Final Study Report

Study Title: Use of 18F-PSMA-11 PET for detection of lesions in iodine refractory thyroid cancers

EU reference number: *2021-000456-19*

Study protocol/CIP code: *BC-09501*

Investigational device / medicinal product: [^{18}F]PSMA-11, also referred to as [^{18}F]AlF-HBED-CC-PSMA or [^{18}F]aluminium fluoride 4,6,12,19-Tetraazadocosane-1,3,7-tricarboxylic acid, 22-[3-[[[2-[[[5-(2-carboxyethyl)-2-hydroxyphenyl]methyl](carboxymethyl)amino]ethyl](carboxymethyl)amino]methyl]-4-hydroxyphenyl]-5,13,20-trioxo-, (3S,7S)

ClinicalTrials.gov identifier: NCT05175404

Sponsor: *Ghent University Hospital*

Contact details sponsor: C. Heymanslaan 10, 9000 Gent

National Coordinator/ Coordinating Investigator: Prof Dr V Schelfhout.

Funder: Cancer research institute Ghent (*CRIG)*

Author:

Date of report: *02/09/2024*

By signing this final study report, I acknowledge that the information is accurate and complete.

Name and signature Coordinating Investigator: Prof Dr V Schelfhout

V. Schelfhout 04.09.2024

Date signature Coordinating Investigator: .....

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Table of content

1. Introduction

Thyroid cancer is the most common endocrine malignancy. Well differentiated thyroid carcinoma (DTC) generally has a good prognosis, partly due to the therapeutic possibility of I-131, which is a well-known, tolerated and effective therapy for these patients. However, a subset of patients presents with tumors that are not or no longer iodine avid, due to the dysfunction or loss of the sodium iodide symporter expression as part of a dedifferentiation process. Survival rates in these patients are worse, especially in patients with metastatic disease. For optimal management, early detection of loco-regional recurrent or metastatic disease is important. Currently, ultrasound and MRI of the head and neck for detection of local recurrence, and CT and ^{18}F-FDG PET/CT scans for detection of metastatic disease are used in the follow-up of patients with radio-active iodine (RAI) refractory DTC. However, all these methods lack sensitivity and specificity in this indication. ^{18}F-PSMA-11 is a novel radiotracer that could be used in this setting. Several case reports have shown accidental uptake in the thyroid in patients with prostate cancer, which turned out to be thyroid cancer. Since prostate specific membrane antigen (PSMA) expression may be higher in dedifferentiated tumors, there may be more value in this patient group. Further, there is scant data on the molecular and clinical characteristics of these PSMA-expressing thyroid carcinomas. Whether in these patients serum PSMA levels might reflect disease burden and thus serve as an additional tumor marker next to thyroglobulin (which in these patients sometimes might be less reliable due to the dedifferentiation process) has until now not been addressed.

PSMA is a type II transmembrane glycoprotein receptor, expressed in normal prostate tissue and to a greater extent in prostate carcinoma, making it a useful target for radionuclide imaging and therapy for prostate cancer. PSMA is also expressed in the neovasculature of other tumors including carcinomas of the lung, kidney, colon and rectum, and the thyroid. Compared to normal thyroid tissue, PSMA is significantly overexpressed in the neovasculature of DTC, especially in the RAI-refractory type, as well as in poorly differentiated and anaplastic thyroid cancer. PSMA expression seems to predict the level of aggressiveness in DTC and predict patient outcome. Several thyroid incidentalomas have been detected on PSMA PET, both fluor and gallium based, performed in men with prostate cancer. ^{18}F-PSMA-11 is a radiotracer developed at the university hospital of Ghent, as an alternative for the already existing ^{68}Ga-PSMA PET-tracers, that can be made on a larger scale. Preclinical, in vivo imaging in mice showed high affinity for the PSMA receptor, even higher than in ^{68}Ga-PSMA-11. A phase 1 trial showed that the molecule is safe to use and has a total radiation dose that is lower than for other PSMA PET agents. A phase 2 trial evaluated an optimal scanning protocol (for prostate cancer), with the proposal of dose administration of 2MBq/kg and image acquisition after 60 minutes. At current, there is only a very limited amount of case reports and studies to determine the usability of PSMA PET in thyroid carcinoma. Taywade et al used a ^{68}Ga-PSMA PET in a patient with metastasized papillary thyroid carcinoma, rising thyroglobulin level and a negative radioiodine scan. PSMA PET revealed uptake in several lymph nodes, as well as in hematogenous metastasis in the brain, lungs and bone. When compared with ^{18}F-FDG PET, the ^{68}Ga-PSMA PET detected more lesions. Lawhn-Heath et al did a study in 12 patients to determine the feasibility of ^{68}Ga-PSMA-11 PET/MRI in thyroid cancer. They included patients with papillary thyroid carcinoma, Hürthle cell carcinoma, poorly differentiated papillary thyroid carcinoma, anaplastic thyroid carcinoma and follicular thyroid carcinoma. In this study PSMA PET was able to detect metastatic thyroid cancer but at a lower rate than FDG PET, with a heterogeneous degree of tracer uptake.

2. Objectives of the study

2.1 Primary objectives

Demonstrate uptake of ^{18}F-PSMA-11 in lesions in a radio-active iodine refractive thyroid carcinoma (RAI-RTC), either local recurrent disease, lymph nodes or distant metastasis.

2.2 Secondary objectives

- Perform a semi-quantitative analysis of radiotracer uptake in lesions.
- Perform a lesion detection rate analysis on organ level.
- Compare uptake of ^{18}F-PSMA-11 in these patients to the uptake of ^{18}F-FDG, on a lesion basis as well as on a patient basis.
- Evaluate the sufficiency of uptake of ^{18}F-PSMA-11 to consider therapy with ^{177}Lu-PSMA in a subset of patients.
- Compare the histological expression of PSMA on the primary tumor with the uptake of lesions on PSMA PET.
- Analyse the correlation between the serum level of PSMA and the uptake on PSMA PET.
- Compare the histological expression of PSMA on the primary tumor with the serum level of PSMA.

3. Investigational Medicinal Product

The investigational medicinal product of 18F PSMA-11 is a sterile solution for intravenous injection and consists of:
- [18F] PSMA-11: 0.1 – 2.5 GBq/mL at time of calibration (active pharmaceutical ingredient)
- Aqua ad injectabilia ad: ≥ 90% V/V (solvent)
- Ethanol (96 % V/V): 10% V/V (co-solvent)
- Potassium dihydrogen phosphate : 0.3 mg/mL (buffer) (*)
- Di-potassium hydrogen phosphate : 0.4 mg/mL(buffer) (*) *(*)added in the form of a concentrated potassium phosphate solution (Kaliphos®) consisting of 0.136 g/ml monopotassium phosphate and 0.174 g/ml dipotassium phosphate*

The preparation of [18F]PSMA-11 sterile solution for injection, is a continuous process, and the pharmaceutical active substance (drug substance) is, as a rule, not isolated.

Manufacturer and distributor:

Cyclotron facility, Department of Nuclear Medicine, UZ Gent
Corneel Heymanslaan 10,
B-9000 Gent
exploitation license BA-0001751.

Universiteit Gent – Universitair ziekenhuis Gent

GMP Unit Radiopharmacy (Unit 4)

Gebouw P8 verdieping -1
Corneel Heymanslaan 10

B – 9000 Gent

License: 1940 IMP

Preparation + dosage + administration

In preparation of the production of the IMP, environmental parameters (HVAC, pressure cascade) are verified. Materials are then transferred from storage area to the grade A laminar air flow using a validated decontamination and disinfection method.

In grade A under aseptic conditions the dispensing kit is assembled and mounted on the dispensing unit and product vials are prepared and properly labelled. Vials and dispensing unit are transferred to a grade A hotcel where formulation and filling of vials will occur.

The drug substance is synthesized and transferred from the synthesizer to the grade A hotcel. The [18F]PSMA-11 solution is passed through a sterilizing filter and collected in the product bulk vial. Here, it is mixed with a diluted potassium phosphate solution to a homogeneous formulation.

Immediately after homogenisation of the bulk, the radioactivity of the bulk is determined with a dose calibrator. The timepoint of measuring the activity of the bulk solution is by definition the reference time (also known as T0 or T-zero) recorded for the produced batch.

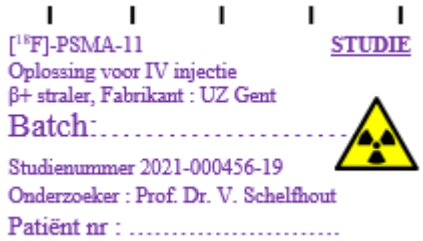
Sterile pyrogene free vials are filled with the product bulk solution by piercing of the rubber stopper. Prior to filling the dispensed volume is passed through a sterilizing end-point filter. Radioactivity in each vial (QC samples, reference samples and product vials) is determined. Vials are then transferred through the vial extraction system and packaged in lead containers.

The finished product in its lead shielding is properly labelled and stored in quarantine until release of the batch.

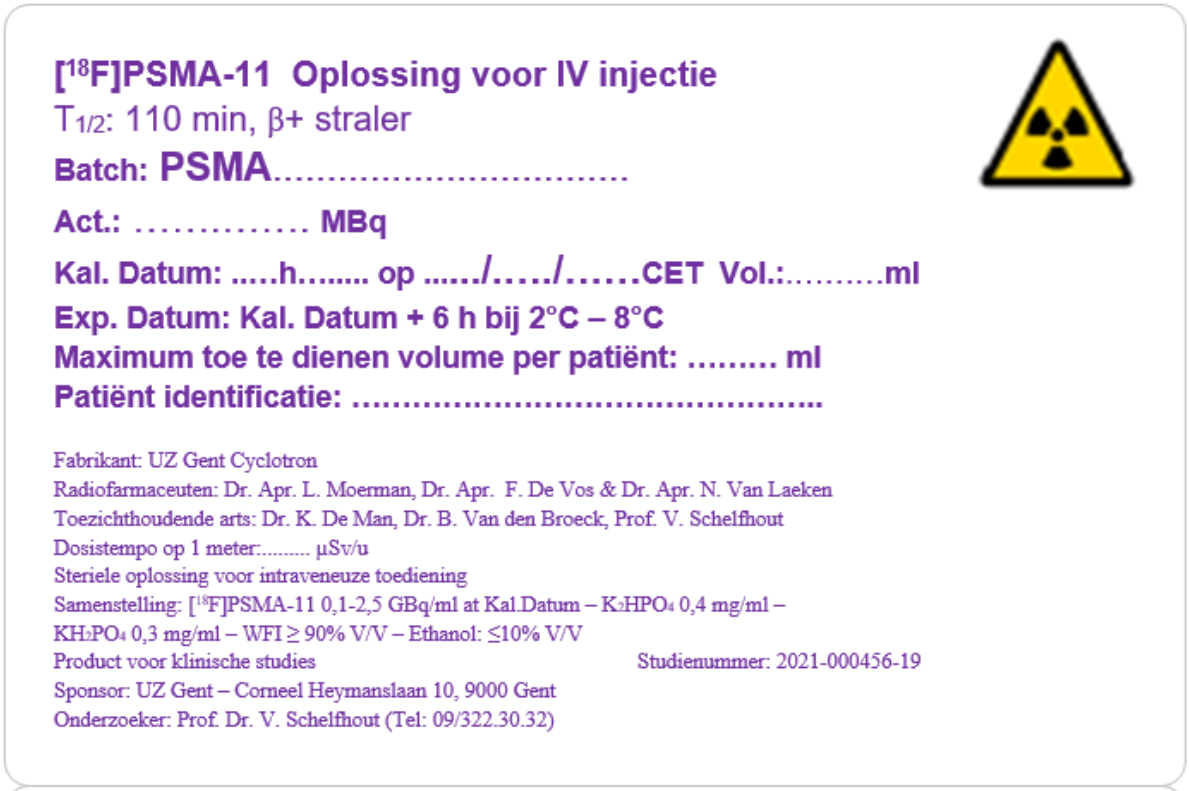
Dose: 2 MBq/kg +- 10%

Administration: intravenous

Primary packaging



Secondary packaging:



Storage conditions of the IMP

The IMP is produced at the cyclotron of the university hospital Ghent. The administration of the IMP is in the department of nuclear medicine of the university hospital Ghent. The drug product vials must be stored in a precooled (≥ 12 hours of storage at ≤ -15°C) lead container, placed in a fridge at 2-8°C. The temperature is logged via the aeroscout system. The time at which the lead containers are placed in the freezer is documented. A check of the minimum period of 12 hours is made via the production report. Storage of the IMP (in pre-cooled lead pot) at 2-8°C also takes place in a GMP refrigerator, which is logged via the aeroscout system. Transfer from IMP: see iDOC 5391.

4. Investigational Medical Device

Not applicable

5. Study Protocol Summary

5.1 Study design

Patients with a radio-iodine refractory thyroidcarcinoma that had an FDG PET/CT in routine clinical setting would get an F-PSMA-11 PET. Before injection of the tracer a serum sample was taken to measure sPSMA. If available immunohistochemistry was performed on resection specimens.

5.2 Inclusion criteria

- Patient is 18 years or older.

- Signed Informed Consent.
- Subject is diagnosed with a histologically confirmed differentiated thyroid carcinoma, that is considered RAI refractory. There is evidence of persisting or recurrent disease, based on serum thyroglobulin levels and/or medical imaging.
- Subject should have a routine clinical ^{18}F-FDG PET/CT performed within two months prior to the study scan.
- Female patients should be either post-menopausal, surgically sterile, or using highly effective contraceptives (methods that can achieve a failure rate of less than 1%: combined hormonal contraception, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence).

5.3 Exclusion criteria

- Patient has a known other active malignancy.
- Subject is potentially pregnant (urinary test can be performed in case of doubt) or breastfeeding.
- Patient is mentally or legally incapacitated.

5.4 Primary endpoint

Demonstrate uptake of ^{18}F-PSMA-11 in lesions in a radio-active iodine refractive thyroid carcinoma (RAI-RTC), either local recurrent disease, lymph nodes or distant metastasis.

5.5 Secondary endpoints

- Perform a semi-quantitative analysis of radiotracer uptake in lesions.
- Perform a lesion detection rate analysis on organ level.
- Compare uptake of ^{18}F-PSMA-11 in these patients to the uptake of ^{18}F-FDG, on a lesion basis as well as on a patient basis.
- Evaluate the sufficiency of uptake of ^{18}F-PSMA-11 to consider therapy with ^{177}Lu-PSMA in a subset of patients.
- Compare the histological expression of PSMA on the primary tumor with the uptake of lesions on PSMA PET.
- Analyse the correlation between the serum level of PSMA and the uptake on PSMA PET.
- Compare the histological expression of PSMA on the primary tumor with the serum level of PSMA.

5.6 Procedures

Moment of screening at the department of endocrinology:

- Explain goal and advantages and disadvantages of the study
- Check inclusion and exclusion criteria if possible

Moment of inclusion at the department of nuclear medicine:

- Signing of informed consent form.
- Urinary pregnancy test if any doubt that an included female patient may be pregnant.

- PET/CT scan with ^{18}F-PSMA-11 at the department of nuclear medicine (within 2 months after the standard of care ^{18}F-FDG PET/CT scan):
- Check signed informed consent form. Check if patient understood the course and risks of the study.

- Collection of venous sample (9 ml) for PSMA serum measurement. This sample should be taken maximum one hour before the injection with ^{18}F-PSMA-11
- Administration of ^{18}F-PSMA-11 (2 Mbq/kg +- 10%) intravenously.
- After 60 minutes (+- 5 minutes): low dose CT scan for attenuation correction and anatomical localization followed by a PET scan from head to midfemoral region, No contrast fluid will be administered.
- Enquiry for any adverse effects: if no adverse effects are reported after the PET/CT scan, the patient can leave the hospital.
-

5.7 Randomisation and blinding

The assignment of the study number will be done by a study investigator. All images from the FDG PET and PSMA PET will be put in a separate image processing program for the visual and semi-quantitative assessment of the images.

After the patient has signed the informed consent document and is included in the study, a study number will be assigned. All information and scan data will be stored under this number. However the PSMA PET images and a report (with statement that the scan was performed under a study protocol) will be added also to the clinical patient files (PACS / EPD), and can be used for patient care if applicable and deemed necessary by the attending physician. So the data will be pseudonimysed.

There will be no randomization or blinding.

5.8 Monitoring and quality measures

Monitoring of the study will be performed in compliance with GCP E6(R2) and the applicable regulatory requirements. The study team will be trained during an initiation visit by the monitor.

6. Study analysis

Sample size calculation: in the study protocol 20 patients were determined to participate. Unfortunately, due to the relative rareness of the disease and unwillingness of several patients to participate in the study, only 8 patients were included.

We performed a lesion-based and patient-based analysis on the PET-images and the semi-quantitative analysis of the images. Descriptive statistics of the population and results were performed. Correlation was searched between the PET-parameters, serologic parameters and immunohistochemistry.

The number of lesions delineated in each organ was limited to 10 on each PET. For each lesion, the maximal standard uptake value (SUV), SUV_{max}, and metabolic tumor volume (MTV) were determined using a margin threshold set at 41% of the SUV_{peak} value. If needed, a manual adjustment of the delineation was made, for example, to exclude physiologic uptake in an adjacent region. Additionally, background SUV_{mean} values were determined in the parotic glands, the mediastinal blood pool, and the liver.

Before injection of the radiolabelled PSMA, a venous blood sample was taken from all patients. All samples were collected, centrifuged, and stored for batch processing. An enzyme-linked immunosorbent assay (ELISA; Assay Genie, Dublin, Ireland) was used to analyze serologic soluble PSMA. The concentration of sPSMA was measured twice, and an average result was calculated.

Histology: For each case, 4-µm-thick sections from a representative block of formalin-fixed, paraffin-embedded tumor tissue were used for immunohistochemical analysis. Immunohistochemistry was performed using an immunostainer (Benchmark XT, Ventana Medical Systems, Tucson, AZ, USA), according to the manufacturer's instructions. The sections were immunostained with a primary monoclonal antibody against PSMA (1:25; EP192; Cell Marque). Visualization was achieved with ultraView Universal DAB Detection kit (Ventana Medical Systems, Tucson, AZ, USA). Appropriate positive and negative controls were used throughout the study. PSMA expression was evaluated by two expert pathologists on immunostained whole tissue sections (Olympus, BX53; 40x magnification). The 3-point PSMA scale proposed by Bychkov et al. was used to score PSMA positivity(37): no detectable endothelial expression or expression in <5% of capillaries was defined as negative (score 0), PSMA expression in 6-50% of capillaries as moderately positive (score 1) and PSMA expression in >50% of capillaries as strongly positive (score 2).

7. Independent Ethics Committee and Competent Authority

OVERVIEW APPROVED DOCUMENTS		
Initial submission: - *Protocol version 1.0, dd. 13-07-2021* - *ICF version 2.0, dd. 29-10-2021* - *Investigator Brochure version 8, dd. 14/10/2021* - *Aanvraagformulier FANC version 1.0 dd 26/04/2021* - *Subject card version 1.0 dd 28/05/2021* - *IMPD version 1.0 dd 26/01/2021* - *Clinical trial application form version 1 dd 13/07/2021* -	***Approval date Central EC: 17/11/2021***	***Approval date FAMPH:***

8. Results

8.1 Subject enrollment and demographics

8 patients were included between 04/02/2022 and 02/09/2022. There were no dropouts after inclusion. Due to the relative rareness of the disease and unwillingness of several patients to participate in the study, only 8 patients were included.

Eight patients (four male, four female) were included in this study, with a mean age of 66 years (+- 7 years). The included patients were diagnosed with follicular TC (n=4), papillary TC (n=2), follicular variant of papillary TC (n=1) or poorly differentiated TC (n=1). At the time of initial diagnosis (between 1988 and 2022), five patients had a high ATA risk score, one had an intermediate ATA risk score, and two had a low ATA risk score. The included patients were considered iodine refractory based on the absence of uptake of RAI in all (n=2) or some (n=1) lesions on a post-therapy scan, absence of uptake of RAI in all lesions on a diagnostic iodine scan (n=3), progressive disease 6 months after treatment with RAI (n=1), or persistent disease despite treatment with maximal dose of RAI

(n=1; cumulative dose 950 mCi). Seven patients were previously treated with RAI, with cumulative activities ranging from 100 to 950 mCi. Two patients were treated with a tyrosine kinase inhibitor at the time of inclusion (PT3: lenvatinib 10 mg and PT7: lenvatinib 14 mg). PT3 had previously been treated with sorafenib 200 mg but this treatment was discontinued due to intolerance. The most recent unstimulated Tg levels ranged from 1.13 µg/dl to 2270 µg/dl with a median of 132.25 µg/dl; none of the patients had Tg antibodies The last patient was included and scanned on 02/09/2022.

8.2 Study specific results

Primary objective:

A total of 30 suspicious lesions were identified on [^{18}F]AlF-PSMA-11 PET, including 2 brain lesions, 2 local lesions, 2 lymph nodes, 12 bone lesions and 12 lung lesions.

Secundary objectives:

- Perform a semi-quantitative analysis of radiotracer uptake in lesions: see table

	Location	Type	PSMA SUV	PSMA MTV	FDG SUV	FDG MTV
Lesion 1	Cerebellum	Brain	8,8	0,44	0	0
Lesion 2	Th4-Th6	Bone	10,07	53,46	4,96	30,04
Lesion 3	Rib 6 L	Bone	14,78	2,72	3,81	0,87
Lesion 4	Thyroid L	Local	9,1	3,3	0	0
Lesion 5	LL R	Lung	6,3	7,57	6,1	6,15
Lesion 6	LL R	Lung	2,6	2,85	3,8	2,93
Lesion 7	LL R	Lung	2,3	3,1	3,4	3,1
Lesion 8	ML R	Lung	0	0	5,8	2,66
Lesion 9	LL R	Lung	0	0	4,6	2,49
Lesion 10	UL L	Lung	2,3	7,55	5,3	8,06
Lesion 11	UL L	Lung	2,9	5,11	2,5	5,76
Lesion 12	LL L	Lung	3,5	6,32	3,3	5,67
Lesion 13	LL L	Lung	4	53,83	8,4	54,33
Lesion 14	LL R	Lung	4,6	5,13	4,3	9,35
Lesion 15	Th10	Bone	3,9	4,14	6,6	5,07
Lesion 16	Acetabulum R	Bone	7	47,39	4	26,34
Lesion 17	UL L	Lung	0	0	14,6	0,96
Lesion 18	UL L	Lung	0	0	30,9	0,87

Lesion 19	UL L	Lung	4,2	5,26	44,9	6,3
Lesion 20	LL L	Lung	0	0	6,2	2,24
Lesion 21	LL L	Lung	0	0	2,3	0,1
Lesion 22	LL L	Lung	0	0	14,1	2,12
Lesion 23	UL R	Lung	2	1,87	29,5	1,93
Lesion 24	UL R	Lung	2,1	1,52	24,7	0,85
Lesion 25	UL R	Lung	0	0	9,8	1,31
Lesion 26	LL R	Lung	4,1	7,71	30,2	6,26
Lesion 27	Thyroid L	Local	2,3	0,77	4,8	0,81
Lesion 28	Th6	Bone	7,5	2,68	7,2	1,89
Lesion 29	Th11	Bone	3,6	0,87	5,3	1,35
Lesion 30	Cervical L ant	Lymph node	2	0,89	2,3	0,46
Lesion 31	Cervical L post	Lymph node	2,3	0,37	0	0
Lesion 32	Retropharyng R	Lymph node	0	0	24,3	0,8
Lesion 33	Brain L	Brain	4,3	3,76	0	0
Lesion 34	Scapula R	Bone	4,2	3,91	0	0
Lesion 35	Th2	Bone	3,1	0,77	0	0
Lesion 36	Th7	Bone	4,5	13,74	4,4	6,87
Lesion 37	Th10	Bone	5,2	10,91	4,2	7,96
Lesion 38	Rib 6 L	Bone	3,7	6,55	2,5	8,16
Lesion 39	Os ilium L	Bone	2,9	247	4,7	324

-

A total of 30 suspicious lesions were identified on [^{18}F]AlF-PSMA-11 PET with a SUV_{max} of 4.7 (1.2 – 14.8). On [^{18}F]FDG PET, 33 lesions were found with a SUV_{max} of 10.11 (2.3 – 44.9). In total, there were 39 lesions on [^{18}F]AlF-PSMA-11 and [^{18}F]FDG PET combined. These results provide a detection rate of 76.9% for [^{18}F]AlF-PSMA-11 PET and a detection rate of 84.6% for [^{18}F]FDG PET.

- Perform a lesion detection rate analysis on organ level. + Compare uptake of ^{18}F-PSMA-11 in these patients to the uptake of ^{18}F-FDG, on a lesion basis as well as on a patient basis.

Twenty-four lesions were visible on both [^{18}F]AlF-PSMA-11 PET and [^{18}F]FDG PET, including one locoregional recurrence, one lymph node, ten bone lesions and twelve lung lesions. Six lesions in five patients were only visible on [^{18}F]AlF-PSMA-11 PET, where two were located in the brain, one was a local recurrence, one was a lymph node, and two were bone lesions. Nine lesions in three patients were only visible on [^{18}F]FDG PET, consisting of eight lung lesions and one lymph node.

On a patient-based analysis, the mean SUV_{max} of all lesions per patient was 3.88 (0 – 11.21) on [^{18}F]AlF-PSMA-11 PET and 7.75 (0-20.72) on [^{18}F]FDG PET. An overview of the patient-based analysis can be found in Table 2. Statistical analysis showed only a significant correlation between total metabolic tumor volume (TMTV) of the lesions on [^{18}F]PSMA and [^{18}F]FDG PET (p-value 0.002). No other significant correlations were found between the mean SUV_{max}, TMTV and Tg levels.

- Analyse the correlation between the serum level of PSMA and the uptake on PSMA PET.

sPSMA levels were measurable in the four male patients with an average of 37.7 ng/mL (SD 17.56, range 20.3 – 55.9). None of these patients had undergone prostatectomy. The four female patients had undetectable sPSMA levels. Correlation analysis showed no significant correlation between sPSMA and other parameters in the male patients.

- Compare the histological expression of PSMA on the primary tumor with the uptake of lesions on PSMA PET + Compare the histological expression of PSMA on the primary tumor with the serum level of PSMA.

Immunostaining proved positive in 5 of the primary TC (PT1, PT2, PT3, PT7 and PT8) (63%) and negative in the remaining 3 (PT4, PT5 and PT6) (37%). Among the 5 positive cases, PSMA expression was scored as moderately positive (score 1) in 3 cases (PT1, PT2 and PT3) and strongly positive (score 2) in 2 cases (PT7 and PT8). Endothelial expression of PSMA was exclusively localized within tumors, but not in the normal or non-neoplastic thyroid. There was no significant correlation between the PSMA-score in the primary tumor and any parameters on either PSMA or FDG PET, as well as no correlation between sPSMA in male patients.

Positive PSMA endothelial expression was observed in all histologically examined metastases: strong (score 2) expression in 2 bone metastases (PT1 and PT8) and one brain metastasis (PT7), moderate (score 1) expression in 2 lung metastases (PT2 and PT3).

- Evaluate the sufficiency of uptake of ^{18}F-PSMA-11 to consider therapy with ^{177}Lu-PSMA in a subset of patients.

When applying the criteria of Hofman *et al.* to determine the eligibility for therapy with ^{177}Lu-PSMA, two patients in our study would be eligible.

9. Safety

No serious adverse events did occur during the study.

10. Device deficiencies

Not applicable

11. Protocol deviations

No protocol deviations have occurred.

12. Discussion and overall conclusions

A total of 39 lesions were identified as suspicious in the cohort of included patients. Of these, [^{18}F]AlF-PSMA-11 PET detected 30 lesions, whereas [^{18}F]FDG PET detected 33 lesions. As such, the detection rate of [^{18}F]AlF-PSMA-11 PET was 76.9% , approaching the 84.6% measured with the current gold standard of [^{18}F]FDG PET. However, despite the higher number and mean tracer uptake of lesions detected by [^{18}F]FDG PET, [^{18}F]AlF-PSMA-11 PET was able to detect 6 lesions that were not detected by [^{18}F]FDG PET. Furthermore, in one out of eight patients, disease localization was achieved only by [^{18}F]AlF-PSMA-11 PET. In general our results are comparable with a recent study in DTC and RAI-TC that also found a lower detection rate in [^{68}Ga]Ga-PSMA-11 compared with [^{18}F]FDG PET.

Additionally, a distinction between the types of lesions detectable by both PET modalities was observed. Generally, bone lesions exhibited higher activity on [^{18}F]AlF-PSMA-11 PET scans compared to [^{18}F]FDG PET scans, while lung metastases typically demonstrated the inverse. Notably, the two brain metastases were only detectable using [^{18}F]AlF-PSMA-11 PET.

In addition to the potential value of targeting PSMA using PET imaging, we also evaluated the value of sPSMA in the serum of patients with RAI-R TC. We hypothesized that an increase in neovasculature formation could impact the amount of protein shed from the tumor, which could be a potential biomarker for tumor growth. However, in this small cohort, sPSMA was only detectable in male patients, while sPSMA remained unmeasurably low in female patients. These results indicate that the most important factor in sPSMA is the presence of prostate tissue.

In five out of eight patients immunostaining showed PSMA expression on the primary tumor at the moment of diagnosis. Of the three patients without PSMA expression on the primary tumor, two did have PSMA-positive lesions at 6 years and 34 years after diagnosis. The thirth patient had one FDG-positive lesion, but without PSMA-uptake. In contrast with the primary tumor, all available metastatic tissue showed PSMA expression. Previous studies have suggested that a higher PSMA overexpression in primary thyroid tumors might predict an increased risk of RAI-refractoriness,

recurrent disease, metastases and resistance to RAI-therapy. Our results could also fit in with this suggestion that a more aggressive disease shows higher PSMA expression.

Limitations: The first limitation is the lack of histological confirmation for lesions that showed discrepancies between [^{18}F]AlF-PSMA-11 and [^{18}F]FDG PET results. Most of these lesions were already confirmed sites of disease recurrence or metastases, but some, such as bone lesions, were not previously identified. However, due to the invasive nature of biopsies, histological confirmation of previously unknown lesions was not part of this study. An important second limitation in this study is that, due to the high efficacy of radioiodine therapy, the incidence of RAI-R TC is relatively low. Even though this study was conducted in a tertiary reference center, only a few patients met the inclusion criteria and were included.

Conclusion: [^{18}F]AlF-PSMA-11 PET imaging demonstrates promising results in patients with RAI-R TC. [^{18}F]AlF-PSMA-11 PET detected six lesions that were not visible on [^{18}F]FDG PET, including a solitary lesion in one patient. These discrepancies indicate a potential role for PSMA-targeted PET imaging in patients with RAI-R TC when other imaging techniques, including [^{18}F]FDG PET fail to locate the source of disease progression. While larger prospective studies are required, these results indicate an important additional role for PSMA PET over the current standard of care in the diagnosis, staging and follow-up of RAI-R TC.

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Appendix 1: Summary of results for lay persons

1. Clinical trial identification

Gebruik van ^{18}F-PSMA PET voor detectie van letsels bij jodiumrefractaire schildkliertumoren.

EU-nummer: 2021-000456-19

Studie nummer: BC-09501

2. Name and contact details of the sponsor

Sponsor: Universitair Ziekenhuis Gent, C Heymanslaan 10, 9000 Gent

Nationale coordinator: prof Dr V Schelfhout

Fonds: CRIG ("Cancer Research Institute Ghent")

3. General information

In deze studie onderzoeken we patiënten met schildklierkanker die niet meer gevoelig zijn voor de behandeling met radioactief jodium (of "jodiumrefractair schildkiercarcinoom"). Bij deze patiënten kunnen we de evolutie van ziekte niet meer betrouwbaar opvolgen met jodium-scans, aangezien de kankercellen geen jodium meer opnemen. Daarom krijgt deze groep patiënten nu vaak een FDG-PET scan (onderzoek waarbij met een kleine hoeveelheid licht radioactief suiker afwijkingen in het lichaam kunnen aangetoond worden via een PET-CT scan). Letsels van deze schildklierkankers zouden mogelijk ook zichtbaar kunnen zijn op een PSMA PET-scan. PSMA of "prostaat specifiek membraan antigen" is een stof die voorkomt bij de aanmaak van nieuwe bloedvaten bij tumoren, onder andere bij schildklierkanker.

Deze klinische studie werd uitgevoerd om een PET/CT met 18F-PSMA-11 (verder PSMA genoemd) te evalueren voor de diagnostiek van letsels bij patiënten met schildklierkanker die niet meer gevoelig zijn voor de behandeling met jodium (jodiumrefractair schildkliercarcinoom). Daarnaast vergeleken we de hoeveelheid van PSMA in het bloed (die we bepalen via een bloedafname) en een bepaling van PSMA op het weefsel van uw schildkliertumor, die bekomen werd bij een eerder uitgevoerde schildkieroperatie.

4. Population of subjects

In deze studie werden 8 patienten geïncludeerd tussen 4 februari 2022 en 2 september 2022. Er zijn geen patiënten uitgevallen na de start van het onderzoek. Van de acht deelnemers waren er vier mannen en vier vrouwen, met een gemiddelde leeftijd van 66 jaar. Ze hadden verschillende vormen van schildklierkanker, waaronder folliculair, papillair en slecht gedifferentieerd carcinoom.

De criteria om aan deze studie te kunnen deelnemen waren: ouder zijn dan 18 jaar, een geïnformeerd deelnemingsformulier ondertekend hebben, een schildkliercarcinoom hebben dat niet (meer) reageert op radio-actief iodium met aanwijzingen voor aanwezige of recidief ziekte, een FDG PET/CT gehad hebben binnen 2 maanden voor de studie en vrouwelijke deelnemers dienden in de menopauze te zijn, steriel of effectieve contraceptie te gebruiken.

De exclusie criteria waren: een andere kanker hebben, mogelijke zwangerschap of een geestelijke handicap hebben.

5. Investigational medicinal products used

18F-PSMA-11

6. Description and frequency of adverse reactions

Er zijn geen bijwerkingen gerapporteerd.

7. Overall results and comments on the outcome of the clinical trial

In alle patienten samen werden er 39 verdachte letsels gevonden in de hersenen, de hals, de longen, het bot en de klieren: met de nieuwe beeldvormingstechniek, PSMA PET/CT, werden 30 letsels gevonden die verdacht waren voor schildkliercarcinoom en was er dus een detectie graad van 77%. De oudere beeldvormingtechniek, FDG PET/CT vond 33 verdachte letsels, met een detectiegraad van 85%. Ondanks de hogere detectiegraad van FDG PET/CT waren er toch 6 letsels enkel zichtbaar op PSMA PET/CT, waarbij de 2 hersenletsels enkel zichtbaar waren op de nieuwe scan. Over het algemeen vertoonden botletsels een hogere opname van PSMA in vergelijking met de FDG beelden.

De hoeveelheid PSMA in het bloed bleek in deze studie geen verband te tonen met de andere studieparameters. In 5 van de 8 patienten die deelnamen aan de studie was er geen PSMA-eiwit zichtbaar op de schildkliertumor zelf, maar in de beschikbare weefselstalen van uitzaaiingen was er wel telkens PSMA aanwezig.

PSMA PET/CT toont dus interessante resultaten, omdat het zes tumoren kon opsporen die niet zichtbaar waren met een andere scanmethode FDG PET/CT. Dit suggereert dat PSMA-gerichte PET-beeldvorming een nuttige aanvulling zou kunnen zijn wanneer andere methoden falen