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WHOLE-BODY RADIOGALLIUM SCANNING FOR STAGING OF
HODGKIN'S DISEASE AND OTHER LYMPHOMAS*

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In 1969, Edwards and Hayes demonstrated the usefulness of ^{67}Ga -citrate as a tumor scanning agent.¹ Subsequently, it was reported that this tracer localizes in Hodgkin's disease as well as in the other malignant lymphoreticular neoplasms.² It also localizes in inflammatory tissue and in certain normal organs and therefore cannot be considered specific for neoplastic tissues. Nevertheless, when a histologic diagnosis of Hodgkin's disease has been established, total-body scanning with ^{67}Ga -citrate can be extremely valuable in determining the extent of disease. Our use of this nuclide in the staging of Hodgkin's disease and other malignant lymphomas has been previously reported.^{4,5} The present communication describes our scanning technique, reviews our results with special emphasis on certain problem areas, and suggests some future modifications in both technique and interpretation which may extend the use of radiogallium scanning in the staging of Hodgkin's disease.

The exact mechanism whereby ^{67}Ga -citrate localizes in tumor tissue is unknown. Following intravenous injection, the tracer is rapidly bound to plasma proteins.⁶ Disappearance of ^{67}Ga -citrate from plasma occurs with a $T_{1/2}$ of approximately 12 hours.⁷ Gallium-67 is identified in the lysosomal fraction of tumor ultracentrifugates,⁸ and believed to localize in a lysosome or lysosome-like organelle.^{9,10} The relative abundance of lysosomal elements in macrophages and other reticuloendothelial cells may explain the affinity of the nuclide for lymphomatous tissue, for other tumors, and for sites of inflammation. Gallium localization in tumor may also be promoted in part by leakage of the gallium-labeled plasma proteins into tumor sites due to increased protein permeability of the tumor vessels.

Technique

Carrier-free ^{67}Ga -citrate is used as the scanning agent. The radionuclide is prepared by deuteron (8 MeV) bombardment of natural zinc (the significant reaction being $^{66}\text{Zn} (d,n)^{67}\text{Ga}$) on the Argonne Cancer Research Hospital's compact cyclotron (Cyclotron Corporation CS-15). Production by this method results in no significant contamination by other long-lived radionuclides.¹¹ A three-millicurie dose of the nuclide is administered to the patient by intravenous injection. The total-body radiation dose from ^{67}Ga -citrate is estimated at 340 millirads per millicurie.¹ The initial scan is performed 72 hours following injection. On the evening prior to scanning, the patient receives two ounces of castor oil to evacuate any tracer that is contained in the feces.

The scan is performed with a dual 5-inch rectilinear scanner using a focused collimator with 9 cm focal length (Ohio Nuclear 38 H). The lower probe scans just below the table top and the upper probe is located two to four centimeters above the patient. The patient is scanned in the supine position from the top of the head to below the knees. A five-to-one "minification" technique is used, which allows the entire study to be recorded on a 14 X 17 inch X-ray film.

The major photon emissions of ^{67}Ga and their intensities are as follows: 93 KeV (40%), 184 KeV (24%), 296 KeV (22%) and 388 KeV (7%).¹² In order to obtain maximum efficiency, the scanner has been modified with three independent pulse height analyzers for each probe. This permits simultaneous scanning of the 94 KeV, 183 KeV and 296 KeV peaks of ^{67}Ga , and allows the whole body scan to be completed in one hour with a maximum information density (over the liver) of 250 counts per square

centimeter. The benefit of the improved statistics achieved by the three pulse height analyzer technique is illustrated by Figure 1. If ^{67}Ga is detected in the colon on the first scan, an enema is administered on the same day or on the day following the first scan and the abdominal region is scanned a second time. If apparent colonic activity is still present, the patient is scanned again on a subsequent day following administration of another enema. Since only the abdomen is re-examined, the time required for rescanning is short, usually less than one-half hour. This method is useful in distinguishing fecal activity from tumor involvement, as illustrated in Figure 2.

On the basis of autopsy findings, ^{67}Ga is localized initially in the spleen, kidney, adrenal, liver, bone, lymph node, colon, and lung of "normal" human adults.¹³ Scans at 72 hours, however, usually reveal significant concentrations of ^{67}Ga only in the liver, bone, nasopharyngeal area, orbital regions and, to a lesser extent, the spleen. The typical normal distribution is illustrated in Figure 3. Activity in the colon is variable and can often be eliminated by adequate evacuation of feces prior to scanning. In the absence of disease, ^{67}Ga is only rarely identified in the kidney or lung. Localization of gallium in the lung appears to be more frequent in patients who have undergone lymphography prior to scanning.

Gallium-67 will also accumulate in any area of inflammation due to infection, mechanical injury, or surgical intervention. We have identified ^{67}Ga activity in the breasts of three female patients, one of whom was recently pregnant.

Since August 1, 1970, we have performed gallium scans on over 100 patients with biopsy-proven Hodgkin's disease or other lymphoma. We have restricted our evaluation of data to cases of Hodgkin's disease (24 cases) or malignant lymphoma of the histiocytic type (6 cases) in whom complete staging or restaging, including laparotomy, was carried out, and to four additional cases in whom complete staging was not carried out because of preoperative identification of extranodal involvement. All scan interpretations were made by two of us (A.G. and P.B.H.) Diagnosis was made by region; e.g., neck, mediastinum, para-aortic, spleen, etc., and each region was diagnosed as either involved or free of disease. The scan diagnosis was compared with information from available biopsies or, in the case of mediastinal involvement, with chest X-ray, and, occasionally, with mediastinoscopy. These results have previously been presented^{4,5,14} and are summarized in Tables 1 and 2.

Evaluation of Disease in the Abdomen

The abdomen was the most difficult area to assess by radiogallium scan, the overall accuracy of identifying involved areas being only fair (60%), with a high incidence of false positive and false negative diagnoses. Certain unique problems exist in evaluating abdominal uptake of ^{67}Ga and these deserve special attention.

The spleen normally has a greater uptake of ^{67}Ga than surrounding tissues. The spleen, although usually visualized on the 72-hour gallium scan, is not prominent in the normal subject. On the posterior scan, gallium uptake in the spleen of normal patients is usually less dense than uptake in the liver. When the spleen is enlarged, its nuclide content increases. This is due, at least partially, to the increase in

volume of the organ, although increased concentration of the tracer may also play a role. Splenomegaly may occur in patients with Hodgkin's disease with or without splenic infiltration. We have frequently mistaken increased splenic uptake of ^{67}Ga due to benign splenomegaly for ^{67}Ga uptake due to tumor infiltration, and apparently there is no simple method for distinguishing between these two causes of increased splenic uptake of ^{67}Ga (see Figure 4). In only one case with normal splenic weight and normal histology was increased uptake in the spleen noted.

The para-aortic region is also difficult to evaluate, with a high incidence of false positive diagnoses. Small amounts of ^{67}Ga present in the midline portion of the transverse colon may cause confusion. Furthermore, lordotic curvature of the spine, combined with the "tomographic" effect of the focused collimator may produce a prominent "lesion" in the anterior view which simulates para-aortic node involvement (see Figure 5). We have come to regard all midline abdominal concentrations of nuclide seen on the anterior view as indeterminate unless concentration is marked. If para-aortic uptake of radionuclide is analyzed as asymmetric or midline, and as dense or faint, the asymmetric, dense accumulations are usually due to tumor involvement, and the faint lesions in the midline do not usually indicate disease.

The liver is a prominent area of radiogallium uptake in normal patients. In consequence, tumor involvement of lymph nodes in the portal region is difficult to identify. Occasionally, however, a lesion in this area may be so prominent that it can easily be detected.

Gallium-67 in the cecum and sigmoid colon may obscure iliac nodes. Equally troublesome is our tendency to interpret activity in these regions

as colonic, when it is actually due to node involvement (see Figure 6). We believe that thorough evacuation of the bowel prior to scanning is of critical importance. If activity is identified as colonic, this must be confirmed by repeated scanning following cleansing enemas. If the colon cannot be completely cleared, at least movement of such activity along its course should be seen before it is interpreted as ^{67}Ga trapped in the feces, rather than within a tumor.

Evaluation of Disease Above the Diaphragm

The overall diagnostic accuracy of tumor involvement in the mediastinum, supraclavicular, neck and axillary regions is good (21 of 24 sites detected), since there is no interference from accumulation of ^{67}Ga in normal organs. Gallium-67 uptake, however, is seen in the nasopharyngeal area of normal patients and should not be interpreted as tumor involvement of Waldeyer's ring. Localized uptake of the agent also occurs normally in the orbital regions. It has been suggested that this activity is actually concentrated in the lachrymal glands,¹⁵ but such localization has not been confirmed. Since other centers have not reported uptake of ^{67}Ga on their scans of the orbital region, it is possible that the uptake of nuclide in this region varies with the method of preparation of the ^{67}Ga -citrate.

Evaluation of Extranodal Regions

Localization of areas of extralymphatic (excluding liver) infiltration of Hodgkin's disease by ^{67}Ga is accurate (5 of 5 cases). Not infrequently, such sites have been undetected by other staging tests, and therefore we believe that the identification of unsuspected Stage IV

disease is the strongest single argument for the use of ^{67}Ga scanning in the staging of patients with Hodgkin's disease or lymphoma (see Figure 7).

Future Developments

The relative success of gallium scanning as a supplemental staging procedure for patients with Hodgkin's disease and other malignant lymphoreticular neoplasms encourages further development of the technique. One relatively simple improvement would be to increase the injected dose of radionuclide from the 3 millicuries present in use to the maximum activity that the scanning instrument can efficiently count, probably about 15 millicuries. The improved photon yield could be translated directly into an improved image quality which should enhance our ability to distinguish normal from abnormal structures, especially in the abdomen. The increased radiation dose to the patient would be tolerable; the total-body dose from a 15 millicurie injection of ^{67}Ga -citrate being approximately 5 rads. Since the diagnosis of lymphoma has already been established and the patient will probably be receiving a significant radiation dose during therapy, the increased hazard associated with the administration of the additional radionuclide would be small.

Another useful refinement would be a more careful description of tumor localization with regard to lateral position and relative scan density. This is especially important in determining abdominal involvement in the region of the para-aortic nodes. A probability factor could then be assigned to all positive localizations. We currently use such a method informally in our reporting of ^{67}Ga scans, tending to give a high degree of certainty to areas of increased uptake which are not in the midline and show a high concentration of gallium, and a low degree of

probability to apparent lesions which are along the midline and have a relatively low concentration of gallium.

Improved scanning equipment may also be helpful. We would prefer a highly efficient detector capable of total-body scanning with tomographic readout in multiple body planes. The tomographic scanner developed by Anger may be suitable for this purpose.¹⁶ Tomography would be particularly helpful in distinguishing activity in the axial skeleton and transverse colon from para-aortic node localization.

Finally, other agents localizing in tumors should be investigated. ¹¹¹In-chloride has been suggested for this purpose.¹⁷ Bismuth-206 is of particular interest, since it demonstrates higher tumor-to-background ratios than any other known agent used for tumor scanning.¹⁸ Unfortunately, its radiations are difficult to collimate and detect with currently available equipment. Special, large-area GeLi detectors may prove suitable for imaging of this radionuclide.¹⁹

Conclusions

In spite of the success we have had with ⁶⁷Ga-citrate scanning, its nonspecificity and localization characteristics limit its uses. Consequently, the "ideal" agent for scanning lymphoma patients has yet to be developed. Nevertheless, total-body scanning with ⁶⁷Ga-citrate is a useful technique in staging patients with Hodgkin's disease and histiocytic-type malignant lymphoma. Experience with 30 patients indicates an overall accuracy of 78%. Although identification of diseases in the abdomen, including spleen, liver, para-aortic nodes and para-iliac nodes, is difficult due to interference from ⁶⁷Ga uptake in the liver, colon, and marrow, identification of disease in lymphatic tissues

above the diaphragm is highly accurate. The gallium scan is particularly useful in identifying unsuspected sites of extranodal involvement. In three patients, the gallium scan was the significant diagnostic study.

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FIGURE CAPTIONS

Figure 1.--A and B--Low information density scan (50 counts/cm²) produced by scanning with the 296 KeV peak of ⁶⁷Ga. Localization of tumor involvement is difficult.

C--High information density scan (230 counts/cm²) produced by simultaneously scanning the 93 KeV, 183 KeV and 296 KeV peaks of ⁶⁷Ga (3 independent pulse height analyzers). Tumor involvement in mediastinum, neck and right iliac region can now be more readily identified. Scan time is the same in both sets of scans. (Note also breast activity and possible para-aortic node involvement.)

Figure 2.--A, B, C--Apparent localization of ⁶⁷Ga in feces (A). However, following two attempts at evacuation with enemas, activity remains (B and C). This strongly suggests tumor involvement rather than fecal localization.

Figure 3. --Normal anterior and posterior ⁶⁷Ga scan 72 hours following intravenous injection of 3 millicuries of ⁶⁷Ga citrate. Note activity in nasopharynx, bone, liver and colon.

- Figure 4.--A --Increased splenic uptake due to lymphomatous involvement of the spleen. On the posterior view, shown here, the spleen is almost as "hot" as the liver. In normal patients, the posterior view of the liver is denser than the posterior view of the spleen.
- B --Increased splenic uptake due to "benign" splenomegaly. No lymphomatous involvement of the spleen was demonstrated by pathologic examination.
- Figure 5. --Prominent lordotic curvature simulating para-aortic node involvement (arrow) in the anterior view. Cervical, mediastinal, splenic right inguinal involvement correctly identified (recent case, not included in Table 1).
- Figure 6. --Iliac node involvement. The activity in the right lower quadrant of the abdomen (arrow) was misinterpreted as representing gallium accumulation in feces in the cecum.

- Figure 7.--A --Chest wall involvement. Re-staging evaluation was otherwise normal. Biopsy of this region revealed tumor infiltration.
- B --Tumor infiltration of left arm. Prior to the scan, the arm swelling was thought to be lymphedema due to lymphatic obstruction in axilla. Biopsy of arm lesion revealed tumor; axilla and spleen also positive.
- C --Severely ill patient with presumed stage IV Hodgkin's disease. Unsuspected lesion in left knee proved most convenient site to biopsy to establish extra-nodal involvement. Splenic, chest, mediastinal and right inguinal lesions are also seen.
- D --Splenic bed involvement. Restaging work-up demonstrated uptake of ^{67}Ga in splenic bed. However, splenectomy had been previously performed. Second laparotomy revealed large tumor mass in splenic bed.