# $^{67}$Ga Scintigraphy

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## 1. Introduction

$^{67}$Ga has been used in nuclear medicine since 1969 for imaging of solid tumours and chronic infections. $^{67}$Ga is cyclotron-produced and is delivered as an isotonic sterile citrate solution for intravenous use. The uptake mechanism for $^{67}$Ga is extremely complex. $^{67}$Ga leaves the circulation to become distributed in the interstitial space before entering the cell through a process of binding and uptake in the cell membrane. The biological behaviour of intravenously administered $^{67}$Ga most resembles that of iron. $^{67}$Ga binds primarily to transferrin, an iron transport protein. The degree of binding depends on the oxidation state, the pH and the solubility of $^{67}$Ga. The transportation of $^{67}$Ga transferrin through the cell wall is normally a slow process requiring late imaging (24-72 h p.i.). However, tumours have blood vessels with greater permeability than normal vessels, allowing earlier imaging to be performed. Moreover, tumours contain a higher concentration of transferrin to which gallium can bind. The presence of this tumour-specific transferrin receptor forms the main uptake mechanism of $^{67}$Ga in tumours. Following uptake in the cell, the complex is converted to ferritin, an iron storage protein accounting for up to 40% of the total concentration of protein in the cell. In a focus of infection, the gallium transferrin complex passes into the extracellular space. The free lactoferrin present in the focus binds to the surface of lymphocytes and macrophages and forms a gallium lactoferrin complex by way of a competitive process that takes place between the lactoferrin and transferrin for binding to gallium. Lactoferrin has a greater affinity for gallium than transferrin. Malignant lymphomas have a high concentration of lactoferrin and therefore take up $^{67}$Ga well. $^{67}$Ga is also taken up via lactoferrin in secretary organs such as the lacrimal, salivary and mammary glands. During lactation, the production of lactoferrin is increased, as is the number of gallium lactoferrin complexes. Bacteria and other pathogenic microorganisms are able to take up gallium directly due to the presence of siderophores; these low molecular weight chelates bind to gallium and facilitate intracellular incorporation.
Scintigraphic imaging is usually planar and whole body. Supplementary SPECT images of the region of interest make the examination both more sensitive and easier to assess.

## 2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

## 3. Indications

The use of gallium scintigraphy as a diagnostic modality within nuclear medicine has become less common due to the increasing use of FDG-PET. Many of the indications listed below are therefore no longer relevant unless a PET scanner is not available for use.

a. Cardiac sarcoidosis

b. Localisation of renal infection
c. Fever of unknown origin with unknown focus and negative PET
In the absence of PET, Gallium scintigraphy is also used for:
d. Tumour detection, staging, follow-up and restaging of malignant lymphoma (Hodgkin's, Non-Hodgkin's, Burkitt and nodular histiocytic lymphoma) andsoft tissue sarcoma. Melanoma, pulmonary carcinoma, mesothelioma, testicular carcinoma, tumours of the head and neck and hepatocellular carcinoma also take up $^{67}$Ga but gallium scintigraphy no longer plays a role in diagnosing these types of tumour.
e. Diagnosis and follow-up of chronic interstitial lung abnormalities including: sarcoidosis, idiopathic pulmonary fibrosis and related diseases. Gallium scintigraphy no longer plays a role in the diagnosis of acute interstitial pulmonary diseases such as pneumocystis carinii pneumonia and cytomegalovirus.
f. Localisation of infection with unknown focus.

**4. Relation to other diagnostic procedures**

a. Gallium scintigraphy is much more sensitive than radiodiagnostic investigations for evaluating the activity of chronic interstitial pulmonary abnormalities and malignant lymphoma. However, PET is more sensitive than either of these modalities, and is also easier to assess due to its higher target to non-target ratio. Acute interstitial pulmonary diseases such as pneumocystis carinii pneumonia or cytomegalovirus are no longer diagnosed using gallium scintigraphy, but via bronchoalveolar lavage.
b. Tumour and infection localisation with an unknown primary focus often takes place after a comprehensive medical history has been taken and the patient has undergone extensive physical, biomedical, microbiological and radiodiagnostic tests. PET is then also preferable to gallium scintigraphy.
c. PET and leukocyte scintigraphy (including labelled monoclonal antibodies) are the investigations of choice to demonstrate a focus of infection in the thorax, abdomen or around a joint prosthesis. However, gallium scintigraphy is preferable for demonstrating a focus of infection in the kidneys. A supplementary gallium scintigram might be considered in the event of negative PET scan results in patients with fever of unknown origin.

**5. Medical information nessecary for planning**

a. Case history/symptoms and abnormalities found on physical examination.
b. Depending on the indication, relevant laboratory test results such as ESR, leukocyte levels, blood count, blood and other cultures, lysozyme, gamma globulin.
c. Results of radiodiagnostic investigations.
d. Cytology and histology results.

**6. Radiofarmacon**

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| Tracer: | $^{67}$Ga gallium citrate |
| Nuclide: | Gallium-67 |
| Activity: | 185 MBq |
| Administration: | intravenous |

**7. Radiation safety**

Animal reproductive studies have not been conducted with Gallium Citrate $^{67}$Ga injection. It is not known whether Gallium Citrate $^{67}$Ga injection can cause foetal harm when administered to a pregnant woman or whether it can affect reproduction capacity. Gallium Citrate $^{67}$Ga should be given to a pregnant woman only if clearly needed. Ideally, investigations using radiopharmaceuticals, especially those elective in nature, in a woman of childbearing capability, should be performed during the first few (approximately 10) days following the onset of menses.

*Nursing mothers*

Gallium Citrate $^{67}$Ga is excreted in human milk; therefore, formula feedings should be substituted for breast feedings. Breast feeding should be interrupted for at least 3 weeks according to ICRP 106

*Pediatric use*

Safety and effectiveness in the pediatric population has not been established.

*Medical personnel*

For medical personnel, there are no specific requirements for working with patients injected with $^{67}$Ga.

**8. Patient preparation/essentials for procedure**

*Patient preparation*

A 48 h waiting period is usually required following injection. Scintigraphic imaging may be performed up to five days post injection. Preparation with laxatives before imaging is usually not helpful.

*Essentials for procedure*

a. Preferably anterior and posterior planar whole body imaging performed with the patient in supine position using a double-headed camera at 48-72 h following injection of the radiopharmaceutical.
b. For cardiac sarcoidosis: Planar, anterior-posterior regional images at 10 min p.i. supplemented by SPECT imaging of the heart region.
c. Supplementary SPECT imaging of the region of interest, the region of suspected abnormality, or of the abdomen in cases of restrictive bowel activity is strongly recommended.
d. Late images of the abdomen (72 and 96 h p.i.) if bowel activity is restrictive and supplementary SPECT images do not provide adequate information. A whole body gallium scintigram generally includes the head to the pelvis. Total head to foot imaging is recommended for sarcoidosis.
e. Marking: It may be helpful to mark any abnormalities to aid physical examination, radiodiagnostic follow-up and/or biopsy.

**9. Acquisition and processing**

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| Energy: | $^{67}$Ga setting, 93 keV, 184 keV, 296 keV |
| Window: | 20% over each peak |
| Collimator: | MEAP |
| Whole body images: | Scan speed 6 cm/min (or 8 cm/min when legs are included) |
| | Matrix size 128x512 |
| Regional imaging: | 10 min per image |

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| | Matrix size 128x128 |
| SPECT: | 60 sec per projection using a double-headed camera. Matrix size 64x64x16 |

**10. Interpretation**

a. The specificity of this examination with regard to infection and tumour localisation is low. Even arthritis, for example, can result in pathological gallium uptake.

b. Increased gallium uptake in the lacrimal and salivary glands in combination with increased gallium uptake in the pulmonary hili and/or mediastinum: high probability of sarcoidosis. At a later stage, sarcoidosis can also result in increased gallium uptake in the lungs, initially with and later without increased gallium uptake in the pulmonary hili. Extrapulmonary localisations are often detected in areas including the supradiaphragmatic and subdiaphragmatic lymph node regions, and in the muscles (lower extremities!) and in the spleen.

c. Diffusely increased pulmonary uptake without pathological uptake in lacrimal and salivary glands and pulmonary hili can indicate sarcoidosis, but also acute or chronic interstitial pulmonary abnormalities.

d. Focally increased pulmonary uptake without pathological uptake in lacrimal and salivary glands can indicate conditions including pulmonary infection, tuberculosis, pulmonary malignancy and pleural malignancy.

e. Asymmetrically increased uptake in lymph node regions: neck, supraclavicular and infraclavicular, axillary, mediastinal, hilar, para-aortic, para-iliac and inguinal can indicate a malignant lymphoma. However, not all malignant lymphomas show increased gallium uptake (depending on the degree of malignancy). Low-grade lymphomas and soft tissue sarcomas show normal to very slightly increased gallium uptake. Gallium scintigraphy can be used to stage malignant lymphoma if no PET scanner is available. Once it is known that a lymphoma takes up $^{67}$Ga, this can serve as a sensitive tool with which to assess the progression or regression of the disease. However, residual abnormalities that no longer contain any activity may remain slightly positive.

f. Special attention must be paid to artifacts such as hot spots caused by contamination from faeces, particularly in the region of a faecal stoma, and hot spots caused by newly formed scar tissue, for example following recent surgery. In such cases, SPECT may provide important supplementary information.

g. Incidental uptake of $^{67}$Ga has been described for meningiomas and asymptomatic radiation induced sialadenitis. Adult respiratory distress syndrome (ARDS) produces diffusely increased pulmonary uptake irrespective of the presence of pneumonia.

h. In AIDS patients, increased $^{67}$Ga uptake in the stomach does not necessarily indicate malignant lymphoma. This is often caused by non-malignant conditions such as cytomegalovirus or non-specific gastritis.

**11. Report**

The report should include a note of the uptake of $^{67}$Ga citrate (physiological or otherwise) in lacrimal, salivary and mammary glands, liver, bone marrow and bowel.

## 12. Literature


- http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=e9ef06a5-5a61-47df-9203-2573454c0591.
- MIRD Dose Estimate Report No.2, J. Nucl. Med. 14:755-6 (1973).