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ORIGINAL ARTICLE

The role of routine imaging procedures in the detection of relapse of patients with Hodgkin lymphoma and aggressive non-Hodgkin lymphoma

Neta Goldschmidt · Omer Or · Martine Klein · Bella Savitsky · Ora Paltiel

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Abstract Despite improved initial therapies, a subgroup of patients with aggressive non-Hodgkin (A-NHL) and Hodgkin lymphomas (HL) will relapse after first remission. The optimal follow-up strategy for the detection of relapse has not been clarified and periodic imaging is not recommended in most written guidelines. We identified 125 patients with HL and A-NHL diagnosed between January 1993 and September 2008 who relapsed at least 1 month after the end of initial therapy. We assessed whether relapse was detected based on clinical signs or periodic computed tomography (CT), [^{18}F] fluorodeoxyglucose positron emission tomography (PET), or combined PET/CT and whether the mode of detection influenced the pattern and outcome of relapsed disease. Overall, most relapses (62%) were diagnosed clinically especially in A-NHL and in patients with extranodal involvement at diagnosis ($p<0.05$); however, relapses of HL occurring after 2001 when PET/CT became available were more commonly detected by routine imaging ($p<0.05$). Imaging-detected relapse was not associated with improved survival. While clinical exam remains the most common mode of detecting relapse, our results suggest a potential role for routine PET/CT surveillance in HL patients; however, survival does not appear to be affected by mode of detection.

Keywords Follow-up · Lymphoma · PET/CT · Relapse · Surveillance

Introduction

Despite the improvements in remission and cure rates of Hodgkin lymphomas (HL) and aggressive non-Hodgkin (A-NHL), relapsed disease after first-line therapy is experienced by up to 30% and 50% of patients with HL and A-NHL, respectively [1, 2]. Second-line therapy in responsive patients is potentially curative, and response to salvage chemotherapy is achieved in up to 80% of patients with HL and 58% of patients with A-NHL [3, 4]. Disease recurrence occurs most commonly in the first 2 years following initial therapy [5]. Thus, it stands to reason that follow-up strategies for patients with these curable lymphomas after first remission should aim to detect relapse at an early stage when tumor burden is low, a fact that may improve survival [6, 7]. There is no current consensus regarding the optimal method to follow HL and A-NHL patients in remission. A common practice based on published guidelines [8–10] include clinical visits (history taking and physical examination) and laboratory evaluation every 3–6 months for 3–5 years and annually thereafter. Imaging studies performed during this follow-up period may include simple radiographs such as chest X-ray or more advanced imaging as computed tomography (CT) scan, gallium scan, and positron emission tomography (PET) or

Neta Goldschmidt and Omer Or authors have equal contribution.

N. Goldschmidt · O. Or · O. Paltiel
Department of Hematology,
Hadassah-Hebrew University Medical Center,
Jerusalem, Israel

M. Klein
Department of Biophysics and Nuclear Medicine,
Hadassah-Hebrew University Medical Center,
Jerusalem, Israel

B. Savitsky · O. Paltiel
School of Public Health,
Hadassah-Hebrew University Medical Center,
Jerusalem, Israel

N. Goldschmidt (✉)
Department of Hematology,
Kyriat Hadassah, P.O. Box 12000, Jerusalem 91120, Israel
e-mail: neta@hadassah.org.il

PET/CT scan. It is clear that PET/CT is a more sensitive tool than the other imaging modalities for detecting disease presence and activity [11, 12]. PET/CT has also demonstrated its importance as an imaging technique for staging of new patients with A-NHL and HL [13, 14] and for interim assessment during induction and salvage treatment [15, 16]. Although there is a temptation to use these sophisticated and currently available techniques for follow-up of patients, it has never been shown that preclinical detection of lymphoma relapse by imaging improves survival [17, 18], and previous studies have stressed the role of clinical symptoms and signs as the primary modes of detecting disease recurrence [19, 20]. Our aims in this retrospective study were to describe the diagnostic modality by which relapse was detected and to evaluate whether the use of PET/CT influenced survival in patients with relapsed HL or A-NHL.

Patients and methods

Patients

We reviewed the clinical records of patients treated in Hadassah for HL and NHL between 1 January 1993 and 1 December 2008. Patients with HL and A-NHL (diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma, Burkitt's lymphoma, and lymphoblastic lymphoma) who relapsed at least 1 month after achieving first complete remission were eligible for inclusion. All patients were older than 18 years at diagnosis and received their initial treatment with curative intent (curative chemo or chemoradiotherapy for HL and anthracycline-based therapy for A-NHL) in our own institution (Hadassah-Hebrew University Medical Center). Patients who transferred to our medical center for their care at the time of relapse or following the initiation of first-line treatment were excluded. The medical records were evaluated for details of initial disease characteristics (date, age, sex, histology, stage, prognostic factors, therapeutic regimen, and date of completion of treatment) and details at relapse (date, site, stage and prognostic factors at relapse, therapeutic regimen, and the diagnostic modality of relapse). In order to assign a risk score for A-NHL, we calculated the International Prognostic Index [21] and dichotomized the score into low risk (IPI 0–2) and high risk (IPI 3–5). Prognostic scores for early HL (stage I and IIA) were calculated according to the European Organisation for Research and Treatment of Cancer (EORTC) scale [22] and for advanced stage (stage IIB, III, and IV), according to the International Prognostic Score (IPS) scale [23]. Clinical detection of relapse was based on symptoms or physical signs, and imaging detection of relapse was done using either CT scan, gallium scan, PET scan, or combined PET/CT scan. Clinical evaluation post treatment was done every 3–4 months in the first 2 years, every 6 months in the three coming years and yearly, thereafter. Imaging follow-up post treatment was done every 6 months in the first 2 years and once more at the end of the third year.

Statistical analysis

We report mean values and standard deviations for continuous variables and percentages for categorical values. Comparisons of disease characteristics between study groups were assessed using the Chi-square test. Characteristics associated with the modality of detection of relapse were included in a multivariate logistic regression model. We tested whether there was an interaction between histology and the year of relapse in relation to the modality of detection of relapse. We assessed survival as a function of the mode of detection of relapse in each histological subgroup using the Kaplan–Meier survival analysis and compared the differences in survival functions using the log-rank test. Only patients whose relapse occurred at least 1 year prior to data collection were included in the survival analysis. The follow-up time began at the date of relapse detection and ended at death or at the date of the last follow-up or November 30, 2009. Finally, we constructed a Cox proportional hazards model examining the independent effect of the disease characteristics and the mode of detection of relapse on survival. Other than the mode of detection, variables chosen to enter the multivariate model were those that were significantly associated with outcome in the univariate analysis as well as other parameters thought to be related to survival. These included prognostic score at diagnosis, prognostic score at relapse, type of lymphoma (HL versus NHL), age at relapse, bone marrow transplant at relapse, mode of diagnosis (clinical versus image), and period of the diagnosis (1993–2000 versus 2001–2009).

Statistical analysis was performed using Statistical Package for the Social Sciences version 17 (Chicago, IL). For all hypotheses tested, a two-sided P value of ≤ 0.05 was considered statistically significant.

Results

Patients' characteristics at diagnosis

The characteristics at diagnosis of the125 patients included in the study are shown in Table 1. Forty-two (34%) patients had HL and 83 (66%) had A-NHL. Of the A-NHL patients, the vast majority (81, 97.6%) had DLBCL, one (1.2%) had peripheral T-cell lymphoma and one (1.2%) had lymphoblastic lymphoma. The mean age of all patients was 50 years (range, 18–90 years; SD, 19.5); however, as expected, age distribution varied greatly among the histologic groups. For instance, 50%

Table 1 Patients' characteristics at diagnosis

Parameter	HL (%)	NHL (%)	All patients (%)
Number of patients	42 (34)	83 (66)	125 (100)
Age			
18–29	21 (50)	10 (12)	31 (25)
30–59	15 (36)	34 (41)	49 (39)
60+	6 (14)	39 (47)	45 (36)
Stage			
I–II	21 (50)	29 (35)	50 (40)
III–IV	21 (50)	54 (65)	75 (60)
B symptoms			
No	15 (36)	45 (54)	60 (48)
Yes	27 (64)	38 (46)	65 (52)
Prognostic score (n=123)			
Low risk	18 (45)	58 (70)	76 (62)
High risk	22 (55)	25 (30)	47 (38)
Extranodal involvement			
No	41 (98)	57 (69)	98 (78)
Yes	1 (2)	26 (31)	27 (22)

Percentages are within histological subtypes

of HL patients were 18–29 years old while 47% of A-NHL patients were older than 60 years. Advanced stage at diagnosis was present in 50% and 65% of the HL and A-NHL patients, respectively while B symptoms were present in 64% of HL patients and in 46% of A-NHL patients. Most (55%) HL patients at diagnosis had a high prognostic score while a high-risk score was observed only in 30% of A-NHL. Extranodal involvement was found in 31% of A-NHL and was rare (2%) in HL.

Patients' characteristics at relapse

Seventy-one patients (57%) relapsed in the first year following treatment, 20 (16%) in the second year and the rest (34, 27%) relapsed thereafter. Detection of relapse was via clinical diagnosis either due to patients' symptoms or to physical signs (clinical detection of relapse) in 78 (62%) patients; whereas, asymptomatic relapse detected via routine imaging (image detection of relapse) was observed in 47 (38%) of patients. Second-line treatment was given as follows: thirty-six patients had second-line salvage therapy (ICE or miniBEAM or DHAP) followed by stem cell transplant (SCT); 11 had standard-dose therapy (CHOP, ABVD, Stanford, and BEACOPP) followed by SCT; 11 patients had high-dose therapy but did not reach BMT due to resistant or progressive disease or co-morbidities; 14 patients had salvage radiation therapy; 42 patients had standard-dose therapy with no further treatment; two had surgery; six had palliative care and in three patients the information is missing.

Table 2 Pretreatment characteristics versus the modality of relapse detection

	Clinical (%)	Image (%)
Histology[a]*		
HL	20 (16.0)	22 (17.6)
A-NHL	58 (46.4)	25 (20.0)
Stage[b]		
HL		
I–II	10 (23.8)	11 (26.2)
III–IV	10 (23.8)	11 (26.2)
A-NHL		
I–II	24 (28.9)	5 (6.0)
III–IV	34 (41.0)	20 (24.1)
B symptoms[b]		
HL		
Absent	6 (14.3)	9 (21.4)
Present	14 (33.3)	13 (31.0)
A-NHL		
Absent	34 (41.0)	11 (13.3)
Present	24 (28.9)	14 (16.9)
Prognostic score (n=123)[b]		
HL		
Low risk	9 (21.4)	9 (21.4)
High risk	10 (23.8)	12 (28.6)
A-NHL		
Low risk	40 (48.2)	18 (21.7)
High risk	18 (21.7)	7 (8.4)
Extranodal involved[b]		
HL		
No	20 (47.6)	21 (50.0)
Yes	0	1 (2.4)
A-NHL*		
No	36 (43.4)	21 (25.3)
Yes	22 (26.5)	4 (4.8)
All*		
No	56 (45.0)	42 (33.5)
Yes	22 (17.5)	5 (4.0)
Period of diagnosis[b]		
HL*		
1993–2000	15 (35.7)	9 (21.4)
2001–2009	5 (11.9)	13 (31.0)
A-NHL		
1993–2000	28 (33.7)	11 (13.3)
2001–2009	30 (36.1)	14 (16.9)
All		
1993–2000	43 (34.4)	20 (16.0)
2001–2009	35 (28.0)	27 (21.6)

*p<0.05 for Chi-square test

[a] The percentages relate to the proportions of the total study population

[b] The percentages relate to the proportions within the category (HL versus A-NHL)

We explored whether parameters present at diagnosis could predict clinical or imaging detection of relapse. Table 2 summarizes the results of this analysis. Factors such as stage, presence of B symptoms, and prognostic score did not significantly predict mode of relapse detection. On the other hand, histology, extranodal involvement, and period of diagnosis were associated with the mode of relapse detection. Most A-NHL patients had a clinical diagnosis of relapse as opposed to imaging diagnosis of relapse ($p<0.05$). Extranodal involvement predicted clinical detection of relapse ($p<0.05$) while patients with HL diagnosed after 2001 were more likely to have been diagnosed by imaging ($p<0.05$). Furthermore, the logistic regression analysis, where the dependant variable was the mode of detection of relapse (Table 3), showed that the type of lymphoma retained its independent effect [odds ratio (OR), 2.65; 95% confidence interval (CI), 1.22–5.78 for HL versus A-NHL, $p<0.05$] while the period of diagnosis relation was of borderline significance.

Next, we explored whether patient characteristics at relapse influenced the way in which relapse was detected (Table 4). As expected, patients with B symptoms at relapse where more likely to be diagnosed clinically and not by imaging ($p<0.05$). Relapse in the years 2001–2009 in HL patients was mostly diagnosed by imaging ($p<0.05$). None of the following parameters at relapse influenced the diagnostic modality: age, time to relapse, stage, prognostic score, site of relapse (old versus new), extranodal involvement, and stem cell transplant.

Since PET/CT imaging has only been available at our institution from the year 2001, we examined relapse detection since its inception in a separate analysis. In the years 2001–2009, 79 (26 HL and 53 A-NHL) patients were diagnosed with relapse. Of these, 25 patients (32%) were diagnosed by PET/CT while 54 patients (68%) had their relapse detected via clinical exam or CT. Nevertheless, the proportion of HL patients diagnosed at relapse by PET/CT was significantly higher (12 patients, 46%) compared to that in NHL (13 patients, 25%) ($p=0.05$). This shows that although clinical diagnosis and less sophisticated imaging is still the primary

Table 3 Logistic regression analysis of the probability of relapse diagnosis by routine imaging

Variable	Number	Percent relapse detected by image	OR	95% CI	*P* value
Type of Lymphoma					
Hodgkin	42	52.4	2.65	1.22–5.78	0.014
Non-Hodgkin	83	30.1	1		
Period of relapse					
1993–2000	46	28.3	1		
2001–2009	79	43.0	2.02	0.91–4.52	0.086

Table 4 Characteristics at relapse versus the modality of relapse detection

	Clinical (%)	Image (%)
Time to relapse		
HL		
0–12 m	13 (31.0)	15 (35.7)
13–24 m	3 (7.1)	3 (7.1)
≥25 m	4 (9.5)	4 (9.5)
A-NHL		
0–12 m	28 (33.7)	15 (18.1)
13–24 m	10 (12.0)	4 (4.8)
≥25 m	20 (24.1)	6 (7.2)
Stage		
HL		
I–II	10 (23.8)	11 (26.2)
III–IV	10 (23.8)	11 (26.2)
A-NHL		
I–II	23 (27.6)	14 (16.9)
III–IV	35 (42.2)	11 (13.3)
B symptoms		
HL		
No	13 (31.0)	18 (42.8)
Yes	7 (16.7)	4 (9.5)
A-NHL *		
No	41 (49.4)	23 (27.7)
Yes	17 (20.5)	2 (2.4)
All*		
No	54 (43.2)	41 (32.8)
Yes	24 (19.2)	6 (4.8)
Prognostic score ($n=117$)		
HL		
Low risk	6 (17.6)	9 (26.5)
High risk	9 (26.5)	10 (29.4)
A-NHL		
Low risk	40 (48.2)	19 (22.9)
High risk	18 (21.7)	6 (7.2)
Site of relapse		
HL		
Old	14 (33.3)	10 (23.8)
New	6 (14.3)	12 (28.6)
A-NHL		
Old	36 (43.4)	19 (22.9)
New	22 (26.5)	6 (7.2)
Period of relapse		
HL *		
1993–2000	11 (26.2)	5 (11.9)
2001–2009	9 (21.4)	17 (40.5)
A-NHL		
1993–2000	22 (26.5)	8 (9.6)
2001–2009	36 (43.4)	17 (20.5)

Table 4 (continued)

	Clinical (%)	Image (%)
Stem cell transplant		
All		
Yes	27 (21.6)	20 (16.0)
No	51 (40.8)	27 (21.6)

The percentages relate to the proportions within the category (HL versus A-NHL)

*$p<0.05$ for Chi-square test

mode of detection of relapse, an increased proportion of HL relapses were detected by PET/CT.

The overall survival after relapse of the 125 patients did not differ significantly whether they were diagnosed by imaging or by clinical signs or symptoms (Fig. 1a); however, it is notable that long-term survival (>6 years) was noted preferentially among patients diagnosed by imaging compared to clinical symptoms and signs. Furthermore, the curve appears to show a plateau after this point in those diagnosed by imaging. Figure 1b and c show the survival in HL and A-NHL, respectively in those diagnosed at relapse via clinical presentation versus imaging. In the HL group, patients diagnosed via imaging appeared to have an improved survival (albeit non-significant), but this was not seen in the A-NHL patients. Excluding the two patients with non-DLBCL, aggressive lymphoma (i.e., one with peripheral T-cell lymphoma and one with lymphoblastic lymphoma) did not change the survival curves.

In a multivariate model, survival was not influenced by the mode of detection of relapse (HR, 1.2; 95% CI, 0.69–2.08, for image versus clinical detection of relapse). After taking into account age at relapse, histology, prognostic score and BMT, the factors which were significantly associated with survival were age >60 (HR, 2.4 in comparison with aged 30–59) (95% CI, 1.22–4.86) and high prognostic score at relapse (HR, 1.8; 95% CI, 1.03–3.19) as well as A-NHL histology (HR, 2.8; 95% CI, 1.27–5.95).

Discussion

In this study, which included 125 patients who experienced relapse after the first complete remission, we found that, overall, the most common mode of detecting relapse remained the clinical exam and not imaging; however, we show that in recent years and in patients with Hodgkin lymphoma, PET/CT imaging appears to be emerging as the dominant way in which relapse is detected.

Our findings are consistent with previous papers which concluded that most relapses are detected by clinical symptoms and not by routine CT imaging [19, 20, 24–26]

Thus, current recommendations for follow-up of lymphoma patients, as published by the National Comprehensive Cancer Network (NCCN) [8] and the European Society for Medical Oncology (ESMO) [9, 10] include mostly clinical and laboratory evaluation. Imaging studies such as chest X-ray and CT scan are not recommended routinely but are indicated in clinical suspected relapses [10]. PET/

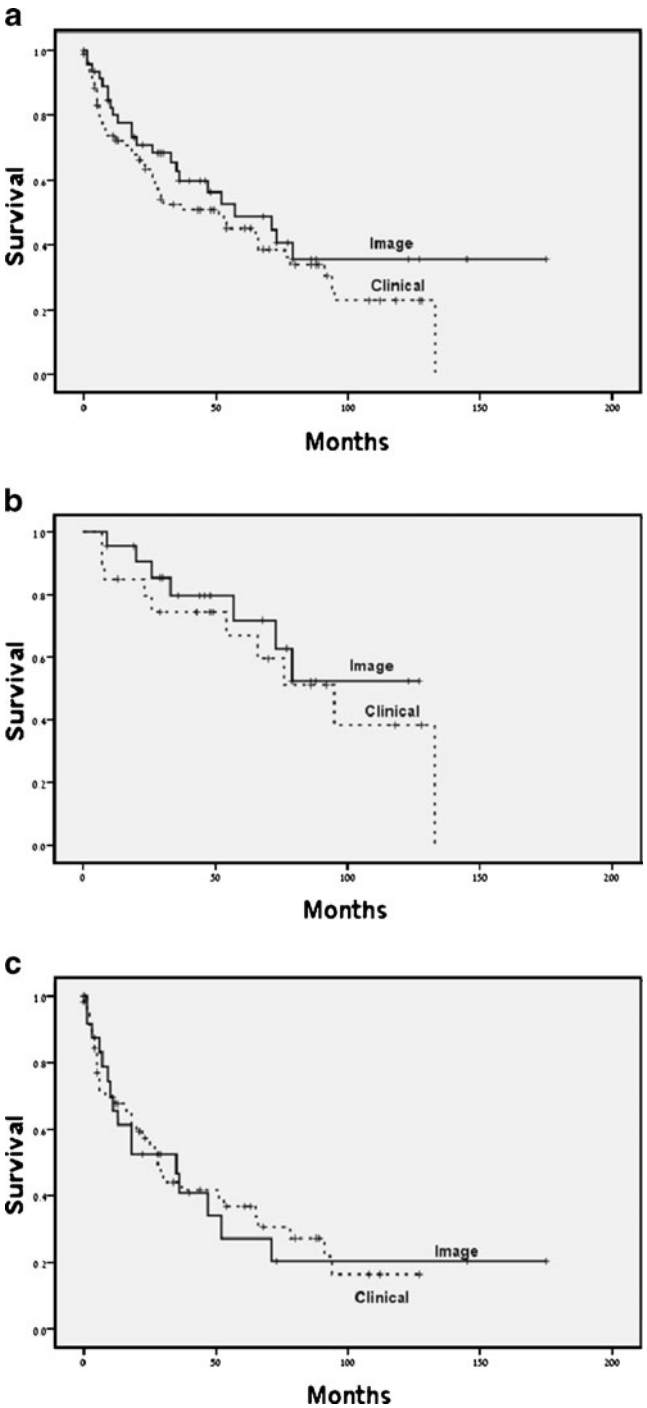

Fig. 1 Survival of patients versus diagnostic modality. **a** All patients, **b** HL patients, and **c** A-NHL patients

CT studies are specifically not recommended in either guideline.

Nevertheless, since PET/CT is a highly sensitive diagnostic modality for staging lymphoma [14] for the evaluation of therapeutic response [14] and for the diagnosis of relapse [27, 28] even at the preclinical stage [29], we and others hypothesized that its use for disease surveillance may bring forward relapse detection and improve prognosis. In our study, we found that significantly more patients with relapsed HL were diagnosed by routine PET/CT (Tables 2 and 4, $p<0.05$) and that the odds ratio to be diagnosed by routine imaging for HL patients compared to A-NHL patients was 2.6 ($p=0.014$, Table 3). No other clinical parameters at diagnosis or at relapse predicted an advantage for PET/CT imaging for follow-up. A-NHL histology and extranodal involvement at diagnosis predicted clinical and not imaging detection of relapse (Table 2). Second-line treatment, in particular SCT, was not associated with the mode of detection (Table 4). Stem cell transplant was done in 47 of the 125 patients (38%). While it is true that SCT is the standard of care for relapsed disease, many patients with relapsed disease are not considered eligible for transplant, and even in the setting of clinical trials, there is a gap between intention to treat with transplant and actual transplants carried out [30].

Despite the fact that PET/CT is a sensitive modality for disease surveillance, it has not yet been shown to improve outcome [18]. Our results may suggest that long-term survival may improve if relapse is diagnosed by imaging (Fig. 1a, note the plateau in the long-term), specifically in patients with HL (Fig. 1b). The small sample size in our study may have resulted in limited power to detect a difference in survival. We did find, as previously shown [6, 7], that age over 60 years and high prognostic score at relapse were associated with worse survival. Worse survival was also found in patients with relapse A-NHL compared to HL.

It should also be noted that although the final sample size in this study was modest, with only 125 meeting the inclusion criteria, the original pool of lymphoma patients sampled was quite large ($n=1992$). With increasingly effective first-line therapies, the number of relapsed patients eligible for aggressive salvage therapy is decreasing [31] and multicentered investigations will be required to accurately estimate prognosis in this relapsed subgroup.

A significant potential weakness in this type of retrospective study is the possibility of lead time bias i.e., earlier diagnosis does not prolong survival but enables knowledge of relapse for a longer time. Only randomized controlled trials with mortality as an outcome will effectively determine whether improved survival after imaging-detected relapse is a true phenomenon or a result of lead time bias.

It is important to point several disadvantages of routine PET/CT studies. While a negative test provides reassurance regarding continued remission due to its high sensitivity, there may be false positive results [27, 32] that may result in unnecessary biopsies. Besides exposing the patient to radiation [33], the multiplicity of imaging tests may be a source of substantial emotional stress, in particular to the patient undergoing invasive biopsies due to false positive results. Another significant shortcoming of frequent PET/CT studies is the economic burden due to the high cost of the procedure. In our institution we calculated that a 5-year follow-up using PET/CT costs four times more than the cost of a clinical follow-up (numerical data not shown). This adds to published data showing that routine CT may not be cost effective for lymphoma follow-up [34].

To conclude, our results support the previous findings that the clinical exam is still the most common modality to diagnose relapse especially in A-NHL patients and in patients with extranodal involvement at diagnosis; however, PET/CT and not clinical exam may emerge as the main mode to diagnose relapse in HL patients in the current era of PET/CT use. Despite this, we could not find a survival advantage for the use of PET/CT in our patients when other parameters that influence survival are taken into account such as age or BMT at relapse. As expected, we did find that patients and disease characteristics such as older age and high prognostic score at relapse are associated with poorer survival. Our results support the need for a large scale, prospective, multicentered clinical trial to assess the appropriate role of PET/CT use in lymphoma surveillance.

Disclosures None

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