Editorial: Residual Mass and Negative Gallium Scintigraphy in Treated Lymphoma: When Is the Gallium Scan Really Negative?

The paper by Israel et al. (*1*) underscores what may be the most important role of gallium-67-citrate ([^{67}Ga]) scintigraphy in the evaluation of the treated lymphoma patient; that is, to assess tracer avidity within a residual mass as an indicator of response to therapy. The assumption made by the authors, and one with which we agree, is that the ^{67}Ga negative post-therapy residual mass indicates a positive therapeutic response and an absence of viable tumor. If, however, such importance is to be associated with the negative ^{67}Ga image result in terms of major therapeutic decisions, we must be absolutely certain that we are accurately depicting the scintigraphic data.

There are few reasons for false-positive ^{67}Ga scans with most of these due to either fecal contents or foci of benign pulmonary uptake. It is the "true-negative" ^{67}Ga image, however, that is the most difficult to document. Concepts engendered by the Israel paper (*1*), which directly affect such interpretations, include tumor heterogeneity, count density, patient positioning, time of imaging, and the role of other radiographic exams; this editorial will discuss each of these points further.

Although the context in which Israel et al. (*1*) present the issue of tumor heterogeneity relates to biopsy technique and implies the potential for histologic heterogeneity as a function of sampling error, ^{67}Ga "tumor heterogeneity" has also been described. Chen et al. (*2*) reported that patients with non-Hodgkin's lymphoma will show varying degrees of gallium tumor avidity depending upon tumor grade; that is, higher grade tumors, such as that seen in Patient 1 of the Israel paper (*1*), demonstrate a greater degree of ^{67}Ga uptake than do low-grade lymphomas. It may be much more difficult then to define a "true-negative" ^{67}Ga scan in a patient with low-grade lymphoma than it would in the patient with high-grade disease. Therefore, it is extremely important when imaging patients with non-Hodgkin's lymphoma to be aware of the histology and, in a sense, "predict" the sensitivity of the test result.

To further compound the problem, since ~30% of patients with indolent low-grade lymphoma will convert to a higher grade of tumor (*3*), it can be expected that varying degrees of ^{67}Ga uptake will be seen in multiple sites within the same patient, i.e., very avid uptake in sites of intermediate- to high-grade disease, and only minimal uptake in sites of low-grade disease. Image interpretation will therefore rely heavily upon: (a) recent biopsy data from the patient under study and (b) anatomic information derived from recent CT scans to direct scintigraphic attention to sites of known bulk disease.

The single most important technical issue related to ^{67}Ga imaging in the context of evaluating the residual mass is that of count density. The optimal way to increase sensitivity and thereby eliminate false-negative image results is to image for an amount of time sufficient to collect a count density which allows definition of subtle foci of active tumor. Administering higher doses of radiogallium, on the order of 8–10 mCi, allows one to acquire these high-count density images, (one million counts per view) in a relatively short time period (*4*).

We recommend that the first set of images be obtained no earlier than 72 hr after ^{67}Ga injection with follow-up studies obtained even as late as 10-14 days postinjection. This format of delayed imaging will result in high tumor-to-background ratios and the subsequent increased sensitivity needed for detecting subtle sites of residual tumor (*5*).

In addition to obtaining delayed images, a further method for increasing image contrast is the use of SPECT (*6*). Again, by administering 8–10 mCi ^{67}Ga doses (rather than 3–5 mCi), SPECT imaging performed beyond 72 hr will yield high count rate studies. SPECT has its greatest utility when the planar images are either negative or suspicious for residual disease; the technique is less useful when planar images are grossly positive. The increased contrast available from ^{67}Ga SPECT images, coupled with the CT scan as an anatomic guide, will commonly convert the negative or suspicious planar image to a positive result.

Patient positioning is also a critical issue when attempting to achieve maximal count densities over an anatomic area of interest. For instance, in the Israel article (*1*), Figures 1B and 2D depict an anterior image of the thorax and abdomen on a single field of view. In these examples, the relative counts contributed by a theoretical disease site in the thorax would be minimal with respect to the entire field of view which includes not only the liver but a high-grade abdominal lymphoma. For this reason, we strongly recommend isolated, static images over each individual anatomic area excluding from the field of view organs with high ^{67}Ga

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avidity. When, for example, the thorax is the anatomic area of clinical interest, static images of this region should be obtained for one million counts with the liver excluded from the field of view. Similarly, when the abdomen represents the area of clinical interest, the gamma camera should be centered over the paraaortic lymph nodes, again excluding the liver from the field of view. At our institution, these one million-count images are routinely obtained when initial planar images are normal in a site of previous disease, or when the CT scan suggests residual lymphoma.

The time of ^{67}Ga imaging refers not only to the interval between tracer injection and initial views, but in a broader context also refers to: (a) the interval between ^{67}Ga injection and most recent chemotherapy administration and (b) the optimal time for radiographic restaging. In animal models, Fletcher et al. (*7*), Chilton et al. (*8*), and Bradley et al. (*9*) showed that both chemotherapy and radiotherapy have a profound effect on the biodistribution of radiogallium. Bekerman et al. (*10*) reported such an effect on image quality in a series of patients who were injected with ^{67}Ga within 24 hr of chemotherapy administration. Based on their experience, Wylie et al. (*11*) recommend a six-week interval between chemotherapy administration and gallium injection.

At our institution, we have adopted a policy which has patients receiving their ^{67}Ga dose one week prior to the next cycle of chemotherapy. For both Hodgkin's and non-Hodgkin's lymphoma, this usually represents a three-week interval from the last therapy treatment. If patients must receive both chemotherapy and ^{67}Ga within a few days of one another, we elect to administer the ^{67}Ga *first* (to allow for tumor fixation) and then at a minimum of 24 hr later, administer the chemotherapy. We must realize that the potential exists for reducing ^{67}Ga sensitivity when this policy is followed.

With respect to time of restaging, we note that in the Israel paper (*1*), Patient 1 was restaged after one cycle of chemotherapy. Our own experience in restaging with ^{67}Ga in intermediate grade diffuse large cell (DLCL) non-Hodgkin's lymphoma suggests that although those patients who will convert to a ^{67}Ga negative study usually do so within one to four cycles of therapy, there was a subset of patients who required five or more cycles of chemotherapy to reach this scintigraphic state. Therefore, a failure to convert to a ^{67}Ga negative study after one cycle of chemotherapy did not predict for ultimate ^{67}Ga negative conversion. Consequently, we recommend ^{67}Ga restaging at the same time that other radiographic restaging modalities are utilized.

Armitage et al. (*12*) recommend such radiologic restaging in the mid-course of chemotherapy in patients with DLCL. Our clinical experience would support this as an appropriate time for the first ^{67}Ga follow-up (*13*).

Although their paper dealt exclusively with non-Hodgkin's lymphoma, Israel et al. (*1*) presented data on the restaging of both Hodgkin's and non-Hodgkin's lymphoma. At this time, we are not aware of any scintigraphic information on the value of restaging Hodgkin's disease prior to the completion of a full course of chemotherapy. This is in contradistinction to patients being evaluated for non-Hodgkin's lymphoma, particularly those with intermediate and high-grade disease who are being aggressively treated to achieve rapid remission. Indeed, these are very different lymphomas with Hodgkin's disease presenting as an orderly, contiguous spread of lymph node involvement in a young patient group with a high cure rate. On the other hand, the non-Hodgkin's lymphomas demonstrate variable histologies, multicentric disease, a highly variable clinical course which can be indolent or rapidly lethal, and a high incidence of extranodal tumor involvement.

The point of residual gallium avidity in patients with Hodgkin's disease is an important concept however. Wylie et al. (*11*) recently showed that the critical issue was not solely the presence or absence of a residual mass, but whether or not ^{67}Ga positivity persisted. Eighty-nine percent of the patients who were ^{67}Ga positive either died or had progressive disease, whereas 88% of these who were ^{67}Ga negative remained in complete remission.

Although Israel et al. (*1*) do not address the false-positive ^{67}Ga scan per se, the concept is worth mentioning again. The overall incidence of false-positive ^{67}Ga scans in the lymphoma population, is low (*4*). Those in the abdomen, will be reduced by delayed imaging; this is because the most common etiology for these findings is radiogallium within the bowel. Subsequent abdominal views will show these foci to either move with time or disappear.

One further potential for false-positive gallium studies in the follow-up of the treated lymphoma patients is that of ^{67}Ga uptake in hilar lymph nodes. This can be manifested as either new sites of ^{67}Ga uptake or sites of persistent abnormal uptake in the face of other known disease sites, which have converted to ^{67}Ga negative with therapy.

Waxman et al. (*14*) have used thallium-201 (^{201}Tl) as the chloride to differentiate hilar uptake due to tumor from that secondary to post-therapy inflammatory change or superimposed sarcoidosis. They showed that those patients with hilar and/or mediastinal malignancy had positive ^{67}Ga and ^{201}Tl studies, whereas those patients who showed ^{67}Ga hilar uptake due to a benign etiology, in general, showed no ^{201}Tl uptake. They used this combination of radionuclides to effectively differentiate malignant from benign adenopathy; our own experience, using ^{201}Tl and ^{67}Ga in this patient population has been identical.

A final concept discussed by Israel et al. (*1*) was that of the utility of the CT scan. They mention in the

presentation of Patient 1 that "... the abnormal CT was falsely positive." We would suggest that most diagnostic radiologists realize the limitations of this anatomic imaging modality and include in the differential diagnosis, along with residual viable tumor, the potential for benign fibrotic change. It is time for us, as diagnostic clinicians, to move away from the competitive aspects of CT versus ^{67}Ga imaging and to view the two modalities as complementary. Indeed, the paper by Israel et al. (*1*) explicitly points out the complementary nature of these two tests. The ^{67}Ga image represents functional information, whereas the CT scan represents anatomic information. It is not a question of which modality is "better" but rather how to best use ^{67}Ga imaging to further elucidate the anatomic mass. We have found the most appropriate way to use these two tests is to interpret both sets of images concomitantly. The CT mass will be defined as: (a) residual tumor by a correspondingly positive ^{67}Ga planar or SPECT image, or (b) fibrosis when the ^{67}Ga images are negative. Additionally, a positive ^{67}Ga focus in a patient with a CT scan initially interpreted as negative will, with reinterpretation, commonly be found to represent a CT mass of borderline size which corresponds in location to the ^{67}Ga finding.

If we believe that anatomic imaging modalities are limited in their ability to differentiate viable tumor from fibrosis and that ^{67}Ga imaging is indeed capable of answering this question then we, as nuclear medicine clinicians, must be compulsive in our efforts to provide accurate data for utilization in patient care decisions. This means knowing the cell type, predicting sensitivity, knowing the location of disease sites, demanding high count density delayed images, using SPECT, and believing our own scintigraphic results.

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