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^{67}GA-SUBTRACTION SCANNING IN HODGKIN'S DISEASE AND LYMPHOMAS

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During the last years a considerable interest has appeared in the staging of Hodgkin's disease (ROSENBERG 1966) and non-Hodgkin's lymphoma using radionuclide methods, ^{67}Ga being the most successful tumor-detecting agent known to date. It localizes well in both lymphoma and Hodgkin's disease as reported by EDWARDS & HAYES (1970), HIGASHI & NAKAYAMA (1972), GREENLAW et coll. (1974) and JOHNSTON et coll. (1977), but also localizes in inflammatory processes and abscesses (BEIHN et coll. 1974). Recently a method was described in which ^{67}Ga subtraction scanning was applied to enhance tumor detection and tumor localization (DELAND et coll. 1975). This method utilized ^{67}Ga as an agent for total body labeling. Additional isotopic materials or agents with different photon emission spectra which selectively localize in lung, liver, bone and spleen are then injected as a second isotopic label which permits the activity and contribution to the image of the lung, liver, bone or spleen to be subtracted. This leaves as a residual image, the abnormal isotope accumulation in e.g., neoplastic or inflammatory tissue. This method was applied to the evaluation of selected patients with Hodgkin's disease and non-Hodgkin's

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lymphoma in this clinic. The present report describes preliminary experiences with this method. The histologic appearances were correlated with capability for detection. The purpose of this comparison was to determine whether the reduction of the normal organ background enhanced the ability to recognize ^{67}Ga true scan abnormalities.

Materials and Methods

The material consisted of 38 patients, 24 with Hodgkin's disease and 14 with non-Hodgkin's lymphoma. All patients had standard evaluation carried out at this University, including history, physical examination, complete blood count, p.a. and lateral chest films and tomography of hilar regions as indicated, lymphangiography (LEE 1969), liver function tests, liver and spleen scans (MILDER et coll. 1975), and urography. In all cases of Hodgkin's disease, laparotomy staging was done (KAPLAN 1972), which included splenectomy, multiple lymph node biopsies, needle and wedge liver biopsies, and bone marrow biopsy. Bone scan or bone radiography were used selectively. In more recent experience with non-Hodgkin's lymphomas, laparotomy staging has been used very selectively (JONES et coll. 1972). All patients were clinically staged according to Ann Arbor staging system (see KAPLAN).

^{67}Ga citrate was obtained as a sterile, pyrogen-free commercial product. A dose of 45 μCi/kg (2–3 mCi) was administered intravenously. ^{67}Ga decays with a $T_{1/2}$ of 78 hours. The scanning procedure was usually performed at approximately 48 to 72 hours after intravenous administration of the nuclide; occasionally scanning was delayed only 30 hours. Standard imaging instruments were used for photoscanning. The ^{67}Ga was performed first. Then the second labeled agent was injected and scanned together with the ^{67}Ga.

^{99}Tc^{m} bone-seeking agents (e.g., Diphosphonate), ^{99}Tc^{m} sulfur colloid and ^{99}Tc^{m} labeled human albumin microspheres were used as bone, liver and spleen and lung scanning agents, respectively. These imaging agents were prepared and injected at appropriate intervals before the scanning procedure. The two scans were then displayed as described in the following.

A dual 12.7 cm total body rectilinear scanner with dual pulse-height analyzers and subtraction feature was utilized. A high energy 19-hole broad focus collimator with 10 cm focal distance was used to collimate the ^{67}Ga gamma ray energies as well as those from ^{99}Tc^{m}. A medium energy, medium focus collimator with a 15.3 cm focal distance was also used to collimate both ^{67}Ga and ^{99}Tc^{m} gamma energies. The photoscans were displayed without minification on 35 cm × 43 cm Kodak safety RP film with a 2 mm line spacing and information density of 500.

All signal pulses corresponding to ^{67}Ga and ^{99}Tc^{m} gamma interactions from the detectors were directed to each position of two pulse-height analyzers. One pulse-height analyzer by use of energy selection permitted the ^{67} Ga 184 and 300 keV photopeak counts to be recorded on the photoscan. The resulting photoscan therefore demonstrates the distribution of ^{67}Ga. The other pulse-height analyzer was cali-

Table 1

Results of ^{67}Ga scans in cases of Hodgkin's disease

Classification	No. of patients	Correlation of positive ^{67}Ga scan in major* involvement sites
Nodular	11	10
Mixed cell	5	4
Lymphocyte predominance	4	3
Recurrent disease	4	3
Total	24	20 (83 %)

* Clinically positive obvious disease by examination, radiography or laparotomy (true positive).

brated to encompass counts of the 140 keV peak of $^{99}Tc^{m}$. Each of these pulse-height analyzers was normalized to 100 per cent over the area of greatest activity over the liver. A subtraction photoscan was produced by subtracting the output of one pulse-height analyzer from the other. The subtraction scan and the ^{67}Ga photoscan were then produced separately and simultaneously. An average information density of 400 counts/cm^2 was maintained on all same. The 90 degree Compton scatter occurs at about 135 keV and no doubt contributes some background ($\sim 5\,\%$) to that detected by the second pulse-height detector. Presently higher counts are being used. Similarly it has become evident that a scintillation camera or Phocon scanning with computer data storage and subtraction is also easily performed with still better demonstration.

Current laparotomy staging methods were used for all patients with Hodgkin's disease (see KAPLAN) and ensured a complete evaluation of the disease for comparison with the accuracy of ^{67}Ga scanning. For the non-Hodgkin's lymphoma, laparotomy staging was not routinely performed and therefore radiographic localization was more important. Independent histologic review of all lymphomas was carried out by the Southeastern Cancer Group (SEG) pathology reviewers. The scan was correlated with the clinical localization of the gross distribution of the disease. That is, the major comparison was limited to true positive cases only, since it has already been shown that detection of inapparent disease by ^{67}Ga is not accurate and many false negatives occur (ADLER 1975, GREENLAW et coll., HORN et coll. 1976, JOHNSTON et coll., MCCAFFREY et coll. 1976).

In the data to be presented, all cases were patients with documented Hodgkin's or non-Hodgkin's lymphoma. Correlation was directed to sites of obvious involvement or abnormality by one or other means of evaluation, including physical examination, biopsy, radiography, laparotomy or similar means.

No effort was made for a site-by-site correlative comparison unless a palpable, radiographic or biopsy proven obvious major abnormality was apparent. It has already been established that microscopic disease and non-obvious disease has a high

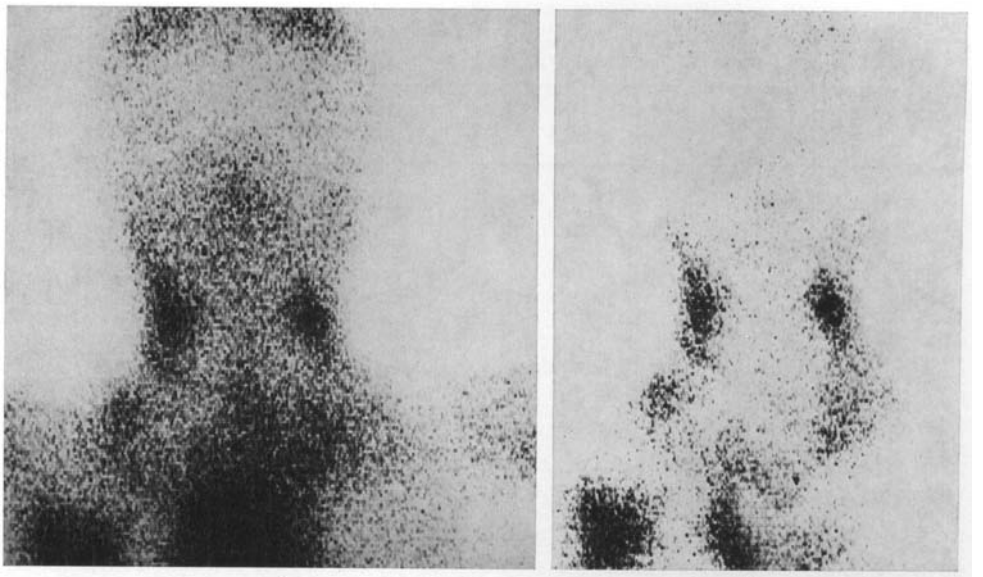

Fig. 1. a) ^{67}Ga scan of neck and chest. b) ^{67}Ca subtraction scan. $^{99}Tc^{m}$ removed bone activity from the ^{67}Ca scan.

frequency of false negatives and moreover is often below the detection sensitivity of the ^{67}Ga method. Thus, the evaluation concentrated on the capability of the subtraction method to recognize obviously diseased sites.

Results

Correlation was found in localization of Hodgkin's disease in patients with proven disease as has been shown by ADLER, GREENLAW, HORN et coll., JOHNSTON et coll., MCCAFFREY et coll. Patients in the present series were distributed through all stages of disease including 4/20 who were recurrent; 20/24 (83 %) had evidence of accumulation in major diseased sites (Table 1), and this experience is compatible with the report by JOHNSTON et coll. A high percentage of the grossly involved, clinically apparent sites showed ^{67}Ga uptake especially for Hodgkin's disease. All histologic types accumulated activity well, and in all patients the accumulation of definite abnormal activity indicated an abnormality. In the neck, chest, axilla (Fig. 1), and groin regions, the ^{67}Ga method correlated well with gross disease involvement as assessed by clinical examination or radiography with or without subtraction. In the abdomen, the subtraction scanning reduced the bone, liver and spleen backgrounds (Figs 2, 3). But the abdomen and the pelvis contain bowel activity, which made the evaluation of the images difficult. The pelvis also has activity in the bladder, which can be subtracted, but subtraction of bone and bladder, made detection of small

Table 2

Results of ^{67}Ga scanning in cases of non-Hodgkin's lymphoma

Classification	No. of patients	Correlation of positive ^{67}Ga scan in major involvement sites*
Well-differentiated	6	4
Moderately to poorly differentiated	4	3
Histiocytic lymphoma	1	1
Unclassified lymphoma	3	0
Total	14	8 (57 %)

* Obvious clinical disease by examination, radiography or laparotomy (true positive).

residual masses difficult unless located in the groin or external iliac node chain. Meticulous bowel preparation greatly reduced bowel background, but this remained a problem due to the background activity contributed. ^{67}Ga made it possible to detect axillary, supraclavicular, hilar-mediastinal, para-aortic, retroperitoneal, iliac, and groin disease (Figs 2, 3). The negative case included one patient with Stage IA disease who had a single involved node excised (cervical) and was negative; 2 had prior irradiation with response and tumor disappearance; one had recurrent disease in bone marrow and was negative (Table 1). No false negatives were observed. After completion of radiation therapy ^{67}Ga localization was negative if response was complete.

The observations showed a diagnostic accuracy of 57 per cent (Table 2) for non-Hodgkin's lymphoma. In all forms of non-Hodgkin's lymphoma involved sites were localized except in the unclassified lymphoma. This included both lymphocytic and histiocytic types and raises the question of the accuracy of tumors placed in the category of unclassified lymphoma. Non-Hodgkin's lymphoma constitutes a much more capricious disease with a much less orderly distribution and more extranodal involvement, as well as microscopic spread. Nonetheless, the disease was detected in nearly all sites including orbit, bone, and nodes of the cervical, axillary, mediastinal, mesenteric, parotid and retroperitoneal regions. Although the disease was excellently localized in some patients (Figs 1–3), false negatives in the neck, abdominal, periaortic and iliac regions were observed. The negative scans were as follows: 3 were considered unclassified lymphoma; 2 well differentiated lymphoma (abdominal nodes); one iliac node and bone marrow involvement (moderately to poorly differentiated).

A single case with histiocytic lymphoma was positive, which has been found for this type of tumor. At the present level of development, abdominal examination was not greatly improved over standard ^{67}Ga scanning although background was greatly reduced. Some difficulty in evaluation of the cervical and hilar region was encountered and did not correlate with physical examination, surgical or radiographic findings.

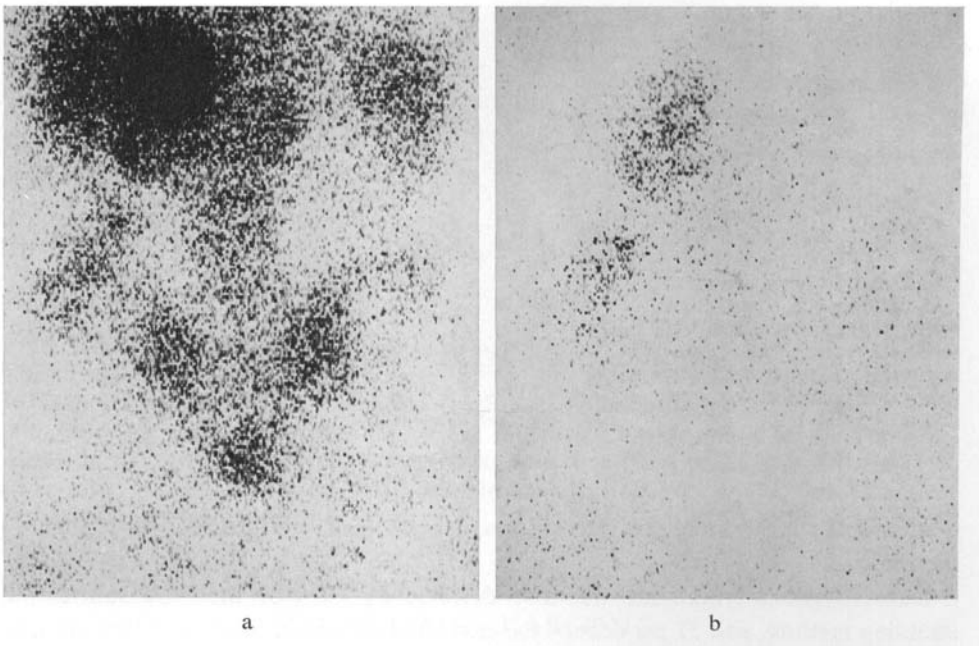

Fig. 2. a) ^{67}Ga scan of abdomen. b) ^{67}Ga subtraction scan. Uptake in liver, spleen, bone and urogenital tract subtracted by $^{99}Tc^{m}$ labeled compound. In (b) uptake in retroperitoneal lymphoma not visible in (a) due to superimposition of hepatic uptake.

Discussion

The purpose was to determine the feasibility of the ^{67}Ga multiple subtraction method in Hodgkin's disease and non-Hodgkin's lymphoma and to correlate the histologic findings and clinical evaluation with the scanning results. The Ann Arbor meeting (see KAPLAN) proposed a staging scheme and suggested that the use of isotope methods such as ^{67}Ga may be a promising procedure for clinical diagnostic evaluation of patients with Hodgkin's disease and lymphoma (Ann Arbor Conference). JOHNSTON et coll. and GREENLAW et coll. reported a 50 to 88 per cent accuracy by positive accumulation of activity in diseased areas. However, the frequency of equivocal scans has limited the evaluation of data obtained by the ^{67}Ga scanning method. Considerable activity also accumulates in normal liver, spleen, bone and bowel, and greatly interferes with the evaluation of abnormalities in sites such as the head, mediastinum, abdomen, para-aortic regions and pelvis (ADLER, EDWARDS & HAYS 1969, 1970, HIGASHI et coll. 1972, MCCAFFREY et coll., LAVENDER et coll. 1971, LEVI et coll. 1975). In the present experience, concentration of ^{67}Ga was found in patients with Hodgkin's disease and the various types of lymphoma, and the results of GREENLAW et coll. and JOHNSTON et coll. were confirmed. A correlation of ^{67}Ga citrate scans with histologic subtypes was found. True positive correlations were

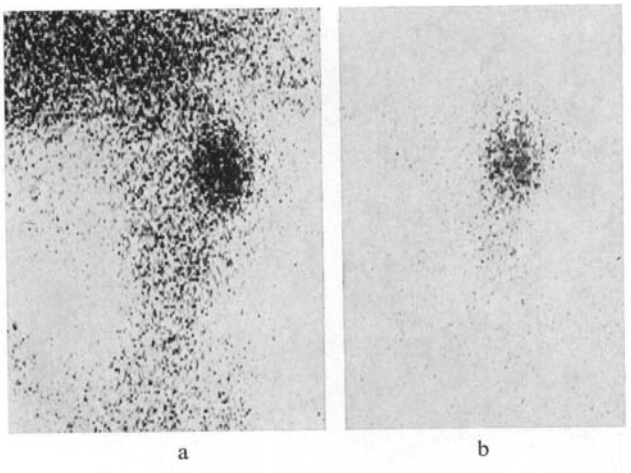

Fig. 3. a) ^{67}Ga scan. Uptake in mid-abdomen in para-aortic, lymph nodes, and tumor. b) ^{67}Ga subtraction scan. The tumor uptake is more evident after removal of uptake in liver, bone, and uro-genital tract

comparable with those of previous reports, being 83 per cent (Table 1) for Hodgkin's disease.

Non-Hodgkin's lymphoma was also detected by ^{67}Ga or the ^{67}Ga subtraction scanning method, and 57 per cent of the cases had uptake in major involved sites. In Hodgkin's disease the sites are usually massively involved, and the lymphoid regions of the body are almost invariably involved. For non-Hodgkin's lymphoma, negative scans appeared to correlate with the smaller lesions, although low or poor uptake of isotope, and perhaps errors in evaluation of pathology (undifferentiated tumors), contributed.

This investigation has focused on detection of obvious disease and the possible contribution of subtraction scanning to detection of abnormalities. Clearly, by reduction of background, detection of abnormalities was facilitated. However, at the present state of development limitations were obvious. The positive scans correlated well with sites of obvious clinical disease (true positive by examination, radiography or laparotomy). Although background was reduced by subtraction scanning, further refinement of instrumentation, greater purity of organ-specific radiopharmaceuticals, higher specific activity of ^{67}Ga and greater versatility in optimizing differential enhancement of the image appears to be necessary. The preliminary results were comparable with present ^{67}Ga scanning, but further improvement is necessary before reduced equivocal scans and improved and accurate tumor detection and localization is possible with this method. One of the important problems is the need for determination of a size threshold for lesion detection as background is reduced.

^{67}Ga scanning is a procedure which is potentially useful for: (1) pretreatment evaluation and determination of the extent of disease; (2) posttreatment follow-up, and (3) detection of recurrence. The multiple isotope subtraction scanning method may permit a more accurate diagnosis of abnormal sites by reducing background

noise. The method can be applied in principle to any imaging system for reduction of background noise.

A better understanding of the radiopharmaceuticals and their metabolism is needed. The cause of increased gallium concentration in tumors and inflammatory tissue is unknown and must be further investigated with animal tumor models and human tissue (SWARTZENDRUBER et coll. 1971).

SUMMARY

Recently a new method was described, the ^{67}Ga subtraction scanning method. ^{67}Ga accumulates in neoplastic and inflammatory tissue. The subtraction method was applied for evaluating 38 patients with Hodgkin's disease and non-Hodgkin's lymphoma. The preliminary experiences are described. It was found that the diagnostic accuracy is comparable to that of ^{67}Ga scanning. The subtraction method offers potential improvement of the accuracy for equivocal scans, but further technological refinement is needed before the method can be widely applicable.

ZUSAMMENFASSUNG

Die neue Methode, ^{67}Ga Subtraktions-Scanning wurde zur Auswertung von 38 Patienten mit Hodgkinscher Krankheit und nicht-Hodgkinschem Lymphom verwendet. Die Methode basiert sich darauf, dass ^{67}Ga sich in neoplastischen und inflammatorischen Geweben anreichert. Die vorläufigen Erfahrungen deuten darauf hin, dass die diagnostische Genauigkeit vergleichbar mit der von ^{67}Ga Scanning ist. Die Subtraktionsmethode ermöglicht eine Verbesserung der Genauigkeit bei unsicheren Scans, es ist jedoch eine weitere technologische Verfeinerung notwendig, bevor die Methode in weitem Umfang verwendet werden kann.

RÉSUMÉ

La nouvelle méthode de scintigraphie par le ^{67}Ga avec soustraction a été utilisée pour examiner 38 malades atteints de maladie de Hodgkin et de lymphome non Hodgkinien. Elle se base sur le fait que ^{67}Ga s'accumule dans les tissus néoplastiques et inflammatoires. Les expériences préliminaires indiquent que l'exactitude du diagnostic est comparable à celle de la scintigraphie par le ^{67}Ga. La méthode de soustraction fournit une amélioration potentielle de l'exactitude pour les scintigraphies douteuses mais des perfectionnements technologiques sont nécessaires avant que cette méthode soit largement applicable.

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