Diagnostic Efficiency of Gallium 67 Citrate Scans in Hodgkin’s Disease

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ABSTRACT

The findings of 49 67Ga citrate scans were correlated with all clinical information obtained by other diagnostic modalities in untreated and treated patients with histopathologically proven Hodgkin’s disease (539 sites). Eleven nodal and extranodal sites were analyzed in terms of sensitivity, specificity, accuracy and, subsequently, by calculations of the posterior probability for the presence of disease at positive and negative sites by scan using Bayes’ theorem. Lowest posterior probabilities for the presence of disease at positive sites were seen in lung parenchyma (66 percent) and spleen (67 percent) in untreated patients and for treated patients in abdominal nodes and inguinal nodes (both 66 percent), whereas the scan was a good method for detecting Hodgkin’s disease at all other sites where posterior probabilities were near 100 percent. Figures for the posterior probability of disease at negative sites by scan showed it was a good modality for ruling out Hodgkin’s involvement in axillary nodes, perihilar nodes, lung parenchyma, inguinal nodes, and bone marrow (all less than 10 percent); however, it was not as satisfactory in ruling out disease in untreated cervical nodes (20 percent), supraclavicular nodes (11 percent), and especially in the intraabdominal sites of spleen (35 percent), abdominal nodes (33 percent), and periaortic nodes (27 percent).

Introduction

Following nearly a decade of use of gallium 67 citrate scans in the diagnosis, staging and treatment of Hodgkin’s disease, controversy remains among practitioners as to their effectiveness and overall contribution in the identification of the disease and involved sites. The role of gallium 67 citrate scans as a useful noninvasive adjunct to other methods of detecting Hodgkin’s disease has been supported by numerous studies.1-16,18-23. Scanning has been shown to be particularly beneficial during the initial staging evaluation of patients prior to treatment in the location of
occult tumor, especially in supra-diaphragmatic nodal sites and in bone. Also stressed is its value in finding unsuspected positive lesions in treated asymptomatic patients returning for routine follow-up, thus allowing early therapy for recurrences. Despite these contributions and others, arguments remain concerning cost-effectiveness, the inability of gallium scans to replace any of the current staging procedures, and the implications of scan findings, such as the probability of disease actually being present at positive or negative sites by scan.

Further investigation of these controversies was accomplished by correlating the findings of gallium 67 citrate scans with clinical information obtained by all other diagnostic modalities in 49 studies with histopathologically proven Hodgkin's disease (539 sites). Analysis of 11 nodal and extranodal sites provided statistical information not only in the traditional terms of sensitivity, specificity, and accuracy but also in using the concepts of posterior probability for the presence of disease at positive and negative sites by scan, as first described by Bayes in McNeil et al. 17

Methods

From March 1974 through December 1977, 49 gallium 67 citrate scans were performed on 34 patients with untreated and treated histopathologically proven Hodgkin's disease at the University of Nebraska Medical Center. Carrier-free gallium 67 citrate was given intravenously as a single dose of between 3 to 5 mCi. In an effort to reduce interference from bowel activity, patients were given laxatives, supplemented on occasion with enemas between injection and scanning. Simultaneous anterior and posterior views were obtained on a five inch dual probe rectilinear scanner with high-energy collimation at 48 hours, 72 hours and, in some cases, 96 and 120 hours after injection. Total body scans were performed with a window spanning 160 to 360 KeV, so as to cover the second and third gamma emissions of 67Ga (184 KeV and 296 KeV). The scans were interpreted independently by two of the authors (EVK and MAQ) without knowledge of the patients' clinical findings. Interobserver discordance by the reviewers of the scans was 10.8 percent on their initial independent evaluations. Where discrepancies occurred in scan interpretations, the cases were reviewed by the authors together to determine the final decision. Positive or negative scan findings were recorded for seven nodal sites, —cervical, supraclavicular, axillary, perihilar, abdominal, periaortic, and inguinal, as well as four extranodal sites, —pulmonary parenchyma, liver, spleen, and bone marrow.

For analysis of the procedure, confirmation of the findings on the gallium scans was made by reviewing the complete medical records of all the patients. Clinically positive sites were based on pathologic, surgical, radiographic, and clinical evaluations within one month of the scan. Radiologic methods included plain films, chest radiography and tomography, UGI and BE examinations, IVPs, lymphangiograms, abdominal ultrasound, and liver-spleen scans.

The following definitions were used in the correlation of gallium scan and clinical results. A true positive (TP) was an area of abnormal uptake confirmed by one or more of the modalities of clinical evaluation in which there was no evidence of inflammation or infection. A true negative (TN) was an area that showed no abnormal uptake and was confirmed to be free of tumor by other means. A false positive (FP) was an area of abnormal uptake not confirmed by clinical evaluation as reflecting the presence of Hodgkin's disease. A false negative (FN) was an area lacking abnormal uptake where disease was determined to be present.
and accuracy, as well as in regard to the posterior probability for the presence of disease at positive and negative sites by scan calculated by using Bayes' theorem.

Sensitivity was defined as the percentage of sites or patients with disease which were detected by gallium scan. Thus:

$$\frac{TP}{TP + FN} \times 100$$

Specificity was defined as the percentage of sites correctly identified by gallium scan as having no disease. Thus:

$$\frac{TN}{TN + FP} \times 100$$

Accuracy was defined as the percentage of correctly classified sites by gallium scanning.

$$\frac{TP + TN}{TS} \times 100$$

where \(TS = \text{total sites}\).

After the gallium 67 citrate scan had been evaluated in terms of the characteristics of sensitivity, specificity, and accuracy, further calculations were performed using Bayes' theorem to determine posterior probability statements about the presence of disease in a particular site examined by the gallium scan. Posterior probability for the presence of disease at a gallium scan positive site was defined as the probability of disease being present in a site after having an abnormal gallium scan at the site:

$$\frac{\text{Sensitivity} \times \text{prevalence of disease}}{\text{Sensitivity} \times \text{prevalence of disease} + [(100-\text{specificity}) \times \text{prevalence of nondisease}]} \times 100$$

Prevalence of disease at a specific site was calculated as $$\frac{TP + FN}{TS} \times 100$$. The closer the result to 100 percent, the higher the probability that the particular site had disease.

Posterior probability for the presence of disease at a gallium scan negative site was defined as the probability of disease being present in a site after having a normal gallium scan at that site:

$$\frac{(100-\text{Sensitivity}) \times \text{prevalence of disease}}{[(100-\text{Sensitivity}) \times \text{prevalence of disease}} + [\text{specificity} \times \text{prevalence of nondisease}]] \times 100$$

Ideally, this figure should have been close to 0 percent.

The previous formulas infer that the posterior probabilities for the presence of disease at gallium scan positive or negative sites are dependent upon the combination of sensitivity, specificity, and prevalence of disease at the site of evaluation. Higher sensitivities and specificities result in increased probabilities for the presence of disease at scan positive sites and decreased probabilities for the presence of disease at scan negative sites. When prevalence of disease is high, the probabilities for the presence of disease increase at scan positive sites; however, the probabilities also increase at scan negative sites. On the other hand, if prev-
TABLE I

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Num-</th>
<th>Posi-</th>
<th>Sensi-</th>
<th>Num-</th>
<th>Posi-</th>
<th>Sensi-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ber</td>
<td>tive</td>
<td>tivity</td>
<td>ber</td>
<td>tive</td>
<td>tivity</td>
</tr>
<tr>
<td>Nodular</td>
<td>11</td>
<td>10</td>
<td>91%</td>
<td>11</td>
<td>9</td>
<td>82%</td>
</tr>
<tr>
<td>sclerosing</td>
<td>9</td>
<td>9</td>
<td>100</td>
<td>13</td>
<td>9</td>
<td>69%</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>3</td>
<td>1/3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predominance</td>
<td>1</td>
<td>1/1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1/1</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>depletion</td>
<td>1</td>
<td>1/1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1/1</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>23</td>
<td>96%</td>
<td>25</td>
<td>19</td>
<td>76%</td>
</tr>
</tbody>
</table>

lence of disease is low, the probabilities for disease decrease at scan negative and also positive sites.

Results

The 49 gallium 67 citrate scans were performed on 34 patients with histopathologically proven Hodgkin’s disease, including 28 males and six females ranging in age from 15 to 76 years, with a median of 31 years at the time of the scan. In table I are listed the sensitivities of gallium 67 scans in patients with untreated and treated Hodgkin’s disease with reference made to the specific histological morphology. One or more positive sites were demonstrated on 96 percent of scans of untreated patients and 76 percent of scans of treated patients.

In table II is shown the analysis of the 11 nodal and extranodal sites evaluated by gallium 67 scans. The overall results, comparing untreated and treated sites, showed sensitivities of 73 percent and 82 percent, specificities of 96 percent and 98 percent and accuracies of 88 percent and 96 percent, respectively. Among untreated patients, the sites of lowest sensitivity were intra-abdominal including liver (67 percent), spleen (40 percent), abdominal nodes (50 percent), and periaortic (25 percent). Above the diaphragm only axillary nodes (67 percent) had a low sensitivity in untreated patients. On scans of treated patients, sensitivities were somewhat lower in sites above the diaphragm and in bone marrow compared with pretreatment scans, —cervical nodes 80 percent (vs 88 percent untreated), supraclavicular nodes 67 percent (vs 94 per-

TABLE II

Analysis of 67Gallium Citrate Scans at Eleven Nodal and Extranodal Sites

<table>
<thead>
<tr>
<th>Areas</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Prevalence of Disease at Site</th>
<th>Posterior Probability for Presence of Disease Gallium Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UnRx</td>
<td>Rx</td>
<td>UnRx</td>
<td>Rx</td>
<td>Postive Site</td>
</tr>
<tr>
<td>Cervical nodes</td>
<td>88%</td>
<td>90%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Supraclavicular nodes</td>
<td>94%</td>
<td>67%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Axillary nodes</td>
<td>67%</td>
<td></td>
<td>100%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Perihilar nodes</td>
<td>90%</td>
<td>75%</td>
<td>100%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Lung parenchyma</td>
<td>100%</td>
<td></td>
<td>75%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Liver</td>
<td>67%</td>
<td></td>
<td>100%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Spleen</td>
<td>40%</td>
<td>100%</td>
<td>85%</td>
<td></td>
<td>67%</td>
</tr>
<tr>
<td>Abdominal nodes</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Periaortic nodes</td>
<td>25%</td>
<td>50%</td>
<td>100%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Inguinal nodes</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>100%</td>
<td>86%</td>
<td>100%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Totals</td>
<td>73%</td>
<td>82%</td>
<td>96%</td>
<td>98%</td>
<td>88%</td>
</tr>
</tbody>
</table>
GALLIUM SCANS AND HODGKIN'S DISEASE

cent), perihilar nodes 75 percent (vs 90 percent), and in bone marrow 86 percent (vs 100 percent). All other treated sites had sensitivities equal to or higher than their untreated counterparts.

Specificity of gallium scans was greater than 90 percent at all sites except lung parenchyma and spleen in untreated patients, which were 75 percent and 85 percent, respectively. Accuracy of scans was above 87 percent at all sites except in lung parenchyma, spleen, abdominal nodes, and periaortic nodes in untreated patients where two-thirds of all false positive and false negative results found in the study occurred.

Overall posterior probability for the presence of disease at gallium scan positive sites was 90 percent and 91 percent, and at negative sites 13 percent and 3.1 percent for untreated and treated, respectively. Among untreated patients, lowest posterior probabilities for the presence of disease at positive sites were seen in lung parenchyma (66 percent) and spleen (67 percent), and for treated patients in abdominal nodes and inguinal nodes (both 66 percent).

The highest posterior probabilities for the presence of disease at gallium scan negative sites in untreated patients were in the intra-abdominal sites of spleen (35 percent), abdominal nodes (33 percent), and periaortic nodes (27 percent), and above the diaphragm in cervical nodes (20 percent) and supraclavicular nodes (11 percent). In treated patients, posterior probability for negative sites was significantly better, the highest being in periaortic nodes (14 percent) and cervical nodes (12 percent).

Discussion

It is generally believed that the detectability of Hodgkin's disease by gallium scan is related in some measure to the histological characteristics of the neoplasm, as well as to whether or not the patient has received chemotherapy and/or radiation treatment.\textsuperscript{15,20} In our patient population, detectability of disease was uniformly high in the untreated group in all histological types except lymphocyte depletion, where no cases were assessed. Sensitivities fell following treatment, consistent with dissolution of disease activity, and resulting in impaired ability for gallium concentration at previously positive sites.

Analysis of the variation in the gallium 67 scan detectability of Hodgkin's involvement at different anatomical locations has been presented frequently in recent literature,\textsuperscript{14,15,16,17,18,19,20,21} with statistics expressed in terms of sensitivity and specificity. This study utilized posterior probability calculations based on formulas combining the factors of sensitivity, specificity, and prevalence of disease at specific sites in our patient population to yield more meaningful information in the evaluation of nodal and extranodal sites examined by the gallium scan. Posterior probability figures for the presence of disease at gallium scan positive or negative sites answered the practical questions of "What is the probability that disease is truly present at a positive site on gallium scan?" or "What is the probability that disease is actually present at a negative site on gallium scan?"

The presence of disease was reliably predicted (greater than 90 percent) by gallium scans at all nodal and extranodal sites except for lung parenchyma and spleen in untreated patients (66 percent and 67 percent, respectively). In treated patients, the abdominal and inguinal nodes predicted disease activity less reliably (66 percent each). Conversely, the absence of disease was reliably predicted by a negative study (posterior probability for the presence of disease at a negative site by gallium scan less than 10 percent) in only six of the 11 sites analyzed in untreated patients. Of particular concern were the posterior probability statistics in the ab-
dominal region of untreated patients where the spleen demonstrated a 35 percent probability of disease in spite of a negative study, and the abdominal and periaortic nodes showed 33 percent and 27 percent, respectively. Thus, there is a significant probability of disease in patients with a negative interpretation at these sites. Additionally, in the untreated group, the cervical (20 percent) and supraclavicular (11 percent) sites were marginally useful. In treated patients, the negative gallium scan site was much more reliable as an indicator for absence of disease. Only the cervical (12 percent) and periaortic (14 percent) nodal sites yielded posterior probabilities for the presence of disease at negative sites greater than the desired result of less than 10 percent.

The findings with respect to the abdominal area are consistent with those of other observers and are most likely due to the poor target to non-target ratio resulting from the excretion of gallium by the intestine. In addition, lesions occurring near normal sites of accumulation of tracer, such as the liver or spleen, appear more difficult to direct accurately.

Conclusions

Based on reliability standards of greater than 90 percent posterior probability for the presence of disease at gallium 67 scan positive sites and less than 10 percent at negative sites, our study concludes that:

1. While gallium scanning provides valuable information in the initial staging of the disease, its value is attenuated by the inability to predict reliably or exclude the presence of disease in all analyzed nodal and extranodal sites.

2. Posterior probabilities for the presence of disease at scan positive sites in untreated patients of 66 percent in lung parenchyma and 67 percent in spleen, as well as 66 percent in the abdominal and inguinal nodes in treated patients, call for additional confirmatory information in these areas.

3. Posterior probabilities for disease at negative sites in the untreated group failed to meet our reliability criteria at five of the 11 sites evaluated, implying a significant probability for disease in spite of negative findings.

4. The most reliable findings relating to the presence or absence of disease were in the treated patient population.

Although gallium 67 citrate scanning offers a safe, noninvasive approach in the diagnostic staging process, it does not replace more traditional methods of evaluation. In areas except the abdomen, it offers a reliable adjunctive role in staging. As demonstrated by the posterior probability statistics, gallium scan is most useful in predicting the presence or absence of disease during the patient's time course after treatment.

References


