The prognostic value of conventional imaging tools to determine how patients with hodgkin lymphoma will respond to treatment

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Abstract

Introduction: This systematic review studies the prognostic value of two conventional imaging tools, sestamibi and gallium scans, for predicting how patients with Hodgkin lymphoma will respond to treatment.  

Methods: The PubMed database was searched for English-language articles that contained the following search terms: (Hodgkin AND [mibi OR sestamibi OR gallium OR spect] AND response). All articles that were identified during this search were included in the study, regardless of date published. The inclusion criteria were as follows: articles that described studies that were limited to Hodgkin patients and that reported the predictive value of conventional imaging tools. Articles about other types of lymphoma and/or those that focused on the diagnostic and staging accuracy of mibi and gallium scans were excluded.  

Result: In total, 14 articles were retrieved. Of these, the majority met the inclusion criteria of the systematic review with the exception of two, which were limited to an examination of the reliability of performing sestamibi scans to predict the response to treatment. All remaining 12 articles considered both the sestamibi scans and the gallium scintigraphy. The results of the systematic review indicate that positive gallium scan results can be proposed as a poor prognostic factor that is associated with partial or full recurrence of Hodgkin disease, a reduction in overall survival rate, and progression-free survival compared with patients with a negative scan.  

Discussion: Both sestamibi and gallium scans revealed high sensitivity and specificity in predicting the response to treatment including complete remission, partial remission, and recurrence of the disease.  

Conclusion: These imaging tools can appropriately assess how Hodgkin patients will respond to chemotherapy. As such, clinicians can use these tools to devise appropriate treatment strategies.

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Introduction

Radiation therapy and chemotherapy alone or in combination have been proposed as the main treatment approaches for patients at an early or advanced stage of Hodgkin lymphoma. In some cases, these therapies have resulted in complete response and prolonged survival (1).
Evaluating how a patient may respond to treatment is important, but difficult, especially in patients with residual radiological abnormalities. Imaging techniques represent a significant and effective method by which therapeutic strategies for patients with Hodgkin disease can be managed.

Gallium-67 citrate uptake is transferrin receptor-dependent, and it can be used to reveal an active metabolic process and also to predict disease activity in residual mediastinal mass following therapy. This tracer is not absorbed in fibrotic or necrotic tissue; however, it is absorbed by avid and viable HL (Hodgkin Lymphoma) tissue. As such, 67Ga is proposed as an indicator of tumor viability (2).

Whole-body 67gallium (67Ga) scintigraphy is a valuable and sensitive imaging tool, not only for the diagnostic purposes of lymphoma, but also for evaluating the response to treatment including complete remission, partial remission, and recurrence of the disease. Although the 67Ga scintigraphy procedure is able to predict how patients with Hodgkin lymphoma may respond to treatment, physiological accumulation of gallium in the intestine limits the efficacy of this imaging tool in abdominal parts of the body (3). As such, a gallium scan is more sensitive for lesions that are located above the diaphragm than it is for abdominal and pelvic diseases (4).

The 99mTc-MIBI (99mTc-methoxyisobutylisonitrile) imaging procedure is recognized to have a prognostic factor regarding response to chemotherapy in various types of malignancies including lung cancer (5), malignant lesions (6), Hodgkin’s and non-Hodgkin’s lymphoma, etc. (7-9). The effectiveness and utility of 99mTc-MIBI scintigraphy has also been investigated in some types of lymphomas. However, these studies have typically employed different methodologies and obtained different results.

This systematic review studied the results described in various articles that focused on the prognostic value of conventional imaging techniques that employed Ga67 and 99mTc-MIBI.

Methods

According to the purpose of this study, the PubMed database was searched using the following keyword strategy: (Hodgkin AND [mibi OR sestamibi OR gallium OR spect] AND response). The inclusion criteria were all articles that studied the prognostic value and sensitivity of gallium scintigraphy and Technetium-99m-sestamibi in predicting response treatment and disease outcome. According to the included studies, response to treatment was reported as complete remission, partial remission, and relapse of the disease. The procedures can be performed before initiating the therapy, during the treatment, or after the treatment. Only English-language articles were included in this systematic review. No limitations regarding date of publication were applied. The exclusion criteria were all the non-English articles that studied patients with lymphomas except Hodgkin and any articles that investigated the diagnostic sensitivity or staging accuracy of the mentioned imaging strategies.

Results

Information regarding the process by which the articles were selected and the number of articles that were included in the final assessment are provided in the flowchart presented in Figure 1.

![Figure 1. Show the strategy of including related articles in the systematic review](image-url)
Table 1. Quality control results of the included studies.

<table>
<thead>
<tr>
<th>NO</th>
<th>Author</th>
<th>Year</th>
<th>Reference</th>
<th>Was the sample of patients assembled at a common point in the course of their disease?</th>
<th>Follow up duration</th>
<th>Were outcome criteria either objective or applied in a 'blind' fashion?</th>
<th>Outcome reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spyridonidis</td>
<td>2013</td>
<td>(10)</td>
<td>Yes</td>
<td>45.5 ± 23.5 M</td>
<td>Yes</td>
<td>Sensitivity/ specificity</td>
</tr>
<tr>
<td>2</td>
<td>Kapucu</td>
<td>1997</td>
<td>(11)</td>
<td>Yes</td>
<td>1-2 yrs</td>
<td>No</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>3</td>
<td>Herman</td>
<td>2007</td>
<td>(12)</td>
<td>Yes</td>
<td>6-54 M</td>
<td>NO</td>
<td>Sensitivity/Specificity/PFS</td>
</tr>
<tr>
<td>4</td>
<td>Ng</td>
<td>2005</td>
<td>(13)</td>
<td>Yes</td>
<td>Median 64 M</td>
<td>No</td>
<td>OS/PFS</td>
</tr>
<tr>
<td>5</td>
<td>Castellani</td>
<td>2003</td>
<td>(14)</td>
<td>Yes</td>
<td>Follow up 13-168 M</td>
<td>Yes</td>
<td>Relapse rate</td>
</tr>
<tr>
<td>6</td>
<td>Brenot-Rossi</td>
<td>2001</td>
<td>(3)</td>
<td>Yes</td>
<td>28-124 yrs</td>
<td>NR</td>
<td>Sensitivity/Specificity</td>
</tr>
<tr>
<td>7</td>
<td>Nikpoor</td>
<td>2000</td>
<td>(15)</td>
<td>Yes</td>
<td>Average follow up:4.5 yrs</td>
<td>Yes</td>
<td>Relapse rate</td>
</tr>
<tr>
<td>8</td>
<td>Delcambre</td>
<td>2000</td>
<td>(16)</td>
<td>Yes</td>
<td>Mean 31 M</td>
<td>NO</td>
<td>CR rate</td>
</tr>
<tr>
<td>9</td>
<td>Ionescu</td>
<td>2000</td>
<td>(17)</td>
<td>Yes</td>
<td>Median 36 M</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Front</td>
<td>1999</td>
<td>(18)</td>
<td>Yes</td>
<td>12-120 M</td>
<td>No</td>
<td>CR/PR rate</td>
</tr>
<tr>
<td>11</td>
<td>Setoain</td>
<td>1997</td>
<td>(19)</td>
<td>Yes</td>
<td>Follow up:6-20 M</td>
<td>No</td>
<td>Sensitivity/Specificity</td>
</tr>
<tr>
<td>12</td>
<td>Hagemeister</td>
<td>1994</td>
<td>(20)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>FFP</td>
</tr>
<tr>
<td>13</td>
<td>King</td>
<td>1994</td>
<td>(21)</td>
<td>Yes</td>
<td>Median 28 M</td>
<td>Not available</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>Anderson</td>
<td>1983</td>
<td>(22)</td>
<td>Yes</td>
<td>10-24 M</td>
<td>NR</td>
<td>Recurrence rate</td>
</tr>
</tbody>
</table>

DFS: disease free survival, PFS: progression free survival, OS: overall survival, CR: complete remission, PR: partial remission, R: recurrence, FFP: freedom from progression, M: month

Discussion

Predicting the possibility of disease recurrence and response to treatment will be beneficial for the improvement of the therapeutic interventions that are administered to patients with lymphoma.

99mTc-MIBI SPECT

According to the extracted data, 99mTc-MIBI imaging is a putative imaging approach for providing prognostic information about chemotherapy response and guiding therapeutic decisions following baseline evaluation of patients with lymphoma. In the study performed by Kapucu et al., the results obtained by conducting 99mTc-sestamibi scintigraphy in patients with complete response
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Reference</th>
<th>Patients</th>
<th>Dose</th>
<th>Therapy response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spyridonidis</td>
<td>2013</td>
<td>(10)</td>
<td>N:47</td>
<td>740 MBq (20 mCi)</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Kapucu</td>
<td>1997</td>
<td>(11)</td>
<td>144</td>
<td>5-10 mCi (185-370 MBq)</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Herman</td>
<td>2007</td>
<td>(12)</td>
<td>N:10</td>
<td>320-360MBq</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Ng</td>
<td>2005</td>
<td>(13)</td>
<td>N:71</td>
<td>37-111 MBq</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Castellani</td>
<td>2003</td>
<td>(14)</td>
<td>N:175</td>
<td>67Ga negative, N:61 67Ga positive, N:13 41 M, 33 F Age range:14-62 yrs</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Brenot-Rossi</td>
<td>2001</td>
<td>(3)</td>
<td>N:74</td>
<td>222 MBq (6 mCi).</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Nikpoor</td>
<td>2000</td>
<td>(15)</td>
<td>N:85</td>
<td>10 mCi (370 MBq)</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Delcambre</td>
<td>2000</td>
<td>(16)</td>
<td>N:62(52 HD, 10 NHL) 39 M, 23 F Median follow up: 32 months</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
<td></td>
</tr>
<tr>
<td>Ionescu</td>
<td>2000</td>
<td>(17)</td>
<td>N:53</td>
<td>Not available</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Front</td>
<td>1999</td>
<td>(18)</td>
<td>N:98</td>
<td>Adults: 8 mCi (296 MBq/Kg) Children: 75 mCi (2.77 MBq/Kg)</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Setoain</td>
<td>1997</td>
<td>(19)</td>
<td>N:33</td>
<td>370 MBq 67Ga-citrate</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Hagemeister</td>
<td>1994</td>
<td>(20)</td>
<td>N:46</td>
<td>8 to 10 mCi</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>King</td>
<td>1994</td>
<td>(21)</td>
<td>N:33</td>
<td>Not available</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
<tr>
<td>Anderson</td>
<td>1983</td>
<td>(22)</td>
<td>N: 21 (43 scans)</td>
<td>7 to 10 mCi</td>
<td>Sensitivity%:specificity% Early T/B: 50-93.9 Late T/B: 85.7-87.9 Washout: 85.7-72.7 Early T/B: 2.22-50.0 Late T/B: 1.82-75.0 Washout: 4.6-7.2</td>
</tr>
</tbody>
</table>

Ga scintigraphy has prognostic value regarding the ability to identify tumor recurrence by scanning the whole body and the ability to distinguish between active tumor and fibrosis tissue. This entails that $^{67}$Ga scintigraphy can be employed to discriminate between patients who are at a low or high risk of malignancy relapse (3,12,25).

Ga $^{67}$ absorption change following treatment is associated with absence or the presence of tumor cells and can evaluate the possibility of lymphoma relapse and the biological aggressiveness of the malignancy, which can change the subsequent optimum treatments (16).

It can be suggested that a sufficient dose of the 370 MBq and high-quality SPECT have prognostic value in terms of malignancy recurrence.

According to a report by Front et al., performing Ga scintigraphy after one cycle of treatment has prognostic value regarding the evaluation of the clinical outcome of the patients and can separate patients with favorable outcome from those with unfavorable outcomes (18). Front et al. were unable to achieve favorable results by performing Ga scintigraphy at the mid-treatment point to predict failure of response to treatment (recurrence or partial remission). As such, they concluded that early Ga scintigraphy following one cycle of treatment could predict the treatment outcome and early change in subsequent therapeutic strategies (18). Eventually, they suggested that the application of lower doses of chemotherapy for patients with negative Ga results after one cycle of treatment would not negatively affect the patients’ survival rates.

Setoain et al. found that $^{67}$Ga showed higher sensitivity and specificity for the detection of malignancy relapse compared with the computed tomography procedure. They suggested that $^{67}$Ga-scintigraphy should be routinely performed as part of the management of patients with HL (19). They also found that patients with Ga+ results had a higher mortality rate than those with Ga-cases (relative risk of 5.2). Similar results have also been confirmed in other studies, despite differences in the disease stage at first screening, types of applied treatment strategy, technique and interpretation of the gallium images, types of applied treatment subsequent positive gallium scan, and the follow-up duration. In all the included studies, HL patients with positive gallium scan were associated with poor clinical prognosis (13,14,17,20,22). As such, the gallium scan results should directly impact any decisions that are made regarding further treatment strategies due to the extent to which they can predict post-treatment risk of recurrence.

Generally, in the case of patients treated following initial presentations and those with recurrent disease, performing $^{67}$Ga scintigraphy has prognostic value for evaluating response to therapy.
and for the early detection of relapse. The absorption rate of Ga can be regarded as an indicator of treatment efficacy. In the study of Castellani et al. (14), this procedure accurately predicted the clinical outcome in 97% of the included patients.

One study reported the normal, borderline, and abnormal uptake of Ga through using sternum and spinal uptake as a reference that reflected bone marrow localization of Ga-67 (15). The researchers suggested that that mild M-H (Mediastinum-Hilar) uptake with intensity less than that of the sternum or spine may indicate post-treatment fibrosis rather than residual tumor. They concluded that the quantitative evaluation of Ga-67 tracer in the M-H area following treatment is greatly sensitive in differentiating between active tumor and benign uptake. Normal and borderline Ga-67 uptake in the M-H area can be associated with a low likelihood of recurrence and indicates better prognosis (15).

Due to the high specificity of 67Ga scintigraphy, the application of high doses of chemotherapy consolidation would be favorable and advantageous for patients with 67Ga+ results. On the other hand, this procedure has low sensitivity in predicting the disease recurrence in patients with negative post-treatment Ga scan, due to incomplete remission or inability to detect the residual malignant tissue. As such, by performing Ga scintigraphy following one cycle of treatment, the accuracy of any prediction may increase. However, performing the Ga scintigraphy mid-treatment or after the completion of the chemotherapy may be associated with lower sensitivity in predicting the outcome.

Conclusion

99mTc-MIBI imaging can be proposed as prognostic criterion for chemotherapy response; however, further studies are needed to confirm these results.

According to the existing literature, the advantage of performing 67Ga scintigraphy for monitoring HL is apparent. This aging tool can appropriately assess the response to chemotherapy and, therefore, play an important role in treatment decisions. A positive gallium scan can be proposed as a poor prognostic factor which is associated with decreased OS, FFTF, and PFS compared with patients with a negative gallium scan.

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Conflict of Interest

The authors declare no conflict of interest.

References


