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Artículo original

Gallium Scan after the Second and Fourth Chemotherapy Cycle is Predictive in Aggressive Non-Hodgkin's Lymphomas

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RESUMEN

Objetivo: evaluar la utilidad del tamizaje con galio como predictor de supervivencia y duración de la respuesta en pacientes con linfoma no Hodgkin agresivo.
Pacientes y método: participaron 190 pacientes con linfoma no-Hodgkin, entre 1992 y 1996, en dos diferentes protocolos de tratamiento con atraciclina. 116 pacientes (61%) tuvieron puntuación Internacional de Pronóstico (IPI) baja y de bajo riesgo intermedio, 74 (39%) la tuvieron alta intermedia y de alto riesgo. Antes del inicio de la quimioterapia todos los pacientes tenían resultados positivos de galio (Ga67), y después de dos (n = 139), cuatro (n = 113) y seis (n = 24) ciclos de quimioterapia se efectuaron exploraciones complementarias. Los pacientes también recibieron radiación en los sitios conocidos con tumor voluminoso.
Resultados: los pacientes en quienes el galio siguió siendo positivo después de dos ciclos de quimioterapia tuvieron una mediana de supervivencia global de sólo 23 meses, comparados con una mediana de 107 meses en quienes las exploraciones de galio fueron negativas (p = .00434). La positividad al Ga67 después de dos ciclos de quimioterapia se asoció con supervivencia libre de enfermedad de 6.6 meses, frente a 106 meses para quienes tuvieron Ga-67 negativo (p =. 00279). Después de cuatro ciclos de quimioterapia, el Ga67 positivo persistente se correlacionó con una media más corta (14.6 meses frente a 102.5 meses, respectivamente, p =. 00092) y supervivencia libre de enfermedad con media más corta (6.2 meses frente a 90 meses, respectivamente, p =. 00006). Mediante análisis de regresión de Cox, el resultado de la gammagrafía con galio es independiente del Índice Pronóstico Internacional (IPI) como un predictor de pobres resultados en el linfoma no Hodgkin agresivo.
Conclusiones: la positividad persistente del tamizaje con galio después de dos, cuatro, o seis ciclos de quimioterapia identifica a grupos de pacientes con gran tendencia a la progresión temprana de la enfermedad y pobre supervivencia global. El efecto parece ser independiente del IPI. El objetivo de esta prueba es identificar la resistencia intrínseca al tratamiento en los pacientes con la enfermedad para que puedan beneficiarse de un esquema más agresivo e innovador, como la intensificación temprana.
Palabras clave: galio, agresivo, linfoma, factores pronósticos.

ABSTRACT

Purpose: To evaluate utility of gallium scans as a predictor of survival and response duration in patients with aggressive NHL.
Patients and Methods: From 1992 to 1996, 190 patients with aggressive non-Hodgkin's lymphoma (NHL) were enrolled in two different anthracyclin-containing treatment protocols. One hundred-sixteen of these patients (61%) had an International Prognostic Score (IPI), of low, and low-intermediate risk; 74 (39%) had high-intermediate and high-risk. All patients had positive gallium scans (Ga67) prior to initiation of chemotherapy, and additional scans were performed after cycles two (n=139), four (n=113), and six (n=24) of chemotherapy. Patients also received radiation to known sites of bulky disease.
Results: Patients whose gallium scan remained positive after two courses of chemotherapy had a median overall survival (OS) of only 23 months compared to a median OS of 107 months for those whose gallium scans turned negative (p=.00434). Similarly, Ga67 positivity after two cycles of chemotherapy was associated with a disease-free survival (DFS) of 6.6 months compared to 106 months for those who had Ga-67 negativity (p=.00279). After four courses of chemotherapy, persistent Ga67- positivity also correlated with a shorter median OS (14.6 months vs. 102.5 months respectively, p=.00092) and a shorter median DFS (6.2 months vs. 90 months respectively, p=.00006). By Cox regression analysis, the result of the gallium scan was independent of the International Prognostic Index (IPI) as a predictor of poor outcomes in aggressive NHL.
Conclusions: Persistent gallium scan positivity after two, four, or six cycles of chemotherapy identifies a group of patients with great tendency for early disease progression and poor overall survival. The effect appears to be independent of IPI. This test targets patients with disease which has intrinsic resistance to their treatment and who may benefit from more aggressive and innovative therapies such as early intensification.
Key words: Gallium Scan, Aggressive Lymphoma, Prognostic Factors.

Aggressive NHLs constitute a heterogeneous group of diseases that afflict individuals of all ages. In spite of notable improvements and better outcome for patients diagnosed from aggressive NHL in the last decade a significant number of them will ultimately die because of lymphoma. The identification of clinical, biological or, recently, genetic features, that identify patients who will not response or relapse after a conventional first-line therapy is very important since it will contribute to a more efficient use of the available drugs and treatment strategies for aggressive NHL, and contribute to a more individualized therapy. Several investigators have defined pretreatment prognostic features that identify patients likely to have short responses to initial chemotherapy and poor overall prognosis. These include, among others, the IPI,_ b2 microglobulin (b2M),2 serum interleukin-6,3 Ki-67,4 and the M D Anderson Tumor Score.[5]

Although not a pretreatment factor, the quality of response to initial treatment is one of the most important prognostic features determining the ultimate outcome of patients with aggressive lymphomas. Those who do not achieve a CR with initial therapy have much lower survival rates than those who do. Various investigators have suggested that patients who achieve early remission during treatment will have longer disease-free survival results.[6-11] However, despite achieving CR, many patients will still relapse, usually within the first two years of initial treatment.[12,13] Some of those who develop relapse will be eligible for potentially curative high-dose chemotherapy with stem cell rescue. If clinicians could successfully identify patients who will not achieve CR or who will likely respond initially to treatment but have a very high relapse-risk before medical signs of disease reoccurrence develop then aggressive strategies involving salvage therapy treatments could be employed in the hopes of improving prognoses.

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Relatively common findings in the treatment of this disease are large tumor masses that slowly shrink with therapy. Distinguishing active tumor from necrotic tissue can be difficult in the evaluation of post treatment residual masses.[14,15,16] Image-guided core biopsy has been useful in this situation, but may not be completely reliable when biopsies are negative for disease.[17] While computed tomography (CT) scans are invaluable for determining the extent of disease at diagnosis, gallium imaging, with or without the use of single photon emission computed tomography (SPECT), and Positron emission tomography (PET) may have a greater specificity for assessing the presence of viable tumor in residual masses of patients with Hodgkin's Lymphoma (HL) and NHL.[18-27]

Multiple investigators have studied gallium imaging during and after chemotherapy treatment and suggested that persistent Ga-67 positivity is a significant adverse prognostic factor.[28-33] Janicek et al reported the significance of persistent Ga-67 positive scans in 30 patients with poor prognosis aggressive NHL and tumor masses ^{3} 10 cm.[28] Another retrospective analysis of 75 patients with HL and NHL, Zinzani et al demonstrated gallium scan usefulness in evaluation of residual mediastinal masses at the completion of therapy.[29] Others have studied whether Ga-67 scanning early during therapy can predict treatment outcomes.[30,31] In these earlier studies, conclusions regarding the predictive utility of gallium scanning has been limited by small patient numbers and scant information on the pretreatment prognostic factor profile of patients studied. In this analysis, we report on the utility of gallium scans after the second, fourth and sixth cycle of frontline chemotherapy in 190 patients with good and poor prognosis aggressive histology NHL.

PATIENT AND METHODS

Eligibility Criteria, Treatment, and Accrual Data

Newly diagnosed patients with aggressive NHL were evaluated at M D Anderson from June 1992 through December 1996 and enrolled on clinical protocols 92-054 and 93-003. These studies were designed to treat patients with intensive chemotherapy. Because of the similarities of the two trials and the concurrent time of patient recruitment, data from these two studies are pooled for analysis purposes.

During this period, 146 patients with high-risk aggressive histology NHL (intermediate grade and immunoblastic lymphomas according to the Working Formulation) were

registered for treatment under protocol 92-054. Patients with an M D Anderson tumor score ³ 3 were eligible. They were treated with alternating triple therapy (ATT) as previously reported.35Seventy-seven patients with similar aggressive histology NHL with a tumor score <3 were treated in protocol 93-003. A tumor score of < 3 is associated with a good prognosis. Patients received CHOP-based chemotherapy for six cycles. Only 190 of the 223 patients from both protocols had positive baseline gallium scans and are subjects of this analysis. All patients received one or more additional gallium scans after their baseline pretreatment scan.

Patient Characteristics (Table 1)

Biopsy slides were reviewed at MD Anderson by one or more experienced hemato-pathologists. Information on Ann Arbor stage, LDH, serum b2 microglobulin, serum albumin, Zubrod's performance status, size of the largest tumor, number of extranodal areas, number of treatment cycles, treatment response, and baseline gallium scans results were collected prospectively. For this report, bulky disease was defined by a mass³ 7 cm.

Table I. Patient Characteristics (n=190)

Patient Characteristics		*Number of Patients (%)*
Age > 60		122 (64%)
Male		107 (56%)
Ann Arbor Stage	I	31 (16%)
	II	52 (27%)
	III	38 (20%)
	IV	69 (36%)
B-symptoms		76 (64%)
Elevated HDL		128 (67%)
Bulky mass> 7 cm		141 (74%)
Zubrod´s Performance Status ≥ 2		38 (20%)
Extranodal sites ≥ 2		38 (20%)
ß2-microglobulin ≥ 3 mg/L		66 (35%)
International Prognostic Index		
Low (0-2)		116 (61%)
High (≥3)		74 (39%)
MDA Tumor Score		
Low (0-2)		77 (41%)
High (≥ 3)		113 (59%)
Dead		87 (46%)
Dead without disease progression		13 (7%)
Dead by mieloysplasia		4 (2%)
Dead by other causes		9 (5%)
Disease Progression		95 (50%)
Alive		102 (54%)
Alive without disease progression		82 (42%)

Gallium Scan Technique

Gallium scans were performed with the intravenous injection of 8 - 10 mCi of Ga-67 citrate with subsequent imaging performed 48-120 hours later. Scans were done before treatment, and 3 weeks after the second or more cycles of chemotherapy. Each patient received 8-10 millicuries of gallium-67 citrate as a bolus injection. Using a dual detector gamma camera, with a medium energy collimator, total body images were performed at a scan speed of 10 cm/min at a minimum of 48 hours after Ga-67 injection. The 93KeV, 184 KeV, and 296 KeV peaks were used with 20% and 10% windows. The image typically had 2 to 4 m counts. SPECT imaging was performed at 48 hours and up to 72 hours, depending upon patient's clinical status. Images were displayed in the transaxial, saggital and coronal views, and results interpretation was performed from hard copy transparencies and interactive console display with volume-rendered three-dimensional images. Interpretations were performed with full knowledge of clinical, laboratory, and other imaging findings.

Criteria for Response

A CR was defined as no detectable evidence of disease by physical examination, x-rays, and CT scans. Bone marrow was confirmed to be free of lymphoma by repeat biopsy if involved by disease prior to the start of treatment. Unconfirmed CR (CRu) was defined as the presence of minimal residual abnormalities on radiographic imaging (a mass <25% of the original volume calculated from the product of two diameters) with no palpable disease on physical examination. Partial response (PR) was defined as a ³ 50% reduction in the product of two diameters of tumor measured by radiological criteria or physical examination. Those who met the above criteria but still had histological evidence of lymphoma by biopsy were designated as having achieved PR. Progressive disease (PD) was defined as any tumor reduction less than 50%, significant tumor growth between courses despite an initial ³ 50% reduction, or lymphoma relapse in a patient achieving CR. Clinical responses lasting less than at least two months were designated PD.

Additional Biopsies

Biopsies of residual masses after the fourth cycle of chemotherapy were performed in 47 patients. Thirty patients had

fine needle aspirations (FNA), seven underwent surgical biopsies, and 10 had both FNA and surgical biopsies.

Statistical Methods

Disease-free survival was calculated with the start of therapy to the time of first relapse, disease progression, or toxic death. Disease progression was not dependent on the status of the gallium scan. Thus, patients with significant tumor reduction and persisting Ga-67 positivity were not considered to have disease progression unless there was clear clinical or radiological evidence. Overall survival was calculated from beginning of therapy until death. Survival analysis was performed using the Kaplan and Meier method.[36] The positive predictive value (PV+) was calculated using the following equation: PV+= TP/(TP+FP), where TP=true-positive and FP=false positive. A test was considered TP when results of the test were positive, and patient had clear evidence of disease relapse or a positive FNA or biopsy after treatment. A test was considered FP when the test was positive without clear disease relapse and with a negative biopsy. Negative predictive value (PV-) was calculated using the following equation: PV-= TN/(TN+FN), where TN=true-negative results and FN=false negative results. A test was considered to be TN when the test results and biopsy (if available) were negative, and no progressive disease occurred. A test was considered to be false negative when results were negative and biopsy (if available) was positive; or if patient developed progressive disease.

Statistical differences observed were assessed using the log-rank test. All p values were two-sided. Overall follow-up duration was calculated from the beginning of treatment to the last day of follow-up evaluation or death.

RESULTS (Table 1)

Of the 190 patients with positive baseline gallium scans, 139 had a gallium scan performed after the second cycle of chemotherapy, and 43 of these remained positive. Fifty-three of the 139 patients did not have additional gallium scans performed afterwards due to disease progression or other reasons including patient or physician preference. One hundred and thirteen patients had gallium scans after the fourth course of chemotherapy resulting in 23 positive scans. Eighty-seven of the 113 patients had gallium scans after both the second and fourth treatment courses. Twenty-four patients did not have scans after the second or fourth course but had gallium scans after the sixth course of chemotherapy due to physician or patient preference.

Only three patients had gallium scans that were initially negative and later positive during repeat testing. All three had disease progression quickly after this observation with DFS of 3.5, 3.9, and 6.6 months. For the purpose of this study, the final gallium scan is defined by the status of the last scan done after course two, four or six of treatment. All patients with positive scans after the second course had an additional scan after course four or six unless disease progression developed. Ten of 43 patients with positive scans after the second course eventually had negative scans following additional courses of treatment.

Responses to Therapy

Eighty-one patients (72%) treated with the ATT regimen achieved CR (44 CR, and 37 CRu). Twenty-six (23%) achieved PR, and six (5%) patients progressed during therapy. Sixty-four (83%) patients treated with CHOP-Bleomycin/OPEN regimen achieved CR (33 CR, and 31 CRu). Ten (13%) achieved PR, and three (4%) progressed on therapy. Of the 95 patients who relapsed or have not responded, 24 patients had autologous bone marrow transplants; eight had allogeneic transplants; and one had both.

Overall Survival and Disease-free survival Results (Tables 1-3)

With a median follow up duration of 88 months for the surviving patients, 87 (46%) patients died. Seventy-four deaths (39%) were due to lymphoma; 13 (7%) died of other causes, including four (2%) of myelodysplasia.

Disease-free survival was significantly affected by the results of post treatment gallium scan status. Of 96 patients with negative gallium scans after the second chemotherapy course, 47 (49%) had PD resulting in a median DFS of 106 months and 3-year DFS of 61% (Figure 1). In contrast, of 43 patients with positive Ga-67 after the second course, 25 (58%) had PD resulting in a median DFS of 6.6 months and a 3-yr DFS of 35% (log-rank p=0.00279). Forty-one (43%) of 96 patients with a negative Ga-67 after the second course have died resulting in a median OS of 111 months and a 3-year OS of 71% (log-rank p=.00017) (Figure 2). Forty-two of 90 patients (46%) who had a negative gallium scan after four cycles of chemotherapy had PD. For those with positive gallium scans after four cycles of treatment, 20 of 23 patients (87%) experienced PD. The median DFS and 3-year DFS was 90 months and 60% respectively for

Table II. Disease-free Survival

	Patients	*Disease Progression (%)*	*Median DFS (months)*	*% 3 year DFS (95% CI)*	*Log-rank p*
Gallium after 2nd course					
Negative	96	47 (49%)	106	61 (51-71)	0,00279
Positive	43	25 (58%)	6,6	35 (21-49)	
Gallium after 4th course					
Negative	90	42 (47%)	90	60 (50-70)	0,00006
Positive	23	20 (87%)	6,2	12 (0-26)	
Gallium Status					
Negative	144	61 (42%)	107	65 (57-73)	0,00001
Positive	56	34 (61%)	6	26 (13-39)	
Low IPI (0-2) Final Gallium Status	88	29 (33%)	NR	73 (64-82)	0,00326
Negative	28	17 (61%)	10,7	28 (20-57)	
Positive					
High IPI (3-5) Final Gallium Status	56	32 (57%)	32	49 (36-62)	0,00028
Negative	18	17 (94%)	3,6	2 (0-16)	
Positive					

NR: Not Reached

Table III. SURVIVAL

	Patients	*Dead (%)*	*Median Survival (months)*	*% 3 year Survival (95% CI)*	*Log-rank p*
Gallium after 2nd course					
Negative	96	41 (43%)	111	71 (63-79)	0,00017
Positive	43	26 (60%)	18	38 (24-52)	
Gallium after 4th course					
Negative	90	42 (47%)	102	66 (56-76)	0,00092
Positive	23	16 (70%)	14,6	26 (7-45)	
Gallium Status					
Negative	144	61 (42%)	111	71 (63-79)	0,00017
Positive	56	27 (48%)	18	38 (24-52)	
Low IPI (0-2) Final Gallium Status	88	27 (31%)	116	82 (78-86)	0,02650
Negative	28	12 (43%)	44,7	52 (3-71)	
Positive					
High IPI (3-5) Final Gallium Status	56	34 (61%)	51	51 (38-64)	0,00114
Negative	18	15 (83%)	6,8	19 (2-26)	
Positive					

the Ga-67 negative group vs. 6.2 months and 12% for the Ga-67 positive group (log-rank p= 0.00006) (Figure 3). The median OS and 3-year OS was 102 months and 66% for the negative group vs. 14.6 months and 26% for the positive group (log-rank p=00092) (Figure 4).

Final gallium scan analysis revealed the following. Of 144 patients who had negative final scans, 61 (42%) had PD; 34 of 56 patients (61%) with positive final gallium scan developed PD. The differences in median DFS and 3-year DFS was 107 months and 65% vs. 6 months and 26% (log-rank p=.0001) (Figure 5). The median OS and 3-year OS was 111 months and 71% vs. 18 months and 38% (log-rank p=.00017) (Figure 6).

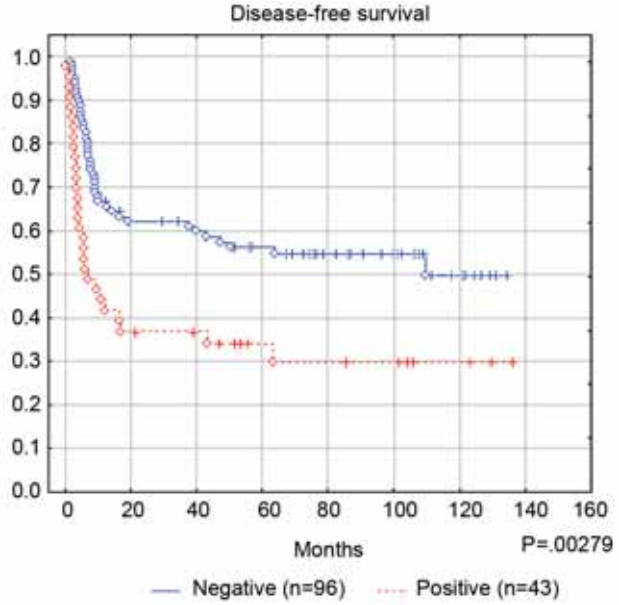

Figure 1. Kaplan-Meier Estimates of Disease-free Survival for Gallium Scans After Cycle Two

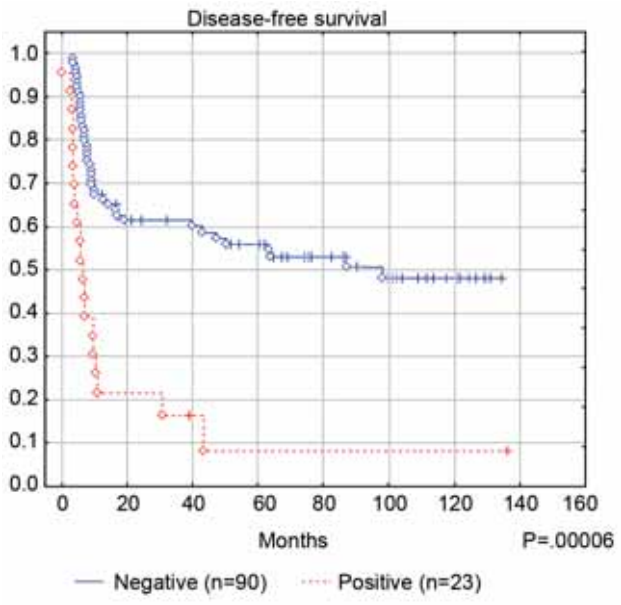

Figure 3. Kaplan-Meier Estimates for Disease-free Survival for Gallium Scans After Cycle Four

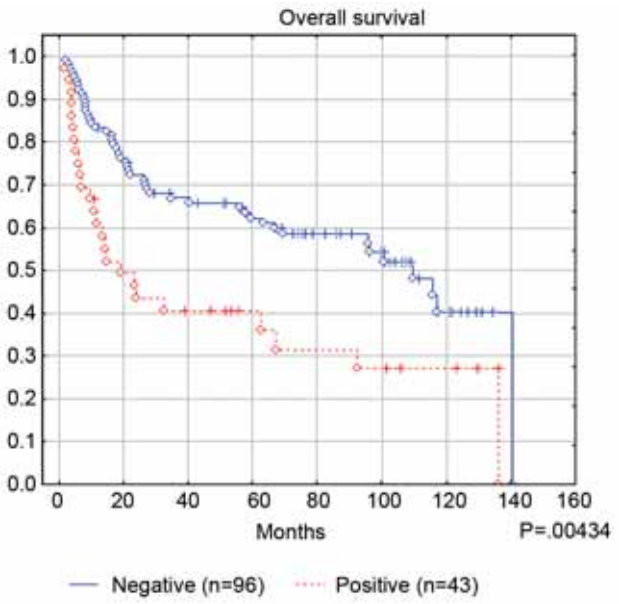

Figure 2. Kaplan-Meier Estimates of Overall Survival for Gallium Scans After Cycle Two

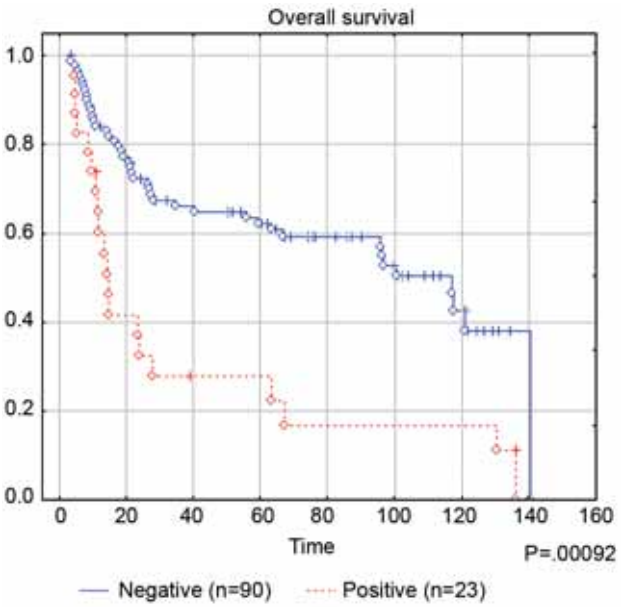

Figure 4. Kaplan-Meier Estimates for Overall Survival for Gallium Scans After Cycle Four

IPI and Gallium Analysis

Patients were analyzed according to low IPI (0-2) or high IPI (3-5) status. In the low IPI group, 28 of 116 patients had positive final gallium scans resulting in a median DFS that was not reached in the Ga-67 negative group vs. 10.7 months for the Ga-67 positive group (table 2). The 3-yr DFS was 73% for the Ga-67 negative group vs. 38% for the Ga-67 positive group (log-rank p= 0.00326). The median

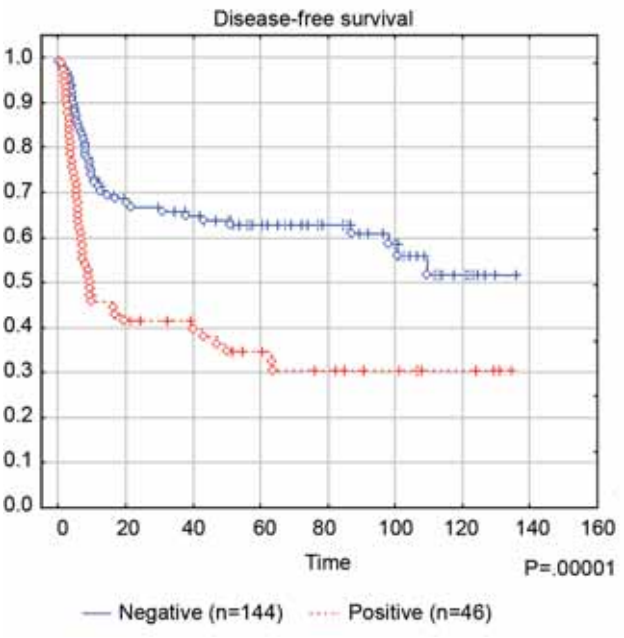

Figure 5. Kaplan-Meier Estimates of Disease-free Survival for the Last Gallium Scan

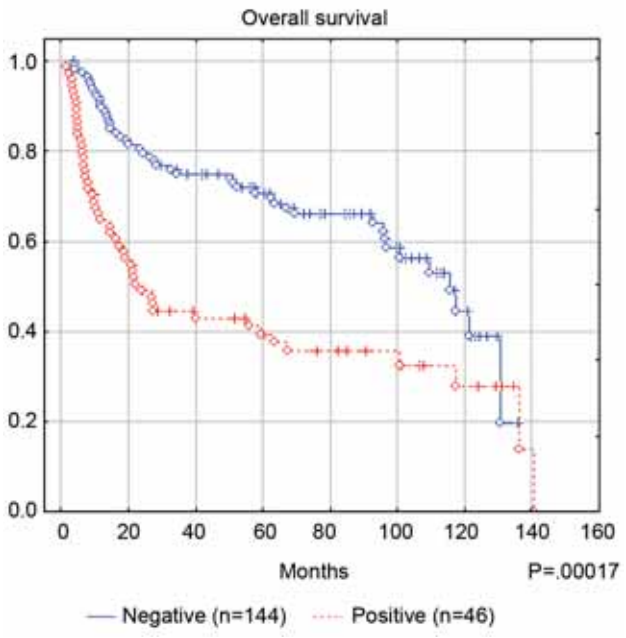

Figure 6. Kaplan-Meier Estimates of Overall Survival for the Last Gallium Scan

OS and 3-yr OS was 116 months and 82% vs. 44.7 months, and 52% for the negative and positive Ga-67 groups respectively (log-rank p= 0.02650) (Table 3).

In the high IPI group, 18 of 74 patients had persistently positive final gallium scans resulting in a median DFS of 32 months for the negative Ga-67 group vs. 3.6 months for the Ga-67 positive group (Table 2). The 3-yr DFS was 49% for the negative Ga-67 group vs. 2% for the positive Ga-67 group (log-rank p= 0.00028). Median OS and 3-yr OS was 50.8 months and 51% for the negative Ga-67 group vs. 6.8 months and 19% for the positive Ga-67 group (log-rank p= 0.00114) (Table 3).

A Cox regression analysis showed that gallium scans performed after the second cycle of chemotherapy were independent of the IPI status (high *vs* low) for predicting failure-free survival (p= 0.001396 and p= 0.000102 respectively). This independence from the IPI status was also seen in scans after the fourth chemotherapy (p= 0.00002 and p= 0.021463) and in the final gallium scan (p= 0.000001 and p= 0.000005).

Predictive Values

The positive predictive value of disease progression of a gallium scan after the second and fourth course of treatment was 67% and 87% (Table 5). Fifty-six patients had persistently positive gallium scans on their last evaluation resulting in a 74% overall positive predictive value. Negative predictive value of the gallium scan after the second and fourth course of treatment was 55% and 53% respectively. One hundred forty-four patients had negative gallium scans at their last evaluation resulting in a 58% overall negative predictive value. Further analysis of patients according to IPI status reveals a positive predictive value of gallium scans of 61% for low IPI and 94% for high IPI patients. The negative predictive value is 67% and 43% for low and high IPI patients respectively.

Landmark Analysis

To assess value of post treatment gallium scans in predicting long term PD, a landmark analysis was performed using the status of the last gallium scan done. A landmark time of six months dated from initiation of treatment was chosen because all patients had completed frontline therapy by this time. Forty-three patients had PD before six months and were excluded. Of the remaining 147 patients, 126 had negative final gallium scans, and 24 had persistently positive gallium scans. The median DFS was not reached, and the 3-year DFS was 74% for the negative Ga67 group.

Table IV. Predictive values

	Patients	*Positive Predictive Value (%)*	*Negative Predictive Value (%)*
Gallium after 2nd course			
Positive	43	67	
Negative	96		55
Gallium after 4th course			
Positive	23	87	
Negative	90		53
Gallium Status			
Positive	56	74	
Negative	144		58
Low IPI (0-2) Final Gallium Status			
Positive	28	61	
Negative	88		67
High IPI (3-5) Final Gallium Status			
Positive	18	94	
Negative	58		43

In contrast, the positive Ga67 group had a median DFS of 40 months and 3-year DFS of 51%. This difference did not meet statistical significance (p=0.087).

DISCUSSION

Gallium scintigraphy has been frequently used at the end of the therapy in NHL and HD to evaluate treatment response, particularly in the setting of residual masses. It offers superior sensitivity to detect residual disease than CT imaging.[28,29,30] Post treatment Ga67 positivity is an adverse prognostic factor for disease-free survival and overall survival.[29] Our study, the largest mid-cycle and post-treatment gallium scanning analysis to date, concludes that persistent Ga67 positivity after cycle two, four, or six of frontline treatment in patients with aggressive NHL with either favorable or poor prognosis is a hallmark for early disease progression. These patients may benefit from an early switch to different therapies and should be strongly considered for novel treatments.

Ten patients who initially had positive Ga-67 scans after cycle two developed negative Ga-67 scans after cycle four. Of these patients, seven eventually had PD after achieving an initial PR while three continued to be disease-free after achieving CR. Only three patients whose gallium scans were initially negative after cycle two developed positive scans upon later testing, and all relapsed shortly afterwards. Based on this small subset of patients, it is difficult to determine when the optimal time to maximize the usefulness of gallium scintigraphy to assess response to a regimen would be. Nevertheless, scans done after treatment cycles two and four were able to delineate with great significance a group of patients likely to have disease progression.

The landmark analysis censoring patients with early PD prior to six months shows that these gallium tests do not reliably predict which patients will have late relapse (beyond six months). It is very likely that the sensitivity of the gallium scan limits its ability to predict these later events. Patients who relapse late probably have a smaller tumor volume that escapes detection of the gallium scan than those who relapse early. Newer, more advanced technologies may provide needed sensitivity to predict later relapses in these patients.

Other tests such as magnetic resonance imaging 37-9 and positron emission tomography (PET) may also be useful in predicting response and disease-free survival.[40] Accumulating evidence shows that PET offers greater specificity and sensitivity over gallium scintigraphy, due to a poor spatial resolution and low sensitivity at the abdominal level of the gallium scan.[40-47] Use of PET in lymphoma treatment has largely superceded gallium scintigraphy at M D Anderson Cancer Center and in many parts of the United States. Because of its greater sensitivity for detecting lymphoma, PET may overcome the inability

Table V. Landmark Analysis Disease-free Survival

	Patients	*Dead (%)*	*Median Survival (Months)*	*3-year Survival (95% CI)*	*Log-rank p value*
Gallium Status					
Negative	125	41 (33%)	NR	74 (66-82)	0,087
Positive	24	12 (50%)	40	51 (31-71)	

NR: Not Reached

of gallium scintigraphy to predict late relapses. However, its cost effectiveness and availability in different clinical settings needs further exploration, and we are currently comparing both procedures in a prospective study for DLBCL at our institution.

The gallium scan status was independent of the M D Anderson Tumor Score and the IPI by Cox regression analysis. As expected by Bayesian statistics, the positive predictive value of a gallium scan done in patients with a worse overall prognosis predicted by a high IPI score was better than in patients with a more favorable pretreatment prognosis. Likewise, the prognostic utility of a positive gallium scan after the fourth chemotherapy course was better than a positive scan after the second treatment course. Patients who are at extremely high risk for early disease progression may possibly be selected through combining multiple prognostic factors such as MD Anderson Tumor Score, IPI, and gallium scan status in the midst of their current chemotherapy treatment.

In conclusion, although gallium scans are been progressively substituted by FDG-PET studies in the management of aggressive NHL, in our experience, the largest series ever analyzed, we have shown that gallium scans done during mid-cycle or at the end of therapy can predict which patients with aggressive NHL have poor prognosis and are likely to have disease progression. Of note was that this results were independent from the most common risk-factor clinical classification employed, the IPI score. In this patients, a change to different, more intense chemotherapy regimens and new treatment strategies is justified. Whether a similar strategy can be adopted with the use of new metabolic imaging techniques need to be clarified, but emerging data from recent series have demonstrated that PET imaging performed in the mid-course of therapy had a predictive value for clinical outcome.[45]

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