Gallium and Infection

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Although radiogallium was initially used for tumor imaging, early clinical studies suggested its potential use as a method of detecting occult inflammatory lesions (*1*). Littenberg and associates (*2*) were the first to explore and popularize this application in the United States. Currently the number of gallium scans performed for the detection of inflammatory disease, is equal to or greater than the number performed to evaluate malignancy. The technique of gallium imaging in inflammatory disease differs somewhat from that used in tumor imaging. The usual dose of Ga-67 used for imaging inflammatory lesions is between 3 and 6 mCi in adults. Bowel preparation, although desirable, may be omitted when the patient's clinical condition precludes its use or when the region of concern is not within the abdomen. Rectilinear scanners are still used, more sensitive instruments, such as the multiple-window large-field camera and the Anger tomoscanner, have become more popular.

There is considerable controversy regarding ideal time for imaging. Hopkins and Mende have suggested that adequate diagnostic images can be obtained as early as 6 hr after injection (*3*). I prefer to wait 24 hr after injection to perform initial imaging. Repeat imaging at 48 or 72 hr is often helpful when bowel preparation cannot be performed or when considerable background activity is present in the initial images. Although most lesions can be reliably identified on the 24-hr image, I have occasionally encountered sites of inflammation that could be unequivocally identified only on the 48- or 72-hr images. Movement of activity in the abdomen between delayed images strongly suggests that the activity is within the bowel lumen rather than in an intra-abdominal lesion. Total-body views are often helpful in identifying unexpected secondary sites of inflammation, but local camera views of specific regions may suffice when the site of suspected infection is definitely localized, when the patient is too ill or uncooperative to withstand prolonged examination, or when delayed images of suspicious areas are required.

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SPECIFIC ANATOMIC REGIONS

Lung. Gallium localization has been associated with virtually all pulmonary lesions in which inflammation is present as either a primary or secondary phenomenon. Such processes include pneumonia, granulomatous lesions (tubercular or mycotic), pneumoconiosis, sarcoidosis, abscess, *Pneumocystis carinii* infection and idiopathic fibrosis (*4–10*). However, gallium uptake is conspicuously absent in uncomplicated pulmonary infarction (*11*).

When the gallium scan of the lung is performed at 24 hr after injection, faint but significant activity throughout the lung is observed in about 50% of normal individuals (*12*). At 48 hr this activity decreases to a level equal to or less than that seen in the abdomen. Therefore, when quantitative estimates are required for the staging of pulmonary disease—e.g., in patients with idiopathic pulmonary fibrosis (IPF)—evaluation of the 48-hr image is preferred. Faint bilateral perihilar activity is also occasionally seen on gallium scans and is of unknown significance.

The most clinically significant applications of nononcologic gallium imaging of the lung are related to early detection of opportunistic infection, distinguishing pulmonary infection from infarction, staging idiopathic pulmonary fibrosis, and evaluating treatment in sarcoidosis. Levenson and associates (*9*) have shown that opportunistic infections, such as *Pneumocystis carinii*, may be detected by diffuse increased uptake of gallium in the lung even though the chest radiograph remains normal. Richman and Bekerman have emphasized that

this diffuse increase in the presence of a normal or near-normal chest radiograph is nonspecific, being seen also in other conditions, including pulmonary drug toxicity and tumor infiltration (*13,14*). Therefore, in the face of clinical symptoms and diffuse pulmonary uptake, pulmonary biopsy is usually indicated to establish a specific diagnosis, even if the chest radiograph is normal.

Niden and colleagues have demonstrated that inflammatory lesions of the lung are almost invariably positive on gallium scan, whereas uncomplicated pulmonary infarcts do not show increased uptake (*11*). They advocate the gallium scan as a method of distinguishing infarction from infection in those cases where the clinical and radiographic findings make differentiation difficult.

Line and his associates (*10*) have found that pulmonary uptake of Ga-67 correlates well with the active phase of idiopathic pulmonary fibrosis (IPF). They have developed a method of quantitating Ga-67 uptake in the lung that takes into consideration the pattern, intensity, and extent of pulmonary uptake and is useful in assessing the effectiveness of treatment in IPF.

Gallium-67 uptake in sarcoidosis does not correlate well with clinical symptoms but does correlate with histologic findings (*4,8,15*). Gallium may therefore be useful in determining the effectiveness of therapy in sarcoidosis. It is possible, however, that this correlation is coincidental and due to steroid inhibition of gallium-67 uptake (*4*). In any case, the fact that lesions in sarcoidosis do accumulate gallium is important for one to bear in mind when evaluating patients for pulmonary malignancies. On at least two occasions I have evaluated scans of patients with suspected mediastinal lymphoma that showed avid uptake by a "tumor" that later proved to be sarcoid. When a combination of perihilar and parotid uptake is seen in an unirradiated patient, the diagnosis of sarcoid must be strongly suspected. Not all patients with sarcoidosis have parotid uptake of gallium-67, but such uptake is rare in untreated patients with lymphoma.

Although gallium uptake in other pulmonary lesions has been documented, its clinical value in these circumstances is unclear. It has been suggested as a method of differentiating active from inactive TB (*4,6*) but clinical experience is limited. Moreover, although its reported sensitivity in detecting pneumoconiosis is 100% (*4*), this study involved patients with radiographically detectable disease.

Abdomen. A large number of clinical studies have been reported concerning the use of radiogallium for detection of intra-abdominal infection (*2,16–27*). A variety of equipment, doses, and techniques were used. In general, most groups report very similar findings, with sensitivity and specificity both in the 90% range (*5*). Also, approximately 20% of positive scans detected a source of infection that was outside of the abdomen. These cases are not included in the sensitivity data. Some investigators have attempted to compare Ga-67 imaging with ultrasound and CT to determine the preferred modality for detecting intra-abdominal lesions (*25–27*). Even though these studies do provide some information, they are frequently misunderstood, and may be misleading. One problem is the definition of an intra-abdominal inflammatory lesion. The gallium scan is capable of detecting abscesses, phlegmon, or peritonitis. Abscesses are usually localized; phlegmon may be localized or may extend along an anatomic pathway limited by the attachment of the abdominal organs to the posterior peritoneum. Peritonitis is associated with a diffuse pattern of abdominal uptake, occasionally limited by anatomic barriers but often extending beyond them (*28,29*). In peritonitis the activity will occasionally surround the liver, a sure sign that the diffuse pattern is not due to Ga-67 within the bowel. However, whereas both ultrasound and CT are sensitive in detecting formed abscesses, they are unreliable for the detection of phlegmon or peritonitis. Therefore, if a study is conducted in which an inflammatory lesion is defined as a formed abscess, the incidence of false-positive gallium-67 scans will be deceptively high. Moreover, if phlegmonous lesions or peritonitis are eliminated from the study group to "correct" for this problem, part of the advantage of the Ga-67 scan over other modalities will be obscured.

If comparative studies are unreliable, what is the proper role of Ga-67 in the evaluation of suspected abdominal infection? The Ga-67 scan is the preferred initial procedure when the location of the site of infection is unclear and plain radiographs and appropriate contrast studies of the bowel fail to identify a focus of infection. In such cases even "suspicious" areas of uptake on early scans can be pursued with other diagnostic modalities. The Ga-67 scan is also preferred when other studies are technically unfeasible—e.g., in the postoperative patient with extensive bowel gas, numerous bandages, or an open wound that prevents proper placement of an ultrasound scanning head. Gallium-67 imaging is also recommended when other studies are equivocal, or when they are normal but the index of suspicion is high. Although current trends militate against the use of multiple examinations with only modest incremental yield, searches for sites of inflammation should represent an exception. These lesions, when misdiagnosed, are associated with high morbidity and mortality. Early correct diagnosis of intra-abdominal infection may not only be lifesaving but may also significantly shorten hospitalization, with consequent cost savings.

Bone and joint. The early experience following the introduction of the Tc-99m bone-imaging agents indicated that they were highly sensitive for the detection of osteomyelitis and joint infections (*30–33*). Subsequent investigations suggest that, in children and perhaps also

adults, the bone scan, although very useful, is neither as sensitive nor as specific as originally believed (*34–38*).

Handmaker and Leonards originally suggested the use of the Ga-67 scan as an adjunct to the bone scan in the diagnosis of osteomyelitis and joint infection (*39,40*). One of the problems in detecting early inflammatory lesions in bone on Tc-99m phosphate scan is that increased intramedullary pressure may tamponade the intraosseous vessels and prevent an increase in bone blood flow. Since Ga-67 is less dependent on increased blood flow for localization, it seems capable of accumulating in such lesions in spite of the tamponade. The high sensitivity of the Ga-67 scan for detection of osteomyelitis and joint infection should not result in abandonment of the conventional bone scan for this purpose. Since the bone scan is fast, gives a low radiation dose to the bone and the body, and has a sensitivity of at least 80% and perhaps closer to 90%, it is clearly the preferred initial study. However, whereas a positive bone scan in the proper clinical setting establishes the diagnosis of infection, a negative study does not exclude it. When infection is suspected and the bone scan is normal, a Ga-67 scan is often indicated. When osteomyelitis is suspected as result of spread from an adjacent area of cellulitis, the Ga-67 scan may be difficult to interpret due to inability to distinguish which activity is in the bone and which in the soft tissues.

Another application of Ga-67 imaging in benign bone and joint disease is the detection of an inflammatory lesion in the presence of underlying bone disease. For example, in the diabetic foot or degenerative ankle that becomes acutely symptomatic, the bone scan is frequently positive. Without comparison studies, however, it is impossible to distinguish acute from chronic lesions. The Ga-67 scan is rarely positive when chronic noninflammatory disease is present. Therefore a positive Ga-67 scan—especially one that is disparate with the bone scan in terms of either extent or intensity of uptake—is strongly suggestive of an active inflammatory process. Rarely, areas of chronic osteomyelitis may take up gallium.

Kidney. Kessler and associates (*43*) were among the first to indicate the high sensitivity and clinical value of Ga-67 imaging in the detection of both renal and perirenal infection. The diagnosis of pyelonephritis is not usually made by Ga-67 scan, since in most cases clinical and laboratory findings are adequate to confirm the presence of renal infection. However, the appearance of renal uptake in a Ga-67 scan may be helpful in making this diagnosis in the occasional case in which symptoms are deceptive and suggest an intra-abdominal site of infection. Gallium-67 scanning is useful in detecting renal and perirenal abscesses as well as infected renal cysts. Recently it has also been shown useful in diagnosing acute lobar nephronia (acute interstitial nephritis) (*44*). This disease is believed to be caused by retrograde urinary infection and with IVP and ultrasound it may be mistaken for a renal tumor or abscess. Characteristic Ga-67 scan findings include (a) a single focus of involvement that is larger than the lesion as described on ultrasound or nepro-tomography; (b) multiple unilateral or bilateral areas of involvement not seen on other studies; or (c) diffuse renal involvement. Establishing the correct diagnosis is important, since antibiotic treatment is usually adequate and unnecessary surgical intervention may be avoided.

Other. Postive Ga-67 scans have been described in several other nonmalignant and inflammatory lesions, including thyroiditis (*45*), Duchenne muscular dystrophy (*46*), and renal amyloidosis (*47*). However, its exact clinical value in detection of these lesions is unclear.

Since Ga-67 uptake in inflammation is nonspecific, a false-positive diagnosis may occur when inflammation or infection is present but not of clinical significance. Any site of injection may concentrate gallium, especially if it is a site of chronic subcutaneous or i.m. injection. Sites of recent BCG administration are "positive" on scan, as are recent surgical wounds. Persistence of activity in surgical wounds is variable, depending on the speed of healing. Activity in most wounds resolves in about 2 wk or less. Asymmetric uptake in a recent surgical wound should raise the possibility of a wound abscess. Sites of implantation of surgical drains and colostomies often have increased uptake on scan. Finally, cutaneous metal retention sutures may cause reaction at the site of insertion or other skin contact, causing Ga-67 uptake that can easily be mistaken for an intra-abdominal lesion.

Although Ga-67 lacks the specificity of other diagnostic tests, it has proven extremely valuable as a diagnostic aid and in many inflammatory diseases. One of the chief problems with gallium has been its localization in bowel—and to a lesser extent in other organs—which may obscure or confuse the detection of lesions. Newer diagnostic procedures, such as specifically radiolabeled leukocytes (*48*), may ultimately supplant Ga-67 imaging for those lesions in which activity in bowel and adjacent organs create diagnostic problems. The preparation of In-111 leukocytes is currently beyond the capability of most small radiopharmacies, but efforts to modify and simplify these methods may eliminate this problem. Also, whereas initial clinical studies with radiolabeled leukocytes are in general encouraging, the specific scope of these agents must be defined. Hence Ga-67 will remain a significant diagnostic aid in the detection of inflammatory disease at least through the immediate future.

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