# Present State and Future Role of Gallium-67 Scintigraphy in Lymphoma

Dov Front and Ora Israel
*Department of Nuclear Medicine, Rambam Medical Center and the Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel*

**Key Words:** gallium-67; lymphoma
**J Nucl Med 1996; 37:530–532**

Several papers have recently been published on the use of $^{67}$Ga scintigraphy in lymphoma—with the emphasis on its value after treatment (*1–7*). These articles provide further evidence of the utility of $^{67}$Ga to monitor patients (*8–14*). The ability of $^{67}$Ga scintigraphy to detect recurrence early during clinical remission, when the tumor load is small and other tests are not sensitive enough for early detection, has been described (*2*).

Recently, we suggested the potential use of $^{67}$Ga scintigraphy to evaluate the rapidity of response to treatment, if there is the possibility to achieve better overall response by changing therapy in patients who do not respond rapidly to first line chemotherapy (*6*). While $^{67}$Ga scintigraphy has a clearly established role in determining whether a lymphoma patient has responded to treatment and in the early diagnosis of a recurrence, the number of articles on this subject is modest. This is somewhat surprising when one considers that lymphoma is a disease that can be effectively treated, particularly when the progress of the disease and its therapy in individual patients can be optimized by $^{67}$Ga. No other test or imaging procedure, other than $^{67}$Ga, can reliably monitor response and provide early detection of disease recurrence. The role of MRI to evaluate lymphoma response to treatment is not yet clear (*15–19*). Fluorine-18-fluorodeoxyglucose and PET also have been used in lymphoma patients (*20,21*). Tritiated deoxyglucose and $^{67}$Ga are both taken up in viable tumor tissue but not in fibrotic or necrotic cells (*22*). PET, however, is technically complex and much more expensive than gallium scintigraphy. The role of gamma cameras using 511 keV collimators to image [$^{18}$F]fluorodeoxyglucose remains to be evaluated.

There are several reasons why $^{67}$Ga is not uniformly and energetically accepted by the nuclear medicine community, although there is a true need for it by oncologists. This is a strange situation; one in opposition to nuclear medicine techniques that are theoretically appealing but clinicians do not readily accept as a means of routine management of their patients (*23,24*). One difficulty in the acceptance of $^{67}$Ga as a worthwhile research subject may be its image as an old, unexciting agent which has been in use for more than 20 years (*6*). Despite this image, several centers are testing new ideas on the use of $^{67}$Ga to solve various problems in the treatment of lymphoma. Understanding the needs of oncologists and the ability to cooperate with them routinely are, of course, helpful (*6,12*). The quality of $^{67}$Ga scintigraphy has improved with the use of higher doses, SPECT with dual-head cameras and delayed as well as whole-body imaging (*6,25–28*). This has contributed to an expanding role in routine clinical nuclear medicine practice.

In the 1970s and early 1980s, $^{67}$Ga was used for diagnosing and staging lymphoma prior to treatment. The need for $^{67}$Ga imaging prior to treatment, however, decreased significantly with the advent of CT, which provided the necessary diagnostic information for staging. In many ways, CT has also replaced lymphography and staging laparotomy in the initial evaluation of patients with lymphoma. Post-treatment, however, CT had false-positive results, showing residual masses in patients who later proved to have a complete therapeutic response (*8–11*). Observations of patients with residual CT masses after treatment who had negative $^{67}$Ga scintigrams and subsequent histologic demonstration fibrosis and/or necrosis, but no viable cancer cells, drew our attention to the possibility of using $^{67}$Ga scintigraphy to evaluate the presence or absence of disease after treatment (*8,22*). Iosilevsky et al. (*22*) observed a relationship between the amount of viable tissue and the amount of $^{67}$Ga and tritiated deoxyglucose uptake after treatment in a tumor model. There was no relationship between tumor size and viability. Treated, small, but completely viable tumors had normal $^{67}$Ga uptake, whereas large, necrotic and fibrotic tumors without malignant cells did not. It was subsequently demonstrated that $^{67}$Ga is a good indicator of tumor response in patients (*8–14*). A statement by Canellos (*29*) on the problem of residual mass versus residual cancer after treatment raised the oncology community's awareness of the problem. Determination of therapeutic response is critical in cancer treatment. Since treatment is best when the tumor load is smallest, $^{67}$Ga can also play an important role in early diagnosis of recurrence (*2*).

Since CT may demonstrate a mass during continuous clinical remission, it has a low sensitivity for detecting recurrence (*30*). Moreover, CT is unable to determine the presence of recurrence until there is significant growth of the mass. Gallium-67 shows tumor viability early in recurrence while the tumor burden is low.

## LIMITATIONS

The limitations of $^{67}$Ga scintigraphy should be clearly recognized and understood and image interpretation should take these difficulties into consideration. One of the basic problems of $^{67}$Ga scintigraphy is its limited sensitivity: the patient with a negative post-treatment $^{67}$Ga scintigram may have a recurrence. In these patients, therapy did not destroy all tumor cells and there is occult malignant tissue not detected by $^{67}$Ga scintigraphy. Neither $^{67}$Ga nor any other noninvasive test can detect the last malignant cell in a tumor after chemo- and radiotherapy. In fact, there is no need to detect the last cell. It is, however, necessary to detect the presence of the mass of cells sufficient to cause a recurrence. There is now evidence that small deposits of lymphoma cells, after therapy, can be subsequently destroyed

Received Mar. 29, 1995; revision accepted Sept. 21, 1995.
For correspondence or reprints contact: Dov Front, MD, PhD, Department of Nuclear Medicine, Rambam Medical Center, Haifa 35254, Israel.

by the body's own mechanisms (*31*). Current procedures cannot detect small deposits of cells which may cause disease recurrence after the patient has achieved an initial complete clinical response and appears to be in continuous clinical remission. Gallium-67 is a useful test to determine if a patient has achieved a complete response by oncological definition. A significant refinement of the diagnosis of malignancy is still necessary for diagnosis of microscopic tumor in vivo.

Another difficulty is the need for quantification of $^{67}$Ga uptake to assess the significance of low $^{67}$Ga uptake. When should low uptake be called abnormal? Experience shows that only a substantial increase in uptake should be defined as abnormal, even if it may cause some reduction of sensitivity (*6*). Expertise in reading $^{67}$Ga images is, of course, important for correct interpretation of scan findings. Nuclear medicine physicians should set their own threshold for the technique used in their own departments. Some lymphomas do not take up gallium at all (non-gallium-avid lymphomas). The existence of non-$^{67}$Ga-avid tumors in some patients dictates the need for pretreatment baseline scintigraphy. No scintigraphic evaluation is possible in patients with non-$^{67}$Ga-avid lymphoma. When $^{67}$Ga scintigraphy is only performed after treatment, it may be negative not only because the patient has achieved a complete response, but also because the lymphoma is non-$^{67}$Ga-avid.

Another major weakness in the use of $^{67}$Ga scintigraphy is that the gallium image is "loaded". In contrast to heart, lung or bone scintigraphy, in $^{67}$Ga scintigraphy, there are several structures which take up $^{67}$Ga. The liver, bone, colon, muscles and other soft tissues all take up $^{67}$Ga, and a good knowledge of normal anatomy is needed to separate abnormal from normal uptake and determine if disease exists (*27*). One must also realize that disease may involve not only the lymph nodes, but also other organs such as the bone, liver, gut, lungs and other soft tissues that normally take up $^{67}$Ga. The colon is a particular problem, and some investigators have limited their studies to the chest only. Delayed planar and SPECT studies at 7 days and planar scintigraphy 2 wk after injection, using high-sensitivity dual-head cameras, essentially solve the problem of uptake in the gut. Diffuse lung uptake can be ignored after treatment since it is a self-limited finding. Even-Sapir et al. (*7*) used SPECT quantitation and found that there is a significant difference in the amount of $^{67}$Ga uptake in mediastinal and hilar lymphoma in contrast with benign hilar uptake in which the uptake is low. This problem, which has been troublesome for some time (*32,33*), has been solved. The problem of thymus activity, however, still remains. Currently, there is no way to suppress $^{67}$Ga uptake in a hypertrophied thymus in young patients.

## FUTURE IMPLICATIONS

In the present era of cost-containment, therapies and diagnostic tests have to be cost-effective and provide data that affect treatment (*34–38*). Traditional indications for performing tests are no longer sufficient. Even in the most advanced countries, limitations are placed on healthcare. Priorities must be established, even for patients with cancer (*37*). Effectiveness can be defined as the cost per life year or as the cost per quality of life year. Treatable malignancies in which cure and long disease-free survival can be achieved should have priority over non-treatable malignancies, for which physicians cannot affect the course of the disease and, ultimately, the patient's quality of life. Lymphoma, however, is a treatable malignancy. Survival is dependent on optimal individualized treatment. In recent years, $^{67}$Ga scintigraphy has shown that it has an increasingly useful role in clinical decision making.

A detailed analysis of the cost-effectiveness of $^{67}$Ga scintigraphy in lymphoma management needs to be done. This could be calculated in the same way oncologic therapy is evaluated in terms of price of prolonging a patient's life (*34*):

Cost per year of life =

price of test/survival with test − survival without test.

This determination will require a multicenter study with matched groups of patients. The cost per year of life, and, if possible, the cost per quality of year of life, should be compared in a group monitored with $^{67}$Ga scintigraphy and possible treatment modification based on the $^{67}$Ga results and a group that did not have $^{67}$Ga scintigraphy. This type of study could provide data (Kaplan Meier plots) which compare survival of patients who had $^{67}$Ga scintigraphy and those who did not.

## CONCLUSION

To be viable and relevant, nuclear medicine must solve real problems in patient care at a reasonable price. Results of $^{67}$Ga scintigraphy in the post-treatment assessment of lymphoma appear to be quite encouraging in terms of clinical relevance. Future studies will determine the role of $^{67}$Ga scintigraphy in prolonging survival and the cost of this intervention.


## ACKNOWLEDGMENTS

We thank Dr. G.M. Kolodny for reviewing the manuscript. Supported in part by a grant from the L. Rosenblatt Foundation for Research in Cancer-Technion Research and Development Foundation, Haifa, Israel.


## REFERENCES


1. Cooper DL, Caride VJ, Zloty M, et al. Gallium scans in patients with mediastinal Hodgkin's disease treated with chemotherapy. *J Clin Oncol* 1993;11:1092–1098.
2. Front D, Bar-Shalom R, Epelbaum R, et al. Early detection of lymphoma recurrence with gallium-67 scintigraphy. *J Nucl Med* 1993;34:2101–2104.
3. Luker GD, Siegel MJ. Mediastinal Hodgkin's disease in children: response to therapy. *Radiology* 1993;189:737–740.
4. King SC, Reiman RJ, Prosnitz LR. Prognostic importance of restaging gallium scans following induction chemotherapy for advanced Hodgkin's disease. *J Clin Oncol* 1994;12:306–311.
5. Hagemeister FB, Purruganan R, Podoloff DA, et al. The gallium scan predicts relapse in patients with Hodgkin's disease treated with combined modality therapy. *Ann Oncol* 1994;5:S59–S63.
6. Front D, Israel O. The role of $^{67}$Ga scintigraphy in evaluating the results of therapy of lymphoma patients. *Semin Nucl Med* 1995;25:60–71.
7. Even-Sapir E, Bar-Shalom R, Israel O, et al. Single-photon emission computed tomography quantitation of gallium citrate uptake for the differentiation of lymphoma from benign hilar uptake. *J Clin Oncol* 1995;13:942–946.
8. Israel O, Front D, Lam M, et al. Gallium-67 imaging in monitoring lymphoma response to treatment. *Cancer* 1988;61:2439–2441.
9. Wylie BR, Southee AE, Joshua DE, et al. Gallium scanning in the management of mediastinal Hodgkin's lymphoma. *Eur J Hematol* 1988;118:1–4.
10. Front D, Israel O, Epelbmm R, et al. Gallium-67 SPECT before and after treatment of lymphoma. *Radiology* 1990;175:515–521.
11. Kaplan WD, Jochelson MS, Herman TS, et al. Gallium-67 imaging: a predictor of residual tumor viability and clinical outcome in patients with diffuse large-cell lymphoma. *J Clin Oncol* 1990;8:1966–1970.
12. Front D, Israel O, Ben-Haim S. The dilemma of a residual mass in treated lymphoma: the role of gallium-67 scintigraphy. In: Freeman L, ed. *Nuclear medicine annual*. New York: Raven Press; 1991:211–220.
13. Front D, Be-Haim S, Israel O, et al. Lymphoma: predictive value of $^{67}$Ga scintigraphy after treatment. *Radiology* 1992;182:359–363.
14. Kostakoglu L, Yeh SDJ, Portlock C, et al. Validation of gallium-67-citrate single-photon emission computed tomography in biopsy-confirmed residual Hodgkin's disease in the mediastinum. *J Nucl Med* 1992;33:345–350.
15. Dooms GC, Hricak H, Moseley ME, et al. Characterization of lymphadenopathy by magnetic resonance relaxation times: preliminary results. *Radiology* 1985;155:691–697.
16. Rahmouni A, Zerhouni EA. Role of MRI in the management of thoracic lymphoma. In: Zerhouni EA, ed. *CT and MRI of the thorax*. New York: Churchill Livingstone; 1990:23–35.
17. Nyman R, Rehn S, Glimelius B, et al. Magnetic resonance imaging for assessment of treatment effects in mediastinal Hodgkin's disease. *Acta Radiol* 1987;28:145–151.
18. Rehn S, Nyman R, Glimelius B, et al. Non-Hodgkin's lymphoma: predicting prognostic grade with MR imaging. *Radiology* 1990;176:249–253.
19. Rahmouni A, Tempany C, Jones R, et al. Lymphoma: monitoring tumor size and signal intensity with MR imaging. *Radiology* 1993;188:445–451.

20. Heokstra OS, Ossenkoppele GJ, Golding R, et al. Early treatment response in malignant lymphoma as determined by planar fluorine-18-fluorodeoxyglucose scintigraphy. *J Nucl Med* 1993;34:1706–1710.
21. Newman JS, Francis IR, Kaminski MS, et al. Imaging of lymphoma with PET with 2-[$^{18}$F]-fluoro-2-deoxyglucose: correlation with CT. *Radiology* 1994;190:111–116.
22. Iosilevsky G, Front D, Betman L, et al. Uptake of $^{67}$Ga-citrate and $^{2}$H-3-deoxyglucose in the tumor model following chemotherapy and radiotherapy. *J Nucl Med* 1985;26: 278–283.
23. Fishman AJ, Strauss WH. When magic bullets ricochet [Editorial]. *J Nucl Med* 1990;31:32–33.
24. Juni JE. Taking brain SPECT seriously: reflections on recent clinical reports [Commentary]. *J Nucl Med* 1994;35:1891–1895.
25. Anderson KC, Leonard RCF, Canellos GP, et al. High-dose gallium imaging in lymphoma. *Am J Med* 1983;75:327–331.
26. Tumeh SS, Rosenthal DS, Kaplan WD, et al. Lymphoma: evaluation with $^{67}$Ga SPECT. *Radiology* 1987;164:111–113.
27. Israel O, Jerushalmi J, Ben-Haim S, et al. Normal and abnormal $^{67}$Ga SPECT anatomy in patients with lymphoma. *Clin Nucl Med* 1990;15:334–345.
28. Front D, Bar-Shalom R, Iosilevsky G, et al. Gallium-67 scintigraphy with a dual-head camera. *Clin Nucl Med* 1995;20:542–548.
29. Canellos GP. Residual mass in lymphoma may not be residual disease [Editorial]. *J Clin Oncol* 1988;6:931–932.
30. Weeks JC, Yeap BY, Canellos GP, et al. Value of follow-up procedures in patients with large-cell lymphoma who achieve a complete remission. *J Clin Oncol* 1991;9: 1196–1203.
31. Surborne A, Longo D, De Vita V, et al. Residual abdominal masses in aggressive non-Hodgkin's lymphoma after combination chemotherapy: significance and management. *J Clin Oncol* 1988;6:1832–1837.
32. Champion PE, Groshar D, Hooper HR, et al. Does gallium uptake in the pulmonary hila predict involvement by non-Hodgkin's lymphoma? *Nucl Med Commun* 1992;13: 730–737.
33. Israel O, Front D. Benign mediastinal and parahilar uptake of gallium-67 in treated lymphoma: do we have all the answers? [Editorial]. *J Nucl Med* 1993;34:1330–1333.
34. Catane R, Catane H, Rozencweig M. Cancer therapy—economic aspects. *Harefuah* 1995;128:182–185.
35. Hornberger JC, Redelmeier DA, Petersen J. Variability among methods to assess patients' well-being and consequent effect on a cost-effectiveness analysis. *J Clin Epidemiol* 1992;45:505–512.
36. Culyer AJ, Jonsson B. Ought cancer treatments to be immune from socio-economic evaluation? An epilogue. *Eur J Cancer* 1991;29A:S31–S32.
37. Hillner BE, Smith TJ. Efficacy and cost-effectiveness of adjuvant chemotherapy in women with node-negative breast cancer. *N Engl J Med* 1991;324:160–168.
38. Grilli R, Oxamn AD, Julian JA. Chemotherapy for advanced non-small-cell lung cancer: how much benefit is enough? *J Clin Oncol* 1993;11:1866–1872.

**CORRECTION**

In the *JNM* December 1995 Table of Contents, the title of the article by Volkow et al. (page 2162) was printed incorrectly. The correct title is, "A New PET Ligand for the Dopamine Transporter: Studies in the Human Brain."