

# A Comparison of Two Technetium-99m-Labeled Radiopharmaceuticals for Lymphoscintigraphy: Concise Communication

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*A comparison of stannous phytate and antimony sulfide colloid, both labeled with Tc-99m, was conducted during the performance of internal mammary lymphoscintigraphy in 46 patients. Thirteen of these patients were randomized to receive both radiotracers in two consecutive studies. The results indicated a statistical difference between agents; Tc-99m antimony sulfide allowed visualization of a greater number of more intense nodes, better delineation of the total length of the internal mammary lymph-node chain, and a more consistent visualization of supraclavicular nodes. Although previously published animal data suggest utility of Tc-99m stannous phytate for lymph-node imaging, Tc-99m antimony sulfide was shown in this clinical comparison to provide a more reliable representation of lymph-node anatomy.*

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Interstitial injections of radioparticulates have allowed the visualization of lymph-node groups not previously demonstrable by routine techniques (1). Critical in the choice of agents for these procedures is the size of the particles; this parameter has been shown to affect both the biological behavior of the tracer and the ultimate quality of the diagnostic study (2). Although gold-198 colloid (5-10 nm) has allowed nodal visualization (3,4), the increased photon flux attained with technetium-99m, along with the absence of unwanted beta radiation, has generated significant interest in the development of a highly effective Tc-99m labeled colloid (5-7). Tc-99m sulfur colloid, with a mean particle size of 300 nm, has provided variable lymphoscintigraphic results (1,6).

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Investigations in our laboratory, using Tc-99m stannous phytate (8) for the quantitation of ascitic fluid volumes, indicated that in the absence of malignant ascites, intraperitoneally administered tracer readily traversed the diaphragm to allow visualization of intrathoracic lymph nodes (9). A recent animal study using this radiocolloid corroborated our initial impressions and also suggested the potential clinical utility of Tc-99m (Sn) phytate for lymphoscintigraphy (10).

Tc-99m antimony sulfide (Tc-Sb<sub>2</sub>S<sub>3</sub>) colloid (11) has undergone extensive clinical evaluation in over 2,000 patients (12) and has been the agent in use at our institution for identification of the internal mammary nodes before radiation therapy (13). However, the cited recent experiences with Tc-99m-Sn-phytate, coupled with the more time-consuming preparation of Tc-Sb<sub>2</sub>S<sub>3</sub>, indicated the need for a comparison of radiopharmaceutical agents in a clinical setting.

**TABLE 1. STUDY DESIGN FOR THE CLINICAL EVALUATION OF Tc-99m-Sn-PHYTATE AND Tc-99m-Sb<sub>2</sub>S<sub>3</sub>**

Agent	Group	Injection order	No. of patients
Phytate	A	phytate only	10
	B	phytate/antimony	6
	C	phytate*/antimony	4
Antimony	D	antimony only	12
	E	antimony/phytate	7
	F	antimony/phytate*	7
TOTAL			46

\* Diluted or concentrated phytate.

#### MATERIALS AND METHODS

Forty-six patients with carcinoma of the breast referred to the Sidney Farber Cancer Institute for location of internal mammary lymph nodes were examined (Table 1). Tc-99m (Sn) phytate\* and Tc-Sb<sub>2</sub>S<sub>3</sub>† were the colloidal preparations used. Injected volumes ranged from 0.2 to 1.0 ml for the phytate and 0.2 to 0.5 ml for the Tc-Sb<sub>2</sub>S<sub>3</sub>. The amount of radioactivity associated with both colloids ranged from 0.5 to 1.2 mCi per injection site. When both agents were to be compared in the same patient, similar amounts of radioactivity were administered.

Of the 46 patients studied, 13 were randomized to receive either Tc-Sb<sub>2</sub>S<sub>3</sub> or phytate as the first of two radiotracers (Table 1, Groups B and E). Following the technique of Ege (1), the subcostal injection of radiocolloid was administered at a point approximately 3.0 cm below the xiphisternum and medial to the mid-clavicular line. With the syringe held at an angle of 45° to the horizontal plane, an injection to a depth of 2.0 to 2.5 cm was made. This deposited the tracer just anterior to the posterior rectus sheath. The side involved by tumor was injected initially. Three hours later, 100,000-count gamma camera scintiphotos were obtained using a low-energy all-purpose collimator‡. Images of the nodes were obtained in the anterior position. After a minimum delay of 24 hr, patients were injected with the second agent, still on the tumor-involved side, and reimaged 3 hr later as on the first day. In a subset of 11 patients (Table 1, Groups C and F) before the addition of Tc-99m to the reconstituted phytate preparations, the kits were either diluted (1:10, 1:20, 1:50) or concentrated (2–5 times) to evaluate a potential alteration of in-vivo colloid formation. Twenty-two patients (Table 1, Groups A

**TABLE 2. NUMBER OF UNILATERAL NODES VISUALIZED WITH Tc-99m-Sn-PHYTATE AND Tc-99m Sb<sub>2</sub>S<sub>3</sub>**

Agent	No. of patients	Patient group	No. nodes	$\bar{X}$ *	s.d.†
Phytate	16	A, B	57	3.6	1.86
Antimony	26	D, E, F	192	7.4	2.67

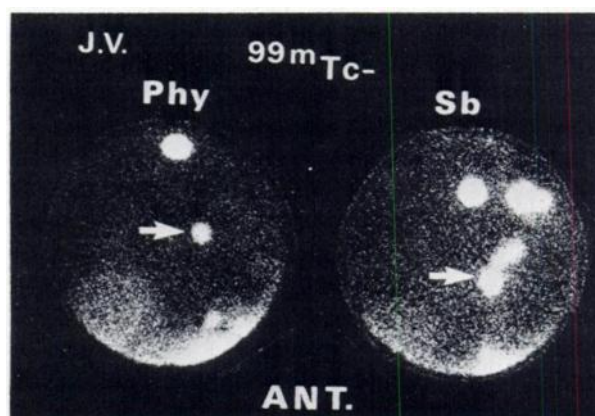
\*  $\bar{X}$  = mean.  
† s.d. = standard deviation.

and D) were imaged with only one agent, 10 with phytate and 12 with Tc-Sb<sub>2</sub>S<sub>3</sub>.

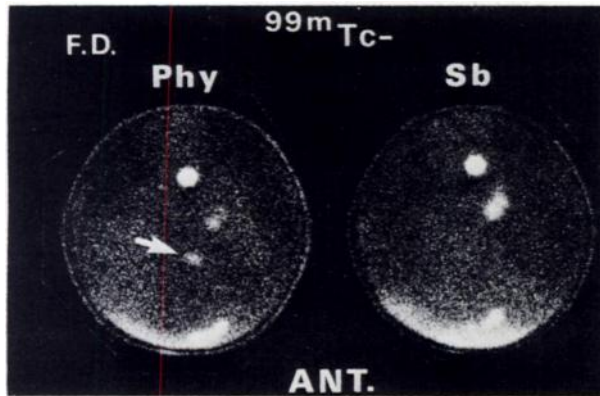
Visualized nodes were identified with reference to interspace and rib location and their distance in centimeters inferior to the sternal notch and lateral to the midline were measured. Following anatomic mapping, nodes were visually graded as to relative brightness on a scale of 1+ (barely perceptible) to 3+ (representing an intensity approximating that of a cobalt marker placed at the sternal notch). Before either unilateral or bilateral lymphoscintigraphic studies, no therapeutic manipulations were performed in any patient.

#### RESULTS

A comparison of the 16 patients receiving a standard preparation of phytate (prepared according to the manufacturer's instructions) (Table 1, Groups A and B) with the 26 patients who received Tc-Sb<sub>2</sub>S<sub>3</sub> (Table 1, Groups D, E, and F) revealed that the mean number of nodes unilaterally visualized by phytate was 3.6 per patient (Table 2). More than twice that number of nodes, 7.4, were seen when



**FIG. 1.** Anterior view of internal mammary lymphatics using Tc-99m (Sn) phytate (left) shows single node (arrow) midway between sternal notch marker and diaphragm. On right, when using Tc-99m Sb<sub>2</sub>S<sub>3</sub>, node is again seen (arrow); however, four additional superiorly positioned nodes are identified.



**FIG. 2.** Anterior view of internal mammary lymphatics with Tc-99m-Sn-phytate (left) allows identification of node (arrow) not seen when patient was studied following injection with Tc-99m-Sb<sub>2</sub>S<sub>3</sub> (right). Note, however, that nodes visualized in scintiphoto on right are much more intense than when imaged with phytate.

Tc-Sb<sub>2</sub>S<sub>3</sub> was used ( $p < 0.01$ ). In those patients given both agents, rarely did phytate reveal a node not seen with Tc-Sb<sub>2</sub>S<sub>3</sub> (Figs. 1 and 2).

A significantly greater number ( $p < 0.05$ ) of more intense nodes—that is, those graded +++ and ++—were seen with Tc-Sb<sub>2</sub>S<sub>3</sub> than with phytate (Table 3). Also, nodes in the supraclavicular area and first and second interspaces were more frequently delineated by Tc-Sb<sub>2</sub>S<sub>3</sub> (Table 4). Neither radiocolloid produced images that suggested any relationship between lymph-node location and relative intensity.

The results from those randomly selected 13 patients (Table 1, Groups B and E) sequentially injected with both phytate and Tc-Sb<sub>2</sub>S<sub>3</sub>, are included in Table 5. The order of radiocolloid administration had no influence on the number, intensity, or anatomic level of lymph nodes visualized. Again, Tc-Sb<sub>2</sub>S<sub>3</sub> produced superior images in all respects.

Varying the concentration of phytate before the addition of Tc-99m (Table 1, Groups C and F) showed some advantage for the diluted material over unaltered phytate preparations. Although the diluted solutions of phytate tended to produce im-

**TABLE 3. CORRELATION BETWEEN LYMPHOSCINTIGRAPHIC AGENT AND SCINTIPHOTO INTENSITY OF NODES**

Agent	No. of patients	Patient group	No. observed nodes	Node intensity*		
				+++	++	+
Phytate	16	A, B	57	39	26	35
Antimony	26	D, E, F	192	47	30	23

\* +++ > ++ > +; + = barely perceptible; +++ = intensity approximating that of sternal notch cobalt marker; ++ = intensity midway between + and +++.

ages that approached Tc-Sb<sub>2</sub>S<sub>3</sub> in the number of nodes visualized, the alterations in concentration in general did not produce the image quality seen with Tc-Sb<sub>2</sub>S<sub>3</sub> with respect to intensity or radiocolloid migration to upper-rib and interspace levels.

#### DISCUSSION

The design of this study allowed a direct comparison between agents, since identical lymph nodes on the tumor side were sequentially evaluated; thus a potential interpretive error due to asymmetric lymph-node chains was eliminated. Also, the injection sequence was randomized in an effort to obviate any potential for either the "filling up" of phagocytic sites and thus the depression of nodal uptake with a second injection, or the potential for the stimulation of reticuloendothelial phagocytic activity by an initial particulate injection that could thereby enhance nodal uptake of a second radiocolloid injection (1,14). If such phenomena exist, they are not perceptible with our imaging techniques.

Although the particle size of colloidal antimony sulfide has been documented by electron microscopy (2), colloidal stannous phytate escapes precise sizing by this technique since it is only upon administration to the patient that the radiopharmaceutical becomes insoluble. Since the Tc-99m-Sn-phytate forms a colloid by reacting with ionic calcium, it is theoretically possible that the continually

**TABLE 4. CORRELATION BETWEEN LYMPHOSCINTIGRAPHIC AGENT AND ANATOMIC LEVEL OF VISUALIZED NODES AT 3 HR**

	No. observed nodes	Patient group	Rib/interspace (%)						
			Xip*	5	4	3	2	1	S.C.†
Phytate	57	A, B	28	12	16	9	19	16	0
Antimony	192	D, E, F	11	11	7	19	24	18	9

\* xip = xiphoid.

† S.C. = supraclavicular.

**TABLE 5. LYMPHOSCINTIGRAPHY RESULTS CORRELATED WITH INJECTION ORDER IN 13 PATIENTS RANDOMLY STUDIED WITH Tc-99m-Sn-PHYTATE AND Tc-99m-Sb<sub>2</sub>S<sub>3</sub>**

Group	Injection order	No. of observed nodes	Node intensity (%)			Rib interspace (%)						
			+++	++	+	Xip	5	4	3	2	1	S.C.
B	1. Phytate	28	29	25	46	25	4	14	7	29	21	0
	2. Antimony	38	37	34	29	16	0	5	3	29	29	18
E	1. Antimony	51	55	27	18	17	0	8	12	22	25	16
	2. Phytate	31	19	23	58	13	3	13	16	26	23	6

available interstitial calcium concentration leads to a radiocolloid particle larger than that desired for lymphoscintigraphy. Attempts to prepare a preformed phytate colloid of small particle size in vitro by the addition of calcium and stabilizer were unsuccessful.

Neither a 1:10 to 1:50 dilution of phytate, which decreases the probability of large-particle formation in vivo, nor a two- to fivefold increase in the concentration of available phytate, potentially producing more abundant colloid formation, showed a difference in scintiscan images. These findings suggest that although the variability in nodal uptake with phytate may be associated with particle size, another yet unidentified parameter may also be of importance.

The data on radiocolloid migration as assessed by the anatomic level of visualized nodes (Table 4) is important since it reflects the propensity for Tc-Sb<sub>2</sub>S<sub>3</sub> to allow definition of the full extent of a nodal chain. This suggests a potential for clinical utility for this agent in the evaluation of nodes that are distant from the injection site. Colloids of a larger size have been shown to remain primarily at the site of interstitial administration, evidencing little tendency for lymphatic migration (6).

Our clinical experiences indicate that Tc-Sb<sub>2</sub>S<sub>3</sub> is currently the radiocolloid of choice for lymphoscintigraphy. Animal models did suggest that phytate was a potentially useful agent (9,10), and sporadic clinical experiences indicated that phytate could approximate the scintiphotos obtained with Tc-Sb<sub>2</sub>S<sub>3</sub> in some patients. However, when compared with Tc-Sb<sub>2</sub>S<sub>3</sub>, the variability encountered with phytate in terms of number and relative intensity of visualized nodes, as well as the lack of visualization of total extent of a nodal chain, support the use of Tc-Sb<sub>2</sub>S<sub>3</sub> for radionuclide lymphoscintigraphy.

#### ADDENDUM

Since the submission of this paper, a similar clinical experience has been reported by Ege (15). Although fewer patients were investigated in that

study, the results support our findings.

#### FOOTNOTES

- \* New England Nuclear Corp., North Billerica, MA.
- † Kindly supplied by G. N. Ege and A. Warbick-Cerone, Dept. of Nuclear Medicine, The Princess Margaret Hospital, Toronto, Ontario, Canada.
- ‡ LEM, Searle Radiographics, Inc., Des Plaines IL.

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