Prognostic Value of Axillary Lymphoscintigraphy in Breast Carcinoma Patients

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Axillary lymphoscintigraphy (AxLS) with bilateral interdigital injection of [^{99m}Tc]antimony sulfide colloid carried out concurrently with internal mammary lymphoscintigraphy in 488 patients with breast carcinoma was evaluated. Patterns of radiocolloid distribution within the ipsilateral axilla and supraclavicular fossa were compared with similar features on the contralateral side to determine whether image characteristics (a) are significantly disrupted by prior surgery, (b) reflect the presence of metastases, and (c) can predict treatment failure. Interpretive criteria for AxLS were refined after correlation of the identified image components with clinical parameters including axillary surgery, lymph node histology and relapse within a follow-up period of 2 years from the study. Results indicate that AxLS is at least as accurate as clinical assessment and provides data predictive of relapse to complement axillary lymph node status although the technique cannot presently replace lymph node sampling for patient staging.

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Since its introduction into limited clinical application in the 1970s, axillary lymphoscintigraphy has had a checkered course, being alternately supported and disclaimed in roles as varied as diagnosis of a breast lump, assessment of axillary involvement and determination of completeness of axillary clearance (*1–11*). Radiopharmaceuticals, injection techniques and scan interpretations have varied and studies have suffered from inadequate histologic correlation, small patient populations, and short follow-up periods. It is therefore not surprising that results have been conflicting and its use in clinical management of patients with carcinoma of the breast has not been defined. Since recent studies suggest that in such patients, treatment of the axilla does little to alter ultimate outcome (*12,13*), a test that could reduce the need for surgical sampling of the axilla and yet offer prognostic information appears very attractive.

In order to address this issue, we have carried out a retrospective analysis of results of axillary lymphoscintigraphy performed in a population of patients with predominantly early stage breast carcinoma to determine the usefulness of the technique and to refine criteria for scan interpretation.

MATERIALS AND METHODS

Between September 1980 and June 1983, axillary lymphoscintigraphy (AxLS) was performed on 488 patients with breast carcinoma and the results were correlated with clinical and pathologic findings. Diverse patient groups were deliberately included in the study to evaluate the appearances, information content, and potential performance of AxLS under varying clinical circumstances. The 488 patients comprised 417 who were being managed with curative intent, 41 with incurable disease at diagnosis, and 30 with local or regional recurrence.

Two patient subsets were analyzed separately. The group of 62 patients with various disease stages who underwent scanning before axillary surgery (designated Pre-Sx) was used to determine the place of AxLS in predicting lymph node metastases pre-operatively. Clinical findings at the time of the study and the status of 345 patients with primary disease or controlled recurrence at a minimum period of 2 years formed the basis for assessing the value of AxLS in predicting disease relapse.

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TABLE 1
Clinical Features of 488 Patients Undergoing Axillary Lymphoscintigraphy (AxLS)

Patient category	Number	Mean age (range)	Operation* %						Stage† %				2 yr F/U	% Recurred
			Bx	PM	SM	PM + AX	SM + AX	MRM	I	II	III	IV		
Primary disease														
Axillary surgery (AxSx)	223	52.6 (23–81)				43	5	52	37	46	14	3	184	36.4
No axillary surgery (No AxSx)	194	60.1 (28–85)		95	5				55	40	4	1	140	33.6
Advanced primary disease	41	55.7 (17–79)	63	10				27				100	NA	NA
Local/regional recurrence	30	58.6 (32–84)	100							NA			21	80.9
Total	488	56.6											345	

* Bx = Biopsy/excision; PM = Partial mastectomy; SM = Simple mastectomy; MRM = Modified radical mastectomy; AX = Axillary surgery; NA = Not applicable.
† Pathological = Axillary surgery; Clinical = No axillary surgery; Stage IV = Local skin involvement; Distant metastases.

In order to study the effect of recent axillary surgery on scan interpretation, it was possible to select from this group, 140 patients who did not have axillary surgery (designated Group I) to compare with 147 patients who had axillary surgery prior to scanning (Group II). Additionally, those patients scanned at the time of first recurrence and followed up for 2 years (Group III) were studied to evaluate the possible role of AxLS in determining management. Clinical details are summarized in Table 1.

AxLS was performed by alternating bilateral interdigital subcutaneous injections of 20 MBq of technetium-99m antimony sulfide colloid ([^{99m}Tc]Sb_2S_3). Anterior images of the chest and axillae were obtained 2½–3 hr later using a large field-of-view gamma camera†. Internal mammary lymphoscintigraphy (IMLS) was performed concurrently using standard techniques described elsewhere (*14*).

As in IMLS, there is great variation in normal axillary anatomy and lymphoscintigraphy. Since criteria for interpreting AxLS have not been well established, those used in interpretation of IMLS were adapted as follows: the number of discrete foci in each axilla was recorded and symmetry of radiocolloid uptake and foci number were graded. If uptake or foci number on the ipsilateral side were greater than or similar to that on the contralateral side, the scan feature was considered equivalent (A). If uptake or foci number were less, the feature was considered mildly (B), moderately (C), or markedly (D) disparate, depending on the degree of asymmetry. Those studies considered markedly disparate showed negligible uptake or 0 to 1 foci.

The pathologic and prognostic significance of the appearance of nodes in the proximal axilla and supraclavicular region was also considered. To "quantitate" this characteristic, a line was drawn from the suprasternal notch to the lowest focus in either axilla and the lines bisected on both sides. Uptake within the proximal half of this distance on the ipsilateral side was compared with that in the corresponding contralateral area, the regions roughly corresponding to the supraclavicular fossae and upper axillae (Fig. 1). Uptake was graded as

FIGURE 1
Typical axillary lymphoscintigrams performed in conjunction with internal mammary lymphoscintigraphy. Method for determining proximal regions is shown. Note variation in number of nodes (A, B) and relation of nodes and regions with respect to skeletal structures demonstrated by preceding bone scan (C)

symmetrical (A), slightly less on the ipsilateral (B-I) or contralateral (B-C) side, or significantly less on the ipsilateral (C-I) or contralateral (C-C) side. The relative importance of these features was then determined by correlation with clinical data. Finally, an overall scan grading was attempted. This incorporated radiocolloid uptake and symmetry of foci, both used in previously reported studies and also included the new feature of "proximal regions". As the "proximal regions" seem less prone to anatomic alteration than the lower axilla, either as a normal variant or following surgery, the characteristic of "proximal region" was given greater weight. If prior surgery had been undertaken, less significance was placed on alterations in the lower axilla. The 4-point grading from definitely normal to definitely abnormal was performed as follows. Symmetry, or only mild asymmetry in one or two characteristics was considered definitely normal, moderate changes being considered probably normal or probably abnormal, depending on the extent, and only marked changes in most characteristics were considered definitely abnormal. Figure 2 illustrates some relevant features. In seven patients (1.4%), the image was of inadequate quality and the study was classified as "equivocal". These patients were excluded from analysis of follow-up data. Reporting of IMLS was performed as described elsewhere (*14*).

The questions we addressed were whether features of foci number and radiocolloid uptake within the ipsilateral axillae, when compared with the contralateral axillae (a) are disrupted by regional surgery, (b) reflect the presence of metastases, and (c) predict treatment failure.

RESULTS

Table 2 illustrates the distribution of scan results within each patient subgroup. The mean number of foci of axillary radiocolloid uptake in the different patient subgroups are shown in Table 3. The findings in the last three subgroups of patients show a slightly lower mean number of foci in the ipsilateral axillae compared with the contralateral axillae, indicating a modest effect of axillary surgery, since these figures are identical in the first two subgroups whose AxLSs were performed before any surgical disruption. While the difference between pre- and postaxillary surgical numbers of foci is <1, the average number of nodes identified in surgical specimens was 8.6 (range 0–24). Therefore, foci demonstrated by AxLS are far less than the number of nodes which constitute the axillary group of lymphatics anatomically, and axillary surgery appears to have only minor effect on the number of nodes as determined by AxLS.

Data on the "ideal" group of 62 PreSx patients who underwent AxLS before axillary surgery and tissue removal are illustrated in Fig. 3. In Fig. 3A, the numbers of ipsilateral and contralateral foci present a normal distribution confirming normal variability and the lack of perfect symmetry between ipsilateral and contralateral axillary lymphatics. Although there is a slight preponderance of positive nodes in the group demonstrating few foci, some patients with greater than average numbers of foci also had involved axillae. Figure 3B illustrates the distribution of positive nodes within each group according to overall scan interpretation, indicating that current interpretive criteria recognize the majority, but not all cases with positive nodes. Figure 3C illustrates how the different components of the interpretive criteria perform in this group of patients. Alterations in each characteristic correlate with nodal pathology but none is diagnostic by itself. While symmetry of uptake and of disposition of nodes between ipsilateral and contralateral axillae does not exclude pathology, there is an association between asymmetry and histologically proven metastases.

Figure 4 illustrates data in 140 patients (Group I) who had no axillary surgery and were followed up for

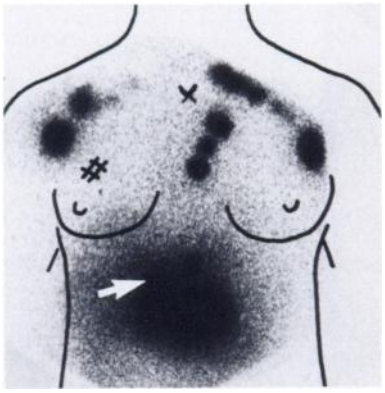

FIGURE 2
Abnormal right axillary lymphoscintigram performed preoperatively in patient with right breast carcinoma (pathology demonstrated positive nodes). Note that major abnormality is in proximal region. Right internal mammary lymphoscintigram is also abnormal; right diaphragmatic node (arrow) indicates satisfactory injection

TABLE 2
Results of AxLS in Patient Subgroups

AxLS	AxSx	No AxSx	Advanced primary disease	Local/regional recurrence	
Def nor	98 (45)*	115 (59)	7 (17)	13 (43)	
Prob nor	39 (17)	36 (19)	4 (10)	5 (17)	
Prob abn	41 (18)	26 (13)	11 (27)	4 (13)	
Def abn	41 (18)	16 (8)	17 (41)	8 (27)	
Equiv	4 (2)	1 (1)	2 (5)	0	
Totals	223	194	41	30	488

*( ) = %.

TABLE 3
Mean Number of Axillary Foci Determined by AxLS

Item	PreSx*		Prim No AxSx†		Prim AxSx Post Sx‡		Adv PostSx§		Rec PostSx¶	
	I**	C††	I	C	I	C	I	C	I	C
Patients	62		194		172		35		25	
Mean number of foci	4.5	4.7	4.8	4.7	3.9	4.7	3.2	4.3	3.6	5.1
Range	(1–9)	(1–9)	(1–9)	(1–9)	(0–8)	(1–9)	(1–6)	(3–8)	(1–10)	(3–9)

* PreSx = Patients from last three categories scanned *before* axillary surgery.
† Prim No AxSx = Scanned after breast surgery; no axillary surgery.
‡ Prim AxSx PostSx = Scanned after breast/axillary surgery for early stage primary disease.
§ Adv PostSx = Scanned after breast/axillary surgery for advanced stage primary disease.
¶ Rec Post Sx = Scanned after biopsy/excision of recurrent disease.
** I = Ipsilateral.
†† C = Contralateral.

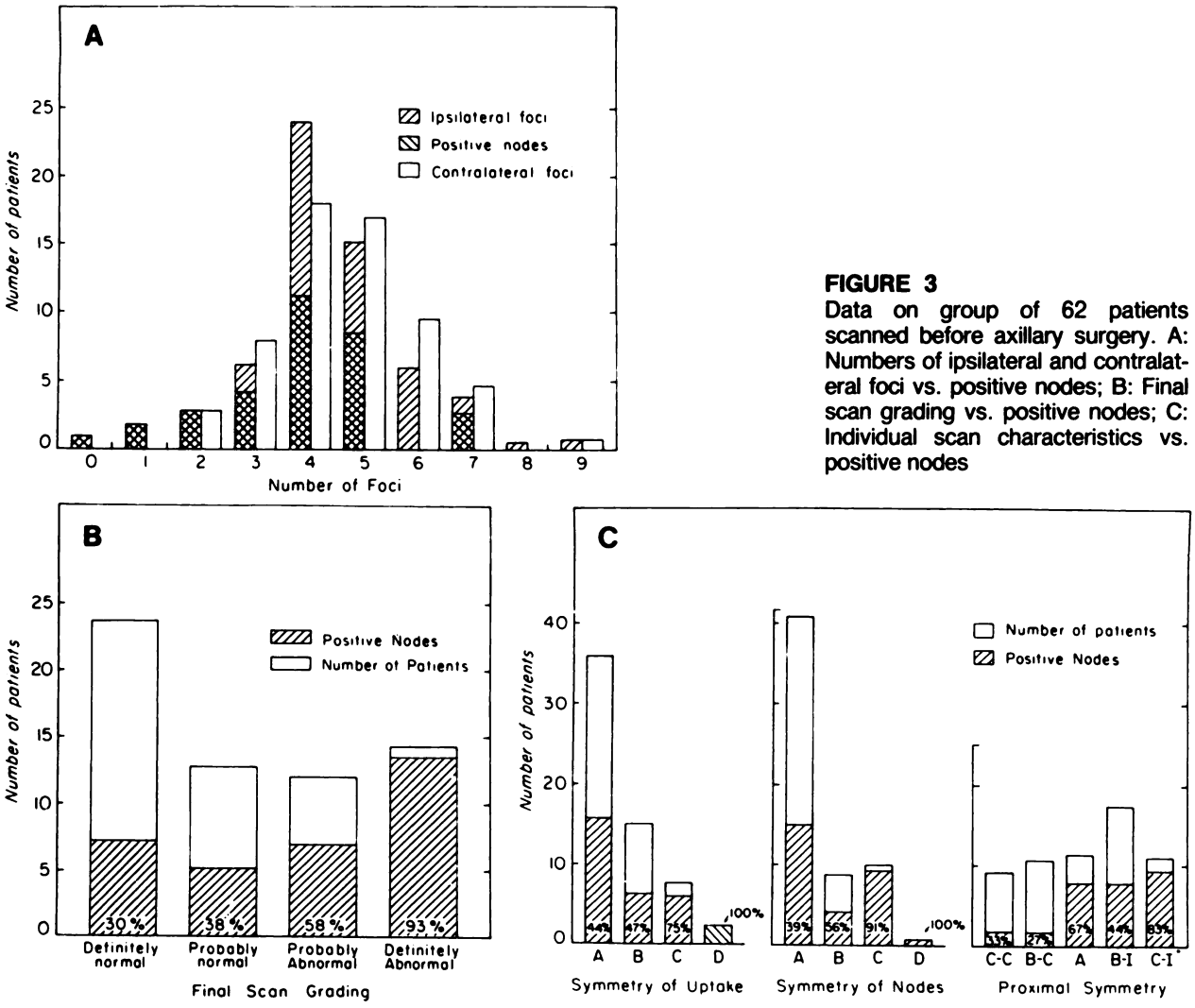

FIGURE 3
Data on group of 62 patients scanned before axillary surgery. A: Numbers of ipsilateral and contralateral foci vs. positive nodes; B: Final scan grading vs. positive nodes; C: Individual scan characteristics vs. positive nodes

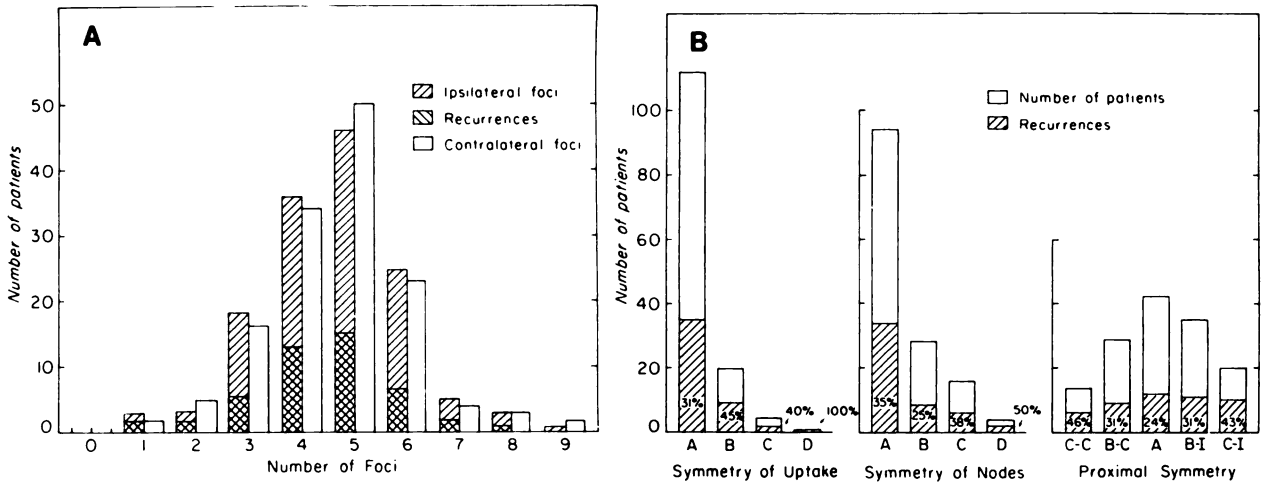

FIGURE 4
Data on group of 140 patients who did not undergo axillary surgery (Group I). A: Numbers of ipsilateral and contralateral foci vs. recurrence; B: Individual scan characteristics vs. recurrence

at least 2 years where recurrence—either local, regional, or distant—was used to evaluate the efficacy of AxLS. A normal distribution of numbers of ipsilateral and contralateral foci is demonstrated in Fig. 4A. Since patients with recurrence are distributed evenly, any feature which is predictive of recurrence does not significantly affect number of foci. In Fig. 4B, the different components of interpretive criteria are related to recurrence. Figures 5A and B illustrate similar data in 147 patients (Group II) who had axillary surgery prior to AxLS and were followed up for 2 years. As was illustrated in Table 3, mild disparity in the numbers of ipsilateral and contralateral foci attributable to surgical disruption can be discerned in the preponderance of ipsilateral axillae with fewer and contralateral axillae with more numerous foci demonstrated in Fig. 5A. There is no significant association between foci number and subsequent recurrence in this group either. In Fig. 5B, different components of interpretive criteria are related to recurrence. For Groups I and II, as with PreSx, individual characteristics are suggestive but not predictive of disease recurrence. The tendency is less strong for those scanned following surgery but still is obvious. Figure 6 illustrates the distribution of patients in Groups I and II according to overall scan interpretation with the incidence of recurrence within each interpretive category, as well as the same data in 21 patients (Group III) studied at the time of their first recurrence and followed up for 2 years.

The overall scan grading for each AxLS, when assessed against pathologic nodal status for the PreSx group (Fig. 3B) and against recurrence rate for Groups I, II, and III (Fig. 6) was more sensitive than any individual characteristic alone. Representative images are illustrated in Figs. 7 and 8. The sensitivity and specificity of AxLS in predicting axillary involvement at subsequent surgery was 76 and 67%, respectively, with positive and negative predictive values of 63% and

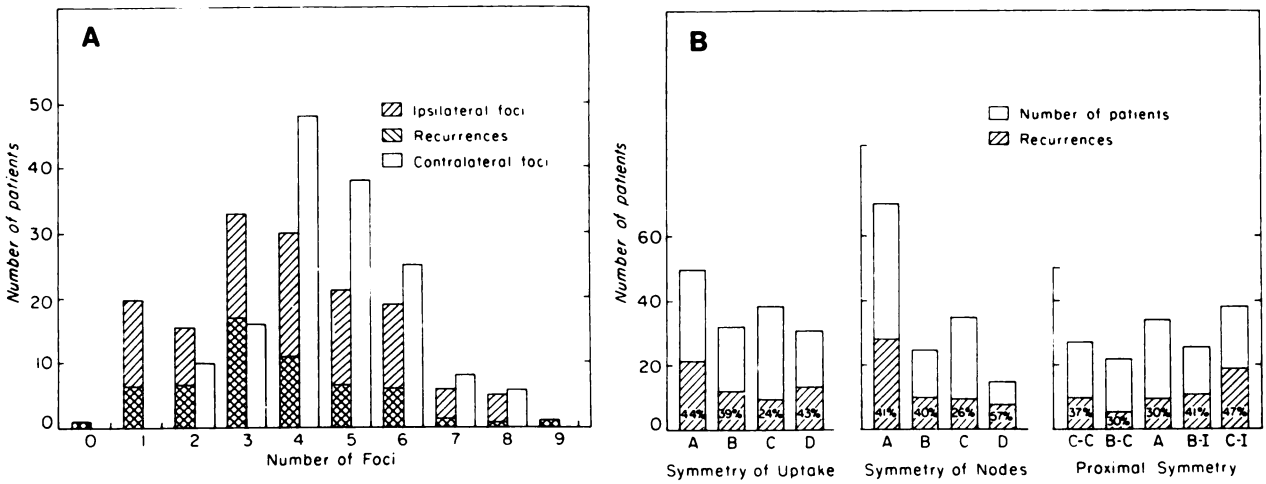

FIGURE 5
Data on group of 147 patients who were scanned following axillary surgery (Group II). A: Numbers of ipsilateral and contralateral foci vs. recurrence; B: Individual scan characteristics vs. recurrence

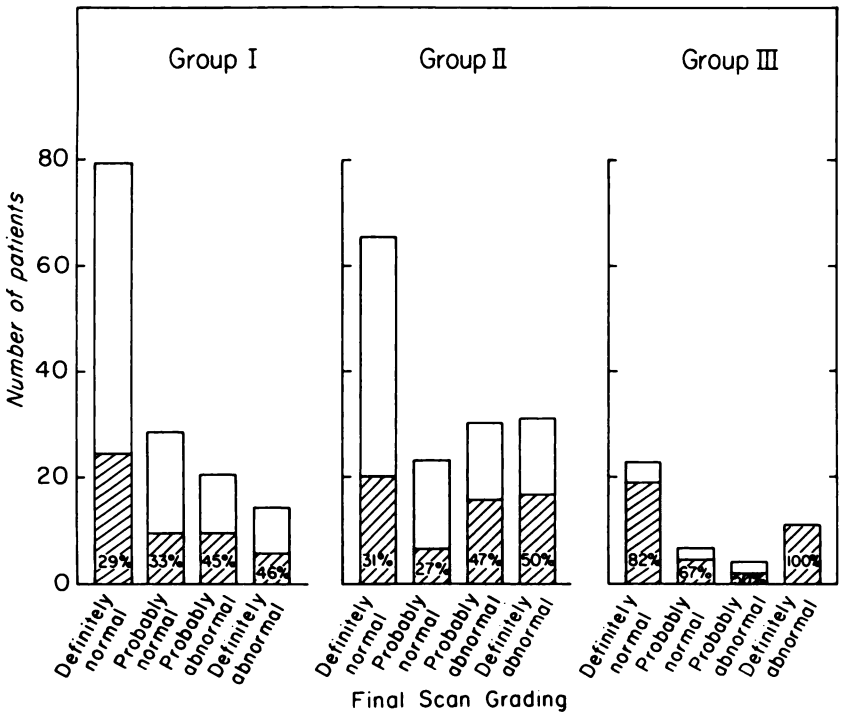

FIGURE 6
Final scan grading vs. recurrence. From left to right: Group I, Group II, and Group III (those scanned at time of first recurrence)

80%. Apart from the group who presented with recurrence, the overall grade also correlated well with relapse rates. If scan grades "definitely" and "probably normal" and "definitely" and "probably abnormal" are combined, the recurrence rates for those with normal and abnormal scans in the overall group of 345 patients with 2 years follow-up are 31% and 51%, respectively. These results compare favorably with the predictive value of pathologic node status of 184 patients who underwent axillary surgery. Of 91 patients with histologically negative axillae, 31 patients (34%) relapsed, and of 93 patients with histologically positive axillae, 36 (39%) relapsed. The most sensitive histologic predictor of relapse was obtained if patients with less than three positive nodes are compared with patients with three or more positive nodes, where relapse rates were 33 and 48%, respectively.

We were also able to compare pathologic nodal status

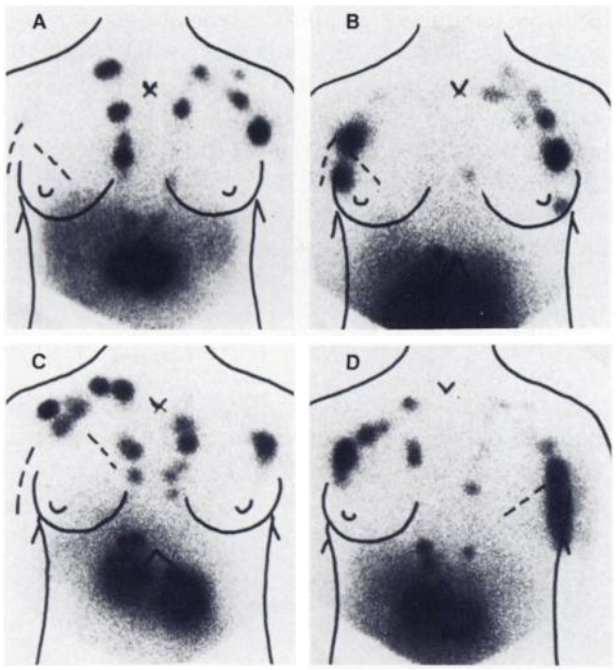

FIGURE 7
Axillary lymphoscintigraphy performed after surgery that included axillary dissection. A: Right axilla negative and no recurrence: note mildly increased proximal uptake; B: Right axilla positive with subsequent recurrence: note markedly decreased proximal uptake; C: Right axilla negative and subsequent recurrence: note markedly increased proximal uptake; D: Left axilla negative and subsequent recurrence; note decreased uptake and possible lymphocele

FIGURE 8
Axillary lymphoscintigram performed after surgery which did not involve axillary dissection. Note decreased uptake in right proximal region and abnormal right internal mammary lymphoscintigram. Local recurrence occurred subsequently. Also note Y-shaped uptake in left proximal region, a common finding

and scan results in predicting relapse in 38 patients from the PreSx group followed up for 2 years. Sixty-five percent with abnormal AxLS relapsed while 57% with positive nodes at surgery relapsed. As only 77% of those with positive nodes had had abnormal scans prior to surgery, this suggests that AxLS may give additional prognostic information.

We further examined the site of relapse. In Group I patients, 76% of the relapses were at a local or regional site. Of the 32 relapses in patients with negative scans, 28 (87%) occurred at local or regional sites. In Group II patients, 58% of the relapses occurred locally or regionally. Thirteen (50%) of the 26 recurrences in patients with normal scans, occurred at the site of the primary lesion.

An abnormal AxLS is more likely to predict distant relapse than a normal AxLS is to exclude regional relapse. Finally, in the group presenting with recurrence, in which AxLS performed poorly, chest wall was the site of recurrence in six (60%) of ten patients with negative scans who recurred subsequently.

Results of IMLS for the 345 patients with 2 years follow-up are given in Table 4 and are similar to those previously reported by Ege and Elhakim (*15*). The results of AxLS and IMLS were combined to assess whether the combination would give improved prediction of relapse. The internal mammary lymphoscintigrams (classed as normal, suspicious, or abnormal) and the axillary lymphoscintigrams (classed as normal or abnormal) were combined to give four grades from I (normal) to IV (abnormal) and the results are given in Table 5. This indicates that the combination of tests gave results superior to either test alone in predicting relapse.

TABLE 5
Combined IMLS/AxLS vs. Recurrence in Patients with Follow-up at Least 2 Years (n = 345)

Category	I	II	III	IV	EQ
Number	182	82	48	27	6
Number recurred	56	38	18	18	
% Recurred	31	46	38	67	

DISCUSSION

In 1973, Antilla et al. (*16*) using [^{99m}Tc]Sb_2S_3 reported clinical application of AxLS for planning axillary portals in the radiation treatment of patients with breast carcinoma. Matsuo (*17*) in 1974, employed the technique for determining the status of the axillary lymphatics pre-operatively with gold-198 injected subcutaneously into the medial surface of the upper arm in 106 patients. Results yielded a 100% true-negative, 69% true-positive, and 34.5% false-positive/negative diagnostic rate. The sensitivity was lower than the value obtained for IMLS in the same group of patients. In 1978 Agwunobi and Boak (*1*) reported the use of AxLS pre-operatively to predict the presence of breast carcinoma in 50 patients with breast masses. In patients subsequently shown to have carcinoma, axillary scans following periareolar injections showed less uptake on the ipsilateral side but results of axillary dissections were not reported. Similar studies tended to confirm the finding of decreased ipsilateral uptake (*2,3*) although the technique did not differentiate reliably between benign and malignant masses (*4–6*). Christensen et al. (*6*) also demonstrated that increased uptake was more characteristic of benign than malignant lesions, but it was concluded from a small number of pathologically examined specimens that the scan findings were independent of the presence of tumor in lymph nodes. Peyton et al. (*7*) also found poor diagnostic accuracy in 19 patients with axillary lymph node metastase. In 143 patients with carcinoma of the breast, Gabelle et al. (*8*) used intratumoral injection of [^{99m}Tc]rhenium colloid preoperatively, and by quantifying the number of foci of uptake, were able to predict the degree of axillary involvement with high specificity and sensitivity. More recently, Osborne et al. (*9*) have employed a novel approach using ^{99m}Tc-labeled liposomes and found good sensitivity and specificity in predicting nodal involvement.

In a prospective study using interdigital and periareolar injection, Hill et al. (*10*) scanned 43 patients with breast cancer and found abnormal scans in 12 out of 18 with nodal involvement and normal scans in 23 out

TABLE 4
Internal Mammary Lymphoscintigraphy vs. Recurrence in Patients with 2 Years Follow-up (n = 345)

Item		Normal	Suspicious	Abnormal	Equivocal
	Number	104	18	18	
No AxSx	Number recurred	34	4	9	
n = 140	% Recurred	33	22	50	
	Number	123	36	23	2
AxSx	Number recurred	41	12	13	1
n = 184	% Recurred	33	33	57	
	Number	10	5	6	
Local/regional recurrence	Number recurred	8	4	5	
n = 21	% Recurred	80	80	83	

of 25 without nodal involvement. Clinical staging by the attending surgeon predicted ten (55%) of 18 patients proven to have axillary lymph node involvement. Bourgeois et al. (*11*) employed AxLS postoperatively to assess completeness of axillary clearance. They employed both interdigital and intercostal injections and showed that few additional nodes were seen following the intercostal injections. Only 35% of patients were confirmed as having complete clearance on the basis of no axillary uptake and these patients subsequently had a lower rate of nodal relapse than those who had remaining lymph nodes visualized.

Variations in purpose, technique, radiopharmaceuticals, and interpretation have detracted from an adequate assessment of the potential realistic role of AxLS in clinical practice, which may assume greater importance in the light of current trends in conservative management of early stage breast cancer.

Interdigital injection appears to be the most universally applicable of all injection sites utilized both before and after breast ± axillary surgery and yields the greatest number of foci, permitting evaluation of several elements contributing to scan interpretation. Our study confirms minimal impact upon interpretive features of the AxLS from previous axillary surgery. Bourgeois et al.'s study (*11*) indicates that little further information is gained by chest wall injection in addition to interdigital injection.

Notwithstanding the diversity of agents available for lymphoscintigraphy (*18*), [^{99m}Tc]Sb_2S_3 is the agent of choice for AxLS in view of the extensive experience with its use in IMLS and particularly since both studies are applicable in the same patient population and should be performed concurrently. Inherent anatomic differences between parasternal and axillary lymphatics necessitate augmentation of criteria utilized in interpretation of IMLS. AxLS may be handicapped by two-dimensional imaging of a three-dimensional compartment and superimposition of structures within it. While the parasternal lymphatics comprise a single chain and alterations in radiocolloid flow secondary to disruption due to tumor involvement can be readily recognized, the lymphatic channels in the axilla are syncytial in nature and tumor involvement of a single node may not have directly observable consequences in radiocolloid flow. A number of scans demonstrate a Y-shaped branching of lymphatics (Fig. 8) and one arm could be involved without interference of flow through the other. Interpretive criteria were expanded to include specifically the "proximal region" since asymmetry of the upper half of the axillae and supraclavicular fossae appeared to correlate with both pathological status and subsequent relapse, although the latter relationship is not a direct one. Increased recurrence rates were found with both markedly increased or decreased uptake in the proximal regions for which the following mechanism is postulated. Nodes containing no tumor or with a good immunological response may show no change in radiocolloid uptake or slight increase in activity, which may be characterized histologically by sinus histiocytosis known to carry a good prognosis (*19*). Metastatic nodes may show increased uptake initially (*17*), but as tumor replaces nodal tissue there is progressive fall in uptake with poor or nonvisualization of nodes. In an animal model, Ege et al. (*20*) have shown that proliferative nodes draining a regional neoplasm but without evidence of metastases, accumulate less radiocolloid than normal nodes, which may be an alternate manifestation of hyperplasia. In addition to these possible physiologic mechanisms, the mechanical effect of increased uptake in nodes resulting from distal obstruction by tumor (as is seen in IMLS) may also be important in some cases.

In patients studied before surgery, the sensitivity and specificity in predicting nodal involvement was similar to the results of palpation reported elsewhere, (*21,22*) and hence, not adequate to allow replacement of axillary sampling by AxLS at present. As indicated earlier, however, the probability of relapse in Groups II and PreSx was predicted at least as successfully using overall scan grading as using nodal status at surgery. On the other hand, AxLS performed poorly in patients presenting with local recurrence, suggesting that previous surgical disruption protects drainage lymphatics from adverse effects of a local recurrence.

Like IMLS, AxLS is a simple, well-tolerated procedure. Studies confirm the extent of normal variability inherent in the lymphatic system. Figure 9 illustrates the reproducibility of AxLS which has been demonstrated in many patients over the years. Unlike IMLS, far fewer individual nodal components of the axilla can be identified with a single interdigital injection of radiocolloid than can lymphatic components of the parasternal chains following a single subcostal injection. The foci displayed on AxLS clearly represent clusters of several individual lymph nodes. This disparity between the number of identifiable nodes and those containing radiocolloid at axillary dissection has been disturbing to some investigators (*7*). Nevertheless, that axillary surgery does not produce more pronounced disruption in the postoperative AxLS attests to the abundance of lymphatic structures which can be evaluated with AxLS. This study supports the likelihood that features concerning those aggregate structures that can be displayed on an AxLS reflect the pathologic and physiologic status of the axilla since an overall scan grading which takes into consideration several parameters has been effective in predicting both nodal involvement and relapse.

IMLS has established predictive value (*23*) and AxLS may provide information complementary to that obtained by clinical examination and surgical sampling of

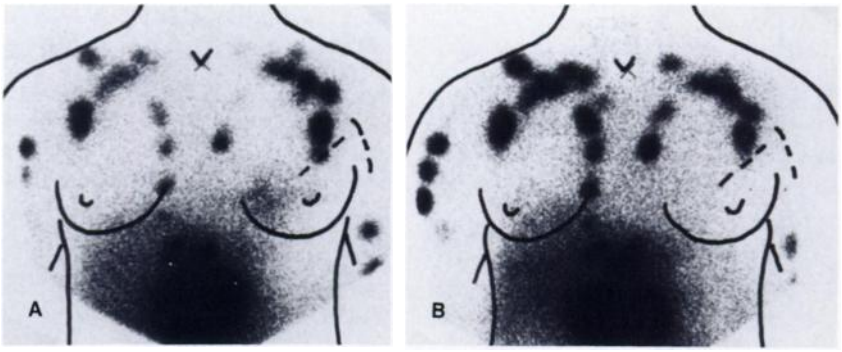

FIGURE 9
Repeat axillary lymphoscintigrams demonstrating reproducibility. Studies were carried out 12 mo apart

the axilla. The availability of tumor specific agents such as monoclonal antibodies, tomographic imaging of the lymphatic network such as may be possible with single photon emission computed tomography and prospective studies to determine histologic correlates of variations in radiocolloid sequestration may introduce the refinements required to enhance the sensitivity and specificity of AxLS in the management of patients with breast carcinoma.

FOOTNOTE

[†]Ohio Nuclear 110.

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