

The impact of monosodium glutamate on ⁶⁸Ga-PSMA-11 biodistribution in men with prostate cancer: a prospective randomized, controlled, imaging study

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ABSTRACT

Background: The prostate-specific membrane antigen (PSMA) has been targeted for PET imaging and radioligand therapy (RLT) in patients with prostate cancer. Xerostomia is a common side effect of RLT due to high salivary gland uptake of PSMA-radioligands. Here we aimed to determine the impact of monosodium glutamate (MSG) administration on PSMA-radioligand biodistribution within healthy organs and tumor lesions by using ^{68}Ga -PSMA-11 PET imaging.

Methods: 16 men with prostate cancer were randomized (1:1) into *oral ingestion* and *oral topical application* ('swishing') arms. Each subject underwent two ^{68}Ga -PSMA-11 PET/CT scans within 14 days under baseline and MSG conditions. Salivary glands and whole-body tumor lesions were segmented using qPSMA software. We quantified tracer uptake via mean and maximum standardized uptake values (SUV_{mean} and SUV_{max}) and compared parameters within each patient.

Results: For the *oral ingestion* arm, salivary gland SUV_{mean}/max decreased on average from Control to MSG scan by $45\pm 15\%$ ($p=0.004$) and $53\pm 11\%$ ($p<0.001$), respectively. Tumor lesions SUV_{mean}/max also decreased by 38% (IQR -67%, -33%) and -52% (IQR -70%, -49%), respectively ($p=0.018$). Swishing had no significant effect on ^{68}Ga -PSMA-11 accumulation in normal organs or tumor lesions.

Conclusion: Oral ingestion but not topical application of MSG reduced ^{68}Ga -PSMA-11 uptake in salivary glands. Tumor uptake also declined, therefore, the clinical application of MSG is unlikely to be useful in the framework of RLT.

Trial Registration: ClinicalTrials.gov NCT04282824

INTRODUCTION

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein highly overexpressed by prostate cancer (PCa) cells (1). In recent years, PSMA became an attractive target for both diagnosis and treatment of PCa (2). After their introduction for whole-body imaging with positron emission tomography/ computed tomography (PET/CT), small molecule PSMA ligands with a DOTA-chelator, such as PSMA I&T or PSMA-617 were labeled with β - (Lutetium-177 [^{177}Lu]) or α -emitting isotopes (Actinium-225 [^{225}Ac]) for therapeutic purposes. PSMA-targeted radioligand therapy (PSMA-RLT) with ^{177}Lu demonstrated significant reductions in serum PSA levels in phase 2 trials of metastatic castration-resistant PCa (mCRPC) (3) and is currently investigated in a phase 3 trial (VISION: NCT03511664). PSMA-RLT with ^{225}Ac (AcPSMA), an alpha emitter with high energy deposition, may have enhanced therapeutic efficacy but has a less favorable toxicity profile (4,5). The most concerning side effects include xerostomia, long-term nephrotoxicity, and myelo-suppression (6-8). In particular, AcPSMA is associated with grade 2 or higher xerostomia which often led to treatment cessation despite initial favorable PSA response (4,5,9,10). Following the preliminary effects of AcPSMA on serum PSA levels, multiple efforts have failed to apply protective measures against salivary gland and kidney toxicity (11-14).

The PSMA-radioligands salivary gland binding and uptake mechanism remains unclear. There appears to be limited target expression by the salivary glands (low/intermediate immunohistochemistry (IHC) PSMA staining intensity, patchy and focal expression limited in extent (5% of SG tissue)) whereas radioligand uptake is very high (15). In contrast, PSMA-targeted radio-antibodies, such as ^{111}In -J591 and ^{177}Lu -J591, do

not accumulate in salivary glands or only at low levels (16). The high accumulation in the salivary glands of the PSMA-radioligands may thus represent an off-target effect (i.e. not related to the PSMA target expression but to the radioligands molecules).

PSMA (also known as glutamate carboxypeptidase II) is targeted by small molecules via interaction of the glutamate moiety of the radioligands (among other features) with its enzymatic region which has high glutamate affinity (17-19). Therefore, it was hypothesized that the administration of monosodium glutamate (MSG), a well-known food additive, could act as a competitor by blocking the binding of the PSMA-targeting radioligands. In a preclinical model, MSG reduced ^{68}Ga -PSMA-11 salivary gland and renal uptake while tumor accumulation was unaffected in LNCap bearing mice (20). Moreover, MSG stimulates salivary flow as shown in a controlled study with up to 1 mL/min of mean salivary flow compared to 0.25 mL/min at baseline (21). We also hypothesized that MSG could be used as an oral salivary flow stimulant to remove accumulated radioligands from the salivary glands.

^{68}Ga -PSMA-11 PET imaging is a rapid, non-invasive, and safe technique that provides reliable estimates of the biodistribution of therapeutic PSMA ligands.

In this imaging-controlled study in men with PCa, we determined the impact of MSG administration on PSMA-radioligand biodistribution in normal organs and tumors by using ^{68}Ga -PSMA-11 PET/CT with and without MSG administration. We tested two administration methods: swishing (i.e. oral topical, to increase the salivary flow) and oral ingestion (for competitive binding).

MATERIAL AND METHODS

Study Design and Patient Population

This was a prospective single-center, open-label, randomized, controlled imaging study conducted at the University of California Los Angeles (UCLA; Los Angeles, CA, USA) using 16 paired PSMA-PET/CT studies with (MSG scan) and without MSG administration (Control scan) within less than 14 days between the two scans. The study was investigator initiated, self-funded and was conducted under an investigational new drug application (IND#130649), approved by the local institutional review board (IRB#18–001776) and registered on clinicaltrial.gov (NCT04282824).

Patients with histopathologically proven PCa who volunteered to undergo two PSMA-PET/CT scans within 14 days and without any treatment change between the two scans were eligible. Patients with prior salivary gland surgery or radiation therapy (RT), a history of salivary gland disease, severe uncontrolled hypertension, known allergic responses to MSG or who were unable to comply with the study procedures were excluded (Supplemental Table 1; appendix p 1). We obtained oral and written informed consent from all patients.

To preclude the potential confounding factor of stimulus effect, patients were initially randomized into two arms based on the type of MSG administration: *Oral ingestion* ($n=8$) and *Swishing* ($n=8$). A second randomization process subdivided the patients into receiving the Control or MSG scan first. Figure 1 depicts the study flowchart.

Procedures

MSG administration

We obtained food grade MSG as sealed salt powder (Ajinomoto). The U.S. Food and Drug Administration has designated MSG as safe (GRAS). Patients randomized to *Oral Ingestion* received 150 mg/kg food grade MSG dissolved in 300mL drinking grade water 30 minutes prior to ^{68}Ga -PSMA-11 injection. Patients randomized to *Swishing* received 0.5M of MSG applied topically to the oral mucosa, which was swished within the mouth for 30 seconds before removing the solution without swallowing. The swishing procedure was repeated at 0, 30, and 45 minutes following ^{68}Ga -PSMA-11 injection.

Image Acquisition

^{68}Ga -PSMA-11 (Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga (HBED-CC)]) was used as the PSMA-ligand and was obtained from the Biomedical Cyclotron Facility at UCLA. ^{68}Ga -PSMA-11 PET/CT imaging was performed according to international guidelines (22). Target injected activity dose was 185 MBq (allowed range 111-259 MBq). Target uptake period was 60 min (allowed range 50-100 min). We applied oral but no intravenous CT-contrast for the control and MSG scans. We acquired images using a 64-detector PET/CT scanner (2007 Biograph 64 Truepoint or 2010 Biograph mCT 64; Siemens). The same scanner was used for both visits. A diagnostic CT scan (200–240 mAs, 120 kV) with 5-mm slice thickness was performed. PET images were acquired in 3D mode from mid-thigh to vertex (whole-body scan) with a time-per-bed position of 2-4 min using a weight based protocol (22). All PET images were reconstructed using attenuation, dead-time, random events, and scatter corrections. PET images were reconstructed with an iterative

algorithm (ordered-subset expectation maximization) in an axial 168×168 matrix on the Biograph 64 Truepoint (2D, 2 iterations, 8 subsets, Gaussian Filter 5.0) and in a 200×200 matrix on the Biograph mCT 64 (3D, 2 iterations, 24 subsets, Gaussian Filter 5.0).

Image Analyses

Board-certified nuclear medicine physicians and radiologists used a PSMA-PET/CT based TNM staging system (PROMISE) to generate clinical reports of the control scans by consensus (23).

Two nuclear medicine physicians (AG, JCa), who were blinded to the study condition (Control vs MSG administration and type of MSG application) used qPSMA to interpret the research MSG and Control PSMA-PET/CT scans by consensus (24). They segmented all detected tumor lesions and normal organs manually. Normal organs included lacrimal glands, parotid glands, submandibular glands, liver, spleen, kidneys, and urinary bladder. Output parameters included SUV_{mean} and SUV_{max} for both tumor lesions and normal organs.

Measurements of Salivary Radioactivity

To assess the effect of MSG on radioligand excretion, we collected saliva from all patients at five time-points following ⁶⁸Ga-PSMA-11 injection at 0 (range: 0-7), 10 (range: 9-17), 30 (range: 28-39), 45 (range: 44-54), and 100 (range: 88-126) minutes. We transferred saliva collected in disposable medication cups to disposable borosilicate test tubes. Samples were weighed and radioactivity was measured in a gamma well counter (Capintec CAPRAC-t, Mirion Technologies, Florham Park, NJ). Background

measurements were generated prior to each patient injection. We assayed ^{68}Ga decay within a range of 10Kev - 1200Kev and recorded time of radioactivity collection and measurement to adjust for tracer decay. We corrected tracer uptake in saliva for background and radioactive decay.

Safety

We monitored safety after the injection of the radiotracer before and after the MSG administration, before and after the scan and recorded blood pressure and heart rate prior to injection of ^{68}Ga -PSMA-11 and directly following completion of the scan. We communicated with all patients within 72 hours following the scan and asked for any untoward side effects or symptoms. Adverse events were documented and evaluated according to Common Terminology Criteria for Adverse Events version 5.0.

Outcomes

The primary objective of this trial was to compare the degree of ^{68}Ga -PSMA-11 uptake in salivary glands with or without MSG administration. A 2-fold reduction after MSG administration was a priori defined as successful reduction in salivary gland PSMA uptake (25). The secondary objectives were (i) to determine the impact of MSG administration on ^{68}Ga -PSMA-11 uptake in normal organs and tumor lesions, (ii) to measure if MSG stimulates ^{68}Ga -PSMA-11 excretion in the saliva, and (iii) to assess the safety of oral MSG ingestion and salivary flow stimulation at the proposed doses.

Statistical Analyses

Radiation doses to the salivary glands from one cycle of AcPSMA or LuPSMA were estimated at 17 Gy and 10 Gy, respectively (9,10,26,27). The commonly applied safe upper limit for external beam salivary gland RT is 32 Gy, which can be reached after 2 cycles of Ac-PSMA (28). Based on these numbers, we aimed to achieve a 2-fold reduction in the ⁶⁸Ga-PSMA-11 accumulation in the salivary glands following MSG administration. The primary endpoint measure was the mean difference of SUVmax and SUVmean in all assessable salivary glands with and without the administration of MSG interventions. Patients were randomized (1:1) using a computer-generated randomization list. The randomization plan used a permuted block design with two blocks of n= 8 (Arm A and B, Supplemental Table 2, appendix p 02).

We report descriptive values as mean \pm standard deviation (SD) or median and interquartile range (IQR) (if data were not normally distributed according to the Shapiro-Wilk test). As each patient serves as his own control, paired T-tests were performed. Differences between paired data that were not normally distributed were determined using Wilcoxon's signed-rank test. The Independent t-test was used to compare the means between unrelated groups. In each analysis, a *P* value of less than 0.05 was considered statistically significant. We conducted all analyses using the IBM SPSS Statistics v26.0 (IBM Corp., Armonk, NY, USA) and R Studio v3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A summary image of each of the 16 cases with all measurements is provided as a Supplemental Patient Summary Images brochure (appendix pp 5-12). One case example (patient #012) is displayed in Figure 2.

Patient Population

Between December 20th, 2019 and April 4th, 2020, 17 patients were screened to identify 16 patients who met the eligibility criteria (Figure 1). One patient declined to participate. Demographics and clinical characteristics of the study population are presented in Table 1. Two of 16 (16%) patients underwent the PSMA-PET/CT scan for initial staging of PCa, seven of 16 (42%) for localization of biochemical recurrence, and seven of 16 patients (42%) for restaging of metastatic disease.

PSMA-PET/CT images

Oral ingestion arm: The mean injected activity was 184 ± 1 and 183 ± 2 MBq for MSG and Control scans, respectively ($p=0.18$). Image acquisition commenced at 61 ± 8 and 61 ± 7 minutes after tracer injection for MSG and Control scans, respectively ($p=0.87$).

Swishing arm: The mean injected activity was 184 ± 1 and 184 ± 1 MBq ($p=0.40$). Image acquisition commenced at 67 ± 15 and 66 ± 14 minutes after tracer injection for MSG and Control scans, respectively ($p=0.87$).

Table 2 summarizes the scans findings and PSMA PET-based staging. Three patients had no visible PCa lesions (one in the oral ingestion arm and two in the swishing arm). There was no change in stage between the control and MSG scans.

⁶⁸Ga-PSMA-11 uptake in Normal Organs

Oral ingestion arm. MSG administration was associated with a significant decrease in ⁶⁸Ga-PSMA-11 accumulation in all normal organs ($p < 0.05$) and a large increase in bladder activity (mean difference +372% SUVmean and +593% SUVmax, Table 3). Of note, ⁶⁸Ga-PSMA-11 uptake decreased by more than 50% in the salivary glands (mean difference -46% SUVmean, -53% SUVmax) with a more prominent effect on the submandibular (mean difference -59% SUVmean, -63% SUVmax) than in the parotid glands (mean difference -33% SUVmean, -34% SUVmax).

Swishing arm. No statistically significant difference in ⁶⁸Ga-PSMA-11 accumulation measured by both SUVmean and SUVmax was observed in normal organs following MSG administration ($p > 0.05$) (Table 3).

⁶⁸Ga-PSMA-11 uptake in Tumor Lesions

Oral ingestion arm. MSG administration was associated with a significant decline in ⁶⁸Ga-PSMA-11 accumulation in tumor lesions (median difference -38% SUVmean and -52% SUVmax; Table 4). Of note, one pelvic bone lesion showed a dramatic decrease in SUVmax (from 46.8 to 4.3) following MSG administration (case MSG05 in appendix p 07).

Swishing arm. No significant difference was observed in tumor accumulation of ⁶⁸Ga-PSMA-11 measured by SUVmean and SUVmax between the two PET scans ($p = 0.11$ and $p = 0.17$, respectively) (Table 4).

The comparison of pooled SUVmean and SUVmax between control and MSG studies for each arm is depicted in Figure 3.

Saliva Radioactivity Measurements

Salivary radioactivity increased over time demonstrating ^{68}Ga -PSMA-11 salivary excretion. The median activity counts following tracer injection for both arms are provided in Supplemental Table 3 (appendix p 03). Figure 4 shows the median saliva counts over the time.

Oral ingestion arm. A significant decrease of salivary activity counts was observed at 45 and 100 min with median reductions -42% and -53%, respectively.

Swishing arm. No significant difference in salivary activity was observed at any time point ($p>0.05$).

Adverse Events

Grade 1 nausea following administration was recorded in one (6%) of 16 patients following oral ingestion of MSG. Five non-study related events were recorded (diarrhea (n=2 in each arm), abdominal discomfort in the swishing arm (n=1; Supplemental Table 4; appendix p 04).

DISCUSSION

This prospective randomized imaging study revealed that oral ingestion of MSG, a food additive, is associated with a significant decrease in ^{68}Ga -PSMA-11 accumulation within normal organs and tumor lesions, whereas topical oral application of MSG has no impact on ^{68}Ga -PSMA-11 biodistribution. The primary endpoint of $\geq 50\%$ decrease in ^{68}Ga -PSMA-11 accumulation in salivary glands was met when expressed as change in SUVmax (53%). However, oral administration of MSG also significantly diminished ^{68}Ga -

PSMA-11 uptake in tumor lesions (52% and 39% decline in SUV_{max} and SUV_{mean}, respectively) and all other organs. A 3-fold increase of ⁶⁸Ga-PSMA-11 signal in the urinary bladder highlighted its rapidly increased urinary excretion after oral MSG administration. Previous work found a repeatability coefficient for SUV measurements in PSMA-PET/CT in the range of 33-38%, which indicates that the reduction in tumor uptake noticed in our patients (>45%) is related to MSG administration (29). The application of MSG to reduce salivary gland toxicity (xerostomia) induced by PSMA-RLT, is therefore unlikely to be a successful clinical strategy.

Various direct attempts to reduce the salivary gland toxicity of AcPSMA have been reported: salivary gland duct dilation and clearance via sialendoscopy (30), vasoconstriction of parotid gland blood vessels through external cooling with icepacks (11,13) and local injection of botulinum toxin A, to suppress saliva formation metabolically (31). Indirect attempts to alter the biochemical mechanism of off-target binding by competition included PSMA inhibitors such as 2-(phosphonomethyl) pentanedioic acid (PMPA) or serum glutamate elevating approaches (20,32-35). Dosimetry data showed that co-administration of oral polyglutamate administration may reduce salivary gland ligand uptake. However, the impact on tumor uptake has not yet been determined (36).

Application of MSG in murine models reduced salivary PSMA radioligand uptake in in a dose-dependent matter without affecting tumor uptake (20). In contrast, oral MSG administration in humans led to significant decreases in tumor uptake. Consistent with our findings a significant decrease of ¹⁸F-DCFPyL accumulation in normal organs and tumor lesions following oral administration of MSG was also observed by others (32). Harsini et al applied a fix dose of 12.7g, while our patients received 150 mg/kg of MSG,

which led to higher dosage (average 15.1g). This might explain the higher impact of MSG on tracer biodistribution observed in our study, which suggest a dose dependent effect of MSG. Despite the MSG dosages were 10-fold higher than MSG concentration in a normal meal ((37)), intake of food containing glutamate (MSG, umami, tomatoes, cheese, mushrooms, etc) may impact the biodistribution of PSMA-radioligands and a potential impact on diagnostic or therapy efficacy cannot be formally excluded. Further studies investigating the impact of food glutamate-containing on imaging and therapy PSMA-radioligands may be warranted.

⁶⁸Ga-PSMA-11 is excreted in the saliva as shown by our measurements. Oral ingestion of MSG led to diminished salivary excretion of ⁶⁸Ga-PSMA-11. This suggests that its off-target accumulation in salivary glands interacts with saliva formation, potentially impacting ductal cell transporters within the glands (15,38). Alternatively, the macromolecular composition of saliva itself may be interacting with PSMA and glutamate, trapping or binding to the molecules causing accumulation in the salivary glands within saliva.

Our study has limitations. First, both the dosing and the timing of MSG administration were chosen empirically based on studies largely concerned with safe dosing of MSG rather than application as blood glutamate modulating tool (39). Second, while not evaluated in this study, tumor burden may play a role in the efficacy of MSG's impact on radioligand distribution. While PSMA-RLT is currently offered in heavily metastasized patients with late-stage mCRPC, our patients were mainly in earlier stages of the disease having low tumor burden. Nevertheless, considering the tumor sink effect,

we expect a higher impact of MSG administration on tumor uptake in patients with high tumor burden (40).

CONCLUSION

Oral administration of MSG successfully decreased ^{68}Ga -PSMA-11 uptake in normal organs including salivary glands and kidneys in human subjects but also reduced tumor uptake significantly. This suggests that MSG strategies that reduce salivary gland toxicity of PSMA-RLT will negatively impact tumor PSMA uptake. Thus, clinical applicability is unlikely. Future investigations evaluating different doses and timing of MSG administration are warranted, considering the possibility that a lower dose may show differential preference for tumor or normal tissue.

CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article exist.

KEY POINTS

Question: What is the impact of monosodium glutamate administration on ^{68}Ga -PSMA11 biodistribution?

Pertinent Findings: This prospective single-center, randomized imaging study which included 16 men with prostate cancer met its primary endpoint, defined as a 50% reduction of ^{68}Ga -PSMA11 accumulation in salivary glands, when monosodium glutamate was administered orally (-53.4% SUVmax, $p < 0.001$). However, the radiotracer reduction in normal organs was accompanied by a significant reduction within tumor lesions (-55.7% SUVmax, $p = 0.061$).

Implications for patient care: Monosodium glutamate is capable of modulating ^{68}Ga -PSMA-11 biodistribution including tumor uptake, which limits its clinical application in the setting of PSMA RLT.

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Figure 1. Study Flowchart.

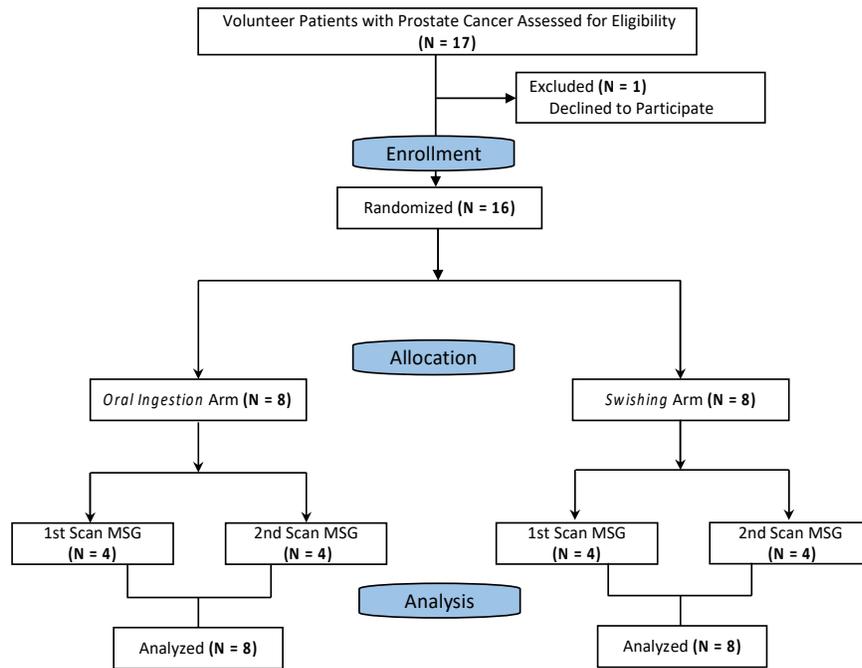


Figure 2. Set of images of a 73-y-old patient with status after radiation therapy (initial PSA of 16 ng/ml, biopsy Gleason score 8, pT2c) and concurrent androgen hormone treatment, currently presenting for rising PSA value (6.27 ng/mL). Following enrollment, patient was randomized to *Oral ingestion* arm and received 18.9 g of monosodium glutamate (MSG) before the second ⁶⁸Ga-PSMA-11 injection. PSMA PET/CT images revealed multifocal prostate involvement, common iliac right and external iliac right pelvic lymph nodes, and multiple bone lesions (corresponding miTNM score: mi T2m(LB, RB, LM, LA, RA) N2(CIR, EIR) M1b(diss)). The maximum intensity projection (MIP) images show an overall decline in ⁶⁸Ga-PSMA-11 accumulation within normal organs as well as tumor lesions on the MSG scan relative to control scan. The axial view images display a relevant case example of a bone lesion with a significant PSMA decrease following MSG administration (SUVmax from 18.6 to 9.2).

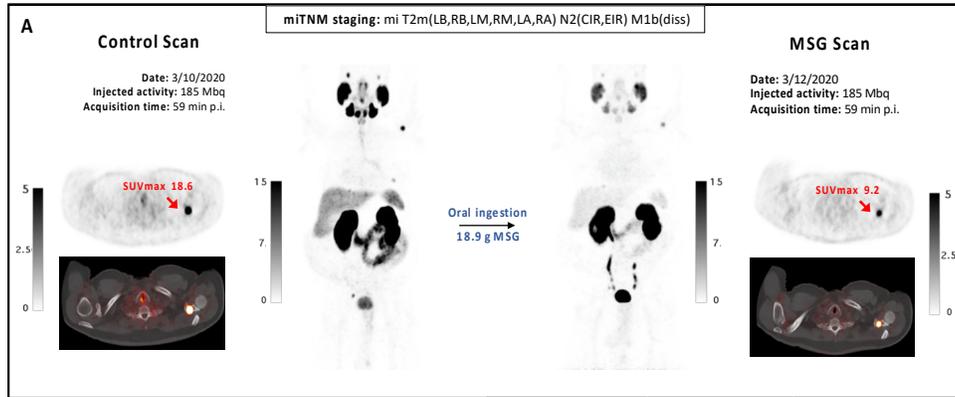


Figure 3. SUVmean (A) and SUVmax (B) of salivary glands, kidneys and tumor lesions in control and MSG studies in *Oral ingestion* and *Swishing* arms.

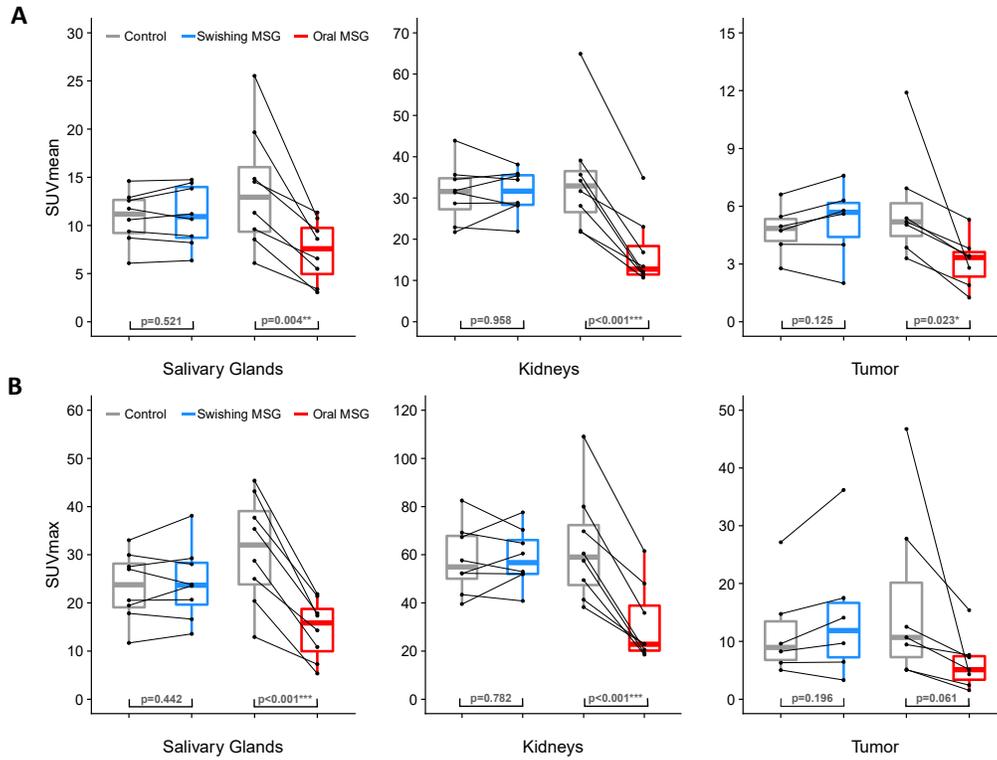
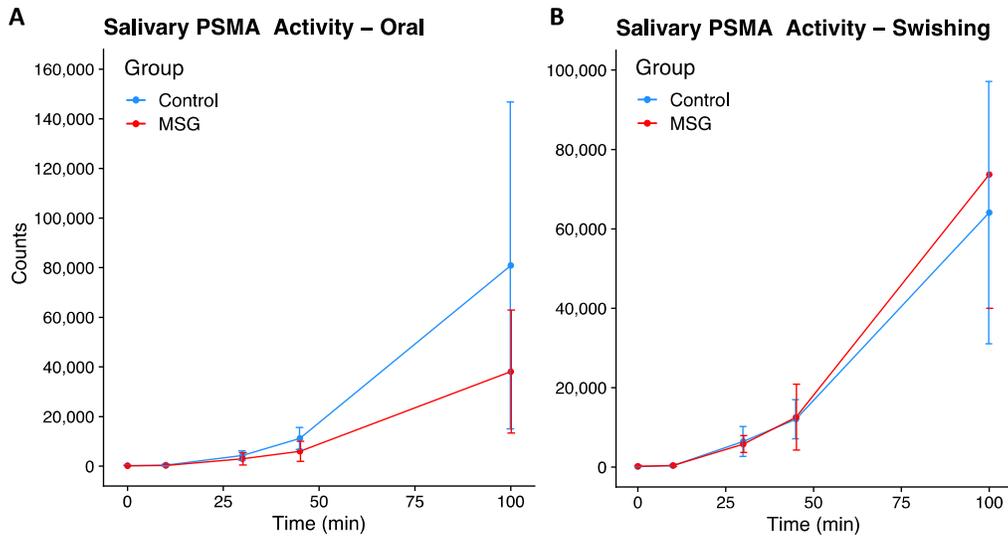


Figure 4. The median changes of ⁶⁸Ga-PSMA11 activity in saliva between Control and MSG group at 0, 10, 30, 45, and 100 minutes following tracer injection for *Oral ingestion* arm (A) and *Swishing* arm (B).



	All patients (N = 16)
Age (years)	72 (56-81)
Time since diagnosis of prostate cancer (years)	7 (0.6-21)
PSA at diagnosis (ng/ml)	36 (2.5-308)
Gleason score at diagnosis*	
<8	7 (44%)
≥8	8 (50%)
T-Stage at diagnosis*	
T1	1 (6%)
T2	11 (66%)
T3	3 (18%)
M status at diagnosis**	
M0	15 (94%)
M1	1 (6%)
Primary treatment†	
Prostatectomy ± lymphadenectomy	7 (49%)
Local radiotherapy	6 (42%)
Systemic treatment	1 (7%)
Salvage Treatment	
None	9 (56%)
Radiotherapy	3 (19%)
Systemic treatment	4 (25%)
Indication for Scan	
Primary Staging	2 (12%)
Biochemical Recurrence	7 (42%)
Metastatic Restaging	7 (42%)
PSA at time of PSMA (ng/ml)	6.2 (0.2-53.7)

Table 1. Patient characteristics. Data are median (Range) or n (%); PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; *Data missing for one patient; ** M1 was defined as metastatic disease (distant metastases); † Data missing for two patients.

Table 2. PSMA PET findings.

Study arm	<i>“Swishing”</i>		<i>Oral ingestion</i>	
	Control	MSG	Control	MSG
⁶⁸Ga-PSMA-11 PET/CT+				
Prostate/prostate bed (T+)	4 (50%)	4 (50%)	5 (63%)	5 (63%)
Pelvic LN (N1)	1 (13%)	1 (13%)	2 (25%)	2 (25%)
Extrapelvic LN (M1a)	1 (13%)	1 (13%)	1 (13%)	1 (13%)
Bone (M1b)	2 (25%)	1 (13%)	3 (38%)	3 (38%)
Visceral (M1c)	0	0	0	0
⁶⁸Ga-PSMA-11 TNM Pattern				
PSMA T0 N0 M0	2 (25%)	2 (25%)	1 (13%)	1 (13%)
PSMA T+ N0 M0	3 (38%)	3 (38%)	2 (25%)	2 (25%)
PSMA T0 N1 M0	0	0	0	0
PSMA T+ N1 M0	1 (13%)	1 (13%)	1 (13%)	1 (13%)
PSMA T+ N0 M1	0	0	1 (13%)	1 (13%)
PSMA T0 N0 M1	2 (25%)	2 (25%)	2 (25%)	2 (25%)
PSMA T0 N1 M1	0	0	0	0
PSMA T+ N1 M1	0	0	1 (13%)	1 (13%)

		Average \pm SD SUVmean				Average \pm SD SUVmax			
		Control	MSG	Changes	p value	Control	MSG	Changes	p value
Oral ingestion (n = 8)	Lacrimal glands	5.5 \pm 2.3	2.6 \pm 0.9	-50.9 \pm 6.5 %	0.001	9.9 \pm 4.7	4.3 \pm 1.6	-55.5 \pm 6.1 %	0.002
	Parotid glands	10.9 \pm 4.1	6.9 \pm 3.3	-32.9 \pm 22.6 %	0.002	19.0 \pm 6.6	13.2 \pm 6.2	-34.1 \pm 21.7 %	0.020
	Submandibular glands	15.9 \pm 5.7	6.6 \pm 2.5	-58.9 \pm 8.9 %	<0.001	29.0 \pm 10.5	10.4 \pm 3.7	-63.2 \pm 9.9 %	<0.001
	Salivary glands	12.1 \pm 4.6	6.8 \pm 3.1	-45.5 \pm 14.6 %	0.004	29.0 \pm 10.5	13.5 \pm 5.9	-53.4 \pm 11.1 %	<0.001
	Liver	4.6 \pm 0.5	2.1 \pm 0.3	-54.2 \pm 5.3 %	<0.001	10.7 \pm 1.3	5.5 \pm 0.4	-50.1 \pm 8.3 %	<0.001
	Spleen	8.1 \pm 2.0	3.0 \pm 0.9	-62.8 \pm 6.9 %	<0.001	13.7 \pm 3.5	5.3 \pm 1.5	-61.5 \pm 8.6 %	<0.001
	Kidney	34.5 \pm 14.8	17.4 \pm 8.8	-51.5 \pm 13.7 %	<0.001	63.6 \pm 25.0	32.7 \pm 16.6	-51.3 \pm 13.3 %	<0.001
	Urinary Bladder	16.0 \pm 8.7	69.1 \pm 34.3	+371.6 \pm 300.2 %	0.004	33.7 \pm 23.9	184.2 \pm 97.5	+593.2 \pm 659.5 %	0.003
Total tumor lesions		6.6 \pm 3.5	3.5 \pm 2.1	-45.0 \pm 19.0 %	0.023	21.5 \pm 19.8	8.2 \pm 8.7	-55.7 \pm 22.0 %	0.061
Swishing (n = 8)	Lacrimal glands	6.5 \pm 1.6	6.0 \pm 2.5	+4.9 \pm 22.0 %	0.625	12.3 \pm 3.2	11.1 \pm 4.6	-5.2 \pm 25.0 %	0.556
	Parotid glands	11.7 \pm 2.2	12.0 \pm 2.7	+0.1 \pm 8.4 %	0.917	22.2 \pm 6.1	22.5 \pm 6.0	+1.9 \pm 10.4 %	0.792
	Submandibular glands	12.8 \pm 3.5	13.4 \pm 3.6	+5.6 \pm 6.8 %	0.061	21.3 \pm 7.0	22.6 \pm 7.3	+7.7 \pm 11.6 %	0.188
	Salivary glands	11.5 \pm 2.3	11.9 \pm 2.9	+1.6 \pm 7.8 %	0.521	25.8 \pm 6.0	26.6 \pm 7.2	+4.3 \pm 12.3 %	0.442
	Liver	4.1 \pm 0.8	4.3 \pm 0.9	+5.7 \pm 17.3 %	0.317	9.8 \pm 1.3	10.4 \pm 3.0	+5.3 \pm 15.7 %	0.321
	Spleen	6.1 \pm 2.0	6.3 \pm 1.7	+6.2 \pm 18.6 %	0.458	10.8 \pm 3.9	10.1 \pm 2.6	-0.3 \pm 15.2 %	0.622
	Kidney	30.1 \pm 8.0	30.1 \pm 5.8	+ 1.9 \pm 13.9 %	0.958	57.1 \pm 15.9	57.6 \pm 13.6	+3.4 \pm 15.8 %	0.782
	Urinary Bladder	20.2 \pm 13.5	24.2 \pm 8.3	+36.5 \pm 41.4 %	0.357	50.6 \pm 42.4	56.4 \pm 20.2	+52.0 \pm 70.0 %	0.651
Total tumor lesions		4.9 \pm 1.1	5.4 \pm 1.6	7.8 \pm 13.8 %	0.125	12.5 \pm 7.7	15.0 \pm 11.3	12.6 \pm 27.8 %	0.196

Table 3. Comparison of ^{68}Ga -PSMA11 uptake in normal organs in Control and MSG scans.

		Median (IQR) SUV of Total Tumor Lesions			
	Parameter	Control	MSG	Changes (%)	<i>p</i> value
Oral Ingestion (n = 7)	SUVmean	5.4 (3.9, 11.4)	3.3 (1.9, 3.8)	-37.8 (-67.3, -32.5)	<i>0.018</i>
	SUVmax	10.7 (6.5, 46.8)	5.1 (2.6, 9.7)	-52.3 (-70.0, -48.5)	<i>0.018</i>
Swishing (n = 6)	SUVmean	4.9 (4.2, 5.5)	5.7 (4.1, 6.3)	13.8 (-4.0, 15.4)	<i>0.116</i>
	SUVmax	9.0 (7.8, 14.8)	11.9 (6.7, 17.5)	17.9 (-14.0, 33.3)	<i>0.173</i>

Table 4. Comparison of SUVmean and SUVmax derived from Control and MSG scans.