for PET/CT(*12*). Nowadays, a simplified production and

a simpler distribution logistics assume great importance, since PSMA-PET imaging is more and more used. Furthermore, several methods of labeling and preparation have been introduced for the production of ^{68}Ga-PSMA-11 ligands(*13*). Since the half-life of ^{68}Ga (68 minutes) is relatively short, reducing production times may significantly increase the available tracing activity in each elution charge. This in turn may be beneficial to a high-volume PET imaging center, as well as decreasing the costs of each examination. Although ^{68}Ga-PSMA-11 ligands are commonly produced via automated synthesis modules and sometimes manual synthesis process are used which are time consuming, a sterile cold kit for ^{68}Ga-PSMA-11 production was recently introduced. In this retrospective study we investigated the impact of two different ^{68}Ga-PSMA-11 synthetic procedures on PET/CT image quality. We also investigated, as secondary aims, the roles played by external factors, including patient age, weight, BMI, injected activity, uptake times and image acquisition methodologies in influencing image quality.

Materials and methods

Patient population

PSMA-PET imaging is an option offered at our Institution to PCa patients within the framework of an investigational new drug (IND) trial (Prot. PSMA PROSTATA; Eudract: 2015 004589 27 OsSC). In our retrospective single-center study we enrolled two groups of consecutive PCa patients (100 patients each) who underwent PSMA-PET. The first group between April and June 2017, the second one between October and December 2017. No patients had a known second primary cancer. The institutional Ethics Committee approved this retrospective study. All participants included in the study, appropriately informed of the purpose of the study, signed a written informed consent.

^{68}Ga-PSMA-11 preparation

Synthesis module

In the first cohort of 100 patients, ^{68}Ga-PSMA-11 production was performed by means of a synthesis module (Modular-Lab Pharm Tracer, Eckert & Ziegler, Germany) equipped with sterile single-use cassettes (C4-GA68-PSMA, Eckert & Ziegler) using the eluate of a GalliaPharm generator (1850 MBq, Eckert & Ziegler, Germany). ^{68}Ga was eluted with 5 ml of 0.1N HCl (Eckert & Ziegler, Germany) and trapped onto a strong cation exchange column for purification. ^{68}Ga was then slowly eluted with 0.8 ml of NaCl 5N/HCl 5.5N solution in a reactor with the precursor PSMA-11 (25 µg, GMP grade, ABX Germany) dissolved in sodium acetate buffer (0.4 ml, pH 4.5). The labeling reaction was carried out at 95°C for 5 minutes. The crude product was diluted with 2 ml of NaCl 0.9% solution and loaded onto C18 column for purification. The product was eluted with 1 ml of ethanol, diluted with 8 ml NaCl 0.9% solution and sterilized by means of a 0.22 µm filter.

Cold kit

For the second group of patients, production runs were performed using a lyophilized sterile cold kit with Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (PSMA-11) (ANMI SA, Liege, Belgium). All necessary materials to perform the radiolabelling are provided with the kit. ^{68}Ga elution was performed in a vacuumed sterile vial (5 ml of 0.1 N HCl, 1850 MBq GalliaPharm generator, Eckert & Ziegler, Germany). In a second sterile vial the lyophilized precursor PSMA-11 (25 µg) was reconstituted with acetate buffer. The precursor solution was then added to the elution vial and the labeling reaction was performed within 5 minutes at room temperature.

Quality control

Radiochemical purity for each batch was performed by high-performance liquid chromatography (HPLC) equipped with radio-detector and UV detector and thin layer chromatography (TLC). HPLC mobile phase was water with 0,1% trifluoroacetic acid (TFA) (A) and acetonitrile with 0,1% TFA (B) with a linear gradient 10-30% (B) in 10 min, the stationary phase was a C8 column (Eclipse XDB-C8, Agilent), the flow rate was 1.5 ml/min and the wavelength was 220 nm. Mobile phase of TLC method was a 1:1 solution of ammonium acetate (77 g/L)/methanol and a silica gel plate was the stationary phase. Ethanol content (only for synthesis module method) was measured by gas chromatography (capillary column CP-Wax 52 CB, Varian). Residual content of ^{68}Ge was evaluated by gamma-ray spectrometry (HPGe detector). Sterility and pyrogen content were tested according to European Pharmacopoeia methods.

PET/CT acquisition and image reconstruction

PET/CT scans were performed between 48 to 114 minutes (mean uptake time: 73 minutes) after the intravenous injection of ^{68}Ga-PSMA-11 using a weight-tailored activity of 2 MBq/kg of body weight in a total volume of 5–10 ml. The average injected activity was 150 MBq (range: 96 - 225 MBq). PET images were acquired in accordance with the Joint SNMMI/EANM procedure guidelines for PCa imaging(*14*). Acquisitions were performed using two different dedicated PET/CT hybrid systems (Discovery STE and Discovery 710; GE Healthcare). All patients were positioned supine on the imaging table, arms above, and acquired from the base of the skull to the mid thighs. PET emission images were recorded for 3 min per bed position in tri-dimensional mode using the Discovery STE (122/200 patients) and Discovery 710 (78/200 patients). All images were corrected for scatter, random coincidence events, system dead time and decay. CT images were used for correction, (employed parameters: 120 kV, 80 mA, 0.8-s tube rotation and 3.75-mm thickness). Attenuation-CT imaging was

performed without intravenous contrast enhancement. PET images were reconstructed using a fully tri-dimensional iterative reconstruction algorithm.

Image interpretation

PSMA-PET images were analyzed using a dedicated workstation, equipped with a commercially available software package (Advantage Workstation 4.6, GE Healthcare), allowing simultaneous and fused reviewing of PET and CT data. Two experienced nuclear medicine specialists independently reviewed all PSMA-PET images, while in case of disagreement final reporting was finalized after reaching a consensus. Any non-physiologic, focal areas of ^{68}Ga-PSMA-11 uptake, higher than the normal background were considered significant and likely sites of disease. Lesions were grouped and recorded according to the PROstate cancer Molecular Imaging Standardized Evaluation (PROMISE) classification; in particular, criteria are separately given for imaging of the prostate bed after RP or after EBRT, for primary staging of cancer, for lymph node imaging and for imaging of visceral bones or organs(*15*). Classification of local tumor is based on extent and organ confinement. Pelvic node metastases are categorized as single involved nodal regions (miN1a) or multiple involved nodal regions. Distant metastases are classified into extrapelvic lymph nodes (miM1a), bone metastases (miM1b) and organ metastases (miM1c). Bone disease is subcategorized as unifocal, oligometastatic, disseminated or diffuse marrow involvement (oligometastatic bone involvement is interpreted when there are max three bone lesions)(*15*). Maximum Standardized Uptake Values (SUVmax) were calculated as a measure of PSMA expression.

Quality assessment

For quality assessment, two other senior nuclear medicine physicians, highly experienced in PCa imaging with at least two years of PSMA imaging practice (Operator 1: SF; Operator 2: PC),

independently reviewed all the 200 PSMA-PET/TC images. Both physicians were unaware of the individual patients' clinical histories and employed synthesis procedure (synthesis module or cold kit). They subjectively assessed the perceived quality of the image. Half of final scoring was obtained after evaluating the images' adherence to five quality parameters, such as optical texture (defined as smoothness vs. graininess of liver uptake), sharpness (vs. blur) at sites of physiological uptake, image detail and contour rendering and perceived image quality in terms of lesion detection. The remaining half was quantified by defining the presence/absence of image artifacts, with particular focus on the presence of the halo artifact, defined as areas of artificially reduced, apparent tracer uptake in the vicinity of structures with intense PSMA uptake (especially kidneys and bladder) in the scatter-corrected images. After final scoring, the included imaging datasets were sub-grouped following a 3-point Likert scale (quality level described as excellent, good or moderate). Regions of interest (ROIs) were drawn around pathological foci and SUVmax was obtained for the most relevant lesions. In case of discordance the operators reviewed the images and reached a consensus. Figures 1 and 2 show a comparison of two ^{68}Ga-PSMA-11 PET/CT acquisitions rated as good and moderate quality respectively using different production procedures.

Statistical analysis

For continuous data mean ± SD, median and inter-quartile range (IQR) were reported, while categorical variables were described using absolute and relative (%) frequencies. Association between image quality and categorical variables were evaluated with Pearson's X^2 test, while for continuous variables (age, weight, BMI, injected dose, time of uptake) Analysis of variance (ANOVA) was used. Due to an extremely asymmetric distribution of PSA, its association with image quality was assessed with the non-parametric Kruskal Wallis test. Finally, significant variables were entered into a multiple logistic regression model, in order to identify independent factor associated to not excellent image quality. For

this purpose, the image quality evaluation was dichotomized into “excellent” vs. “not excellent” (good plus moderate) judgment. In order to avoid collinearity between weight and the BMI only the first one was considered in the model. Model goodness of fit was evaluated with the Hosmer and Lemeshow test. Statistical analysis was conducted with Stata statistical software version 13 (StataCorp, College Station, TX) and a p value lower than 0.05 was considered significant.

Results

Patient population characteristics

Among 200 patients the median age was 70 years (IQR: 64 - 74) and median serum PSA level at the time of PSMA-PET was 0.9 ng/mL (IQR: 0.4 - 2.2 ng/mL). Regarding PCa indication, 7/200 (4%) patients were referred to PET for primary staging, 168/200 (84%) to restage during biochemical recurrence and 25/200 (12%) to restage in castration-resistance. Complete clinical data are reported in detail in Table 2. Patient weight was on average 79.8±11.5 kg (range: 54 - 155). Average body mass index (BMI) for each patient was 26.7±3.7. None of the patients experienced immediate adverse reactions relating to the procedure.

^{68}Ga-PSMA-11 preparation and quality control

Synthesis yield with the automatic module was >80% corrected for the decay in 20 minutes. Radiochemical purity was >98%, ethanol and residual ^{68}Ge content complied with European Pharmacopoeia specifications. The product was sterile and non-pyrogenic. Synthesis yield with cold kit was 99.9% corrected for the decay (all ^{68}Ga activity coming from generator was available as radiopharmaceutical). Radiochemical purity was >98% and the product was found to be ethanol free, sterile and non-pyrogenic. Residual content of ^{68}Ge complied with the specification of the European Pharmacopoeia.

Image interpretation

^{68}Ga-PSMA-11 PET/CT was positive in 103/200, resulting in an overall positivity rate of 52%. Local recurrence within the pelvis was reported in 26% (52/200) of cases while distant metastases were identified in 26% (51/200) of patients. All identified pathologic foci corresponded to anatomic abnormalities on CT. In detail, 30/200 pathological lesions (15%) were localized on the prostate gland/bed site (T/Tr) and SUVmax ranged from 3.1 to 27.9. Forty-one/200 patients (21%) had pathologic pelvic nodes (N1), SUVmax ranging from 2.2 to 47.8. Twenty-two/200 (11%) of patients showed distant lymph node involvement (M1a) with SUVmax ranging from 3.3 to 50.5. Thirty-seven/200 (19%) patients showed bone involvement (M1b); SUVmax ranged from 1.9 to 43.0. In 4/200 (2%), PSMA-PET detected visceral metastases (M1c): 2/4 in the lungs and 2/4 in the liver; recorded SUVmax was 15.9.

Image quality and association with patient characteristics

Both operators considered all the examinations as diagnostic. In case of discordance, the operators reviewed the images and reached a consensus. The two operators rated 79 (39.5%) images as excellent, 95 (47.5%) as good and 26 (13%) as moderate (Table 3). Fifty/200 (25%) patients showed the presence of artifacts (Figure 3): 15/100 within the kit-group (15%) and 35/100 within the module-group (35%). In 3/200 (1.5%) there was blood extravasation at the injection site (commonly brachial). There was no significant difference between kit and automated synthesis module in evaluating ratings (p=0,13) although in the kit group the percentage of images rated "excellent" was higher (45% vs. 34%) (Table 3). A direct comparison of the novel cold kit-based 68Ga- PSMA-11 with the clinically established module-based 68Ga-PSMA-11 was made in some patients belonging to the same cohort of PCA, in particular the BRC (168 patients). We found no significant difference in image quality between kit and

cassette (p=0.344); the percentage of excellent images is higher in the kit vs cassette group (43.5% vs 31.1%). There were also no significant differences between production modalities in the overall report conclusions (in terms of presence\absence of pathologic uptake). Regarding patient characteristics, correlation with age was statistically significant (p=0.04). Within the group where images were rated as "excellent" the age was on average lower. However, when considering modular and kit synthetic protocols separately, in the former group there was a direct proportion between increase in age and lower image quality and the difference between the three levels (excellent, moderate, poor) was statistically significant (p=0.03); while in the latter group of patients (cold kit employed), the association between image quality and age was not significant. Clearer, significant correlations were on the other hand found between overall image quality and other variables such as weight, BMI and uptake times ($p<0.01$). The higher those three parameters were, the lower the image quality was, regardless of the employed production system, although when the cold kit was in use, variability in uptake times was found to be less relevant. Moreover, the increase in injected activity was significantly related to better image quality (p=0.02), although when considering modular and kit synthetic protocols separately, the association was significant only in the latter. Conversely, serum PSA levels, as well as the employed PET/CT system had no significant impact on image quality. According to multivariate regression analysis, after the dichotomization of image quality as “excellent” and “not excellent”, increases in patient age (+5 years: OR=1.40; CI 95%=1.12-1.75), patient weight (+5 kg: OR=1.89; CI 95%=1.53-2.32), ^{68}Ga-PSMA-11 uptake times (+10 minutes: OR=1.45; CI 95%=1.08-1.96) and injected activity (-10 Mbq: OR=1.28; 95%CI 1.07-1.52) were significantly associated with a "not excellent" image quality (Table 4).

Discussion

Our retrospective analysis of 2 different cohorts of heterogeneous PCa patients showed no statistically significant difference between PSMA-PET image quality (p=0.18). Nevertheless in the kit-group the percentage of images rated "excellent" was slightly higher than the module-group; this may be due to a lower percentage of halo artifacts within the kit-group compared to the module-group (15% vs. 35%). Thus in our study 2 different ^{68}Ga-PSMA-11 synthesis procedures, either modular or employing a cold kit, did not influence image assessment. Nevertheless, impactful factors on PSMA-PET image quality were found to be patient weight, patient age and uptake times. For higher values of these 3 parameters, the image quality worsened, regardless of the production method used. There was no significant association between image quality and ^{68}Ga-PSMA-11 injected activity in a setting where we administered 1.8-2.2 MBq of tracer per kilogram of body weight, in compliance with the EANM procedure guidelines, with injected activities under no circumstances falling below 50 MBq per patient; individual PET/CT tomograph and serum PSA levels at time of scan. However, only few scans were rated as "moderate" in quality and none was judged so poor to be described as non-diagnostic. Traditionally, ^{68}Ga-PSMA-11 can be prepared using a ^{68}Ge / ^{68}Ga generator and a manual synthesis module. Already Nanabala *et al.* studied its stability and radiochemical purity and the product was found to be extraordinarily stable, ensuring at the same time a high standard of radiological safety of the operator. In addition, the generator and the modules can be operated several times a day, the production of the radiopharmaceutical is relatively simple, economical and can be performed by an expert technologist (*16*). However, several studies are currently supporting the feasibility and operational safety of a new radiopharmaceutical, THP-PSMA, labeled in a single step with cold reconstitution by the means of a kit. In particular, in a phase 1 study comparing two different cohorts of patients receiving respectively one PSMA-11 and one THP-PSMA, Hofman *et al.* demonstrated that THP-PSMA is safe and has a favorable bio distribution for clinical imaging(*17*). Moreover, Derlin *et*

al., in a retrospective study, found suitable *in vivo* uptake characteristics of THP-PSMA (kit-based) and suggested the feasibility of its wider application, with a higher patient throughput(*18*). Our data support the hypothesis that ^{68}Ga-PSMA-11 cold kit production may be a promising tool, as previously suggested by Beheshti *et al*(*12*) without a detrimental effect on image quality in everyday clinical routine. Kit formulations may allow for a local, on-demand production overcoming the issues posed by the complexity of synthetic procedures, while resulting in higher yields with a standardized, high degree of radiochemical purity. Additionally, in situations of high demand, employing kits may free all generator-based ^{68}Ga activity for modular synthesis, significantly increasing the available radiopharmaceuticals on a daily basis, with a comparable degree of radiochemical purity among all injected tracer. ^{68}Ga-PSMA-11 cold kit may be easily implemented in a clinical radio-pharmacy, the main advantages being less operational complexity, no installation or maintenance costs, no need for additional staff training or for additional reagents. Furthermore, employing a kit might significantly speed up production, cutting operational times (no need for module and reagents preparation, no generator eluate and product purification) and overall costs, thus making the sterile cold kit a valid alternative to the synthesis module for the preparation of ^{68}Ga-PSMA-11 in clinical practice. Table 5 shows the main advantages and disadvantages of automated synthesis module production vs Kit-based ^{68}Ga-PSMA-11 production. Although our results seem to support the above conclusions, our study suffers from a few limitations, including its retrospective design, a suboptimal agreement between two independent readers and the heterogeneity of our cohorts of patients, which included different stages of prostate disease.

Conclusions

No significant differences were found on image quality between 2 groups of PCa patients investigated with ^{68}Ga-PSMA-11 PET/CT, employing different synthesis procedures in the production of the

administered ^{68}Ga-PSMA-11 radiotracer, namely cold kits and synthesis modules. Increase in patient age, patient weight, reduced injected activity and ^{68}Ga-PSMA-11 uptake times was significantly associated with a "not excellent" image quality. Our results suggest that cold kit synthesis procedures may be successfully implemented for the preparation of ^{68}Ga-PSMA-11 for clinical use in the imaging of PCa patients.

Disclosure

Cold kits were provided, free of charge, by ANMI SA, Liège, Belgium.

Key points

- QUESTION: are there significant differences between different synthesis procedures in term of final image quality in ^{68}Ga-PSMA-11 PET/CT?
- PERTINENT FINDINGS: this is a retrospective single-center cohort study comparing two groups of 100 patients each. No significant differences were found in terms of image quality between the two groups.
- IMPLICATIONS FOR PATIENT CARE: although comparable in quality to standard procedure, kit-based synthesis may allow for a more widespread diffusion of PSMA-ligand PET imaging.

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Figures and Tables

Table 1. Overview of several molecular PSMA-targeted agents and radioisotopes.

RADIOISOTOPES	**PSMA LIGANDS**	
^{123}I	MIP-1072 and MIP-1095	First agents employed for SPECT imaging
^{99m}Tc	MIP-1404 and MIP-1405	
^{18}F	DCFBC	First agents for PET imaging
^{68}Ga	PSMA-11	
^{68}Ga, ^{177}Lu, ^{255}Ac	PSMA-617	Theranostic ligands
^{68}Ga, ^{177}Lu, ^{111}In	PSMA-I&T	
^{18}F	18F-DCFPyL	Second generation of tracers labelled with ^{18}F
^{18}F	18F-PSMA-1007	

Table 2. Patients characteristics (n=200).

	Mean ± SD	**Median**	**IQR**
Age (y)	69 (8)	70	64 - 74
Weight (kg)	80 (11)	79	72 - 87
BMI	26.7 (4)	26.2	24.0 – 29.0
Injected activity (MBq)	160 (21)	157	150 - 174
Uptake time (min)	73 (13)	70	65 - 82
PSA PET (ng/mL)	10.4 (72.9)	0.9	0.4 – 2.2
	Frequency		**%**
Clinical indication			
Primary staging	7/200		4
Biochemical recurrence	168/200		84
CRPC	25/200		12
PET device			
Discovery 710	78/200		39
Discovery STE	122/200		61

Notes: BMI: body mass index; CRPC: castration-resistant prostate cancer.

Table 3. Association between ^{68}Ga-PSMA-11 production and image quality.

	MODULE	KIT	TOTAL
EXCELLENT	34	45	79 (39.5%)
GOOD	49	46	95 (47.5%)
MODERATE	17	9	26 (13.0%)
TOTAL	**100**	**100**	**200**

Table 4. Estimated under logistic regression models for the presence of not excellent images quality.

	Simple Logistic Model			Multivariable Logistic Model		
Not excellent images quality	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Age (5 years increase)	1.25	1.04 – 1.50	0.015	1.40	1.12 – 1.75	0.003
Weight (5 kg increase)	1.63	1.37 – 1.94	<0.001	1.89	1.53 – 2.32	<0.001
Uptake time (10 min increase)	1.40	1.09 – 1.80	0.008	1.45	1.08 – 1.96	0.013
Injected activity (10 Mqb decrease)	1.20	1.04 – 1.38	0.013	1.28	1.07 – 1.52	0.006

Table 5. Main advantages and disadvantages of automated synthesis module production vs. Kit-based ^{68}Ga-PSMA-11 production.

^{68}Ga-PSMA-11 Preparation	**Synthesis module**	**Kit**
Yield (%) corrected for the decay	>80	99.9* *all ^{68}Ga activity from the generator available as radiopharmaceutical
Time of synthesis (min)	20	10
^{68}Ga/^{68}Ge eluate and product purification	Need to eluate and product purification	No eluate and product purification
Preparation of reagents before synthesis	Need to cassette and reagents preparation	All necessary materials are provided with the kit
Installation and maintenance issues	Need to module installation and maintenance	No need to module installation and maintenance
Operational complexity	Need to staff training	Need to staff training but less operational complexity
RCP (%)	>98	>98
^{68}Ge content (%)	0,00001	0,0001%
Ethanol content	Complied with Eur. Pharm. specifications	Not present
Sterility and pyrogen content	Complied with Eur. Pharm. specifications	Complied with Eur. Pharm. specifications

Figure 1. Comparison of two ^{68}Ga-PSMA-11 PET/CT acquisitions rated as good quality using different production procedures.

1) ^{68}Ga-PSMA-11 synthetized with sterile cold kit. 68 years-old patient with extracapsular PCa at the time of diagnosis. iPSA 6.1 ng/mL. GS 7 (4+3). EBRT in 2012 and BAT for two years until 2014. BCR during 2015. dtPSA < 6 months. PSA at the time of PET/CT: 2,5 ng/mL. **1a** coronal PET, **1b** sagittal PET, **1c** axial PET, **1d** Maximum intensity-projection, **1e** fused PET/CT of the abdomen and **1f** fused PET/CT of the pelvis.

2) ^{68}Ga-PSMA-11 synthetized with automated synthesis module. 72 years-old patient with PCa GS 8 (4+4). iPSA 6,9 ng/mL. RP nerve-sparing and pelvic LAD in 2017. pT3a pN1. PSA persistence two months after surgery. PSA at the time of PET/CT: 1.19 ng/mL. **2a** coronal PET, **2b** sagittal PET, **2c** axial PET, **2d** Maximum intensity-projection, **2e** fused PET/CT of the abdomen and **2f** fused PET/CT of the pelvis.

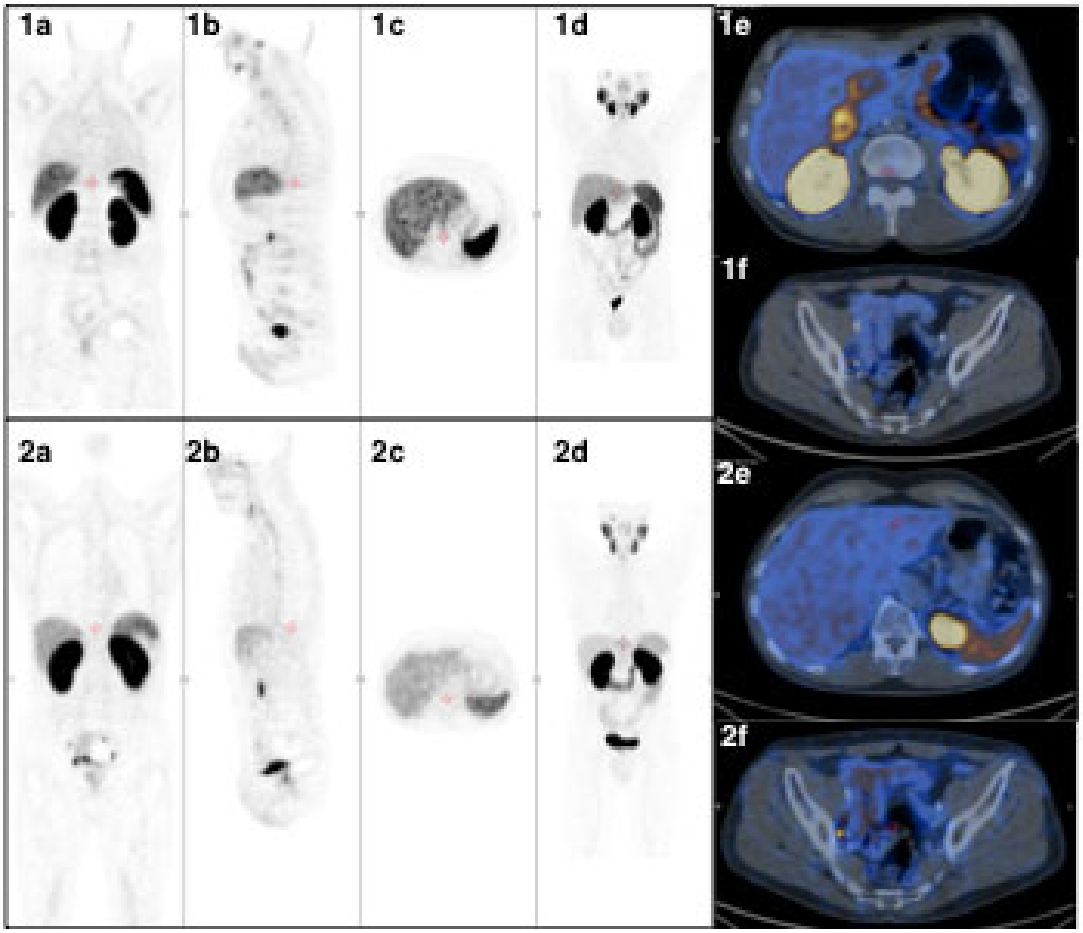
1a
1b
1c
1d
1e
1f
2a
2b
2c
2d
2e
2f

Figure 2. Comparison of two ^{68}Ga-PSMA-11 PET/CT acquisitions rated as moderate quality using different production procedures.

1) ^{68}Ga-PSMA-11 synthetized with sterile cold kit. 81 years-old patient with PCa GS=8 (4+4), underwent RP in 2009. pT4pN1 (1/10), R0, iPSA=10.67. Adjuvant RT on prostate bed and pelvic lymph nodes and BAT. During 2016 stereotactic RT on iliac lymph nodes. PSA at the time of the PET/CT: 1.19 ng/mL. **1a** coronal PET, **1b** sagittal PET, **1c** axial PET, **1d** Maximum intensity-projection, **1e** fused PET/CT of the abdomen and **1f** fused PET/CT of the pelvis.

2) ^{68}Ga-PSMA-11 synthetized with automated synthesis module. 76 years-old patient with PCa. GS 9 (5+4). 2014 RP and pelvic LAD. iPSA 7.5 ng/mL. pT3b R+ N2 (8/20) M0. EBR on prostate bed. PSA at the time of PET/CT: 5.92 ng/mL. **2a** coronal PET, **2b** sagittal PET, **2c** axial PET, **2d** Maximum intensity-projection, **2e** fused PET/CT of the abdomen and **2f** fused PET/CT of the pelvis.

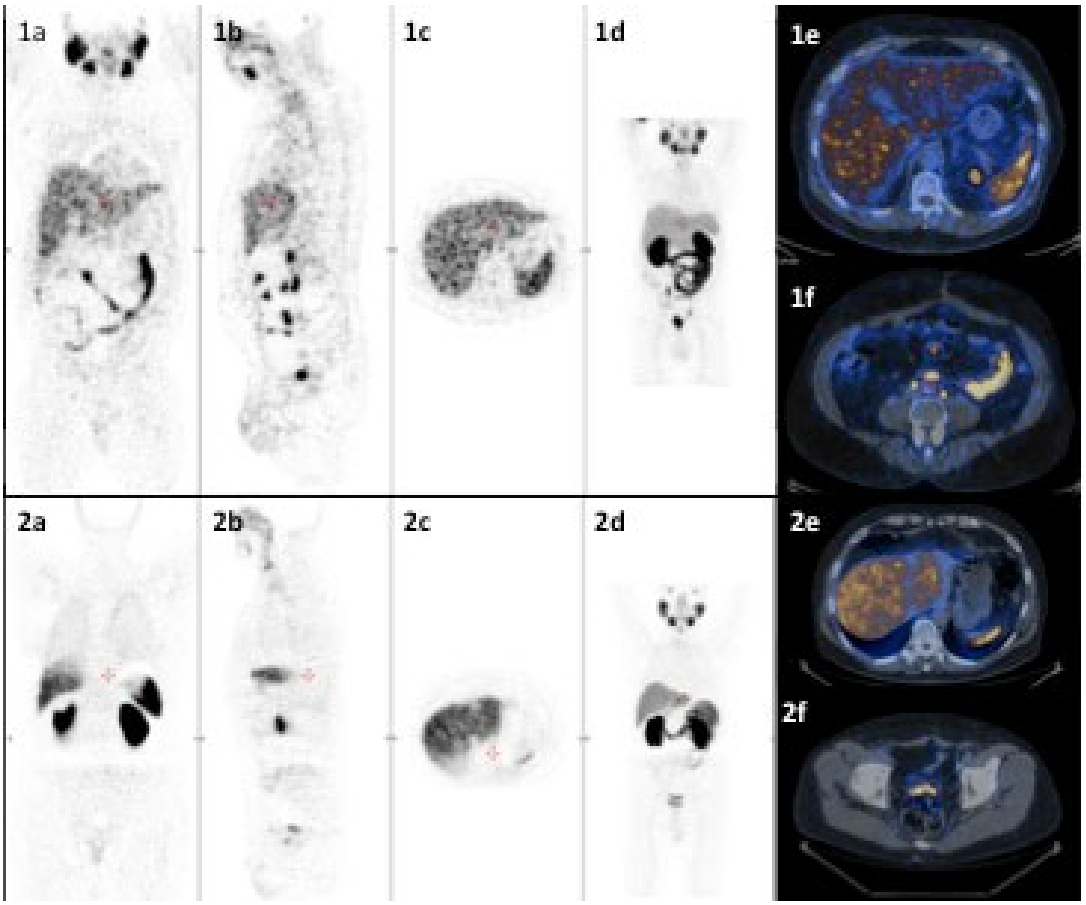
1a
1b
1c
1d
1e
1f
2a
2b
2c
2d
2e
2f

Figure 3. Presence of Halo artifact on PET/CT images.

Occurrence of scatter artifact around the kidneys in ^{68}Ga-PSMA-11 PET/CT. **a** Maximum intensity-projection, **b** coronal PET, **c** sagittal PET, **d** axial PET, **e** fused PET/CT of the abdomen at the level of the kidneys with high urinary tracer activity causing the artifact.