Abstract

Introduction: In this systematic review we studies the prognostic value of two conventional imaging tools (sestamibi and gallium scans) for predicting the response to treatment in patients with Hodgkin lymphoma.

Methods: English language articles with no time limitation relevant to the purpose of this systematic review were searched in PubMed based on the following search strategy: Hodgkin AND (mibi OR sestamibi OR gallium OR spect) AND response. Inclusion criteria were all the articles which included only Hodgkin patients and reported the predicting value of conventional imaging tools. Articles about other types of lymphoma and those focused on diagnostic and staging accuracy of mibi and gallium scans were all excluded.

Results: Totally 14 articles were retrieved which were the most relevant reports. Only 2 out of 14 articles were about the reliability of performing sestamibi scans on predicting the response to treatment; other included articles were about the gallium scintigraphy. Positive gallium and sestamibi scan results can be proposed as a poor prognostic factor which is associated with partial or recurrence of the disease, decreased overall survival, and progression free survival compared with patients with 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 the response to chemotherapy and change the following treatments strategy.

Keywords: Sestamibi, Hodgkin lymphoma, Gallium scintigraphy
Introduction

Radiation therapy and chemotherapy alone or in combination have been proposed as the main treatment approaches for patients at early and advanced stage of Hodgkin lymphoma, which may lead to complete response and prolonged survival (1).

Evaluation of response to treatment is significant but difficult, especially in patients with residual radiological abnormalities. Imaging techniques are important and effective on managing therapeutic strategies for patients with Hodgkin disease.

Gallium-67 citrate uptake is transferrin receptor dependent which can reveal active metabolic process and also predict disease activity in residual mediastinal mass following therapy; this tracer is not absorbed in fibrotic or necrotic tissue, however it is absorbed only by avid and viable HL tissue. In this regard $^{67}$Ga is proposed as an indicator of tumor viability (2).

Whole-body $^{67}$gallium ($^{67}$Ga) scintigraphy is valuable and sensitive imaging tool not only for diagnostic purposes of lymphoma, but also for evaluating the response to treatment including complete remission, partial remission, and recurrence of the disease. Although $^{67}$Ga scintigraphy procedure is able to predict the response to treatment of patients with Hodgkin lymphoma, physiological accumulation of gallium in the intestine limits the efficacy of this imaging tool in abdominal parts (3). Gallium scan is more sensitive for lesions situated above the diaphragm than for abdominal and pelvic diseases (4).

($^{99m}$Tc-methoxyisobutylisonitrile) $^{99m}$Tc-MIBI imaging procedure has been known as 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 $^{99m}$Tc-MIBI scintigraphy has been also investigated in some types of lymphomas. These studies are different regarding the methodology and the obtained results.
In this systematic review we studied the results obtained in various articles focused on the prognostic value of conventional imaging techniques using Ga67 and 99mTc-MIBI.

Methods

According to the purpose of this study relevant articles were search in PubMed based on the following search strategy including: hodgkin AND (mibi OR sestamibi OR gallium OR spect) AND response. Inclusion criteria were all the articles which studied the prognostic value and sensitivity of gallium scintigraphy and Technetium-99m-sestamibi in predicting response to 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 procedure can be performed before initiating the therapy, during the treatment, or after the treatment. Only English language articles with no date limitation were included in this systematic review. Exclusion criteria were all the none-English articles which studied patients with lymphomas except Hodgkin and articles which investigated the diagnostic sensitivity or staging accuracy of the mentioned imaging strategies.

Information regarding selection of the related articles and the number of articles eventually included are provided in flow chart below.
According to the search strategy, inclusion, and exclusion criteria applied here, totally 14 articles could be included in our systematic review. Only 2 out of 14 articles evaluated the prognostic value of sestamibi imaging on Hodgkin patients and 12 remained articles were about the potential of the gallium scan in predicting the response to treatment in these patients.

Supradiaphragmatic lesions were evaluated in all the articles studied the prognostic value of mibi. Regarding 99mTc-mibi, due to physiological tracer accumulation in intra-abdominal organs, abdominal SPECT was not performed in patients with both supradiaphragmatic and subdiaphragmatic lesions.

Lymphomas were classified according to the World Health Organization classification.
Quality control of the included studies is performed based on Oxford Centre for Evidence Based Medicine and summarized in Table 1. Data are presented as the sensitivity and specificity of both studies imaging tools on predicting the response to treatment and recurrence of the lymphoma. Data regarding the author, reference number, patients’ characteristics, tracer dose, outcome (sensitivity and specificity of imaging procedure in predicting response to first-line therapy and final outcome which can be lymphoma-specific survival, overall survival, disease or progression free survival) are summarized in Table 2.

**Table 1.** Quality control results of the included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year 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>Spyridonidis, 2013, (10)</td>
<td>Yes</td>
<td>45.5 T 23.5 M</td>
<td>Yes</td>
<td>Sensitivity/ specificity DFS</td>
<td></td>
</tr>
<tr>
<td>Kapucu, 1997,(11)</td>
<td>Yes</td>
<td>1-2 yrs</td>
<td>No</td>
<td>Sensitivity</td>
<td></td>
</tr>
<tr>
<td>Herman, 2007, (12)</td>
<td>Yes</td>
<td>6-54 M</td>
<td>No</td>
<td>Sensitivity/specificity PFS</td>
<td></td>
</tr>
<tr>
<td>Ng, 2005, (13)</td>
<td>Yes</td>
<td>Median 64 M</td>
<td>No</td>
<td>OS/PFS</td>
<td></td>
</tr>
<tr>
<td>Castellani, 2003, (14)</td>
<td>Yes</td>
<td>Follow up 13-168 M</td>
<td>Yes</td>
<td>Relapse rate Mortality rate</td>
<td></td>
</tr>
<tr>
<td>Brenot-Rossi, 2001,(3)</td>
<td>Yes</td>
<td>28-124 yrs</td>
<td>NR</td>
<td>Sensitivity/specificity OS/DFS</td>
<td></td>
</tr>
<tr>
<td>Nikpoor, 2000(15)</td>
<td>Yes</td>
<td>Average follow up:4.5 yrs</td>
<td>No</td>
<td>CR/R rate</td>
<td></td>
</tr>
<tr>
<td>Delcambre, 2000,(16)</td>
<td>Yes</td>
<td>Mean 31 M</td>
<td>NO</td>
<td>CR rate</td>
<td></td>
</tr>
<tr>
<td>Ionescu, 2000,(17)</td>
<td>Yes</td>
<td>Median 36 M</td>
<td>-</td>
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</tr>
</tbody>
</table>
Table 2. Summarized information of the included studies regarding the prognostic value of sestamibi and gallium scans in Hodgkin patients

<table>
<thead>
<tr>
<th>Author year reference</th>
<th>Patients</th>
<th>Dose</th>
<th>Therapy response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spyridonidis, 2013, (10)</td>
<td>N:47 (16 HL, 31 NHL) 32 M,15 F Age range: 17-87 yrs Follow up: 45.5 T 23.5 Months</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: 48.4 -72.7 + 99mTc-sestamibi OR (CR):14/16 with HL 3/8 with NHL Sensitivity%:70%</td>
</tr>
<tr>
<td>Kapucu, 1997, (11)</td>
<td>N:24 (16 HL, 8 NHL) 13M,11F Age range: 1-17yrs</td>
<td>5-10 μci (185-370 MBq) 99mTc-sestamibi Uptake ≥ 2+: +</td>
<td></td>
</tr>
<tr>
<td>Herman, 2007, (12)</td>
<td>N:30 17M,13F Age:19-50 yrs</td>
<td>320–360MBq</td>
<td>Sensitivity for predicting relapse: 50% Specificity for predicting relapse: 88.5% 2-yr PFS Ga+: 92.8% Ga+:60.5%</td>
</tr>
<tr>
<td>Ng, 2005, (13)</td>
<td>N:175 93M,82F Age: 9–71yrs</td>
<td>-</td>
<td>5-year OS (Ga+: 97%) (Ga+:53%) 5-year PFS (Ga+: 93%) (Ga+:38%)</td>
</tr>
<tr>
<td>Author</td>
<td>Year, (Volume)</td>
<td>Sample Size</td>
<td>Description</td>
</tr>
<tr>
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<tr>
<td>Brenot-Rossi, 2001,(3)</td>
<td></td>
<td>N:74</td>
<td>$^{67}$Ga negative, N:61 $^{67}$Ga positive, N:13 41 M, 33 F Age range:14-62 yrs</td>
</tr>
<tr>
<td>Nikpoor, 2000(15)</td>
<td></td>
<td>N:85</td>
<td>38M,47F Age range 16-76 yrs</td>
</tr>
<tr>
<td>Delcambre, 2000,(16)</td>
<td></td>
<td>N:62(52 HD, 10 NHL) 39 M, 23 F Median follow up: 32 months</td>
<td>185–220 MBq</td>
</tr>
<tr>
<td>Ionescu, 2000, (17)</td>
<td></td>
<td>N:53</td>
<td>Not available</td>
</tr>
<tr>
<td>Front, 1999,(18)</td>
<td></td>
<td>N:98</td>
<td>50M,48F Age range:5-76 yrs</td>
</tr>
</tbody>
</table>

Hagemeister, 1994, (20) | N:46 | 8 to 10 MCI | 3-year FFP Ga\(^+\):70% Ga\(-\):100%

King, 1994, (21) | N:33 | Not available | RFS (Ga\(^+\):8%), (Ga\(-\):75%)

Anderson, 1983, (22) | N: 21 HL(43 scans) | 7 to 10 mCi | Active disease Ga\(^+\): 29/29 Ga\(-\):1/14

N: number. M: male, F: female, HL: Hodgkin, NHL: non-hodgkin, T/B: tumor-to-background, Early (20 minutes), Late (120 minutes), Washout: 2 hours, Ga\(^+\): \(^{67}\text{Ga}\) negative group, Ga\(-\): \(^{67}\text{Ga}\) positive group, DFS: disease free survival, PFS: progression free survival, OS: overall survival, CR: complete remission, PR: partial remission, PD: progressive disease, FFP: freedom from progression, Follow up: NA, R:relapse, M: mortality, normal: no residual mediastinum–hilar (M–H) uptake, borderline: M–H residual uptake was less than that of sternum or spine, abnormal: residual M–H residual uptake was more than that of the sternum or spine, RFS: recurrence free survival

**Discussion**

Predicting the possibility of disease recurrence and response to treatment for rapid onset of the subsequent treatment will be beneficial for the improvement of the 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. It is found that patients who had complete response to chemotherapy showed significantly different findings in 9mTc-sestamibi scintigraphy than patients who had partial or no response. In the study performed by Kapucu et al, results obtained by conducting 99mTc-sestamibi scintigraphy in patients with complete response to treatment were significantly different compared with results obtained from 99mTc-sestamibi scintigraphy in patients with partial or no response to chemotherapy (23). According to that article, regardless of the lymphoma type, all the cases with positive 99mTc-sestamibi imaging (lesions positively detected) revealed complete response to treatment, however those with negative 99mTc-sestamibi (the inability to demonstrate lymphoma lesions) showed partial or no response to treatment (23). It is might be possible that overexpression or increased functioning of Pgp molecules and subsequently outward transportation of sestamibi molecules from tumor cells be associated with negative 99mTc-sestamibi results in patients with poor response to therapy (23).

It is also proposed that Technetium-99m-sestamibi accumulation is greater in HD lesions than NHL.

In the study performed by Spyridonidis et al. among considered scintigraphic indices (early T/B, late T/B, and 2 hours washout) late T/B ratio was associated with higher prognostic value over clinical prognostic factors including age, lymphoma type, Ann Arbor stage, and lactate dehydrogenase levels. Delayed 99mTc-mibi uptake is proposed as independent and incremental prognostic factor of time to disease progression and lymphoma related death, while compared with other scintigraphic indices and clinical prognostic factors (10).
Eventually it is concluded that prescreening with 99mTc-sestamibi has prognostic value regarding the response to treatment and clinical outcome of patients with HL.

**Gallium**

Although small number of residual cells can be sufficient for the recurrence for HL, developing of cell masses enough to cause the relapse take long time. Delayed relapse is a characteristic of the HL, so the study of Castellani et al covered almost 15 years of follow up for included patients (14). Gallium-67 citrate is known as a viability factor which is absorbed only by cancer tissue and not by fibrotic or necrotic tissues. Ga scintigraphy procedure is based on the absorption of this ferric ion analogue by tumor cells; especially the white blood cells. It is assumed that the absorption of Ga$^{67}$ is related to the cells proliferation rate; more aggressive tumors shows higher absorption, however well-differentiated types have lower absorption rate (24). Several advantages have been proposed following performing $^{67}$Ga scintigraphy as a tumor viability factor such as the ability of identifying tumor recurrence by scanning whole body and distinguishing between active tumor and fibrosis tissue; discriminating between patients at 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 sufficient dose of the 370 MBq and high quality SPECT have prognostic value regarding the malignancy recurrence.

According to the report of 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 could not achieve favorable results by performing Ga scintigraphy at midtreatment period due to high chance of failure of response to treatment (recurrence or partial remission),
so proposed the association between early Ga scintigraphy following one cycle of treatment with better predicting the treatment outcome and early change in subsequent therapeutic strategies (18). Eventually they suggested the application of lower doses of chemotherapy for patients with negative Ga results after one cycle of treatment would not negatively affect the survival of patients.

Setoain et al, $^{67}$Ga showed higher sensitivity and specificity for detection of malignancy relapse compared with computed tomography procedure; they have suggested $^{67}$Ga-scintigraphy to be performed routinely during the management of patients with HL (19). They also showed higher mortality rate for patients with Ga$^+$ results compared with Ga$^-$ cases (relative risk of 5.2). Similar results have been also confirmed in other studies, despite their differences regarding 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). So the gallium scan results can change the decision for further treatment strategies due to its great value in the post-treatment assessment of recurrence.

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

One study was reported in different way based on the normal, borderline, and abnormal uptake of Ga; sternum and spinal uptake was used as a reference in that study which reflects bone marrow localization of Ga-67 (15). They suggested that that mild M–H uptake with intensity less than that of the sternum or spine may indicates post-treatment fibrosis rather
than residual tumor. They concluded that quantitative evaluation of Ga-67 tracer level 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 low likelihood of recurrence and indicates better prognosis (15).

Due to high specificity of $^{67}$Ga scintigraphy, treating with high doses of chemotherapy consolidation would be favorable and advantageous for patients with $^{67}$Ga$^+$ results. On the other hand this procedure has low sensitivity in predicting the disease recurrence which is because of disease relapse occurrence in patients with negative post treatment Ga scan, due to incomplete remission or inability to detect the residual malignant tissue. So by performing Ga scintigraphy following one cycle of treatment the accuracy of predicting outcome might be increased, however mid treatment or after the completion of the chemotherapy Ga scintigraphy may be associated with lower sensitivity in predicting the outcome.

**Conclusion**

$^{99}$mTc-MIBI imaging can be propose as prognostic criterion for chemotherapy response, however further studies are needed to confirm these results.

According to the literature, the advantageous of performing $^{67}$Ga scintigraphy for monitoring HL is apparent. This imaging tool can appropriately assess the response to chemotherapy and change the following treatments. Positive gallium scan can be proposed as a poor prognostic factor which is associated with decreased OS, FFTF, and PFS compared with patients with negative gallium scan.

**References**


