Clinical pretreatment risk factors and prediction of outcome using gallium 67 scintigraphy in patients with Hodgkin's lymphoma

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Abstract. This study was conducted to investigate the prognostic effect and implications of gallium 67 scintigraphy (gallium scan) at mid-treatment and at the end of first-line treatment in patients with early- and advanced-stage Hodgkin's lymphoma (HL). A total of 216 HL patients were included in the study. Gallium scan was performed at mid-treatment and at the end of first-line treatment. The overall survival (OS) and event-free survival (EFS) were calculated using the Kaplan-Meier method. The log-rank test was used to identify univariate predictors of EFS and OS. For early-stage disease, bulky mediastinal involvement (yes vs. no, 98 vs. 79%, respectively; P=0.01), erythrocyte sedimentation rate (good vs. adverse, 98 vs. 88%, respectively; P=0.03), presence of B symptoms (no vs. yes, 94 vs. 78%, respectively; P=0.006), post-chemotherapy disease status [complete response (CR) vs. unconfirmed CR (uCR) vs. partial response (PR) vs. progressive disease (PGR), 95 vs. 90 vs. 87 vs. 0%, respectively; P<0.01] and gallium scan at mid-treatment and at the end of treatment (negative vs. positive, 88 vs. 20%, P<0.001; and 85 vs. 10%, P<0.001, respectively) significantly affected the EFS. In addition, age (<50 vs. ≥50 years, 96 vs. 78%, respectively; P=0.01), presence of B symptoms (no vs. yes, 97 vs. 87%, respectively; P=0.03), post-chemotherapy disease status (CR vs. uCR vs. PR vs. PGR, 95 vs. 90 vs. 90 vs. 0%, respectively; P<0.01) and gallium scan results at mid-treatment and at the end of treatment (negative vs. positive, 87 vs. 60%, P<0.001; and 95 vs. 0%, P<0.001, respectively) significantly affected the OS. For advanced-stage disease, Hassenclever index (1-3 vs. 4-6, 80 vs. 57%, respectively; P=0.05) and gallium scan results at mid-treatment and at the end of treatment (negative vs. positive, 84 vs. 18%, P<0.001; and 84 vs. 0%, P<0.001, respectively) significantly affected the EFS, whereas age at diagnosis (<50 vs. ≥50 years, 92 vs. 78%, respectively; P=0.04), Hassenclever index (1-3 vs. 4-6, 86 vs. 61%, respectively; P=0.04) and gallium scan results at mid-treatment and at the end of treatment (negative vs. positive, 98 vs. 40%, P<0.001; and 97 vs. 23%, P<0.001, respectively) significantly affected the OS. On the multivariate analysis, gallium scan at the end of first-line treatment retained statistical significance in terms of EFS and OS. In conclusion, post-chemotherapy gallium scan is an important prognostic factor in patients with early- or advanced-stage HL and a predictor of adverse outcome.

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Introduction

The majority of the patients diagnosed with Hodgkin's lymphoma (HL) may be succesfully treated with radiotherapy (RT) or conventional-dose chemotherapy, with 70% remaining alive at 10 years following diagnosis (1-3).

For patients with relapsed and refractory HL, second-line chemotherapy followed by autologous stem cell transplantation (ASCT) and a non-myeloablative conditioning regimen followed by allogeneic transplantation are currently considered to be viable therapeutic options (4).

Clinical risk factors are an expression of disease sensitivity and may indicate the patient's ability to respond to treatment. There is a considerable amount of retrospective information available in this respect for patients with HL (5-10) and the response of lymphoma to chemotherapy is considered by several authors as one of the most significant factors (8,11,12). Functional imaging techniques, such as gallium 67 (^{67}Ga) scintigraphy (gallium scan) or positron emission tomography (PET) with 2-(^{18}F)-fluoro-2-deoxy-D-glucose, may be used to monitor the effect of treatment on lymphoma tissues (13-16).

Strong evidence has been accumulating, indicating that assessment of response after 1 or 2 cycles of chemotherapy, or after the end of first-line therapy, particularly with metabolic imaging methods such as gallium scan and, more recently, with

PET, may identify patients with poor prognosis, for whom early treatment intensification may be considered (13-17). In this study, we present the results of a two-center retrospective study, in which we analyze the prognostic effect and implications of gallium scan at mid-treatment and at the end of first-line treatment in patients with early- and advanced-stage HL.

Patients and methods

Patient characteristics. This study included 216 HL patients who were treated between 1991 and 2004 at the University Hospital of Salamanca (Salamanca, Spain) and the Puerta de Hierro University Hospital (Madrid, Spain). The local Ethics Committees of the participating centers approved the study protocol, taking into consideration the existing regulations at that time. The patient characteristics are summarized in Table I. The patients included 117 (54.2%) men and 99 (45.8%) women, with a median age of 37 years (range, 11-80 years). All the patients had histological evidence of HL confirmed by hematopathologists at the treating hospital; 148 patients (68.5%) had nodular sclerosis, 53 (24.5%) mixed-cellularity and 7 (3.3%) lymphocyte-predominant types. A total of 79 patients (36.6%) presented with B sympthoms at diagnosis and 144 (67.0%) were diagnosed with stage I or II disease. As regards the extension of the lymphoma, 69.0% of the patients did not exhibit bulky disease, whereas only 35 patients (16.0%) exhibited extranodal disease.

Treatment. The treatment details are described in Table II. Considering the 144 patients with early-stage disease who completed the induction therapy, 27 (18.7%) received RT alone, 82 (57.0%) 3 cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) followed by RT and 35 (24.3%) received mechlorethamine, vincristine, procarbazine and prednisone (MOPP) followed by RT. Among the 72 advanced-stage patients, 58 (80.6%) received 3-8 cycles of ABVD and 13 (18.0%) 6-8 cycles of MOPP and components of the ABVD regimen without dacarbazine (MOPP/ABV regimen). One patient received methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin (MACOP-B regimen). Finally, 55 patients (76.4%) received consolidation treatment with RT following chemotherapy.

Restaging gallium. Patients were considered eligible for the study when they had a ^{67}Ga-avid lymphoma established by a baseline gallium scan prior to treatment and a gallium scan for restaging performed midway through chemotherapy (114 patients, 52.7%) and/or at the end of the first-line treatment (204 patients, 94.4%). This cohort of patients were treated before PET was available at our institution; therefore, none of the patients underwent PET. Four patients (1.8%) underwent mid-chemotherapy gallium scan alone, 94 patients (43.5%) underwent end-first-line treatment gallium scan alone and 110 patients (51.0%) underwent both examinations. Apart from one, all patients with a positive restaging gallium scan at the end of treatment received additional chemotherapy or underwent high-dose therapy with stem-cell rescue.

Clinical response following chemotherapy. Clinical response following treatment was determined based on the computed tomography (CT) scan or physical examination findings at the end of chemotherapy or RT, using the guidelines developed by the International Workshop on Response Criteria for non-HL (18). A complete response (CR) was defined as negative physical examination and residual disease of ≤1 cm; an unconfirmed CR (uCR) was defined as >75% reduction in tumor volume, with residual disease of ≤2 cm; a partial response (PR) was defined as >50% reduction in tumor volume; stable disease was defined as <50% reduction in tumor volume; and progressive disease was defined as an increase in the size of initial disease or development of new foci. Relapsed disease was defined as further disease progression or appearance of new disease foci after a response had been achieved with the initial course of treatment.

Table I. Clinical characteristics at diagnosis.

Characteristics	Patient no. (%) (n=216)
Age, years	
Median (range)	37 (11-80)
Gender	
Male	117 (54.2)
Female	99 (45.8)
Histological type	
Nodular sclerosis	148 (68.5)
Mixed-cellularity	53 (24.5)
Lymphocyte-predominant	7 (3.3)
Other	8 (3.7)
ECOG PS	
0, 1	180 (84.0)
2-5	36 (16.0)
B symptoms	
No	79 (36.6)
Yes	137 (63.4)
Ann Arbor stage	
I-II	144 (67.0)
III-IV	72 (33.0)
Bulky disease	
No	149 (69.0)
Yes	67 (31.0)
Bone marrow involvement	
No	201 (93.0)
Yes	15 (7.0)
Extranodal disease	
No	181 (84.0)
Yes	35 (16.0)
Positive CT at diagnosis	216 (100.0)
Positive ^{67}Ga scan at diagnosis	216 (100.0)

^{67}Ga, gallium 67; ECOG PS, Eastern Cooperative Oncology Group performance status; CT, computed tomography.

^{67}Ga imaging. For gallium scan studies, the patients received 7-10 mCi (259-370 MBq) intravenous injection of ^{67}Ga citrate and imaging was performed at 72 h. Whole-body anterior and posterior planar images were acquired with a dual-head camera attached to a medium-energy collimator and 3 energy peaks of 93, 184 and 296 keV (20% window), using a 256x768 matrix and a scanning speed to achieve an information density of >1,500,000 counts for each view. In addition, single-photon emission CT (SPECT) of the chest, abdomen and pelvis was performed with the same camera at 3˚ intervals and 25 sec/stop using 64x64 matrix. Reconstruction of the SPECT data was performed using a low pass pre-filter (order 5.0, cut-off 0.31) and transverse reconstruction with a ramp filter. Attenuation correction was not applied and the files were reconstructed in transverse, sagittal and coronal planes. Additional delayed images were obtained in selected patients in whom the SPECT images failed to differentiate between normal and abnormal bowel activity. Nuclear medicine physicians did not have access to the CT images or results when evaluating the gallium scans. The gallium scan was considered positive for the presence of disease when abnormal focal or diffuse uptake of ^{67}Ga was observed in a localization incompatible with normal structures and unexplained by other causes. Diffuse lung uptake (19) and bilateral perihilar uptake (20) were not considered to indicate the presence of lymphoma.

Statistical analysis. In order to identify the factors that affected outcome, the following clinical and biological characteristics were evaluated in univariate and multivariate analyses: Gender, age, Eastern Cooperative Oncology Group performance status, Ann Arbor stage, size of tumor, bulky disease, presence of B symptoms, bone marrow involvement, number of extranodal sites, erythrocyte sedimentation rate (ESR), lactate dehydrogenase, β2-microglobulin, copper and ceruloplasmin levels, number of leukocytes and lymphocytes and hemoglobin levels. Finally, CT and gallium scan results after 3 cycles of treatment and at the end of induction therapy were included.

Comparison of response rates was performed using the χ^2 test. The patients were analyzed with respect to event-free survival (EFS) and overall survival (OS). OS was calculated from the day of diagnosis to the day of death or last follow-up. EFS was calculated from the day of diagnosis to the day of treatment failure (relapse, progression or no response to induction therapy). Probabilities were estimated using the Kaplan-Meier method. Differences between groups according to the different covariates were analyzed by the log-rank test. A forward stepwise Cox proportional hazards regression model was used for multivariate analysis. All the P-values reported were two-sided and $P<0.05$ was considered to indicate statistically significant differences.

Results

Follow-up and survival. The median follow-up time for the 216 patients was 107 months. The 5-year Kaplan-Meier OS and EFS estimates were 91 and 82%, respectively. The corresponding OS and EFS estimates for the 144 patients with stage I-II disease at diagnosis were 92 and 87%, respectively, whereas the corresponding OS and EFS for the 72 patients with stage III-IV disease were 86 and 77%, respectively.

Table II. Induction treatment.

First-line treatment	Patient no. (%)
Early stage (n=144)	
RT alone	27 (18.7)
ABVD x 2/3 + RT	82 (57.0)
MOPP x 2/3 + RT	35 (24.3)
Advanced stage (n=72)	
ABVD x 6/8	58 (80.6)
MOPP-ABV x 6/8	13 (18.0)
MACOP-B	1 (1.4)
RT bulky	55 (76.4)

RT, radiotherapy; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; MOPP, mechlorethamine, vincristine, procarbazine and prednisone; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin.

Restaging gallium scan and clinical response following chemotherapy. The results of restaging gallium scanning are presented in Table III. Among the 114 patients who underwent a mid-chemotherapy gallium scan, 12 (10.5%) had a positive result. For the 204 patients who underwent a post-chemotherapy gallium scan, the results were positive in 10 (4.9%). Among the 110 patients who underwent both a mid- and a post-chemotherapy gallium scan, 5 patients (4.6%) had a positive scan midway through treatment and became negative after treatment; 2 patients (1.8%) had a negative gallium scan at mid-chemotherapy and became positive at the end of chemotherapy; and in 5 patients (4.6%), the results were positive in both mid- and post-chemotherapy gallium scans. The remaining 98 patients (89%), had negative results at both time points.

Based on the CT scan or physical examination findings, 206 patients (94%) achieved complete or uCR after first-line treatment, 4 patients (2%) had PR and 6 patients (4%) had progressive disease,without any patient achieving stable disease. All 10 patients with a positive gallium scan at the end of first-line treatment had progressive disease, 80% of whom succumbed due to disease progression and 20% were rescued with treatment. Of the 194 patients with negative gallium scan at the end of treatment, 23 (11.8%) suffered an event, whereas 141 of them exhibited CR (72.6%) and 53 uCR (27.3%).

Treatment outcome in patients with a positive restaging gallium scan. Of the 216 patients included in the series, 16 presented a positive gallium scan result and treatment was changed in 4 (25%) patients after 2 cycles of chemotherapy. The 4 patients were rescued with chemotherapy and ASCT. Another 3 patients (18.7%) continued with the first-line treatment despite the gallium scan findings at mid-treatment, with repeat positive results at the end of first-line treatment, and received rescue chemotherapy followed by TASPE. Of

Table III. Restaging gallium scan and clinical response following chemotherapy.

A, Gallium scan

Time point	Positive (%)	Negative (%)
Mid-treatment (n=114)	12 (10.5)	102 (89.5)
End of treatment (n=204)	10 (4.9)	
Mid-end treament (n=110)[a]	Positive to negative, 5 (4.6)	Negative to positive, 2 (1.8)
	Positive-positive, 5 (4.6)	Negative-negative, 98 (89.0)

B, Clinical response to treatment[b]

Type of response	No. (%)
CR/uCR	206 (94.0)
PR	4 (2.0)
PGR	6 (4.0)

[a]Conversion of gallium scan results during treatment: From positive at mid-treatment to negative at the end of first-line treatment; from negative to positive result after induction treatment; and those who maintained the same gallium scan results during the entire duration of the induction treatment. [b]Clinical response based on computed tomograhy scan results and clinical examination findings. CR, complete response; uCR, unconfirmed CR; PR, partial response; PGR, progressive disease.

these 7 patients, 3 remained alive and disease-free at the last follow-up (2 of whom had positive gallium scan results at the end of first-line treatment). The remaining 4 patients succumbed to progressive lymphoma. Of the 9 patients with positive gallium scans and without change of treatment, 6 patients succumbed, 2 of whom due to secondary neoplasms. Of the remaining 3 cases, 1 should be considered a false-positive result secondary to RT, the second patient suffered a late relapse and remained lymphoma-free following conventional rescue treatment plus consolidation with RT, whereas the third patient became negative (after a mid-treatment positive result) following 4 more chemotherapy cycles and consolidation RT of bulky mediastinal disease, and remained disease-free at the last follow-up.

Univariate analysis of stage I-II patients. The significant variables in the univariate analysis are listed in Table IV. For stages I-II, the analysis was restricted to 144 patients. The variables included in the analysis were gender, age at diagnosis, bulky mediastinal involvement, B symptoms, ESR, post-chemotherapy status, and gallium scan at mid-treatment and at the end of first-line treatment.

The factors found to significantly affect the EFS were bulky mediastinal involvement (yes vs. no, 98 vs. 79%, respectively; P=0.01), ESR [good vs. adverse (>50 without or >30 with B symptoms), 98 vs. 88%, respectively; P=0.03], presence of B symptoms (no vs. yes, 94 vs. 78%, respectively; P=0.006), post-chemotherapy disease status (CR vs. uCR vs. PR vs. PGR, 95 vs. 90 vs. 87 vs. 0%, respectively; P<0.01) and gallium scan results at mid-treatment and at the end of treatment (negative vs. positive, 88 vs. 20%, P<0.001; and 85 vs. 10%, P<0.001, respectively). As regards OS, the factors with statistical significance included age (<50 vs. ≥50 years, 96 vs. 78%, respectively; P=0.01), presence of B symptoms (no vs. yes, 97 vs. 87%, respectively; P=0.03), post-chemotherapy disease status (CR vs. uCR vs. PR vs. PGR, 95 vs. 90 vs. 90 vs. 0%, respectively; P<0.01) and gallium scan results at mid-treatment and at the end of treatment (negative vs. positive, 87 vs. 60%, P<0.001; and 95 vs. 0%, P<0.001, respectively).

Univariate analysis of stage III-IV patients. For stage III-IV disease, the analysis was restricted to 72 patients and the results are listed in Table IV. The variables included in the analysis were gender, age at diagnosis, Hassenclever index classified into two groups according to risk (1-3 vs. 4-6), and gallium scan at mid-treatment and at the end of first-line treatment.

The factors found to significantly affect the EFS were Hassenclever index (1-3 vs. 4-6, 80 vs. 57%, respectively; P=0.05) and gallium scan results at mid-treatment and at the end of treatment (negative vs. positive, 84 vs. 18%, P<0.001; and 84 vs. 0%, P<0.001, respectively). Age at diagnosis (<50 vs. ≥50 years, 92 vs. 78%, respectively; P=0.04), Hassenclever index (1-3 vs. 4-6, 86 vs. 61%, respectively; P=0.04) and gallium scan results at mid-treatment and at the end of treatment (negative vs. positive, 98 vs. 40%, P<0.001; and 97 vs. 23%, P<0.001, respectively) were the factors significantly affecting OS.

Multivariate analysis. Considering patients with stage I-II disease, only gallium scan results at the end of first-line treatment retained statistical significance in the Cox regression model [P<0.001, hazard ratio (HR)=2.1 and 95% confidence interval (CI): 1.91-7.9 for EFS; and P=0.03, HR=1.9 and 95% CI: 1.08-5.8 for OS]. Similarly, when considering stage III-IV patients, gallium scan at the end of treatment retained statistical significance (P=0.028, HR=3 and 95% CI: 1.07-3.4 for EFS; and P=0.003, HR=4 and 95% CI: 1.45-6.07 for OS) (data not shown).

Table IV. Univariate analysis of prognostic factors.

Prognostic factors	Patient no.	Cumulative EFS (%)	P-value	Cumulative OS (%)	P-value
Stages I-II (n=144)					
Post-chemotherapy status			**<0.001**		**<0.001**
Complete response	117	95		95	
Unconfirmed complete response	20	90		90	
Partial response	4	87		90	
Progressive disease	3	0		0	
Age at diagnosis, years			0.9		**0.01**
<50	128	86		96	
≥50	16	88		78	
Gender			0.9		0.9
Male	71	86		92	
Female	73	85		94	
Bulky involvement			**0.01**		0.07
Yes	52	98		90	
No	92	79		93	
B symptoms			**0.006**		**0.03**
Yes	49	78		87	
No	95	94		97	
Erythrocyte sedimentation rate			**0.03**		0.6
Good	84	98		94	
Adverse[a]	60	88		92	
Mid-treatment gallium scan			**<0.001**		**<0.001**
Negative	67	88		87	
Positive	5	20		60	
End-treatment gallium scan			**<0.001**		**<0.001**
Negative	136	85		95	
Positive	2	10		0	
Stages III-IV (n=72)					
Gender			0.3		0.07
Male	46	79		82	
Female	26	75		80	
Age at diagnosis, years			0.4		0.04
<50	52	82		92	
≥50	20	76		78	
Hassenclever index[b]			**0.05**		**0.04**
1-3	57	80		86	
4-6	15	57		61	
Mid-treatment gallium scan			**<0.001**		**<0.001**
Negative	35	84		98	
Positive	7	18		40	
End-treatment gallium scan			**<0.001**		**<0.001**
Negative	59	84		97	
Positive	7	0		23	

[a]>50 without B symptoms or >30 with B symptoms. [b]Hassenclever index classified in two groups according to prognosis. EFS, event-free survival; OS, overall survival; P-values in bold print denote statistically significant differences.

Survival analysis. A total of 22 patients had succumbed to the disease at the time of the analysis. Of these, 9 patients succumbed to progressive HL, 7 secondary to infectious complications (3 of whom were under treatment with high-dose chemotherapy and stem cell transplantation), and 1 patient secondary to the bleomycin pulmonary toxicity. The

remaining 5 patients developed secondary neoplasms (4 solid tumors and 1 myelodysplastic syndrome with a high-grade International Prognostic Scoring System score).

Discussion

This study reports the results of gallium scan and other prognostic factors in 216 patients with stage I-IV Hodgkin's disease following first-line treatment with chemotherapy and/or RT. Long-term treatment efficacy and predictors of relapse were included in the analysis. The 91 and 82% 5-year OS and EFS were in concordance with previous reports (21-23). A variety of patient, disease and laboratory factors have been shown to affect the outcome of HL patients. For patients with early-stage disease, age, extranodal involvment, bulky disease and ESR among others have been associated with long-term prognosis (24-26); for advance-stage cases, Hassenclever index has been found to be the most significant predictor of outcome (26-29).

A number of these prognostic indicators lost their prognostic significance in the context of combined modality therapy with higher disease control rates. CT has been considered the gold standard for restaging patients with lymphoma (30). Considering the common finding of persistent masses on CT scan, the assessment of response and, consequently, the disease status, often represent a problem among patients diagnosed with HL due to the difficulties in distinguishing fibrotic tissue from active disease (31). In addition to PET scan, which is a technique based on tumor metabolic rate to distinguish fibrotic tissue from residual masses (32,33), gallium scan has been successfully used for several years for this purpose in patients with HL following standard chemotherapy and prior to autologous hematopoietic transplantation (34,35).

In the present study, the most important predictor for EFS and OS was gallium scan results during and after chemotherapy. Considering a global analysis of prognostic factors, only gallium scan at the end of the first-line treatment retained statistical significance in the multivariate analysis. Other authors have reported similar results in this respect (36-38), although there is significant heterogeneity in the series and the majority refer to high-grade lymphomas, particularly non-HL. Ng *et al* (39) reported similar results in HL series with the limitation of the univariate analysis to early stages, including patients treated with ABVD alone and with a high proportion of RT-treated patients. Our series analyzed both groups and several described prognostic factors for early and advanced stages; according with our results, gallium scan at the end of treatment should be considered to be the strongest prognostic factor.

Considering the presence of residual gallium scan avidity as an adverse predictor of outcome, the optimal therapeutic approach for this group of patients who do not achieve CR at mid-treatment or at the end of first-line treatment has not yet been clearly determined.

In conclusion, the results of the present study confirm the significance of functional imaging techniques in the prognostic evalution of patients with HL. Post-chemotherapy restaging gallium scan results were highly predictive of treatment outcome, with more statistically significant implications compared with other classic established prognostic factors in patients with early- or advanced-stage disease. Considering patients with positive results at mid- or end-treatment, high-dose therapy with stem cell rescue is a viable rescue therapy option for refractory patients, although not necessarily for all patients, considering the clinical and biological characteristics of this type of lymphoma; each case should be considered individually, taking into consideration disease response, extension and biological activity. However, futher studies are required to obtain more solid conclusions. In the PET era, gallium scan remains a viable option for the accurate prognostic characterization of this group of patients.

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