Comparison of Gallium-67-Citrate and Thallium-201 Scintigraphy in Peripheral and Intrathoracic Lymphoma

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We performed this study in an attempt to reconcile the differences with respect to 67Ga uptake as a function of tumor grade and type in the literature, as well as to determine the sensitivity of 201Tl uptake in both Hodgkin's and non-Hodgkin's lymphoma. **Methods:** Thirty-six (9 with low-grade lymphoma, 11 with intermediate-grade lymphoma, 4 with high-grade lymphoma and 12 with Hodgkin's lymphoma) patients underwent both 67Ga and 201Tl scintigraphy. Biopsies were done on all patients. A semiquantitative rating system was used to make statistical comparisons for thallium versus gallium in all lymphoma subgroups, as well as comparisons of thallium and gallium to themselves in all subgroups. **Results:** Patient sensitivity was only 56% and site sensitivity was 32% in patients with low-grade lymphoma. Conversely, 201Tl sensitivity was 100%, respectively, for patients and sites. The difference between 201Tl and 67Ga sensitivity in patients with low-grade lymphoma on a site basis was statistically significant. When compared to itself in lymphoma subgroups, 201Tl was found to be statistically more avid for low-grade lymphoma than for intermediate, high or Hodgkin's lymphoma. Gallium-67 sensitivity for low-grade lymphoma was significantly less than for Hodgkin's and intermediate grade lymphomas. No significant differences were found when 201Tl and 67Ga were compared in the intermediate, high or Hodgkin's lymphoma groups. **Conclusion:** Thallium-201 demonstrates significantly greater tumor avidity in the low-grade lymphoma group compared to 67Ga citrate. Gallium-67-citrate appears relatively nonavid for low-grade lymphoma compared to 201Tl and is statistically inferior in detecting low-grade lymphoma in comparison to its ability to detect intermediate or high-grade lymphomas. Gallium-67-citrate should not be considered dependable in evaluating patients with low-grade lymphoma. Neither 201Tl or 67Ga is dependable in the evaluation of low-grade lymphoma within the abdomen, since gallium avidity for low-grade lymphoma is low and gastrointestinal excretion of 67Ga is poorly controlled.

**Key Words:** gallium-67-citrate; thallium-201; lymphoma; scintigraphy


Gallium-67-citrate has been extensively used in evaluating patients with lymphoma (1-22). The statistical information regarding sensitivity and specificity generated for lymphoma have been reported for Hodgkin's lymphoma and non-Hodgkin's lymphoma, with only minimal attention focused on sensitivity and specificity based upon tumor grade or type. Gallium-67 tumor avidity has been used to determine tumor viability in diffuse large-cell lymphoma and Hodgkin's disease (14-21). In contrast, 67Ga tumor avidity has not been used to evaluate tumor viability in low-grade lymphoma. There is some controversy in the few studies which have addressed the issue of 67Ga uptake according to tumor grade or type (8,9). There is limited information on 201Tl accumulation in lymphoma as a general topic (23-27). We performed this study to reconcile differences with regard to 67Ga uptake in lymphoma in the literature, as well as to determine the efficacy of 201Tl uptake in both Hodgkin's and non-Hodgkin's lymphoma.

**MATERIALS AND METHODS**

Thirty-six patients with a biopsy-proven diagnosis of lymphoma were enrolled in the study. Nine patients were diagnosed as having low-grade lymphoma, 11 with intermediate-grade, 4 with high-grade, and 12 with Hodgkin's lymphoma. Biopsies were obtained on each patient from the least invasive site necessary to make the diagnosis of lymphoma. Most frequently, biopsies were done in the cervical, supraclavicular or inguinal regions. When necessary, biopsies were done invasively using CT-guided biopsy techniques or by direct surgical exploration.

Scintigraphic studies were performed within 14 days of the biopsy, with several patients biopsied following scintigraphy. If uptake was noted at the biopsy site, it was considered as a biopsy effect, as opposed to tumor, unless multiple areas at the site were present. Biopsies were limited to one site per patient.

All patients underwent 67Ga and 201Tl scintigraphic studies prior to chemo- or radiation therapy. The studies were performed within one week of each other. Twenty-five patients, however, had more than a single region demonstrating abnormality on 201Tl or 67Ga. These additional areas were not confirmed with biopsy. A site was considered as positive on 201Tl or 67Ga images if confirmation was obtained with CT, MRI, x-ray, physical examination or biopsy.

All patients had at least one area of adenopathy demonstrated on physical examination, x-ray, CT or MRI. Patients with recurrent lymphoma, only central nervous system lymphoma or only abdominal disease were excluded from the study.

**Thallium Scintigraphy**

Images were acquired with a large field of view Anger camera with high-resolution collimation beginning 2 min postinjection of 3 mCi 201Tl. Two sequential anterior images of the chest with the arms raised above the head were obtained. These were followed by images of the abdomen and pelvis with a final image of the chest acquired approximately 1 hr postinjection. When necessary, 10-min oblique projections with the arms raised above the head were obtained to separate underlying structures such as the heart from suspected tumor areas.

Data were acquired using an 80-kV photopeak with a 20% window. Digital images were acquired and displayed using a 256 × 256 matrix.

**Gallium Scintigraphy**

Immediately following the 201Tl study, patients were injected with 6-10 mCi 67Ga-citrate and scanned 2 and 4 days postinjection. Gallium-67 photopics of 93, 184 and 296 keV with a 20% window were used to acquire the data. Images were acquired and displayed using a 256 × 256 matrix. Anterior and posterior total-body scans were obtained at a scan speed of 10 cm/min. High-resolution spot images of the chest, abdomen and pelvis were obtained when necessary using a preset time of 10 min.
Sensitivity for Thallium-201 and Gallium-67 in Lymphoma by Cell Type

<table>
<thead>
<tr>
<th>Lymphoma Type</th>
<th>Sensitivity (Patient)</th>
<th>Sensitivity (Site)</th>
<th>Sensitivity (Patient)</th>
<th>Sensitivity (Site)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade</td>
<td>9/9 (100%)</td>
<td>34/34 (100%)</td>
<td>5/9 (56%)</td>
<td>11/34 (32%)</td>
</tr>
<tr>
<td>Intermediate Grade</td>
<td>11/11 (100%)</td>
<td>36/46 (83%)</td>
<td>11/11 (100%)</td>
<td>33/46 (72%)</td>
</tr>
<tr>
<td>High Grade</td>
<td>3/4 (75%)</td>
<td>8/9 (88%)</td>
<td>4/4 (100%)</td>
<td>7/8 (78%)</td>
</tr>
<tr>
<td>Hodgkin's</td>
<td>12/12 (100%)</td>
<td>25/28 (89%)</td>
<td>12/12 (100%)</td>
<td>21/28 (75%)</td>
</tr>
</tbody>
</table>

Total Patients = 36
Sites = 17

Rating System for Thallium-201 and Gallium-67

Comparative Studies

A semiquantitative rating system was used to compare \( \text{\(^{67}\text{Ga}\)} \) and \( \text{\(^{201}\text{TI}\)} \) studies. Background activity in the axillary area was compared with \( \text{\(^{201}\text{TI}\)} \) and \( \text{\(^{67}\text{Ga}\)} \) activity within the abnormal sites. A five-point rating system was used in which zero indicated activity within the lesion to be equivalent to background within the axilla (no detectable lesion): 1+ = equivocal, 2+ = definite lesion activity greater than the axillary soft-tissue background (1+ and 2+ values are for both thallium and gallium). For \( \text{\(^{201}\text{TI}\)} \), 3+ = activity within the lesion equal to thyroid activity on the initial image (2–12 min postinjection) and 4+ = activity greater than thyroid. For \( \text{\(^{67}\text{Ga}\)} \), 3+ = activity equal to sternum and 4+ = \( \text{\(^{67}\text{Ga}\)} \) uptake in the lesion greater than sternum.

All studies were graded by three physicians who were blinded to all patient data. An average value was then determined for each site.

Pathologic Tumor Grading

The biopsy specimens were graded by an experienced pathologist according to the working formulation for non-Hodgkin's lymphomas. The grades included low, intermediate and high. The diagnosis for Hodgkin's was established pathologically by accepted criteria.

Statistical Analysis

Sensitivity was calculated for each subgroup of lymphoma. Data were analyzed with respect to patient sensitivity and specificity, as well as site sensitivity.

The data were analyzed to determine the relationship of \( \text{\(^{201}\text{TI}\)} \) to \( \text{\(^{67}\text{Ga}\)} \) avidity in each of the lymphoma subgroups, including high-grade, intermediate grade, low-grade and Hodgkin's. In addition, the relationship of \( \text{\(^{201}\text{TI}\)} \) activity within a specific subgroup compared to other subgroups was studied as well as the relationship of \( \text{\(^{67}\text{Ga}\)} \) within a specific subgroup compared to activity within other subgroups.

Comparison of \( \text{\(^{201}\text{TI}\)} \) and \( \text{\(^{67}\text{Ga}\)} \) within each group was studied using Wilcoxon's rank sign procedure. Wilcoxon's procedure was used since the data were not normally distributed and Wilcoxon's procedure has no requirement for normal distribution.

Comparisons of \( \text{\(^{201}\text{TI}\)} \) and \( \text{\(^{67}\text{Ga}\)} \) for the different groups were studied using the Kruskal-Wallis procedure. In addition, Konover's procedure was used to examine any individual group differences determined by the Kruskal-Wallis procedure. A Spearman's rank correlation procedure was used to measure the relationships between \( \text{\(^{201}\text{TI}\)} \) and \( \text{\(^{67}\text{Ga}\)} \) within each group to see if correlations within each group existed.

Determination of Regional Abnormalities

To compare \( \text{\(^{201}\text{TI}\)} \) and \( \text{\(^{67}\text{Ga}\)} \) activity in abnormal tissue, the body was divided into selected areas. The areas or sites included were the right and left cervical-supraclavicular region, right and left axilla, right and left mediastinum, right and left inguinal region and the extremities. The brain was not included in this series because of blood-brain barrier considerations; the abdomen was not included because of unpredictable gastrointestinal activity which significantly impaired interpretation of the \( \text{\(^{201}\text{TI}\)} \) studies.

An area with multiple focal abnormalities was considered as having a single site abnormality for statistical evaluation. In addition, if a site abnormality was recorded for isotope A and read as normal for isotope B, then isotope B was recorded as a 0 and was considered to have missed the tumor. These false-negative readings were confirmed with other imaging modalities such as CT, MRI or radiography, as well as clinical examination.

RESULTS

The results are summarized in Table 1. Patient sensitivity for \( \text{\(^{67}\text{Ga}\)} \), defined as at least one positive site in any given patient, was low in the low-grade lymphoma subgroup with no detectable abnormalities in four of nine patients. Conversely, \( \text{\(^{201}\text{TI}\)} \) abnormalities in these four patients were observed in more than one location. Site sensitivity for \( \text{\(^{67}\text{Ga}\)} \) in low-grade lymphoma patients was only 32% (11/34). For intermediate, high-grade and Hodgkin's lymphoma, \( \text{\(^{67}\text{Ga}\)} \) sensitivity on a per patient basis was high, with 27 of 27 patients demonstrating at least one abnormality.

Comparison by sites of \( \text{\(^{201}\text{TI}\)} \) and \( \text{\(^{67}\text{Ga}\)} \) activity within each lymphoma subgroup using the Wilcoxon's sign rank procedure demonstrated \( \text{\(^{201}\text{TI}\)} \) ratings for the low-grade non-Hodgkin's lymphoma group to be significantly higher than \( \text{\(^{67}\text{Ga}\)} \) (p < 0.0005). The \( \text{\(^{201}\text{TI}\)} \) and \( \text{\(^{67}\text{Ga}\)} \) ratings were not significantly different for the intermediate, high or Hodgkin's lymphoma groups.

Thallium-201 and \( \text{\(^{67}\text{Ga}\)} \) scans from a patient with low-grade lymphoma are compared in Figure 1. The blind reading of the \( \text{\(^{67}\text{Ga}\)} \) scan was initially interpreted as normal while the \( \text{\(^{201}\text{TI}\)} \) scan demonstrated multiple sites of abnormality with high intensity relative to background activity. Following a review of the \( \text{\(^{67}\text{Ga}\)} \) study, and after correlation with the \( \text{\(^{201}\text{TI}\)} \) scan, low-level \( \text{\(^{67}\text{Ga}\)} \) activity could be detected in the neck and axilla. Many of the sites contained more than one lesion.

A comparison of a \( \text{\(^{67}\text{Ga}\)} \) and \( \text{\(^{201}\text{TI}\)} \) in a patient with an intermediate grade lymphoma is depicted in Figure 2. The groin abnormalities are best visualized with \( \text{\(^{201}\text{TI}\)} \), whereas the neck and chest findings are similar with both isotopes. Figure 3 illustrates the superiority of \( \text{\(^{67}\text{Ga}\)} \) detection in the chest, but superior \( \text{\(^{201}\text{TI}\)} \) detection in the inguinal region, in a 84-yr-old man with high-grade immunoblastic lymphoma.

Comparison of \( \text{\(^{201}\text{TI}\)} \) and \( \text{\(^{67}\text{Ga}\)} \) in Hodgkin's disease is shown in Figure 4 in a patient with cervical and mediastinal tumors. The findings are similar with both agents. There is improvement in the neck evaluation on the delayed \( \text{\(^{201}\text{TI}\)} \) study due to washout of surrounding soft tissue, including thyroid.
Comparison of $^{201}$TI uptake for different groups using the Kruskal-Wallis procedure demonstrated that $^{201}$TI avidity for low-grade lymphoma was significantly higher than for intermediate, high or Hodgkin’s lymphoma ($p = 0.002$). Thallium uptake for intermediate, high or Hodgkin’s groups did not demonstrate a statistically significant difference.

A comparison of $^{67}$Ga for different groups was also performed using the Kruskal-Wallis procedure. Gallium-67 sensitivity for low-grade lymphoma was significantly less than for Hodgkin’s and intermediate grade lymphomas ($p = 0.007$).

Gallium sensitivities for intermediate, high or Hodgkin’s lymphoma were not significantly different.

There was no correlation of $^{201}$TI to $^{67}$Ga within specific tumor subgroups based on Spearman’s range correlation.

**DISCUSSION**

Thallium accumulation has been described in a number of tumors, including lymphoma (23–43). The mechanism of
uptake is not clear, but it has been postulated that several mechanisms are involved in tumor accumulation, including the ATP-ase sodium potassium pump, a co-transport system, calcium channel mechanisms, blood flow and tumor viability (31,33,43,48–55). The mechanism for 67Ga accumulation in tumors is still uncertain, but several studies indicate that the mechanism for 201Tl and 67Ga accumulation are independent (53,56–59). The sole intent of the study was to characterize 67Ga and 201Tl scintigraphy in patients with Hodgkin’s as well as non-Hodgkin’s lymphoma.

Thallium SPECT imaging was initially evaluated in this series but was discontinued because of the relatively poor image quality obtained from administration of 3 mCi 201Tl. Thallium SPECT images generally resulted in detection of major thallium-avid regions, but image interpretation was considered difficult because of significant noise generated during image reconstruction. The noise was thought to be due to the low photon yield resulting from a 3-mCi injection of 201Tl.

This study demonstrates a significant (p < 0.0005) disparity between 67Ga and 201Tl accumulation in the low-grade lymphoma group, with 67Ga demonstrating low or absent uptake and 201Tl moderate to marked avidity. Thallium-201 tumor intensity was also significantly higher in the low-grade lymphoma group when compared to other lymphoma subgroups (p < 0.002). In Hodgkin’s lymphoma patients, there was a statistically significant difference between 201Tl and 67Ga detection in areas outside the abdomen.

The sensitivity for detection of lymphoma reported in this series was confirmed by biopsy for the patient sensitivity subgroups. Sensitivity for lymphoma subgroups on a site basis was not confirmed by biopsy in all areas because each patient only underwent a single biopsy even though they may have had multiple sites demonstrating 201Tl and/or 67Ga avidity. A true-positive reading was recorded for areas demonstrating 201Tl or 67Ga avidity if the biopsy was positive or if a mass abnormality was detected on CT, MRI, radiograph or physical examination. The potential for sensitivity error in the site subgroup is present and governed by the assumptions that mass abnormalities discovered on x-ray correlate imaging techniques or physical examination represent true-positive findings. If abnormalities observed on 201Tl or 67Ga scintigraphy were not confirmed by biopsy, other correlative imaging techniques or physical examination, then the 201Tl and 67Ga findings were considered to be false-positive and were not included for calculation of sensitivity. Overall, site sensitivity would be falsely reduced for 201Tl and 67Ga by these assumptions.

There are only limited data for lymph node size which may be detected using 201Tl in patients with low-grade lymphoma. In this series, it was difficult to determine the relationship between thallium avidity and lymph node size. Patients generally underwent biopsy prior to imaging. Therefore, no direct correlation could be made on the lymph nodes removed prior to scintigraphy. In three patients who underwent biopsy following a scintigraphic procedure, the nodes taken from the general area of scan positivity were 4–16 mm. The nodes were matted and probably superimposed on one another during imaging, which made it difficult to define the size of the smallest node that could be detected.

A major disadvantage in the use of 201Tl to evaluate lymphoma was the unpredictability of gastrointestinal secretion which did not appear to clear on multiple delayed images performed 2–7 days postinjection. This may be due to a recycling of 201Tl with continuous bowel excretion. Delayed 67Ga imaging appeared to be a superior technique for evaluating the abdomen in the intermediate and high-grade lymphoma groups.

Kaplan et al. determined 67Ga-citrate to be a predictor of tumor viability in patients with diffuse large-cell lymphoma (37). Gallium-67 viability has not been applied to lower grade lymphomas possibly because of the lack of 67Ga accumulation in this lymphoma group.

CONCLUSION

Thallium-201 appears to be a promising radiopharmaceutical for the detection of low-grade lymphoma and warrants further study to evaluate its use as an indicator of therapeutic response.

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