

## Comparison between early and delayed images of $^{67}\text{Ga}$ scintigraphy for evaluation of recurrent lymphoma

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### ABSTRACT

**Introduction:** Despite widespread use of  $^{67}\text{Ga}$  Gallium for lymphoma evaluation, timing of imaging after injection is a matter of controversy and to the extent of our knowledge no direct comparison has been made between early and delayed gallium images. We aimed to compare 24 and 48 hours post injection planar gallium imaging for evaluation of lymphoma recurrence.

**Methods:** 255 patients suspicious of recurrent lymphoma were included in the study. Twenty four and 48 hours post injection (10 mCi) whole body Gallium imaging was performed. Semi-quantitative evaluation (background corrected) was carried out in positive whole body  $^{67}\text{Ga}$  Gallium scans. Diagnosis of recurrence was made by combination of clinical or pathologic examination if possible. In 59 patients the final diagnosis was made by tissue biopsy. In case of uncertain diagnosis, follow up of the patients (mean duration of 13 months) was used. The diagnosis was finally made by the referring hematologist.

**Results:** Whole body gallium scintigraphy was positive in 115 out of 150 patients with recurrence (sensitivity of 76%). Comparison of the 24 and 48 hour images did not show any new lesion in the 48 hour images. However, delayed 48 hours images were required for definite detection of the gallium avid lesions in the abdominal and pelvic areas in 40 patients. Semi-quantitative evaluation of the lesions showed higher lesion to background ratio for 48 compared to the 24 hour images ( $p < 0.001$ ).

**Conclusions:** Considering higher lesion to background activity in the 48 hour images, delayed whole body  $^{67}\text{Ga}$  Gallium imaging may be more desirable for diagnosis of recurrent lymphoma, however 24 hour images may be sufficient. Delayed imaging can be reserved for suspicious activities (such as in abdominal images). This strategy can save time and is more convenient for the imaging centers.

**Keywords:**  $^{67}\text{Ga}$  Gallium, SPECT, Planar imaging, Lymphoma, Time of Imaging

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## INTRODUCTION

One of the most common hematopoietic system malignancies is lymphoma, which is distinguished by lymphadenopathy in various parts of the body (1, 2).

Although cross-sectional studies such as CT scanning are in increasing use for management of lymphoma, these procedures are not adequate enough to evaluate recurrence or disease resistance after treatment (3).

A shortcoming of anatomical imaging such as CT scan is difficulty in differentiating between residual tumor masses and non-viable necrotic tissues (4, 5).

Nuclear medicine procedures play an important role in these situations including FDG-PET,  $^{67}\text{Ga}$ , etc (6, 7).

Gallium is a tumor-imaging agent which presents important prognostic and diagnostic information regarding lymphoma (8-10). Its uptake is an indicator of the presence of viable lymphoma tissue while in fibrotic and necrotic tissue gallium scan is negative (11). In addition, gallium scan has a high sensitivity and specificity in order to diagnose the early recurrence of lymphoma (12-14). SPECT scanning is routinely used and significant evidence illustrates that SPECT method improves the sensitivity and specificity of  $^{67}\text{Ga}$  imaging not only before but also after treatment (3).

Timing of imaging after injection is a matter of controversy. Although guidelines and several studies recommend delayed imaging (after 48 hours) for better detection of  $^{67}\text{Ga}$  avid lesions (with increasing target to background ratio), to the extent of our knowledge no direct comparison has been made between early and delayed gallium imaging (10, 15-19).

In the current study, we compared 24 and 48 hours post injection planar gallium imaging in patients referred to our department for evaluation of lymphoma recurrence.

## METHODS

255 patients referred to our department for evaluation of suspicious recurrent lymphoma with  $^{67}\text{Ga}$  scintigraphy (from April 2004 to January 2009) were included in the study. Intravenous Gallium-67 was used for all patients with the dose of 10 mCi. Twenty four and 48 hours post injection whole body imaging was performed for the patients using dual head variable angle gamma camera (E.CAM Siemens). All patients used mild laxative (Milk of Magnesia (MOM)) during the acquisition days. In case of any suspicious activity (for example in the abdomen), complementary projections as well as delayed imaging were done. Four  $^{67}\text{Ga}$  photopeaks with 20% window (93, 184, 300, and 393 KeV) were used and the camera was equipped with a medium energy collimator. Whole body scanning was performed at the speed of 10 cm/min. Two nuclear medicine physicians reviewed the images independently in retrospect. Twenty four and 48 hour whole body image sets were evaluated regarding any activity outside the normal distribution of the  $^{67}\text{Ga}$  in the body. In case of any disagreement, the third nuclear medicine specialist opinion was requested. Semi-quantitative evaluation (background corrected) was also performed in positive whole body  $^{67}\text{Ga}$  scans by placing ROIs on the active lesions as well as on the thigh soft tissue on both sets of 24 and 48 hour images. Lesion to background ratio was calculated as (total counts of lesion ROI-total count of a same size thigh ROI) divided by total count of a same sized thigh ROI.

Diagnosis of recurrence was made by combination of clinical (palpable lymph nodes, presence of symptoms such as fever, night sweating, anorexia, or weight loss, elevated liver function tests and Erythrocyte Sedimentation Rate (ESR)) and imaging

findings (chest X-Ray, CT scan, ultrasound examination) or pathologic examination if possible (2). In 59 patients the final diagnosis was made by tissue biopsy. Any new lymphadenopathy in the CT scan in the proper clinical setting was considered as recurrence. In case of uncertain diagnosis, follow up of the patients (mean duration of 13 months) was used. The diagnosis was finally made by the referring hematologist.

Data were analysed by SPSS version 11.5. Continuous variables were shown as mean  $\pm$  standard deviation (SD). Paired t-test was used for comparison of means between 24 and 48 hour images.  $P=0.05$  was set as the threshold of statistical significance.

## RESULTS

Baseline characteristics of the patients are shown in Table 1. The age range of the patients was 11-60 years.

Lymphoma recurrence was the final diagnosis in 150 patients. The anatomical location of the recurrence and  $^{67}\text{Ga}$  positivity rate for each location is presented in Table 2.

For supra-diaphragmatic and infra-diaphragmatic lymphadenopathies the sensitivity of scintigraphy was 77.5% (131/169) and 66.6% (12/18) respectively.

The whole body  $^{67}\text{Ga}$  scintigraphy was positive in 115 out of 150 patients with recurrence (sensitivity of 76% ([70%-83%] with 95% confidence intervals)). Comparison of the 24 and 48 hour image sets did not show any new lesion on the 48 hour images. However, delayed 48 hours images were required for definite detection of the  $^{67}\text{Ga}$  avid lesions in the abdominal and pelvic areas in 40 patients. Semi-quantitative evaluation of the lesions showed the mean lesion to background ratio of  $2.3\pm 1.1$  and  $3.1\pm 0.9$  for 24 and 48 hour images respectively ( $p<0.001$ ) (Figure 1).

## DISCUSSION

It is shown that early detection of lymphoma can increase the chance of long-term survival of the patients (10). The superior imaging modality for lymphoma imaging is  $^{18}\text{F}$ -FDG PET (20), but procedures such as  $^{67}\text{Ga}$  study are still in use in those centers not equipped with PET facility.

**Table 1.** Baseline characteristics of the patients.

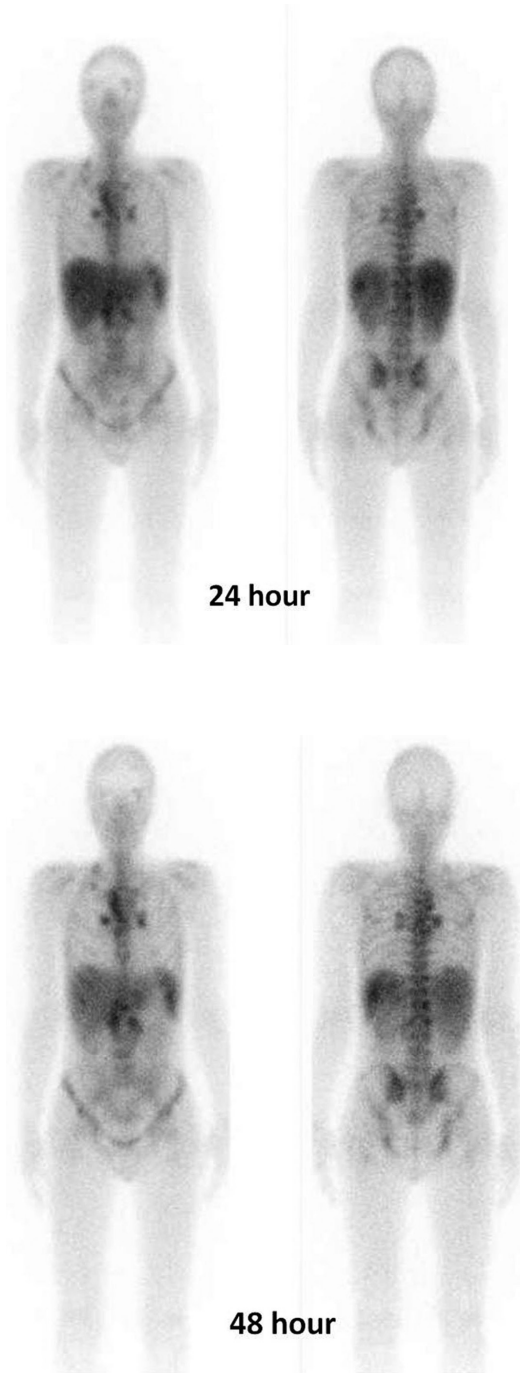
		Number of patients with recurrence	Number of patients with positive $^{67}\text{Ga}$ -Scan	P value
<b>Age</b>	24.3 $\pm$ 14 years	N/A	N/A	N/A
<b>Gender</b>				>0.05
Female	115	76	58	
Male	140	74	57	
<b>Lymphoma Type</b>				>0.05
Hodgkin's	101	65	50	
Non-Hodgkin's	149	85	65	
Indolent	5	1	1	
Aggressive	144	84	64	

Early detection of lymphoma can be achieved by several methods such as routine clinical examination, and lab or imaging findings. Several studies showed that  $^{67}\text{Ga}$  scintigraphy especially with the SPECT method can detect lymphoma recurrence more efficiently than the other methods (such as clinical examination and CT scanning) (12, 13, 21-24).

**Table 2.** Rate of  $^{67}\text{Ga}$  positivity for different anatomical locations of recurrence.

Site	Number of patients	Patients with positive scintigraphy
<b>Lymphadenopathy</b>		
Neck	27	26(96.2%)
Supraclavicular	7	7(100%)
Axillary	10	7(70%)
Intra-thoracic	125	101(80.8%)
Retro-preitoneal	12	7(58.3%)
Inguinal-pelvic	6	5(83.3%)
<b>Visceral</b>		
Liver	3	3(100%)
Lung	9	7(77.7%)
Spleen	9	6(66.6%)
Bone	2	1(50%)

Our study showed 76% overall sensitivity for detection of lymphoma recurrence which is in accordance to the other studies (3). Different genders and types of lymphoma (Hodgkin's and NHL) did not show any statistically significant difference regarding sensitivity for recurrence detection. This is also in accordance to other studies (24-27). Although it is reported that sensitivity of  $^{67}\text{Ga}$  scintigraphy depends on the histological sub-type of the lymphoma with higher sensitivity in aggressive types, in our study the number of patients with indolent lymphoma was not high enough to make any conclusion in this regard (28).



**Figure 1.** 24 and 48 hour whole body  $^{67}\text{Ga}$  scintigraphy images of a patient with recurrent lymphoma. Note higher lesion to background activity of the 48 hour images in the thoracic as well as abdominal lesions.

The anatomical location of lymphoma lesions also affects the sensitivity of  $^{67}\text{Ga}$  scintigraphy for diagnosis. It is reported that supra-diaphragmatic lesions are more likely to be detected by  $^{67}\text{Ga}$  imaging compared to the sub-diaphragmatic involvement (18, 29, 30). This was also true in our study. For supra-diaphragmatic and infra-diaphragmatic lymphadenopathies the sensitivity of scintigraphy was 77.5% (131/169) and 66.6% (12/18) respectively. It is also shown that sensitivity of lesion detection was higher in neck and mediastinum compared to the retroperitoneal region or axilla (29). Our study also showed the same finding (sensitivity of 96.2% and 80.8% for neck and mediastinal lymph nodes and 70% and 58.3% for axillary and retroperitoneal lymph nodes). The lower sensitivity for the lesions in the sub-diaphragmatic area is most likely due to interfering activity of the  $^{67}\text{Ga}$  in the abdomen specially colon (29). It is worth mentioning that our study suffered from low sample size in the axillary and retroperitoneal lymph nodes likely affecting the results.

$^{67}\text{Ga}$  has been used for imaging different tumors since approximately 25 years ago (15) for staging (30), detecting progression or relapse (12), predicting of outcome (26) and response to therapy (18). The physical half-life of gallium-67 is 78 hours and during the first 24 hours after injection about 10-15% of injected dose of gallium is excreted by kidneys. After this time gastrointestinal tract is the principal way of excretion. This is the main reason that imaging of abdominal tumors can be problematic in some patients. 48 hours after injection, almost 75% of injected gallium remains in the patient's body and is distributed among different body organs such as soft tissues, bone, bone marrow and liver (16). Generally, initial images are obtained 18-72 hours post injection. Delayed images at 96 hours or later (5-10 days after injection) may be necessary for

clearance of nonspecific body activities and also in abdomen imaging (routine renal and colonic activity can alter scintigraphies of abdomen). Early images, at 4-6 hours post injection, are also helpful in acute inflammation in order to omit extensive bowel activity (15, 19).

Despite the recommendation of delayed imaging in the tumor imaging with  $^{67}\text{Ga}$ , direct comparison between early and delayed images has not been studied before (17, 18). In the present study 48 hour whole body scintigraphy did not show any new lesion which was not apparent on the early images. However, semi-quantitative evaluation showed statistically significant increase in lesion to background ratio on the 48 hour images compared to the 24 hour image sets. This is due to clearance of the radiotracer from the interstitial tissues and can help to detect abnormal gallium avid lesions more easily (16).

Another aspect of  $^{67}\text{Ga}$  scintigraphy is imaging of the abdominal lesions. As mentioned above,  $^{67}\text{Ga}$  is excreted through kidneys and colon and this can cause problem in differentiation of abnormal Gallium-avid lesions from physiological activity in the colon or urinary tract. Delayed imaging is very helpful in this situation. Abnormal activity would not move as the time passes despite movement of the excreted tracer in the colon (15, 19). Our study also showed the same finding. Delayed imaging was necessary for definite differentiation of the excreted tracer in the colon from Gallium avid lesions in the abdomen in 40 patients.

## CONCLUSION

Considering higher lesion to background activity in the 48 hour images, delayed whole body  $^{67}\text{Ga}$  imaging may be more desirable for diagnosis of lymphoma recurrence, however 24 hour images would could be sufficient and delayed imaging can

be reserved for suspicious activities (such as abdominal uptakes). This strategy can save time and more convenient for the patients.

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