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Biodistribution of Ga 68 Psma in Normal Organs of Patients with Prostate Carcinoma

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Abstract

Background: There have been different biodistribution of Ga-68 PMSA in normal organs.

Methods: SUVmax and SUVmean values was evuluated of 66 patients who underwent Ga-68 PSMA, without radical prostatectomy, relapse in the prostate gland, extensive metastasis, or metastasis in the target.

Results: The SUVmax and SUVmean values of the patients included in the study were determined to range from high to low as bladder, kidney, submandibular gland, parotid salivary gland, duodenum 3rd part, jejunum, spleen, liver and lachrymal gland. The highest uptake was observed in the bladder, kidneys and salivary gland.

Conclusion: High PSMA expressions were observed in the kidney, salivary glands and duodenum 3rd part, medium PSMA expressions were observed in the liver and lachrymal glands, low PSMA expressions were observed in normal prostate tissue, stomach, ileum and pancreas and no PSMA expression was observed in cerebral and cerebellar cortexes. The bladder should be emptied before examination and reporting and the proximal small bowel should be examined more carefully as it can show higher PSMA expression.

Keywords: Prostate Cancer, Ga-68 PMSA, Biodistribution, Normal organs

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Abstract

As prostate specific membrane antigen (PSMA) is highly expressed in prostate cancer cells when compared to other tissues, this protein allows the detection of prostate carcinoma and follow-up of the result of treatment. In this study, it was aimed to understand normal biodistribution of Ga68 PSMA in normal organs. From a total 209 patients, Ga68 PSMA PET CT examination was applied between November 2014 and June 2016 to 66 patients with prostate carcinoma, who had not had local prostatectomy, and were determined with local recurrence on the prostate gland and slight metastasis. The mean age was 69.39±8.71 years (range 47-84) with a median Gleason score (GSC) of 8.16 (range 7-10) and a median prostate-specific antigen (PSA) level of 28.3 ng/ml (range 0.02-111.8 ng/ml). An intravenous solution of 4 mCi Ga68 PSMA was administered to the patients. A non-contrast-enhanced whole body CT scan was performed with 5 mm slices at 1 hr following the tracer injection. Immediately after CT scanning, a whole body PET was acquired. The mean and maximum standardized uptake values (SUVmean, SUVmax) of the brain, lachrymal glands, submandibular gland, parotid glands, thyroid gland, upper lobe of the right lung, mediastinal blood pool, stomach, spleen, liver, abdominal aorta, pancreas head, kidneys, duodenum 3rd section, jejunum, ileum, transverse colon, right iliac bone, gluteal muscle, bladder, prostate gland, and femur were analyzed 1 hour post injection. The highest uptake was observed in the bladder, kidneys and salivary glands and duodenum respectively. There was no Ga-68 PSMA uptake in the brain and lung tissues. It was concluded that the bladder must be empty before imaging and care must be taken when reporting abdominal lymph node activity as high normal duodenal activity may suppress abnormal activities in this region.

Introduction

Prostate-specific membrane antigen (PSMA) is a type II transmembrane protein which is highly expressed in prostate carcinoma (PC) cells when compared to other PSMA expressing tissues such as the salivary gland, kidneys or duodenum. Therefore, this protein provides a highly specific target for prostate carcinoma imaging and therapy [1,2,3,4].

Many imaging methods using PSMA as an antigen target have been used previously[5]. For example, the antibody capromab peptide was labeled with In-111 for scintigraphy. This molecule and second generation antibodies targeting the extracellular domains of PSMA had similar problems, such as high radiation exposure due to the long half-life of In-111 or long circulation time leading to high background signals and reduced detection rate. More recently, Ga-68 labeled Glu-NH-CO-NH-Lys-(Ahx)-[Ga-68(HBED-CC)](Ga-68 PSMA) ligand have been developed for PET imaging[6]. Initial experiences with Ga-68 PSMA have suggested that this novel tracer can detect prostate carcinoma relapses and metastases with high contrast by targeting the extracellular domain of PSMA. The aim of this study was to investigate the biodistribution of this PSMA ligand in normal human tissues.

Material and Methods

Patient characteristics

Of the 209 patients who underwent Ga-68 PSMA in our clinic between November 2014 and June 2016, this study evaluated the SUVmax and SUVmean values of 66 patients without radical prostatectomy, relapse in the prostate gland, extensive metastasis, or metastasis in the target areas. The mean age was 69.39±8.71 years (range, 47-84 years) with a median Gleason score (GSC) of 8.16 (range, 7-10) and a median prostate-specific antigen (PSA) level of 28.3 ng/ml (range, 0.02-111.8 ng/ml).

Imaging

Images were obtained with the Ga-68 labeled HBED-CC conjugate of the PSMA-specific pharmacophore Glu-NH-CO-NH-Lys that was synthesized as described in the studies of Eder M et al.[7]. Ga-68 was obtained from Ge68-Ga68 radionuclide generator 4 and mixed with the HBED-CC conjugate as previously published [4,7]

4 mCi Ga68 PSMA mixed solution was intravenously injected to the patients. A non-contrast-enhanced whole body CT scan was performed with 5 mm slices 1 hr after the tracer injection. An increment of 0.8 mm was used to reconstruct images with a B31 kernel. Immediately after CT scanning, a whole body PET was acquired in 3D (matrix 256x256) using 3 min acquisition time with a 15.5 cm field of view (FOV) for each bed position. The emission data were corrected for random, scatter and decay. Reconstruction was conducted with an ordered subset expectation maximization algorithm (OSEM) with 4 iterations/8 subsets and Gauss-filtered to an in-plane spatial resolution of 3 mm at full-width at half maximum (FWHM). Attenuation correction was performed using the non-enhanced computed tomography data. PET and CT were performed using the same protocol for every patient on a Biog-

raphy 6 PET CT scanner (Siemens Biograph 6, Knoxville, USA).

Image analysis

The mean and maximum standardized uptake values (SUVmean, SUVmax) of the brain, lachrymal glands, submandibular gland, parotid glands, thyroid gland, upper lobe of the right lung, mediastinal blood pool, stomach, spleen, liver, abdominal aorta, pancreas head, kidneys, duodenum 3rd section, jejunum, ileum, transverse colon, right iliac bone, gluteal muscle, bladder, prostate gland, and femur were analyzed 1 hour post injection. Circular regions of interest were drawn around areas with focally increased uptake in trans axial slices and automatically adapted to a three-dimensional volume of interest (VOI) with e. soft software (Siemens) at a 70 % isocontour.

Statistical analysis

The mean, standard deviation, the highest and the lowest values of SUVmax and SUVmean values that were received from the tissues by drawing the volume of interest (VOI) were calculated.

Results

The SUVmax and SUVmean values of the patients included in the study were determined to range from high to low as bladder, kidney, submandibular gland, parotid salivary gland, duodenum 3rd part, jejunum, spleen, liver and lachrymal gland. The highest uptake was observed in the bladder, kidneys and salivary gland. The SUVmax values for the bladder, kidneys and salivary gland were 58.06±25.95, 37.63 ± 12.53 and 12.61 ± 4.91, respectively.

The SUVmax values for the duodenum, jejunum, liver, spleen, lachrymal glands and prostate were 10.22 ± 3.63, 8.21±2.89, 7.18 ± 2.46, 5.65 ± 1.78, 5.58 ± 2.16. and 3.68 ± 1.40. respectively.

No activity was observed in the brain tissue and lungs in the visual evaluation.

The average SUVmean and SUVmax values of the different tissues in all 66 patients analysed (1h p.i.) are listed in Table 1 and summarized in Fig 1.

Table 1 SUVmax SUVmean values mean and standard deviations of 66 patients

Brain parenchyma	0.57±0.26 (0.05-1.11)	0.12±0.06 (0.03-0.29)
Lachrymal gland	5.58±2.16 (2.52-10.36)	2.57±0.82 (1.46-4.68)
Parotid salivary gland	10.82±3.08 (6.56-17.39)	6.93±1.90 (4.86-14.48)
Submandibular gland	12.61±4.91 (3.94-23.38)	8.48±3.37 (2.71-16.10)
Thyroid gland	1.78±0.65 (0.8-3.18)	1.22±0.45 (0.49-2.28)
Pulmonary artery	2.18±0.71 (0.63-3.6)	1.42±0.43 (0.45-2.36)
Right lung upper lobe	0.60±0.20 (0.16-1.14)	0.36±0.16 (0.07-0.81)
Stomach	3.19±0.99 (2.03-5.87)	1.73±0.50 (1.09-2.83)
Liver	5.65±1.78 (3.15-9.50)	3.90±1.49 (1.96-8.05)
Spleen	7.18±2.46 (3.61-12.06)	5.47±2.12 (2.46-10.03)
Abdominal aorta	2.73±0.67 (1.61-4.49)	1.74±0.39 (0.83-2.56)
Pancreas	2.87±0.80 (1.51-5.35)	1.93±0.64 (0.98-3.81)
Kidney parenchyma	37.63±12.53 (10.37-64.90)	25.67±7.92 (8.16-41.06)
Duodenum 3rd Section	10.22±3.63 (4.06-17.9)	7.16±2.51 (3.08-12.98)
2nd lumbar vertebra	1.91±0.58 (0.72-3.12)	1.16±0.41 (0.48-2.23)
Jejunum	8.21±2.89 (2.90-13.76)	5.79±1.95 (2.0-9.45)
Ileum	2.96±1.48 (1.09-6.98)	1.88±0.90 (0.51-3.91)
Transverse colon	1.96±0.75 (0.91-3.96)	1.08±0.56 (0.46-2.84)
Right iliac bone	1.16±0.42 (0.68-2.66)	0.63±0.15 (0.36-0.94)
Gluteal muscle	0.87±0.84 (0.42-1.87)	0.43±0.17 (0.18-0.82)
Bladder	58.06±25.94 (16.34-121)	46.24±22.45 (14.56-106.10)
Prostate gland	3.68±1.40 (1.27-6.53)	2.58±0.61 (0.95-4.24)
Femur	0.87±0.26 (0.19-1.47)	0.50±0.17 (0.11-0.94)

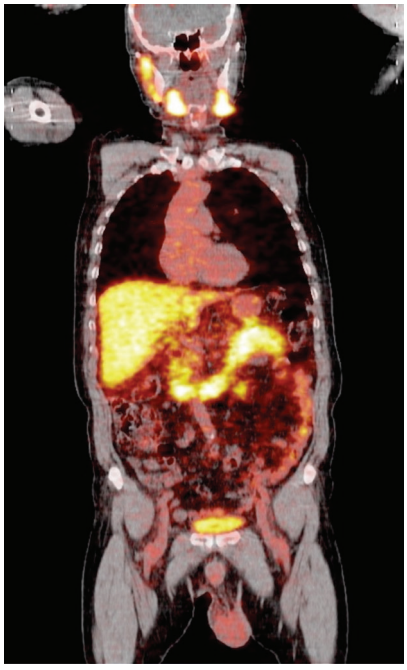

Figure2: A patient with normal biodistribution of Ga-68 PSMA 1 h after injection. Accumulation is seen in the lachrymal and salivary glands, liver, spleen, bowel, kidneys and bladder

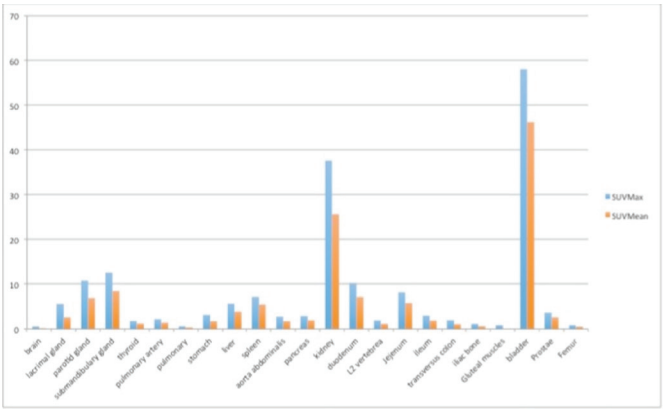

Figure1: SUVmax and SUVmean values of several organs. The highest uptake was observed in the bladder, kidneys and salivary gland.

Discussion

PMSA is a cell surface protein which is expressed at high levels in prostate carcinoma cells when compared to other PSMA-expressing tissues[1,8,9]. Therefore, this protein may serve as a target for imaging and therapy of prostate cancer. PSMA expression, mostly at low levels, has been reported for various tissues[1,8].

There has been observed to be intense PSMA in the neovascular capillary endothelium in the peritumoral areas in some types of epithelial tumors[10].

In the present study, significantly high PSMA expressions were observed which were determined to range from the highest to the lowest in kidney, salivary glands, duodenum 3rd part, proximal jejunum, spleen, liver, and lachrymal glands.

Higher PSMA expression was observed in normal prostate tissue, stomach, ileum and pancreas than in the blood pool (pulmonary artery and abdominal aorta), and lower PSMA expression was observed in the colon and normal bone compared to the blood pool. No PSMA expression was observed in brain and muscle tissues.

No difference was determined in the ranking of the SUVmax and SUVmean values in this study, but a difference originating from the VOI was determined.

The highest SUV value was observed in the bladder, and the bladder should certainly be emptied before the examination as the rate of local relapse is high in prostate cancer and because of the high activity of the bladder in the diagnosis of primary prostate cancer. In the present study, the highest PSMA expression was observed in the kidney cortex and this was due to high PSMA expression in the proximal renal tubule cells[1].

After the kidneys and salivary glands, high PSMA expression was observed in the duodenum 3rd part and the jejunum proximal, and this finding supports the detection of PSMA mRNA transcripts in the protein extracts obtained from the duodenum and small bowel segments in previous studies[10,11]. In addition, high PSMA expression was observed in the duodenum and jejunum in a study performed with PSMA mouse monoclonal antibody CYT-351[1]. In another study performed with monoclonal antibodies showing folate hydrolase activity, it has also been determined that the duodenum increased folate hydrolase activity[12].

Duodenal and proximal jejunal high PSMA expressions have been shown to complicate the evaluation of the lymph nodes in the para-aortic, paracaval and interortocaval regions.

In the current study, colonic activity was not found to be higher than duodenal and jejunal activity in any of the patients. However, in another study in literature, colonic activity was found to be higher than small bowel activity in 4 patients and this was associated with a high neuroendocrine cell population in colonic crypts and physiological regeneration areas[6]. In the present study, the reason for higher stomach and pancreas activity than colonic activity can be attributed to a greater number of neuroendocrine cells in the pancreas and stomach[1,8].

Although there are studies in literature showing folate hydrolase activity to be high in brain tissue[10], no PSMA expression has been observed[6]. Similarly, no PSMA expression was observed in brain tissue in the current study.

Conclusion

In this study, the biodistribution of Ga-68 labeled Glu-NH-CO-NH-Lys-(Ahx)-[Ga-68(HBED-CC)](Ga-68 PSMA) in 66 patients was presented.

The results showed that high PSMA expressions were observed in the kidney, salivary glands and duodenum 3rd part, medium PSMA expressions were observed in the liver and lachrymal

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glands, low PSMA expressions were observed in normal prostate tissue, stomach, ileum and pancreas and no PSMA expression was observed in cerebral and cerebellar cortexes. The bladder should be emptied before examination and reporting and the proximal small bowel should be examined more carefully as it can show higher PSMA expression.

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