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Biodistribution on Tc-99m labeled somatostatin receptor-binding peptide (Depreotide, NeoTec) planar and SPECT studies

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Purpose: To determine the biodistribution of Tc-99m labeled somatostatin receptor-binding peptide (Depreotide) on planar and SPECT studies of the thorax and upper abdomen in order to improve diagnostic accuracy. ***Methods and Materials:*** Retrospectively 29 planar and SPECT studies from 28 patients (all males, average age of 65.79) were reviewed. All the patients had been referred for evaluation of solitary pulmonary nodules. Two to four hours after IV injection of 555- to 740-MBq (15–20 mCi) Tc-99m Depreotide, anterior and posterior total body images, and anterior, posterior, right lateral and left lateral planar images were obtained, and thoracic SPECT was acquired with a three-head gamma camera. The degree of uptake in the lungs, thoracic cage, and organs of the upper abdomen was rated from "0" to "++++". ***Results:*** The range of normal activity in the thorax includes cardiac, "0"; pulmonary, "+"; rib, "+/++"; sternum, "++"; vertebrae, "++". The degree of normal activity seen in the upper abdominal organs includes liver and spleen, "+++", and kidneys, "+++/++++". Eight patients with emphysema had diffuse pulmonary uptake graded as "+/++". One patient with left pneumonectomy and radiation therapy to the left hemithorax had photon-deficiency in the left hemithorax and decreased to absent uptake including the vertebrae and ribs. Although some cases had background pulmonary uptake of Tc-99m Depreotide, the bone/bone marrow activity of the thoracic cage including the ribs, sternum, and thoracic spine is sufficiently great enough to produce a clear distinction between bone and lung in the thoracic cavity that gives high-contrast resolution on SPECT. ***Conclusions:*** The intensity of radioactivity in the sub-diaphragmatic organs such as the liver, spleen, and kidneys provides useful guidance for the categorization of pulmonary lesions. The uptake of land marks such as the sternum, which is anteriorly located, and the thoracic vertebrae, which are posteriorly located in the thoracic cage, can be used in the localization of a Depreotide avid tumor.

Key words: Tc-99m Depreotide, planar images, SPECT, liver uptake, lung uptake, spleen uptake, renal uptake

INTRODUCTION

Tc-99m labeled somatostatin receptor-binding peptide (Depreotide) has received US Food and Drug Administration approval for use in the imaging of suspected malignant tumors in the lung. This agent has been utilized in the evaluation of solitary pulmonary nodules and has shown a specificity of 73.1% to 88% and a sensitivity of 93% to 96.6% for detection of malignant solitary pulmonary nodules.[1,2] The authors therefore concluded that Depreotide is a safe and useful method for the non-invasive evaluation of solitary pulmonary nodules with a sensitivity and accuracy comparable to that reported for FDG PET.[1] In comparison with Depreotide and F-18 FDG PET, a preliminary analysis of 40 subjects indicated that the findings in Depreotide and FDG PET in patients suspected of

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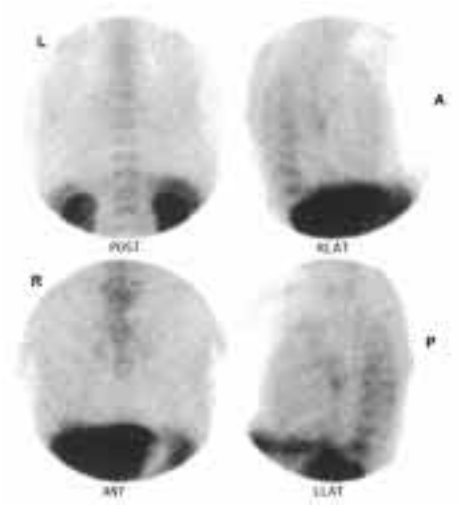

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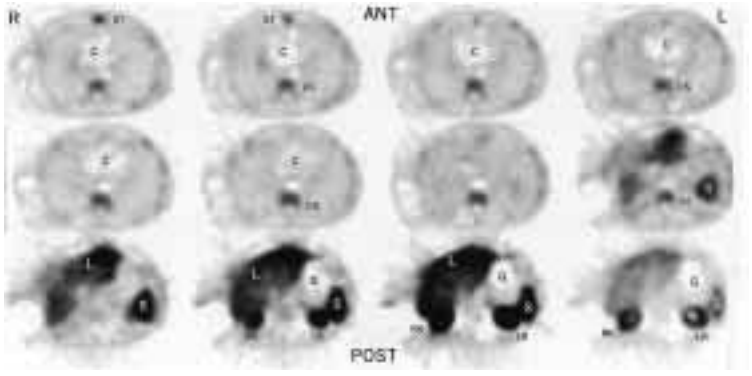

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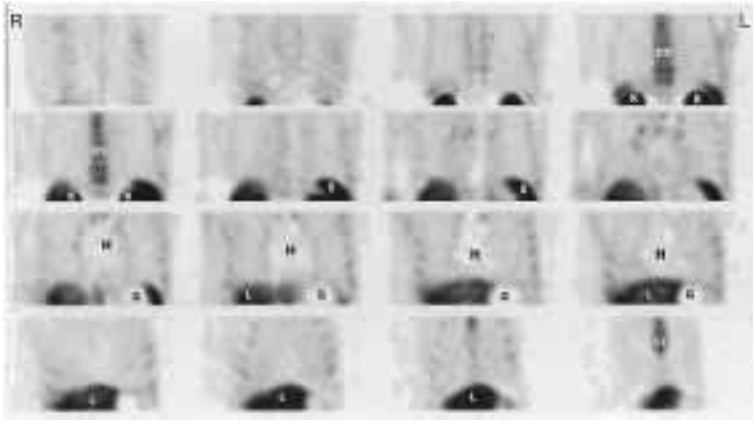

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Fig. 1 A: Planar images of the abdomen and thorax: Planar thoracic and upper abdominal images of the anterior (ANT), posterior (POST), right lateral (RLAT), and left lateral thorax (LLAT) show mildly increased activity in the sternum, thoracic and upper lumbar vertebrae, and ribs, background activity in the lungs; activity in the liver, spleen and kidneys is much higher than that in the vertebrae.
B: SPECT of the thoraco-abdominal region: Transaxial sections of thoraco-abdominal SPECT (from the upper left to the lower right) show a photon-deficient cardiac area in the upper panel, sternum (ST) anteriorly located, and dorsal vertebra (DS) posteriorly located, and much more uptake in the liver (L), spleen (S), and kidneys (RK and LK). Renal activity is more accumulated in the cortical area as seen in the right lower slice. C: SPECT of the thoracic-abdominal region: Coronal sections of thoraco-abdominal SPECT (from the upper left to the lower right) show well delineated activity of the vertebrae (DS), sternum (ST), and ribs, background activity of the lungs that stands out from the photon-deficient heart area (H), higher activity in the liver (L), spleen (S), and kidneys (K), and a photon-deficient area in the gastric (G) area in the left upper abdomen.

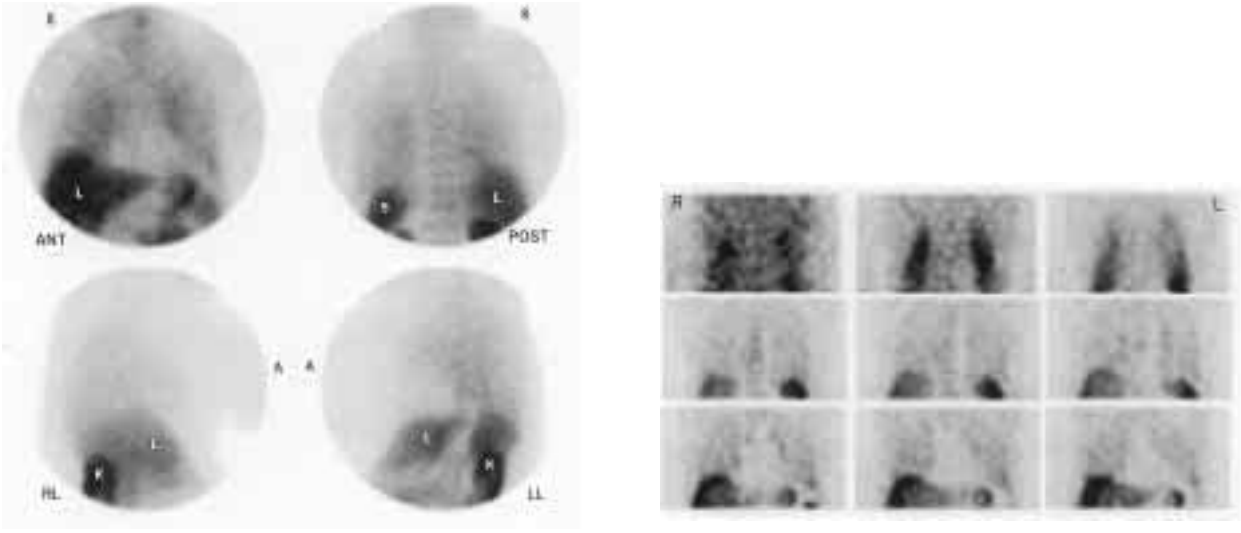
having lung cancer were very similar for both diagnosis and staging.[3] Based on these results, it is likely that Depreotide will be used with increasing frequency in the evaluation of solitary lung nodules.[4] Depreotide as a tumor-imaging agent is relatively new, and because the normal biodistribution of this imaging agent in the human body is not well documented; thus we undertook this study. The study is not intended to evaluate tumor detection in terms of sensitivity, specificity, and accuracy.

MATERIALS AND METHODS

We retrospectively reviewed 29 studies of 28 male patients who had undergone Tc-99m Depreotide planar and SPECT studies. This study included one case study that has been previously reported.[5] Twenty-eight patients were referred for the evaluation of malignancy in a solitary pulmonary nodule; one patient had two studies in a one-week interval. All 28 patients were males and ranged in age from 44 to 82 years with an average age of 65.79 years.

Radiopharmaceutical preparation:
Vials of a lyophilized formulation containing 50 μg Depreotide (Diatide, Inc; Londonerry, NH) were prepared by reconstituting a kit with up to 50 mCi (1.85 GBq) Tc-99m pertechnetate injection and heating the resulting solution in a boiling water bath for 10 minutes according to instruction in the package insert.[6] After cooling to room temperature 10–15 for minutes, the solution was visually inspected for clarity and particulates, and chromatographic quality control testing was performed. By an instant thin layer chromatography method, the radiochemical purity of Depreotide was not <90%. Within 6 hours of kit preparation, 15 to 20 mCi (555 to 740 MBq) of Depreotide was intravenously injected into each patient.

Planar and SPECT imaging:
Two to four hours after IV injection of Tc-99m Depreotide,



A **B**

Fig. 2 A: (H9242) Mildly and diffusely increased uptake in the lungs on planar images. Anterior (ANT) and posterior (POST) views show mildly and diffusely increased radioactivity in both lungs, which is graded as "+/++", and a prominent cardiac area of photon-deficiency in the anterior projection and thoracic and upper lumbar vertebrae identifiable in the posterior projection; activity in the liver (L), spleen (S), and kidneys (K) is higher than that in the lungs and vertebrae. Left lateral (LL) and right lateral (RL) views show mild and diffuse uptake in the lungs, higher radioactivity in the liver, spleen, and kidneys; renal activity is most prominent. B: Mildly and diffusely increased uptake in the lung on SPECT: Coronal sections from the posterior to the anterior direction: symmetrically and diffusely increased uptake in both lungs, designated as "+/++", is shown in the upper panel; in the bottom panel, there is a photon-deficient area representing the cardiac zone surrounded by the lungs, and upper boarder of the liver.

anterior and posterior total body images, and anterior, posterior, right lateral and left lateral planar of thoracic images were obtained; and SPECT was acquired by means of a three-head gamma camera (Prism, Phillip) using an all purpose collimator, and SPECT centered at the thorax was acquired in a $128 \times l28$ matrix, with 360 degree acquisition, each stop consisting of 20 to 30 seconds for 25 minutes altogether. SPECTs were reconstructed in conventional axial, sagittal, and coronal projections.

All planar and SPECT images were reviewed and interpreted by two experienced nuclear medicine physicians independently. In addition to determining the presence or absence of a focal lung lesion with increased uptake, all images were evaluated for radioactivity in the cardiac region, both lungs, thoracic cage including the bone/bone marrow of the sternurn, ribs, and thoracic vertebrae as well as in the visible abdominal organs such as the liver, spleen, kidneys, and bowel.

RESULTS

The table summarizes the biodistribution of Tc-99m Depreotide in the thoraco-abdominal region all 29 studies of all 28 patients. Radioactivity in the thorax and upper abdomen was observed and graded as "0", "+", "++", "+/++", "+++", and "++++" depending on the intensity of radioactivity. Figure 1A showed the planar thoracic and upper abdominal images of the anterior posterior, right lateral, and left lateral projections; when activity in the cardiac region was absent or photon-deficient was it designated as "0" (Figs. 1B and 2B). The very faint diffuse background uptake seen in both lungs was designated as "+". The mild activity seen in the ribs was designated as "+/++". The radioactivity in the sternum, and thoracic spine is designated as "++". Moderate to marked uptake in the liver and spleen was designated as "+++" and the marked uptake in the kidneys was designated as "++++".

Twenty studies of 28 patients demonstrated normal background activity (+) of both lungs. Eight patients with pulmonary emphysema (cases 11, 12, 14, 15, 17–20 on the table), as shown on CT of the chest had diffuse pulmonary uptake graded as "+/++" that obscured rib activity (Figs. 2A & 2B). Another patient with moderate to severe emphysema was complicated with emphysematous blebs formation in the apical regions, and his planar thoracic images (Fig. 3A) and SPECTs (Figs. 3B & 3C) demonstrated absence of activity in the apical region. This patient's concurrent CT of the chest (Fig. 3D) showed emphysematous blebs in the apical regions.

The graded categories can be used for anterior, poste-

Table 1

No.	Age	Clinical diagnosis	Tc-99m-Depreotide Planar/SPECT uptake							
			Car	Pul	Rib	Stm	Ver	Liv	Spl	Kid
1	66	nodule R upper chest wall	0	+	++	++	++	+++	+++	++++
2	71	6-cm mass in LUL	0	+	++	++	++	+++	+++	++++
3	56	L supraclavicular mass	0	+	++	++	++	+++	+++	++++
4	66	3-cm mass in LUL	0	+	++	++	++	+++	+++	+++
5	53	mass in R bronchus	0	+	++	++	++	+++	+++	++++
6	69	nodule in R apex	0	+	++	++	++	+++	+++	++++
7	73	LLL mass	0	+	++	++	++	+++	+++	++++
8	76	R lung mass	0	+	++	++	++	+++	+++	++++
9	72*	nodule in RLL	0	+	++	++	++	+++	+++	++++
10	72*	nodule in RLL	0	+	++	++	++	+++	+++	++++
11	76	nodule in LLL	0	+/++	++	++	++	+++	+++	++++
12	76	residual scarring in RML	0	+/++	++	++	++	+++	+++	++++
13	73	nodules in RUL and RLL	0	+	++	++	++	+++	+++	+++
14	61	mass in the LLL	0	+/++	++	++	++	+++	+++	++++
15	75	7 mm nodule in RLL	0	+/++	++	++	++	+++	+++	++++
16	67	12 cm nodule in RLL	0	+	++	++	++	+++	+++	++++
17	49	1 cm nodule in LUL	0	+/++	++	++	++	+++	+++	++++
18	73	2 nodules in RML	0	+/++	++	++	++	+++	+++	++++
19	76	a nodule in LUL	0	+/++	++	++	++	+++	+++	+++
20	67	a less 1 cm nodule in LUL	0	+/++	++	++	++	+++	+++	++++
21	53	2 nodules in RUL	0	+	++	++	++	+++	+++	++++
22	82	a nodule in RML	0	+	++	++	++	+++	+++	++++
23	44	a nodule in right apex	0	+	++	++	++	+++	+++	++++
24	66	a 3 cm LUL mass	0	+	++	++	++	+++	+++	++++
25	51	3.5 × 5 cm RLL	0	+	++	++	++	+++	+++	++++
26	55	1.7 cm RLL	0	+	++	++	++	+++	+++	++++
27	77	1.5 cm superior seg LLL	0	+	++	++	++	+++	+++	++++
28	64	a 1.1 cm in LLL	0	+	++	++	++	+++	+++	++++
29	53	a 0.6 × 1.3 cm in LUL	0	+	++	++	++	+++	+++	++++

NOTES: Car, cardiac; Pul, pulmonary; Stm, sternum; Liv, liver; Spl, spleen; Kid, kidney; R, right; LUL, left upper lobe; Pul, pulmonary; RLL, right lower lobe; RML, right middle lobe
Intensity of uptake: 0, photon-deficiency; + or +/++, background; ++, mild; +++, moderate; and ++++, severe.

rior and lateral planar images (Figs. 1A, 2A & 3A) and SPECT images (Figs. 1B & C, Fig. 2B, and Figs. 3A & 3B). Total body images showed higher activity in the abdominal organs in the liver, spleen, and kidneys; the highest activity is in the kidneys (Figs. 1B, 1C, 2A & 3). Anterior and posterior total body images demonstrated bowel activity in the abdomen in addition to the well-visualized liver, spleen and both kidneys, and a focal area of increased uptake in the medial aspect of the left chest was depicted (Fig. 4A). Anterior and posterior images of the head showed skull activity without intra-cranial uptake (Fig. 4B). SPECT of the thorax of this patient to demonstrate the pulmonary lesion was exhibited in Figures 4C & D.

DISCUSSION

Depreotide is currently being used for the detection of malignancy in solitary pulmonary nodules. We have made several observations regarding the relative intensity of uptake and potential relevance of these observations during our use of these scintigraphic and single photon emission tomographic techniques. We understood that males and only 29 studies of 28 patients limited the populations of our patients. The highest uptake noted is in the kidneys and accumulation of tracer is primarily in the renal cortex as shown in Figure 1B. The next highest uptake was seen in the liver and spleen, which have equal intensity on SPECT as shown on Table 1. In the thorax, there is mild uptake noted in the thoracic vertebrae, ribs and sternum. The lungs showed faint background uptake, and activity in the region of the heart is even less than background activity and is designated as “0”. Therefore, except for liver and spleen uptake, a Depreotide study is similar to bone scintigraphy; but bone/bone marrow activity is much less than that of the bone scan. The very faint uptake in the normal lungs makes Depreotide especially suitable for detection of lung cancer, which avidly takes up of the tracer. Another unique aspect of Tc-99 Depreotide is the lack of uptake of tracer in the brain as

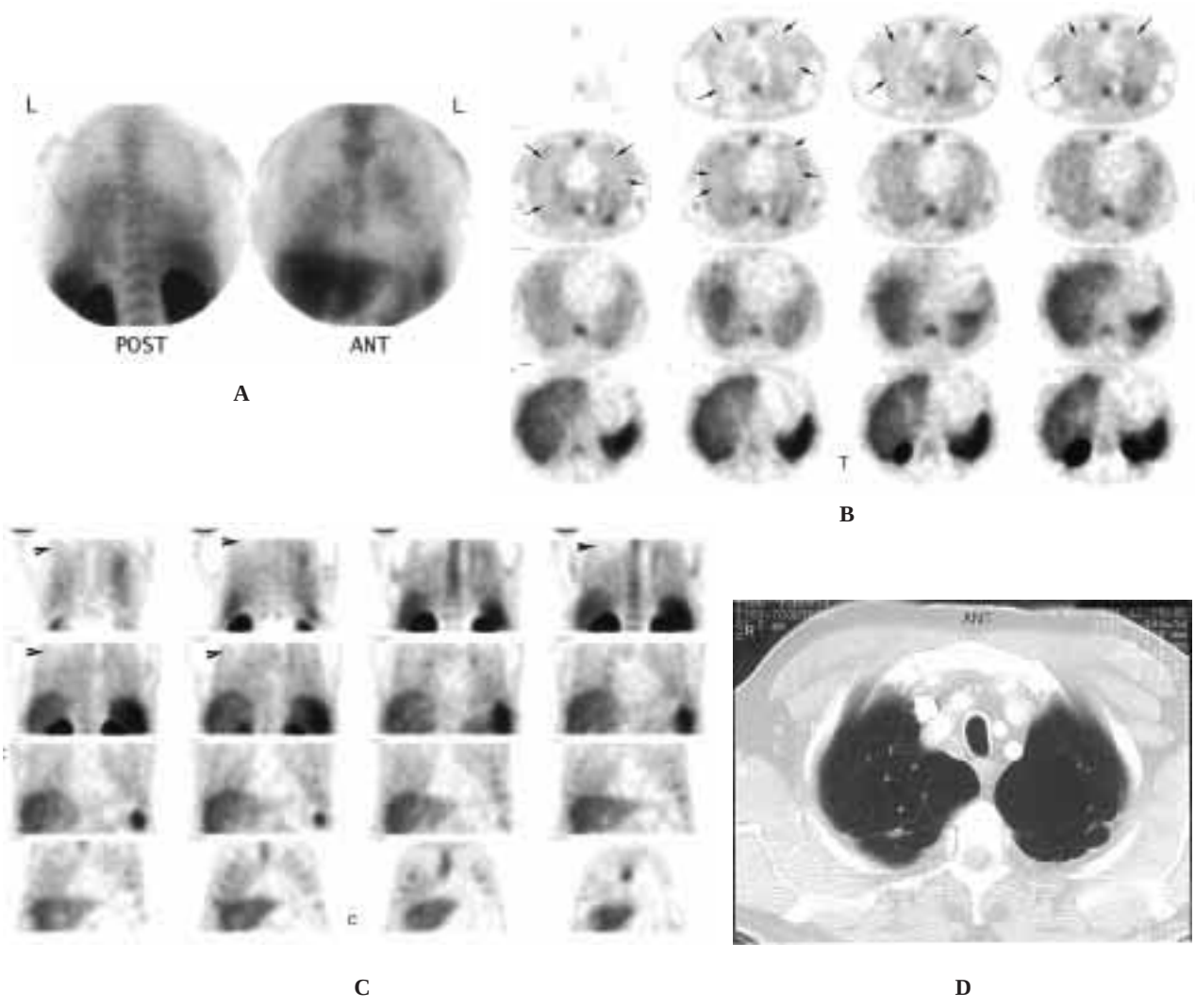


Fig. 3 A: Mildly and diffusely increased uptake in both lungs with the absence of uptake in apical regions especially on the right apex on anterior (ANT) and posterior (POST) planar images. B: Photon-deficient areas, as indicated by arrows, in both apical regions in the mildly and diffusely increased uptake in both lungs are shown in transverse section of SPECTs: the cold area is more apparent in the right apex. C: Open arrowheads, on coronal section of SPECTs, indicate photon-deficient areas. D: Emphysematous changes in the apex of both lungs are shown on a chest.

shown in Figures 4A & B. The Depreotide images show skull activity equal to that of the vertebrae, but without normal brain uptake (Fig. 4B), making it potentially useful for detection of cerebral metastases.

The range of normal biodistribution of Tc-99m Depreotide demonstrated in the cardiac region, the lungs, and bone/bone marrow of the thoracic cage, the liver, spleen and kidneys could serve as a reference for the detection of abnormal radiotracer localization in the lungs. For example, if activity in is equal to the activity in the cardiac area that may be considered as a photon-deficient area. If the lesion is of equal of radioactivity equal to the bone/bone marrow activity of the vertebrae or sternum this would indicate mildly increased uptake. When the lesion is of radioactivity equal to that of the liver or spleen, then the lesion has moderately increased uptake. If activity in the lesion is equal to or higher than that in the kidneys, then the lesion has noticeably increased uptake. If the lesions had activity equal to or higher than that of the liver or spleen, then these lesions were called positive for malignancy (Fig. 4). Three dimensional displays of the thorax (Fig. 4C) shows a large area of increased uptake with a central photopenia area; normal activity of the sternum anteriorly and vertebrae posteriorly can be used as landmarks to localize abnormal areas of uptake in the thorax. SPECTs (Fig. 4D) of the thorax showed an area with a rounded photon-deficient lesion in the superior-lateral aspect of the cardiac area, in which appeared to be the area of no uptake.

Depreotide is synthetic somatostatin analog with a low

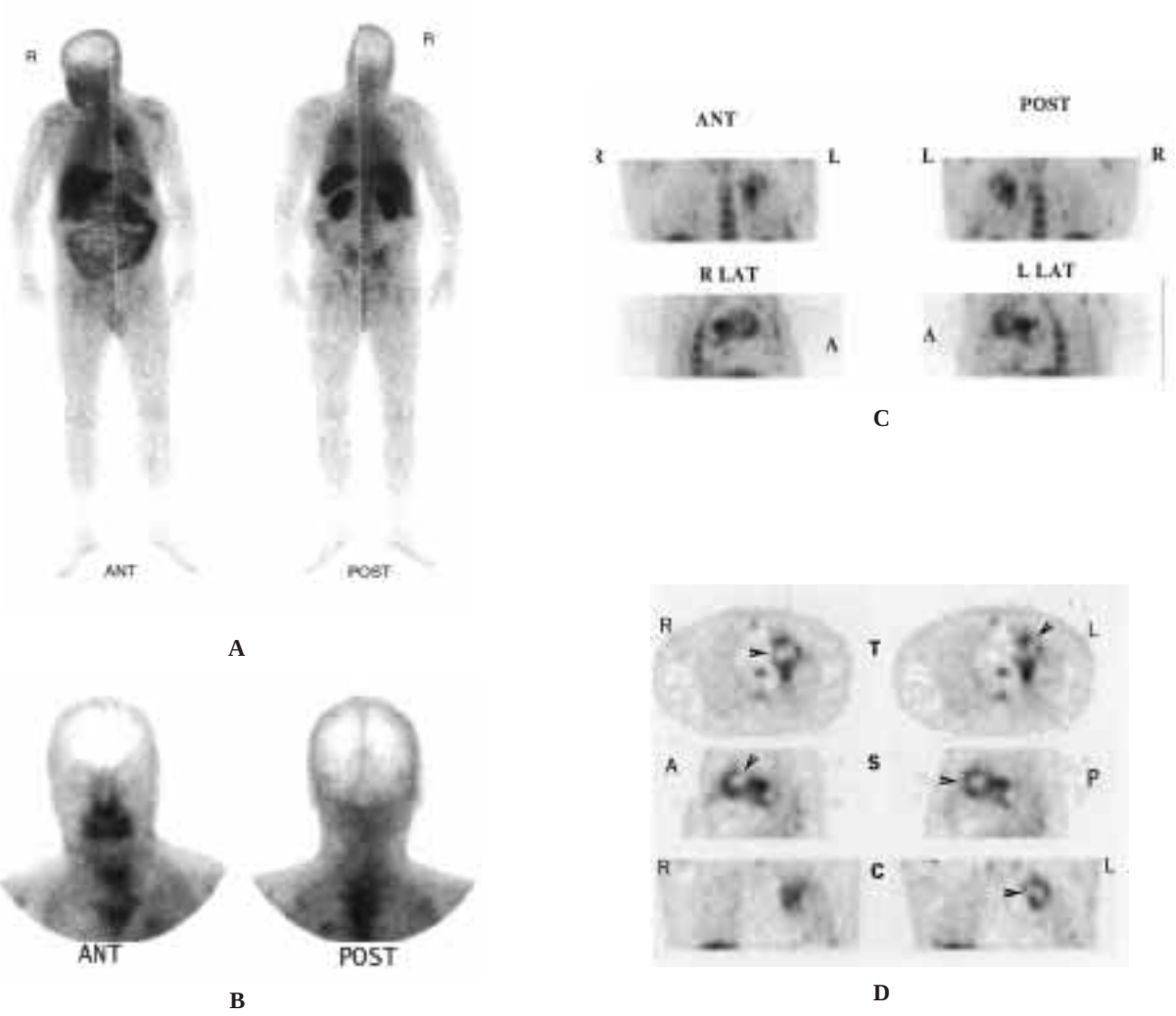


Fig. 4 A: Anterior (ANT) total body image shows mildly increased uptake on the both lungs, moderate to severe uptake in the liver, and some bowel activity. A posterior (POST) total body image shows mildly increased uptake in the lungs and the spine, and pelvic bones including sacro-iliac joints, good visualization of the liver, spleen, and both kidneys. Note that there is skull activity similar to that of the vertebrae, but no area of radioactivity in the intra-cranial cavity. B: Anterior and posterior head images show skull activity without intra-cranial uptake. C: A large mass with photon-deficient area in the right upper lung on three dimensional displays: SPECTs of the thorax, with volume three dimensional anterior (ANT), posterior (POST) and right lateral (R LAT), and left lateral (L LAT) show a large area of increased uptake with a central photon-deficient area, as indicated by arrows, in the right upper lung. D: SPECTs demonstrating a mildly and diffusely increased uptake in the lung on transaxial (T), sagittal (S), and coronal (C) sections show an area with a rounded photon-deficient (as indicated by open arrowheads) lesion in the superior-lateral aspect of the heart, in which there appears to be the area of no uptake. R, right; L, Ieft; A, anterior; and P, posterior.

molecular weigh of 1,358 and the binding domain for somatostatin receptor SSTR subtypes 2, 3 and 5.[7,8] In animal studies, mostly the kidneys clear Tc-99m Depreotide. In a comparison of Tc-99m P587 and Tc-99m Depreotide, the images at 1 hr indicated that about 40% of Tc-99-P587 activity was in the gastrointestinal tract, 25% in the urinary bladder, and only 6% in the kidneys. In contrast, 30% of Tc-99m Depreotide activity was in the kidneys, 20% in the urinary bladder, and less than 5% in the gastrointestinal tract. Therefore, distribution of Tc-99m Depreotide showed almost no gastrointestinal activity with predominantly renal excretion.[8] Because of low gastrointestinal uptake, Tc-99m Depreotide has been selected for clinical studies but some bowel activity was well visualized on total body or abdominal images in several of our cases (Fig. 4A).

Although there has been no prior report of lung uptake and bone/bone marrow uptake in Tc-99m Depreotide

scintigraphy,[1,2] we do normally visualize the vertebrae, sternum, and ribs. The exact mechanism of the Tc-99m Depreotide localization in these areas is unknown; however, this uptake may be due to osteoblastic bone activity, bone marrow localization, or both.

In our series, normal biodistribution in the lungs was categorized as background activity (graded as +); the lung appears to be one of the organs of normal biodistribution of Depreotide. However, 8/28 patients with emphysema (cases 11, 12, 14, 15, 17, and 18–20) and had diffuse pulmonary uptake graded as mildly increased (+/++) in both lungs as shown on Figure 2. In emphysematous blebs areas as shown on Figures 3A, B and C, there was absent radioactivity and they might be graded as "0", the same as activity in the cardiac region. The absence of radioactivity in the emphysematous blebs was in contrast to rest of the lungs, in which showed mildly and diffusely increased uptake graded as (+/++), this is also indirectly indicating enhanced lung tissue uptake in the patients with emphysema. The mechanism of this mildly and diffusely increased uptake in the lungs in patients with emphysema is unknown and deserves for further investigation.

Although our study was limited to males and only 29 studies of 28 patients, the study might be summarized as the follows: (a) The degree of normal activity in the thorax includes cardiac, 0; pulmonary, +; rib, +/++; sternum, ++; and vertebrae, ++; (b) The degree of normal activity in the upper abdominal organs includes liver and spleen, +++, and kidneys, ++++; (c) The normal activity in the skull had an intensity similar to that of the vertebrae without any accompanying activity in the intra-cranial cavity (unlike F-18 FDG normal localization in the brain, Depreotide may used for cerebral metastasis from the lungs); (d) Diffuse pulmonary activity might be categorized into two degrees: background activity "+", and mild uptake, "+/++", in patients with emphysema; (e) Because of normal bowel activity on top of high uptake in the abdominal organs (the liver, spleen and both kidneys), Depreotide imaging is not suitable for detection of a lesion located in the abdomen.

Tc-99m Depreotide, a relatively new radiopharmaceutical agent, has a safety profile. Of 647 patients evaluated, one or more adverse events occurred in only 4.5% of all enrolled patients[6]; the most commonly reported adverse events were headache (1.0%), dizziness (0.8%), flushing (0.5%), and low incidence (1% or less) of transient and clinically insignifi-cant changes in ALT, WBC count, and eosinophil count after following administration.[1] There were no noted drug interactions in patients receiving Tc-99m Depreotide and concomitant medication.[1] Of our 29 study patients, none had any adverse events.

CONCLUSION

Despite there is pulmonary background uptake in Tc-99m Depreotide images, the bone/bone marrow activity of the thoracic cage including the ribs, sternum, and thoracic spine produced clear or virtually absent radioactivity in the intra-thoracic cavity that gives high-contrast resolution on SPECT. A photon-deficient area in the cardiac region may make Tc-99m Depreotide superior to FDG-PET, since FDG is normally localized in the heart, to evaluate a possible solitary pulmonary nodule and invasion of the mediastinum. And the intensity of radioactivity in the sub-diaphragmatic organs such as the liver, spleen and kidneys is a useful guide in categorizing pulmonary lesions. The landmarks of the sternum, at its anterior located, and the thoracic vertebrae, as their posteriorly located of the thoracic cage, can be used to guide the location of a Depreotide-avid tumor.

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