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# Radiolabeled Octreotide for the Demonstration of Somatostatin Receptors in Malignant Lymphoma and Lymphadenopathy

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This prospective study evaluated somatostatin receptor-specific scintigraphy as a clinical tool for routine detection of malignant lymphoma. **Methods:** Forty-one consecutive patients were examined using  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide. Thirty-four patients had diagnoses of Hodgkin's disease ( $n = 11$ ) or non-Hodgkin's lymphoma ( $n = 23$ ) previously verified and staged by hematology, histology and imaging methods (CT, chest x-ray and abdominal ultrasonography). The remaining seven patients initially suspected of presenting lymphoma ( $n = 5$ ) or lymphoma recurrence after chemotherapy and radiotherapy ( $n = 2$ ) were subsequently shown to have other diseases. Planar images were recorded 4, 24 and 48 hr after intravenous injection and evaluated without knowledge of other results. In case of negative planar scintigraphy, additional SPECT images were obtained. Since these failed to increase sensitivity, they were omitted after 15 negative recordings. **Results:** Octreotide scintigraphy did not yield false-positive results. The sensitivity for detecting Hodgkin's disease was 70% and varied from 88% in the neck and chest to 13% in the abdomen and pelvis. The sensitivity for non-Hodgkin's lymphoma was not influenced by localization and amounted uniformly to 35% but varied with the degree of malignancy between 44% (high-grade) and 29% (low-grade malignancy). **Conclusion:** Our results suggest that radiolabeled octreotide is better suited to characterize somatostatin receptor expressing lymphomas than to localize lesion sites. It is useful for imaging Hodgkin's disease, especially above the diaphragm.

**Key Words:** octreotide scintigraphy; lymphoma; lymphadenopathy

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A variety of neuroendocrine and other tumors, as well as several granulomatous diseases are known to express membrane receptors for somatostatin (1-5). Somatostatin receptors (SR) of variable affinity are also expressed by the lymphopoietic system. Reubi and coworkers have demonstrated that lymphomas can be detected by scintigraphy because activated lymphocytes, macrophages and leuko-

mic cells may express SR in sufficient density (6). However, the clinical value of  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide scintigraphy for the detection of malignant lymphoma has not been established (7). It seems possible that the method is better suited to characterize than to localize lesion sites. Therefore, our study evaluated whether the SR-expression of various malignant lymphomas may be reliably used for scintigraphic visualization by  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide and thus be of potential value for clinical management.

## METHODS

### Patients

Forty-one consecutive patients who presented to our department with either proven or suspected lymphoma were investigated by SR-specific scintigraphy. Thirty-four patients had verified Hodgkin's disease ( $n = 11$ ) or non-Hodgkin's lymphoma ( $n = 23$ ). These diagnoses had been substantiated by histological and immunohistological methods. All patients underwent computerized tomography (CT) of head, chest, abdomen and pelvis, as well as chest x-rays and some patients underwent abdominal ultrasonography. Malignant lymphomas were graded in accordance to Lukes and Butler (8) and the updated Kiel classification (9). The remaining seven patients were only suspected of presenting malignant lymphomas ( $n = 5$ ) or lymphoma recurrences ( $n = 2$ ). Seven patients had received chemotherapy and radiotherapy prior to scintigraphy. The study protocol was approved by the Ethics Committee of Karl-Franzens-University in Graz. All patients gave informed written consent.

### Scintigraphy

Planar images from anterior and posterior views (matrix 256,256; 300,000 cts/frame for neck and chest, 500,000 cts/frame for abdomen and pelvis) were recorded 4, 24 and 48 hr after intravenous administration of 10  $\mu\text{g}$  of  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide (OctreoScan<sup>®</sup>, Mallinckrodt Medical, Petten, The Netherlands) labeled with 120-150 MBq of  $^{111}\text{In}$ . For special planar abdominal recordings, lead shielding was used to reduce hepatic and lienal interference. Prior to the late 24 and 48 hr recordings, laxatives were given to reduce the background activity caused by hepatobiliary elimination of radioactivity. SPECT images (4 hr after injection; 64  $\times$  64 matrix) were recorded only in patients with negative planar scintigrams. The scintigrams were first read by two experts in nuclear medicine without knowledge of the clinical

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data. After the study, all scintigrams were re-examined and compared with clinical and radiological data, the CT images serving as a gold standard. The results of ultrasonography and x-ray served as complimentary tools.

Lymphoma-background quotients (LBQs) were computed by only one expert as follows: the gamma count within a circular region of interest (ROI) inside a lymphoma and encompassing its center of mass was divided by the lowest gamma count within a neighboring or contralateral background area of equal size.

## RESULTS

According to the physiological distribution and metabolism of somatostatin, the administration of  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide results in the accumulation of radioactivity within the thyroid, the pituitary gland, the spleen, liver, intestinal contents, kidneys and urinary bladder either due to the receptor status of target tissues or to the elimination of the radioligand. Additional radioactivity in organ-like configuration was regarded as indicative for the presence of lesions caused by SR-expressing pathologic tissue.

Table 1 shows the radiologic and scintigraphic results of our patients with Hodgkin's disease (HD). Three of them had recurrences after previous treatment. Taking into account the number of lesion sites correctly identified, the sensitivity of the SR-scintigraphy demonstrated striking differences within different parts of the body. It rose from 78% (7/9) within the neck region to 94% (15/16) within the chest and dropped to 17% (1/6) within the abdomen and to 0 (0/2) in the pelvis. The portion of the body above the diaphragm presented a sensitivity of 88% (22/25) as compared to a combined sensitivity of 13% (1/8) for the abdomen and pelvis. The scintigraphic sensitivity of all lesions combined was 70% (23/33). Eight patients (73%) demonstrated scintigraphically detectable lesions. All three previously treated patients showed nodular sclerosing HD, one proved to be positive and two yielded false-negative results, later verified by biopsy.

The smallest supradiaphragmatic lymphoma correctly

identified by scintigraphy had a diameter of approximately 2 cm as compared to the critical size of 1 cm detectable by CT. The size of the largest missed lymphoma, situated within the abdomen, was  $7 \times 4$  cm. Figure 1 shows the 4-hr planar chest scintigram of Patient 5 and the corresponding x-ray. Both demonstrate a bulky infiltration within the mediastinum and a small lesion within the right supraclavicular region. Only scintigraphy shows an additional faint activity over the heart which was later verified by CT as a pericardial infiltration.

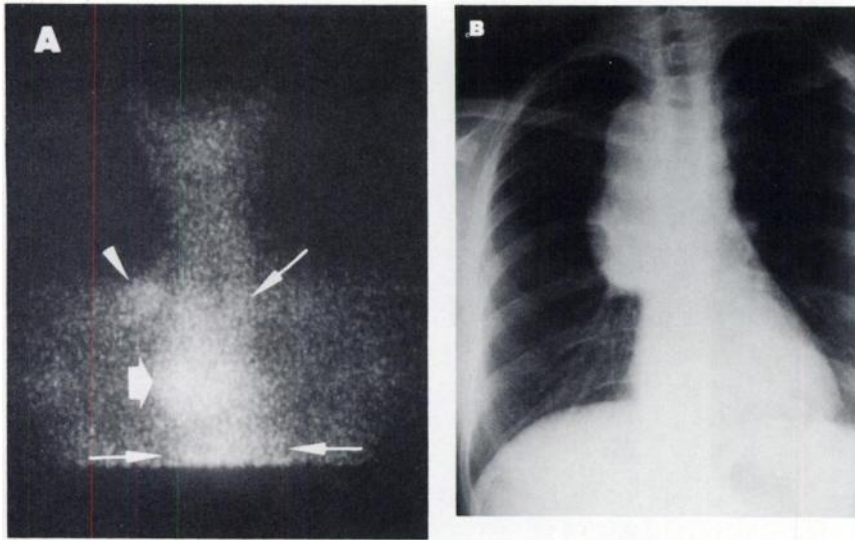
Our 23 patients with non-Hodgkin's lymphoma are summarized in Table 2. Two of them had recurrences after previous treatment. In general, the sensitivity of the SR-scintigraphy was lower than in HD, but did not vary considerably between different parts of the body. As far as the number of lesion sites is concerned, the sensitivity varied from 11% (1/9) within the neck region to 45% (9/20) in the chest and dropped to 36% (9/25) within the abdomen and to 25% (1/4) in the pelvis. The neck and thorax together presented the same sensitivity of 35% (10/29) as the lower half of the body. Of the 23 patients, 13 (57%) demonstrated scintigraphically detectable lesions. Six of ten patients (60%) with high-grade malignant lymphoma and seven of twelve (58%) with lymphoma of low-grade malignancy were positive by scintigraphy. Comparing the number of lesion sites, 44% of highly malignant lymphomas (10/23) versus 29% of lymphomas with low-grade malignancy (10/35) were detected by scintigraphy. In one case, the degree of malignancy was not determined histologically. Of the two previously treated patients, only the one presenting lymphoma of low-grade malignancy yielded a partly positive result.

The smallest lymphoma in non-Hodgkin's lymphoma patients correctly located within the thorax by scintigraphy had a diameter of approximately 2 cm. The largest non-visualized lesions were pathologic lymph nodes occupying an abdominal area measuring  $8 \times 5$  cm. Bone marrow

**TABLE 1**  
Patients with Verified Hodgkin's Disease

Patient no.	Age (yr)	Type	Pretreatment	Neck		Thorax		Abdomen		Pelvis		Result
				R	S	R	S	R	S	R	S	
1	73	nod. scleros.	-	2	2							pos
2	49	nod. scleros.	-	1	1							pos
3	54	nod. scleros.	-	1	0							neg
4	34	nod. scleros.	+			2	2					pos
5	33	nod. scleros.	-			3	3					pos
6	40	mixed cell.	-	2	2	3	3					pos
7	22	nod. scleros.	+			1	0	1	0			neg
8	19	nod. scleros.	-	2	2	3	3	1	1			pos
9	23	nod. scleros.	-			3	3	1	0			p. pos
10	64	mixed cell.	-	1	0	1	1	2	0	1	0	p. pos
11	32	nod. scleros.	+					1	0	1	0	neg

R = number of sites found positive by radiology (CT supplemented by chest x-ray and abdominal ultrasonography); S = number of sites found positive by SR scintigraphy; and p.pos = partly positive.



**FIGURE 1.** Thorax of Patient 5. (A) 4-hr scintigram shows pericardial infiltration (arrows), bulky mediastinal disease (bold arrow) and a right supraclavicular lymph node (arrow-head). (B) Corresponding x-ray with mediastinal mass.

infiltrations with up to 90% malignant cells were also not identified by scintigraphy.

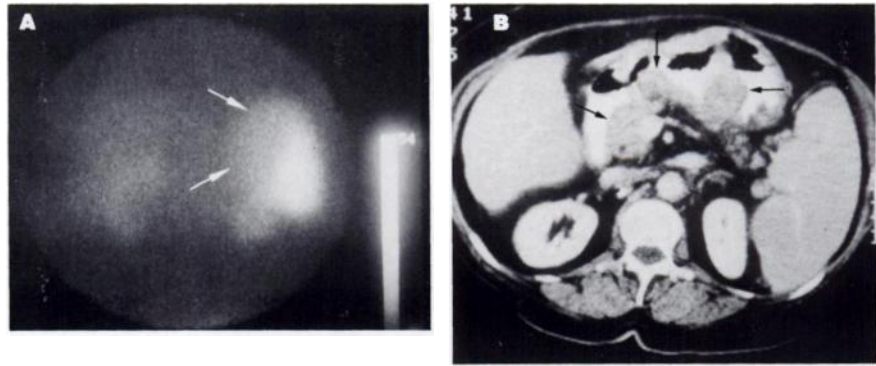
Figure 2 shows the abdomen of Patient 20. The scintigram demonstrates splenomegaly with enhanced octreotide uptake and medially another faint activity which the corresponding CT confirmed as a polypoid infiltration of the posterior gastric wall.

Data on the remaining seven patients are represented in Table 3. Two patients were suspected to have recurrences of lymphoma and yielded two true-negative scintigraphic results. The suspected lesions were later verified as scar tissue by histology. Of the five remaining patients suspected to have lymphoma, three demonstrated scintigraphically detectable SRs expressed by blastcells of CML, sar-

**TABLE 2**  
Patients Presenting with Verified Non-Hodgkin's Lymphoma

Patient no.	Age (yr)	Type	Pretreatment	Neck		Thorax		Abdomen		Pelvis		Result
				R	S	R	S	R	S	R	S	
12	66	hm	-	1	1							pos
13	45	hm	-	1	0							neg
14	62	hm	-	2	0	1	0					neg
15	61	lm	-			2	2					pos
16	79	hm	-			2	2					pos
17	73	hm	-			3	3					pos
18	61	hm	-			1	1					pos
19	59	lm	+			1	1	1	0			p. pos
20	73	hm	-			2	0	2	2			p. pos
21	58	lm	-			1	0	2	1			p. pos
22	67	lm	-			1	0	2	0			neg
23	64	lm	-			2	0	2	0			neg
24	62	lm	-			2	0	1	0			neg
25	27	lm	-					2	0	1	0	neg
26	43	hm	-					1	1			pos
27	58	lm	-					3	2			p. pos
28	28	lm	-	1	0	1	0	1	0	1	0	neg
29	51	lm	-					3	1	1	1	p. pos
30	80	?	-	2	0			3	0			neg
31	67	lm	-	2	0			1	1			p. pos
32	84	lm	-					1	1			pos
33	64	hm	-			1	0					neg
34	72	hm	+							1	0	neg

R = number of sites found positive by radiology (CT supplemented by chest x-ray and abdominal ultrasonography); S = number of sites found positive by SR scintigraphy; lm = low-grade malignancy; hm = high-grade malignancy; and ? = unclassified.



**FIGURE 2.** Abdomen of Patient 20. (A) 4-hr scintigram shows the faint uptake in the liver, intensive uptake in the spleen and activity in the area corresponding to the gastric wall (arrow). (B) Corresponding CT. Arrow points to polypoid configuration of posterior gastric wall.

coid and tuberculosis. One patient with sarcoidosis had a false-negative result and the patient with Castleman's disease had a negative result.

Figure 3 shows a chest scan of Patient 40 who was initially suspected of having lymphoma which finally was verified as tuberculosis. The scintigram displays a distinct uptake of the radioligand on the right of the median plane caused by lymph nodes as demonstrated by the corresponding x-ray. The LBQ of these lymph nodes increased from 2.4 after 4 hr to 3.8 after 24 hr and fell again to 3.1 after 48 hr. In contrast, the LBQs in HD and non-Hodgkin's lymphoma did not vary with time. The mean values  $\pm$  s.d. ( $n = 10$ ) were  $2.6 \pm 1.2$  (4 hr),  $2.0 \pm 0.7$  (24 hr), and  $2.1 \pm 0.5$  (48 hr). Spleens accumulated the radioligand in a variable fashion depending on size as shown by the respective 4-hr LBQs:  $4.1 \pm 1.6$  (normal size;  $n = 22$ ) as compared to  $7.3 \pm 2.5$  (splenomegaly;  $n = 6$ ;  $p < 0.001$ ). However, three spleens of normal size yielded LBQ values similar to those in patients with splenomegaly ( $7.7 \pm 1.4$ ).

SPECT ( $n = 15$ ) was performed on patients with negative planar scintigrams in an attempt to acquire additional information, but failed to reveal additional lesion sites.

After these results had been recorded, all scintigrams were re-examined with knowledge of the patients' clinical data. Only one additional lesion site was detected in the abdomen of Patient 9.

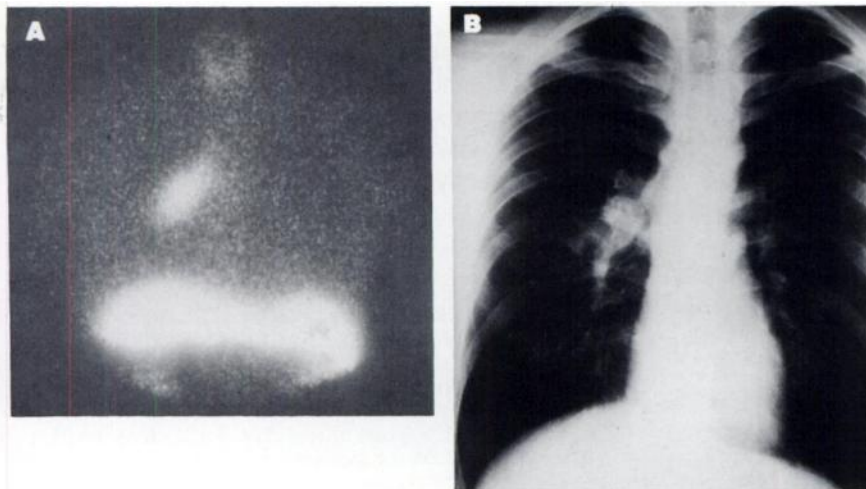
## DISCUSSION

Our prospective study of 41 consecutive patients with proven or suspected lymphoma intended to evaluate as a controlled blind investigation the diagnostic potential of  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide scintigraphy for routine visualization of somatostatin receptors expressed by lymphomas of various types. The method is known to be specific for this type of membrane receptor (6,10). With regard to somatostatin receptors, the study yielded no false-positive results. Of course this scintigraphic method cannot differentiate whether receptor expression is due to lymphoma or lymphadenopathy in granulomatous diseases. The critical size required for positive lymph node detection was about 2 cm. Such lymph nodes were more frequently determined within the neck region and thorax than within the abdomen and pelvis. Many of the infradiaphragmatic lesions were missed probably due to the physiological accumulation of the labeled octreotide by liver and spleen, as well as its elimination via bile and kidneys. These background activities considerably hamper the identification of smaller targets within the respective area. The sensitivity for HD reflects this circumstance and varied from 88% (supradiaphragmatic) to 13% (infradiaphragmatic) when the number of lesions detected by CT is taken into account. Comparable local differences in sensitivity have been recently reported (11).

**TABLE 3**  
Patients with Suspected Lymphoma or Lymphoma Recurrence

Patient no.	Age (yr)	Type	Pretreatment	Neck		Thorax		Abdomen		Pelvis		Result
				R	S	R	S	R	S	R	S	
35	38	Scar tissue	+					1	0			neg
36	35	Scar tissue	+			1	0					neg
37	67	CML	-	4	4	2	2	1	1			pos
38	49	Sarcoidosis	-			1	0	1	0	1	0	neg
39	34	Sarcoidosis	-			1	1					pos
40	23	Tuberculosis	-			1	1					pos
41	73	Castleman's disease	-	1	0							neg

R = number of sites found positive by radiology (CT supplemented by chest x-ray and abdominal ultrasonography); and S = number of sites found positive by SR scintigraphy.



**FIGURE 3.** Thorax of Patient 40. (A) 4-hr scintigram shows activity in lymph nodes in the right hilar region. (B) Corresponding x-ray with right hilar adenopathy.

The lesion-related sensitivity for non-Hodgkin's lymphoma was distinctly lower than that for HD. It amounted to 35% regardless of the localization of lesions. Local differences were less prominent probably because enlarged and hyperactive spleens were frequently encountered. However, three patients presented spleens of normal size but with LBQ values elevated to the LBQ range of splenomegaly. Without additional relevant data (CT, ultrasonography), increased LBQ values alone do not justify a diagnosis of splenomegaly. The hyperactive spleen seems to remove a major portion of the circulating radioligand, thus leaving a concentration of octreotide too low for visualization of smaller peripheral pathologic lymph nodes. The sensitivity for non-Hodgkin's lymphoma was distinctly influenced by histologic status. Lymphomas of high-grade malignancy showed a sensitivity of 44% as compared to 29% related to lymphomas of low-grade malignancy. It seems that lymphomas of high-grade malignancy tend to express a higher density of SR which has also been autoradiographically demonstrated by Reubi et al. (6). Bone marrow infiltrations with malignant cells of up to 90% were not visualized by SR scintigraphy. This might be due to densities and/or affinities of SR too low for distinct visualization. The same properties of receptors may also be responsible for the failure to detect even larger targets of up to 8 cm as was the case in our patients with non-Hodgkin's lymphoma.

Higher sensitivities for both HD and non-Hodgkin's lymphoma up to 100% have been reported (6,11,12). In our study,  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide scintigraphy of HD within the chest reached a sensitivity of 94% and dropped significantly within the infradiaphragmatic region. The sensitivity for non-Hodgkin's lymphoma was distinctly lower and differentiated between lesions of high and low-grade malignancy.

Five patients initially suspected of presenting lymphoma were later verified to present various lymphadenopathies. Three of them expressed SRs in a sufficient density and/or affinity to yield positive scintigrams. Thus, it must be em-

phasized that this scintigraphic method does not obviate the need for a histological diagnosis as is customary in the clinical workup of patients with lymphoma or lymphadenopathy.

We mainly evaluated planar images 4, 24 and 48 hr after intravenous injection. The LBQs computed for both lymphoma types did not increase with time. The target-to-background contrast tended to decrease thus indicating an early saturation of SR parallel to a rapid clearance of the radioligand. Therefore, the 48-hr images can be omitted without loss of information.

SPECT images were only performed in patients with negative planar results. In our study, SPECT never changed an apparently negative SR status of a patient into a positive SR status, and did not increase the patient-related sensitivity of the method. SPECT was therefore discontinued after 15 negative recordings because the additional acquisition time (~60 min per body area) interfered with the patients' schedule and was not practical in a clinical setting. For the same reason, SPECT recordings after positive planar imagings were also omitted because of the possible increase in sensitivity is known to be quite limited. Similarly, a second review of all scintigrams with knowledge of the lesion sites detected by other imaging modalities (CT as gold standard complemented by x-ray and sonography) did not substantially improve the sensitivity of octreotide scintigraphy.

In the literature,  $^{67}\text{Ga}$  scans, nonspecific scintigraphy and immunoscintigraphy have been reported as also being useful for imaging HD and non-Hodgkin's lymphoma lesions. However, each method seems to have certain limitations with regard to sensitivity and specificity, which is important to consider when the appropriate agent for the detection of specific lymphoma types is determined. Gallium-67 scintigraphy has been reported as a suitable imaging method for HD and non-Hodgkin's lymphoma with a sensitivity of up to 85% and a specificity of up to 98% prior to treatment (13), but it takes at least 48 hr before imaging can commence. The radiopharmaceutical has been found to be

useful for monitoring response to treatment, especially in differentiating between residual masses consisting of still viable tumor or scar tissue although benign uptake also seems to be possible. Gallium-67 is taken up especially by HD and intermediate-grade non-Hodgkin's lymphoma while  $^{201}\text{Tl}$  is thought to be highly avid for low-grade non-Hodgkin's lymphoma (14,15). However, there is no conclusive evidence for the tumor specificity of both radiopharmaceuticals and, in addition, their physiological distribution and elimination patterns may hamper the detection of lesion sites. Therefore, a careful objective evaluation of the difference in uptake between  $^{67}\text{Ga}$  and  $^{201}\text{Tl}$  in lymphoma and in nontumor tissue seems to be still necessary (16). Several immunoconjugates have been proposed for lymphoma detection. Immunoscintigraphy with a  $^{99\text{m}}\text{Tc}$ -labeled Fab' fragment against B cells showed a sensitivity of 60% for non-Hodgkin's lymphoma sites in eight patients, the sensitivity being influenced by the mass of tumor tissue present (17). A HRS-3 Hodgkin-associated Mab labeled with  $^{131}\text{I}$  detected nodal, bone marrow, splenic and muscle HD lesions with a sensitivity of 87% in 16 patients (18). An  $^{111}\text{In}$ -labeled Mab directed against eosinophil peroxidase localized specifically HD and non-Hodgkin's lymphoma lesions infiltrated by eosinophils (19). This immunoconjugate demonstrated a sensitivity similar to that of  $^{67}\text{Ga}$  but proved to be superior in detecting tumor masses with eosinophilia below the diaphragm, particularly in the spleen and bone marrow. Scintigraphy with suitably labeled immunoconjugates offers the advantage of same-day imaging but may be hampered by HAMA response especially after multiple Mab applications.

In comparison,  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide scintigraphy demonstrated higher sensitivity for HD, especially within the neck and thorax than in the lower half of the body. The sensitivity for non-Hodgkin's lymphoma was generally lower depending on the grade of malignancy. This method seems to be able to specifically characterize lymphoma tissue as expressing somatostatin receptors. Therefore,  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide scintigraphy should be valuable for monitoring changes in SR expression due to therapy when the octreotide avidity of the tumor has been ascertained prior to treatment. Like  $^{67}\text{Ga}$ , but unlike CT,  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide scintigraphy also differentiates between residual masses consisting of viable tumor due to SR expression and masses consisting of fibrous or necrotic scar tissue. As preliminary trials have shown, an improvement of the method's sensitivity could be achieved by doubling the applied amount of  $^{111}\text{In}$ -DTPA-D-Phe-1-octreotide and using double-head camera systems in order to increase lesion-to-background contrast and to shorten recording times. A further improvement of sensitivity seems possible when the ligand uptake by abdominal organs is reduced. A marked decrease of lienal

uptake and a less effected hepatic uptake has been reported after application of unlabeled octreotide prior to scintigraphy (20). The limited availability of  $^{111}\text{In}$  is a further handicap for this method. Its substitution by  $^{99\text{m}}\text{Tc}$  would assure same-day images, an advantage in case of urgent pretreatment scintigraphy.

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