

# Significance of splenic uptake on somatostatin receptor imaging studies

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## Abstract

Spleen shows a high physiological uptake on radionuclide somatostatin receptor (SSTR) imaging studies. Autoradiography and immunohistochemistry studies showed that SSTRs are mainly located in the red pulp of the spleen. In this review article we will summarize the significance of splenic uptake in SSTR imaging studies and will also present high resolution splenic images of Ga-68 DOTANOC PET in which splenic distribution of the radiotracer appears to be correlating with the distribution of red pulp.

**KEY words:** Spleen, somatostatin receptor, SSTR, radionuclide, red pulp, scintigraphy, Ga-68 DOTANOC

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## Anatomic and physiologic considerations of spleen

The spleen is a pulpy, oval shaped, dark red to blue-black colored, fist sized organ located in the left upper quadrant of the abdomen. Spleen is a highly vascular organ. It has 2 main compartments, the red pulp and the white pulp, which have distinct function and morphology. 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 is composed of periarteriolar lymphoid sheath, the follicles, and the marginal zone. Spleen lacks afferent lymphatic vessels. Through efferent vessels lymphocytes migrate to the splenic lymph nodes. Immune responses to blood-borne antigens occurs in the white pulp [1]. The spleen is the largest secondary lymphoid organ which carries about one-fourth of the body's lymphocytes [1].

## Somatostatin and somatostatin receptors

Somatostatin (SST) is a regulatory peptide which is secreted by various tissues, mainly digestive system (delta cells in pancreatic islets, duodenum and pyloric antrum) and also nervous system (neuroendocrine cells). SST exhibits various neuroendocrine, gastrointestinal and neuromodulatory effects. SST has two biologically active forms; SST14 and SST28.

Major action of SST is inhibition of hormone secretion from the pituitary gland, the pancreas and other endocrine tissues and exocrine secretions in various sites [2]. SST inhibits release of growth hormone, prolactin, thyroid-stimulating hormone (TSH), and adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, insulin and glucagon from the pancreas and gastrin, vasoactive intestinal peptide, secretin and cholecystokinin from the gastrointestinal tract. Inhibitory effects of SST on various gastrointestinal functions include gastric acid secretion, gastric emptying, and intestinal motility. Its neuromodulatory effects are involved in learning, cognitive functions, locomotor activity, anxiety, and depression [3]. SST also exerts antiproliferative actions on normal and cancer cells via inducing cell cycle arrest and apoptosis and also takes part in immunoregulation [4–6].

SST exerts its effects through binding to SST receptor (SSTR) subtypes. There are 5 SSTR subtypes: SSTR1, SSTR2A and B, SSTR3, SSTR4 and SSTR5. SSTRs belong to the G protein coupled receptor family and widely expressed in normal tissues and solid tumors [7].

SSTR subtypes are expressed throughout the human body, including the central nervous system, gastrointestinal tract, pancreas, kidney, prostate, thyroid, and most lymphatic tissues including gut-associated lymphatic tissue, spleen and thymus.

Autoradiography and immunohistochemistry studies demonstrated that SSTRs were mainly located in the red pulp of the spleen which contains diffusely distributed SSTRs [8–10]. 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%) [11]. Significantly higher expression of SST2A mRNA in the spleen was demonstrated by quantitative reverse transcription polymerase chain reaction [12]. Fluorescence immunocytochemistry revealed the presence of SST-positive cells in clusters inside the white pulp

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and more dispersed within the red pulp of the spleen of both the rat and the chicken [13].

SSTRs have also been identified in a large number of human tumors, mainly in a high density in neuroendocrine tumors (NETs) such as pituitary adenoma, pancreatic islet cell tumor, carcinoid, pheochromocytoma, paraganglioma, medullary thyroid cancer, and small cell lung carcinoma and tumors of the nervous system including meningioma, neuroblastoma, and medulloblastoma [14, 15]. The other tumors such as lymphoma, breast cancer, renal cell cancer, hepatocellular cancer, prostate cancer, sarcoma, and gastric cancer, may also express SSTRs [15].

## Radionuclide SSTR imaging

Radionuclide SSTR imaging is used for the detection, localization, staging and in follow-up of NETs. It is useful in the selection of patients for SSTR based therapy with cold or radiolabeled SST analogs [16, 17]. It helps monitoring response to treatment [18]. It may be used in other non-NET tumors expressing SSTRs such as lymphoma and in active inflammatory disorders such as sarcoidosis [19, 20].

SSTR imaging with radiolabeled SST analogs have been used since late 1980s. In early studies I-123 Tyr-3-Octreotide was used which was later replaced by In-111 pentetretotide (Octreotide scintigraphy, OctreoScan). Currently, there are new Ga-68 labeled SST analogs for positron emission tomography (PET) imaging [21]. I-125 TYR(3)-octreotide was studied for hand held gamma probe tumor detection [22]. Tc-99m labeled SST analogs are also available but not commonly used [23].

The main SSTR subtype(s) targeted by various radiotracers are as follows: SSTR2 and SSTR5 by In-111 pentetretotide, SSTR2 by Ga-68 DOTATATE, SSTR2 and SSTR5 by Ga-68 DOTATOC, and SSTR2, SSTR3 and SSTR5 by Ga-68 DOTANOC.

Conventional SSTR imaging with In-111 pentetretotide is still widely used in the detection of NETs. However, new Ga-68 labeled PET radiotracers have been increasingly used and replacing conventional SSTR imaging in many centers due better properties of both the PET radiotracers and PET cameras over In-111 pentetretotide and gamma cameras with single photon emission computed tomography (SPECT) imaging. Studies have shown the superiority of PET imaging with Ga-68 DOTA peptides over SPECT imaging with In-111 pentetretotide for NETs [24, 25].

As compared to In-111 pentetretotide imaging, PET scan with Ga-68 DOTA peptides detects more lesions, shows higher uptake in the lesions and provides shorter time of acquisition and lower radiation exposure [24, 26].

## Splenic uptake on SSTR imaging studies

Spleen shows the highest physiological uptake on radionuclide SSTR imaging studies using any of the available radiolabeled SST analogs and it receives the highest radiation dose (critical organ). The reported radiation dosimetry results for the spleen using In-111 pentetretotide are 0.57 mGy/MBq (2.1 rad/mCi) in adults, 0.79 mGy/MBq (2.9 rad/mCi) in 15 year old children, and 1.8 mGy/MBq (6.7 rad/mCi) in 5 year old children [27]. Splenic radiation dose in Ga-68 DOTANOC PET studies (without including CT) is 0.0725 mGy/MBq (0.269 rad/mCi) [28].

Studies have shown that SSTRs are mainly located in the red pulp of the spleen. However, it is not very clear that where exactly in red pulp SSTRs are located. Following SST administration there was a marked constriction of the splenic vascular bed with 50% decrease in blood flow which was suggested that this effect of SST was due to a direct action on vascular receptor sites [29]. Given high amount of SSTRs in the spleen, it is expected SSTRs to be located also on other sites in red pulp in addition to vascular structures.

To better assess splenic involvement by SSTR positive tumors, intensity of the image setting should be reduced. Due to intense uptake in the spleen, tumors with low or moderate SSTR expression may be missed or seen as cold defects. Uptake in the accessory spleen or splenosis may cause false positive result for SSTR positive tumors [30]. Studies have reported that radiotracer uptake in splenosis is less than the normal splenic uptake [31, 32].

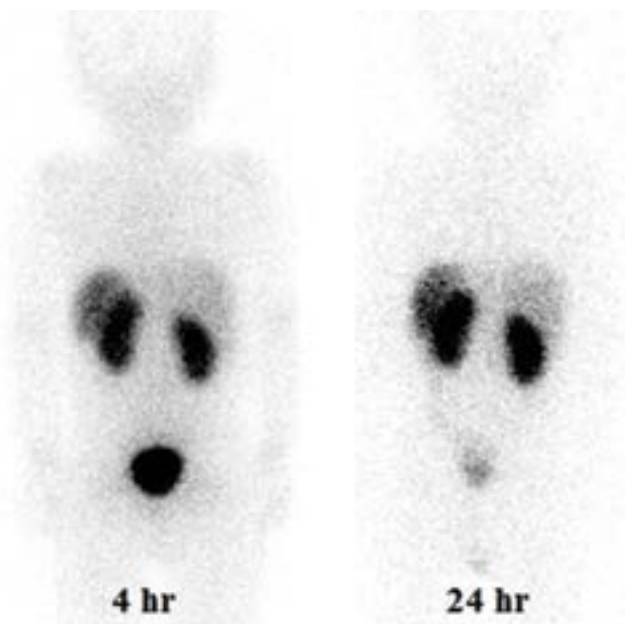
Spleen receives the highest mean absorbed dose during peptide receptor radionuclide therapy. Hematological toxicity according to hemoglobin counts was moderately but significantly correlated with total absorbed spleen dose which supported the possibility that radiation exposure of the spleen affects overall hematological response during Lu-177 DOTATATE treatment [33]. On the other hand, a previous study has reported that hematological toxicity after peptide receptor radionuclide therapy is not related to the radiation dose to the spleen [34]. In patients with NET undergoing peptide receptor radionuclide therapy, the uptake of Ga-68 DOTATOC in spleen and other normal tissues was not significantly different in pre and post-treatment [35].

Radionuclide SSTR imaging studies should be interpreted cautiously for treatment response evaluation in patients who underwent splenectomy after initial treatment. It was reported that there was higher uptake of Ga-68 DOTATOC in tumors and some normal tissues such as kidneys and adrenals after splenectomy [36].

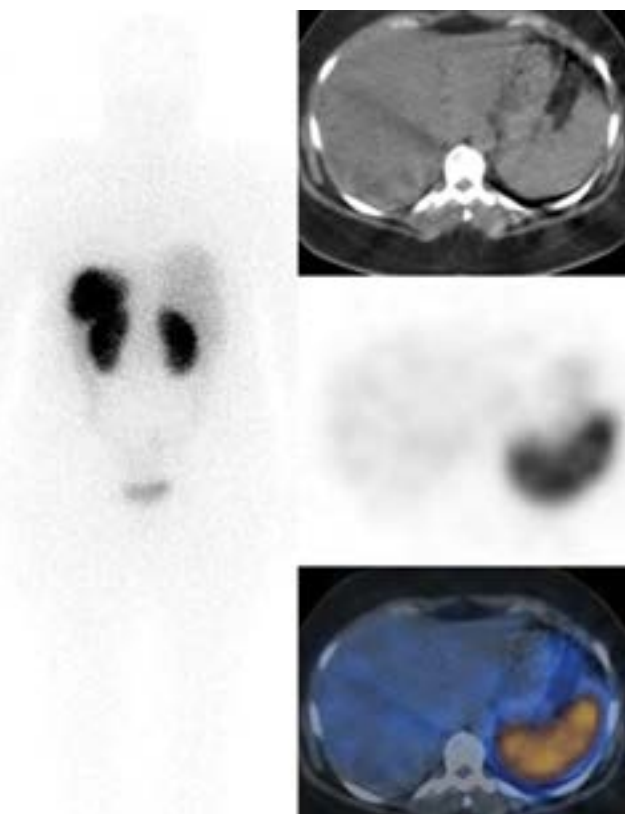
In certain situations splenic uptake can be lower than the expected normal uptake. Treatment with cold SST analogs usually reduces splenic uptake of radiotracers for SSTR imaging [27, 37–39]. Several studies showed that treatment with cold SST analogs reduced the uptake in the spleen as well as in liver and kidneys, but it did not affect or even increased the uptake in the tumor [37–39]. Dörr et al. reported that liver, spleen, and kidney uptake were decreased during octreotide treatment but increased on lanreotide therapy, and tumor accumulation was intensified in majority of the patients [40].

Low physiological splenic uptake of Ga-68 DOTANOC has been reported in a newborn [41]. Authors of this case suggested that incomplete/immature expression of the SSTR in early life could be the reason for low splenic uptake. In-111 pentetretotide images of one of our patients who is a 7 year old child demonstrate less intense uptake in the spleen as compared normal which could be due to treatment with SST analogs (Fig. 1).

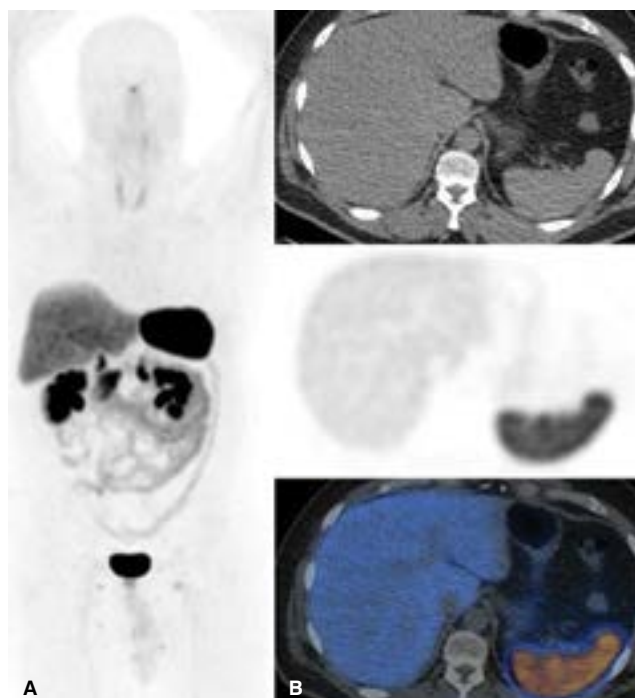
Spleen can be used as a reference to calculate tumor to spleen uptake ratio for estimation of SSTR density in tumors. Kratochwil et al. assessed the SSTR2 expression of the liver metastases in NET patients at baseline and after peptide receptor radiation therapy by measuring SUVmax, tumor to spleen ratio (T/S ratio), and tumor to liver ratio (T/L ratio) using Ga-68 DOTATOC [42]. Using the receiver operating characteristic curves, SUVmax was found a better metric than both T/L ratio and T/S ratios as a stratification criterion in this study. In another study with Ga-68 DOTATATE, SUVmax and



**Figure 1.** Four and 24 hr In-111 pentetreotide posterior whole body images of a 7 year old child illustrate less intense splenic uptake than the normal



**Figure 2.** In-111 pentetreotide posterior whole body image and selected transaxial CT, SPECT, and SPECT/CT fusion images of the spleen. Note the high physiological uptake in the spleen with slight heterogeneous distribution



**Figure 3.** Ga-68 DOTANOC whole body MIP (A), and selected transaxial CT, PET, and PET/CT fusion (B) images. PET images demonstrate physiological high uptake in the spleen. Compare the better image resolution of Ga-68 DOTANOC with In-111 Octreotide images in Figure 2. Note the slightly more prominent uptake in the periphery of the spleen which is likely from subcapsular red pulp. Areas showing less degree of uptake more centrally in the splenic parenchyma could be from splenic vascular structures and/or white pulp

tumor-to-spleen SUV ratio (SUV T/S) were used to assess for the early prediction of response to SST receptor-mediated radionuclide therapy in patients with well-differentiated NETS [43]. Percentage change in SUV scores after PRRT relative to baseline (DeltaSUV) was calculated. Delta SUV(T/S) was superior to Delta SUV (max) for prediction of outcome.

On SSTR images spleen shows diffuse high uptake with mild heterogeneity. In various studies with Ga-68 DOTATOC, standardized uptake value (SUVmax) (mean  $\pm$  standard deviation) in normal spleen was reported to be as  $22.0 \pm 10.0$ ,  $28.8 \pm 12.5$  and  $31.1 \pm 10.9$  [11, 31, 44]. SSTR PET images provide higher resolution spleen images than SSTR SPECT does (Fig. 2–4). Reducing intensity of the image settings helps better assess distribution of activity in the splenic parenchyma. On Ga-68 DOTANOC PET images, slightly heterogeneous distribution of activity with small areas showing less uptake than the rest of the parenchyma are likely due to vascular structures or regions of white pulp. Slightly more prominent uptake in the periphery of the spleen (subcapsular) and throughout parenchyma is likely from red pulp.

Because of high splenic uptake, SSTR imaging, particularly with PET radiotracers, may be an alternative to standard radionuclide splenic imaging studies with Tc-99m heat damaged RBCs or Tc-99m



**Figure 4.** Ga-68 DOTANOC and selected transaxial CT, PET, and PET/CT fusion images demonstrate the distribution of radiotracer in the spleen which is correlating with distribution of red pulp as also shown in Figure 3

sulfur colloid (Tc-99m SC). Standard radionuclide splenic imaging studies are the procedure of choice to image spleen, however, they have certain limitations. Tc-99m heat damaged RBC study is laborious, time consuming, and requires strict sterile technique [45]. Insufficient or excessive damage to RBCs can also cause sub-optimal study. Colloid scan with Tc-99m SC is less sensitive than selective splenic imaging in the identification of small splenic tissues because intense hepatic uptake can obscure small splenic tissues [46]. PET images of spleen with Ga-68 DOTA peptides have better resolution than standard radionuclide SPECT images of the spleen. PET study is also quicker and easier to perform. Radiation dose to spleen also appears to be lower with Ga-68 DOTANOC PET imaging (without including CT) than with Tc-99m heat damaged RBC scintigraphy [27, 28]. However, the main limitations of PET imaging of spleen with Ga-68 DOTA peptides are the high cost and limited availability of this radiotracer.

## Conclusion

Spleen shows a very high uptake in radionuclide SSTR imaging studies. Significance of splenic uptake on SSTR imaging studies have been summarized in this article. In addition it was noted that Ga-68 DOTA peptides provide high resolution images of the spleen which appears to be correlating with the distribution of red pulp. Because of high splenic uptake and excellent image quality, particularly with PET tracers, SSTR imaging may be an alternative to standard radionuclide splenic imaging studies to assess the spleen and detect accessory spleen and splenosis.

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