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QUANTITATIVE LYMPHOSCINTIGRAPHY FOR DETECTION OF METASTASES TO THE INTERNAL MAMMARY LYMPH NODES

Biokinetics of $^{99}Tc^{m}$-sulphur colloid uptake and correlation with microscopy

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Approximately 8 per cent of metastasizing primary mammary carcinoma are at the time of operation spread to the internal mammary lymph nodes but not to the axillary nodes (URBAN & MARJANI 1971). Since biopsy of the internal mammary nodes is not generally performed at the ablation, a number of cases are wrongly classified as clinical stage T1N0. Although biopsy of the internal mammary nodes has been carried out in a few series (HAAGENSEN et coll. 1972) this is most frequently performed on one side only and not always in all the intercostal spaces. Besides, the procedure is time-consuming and not without risk to the patient.

Therefore, a safe and simple diagnostic procedure for demonstrating invasion of the internal mammary lymph nodes would be of great value in the treatment of mammary carcinoma. It would allow proper clinical staging as basis for a rational treatment. At lymphoscintigraphy, absence of active colloid accumulation to a lymph node has been considered indicative of malignant invasion (EGE 1976, GÖRANSSON & JONSSON 1974a, b). The reliability of this method has been tested by performing a second scintigraphy some days after the first one and comparing

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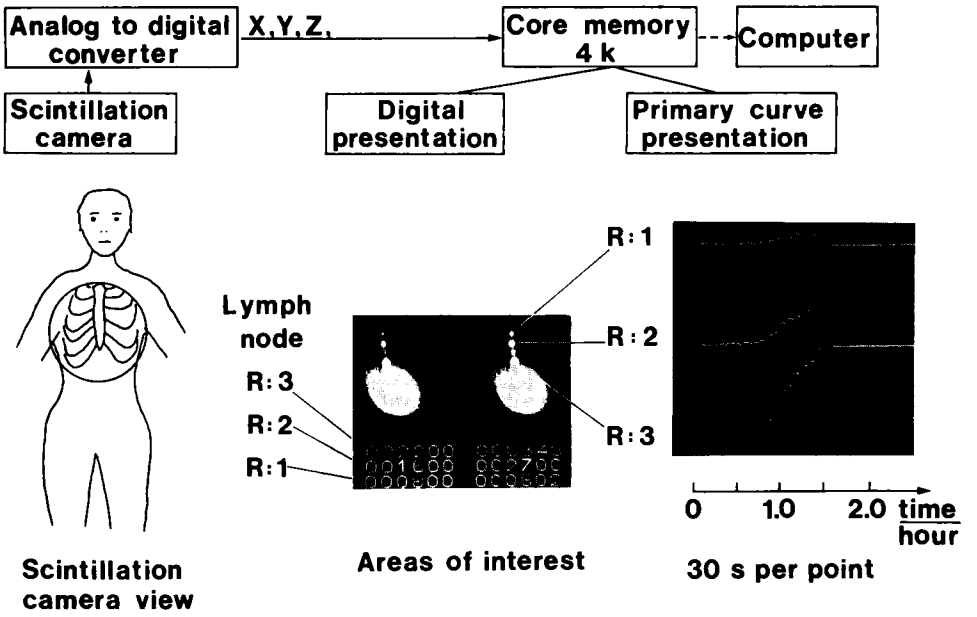

Fig. 1. Scintillation camera and data acquisition scheme. Time–activity curves obtained from patient No. 1 in whom 3 nodes with accumulation were clearly visible. To the right the accumulation curves for the 3 nodes.

the results (EGE). Thus, good to fair reproducibility was observed in 94 per cent of the cases (EGE). A similar reproducibility has also been recorded when hyaluronidase was added to the colloid (GÖRANSSON & JONSSON).

The authors mentioned assumed that no accumulation of the colloid in a lymph node implied gross metastasis to the node. However, it is possible to assume, until proved otherwise, that a non-malignant lymph node sometimes does not accumulate the colloid, or that microscopic invasion does not reduce the uptake. One solution to this essential problem is to perform lymphoscintigraphy and compare the results obtained with those at microscopy of the nodes. Such a procedure was therefore considered necessary before the lymphoscintigraphic method was applied routinely at this hospital.

Material and Methods

Injection procedure. The material consisted of 6 females with primary carcinoma of the breast, one with axillary metastases at the time of operation. The diagnosis was made preoperatively by aspiration biopsy and confirmed postoperatively by conventional microscopy. The $^{99}Tc^{m}$-sulphur colloid was prepared from 48 μmol of sodiumthiosulfate ($Na_2S_2O_3 \cdot 5H_2O$) and 9 μmol of potassium perrhenate ($KReO_4$) according to PERSSON & NAVERSTEN (1970). The mean particle size of the colloid is 0.6 ± 0.2 μm.

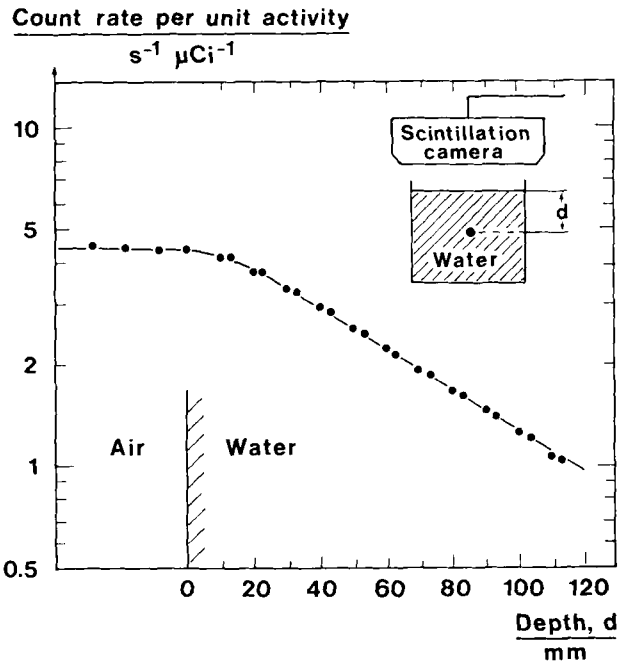

Fig. 2. Calibration factor for the lymph node phantom as a function of depth in water. The scintillation camera was equipped with a parallel 16000-hole collimator. A 35 per cent energy window was centered over the 140 keV full energy peak.

Biokinetic measurements. The general set up of the scintillation camera system appears in Fig. 1. The patients were examined in supine position under the scintillation camera equipped with a parallel 16 000-hole collimator. The injection sites covered with 2 mm lead were placed in the lower part of the camera view. Sequential scintigrams at a rate of two frames per min were recorded on a magnetic tape for $1\frac{1}{2}$ h after the injection. When the recording was terminated, curves of activity accumulation were derived from assumed lymph node and background areas.

In order to determine the uptake of the labelled colloid in the lymph nodes quantitatively, corrections must be made for the attenuation of the radiation in the intermediate tissue. This correction was performed using both anterior and posterior measurements two hours after the injection. The count rate observed from the node at anterior view is ϕ_A and the corresponding count rate at posterior view is ϕ_P. If the center of activity lies at a depth d from the anterior surface, and l is the thickness of the patient, the count rates can be expressed by the equations:

$$\phi_A^d \simeq \phi_A^0 \cdot f(x_A) \cdot \exp(-\mu_{eff} \cdot d) \quad (1)$$

$$\phi_P^{l-d} \simeq \phi_P^0 \cdot f(x_P) \cdot \exp[-\mu_{eff} \cdot (l-d)] \quad (2)$$

where μ_{eff} is the effective attenuation coefficient and ϕ^0 the count rate with the activity free in air, i.e. at zero depth. The distance-response function of the scintilla-

Table 1

The distribution of dissected internal mammary nodes. L1 means left intercostal space number 1, i.e. the space between the first and second left ribs. L2 is second intercostal space, etc. R1 means first right intercostal space. + means that the space in question was dissected and material for microscopy was obtained. − means that the space was not dissected

Patient No.	Intercostal space:					
	L1	L2	L3	R1	R2	R3
1	−	−	−	+	+	+
2	−	−	−	+	+	+
3	+	+	+	−	+	+
4	−	+	−	−	+	−
5	−	+	−	−	+	−
6	−	+	+	−	+	+

tion camera and the collimator in question, f(x), is in the present case when using a parallel hole collimator constant to approximately 1.0.

By combining the equations (1) and (2) the following expression is obtained:

$$\ln\left\{\frac{\phi_A^d}{\phi_P^{l-d}}\cdot\frac{\phi_P^0\cdot f(x_P)}{\phi_A^0\cdot f(x_A)}\right\} = -2\mu_{eff}\cdot d + \mu_{eff}\cdot l \tag{3}$$

The ratio $\frac{\phi_P^0\cdot f(x_P)}{\phi_0^A\cdot f(x_A)}$ is very close to 1.0.

Thus, the expression can be further simplified as:

$$d = \frac{1}{2}\left\{l - \frac{1}{\mu_{eff}}\ln\left(\frac{\phi_A^d}{\phi_P^{l-d}}\right)\right\} \tag{4}$$

The effective attenuation coefficient, μ_{eff}, was determined in water with a lymph node phantom (volume: 0.1 ml). With a 35 per cent energy window centered over the 140 keV full energy peak a value of 0.14 cm^{-1} was obtained.

With the depth of the lymph node in the patient known, the activity in the node was derived using the calibration factor from Fig. 2. This calibration factor was obtained in a similar way as the attenuation coefficient. A static data image was taken four hours after the injection. The spots with increased activity supposedly representing nodes were marked on the scintigram and also on the skin of the patient for guidance to the surgeon.

Operation technique. One day after the lymphoscintigraphy the patients were operated upon with a modified radical mastectomy which preserved the pectoral muscles but cleared the axilla. A transverse skin incision was used. By lengthening

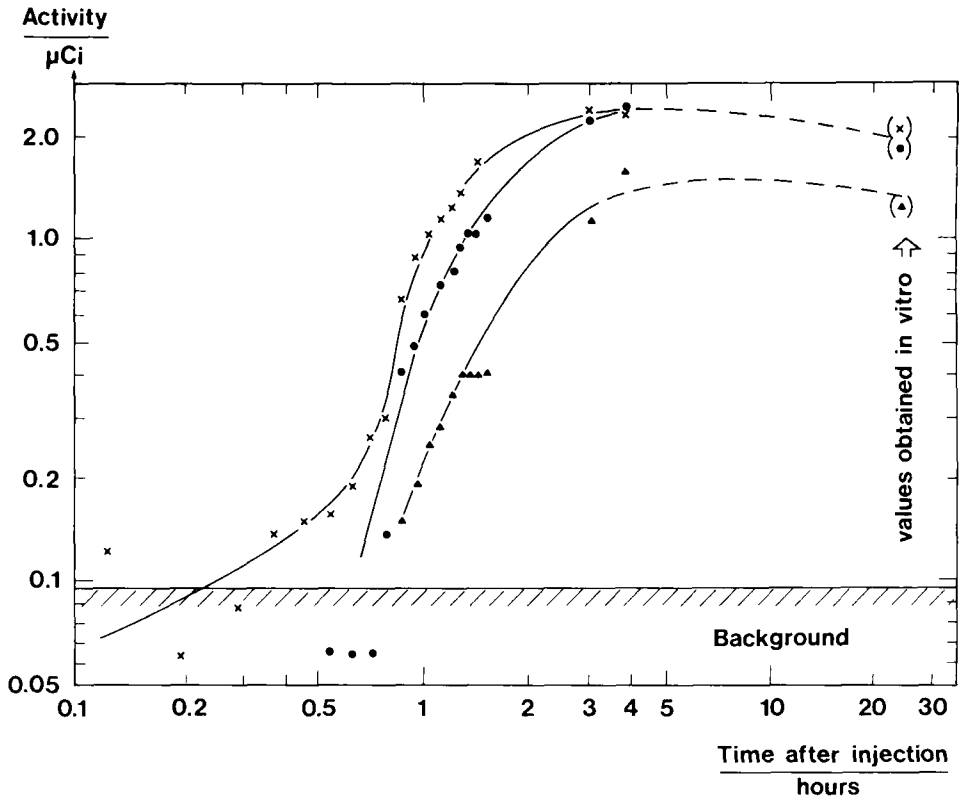

Fig. 3. Genuine uptake of $^{99}Tc^{m}$-sulphur colloid into the right parasternal nodes of patient No. 1. The curves are corrected for background activities, physical half life of $^{99}Tc^{m}$ and tissue attenuation. Triangles (▲) indicate accumulation into intercostal node No. 1 (node between first and second rib), dots (●) indicate incorporation into node No. 2 and crosses (×) into node No. 3. The activity injected at the right injection site was 720 μCi.

the skin incision to the midline and by undermining the subcutis, the three first intercostal spaces could be explored bilaterally along the sternum (HAAGENSEN et coll.). The major pectoral muscle was mobilized from medial; the intercostal muscles and membranes were incised, and the lymph gland was dissected free and removed. Before removal, the distance between the skin surface and the gland was measured with a ruler. Each node was then inserted into a separate plastic test tube with fixative, measured for activity, then sectioned and stained with haematoxylin-eosin and examined by light microscopy. Due to shortage of time or technical difficulties, it was not possible to dissect the six intercostal spaces in all the patients. However, all spaces with scintigraphic activity on the mastectomy side were explored. The distribution of the dissected glands from each patient is given in Table 1.

Post-operative measurements. Four hours after the operation a new static scintillation camera measurement was made to confirm that the removed glands were

Table 2

Results of measurement of depth of lymph nodes from the anterior skin surface by three different methods in patient No. 1

Lymph nodes	Depth (mm)			Calibration factor calculated from anterior and posterior measurements ($s^{-1} \cdot \mu Ci^{-1}$)
	Antero-posterior view	Lateral view	Operation left side	
R1	55	(*)	50	2.4
R2	55	(*)	—	2.4
R3	29	37	30	3.4

* No measurement possible due to background

identical with those recorded before the operation. The activity content of the lymph nodes removed at the operation was measured separately with a NaI(Tl)-crystal ($\phi = 7.5$ cm $\times$ 7.5 cm) housed in a lead shield. The activity of the node was calculated by comparing the count rate from the node with a standard prepared from a $^{99}Tc^{m}$-colloid vial identical with that used for injection.

Results

The biokinetic behaviour of the uptake of the $^{99}Tc^{m}$-sulphur colloid in the lymph nodes of Patient No. 1 (Table 1) is given in Fig. 3. No significant activity above the background was recorded until $\frac{1}{2}$ h after the injection. The observed uptake is corrected for background activity and physical half life and it thus reflects the biologic behaviour.

The uptake in a node appears to vary with the distance from the injection site, the most superior node having the longest delay until uptake commences. This probably reflects the flow in the lymph vessels and consequently offers a possibility to estimate the flow rate. The activity uptakes into the three nodes 4 hours after injection were 1.5, 2.4 and 2.4 μCi, respectively, or 0.2 and 0.3 per cent of the activity injected at a given site.

The rate of accumulation was much slower in the other 5 patients, and no uptake was recorded during the first $1\frac{1}{2}$ h.

Depth of lymph nodes and accumulation of activity. Depths ranging from 20 to 110 mm from the anterior surface of the thorax were recorded with the anterior and posterior measurements. These depths were confirmed by lateral projections when the site of each node activity was marked on the anterior surface of the thorax with a ^{57}Co point source. Measurements at the operation also confirmed these observations. Results from patient No. 1 appear in Table 2.

Table 3

Distribution of accumulation of $^{99}Tc^{m}$-sulphur colloid into lymph nodes of the internal mammary chain in 6 patients

	Uptake	No uptake	No. of nodes
Microscopic normal node	9	7	16
Malignant node	—	3	3

The activities in the lymph nodes 4 h after the injection of the colloid were calculated in 4 patients. The values ranged from 0.1 to 2.4 μCi. This corresponds to 0.01 and 0.3 per cent of the injected amount of colloid per injection site.

Static images. Although the amount of activity accumulated in the lymph nodes was small, good images were obtained and especially so when the injection sites were covered with lead (Fig. 4). The colloid particles used for injection in this patient were of a slightly smaller average size than in previous colloids.

Correlation between activity uptake and microscopy of nodes. The scintillation camera measurements were compared with the findings at microscopy (Table 3). No activity was recorded in malignant nodes. Three such nodes from patient No. 2 were massively infiltrated with carcinoma with virtually no lymph tissue left. Nine normal lymph nodes, where the normality is defined as node without malignant invasion or inflammation, showed substantial accumulation of activity. However, no accumulation occurred in six similar normal nodes. No histologic differences between those two groups existed. No lymph node with both malignant invasion and nuclide uptake was encountered.

Discussion

The method described is simple and permits recording of accumulation of nuclide agents into the lymphatics. It not only permits static images to be made, but also offers possibilities of dynamic examinations, i.e. the rate of the activity accumulation and the estimation of the true activity uptake. These parameters may be important in the investigation of the lymphatics in normal and pathologic conditions.

Depth determination of the accumulating node is important, firstly for the estimation of the tissue attenuation and, secondly, for proper localisation. In the present patients mediastinal nodes were observed and could easily have been erroneously considered as sternal nodes.

The static images produced confirm the observations of GÖRANSSON & JONSSON (1974 b) and EGE to the extent that scintigrams of the internal mammary lymph nodes were successfully accomplished. However, a high frequency (7/16) of absent

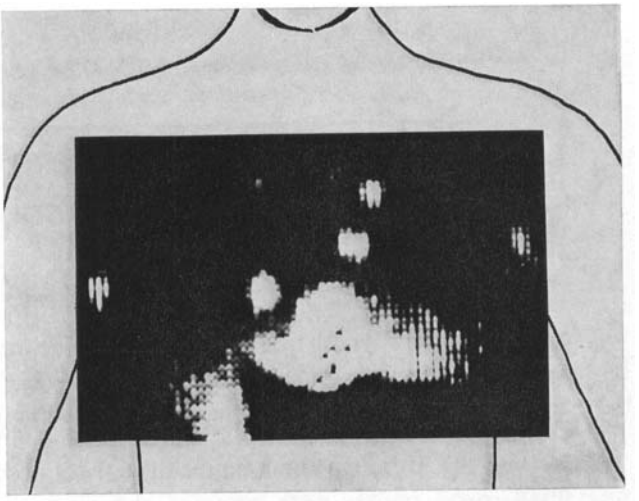

Fig. 4. Static image 4 hours after the injection of $^{99}Tc^{m}$-sulphur colloid in a patient. Uptake into 3 parasternal nodes to the left of the sternum and into 2 nodes to the right. Accumulation into each axilla from the site of subcutaneous injection 1 cm from the xiphoid process.

uptake of the sulphur colloid into normal lymph nodes was detected. Since absence of incorporation indicates inflammation or malignant invasion, the use of the present $^{99}Tc^{m}$ sulphur colloid involves a high risk for overdiagnosis. When this was revealed, further examination of patients was considered unethical, which accounts for the small number of patients.

When nodes were completely infiltrated, no accumulation of activity was observed. No node with partial infiltration was found. Thus, the question whether a partially infiltrated node would incorporate the colloid, resulting in an erroneous impression of normality, cannot be answered.

The frequent failure of normal glands to incorporate the sulphur colloid shows that a species difference between man and rabbit exists. GÖRANSSON & JONSSON (1974 a) invariably found accumulation in rabbit nodes, but this was not so in the present 6 patients. Results from animals should thus be applied to human beings with great care.

However, when the particle size of the colloid was modified by excluding the perrhenate from the kit and reducing the boiling time from 3 to 1 minute, rapid uptake into lymphatics occurred. (Fig. 4). This observation, as well as the small amount of colloid taken up by the lymph nodes from the site of injection and the large percentage of normal nodes without accumulation, indicate that dynamic lymphoscintigraphy with colloids of smaller particle size may be a simple and reliable method of examining the functional condition of the lymphatic system.

Further comparative investigations in rabbits of the uptake of colloids of various size in the parasternal lymph nodes confirms this opinion (PERSSON et coll. 1978, STRAND & PERSSON 1978).

The present results demonstrate that it is necessary to compare and correlate new diagnostic procedures with pathologic findings.

SUMMARY

Dynamic quantitative activity determination and accurate scintigraphic localization of parasternal lymph nodes were obtained from antero-posterior measurements with a scintillation camera. The scintigraphic observations were compared with microscopy of the nodes removed at operation. The $^{99}Tc^{m}$-sulphur colloid indicated a high frequency (7/16) of absent uptake in normal lymph nodes. However, the technique used indicates that a similar technique with smaller particle size may be a useful method for proper classification of the clinical stage of carcinoma of the breast.

ZUSAMMENFASSUNG

Eine dynamische quantitative Aktivitäts-Bestimmung und eine genaue szintigraphische Lokalisation der Parasternal-Lymphknoten wurden durch antero-posteriore Messungen mit der Szintillationskamera erhalten. Die szintigraphischen Observationen wurden mit der Mikroskopie der Lymphknoten, die bei der Operation entfernt worden waren, verglichen. Das $^{99}Tc^{m}$-S Kolloid wurde in einer hohen Frequenz (7/16) in normalen Lymphknoten nicht aufgenommen. Jedoch deutet die verwendete Technik darauf hin, dass eine ähnliche Technik mit kleinerer Partikelgrösse eine brauchbare Methode zur richtigen Klassifikation des klinischen Stadiums des Brust-Karzinoms sein kann.

RÉSUMÉ

Des mesures faites dans le sens antéro-postérieur avec une caméra à scintillation a permis la détermination dynamique quantitative de l'activité et la localisation scintigraphique précise de ganglions lymphatiques parasternaux. Ces résultats scintigraphiques ont été comparés avec l'examen microscopique des ganglions enlevés à l'opération. Le colloïde au $^{99}Tc^{m}$-S a montré une grande fréquence (7/16) de défaut de fixation dans des ganglions lymphatiques normaux. Cependant la technique utilisée montre qu'une technique similaire avec une dimension de particules plus petites peut être une méthode utile pour une classification adéquate du stade clinique du carcinome du sein.

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