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Effect of external cooling on Lu-177 PSMA uptake for parotid glands

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Abbreviated Title: Parotid gland external cooling for PRLT

ABSTRACT

Metastatic castration-resistant prostate cancer (mCRPC) patients have been started to treat with prostate-specific membrane antigen (PSMA) targeted radioligand therapy (PRLT), especially with Lu-177 PSMA-617 in recent years. But, side effects of PRLT against salivary glands, limits the treatment safety. Current study aims to show the effect of external cooling with icepacks on Lu-177 PSMA-617 uptake in parotid glands (PGs). **Methods:** Nineteen patients (Mean age 72.9 years) who had pre-treatment Gallium-68 (Ga-68) PSMA-11 Positron emission tomography/Computed tomography (PET/CT) with mCRPC referred for the first time for Lu-177 PSMA-617 treatment were included. Maximum and mean standard uptake values (SUVmax and SUVmean) of right (R) and left (L) PGs were measured on Ga-68 PSMA PET/CT before treatment without ice-pack applications. Before the initiation of PRLT, frozen icepacks were fixated unilaterally (all right sided) on PGs' of patients and applied approximately 5 hours. 4th and 24^{th} h of PRLT, whole body planar scintigraphy images and 4^{th} hour head/neck region single photon emission computed tomography/ computed tomography (SPECT/CT) scans were acquired after injection of Lu-177 PSMA-617. Region of interest (ROI) for R and L PGs and volume of interest (VOI) of SPECT counts, volume of CT of 4^{th} hour R and L PGs were calculated. **Results:** Before the PRLT, Ga-68 PSMA-11 PET/CT scan without icepack application, showed no statistical significance between R and L PGs' SUVmax or SUVmean variables ($p>.05$). In the 4^{th} and 24^{th} hour of PRLT, on the planar images externally cooled R PGs' ROI's did not demonstrated any statistical difference when compared with L PGs which were not externally cooled($p>.05$). SPECT/CT images in the 4^{th} hour of PRLT had no statistical difference between R and L PGs' VOI counts. In addition, volumes of R and L PGs did not show any statistical difference between the glands ($p>.05$). **Conclusion**: External cooling of PGs in order to reduce Lu-177 PSMA-617 uptake with icepacks is not working at all. **Key Words:** Lu-177, PSMA, Prostate Cancer, Parotid, Ice-pack

INTRODUCTION

Although many treatment modalities have been developed for metastatic castration-resistant prostate cancer (mCRPC), expected survival of patients is usually less than 20 months (*1*). Prostate-specific membrane antigen (PSMA) which is a 750-amino acid type II transmembrane glycoprotein, is a promising target for the diagnosis with Gallium-68 (Ga-68) and radioligand therapy with Lutetium-177 (Lu-177) of mCRPC (*2-7*). Besides, prostate carcinoma (PC) cells, especially poorly differentiated types, express PSMA up to 100–1000 times higher when compared with benign prostate tissue (*7-9*), which makes it an ideal and important target for imaging and treatment modalities (*3,9-11*).

Ga-68 PSMA-11 positron emission tomography/computed tomography (PET/CT) is a highly sensitive and specific diagnostic tool, especially in poorly differentiated PC which also provides valuable information that can be used to select patients for PSMA targeted radioligand therapy (PRLT) and therapy monitoring (*12*). mCRPC have been started to treat with PRLT since recent years (*12,13*). PRLT with Lu-177 PSMA is safe with a relatively low toxicity (*5,14-19*). Lu -177 PSMA-617 is a low molecular weight ligand which binds to the cell surface of PC cells and transported into the cell by receptor-mediated endocytosis, emitting short-range beta particles (*20*), local radiation of both primary tumor and metastases and also providing tumor radiation and gamma emission allowing uptake quantification by scintigraphy thereafter (*7,21*). However, the PSMA receptor is expressed at very high levels in normal tissues such as the kidneys (proximal tubules), the jejunum (brush border), salivary and lacrimal glands (*2,21-23*).

Salivary glands are radiosensitive organs and physiological high binding of PSMA ligands may cause undesirable side effects (*19,24*). Development of xerostomia is a frequent but mild to moderate side effect after PRLT of mCRPC which decreases the patient's quality of life (*19,25-27*). External cooling is suggested to cause vasoconstriction, reduce blood flow, and decrease PSMA binding to prevent radiation toxicity of the salivary glands (*5,14,16,18,28-32*). Transient xerostomia or hypogeusia were reported in 4–87% of patients with or without external cooling with icepacks (*14,26,31,33*). In a recently published study, Ga-68 PSMA-11 PET/CT salivary gland uptake was suggested to be a simulation model just before PRLT (*7*). To date, there has been no established evidence that cooling indeed decreases Lu-177 PSMA-617 uptake in the

salivary glands. In the present study, we aim to clarify the effect of cooling with icepacks on Lu-177 PSMA-617 uptake in parotid glands.

MATERIALS AND METHODS

Study Population

Patients who had pre-treatment Ga-68 PSMA-11 PET/CT with mCRPC referred for Lu-177 PSMA-617 treatment were included in this prospective investigational study from May 2018 to October 2018. Patients with previous or concurrent diagnosis of any other primary malignancy and/or if they had been pre-treated with radiotherapy techniques to head and neck region, patients previously treated with PRLT, patients with renal or urinary disorders or patients who could not able to apply ice–packages were excluded. Additionally, if the duration between PRLT and pre-treatment Ga-68 PSMA-11 PET/CT were >45 days, those patients were also excluded. Nineteen patients (Mean age 72.9 years, range 62-81 years) who underwent routine clinical staging, including physical and urological examination, complete blood count and biochemical tests were included in the current study. The local ethics committee approved this study (2018-1419) and all subjects signed a written informed consent.

Ga-68 PSMA-11 PET/CT Examination and Analysis

The Ga-68 PSMA-11 was in-house synthesized in Trasis synthesis module (Ant-Belgium) with an ITG semi-automated generator (Germany, Munich) which was stable in vitro and with radiochemical purity > 99% after 2h of radiolabeling. In-house generated Ga-68 PSMA-11 (median 175 MBq, range 77–350) was injected intravenously and patients were let rest during distribution of the radiotracer in a comfortable quite room. They were asked to empty their bladder immediately before the scan. No icepacks were applied before PET/CT scans in order to make them as control scans.

PET/CT images were acquired using mCT 20 excel LSO (Siemens molecular imaging; Hoffmann Estates, IL, USA). Combined PET/CT image acquisition began approximately 60 min. after Ga-68 PSMA-11 injection from vertex to the mid-thigh, CT was performed with 140 kV, 80 mA, and 3.75 mm slice thickness. PET scan was performed with the same position. The emission scan time was 3 min. /bed position; and six to seven bed positions covered the scanning range.

Transaxial, sagittal, and coronal images and fused images were analyzed on workstation (Syngo.via; Siemens Molecular Imaging). Quantitative image analyses were carried out by two nuclear medicine physicians (B.Y. and S.N.) with significant experience in reading Ga-68 PSMA-11 PET/ CT scans (average 8 reads/month individually). Maximum and mean standard uptake values (SUVmax and SUVmean) of right and left parotid glands (PG) were measured by placing a 3D volume of interest (VOI) (Fig. 1). Salivary glands were delineated using a 10% threshold of the maximum pixel value within the VOI (isocontour) (*7,21*). Also SUVmax and SUVmean values of cranium (around a region between vertex-glabella; for background values) were noted in areas where homogenous uptake without any evidence of metastasis was observed. Measurements were corrected for lean body mass, according to the formula as defined in the EANM guidelines (*34*).

Application of Icepacks

One hour before the initiation of PRLT, 500 ml intravenous hydration with saline was started. Also at the same time frozen icepacks, covered with dry towel were fixated unilaterally (all right sided) on PGs' of patients. The icepacks were applied until 4 hours after termination of the treatment without any cessation (approximately 5 hours). Icepacks were replaced with new ones in every 30 minutes.

Preparation and Administration of Lu-177 -PSMA-617

The Lu-177 PSMA-617 was in-house synthesized in Trasis synthesis module (Ant-Belgium) which was stable in vitro and with radiochemical purity > 99% after 2h of radiolabeling. Lu-177 PSMA-617 (mean 5.3± 14.6 GBq, range 3.7 – 7.7 GBq), diluted in 100 mL physiological saline was administered slowly in an intravenous infusion for over 15-20 minutes. After the termination of infusion, all patients received intravenous hydration (1000 mL of 0.9 % NaCl; flow 250mL/h) for 4 hours.

Scintigraphy and Analysis

Whole-body and single photon emission computed tomography/ computed tomography (SPECT/CT) imaging were performed with AnyScan SPECT/CT (Mediso Medical Imaging

Systems, Budapest, Hungary) scanner with a medium-energy general purpose collimator, a 20% energy window, a peak at 208 keV, a scan speed of 15 cm/min for whole-body imaging, and 32 frames with a 40 s exposure time per frame for each tomographic scan with 16 slice CT with ≤ 10 kW non-diagnostic CT. Whole-body scintigraphy was acquired after 4 and 24h of PRLT and head/neck region SPECT/CT scans were acquired at 4th hour after injection of Lu-177 PSMA-617.

Quantitative image analyses were carried out by a nuclear medicine physician (B.Y.) on a workstation (InterView™ FUSION Ultimate Processing Workstation with InterView™ XP Planar and InterView™ FUSION Multimodality Processing Software). Region of interest (ROI) were drawn manually for R and L PGs, and cranium (around vertex-glabella; for background counts) for 4th and 24th hour planar scintigraphic images of both anterior and posterior images (Fig. 2). Geometric means were calculated for each variable by using anterior and posterior count values. VOI of SPECT counts and volume of CT of 4th hour R and L PGs were calculated also (Fig. 3).

Statistical Analysis

All statistical analyses were performed using SPSS software (Version 20.0; SPSS Inc., New York, NY) with a value of $p<.05$ considered to be significant. Paired T test was used to compare right (R) and left (L) PG uptakes for Ga-68 PSMA-11 PET/CT variables (SUVmax and SUVmean) without icepack application. Again paired T test was used to compare 4h and 24 h R and L PG uptakes of planar scintigraphy images after unilateral (R sided) icepack applications. Also 4th hour SPECT VOI counts of R and L PG and volume of R and L PG were compared with paired T test. Furthermore, R and L PG counts of 4th hour planar scintigraphic images and R and L PG SUVmax and SUVmean values were divided by background counts and values of each patient in order to find R-C (Right PG count / Cranium Count) PG and L-C (Left PG count/ Cranium count) PG ratios. These values (R-C Planar PG vs L-C Planar PG; R-C SUVmax PG vs L-C SUVmax PG; R-C SUVmean PG vs L-C SUVmean PG) were also compared with paired T test.

RESULTS

Descriptive statistics for variables of both PET/CT and SPECT/CT images were shown in Table 1. Comparison of R and L PGs' count and volume variables according to application of icepacks and according to background were shown in Table 2.

Before the PRLT, Ga-68 PSMA-11 PET/CT scan without icepack application, showed no statistical significance between R and L PGs' SUVmax or SUVmean variables ($p>.05$).

In the 4^{th} and 24^{th} hour of PRLT, on the planar images externally cooled R PGs' ROI's did not demonstrate any statistical difference when compared with L PGs which were not externally cooled($p>.05$). Furthermore, there was not any statistical difference between R and L PGs' VOI counts on SPECT/CT images in the 4^{th} hour of PRLT. In order to dismiss intra-patient volume differences of R and L PGs, we calculated volumes of R and L PGs and could not show any statistical difference between the glands ($p>.05$).

Additionally, R/C (Right PG/ Cranium) PG and L/C (Left PG / Cranium) PG counts ratios were compared and no statistical significance was found on planar post-therapeutic 4^{th} hour scintigraphic images. And also we could not demonstrate any statistical significance when we compared R/C (Right PG / Cranium) SUVmax PG vs L/C (Left PG / Cranium) SUVmax PG and R/C (Right PG / Cranium) SUVmean PG vs L/C (Left PG / Cranium) SUVmean PG.

DISCUSSION

The present study shows no significant differences in Lu-177 PSMA- 617 uptake comparing the intra-patient unilateral icepack applications versus no icepack applications on PGs. With these results we claim that external cooling of the salivary glands seems no impact on PG PSMA targeted radioligand uptake.

Although the salivary gland cells' proliferation rate is slow, they are radiosensitive organs (*19,35*). PRLT is a recently developed entity but protection of salivary glands from radiation toxicity has been area of interest of nuclear medicine and has been in the papers since radioiodine therapy effects of thyroid cancer patients had been published (*36*). Radioiodine accumulation mechanism is different in salivary glands than PSMA targeted therapy, so different methods to prevent from radiation toxicity have been described for both radioistopes. I-131 emits two types of radiation in which beta minus is used for treatment with maximum energy of 812 KeV (0.7%; 606 Kev, 89.3%). Its physical half-life is 8.07 days and penetration of electrons in soft tissue is

about 1 mm with maximum of 2.4 mm (*37-39*). Lu-177 is a medium-energy β-emitter (490 keV) with a maximum energy of 0.5 MeV, with a mean range of 0.7 mm and maximum range of 2.1 mm in soft tissue; has a half-life of 6.7 days (*40*). Although these properties are relatively similar for both radioactive isotopes, Lu-177 PSMA uptake in salivary glands is very high with transmembrane receptor binding mechanism. For protection of radioiodine toxicity sialogogues (vitamin E, lemon juice, etc), pilocarpine and amifostine, or parotid gland massage have been shown to reduce damage to salivary glands significantly whereas chewing gum had no protective effects (*36,41- 47*). The main purpose for those trials were to prevent acute and chronic sialadenitis, xerostomia and hypogeusia.

Salivary glands are shown to have the highest PSMA binding in normal healthy tissues (*19,35*). Irreversible salivary gland damage with regard to radiation toxicity is one of the anxieties that nuclear medicine physicians struggle when planning PSMA targeted therapies for mCRPC patients. Damage to the salivary glands and the development of xerostomia is a frequent side effect of radiation therapy which decreases the patient's quality of life (*19,35*). Although, initial studies demonstrated that salivary glands were not the dose-limiting organs with a mean absorbed dose of 1.4 Gy/GBq of Lu-177 PSMA-617, taking precautions to prevent salivary gland toxicity during targeted therapy has been recommended (*24,35*). In some recent studies, icepack collar was used during Lu-177 PSMA 617 treatment to induce vasoconstriction and reduce PSMA binding to the salivary glands (*5,14,16,30–32*). Transient xerostomia or hypogeusia were reported in both patient groups with or without icepacks (*14,26,31*). In a recently published prospective study, which did not use icepacks, grade 1 xerostomia was observed with a higher rate but no grade 3-4 toxicity was observed in which symptoms were relieved with salivary substitute gels (*33*). But in these studies only clinical results were evaluated without image based analysis and those studies did not have the opportunity to compare patient based differences between parotid glands according to icepack applications. On the other hand, these studies support current study's results in which we could not find any uptake differences in between with or without icepacks of PGs.

van Kalmthout et al. investigated the effect of external cooling of PGs on PSMA uptake for Ga-68 PSMA-11 PET/CT and suggested that some significant differences in SUVmax and SUVpeak between the cooled and non-cooled parotid gland (*7*). Bohn et al. (*48*) also studied external cooling effect of PGs on PSMA uptake for patients undergoing Ga-68 PSMA-11

PET/CT. And these two studies claimed that external cooling with icepacks seems to reduce Ga-68 PSMA-11 uptake in the parotid glands. They were only models that would give an idea for PSMA targeted therapies. Besides PMSA ligands used for Ga-68 and Lu-177 are different; so these differences may cause different reactions across ice-packs. But in both Lu-177 PSMA-617 treatment and Ga-68 PSMA-11 imaging salivary glands have high uptakes which may rule out these PSMA ligand differences. Ahmadzadehfar et al. (*15*) compared baseline and after single cycle Lu-177 PSMA-617 therapy of salivary gland functions with dynamic salivary gland scintigraphy with Technetium-99m (Tc-99m) pertechnetate in order to see the protective effect of external cooling. Comparison of baseline with follow-up salivary gland scintigraphy did not show any change in the uptake and clearance of Tc-99m pertechnetate of the salivary glands which also supported the findings of our study.

We know that kinetic of the radiotracers are different. So modelling of Ga-68 PSMA-11 for Lu-177 PSMA may not give the same results. Ga-68 PSMA-11 has a relatively rapid blood clearance and a relatively slow early elimination phase (*7,49*). On the other hand, Lu-177 PSMA-617 has long half life and uptake of Lu-177 PSMA-617 from interstitial or intracellular space into the salivary glands is relatively slow (*7*). Apart from these, labeling of PSMA-targeting antibodies such as J591 instead of small molecules such as PSMA-617 (molecular weights150 vs.1.4 kD, respectively) might be able to lower the PSMA uptake and decrease the risk of sialotoxicity (*25,50,51*).

It was estimated that the reduction of PSMA uptake in salivary glands by cooling during a relatively short period of time can be anticipated to be even less effective in PSMA targeted therapies and they suggested that long-term application of icepacks during the therapeutic procedure could be considered (*7*). In the present study, patients were exposed to external cooling for approximately 5 hours which was relatively long period. Even this period of application made patients feel discomfort and they wanted to terminate the cooling procedure. So extending the cooling time seems difficult to carry out.

New strategies have been suggested or developed in order to prevent salivary gland toxicity of PSMA targeted radioligands. In a recent case report, intraparenchymal injections of 80 units of botulinum toxin into PG unilaterally 45 days prior to Ga-68 PSMA PET/CT was shown to decrease SUVmean up to 64% as compared with baseline (*52*). This approach may become a promising method for radioprotection of the salivary glands during PSMA radioligand therapy

which needs further investigation. Short-acting anticholinergic agents, and local anesthetics, injected into salivary glands in pre-clinical trials also gave promising data (*53*). Local application of cold compounds or inhibitors of PSMA such as 2-(phosphonomethyl) pentanedioic acid had been also investigated (*54*). Due to the high blood supply of PGs, systemic absorption from intraparenchymal application of 2-(phosphonomethyl) pentanedioic acid may cause potential inhibition of PSMA-targeted tumor cells which needs further consideration (*25*). Gene- and stem cell therapy, have been suggested to prevent xerostomia and this may solve the problem in the near future (*24*). Besides, patient-specific dosimetry may help successful tumor dosing and prevent organ toxicity (*19,35*).

To our knowledge, this is the first prospective study which had the chance to compare external cooling effects in intra-patient basis. In order to control the effect of the external cooling, pre-treatment differences in intra-patient analysis were possible with Ga-68 PSMA PET/CT. Intra-patient volume based analysis was calculated with SPECT/CT to eliminate volume-based differences. We also had the chance to compare intra-patient effect of external cooling with exclusion of physiological differences which can differ from one patient to another.

CONCLUSION

External cooling of PGs in order to reduce Lu-177 PSMA-617 uptake with icepacks seems not working at all. Alternative methods in order to prevent PRLT effects on salivary glands in patients undergoing Lu-177 PSMA therapy for mCRPC is needed.

CONFLICT OF INTEREST

The authors declare that they have no financial or non-financial competing interests.

KEY POINTS

- QUESTION: Does external cooling with icepacks on parotid glands really reduce the uptake of Lu-177 PSMA-617 in the glands?

- PERTINENT FINDINGS: In this prospective investigational study, external cooling of parotid glands unilaterally in 19 prostate cancer patients treated with Lu-177 PSMA-617 had no statistical significance when compared with the opposite glands which had no cooling effects.

- IMPLICATIONS FOR PATIENT CARE: External cooling of PGs in order to reduce Lu-177 PSMA-617 uptake with icepacks is not working. Alternative methods, in order to prevent PRLT effects on salivary glands is needed.

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Table 1: Descriptive variables of patients

Variable	Mean±SD	Range
Age (years)	72.9±5.2	62 – 81
SPECT/CT variables		
R PG Planar (4. Hour) (count)	11602±5811	1749 – 28073
L PG Planar (4. Hour) (count)	10991±6016	2116 – 20545
R PG Planar (24. Hour) (count)	9240±5540	1350 – 24389
L PG Planar (24. Hour) (count)	8759±5374	883 - 20056
R PG SPECT (4. Hour) (count)	82627±49428	29199 – 187765
L PG SPECT (4. Hour) (count)	86349±53180	36320 – 190580
R PG CT (4. Hour) (mm^3)	17820±7074	10263 - 29641
L PG CT (4. Hour) (mm^3)	17163±6715	8696 – 29259
Cranium planar AP (4. Hour) (count)	8233±4782	2298 - 19972
Ga-68 PSMA PET/CT variables		
R PG SUVmax	17.1±7.8	5.4 – 29.4
L PG SUVmax	17.6±8.4	5.6 – 27.4
R PG SUVmean	6.1±4.4	2 – 18.9
L PG SUVmean	5.8±3.7	1.9 – 15.8
Liver SUVmean	4.7±1.6	1.7 – 7.6
Spleen SUVmean	6.6±1.6	3.9 - 9.3
Cranium SUVmax	2.1±0.6	0.9 – 3.1
Cranium SUVmean	0.2±0.07	0.1 – 0.3

(R: Right; L: Left; PG: Parotid Gland; SPECT: Single Photon Emission Computed Tomography; CT: Computed Tomography; Ga-68: Gallium 68; PSMA: Prostate Specific Membrane Antigen; SUV: Standard uptake value)

Table 2: Statistical analysis according to ice-pack application

Variable	*p* value	95 % CI	Std. Deviation
R/L PG Planar (4th hour)	0.572	-1619 – 2841	4626.75
R/L PG Planar (24 th hour)	0.314	-495 – 1456	2023.65
R/L PG SPECT (4 th hour)	0.270	-10582 – 3144	14239.43
R/L PG CT Volume (4 th hour)	0.481	-1261 – 2573	3977.60
R/L PG SUVmean	0.524	-0.67 – 1.27	2.00
R/L PG SUVmax	0.575	-2.13 -1.22	3.47
R-C/L-C PG Planar (4th hour)	0.104	-.074 - .722	0.8
R-C/L-C PG SUVmean	0.556	-2.5 – 4.56	7.4
R-C/L-C PG SUVmax	0.08	-2.39 - .13	2.6

(R: Right; L: Left; PG: Parotid Gland; SPECT: Single Photon Emission Computed Tomography; CT: Computed Tomography; SUV: Standard uptake value)

Figure Legends

FIGURE 1. SUVmax and SUVmean on Ga-68 PSMA-11 PET/CT imaging of right and left parotid glands without any external cooling revealed no differences. Shown are Maximum-intensity-projection PET (A), transaxial fused PET/CT (B), and CT (C) images.

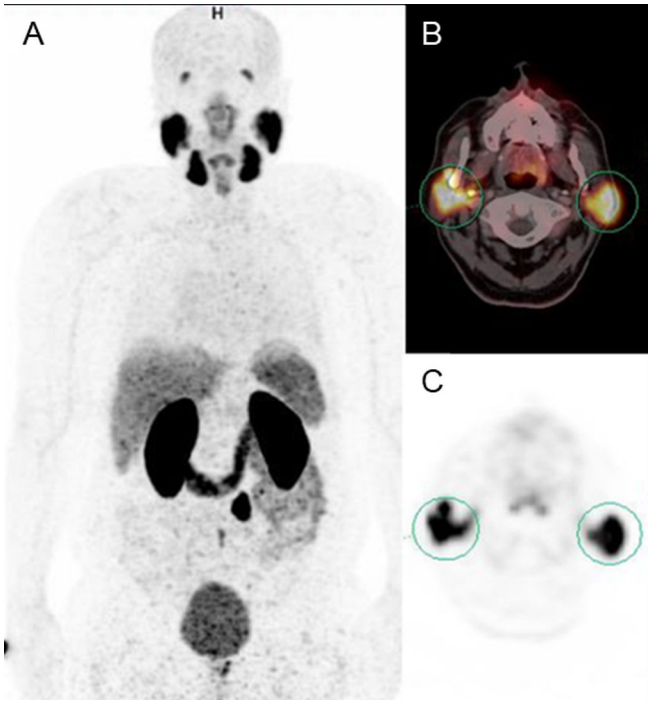

FIGURE 2. Region of interest (ROI) measurements on Lu-177 PSMA-617 uptake (A, anterior; B, posterior) in both parotid glands and cranium in a patient who was scanned with a right-sided icepack. No differences in radioligand uptake were observed, when comparing the cooled (right) to the non-cooled (left) side.

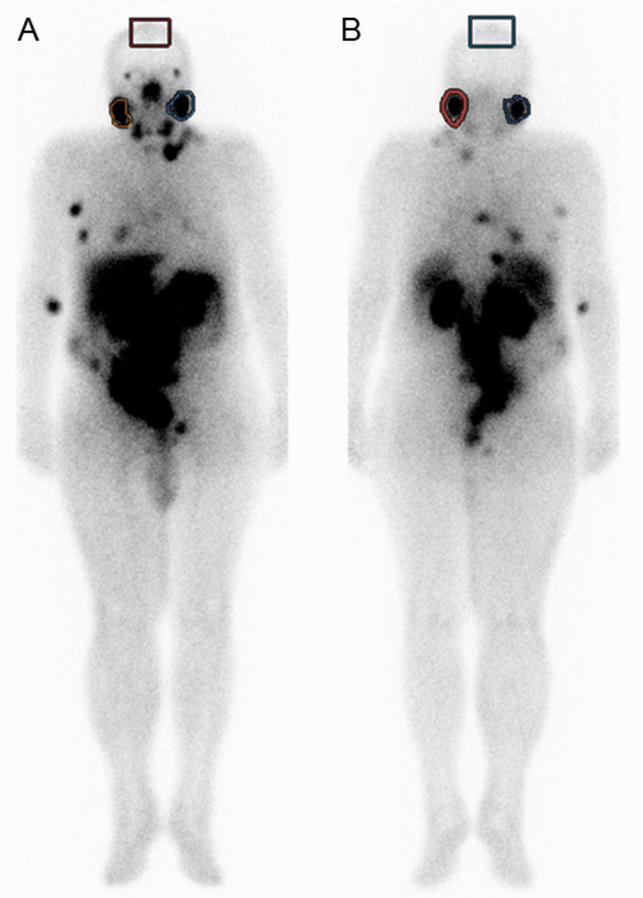

FIGURE 3. Volume of interest (VOI) (count) and volume (mm^3) calculations of Lu-177 PSMA-617 SPECT/CT images respectively, revealed no difference for neither count nor volume parameters. Shown are transaxial SPECT (A), CT (B),fused SPECT/CT (C), and coronal SPECT (D) images.