

Society of Nuclear Medicine Procedure Guideline for Gallium Scintigraphy in the Evaluation of Malignant Disease

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I. Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in recommending, performing, interpreting and reporting the results of gallium-67 citrate (Ga-67) imaging in the evaluation of patients with malignant disease.

II. Background Information and Definitions

- A. Ga-67 is a group IIIA metal which has been used for imaging a variety of solid neoplasms for more than 25 years.
- B. Ga-67 imaging of neoplastic disease has shown the greatest utility in imaging lymphoma. The guideline will concentrate on the use of this technique in lymphoma although the technical aspects of image collection and processing may be applied to the imaging of other neoplastic diseases.
- C. Ga-67 has proven useful in the management of patients with lymphoma for:
 - 1. Staging the extent of disease;
 - 2. Detecting relapse or progression of disease;
 - 3. Determining response to therapy;
 - 4. Predicting outcome.
- D. Meaningful compilation of sensitivity and specificity for imaging lymphoma is difficult because of differences in technique, differences in reporting the data regarding the number of lesions detected, or the number of cases detected, and variations in nomenclature and reporting of histopathology. Further, most "gallium avid" lesions are not examined by biopsy.

III. Common Indications

- A. Lymphoma
 - 1. Hodgkin's Disease (HD)

The overall sensitivity and specificity of Ga-67 for the detection of Hodgkin's disease is about 90%, exceeding other imaging modalities such as CT or MRI.

When CT shows residual soft tissue mass after therapy, Ga-67 scintigraphy accurately predicts tumor viability.

2. Non Hodgkin's Lymphoma (NHL)

In NHL, Ga-67 localization correlates with cell type and proliferative rate of the tumor. Diffuse large cell lymphomas (DLCL) which include diffuse histiocytic lymphoma (DHL) and poorly differentiated lymphocytic lymphoma (PDLL) represent about two-thirds of newly diagnosed lymphomas and are very gallium avid. Kaplan et al. prospectively evaluated the ability of gallium to define residual disease and predict outcomes in 37 consecutive patients with DLCL. They concluded that continued Ga-67 uptake during therapy predicted a poor outcome. Most of the intermediate grade lymphomas and all of the high grade lymphomas demonstrate high gallium avidity. For example, small non-cleaved cell lymphoma (Burkitt's lymphoma) shows avid Ga-67 localization. In contrast to the other cell types, low grade lymphomas such as well-differentiated lymphocytic lymphoma (WDLL) have been found to have poor Ga-67 avidity.

3. Recurrence, Restaging, Management, and Outcomes in Both HD and NHL

Histology is almost always known prior to ordering Ga-67 imaging. Thus, an optimal test sequence can be tailored to each patient. Furthermore, in advanced stage disease management and outcome can be influenced by the unique information provided by the Ga-67 scan. Front et al have studied the predictive value of Ga-67 in approximately 100 patients with HD and NHL. They documented the utility of gallium scanning in restaging patients and predicting survival. The test has much to offer in patients with aggressive lesions, advanced stage, or whose management is otherwise problematic. In these patients it is necessary to know: (a) the gallium avidity of the tumor; (b) the response of the tumor to therapy; and (c) the timing of the therapeutic response. Answers to these questions require performance of sequential studies before, during and after therapy. Any patient for whom the gallium scan is considered part of the work-up of their disease should undergo a baseline study before therapy.

B. Additional tumors that have been shown to be gallium-avid include:

1. Lung cancer
2. Melanoma
3. Hepatocellular carcinoma
4. Sarcoma
5. Testicular tumors

6. Multiple myeloma
7. Head and neck tumors
8. Neuroblastoma

The utility of Ga-67 scanning in patients with these tumors is not addressed in this guideline.

IV. Procedure

A. Patient Preparation

1. Bowel preparation is optional. (See V.C.)
2. Oral laxatives before to imaging may decrease activity in the bowel. Bulk in the diet facilitates transit of Ga-67 through the gut.

B. Information Pertinent to Performing the Procedure

1. A relevant history and physical examination are prerequisites to Ga-67 tumor imaging. Relevant pathological, radiological, and laboratory data should be correlated.
2. Specific attention should be directed to:
 - a. Tumor cell type, size and location;
 - b. Degree of transferrin saturation (e.g., hemolysis or recent transfusion);
 - c. Interfering drugs such as recent chemotherapy treatment with iron preparations, chelation therapy, or recent MRI with gadolinium contrast agent;
 - d. Recent surgery, radiotherapy, diagnostic procedures, or trauma;
 - e. Presence of inflammatory lesions or infectious processes.

C. Precautions

None

D. Radiopharmaceutical

1. Ga-67 has a half-life of 78 hr. It is supplied as the soluble citrate salt in the +3 oxidation state. The principal photopeaks of Ga-67 are 93.3 (37.0%), 184.6 (20.4%), 300 (16.6%), and 393.5 (4.64%) keV.
2. Normal biodistribution: About 10-15% of the injected dose is excreted by the

kidneys during the first 24 hr after injection. After this the principal route of excretion is via the bowel.

3. By 48 hr after injection about 75% of the dose remains in the body and is distributed among the liver, bone and bone marrow, and soft tissues. The normal distribution is variable and also includes nasopharyngeal, lacrimal, salivary, breast (especially lactating or stimulated), thymus and spleen.
4. Mechanism of localization
 - a. Uptake of Ga-67 appears to correlate with the presence of the transferrin receptor, CD71, which may be a marker for gallium avidity.
 - b. Lactoferrin also binds Ga-67.
5. Radiation Dosimetry

Radiation Dosimetry in Adults

| Radiopharmaceutical | Administered Activity MBq (mCi) | Organ Receiving the Largest Radiation Dose mGy MBq (rad per mCi) | Effective Dose mSv per MBq (rem per mCi) |
|---------------------|---------------------------------------|--|--|
| Ga-67 ¹ | 185-370 (5-10) | 0.59 Bone Surface (2.2) | 0.12 (0.44) |

¹ ICRP 53, page 142

Radiation Dosimetry in Children (5 year old)

| Radiopharmaceutical | Administered Activity MBq (mCi) | Organ Receiving the Largest Radiation Dose mGy per MBq (rad per mCi) | Effective Dose mSv per MBq (rem per mCi) |
|---------------------|---------------------------------------|--|--|
| Ga-67 ¹ | 3.7-7.4 (0.1-0.2) | 2.3 Bone Surface (8.5) | 0.38 (1.4) |

¹ Treves, Chapter 26, Radiation Dosimetry in Pediatric Nuclear Medicine

E. Image Acquisition

1. A large field of view multipeak gamma camera with adequate shielding of the head should be used. A medium (preferred) or high energy collimator is used to perform planar or SPECT imaging. Newer instruments are well suited for gallium imaging and produce excellent clinical studies compared to older equipment. Photopeak settings should be as recommended by the manufacturer or on site determination. Use of a 20% window at 93 keV and 15% at 187 keV

was best in one phantom study.

2. Initial images are obtained at 48-72 hr post injection. Later images obtained 5 to 10 days after injection may be helpful as this allows clearance of nonspecific activity from the body and enhanced target to background in the images.
3. Typical imaging times are 10-20 min per view. For planar images of the chest it is desirable to have as many as 2,000,000 counts while spot views of the abdomen and pelvis should be acquired for approximately 1,500,000 counts. Lateral head and neck views should then be acquired for approximately 600,000 counts. Special attention should be placed in getting the chest and pelvic views without the liver in the field of view.
4. For whole-body imaging, anterior and posterior views are needed. A scanning speed to achieve an information density of greater than 450 counts/cm² or greater than 1,500,000 counts for each view is suggested.
5. The increased contrast resolution of SPECT may be helpful in obtaining studies that allow subtle lesion detection in the chest and abdomen. SPECT imaging parameters should be as recommended by the instrument manufacturer or site specific protocol. The importance of SPECT is emphasized as the reconstruction of multiple planes is critical in assessing subtle lesions in the chest and abdomen.

F. Interventions

None other than bowel preparation, which is optional.

G. Processing

1. Filter selection for SPECT images is dependent on the equipment and the user. This should be determined on site.
2. Three dimensional volume images displayed in a cine sequence may be helpful in visualizing abnormalities (dynamic kinetic effect), so step-and-shoot mode is preferred.

H. Interpretation Criteria

1. Interpretation of the Ga-67 scan requires knowledge of the physiologic distribution of activity in liver, spleen, bone marrow, bone, gut, soft tissues and glandular tissues (lacrimal, salivary, nasopharyngeal and mammary).
2. Correlation with other imaging modalities is essential.
3. Quantitative interpretive criteria for distinguishing benign from malignant etiology of hilar uptake have been proposed.

I. Reporting

The report should include:

1. Whether the distribution of Ga-67 is physiologic as described in IV.H.1.
2. All abnormal areas of uptake should be enumerated and if possible characterized as:
 - a. Malignant
 - b. Benign but abnormal (e.g., infected surgical wound)
 - c. Artifactual (e.g., fecal contamination of the gluteal region)
3. Correlation with other imaging modalities and clinical history.

J. Quality Control

1. Quality control for the gamma camera and image display are as enumerated by the *Society of Nuclear Medicine Procedure Guideline for General Imaging*.
2. Demonstration of spatial registration in multiple energy windows may be required to optimize image quality.

K. Sources of Error

1. Other diagnostic studies may be required to define the underlying pathology when either tumor or inflammation may be the cause of the uptake. See the *Society of Nuclear Medicine Procedure Guideline for Gallium Scintigraphy in Inflammation*.
2. Patient motion frequently occurs with long imaging times. This can be minimized by careful positioning and ensuring patient comfort prior to image acquisition. Motion correction software may be helpful in restoring motion degraded SPECT images.
3. Residual bowel activity may be mistaken for disease or obscure underlying lesions in the abdomen. SPECT may help to distinguish bowel activity from an abdominal or pelvic tumor.
4. Faint pulmonary hilar uptake may be seen in adult patients, particularly smokers. More prominent hilar uptake can also be observed following chemotherapy and radiation therapy.
5. Thymic hyperplasia may be visualized in the anterior mediastinum and is known

to occur as a rebound response after chemotherapy. Occasionally, uptake in the mediastinum and other sites occurs for unknown reasons.

6. Chemotherapy may decrease gallium uptake. Gallium studies should be performed prior to induction chemotherapy or at least 3 wk after the last course of chemotherapy.
7. Gadolinium used for MRI contrast enhancement has been observed to decrease Ga-67 localization when given within 24 hr of injection.
8. Iron administration may alter the biodistribution of Ga-67 by competing for transferrin receptor sites in plasma and tissue.
9. Bone marrow harvest may cause uptake at the site of the procedure.
10. Well differentiated lymphocytic lymphoma usually does not accumulate Ga-67. Low-grade lymphomas may be better visualized with thallium-201 or technetium 99m-MIBI, or FDG/PET.

V. Issues Requiring Further Clarification

- A. Economic and therapeutic implications of using Ga-67 for imaging the lymphomas.
- B. Is the transferrin receptor (CD71) a reliable marker for gallium avidity in lymphoma and other tumors? If so can this information be used to guide the work-up and management of CD71 positive tumors?
- C. Whether the use of “bowel preparation” is of clinical utility is not agreed upon by experts.
Preparation with oral laxatives prior to imaging is controversial. Studies have revealed either no significant difference in Ga-67 interference or low rates of compliance. Although in theory, laxatives and high bulk diets may facilitate transit of Ga-67 through the bowel and decrease radiation burden, there are no studies which document that this is clinically significant. Further, in the patient who has been treated with chemotherapy or is immunosuppressed, vigorous catharsis may be associated with sepsis due to break down of the intestinal epithelial defense mechanisms.
- D. Advantages and disadvantages of Ga67 imaging as compared to FDG/PET.

VI. Concise Bibliography

For a more comprehensive bibliography refer to previous version 1 and 2. The following recent publications are relevant and appended to previous versions.

- A. Delcambre C, Reman O, et al. Clinical relevance of gallium-67 scintigraphy in lymphoma before and after therapy. *Eur J Nucl Med.* 2000;27:176-184.
- B. Frohlich DEC, Chen JL, et al. When is hilar uptake of ⁶⁷Ga-citrate indicative of residual disease after chop chemotherapy? *J Nucl Med.* 2000;41:269-274.

- C. Front D, Bar-Shalom R, et al. Aggressive non-hodgkins lymphoma: early prediction of outcome with ⁶⁷Ga scintigraphy. *Radiology*. 2000;214:253-257.
- D. Ha CS, Choe J, et al. Agreement rates among single photon emission computed tomography using gallium-67: computed axial tomography and lymphangiography for Hodgkin's disease and the correlation of image findings with clinical outcome. *Cancer*. 2000;89:1371-1379.
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- I. Rehm PK. Gallium-67 scintigraphy in the management of Hodgkin's disease and non-Hodgkin's lymphoma. *Cancer Biother Radiopharm*. 1999;14:251-262.
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- M. Zizani PL, Magagnoli M, et al. Diagnostic role of gallium scanning in the management of lymphoma. *Acta Haematologica*. 1999;84:604-607.
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VII. Disclaimer

The Society of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high quality nuclear medicine procedures. These generic recommendations cannot be

applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialized practice setting may be quite different than the spectrum of patients seen in a more general practice setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, the resources available to care for patients may vary greatly from one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

Advance in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.

VIII. Last House of Delegates Approval Date: June 23, 2001

IX. Next Anticipated Approval Date: June 2004

X. Appendix: Description of Guideline Development Process

A. Guideline Development Subcommittee:

B. Task Force Chair and Members 2001:

Stephen P. Bartold, MD - Chair; Kevin J. Donohoe, MD; James W. Fletcher, MD;
Thomas P. Haynie, MD; Robert E. Henkin, MD; Annick D. Van Den Abbeele, MD;
and Edward B. Silberstein, MD.

C. History of House of Delegates Approval Dates

Version 1.0 - January 14, 1996

Version 2.0 - June 7, 1998

Version 3.0 – June 23, 2001

D. Revision History

1. Version 2.1

a. Names of each detailed reviewer and the percentage of lines with which the reviewer agreed: Task Force Members 2001

Kevin J. Donohoe, MD (94%); Thomas P. Haynie, MD (95%);
Robert E. Henkin, MD (99%); Otto Lang, MD (EANM) (97%); and
Edward B. Silberstein, MD (97%).

b. Names of other reviewers:

Helena R. Balon, MD (97%).

c. Line-by-line listing of all comments and the action taken on each Comment (Fully Implemented; Partially Implemented; Not Implemented).

See Comment Report on file – *Procedure Guideline for Gallium Scintigraphy in the Evaluation of Malignant Disease.*

d. Date completed:

May 29, 2001

e. House of Delegates Approval Date: June 23, 2001

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