

# Can $^{68}\text{Ga}$ -DOTA Peptides Be Potential Radiotracers for PET Imaging of the Spleen?

Ismet Sarikaya<sup>1</sup>, Abdelhamid H. Elgazzar<sup>1</sup>, Ali Sarikaya<sup>2</sup>, Naheel Alnafisi<sup>3</sup>, and Saud Alenezi<sup>1</sup>

<sup>1</sup>Department of Nuclear Medicine, Kuwait University Faculty of Medicine, Safat, Kuwait; <sup>2</sup>Department of Nuclear Medicine, Trakya University Faculty of Medicine, Edirne, Turkey; and <sup>3</sup>Department of Nuclear Medicine, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait

On radionuclide somatostatin receptor imaging studies, the spleen shows high physiologic uptake. Reducing the intensity of the image settings helps to better assess the distribution of radiotracer in the spleen. In our routine studies, we incidentally recognized that  $^{68}\text{Ga}$ -DOTANOC PET provides higher-resolution splenic images than  $^{111}\text{In}$ -octreotide SPECT. Autoradiography and immunohistochemistry studies have shown that somatostatin receptors are located mainly in the red pulp of the spleen. The distribution of  $^{68}\text{Ga}$ -DOTANOC in the spleen appears to correlate with the distribution of red pulp. In this article, we present  $^{68}\text{Ga}$ -DOTANOC PET/CT spleen images of our patients.

**Key Words:** spleen; somatostatin receptor; red pulp;  $^{68}\text{Ga}$ -DOTANOC; PET/CT

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**S**omatostatin receptor (SSTR) imaging with radiolabeled somatostatin analogs has been used since the late 1980s. It is used mainly for the detection, localization, staging, and follow-up of neuroendocrine tumors.  $^{123}\text{I}$ -Tyr-3-octreotide was used in early studies but later was replaced by  $^{111}\text{In}$ -pentetreotide (octreotide scintigraphy [OctreoScan; Mallinckrodt]). Currently, there are new  $^{68}\text{Ga}$ -labeled somatostatin analogs for PET imaging (1). Conventional SSTR imaging with  $^{111}\text{In}$ -pentetreotide is still widely used in the detection of neuroendocrine tumors, but new  $^{68}\text{Ga}$ -labeled PET radiotracers ( $^{68}\text{Ga}$ -DOTATATE,  $^{68}\text{Ga}$ -DOTATOC, and  $^{68}\text{Ga}$ -DOTANOC) have been increasingly used and replacing conventional SSTR imaging in many centers because PET cameras have better properties than  $\gamma$ -cameras with SPECT imaging and the radiotracers have better properties than  $^{111}\text{In}$ -pentetreotide. Compared with  $^{111}\text{In}$ -pentetreotide imaging, PET with  $^{68}\text{Ga}$ -DOTA peptides detects more lesions, shows higher uptake in

the lesions, and provides a shorter acquisition time and lower radiation exposure (2,3).

High splenic uptake on radionuclide SSTR imaging studies is a physiologic finding. Because we incidentally recognized that splenic images are of higher resolution with  $^{68}\text{Ga}$ -DOTANOC PET/CT than with  $^{111}\text{In}$ -octreotide, we decided to present spleen images of our patients in this article.

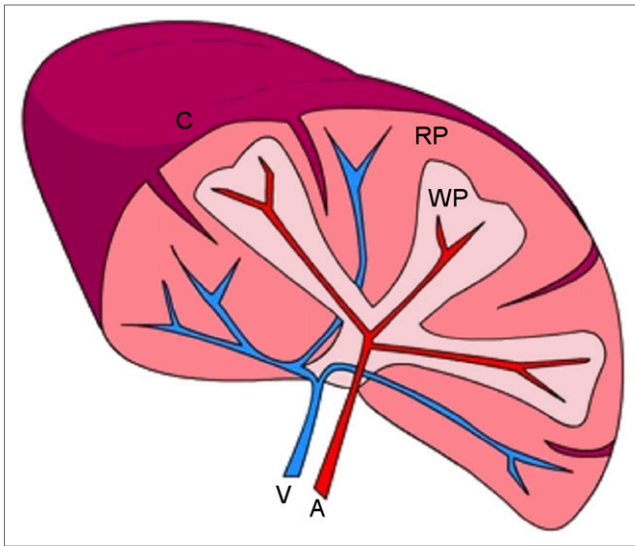
## MATERIALS AND METHODS

$^{68}\text{Ga}$ -DOTANOC PET/CT images were obtained for 7 patients with suspected or biopsy-proven neuroendocrine tumors. Radiolabeling was performed at another institute (Kuwait Cancer Control Center). Images were obtained on a Philips time-of-flight PET/CT camera. PET images were obtained 60 min after intravenous injection of 111–185 MBq (3–5 mCi) of  $^{68}\text{Ga}$ -DOTANOC. Before PET image acquisition, a low-dose CT scan was obtained for attenuation correction and anatomic localization purposes. The PET acquisition was 3 min per bed position from skull base to mid thigh. The images were corrected for attenuation on the basis of the CT data, reconstructed using a standard iterative algorithm, and reformatted into transaxial, coronal, and sagittal views. Maximum-intensity-projection images were also generated. Both attenuation-corrected and uncorrected PET images, as well as PET/CT images, were visually evaluated. Because of intense uptake in the spleen, the intensity of the image settings was reduced to better assess the distribution of activity in the splenic parenchyma.



**FIGURE 1.**  $^{68}\text{Ga}$ -DOTANOC whole-body PET maximum-intensity projection demonstrates normal distribution of activity in spleen, liver, pituitary gland, adrenal glands, pancreatic head, and bowel, with excreted activity in kidneys and bladder.

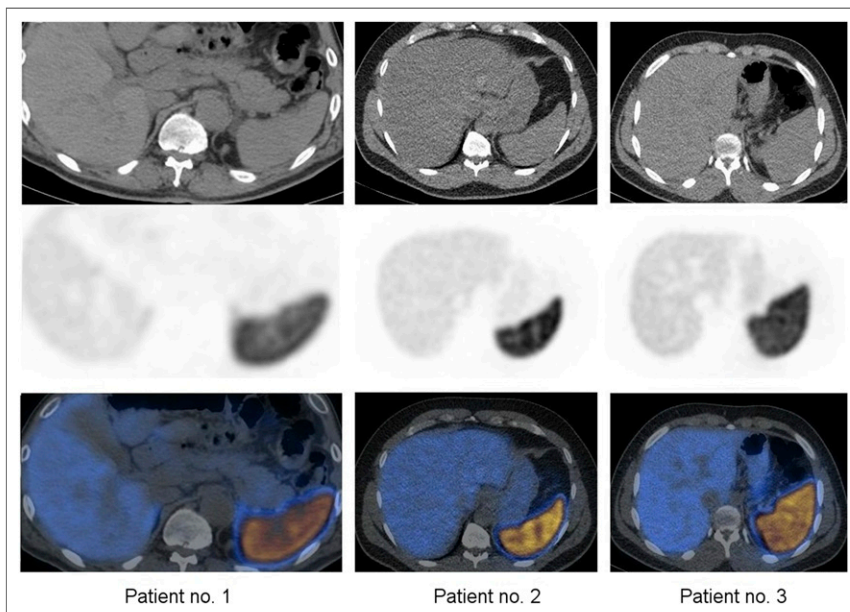
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For correspondence or reprints contact: Ismet Sarikaya, Department of Nuclear Medicine, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat, Kuwait 13110.  
E-mail: isarikaya99@yahoo.com  
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**FIGURE 2.** Basic anatomy of spleen: red pulp (RP), white pulp (WP), vein (V), artery (A), and splenic capsule (C).

## RESULTS

Five patients were male (aged 16, 28, 41, 55, and 62 y), and 2 were female (aged 48 and 73 y). Figure 1 shows a normal distribution of  $^{68}\text{Ga}$ -DOTANOC, Figure 2 shows basic splenic anatomy, Figure 3 shows  $^{68}\text{Ga}$ -DOTANOC PET/CT images of the spleen in 3 of our patients, and Figure 4 shows  $^{111}\text{In}$ -pentetreotide images for comparison with the  $^{68}\text{Ga}$ -DOTANOC images. On  $^{68}\text{Ga}$ -DOTANOC



**FIGURE 3.** Selected transaxial CT (top),  $^{68}\text{Ga}$ -DOTANOC PET (middle), and  $^{68}\text{Ga}$ -DOTANOC PET/CT (bottom) images of 3 patients. PET demonstrates physiologic high uptake in spleen, with slight heterogeneous distribution of activity. Slightly more prominent uptake in periphery of spleen and focally throughout splenic parenchyma is likely due to subcapsular and parenchymal red pulp. Central and hilar areas showing less uptake are likely due to splenic vascular structures or white pulp.

PET/CT images, the spleen shows high uptake with a slightly heterogeneous distribution in the parenchyma. Areas showing more prominent uptake in the parenchyma and subcapsular region are probably due to red pulp, because they correlate with the distribution of the red pulp. Small areas of lower uptake located more centrally and in the hilar region likely represent vascular structures and white pulp.

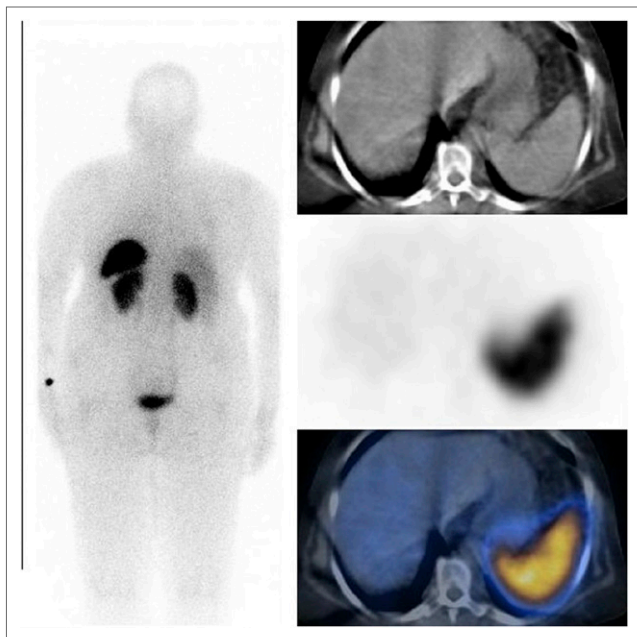
In our patients, the  $\text{SUV}_{\text{max}}$  of the spleen and the waiting period between the  $^{68}\text{Ga}$ -DOTANOC injection and the acquisition start were, respectively, 41.3 and 60 min, 41.4 and 95 min, 58.8 and 76 min, 62.1 and 80 min, 67.7 and 93 min, 69 and 129 min, and 70.4 and 109 min.

## DISCUSSION

The spleen has 2 main compartments, the red pulp and the white pulp (Fig. 1). The red pulp is a blood filter that removes foreign materials and damaged and aged red blood cells (RBCs) from the circulation. It is also a storage site for iron, RBCs, and platelets. White pulp surrounds the central arterioles and comprises a periarteriolar lymphoid sheath, the follicles, and the marginal zone. Immune responses to blood-borne antigens occur in the white pulp (4).

Autoradiography and immunohistochemistry studies have demonstrated that SSTRs are located mainly in the red pulp of the spleen (5–7). Reubi et al. reported that red pulp contains diffusely distributed SSTRs (7). The most abundant SSTR subtype in the spleen was SSTR2 (79.7%), followed by SSTR1 (19.6%), SSTR4 (0.6%), SSTR3 (0.1%), and SSTR5 (0.0%) (8). Quantitative reverse transcription polymerase chain reaction also has shown a significantly higher expression of SSTR2A messenger RNA in the spleen (9). Fluorescence immunocytochemistry has revealed somatostatin-positive cells in clusters within the white pulp and in a more dispersed pattern within the red pulp in both rats and chickens (10). In one study, there was a marked constriction of the splenic vascular bed after somatostatin administration, with a 50% decrease in blood flow; the investigators suggested that this effect of somatostatin was due to direct action on vascular receptor sites (11). Given the high amount of SSTRs in the spleen, somatostatin is expected to locate SSTRs on other sites in red pulp in addition to vascular structures.

$^{68}\text{Ga}$ -DOTANOC PET/CT provides high-quality images of the spleen. The distribution of  $^{68}\text{Ga}$ -DOTANOC appears to correlate with the distribution of red pulp in the spleen. Given the



**FIGURE 4.**  $^{111}\text{In}$ -pentetretotide posterior whole-body and selected transaxial CT, SPECT, and SPECT/CT images. Physiologic uptake in spleen is high and image resolution poor, compared with higher-resolution  $^{68}\text{Ga}$ -DOTANOC images.

excellent splenic images provided by SSTR PET/CT with  $^{68}\text{Ga}$ -labeled DOTANOC or other DOTA peptides, this modality may be an alternative to standard radionuclide splenic imaging studies with  $^{99\text{m}}\text{Tc}$ -labeled heat-damaged RBCs (selective spleen scintigraphy) or  $^{99\text{m}}\text{Tc}$ -sulfur colloid. Although standard radionuclide splenic imaging studies are the procedure of choice to image the spleen, they have certain limitations.  $^{99\text{m}}\text{Tc}$ -labeled heat-damaged RBC studies are laborious and time-consuming and require strict sterile technique (12). Insufficient or excessive damage to RBCs is not uncommon and can cause a suboptimal study. Colloid scans with  $^{99\text{m}}\text{Tc}$ -sulfur colloid are less sensitive than selective spleen imaging in the identification of small splenic tissues (13). High hepatic uptake in colloid scans can mask the visualization of adjacent small splenic tissues. PET imaging of the spleen with  $^{68}\text{Ga}$ -DOTA peptides not only provides higher-quality images than selective spleen SPECT imaging but also is quicker and easier to perform. The radiation dose to the spleen also appears to be lower with  $^{68}\text{Ga}$ -DOTANOC PET imaging (without including CT) than with  $^{99\text{m}}\text{Tc}$ -labeled heat-damaged RBC scintigraphy, at 0.0725 mGy/MBq (0.269 rad/mCi) versus 0.56 mGy/MBq (2.1 rad/mCi), respectively (14,15). However, the main limitations of PET/CT imaging of the spleen with  $^{68}\text{Ga}$ -DOTA peptides are the high cost of this study and the limited availability. Currently, PET/CT cameras are widely

available, but preparation of these radiotracers requires a costly  $^{68}\text{Ga}$  generator and a radiolabeling synthesis unit.

## CONCLUSION

SSTR imaging with PET radiotracers provides high-resolution splenic images, and we expect that it can be an alternative to standard radionuclide splenic imaging studies to assess morphologic abnormalities of the spleen and detect splenosis and accessory spleen. However, the main limitations of PET/CT imaging of the spleen with  $^{68}\text{Ga}$ -DOTA peptides are the high cost and limited availability.

## DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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