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Diagnostic role of gallium scanning in the management of lymphoma with mediastinal involvement

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ABSTRACT

Background and Objective. **Therapy of both Hodgkin's disease (HD) and aggressive non-Hodgkin's lymphoma (NHL) with mediastinal presentation at the time of diagnosis is frequently followed by radiological detection of residual masses. Computed tomography (CT) scanning is generally unable to detect the differences between tumor tissue and fibrosis. Gallium-67-citrate single photon emission (^{67}GaSPECT) can potentially differentiate residual active tumor tissue from fibrosis.**

Design and Methods. **Seventy-five patients with HD or aggressive NHL presenting mediastinal involvement (64% with a bulky mass) were studied with CT and ^{67}GaSPECT at the end of combined modality therapy (chemo- and radiation therapy).**

Results. **After treatment, 3/3 (100%) patients with positive ^{67}GaSPECT and negative CT scan relapsed while only 1/18 (6%) patients with both negative ^{67}GaSPECT and CT scan did so. At the same time, 54 patients had a positive restaging CT scan (abnormal mass < 10% of size of initial mass). Of these patients, 13 had a positive ^{67}GaSPECT, 10 of whom (77%) relapsed; 41 had a negative ^{67}GaSPECT of whom 5 (12%) relapsed. The 4-year actuarial relapse-free survival rate was 90% for those with negative scans compared with 23% for gallium-positive patients ($p < 0.000000$).**

Interpretation and Conclusions. **In lymphoma patients with mediastinal involvement, ^{67}GaSPECT should be considered, at least in patients who are CT positive, the imaging technique of choice for monitoring and differentiating the nature of any residual masses.**

Key words: Hodgkin's disease, aggressive NHL, ^{67}GaSPECT, bulky mediastinum

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Over the last 20 years third generation chemotherapy regimens,[1-3] autologous bone marrow transplantation[4-6] and multimodality chemo-and radiation therapy programs[7-9] have attenuated the negative impact of presentation with bulky mediastinal lymphomatous disease on complete response (CR) and disease-free survival rates.[10-11] Nevertheless, evaluation of the presence or absence of active residual mediastinal disease following treatment still represents a difficult diagnostic problem. Although conventional computed tomography (CT) chest scans most often reveal residual post-treatment abnormalities and provide much information regarding size and distribution of lesions, they do not always adequately distinguish active disease from benign changes such as fibrosis, necrosis or inflammation. Proper evaluation of whether or not there is active residual disease is important, since adequate treatment can often lead to cure or have a significant impact on the clinical outcome. Gallium-67-citrate single photon emission (^{67}GaSPECT) has been proposed as an additional examination because of its ability to provide information about the nature (fibrosis/necrosis vs. residual disease) and activity of masses.[12-25] However, extensive studies on large series of patients focusing on the clinical impact of the use of ^{67}GaSPECT have yet to be reported. We performed a retrospective study of 75 patients with aggressive non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) with mediastinal involvement at the time of diagnosis who underwent ^{67}GaSPECT for routine restaging following treatment with chemotherapy and radiotherapy at our institution.

Design and Methods

Between February 1992 and December 1996, 75 patients with HD or aggressive NHL were treated at our Institute with induction chemotherapy and radiation. The main protocol inclusion requirement was initial mediastinal disease with an area of tumor involvement ≥ 5 cm in size. Criteria for entry into the study included: no prior therapy; histologic diagnosis of HD or aggressive NHL according to the

R.E.A.L. classification;[26] an ECOG[27] performance status score of <3; normal hepatic, renal, and cardiac function. Radiological clinical staging with evaluation of tumor size included CT and ^{67}GaSPECT. CT was monitored at diagnosis (before therapy), at the end of chemotherapy, and 2 months after radiotherapy; ^{67}GaSPECT was monitored at the time of diagnosis and at the end of chemotherapy and 3 months after radiotherapy (if conducted earlier ^{67}GaSPECT can provide false negatives). The remaining staging procedures included bone marrow biopsy, hematologic and biochemical survey, and bipedal lymphangiography (for HD patients only). The extent of mediastinal disease was defined by a mediastinal mass ratio (MMR), calculated by measuring the maximum intrathoracic diameter; an MMR that exceeded one third was considered as bulky.

Patients' characteristics are shown in Table 1. Thirty-seven patients had HD and 38 patients aggressive NHL (35 males, 40 females; median age 29 years, range 15-67 years). All patients were previously untreated. Forty-eight (64%) patients presented with bulky mediastinal disease. HD patients were treated with 4 or 6 cycles of ABVD[28] regimen (related to the initial staging) and aggressive NHL patients with the MACOP-B[1] regimen. After the completion of either chemotherapy program, all patients received radiation therapy to the mediastinum with a tumor dose of 36 Gy.

Imaging

CT scans of the chest, abdomen, and pelvis were obtained using a third generation General Electric scanner (GE Medical Systems, Milwaukee, WI, USA). All the regions were scanned at 10×10 mm intervals; scan time was 2 sec. Intravenous contrast material (a bolus of 100-150 mL of non-ionic contrast medium) was used in all patients.

^{67}GaSPECT study was performed using high-doses (370 Mbq) of ^{67}Ga-citrate. The acquisition was carried out 68h after injection, with high-quality images [triple energy peaks; MEGP collimators: planar in anterior and posterior views (500 Kcounts Apex SP6, Elscint, Israel)] plus SPECT (360-degree rotation, 120 projection, 30 sec × step) (Prism 3000, Picker, Ohio, USA).

Evaluation of response

CR was defined as being a complete regression of all assessable disease. Good partial response (PR) was defined as a > 90% reduction (in terms of residual mediastinal mass) of the size of clinically apparent disease without any evidence of regrowth on completion of induction therapy. For the purposes of this report, results of ^{67}GaSPECT were not considered when assigning response status following therapy. All patients had a positive ^{67}GaSPECT at the time of diagnosis and at least one documented ^{67}GaSPECT after the completion of combination therapy.

The relapse-free survival curve was calculated using the Kaplan-Meier method[29] (relapse-free survival was defined as the period from the end of therapy to the time of first relapse). The statistical significance of differences observed was assessed using the log-rank test.[30]

Table 1. Patients' characteristics.

Number of patients (HD/aggressive NHL)	75 (37/38)
Age (years)	
median	29
range	15-67
Sex	
M	35 (47%)
F	40 (53%)
Symptoms	
no	56 (75%)
yes	19 (25%)
Stage	
I-II	49 (65%)
III-IV	26 (35%)
Bulky mediastinal disease	48 (64%)

Table 2. ^{67}GaSPECT and CT: relationship to clinical outcome.

	N. pts	*CCR*	*Relapse*
CT$^-$ /^{67}GaSPECT$^+$	3	0	3 (100%)
CT$^-$ /^{67}GaSPECT$^-$	18	17	1 (6%)
CT$^+$ /^{67}GaSPECT$^+$	13	3	10 (77%)
CT$^+$ /^{67}GaSPECT$^-$	41	36	5 (12%)

CCR = continuous complete response.

Results

The imaging outcome, which provided 4 possible situations, is summarized in Table 2. CT scan was negative in 21/75 (28%) patients. Of these, 3/21 patients (2 HD and 1 aggressive NHL) were ^{67}GaSPECT$^+$ at the end of the multimodality therapy: these 3 (100%) patients all had a mediastinal relapse (at 8, 11 and 15 months). Of the other 18/21 patients, who all had a negative CT scan associated with negative ^{67}GaSPECT, only 1/18 (6%) relapsed (after 18 months with lung and neck localizations of HD).

Of the 54/75 (72%) patients who were CT$^+$ (all ≤10% of the initial tumor volume), 48 (89%) had had bulky mediastinal involvement at the time of diagnosis. At ^{67}GaSPECT, 13/54 (24%) patients were positive, and of these 10/13 (77%) patients relapsed (nine within 5 months of the positive ^{67}GaSPECT scan and one at 10 months). The remaining 3 patients (2 aggressive NHL and 1 HD) are currently in CR after 14, 33, and 53 months. By contrast, at a median follow-up of 28 months we have observed only 5 (12%) relapses among the 41 ^{67}GaSPECT$^-$ patients. These 5 patients all relapsed within 15 months (all in previously involved sites of disease). The 4-year actuarial relapse-free survival rate for negative ^{67}GaSPECT is

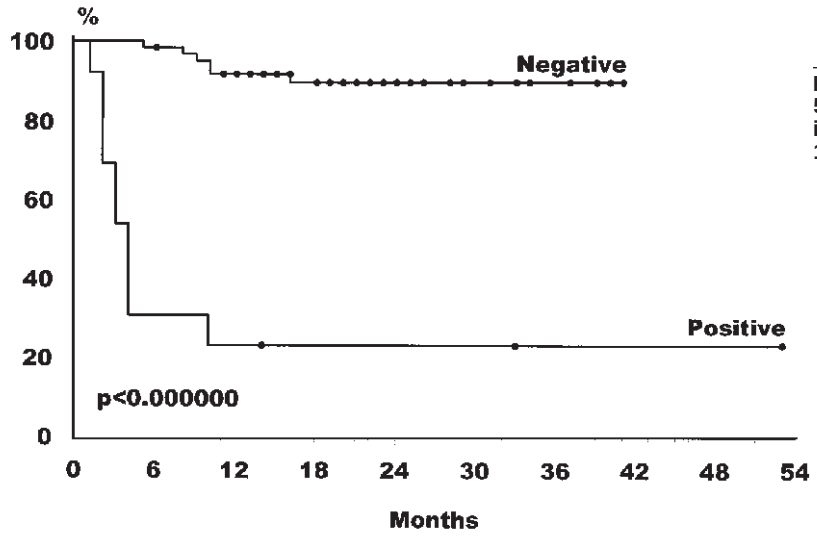

Figure 1. Relapse-free survival curves of 54 patients with positive CT scan according to gallium scan results (^{67}GaSPECT$^+$, 13 patients; ^{67}GaSPECT$^-$, 41 patients).

90%, as compared with 23% for restaging positive ^{67}GaSPECT patients (p <0.000000) (Figure 1). It is remarkable that all the positive ^{67}GaSPECT sites coincided with anatomic mediastinal locations where there had been pretreatment involvement with HD or aggressive NHL, and in all cases initial relapse occurred exclusively at positive ^{67}GaSPECT sites.

Discussion

Few clinical tools are available to help identify patients in apparent CR or PR who have occult residual disease. Incomplete regression of a lymphomatous mass despite apparently effective therapy constitutes a major problem in the treatment of lymphoma, especially in patients presenting with a bulky mediastinal mass. In many cases, such residual masses consist of residual fibrotic tissue with no active lymphomatous component, while in other cases active residual disease may still be present. This dilemma may occur after combined modality treatment (chemotherapy and radiation therapy) in both HD and aggressive NHL patients with mediastinal involvement. Recently, some reports[12-25] have stressed the potential usefulness of ^{67}GaSPECT scanning for discriminating between active residual tumor and benign fibrous tissue.

To our knowledge the present study is one of the largest currently available focusing on the real efficacy of ^{67}GaSPECT scanning in the qualitative evaluation of residual mediastinal masses detected by CT. As expected, CT revealed a considerable percentage of residual masses in the mediastinum after chemotherapy and radiation therapy (a persistent mass constituting ≤10% of the initial disease mass was present in 72% of our patients, 89% of whom had had bulky mediastinal involvement at the time of diagnosis). Among the 13 CT$^+$, ^{67}GaSPECT$^+$ patients, 10 (77%) relapsed in the ^{67}GaSPECT$^+$ sites. This figure strongly contrasts with the 5/41 (12%) relapses among the CT$^+$, ^{67}GaSPECT$^-$ patients (p <0.000000). Moreover, it is noteworthy that all 3 CT$^-$ patients who turned out to be ^{67}GaSPECT$^+$ relapsed within 15 months in mediastinal sites where disease had been present at diagnosis. Finally, further evidence that ^{67}GaSPECT$^+$ restaging revealed induction failure was supplied by the rapidity with which the positive cases relapsed: all ^{67}GaSPECT$^+$ patients developed clinical disease within a few months of completing the combined modality treatment.

Thus, our study on a large number of patients with mediastinal involvement (2/3 of whom had a bulky mass) provides definitive confirmation of ^{67}GaSPECT's utility as a specific tool for discriminating fibrotic and tumor tissue and therefore its validity in the follow-up of mediastinal masses in these lymphomas. This restaging technique allows identification of the subset of patients with residual radiographic abnormalities who need no further therapy (^{67}GaSPECT$^-$) and of poor prognosis patients who do require further treatment.

We conclude that ^{67}GaSPECT is extremely valuable for discriminating between residual tumor and fibrosis/necrosis in HD/aggressive NHL patients who had a positive mediastinal CT scan after combined modality therapy. Furthermore, ^{67}GaSPECT is capable of detecting residual mediastinal disease that goes undetected at CT. Nevertheless, ^{67}GaSPECT needs to be used in combination with CT scan to optimize restaging in qualitative and quantitative terms. Thus, we think that ^{67}GaSPECT should become mandatory at least in patients who are CT positive. In those patients with positive ^{67}GaSPECT restaging, local biopsy can be performed to evaluate residual disease so that suitable salvage therapy may be started as early as possible.

Contributions and Acknowledgments

PLZ, GF, NM designed the study. MZ performed all CT scans. RF, RG carried out all ^{67}GaSPECT. MM, FG, MB and PA were

involved in clinical assessment of the patients. PLZ wrote the paper. ST was responsible for the revision of the paper.

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Disclosures

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