Integration of CT-Based Measurements into Surveillance PET/CT in Patients with Diffuse Large B Cell Lymphoma

Noa Lavi MD[1], Gali Shapira MD[2], Ariel Zilberlicht MD[4,7], Noam Benyamini MD[1], Dan Farbstein MD[4], Eldad J. Dann MD[1,4], Rachel Bar-Shalom MD[3] and Irit Avivi MD[5,6]

Departments of [1]Hematology & Bone Marrow Transplantation, [2]Radiology and [3]Nuclear Medicine, Rambam Health Care Campus, Haifa, Israel
[4]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[5]Department of Hematology and Bone Marrow Transplantation, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

ABSTRACT: **Background:** Despite the lack of clinical studies supporting the use of routine surveillance FDG-positron emission tomography (PET) in patients with diffuse large B cell lymphoma (DLBCL) who achieved remission, many centers still use this strategy, especially in high risk patients. Surveillance FDG-PET computed tomography (CT) is associated with a high false positive (FP) rate in DLBCL patients.

Objectives: To investigate whether use of specific CT measurements could improve the positive predictive value (PPV) of surveillance FDG-PET/CT.

Methods: This retrospective study included DLBCL patients treated with CHOP or R-CHOP who achieved complete remission and had at least one positive surveillance PET. CT-derived features of PET-positive sites, including long and short diameters and presence of calcification and fatty hilum within lymph nodes, were assessed. Relapse was confirmed by biopsy or consecutive imaging. The FP rate and PPV of surveillance PET evaluated with/without CT-derived measurements were compared.

Results: Seventy surveillance FDG-PET/CT scans performed in 53 patients were interpreted as positive for relapse. Of these studies 25 (36%) were defined as true-positive (TP) and 45 (64%) as FP. Multivariate analysis found long or short axis measuring ≥ 1.5 and ≥ 1.0 cm, respectively, in PET-positive sites, International Prognostic Index (IPI) ≥ 2, lack of prior rituximab therapy and FDG uptake in a previously involved site, to be independent predictors of true positive surveillance PET (odds ratio 5.4, 6.89, 6.6, 4.9, $P < 0.05$ for all).

Conclusion: PPC of surveillance PET/CT may be improved if used in selected high risk DLBCL patients and by combined assessment of PET and CT findings.

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KEY WORDS: diffuse large cell B cell lymphoma (DLBCL), surveillance PET, computed tomography (CT), relapse, positive predictive value (PPV)

The benefit of using a surveillance strategy for early detection of disease recurrence depends on the probability of disease relapse, the sensitivity and specificity of the test, and the prognostic value of preclinical detection of relapse [1]. The incidence of relapse in patients with diffuse large cell B cell lymphoma (DLBCL) treated in the rituximab era approaches 40%, with most relapses occurring during the first 2 years after completion of therapy [2]. The ESMO and Lugano guidelines [3,4] recommend following DLBCL patients who achieve clinical remission and reserving imaging studies for the individuals exhibiting clinical features suggestive of relapse. Similarly, the National Comprehensive Cancer Network (NCCN) recommends following high risk patients who initially presented with an advanced disease, and performing computed tomography (CT) scans not more often than every 6 months for up to 2 years after completion of treatment [3-6]. However, despite these recommendations, many centers employ routine surveillance positron emission tomography (PET) scans, aiming to detect early preclinical disease progression, especially in high risk patients who are more likely to relapse.

The diagnosis of relapse either by CT or PET is based on visualization of lesions and/or uptakes, fulfilling well-defined criteria (Cheson response criteria and Lugano classification) [4,5]. The sensitivity of surveillance CT scans varies from 26% to 100% (average 62%), whereas specificity ranges between 35 and 100% (average 92%) [1]. Although the sensitivity of surveillance FDG-PET scans reaches 100% [7-9], he disadvantages of this technique are high rates of false positive (FP) results and a low positive predictive value (PPV) of up to 21% only, as reported in some publications [7]. Such caveats have become even more prominent since the introduction of rituximab, which appears to induce marked inflammatory responses resulting in FP uptakes [9,10]. These limitations, together with the lack of a proven survival benefit, prevent extensive use of the imaging surveillance strategy for following patients with DLBCL in remission [11,12]. Moreover, the feasibility of using surveillance PET scans in high risk patients remains debatable. Nevertheless, in this high risk population, an imaging approach capable of providing high specificity and sensitivity is still

needed, which would avoid undesirable diagnostic procedures, over-treatment and unjustified mental stress.

The integration of CT-related parameters into the interpretation criteria of PET-positive surveillance studies may offer an approach that meets both sensitivity and specificity criteria. Data derived from the Hodgkin lymphoma (HL) setting suggest that combining CT and PET strategies may indeed improve the specificity of surveillance scans [13]. Studies evaluating this combined imaging approach in the DLBCL setting are limited. The aim of the current study was to investigate whether the application of specific CT morphologic measurements could reduce the FP rate and improve the PPV and clinical applicability of surveillance FDG-PET/CT in detecting DLBCL relapse.

PATIENTS AND METHODS

The study was approved by the Institutional Review Board of the Rambam Health Care Campus, Haifa, Israel (approval # 0039-10 RMB). The institutional database was retrospectively searched for adult patients with newly diagnosed DLBCL, treated with CHOP or CHOP-R during the years 1995–2002 and 2003–2007, respectively, who achieved complete remission (CR) defined by CT (1995–2000) or by PET/CT (2000–2007) according to response criteria devised by Cheson et al. [5,14]. The patients underwent repeated surveillance PET/CT studies during 2000–2009 according to the departmental protocol used at that time, i.e., at 6 month intervals in the first and second years of CR (except for a few patients who had an additional scan at 3 months post-treatment), and one scan per year over the next 5 years of CR, with a maximal surveillance PET period of 7 years from the end of treatment, or when relapse was suspected [9]. All positive surveillance PET scans suggestive of disease relapse were further evaluated. Relapse, defined as disease recurrence within ≥ 3 months after therapy completion, was confirmed histologically when feasible. However, when biopsy was technically not feasible, clinical reassessment, including a repeated PET study, was performed, and relapse was identified in the presence of disease progression.

FDG-PET/CT TECHNIQUE AND RESULT INTERPRETATION

All FDG-PET studies were performed using a PET/CT system combining a dedicated PET scanner and a multi-slice CT (GE Discovery LS, GE, Milwaukee, USA), 60–90 minutes after injecting 370–555 MBq18F-FDG. Patients were instructed to fast for at least 4 hours and their blood glucose was measured to ensure a serum level lower than 11 mMol/L prior to injection. All PET/CT scans were performed without injection of intravenous contrast media, according to the policy of our institution. The PET/CT methodology was not changed during the entire period of the study. Each of the original surveillance PET/CT studies was reviewed visually by a team of at least two nuclear medicine physicians experienced in PET/CT reading, who were cognizant of updated clinical data and prior imaging results for each patient. In all cases, consensus regarding the final report was reached among the readers. The surveillance PET/CT was considered negative for the presence of lymphoma on visual review when no foci of increased FDG uptake were revealed, other than those related to physiologic bio-distribution of the tracer or to a known or presumed benign process. A mild FDG uptake, involving calcified lung hilar nodes or small peripheral lymph nodes (head and neck, axilla and inguinal region) characterized by morphologically benign imaging features, was also considered negative. Any other foci of increased FDG uptake compared to the background (using the mediastinal blood pool activity as the reference background activity) were considered abnormal and suspicious of relapse. A positive surveillance PET scan was defined as true positive (TP), and a negative scan was considered false negative (FN) if relapse was confirmed within the first 6 months after imaging.

CT-RELATED MEASUREMENTS AND INTERPRETATION

All sites determined as positive by surveillance PET scans were evaluated. CT-derived features of PET-positive sites were assessed, including long and short diameters (cm), and the presence of calcification and fatty hilum within lymph nodes. According to the revised response criteria for malignant lymphoma (Cheson criteria) [5], lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the length of the short axis. A lymph node with a long axis ranging from 1.1 to 1.5 cm should be considered abnormal only if its short axis is longer than 1.0 cm. Moreover, lymph nodes with a short axis of ≤ 1.0 cm will not be considered indicative of relapse or progressive disease [5]. The long and short axes of lymph nodes with abnormally increased FDG uptake were measured and their definition as suspicious of relapse was based on the Cheson criteria. Additional CT-related features, commonly considered typical of reactive lymph nodes, including the presence of nodal fatty hilum and calcifications, were also assessed. These characteristics were interpreted as suspicious of benign processes, regardless of the lymph node size.

DATA ANALYSIS

Surveillance PET scans assessed with versus without concurrent use of CT-derived measurements were compared, focusing on FP rate and PPV of these two approaches for determining relapse.

STATISTICAL ANALYSIS

Data were analyzed using SPSS version 18. Descriptive statistics in terms of frequencies and standard normal distribution of quantitative variables were tested using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to analyze differences in "abnormally distributed" variables. Fisher's exact test was used to determine the relation between categorical variables. Logistic regression was employed to determine the

variables predicting a FP result. $P < 0.05$ was considered statistically significant.

RESULTS

Data of 137 patients with DLBCL who achieved CR were reviewed. Eighteen patients in whom surveillance PET scans were not performed in remission were excluded from further analysis. A total of 119 patients treated with CHOP-R (84, 71%) or CHOP only (35, 29%) underwent 423 surveillance PET scans between 2000 and 2009. Of these PETs 340 (80%) were interpreted as negative for relapse, with no evidence for disease recurrence during a further follow-up of at least 6 months, indicating a FN rate of 0% and negative predictive value (NPV) of 100%. Eighty-three follow-up PET scans (FU-PETs) (20%) performed in 63 patients were interpreted as positive for relapse. Thirteen positive PET studies in 12 patients were excluded from the analysis due to poor quality of CT scans, insufficient for adequate morphologic evaluation. Seven of these cases were false positive and 6 were true positive. The study therefore included 70 scans (17 in patients treated with CHOP and 53 in subjects receiving CHOP-R), performed in 51 patients (15 in the CHOP cohort and 36 in the CHOP-R group) that were evaluated for CT-associated characteristics.

Relapse was eventually confirmed in 25 of the 51 evaluable patients, either histologically (n=10) or by repeated PET/CT scans (n=15), demonstrating disease progression.

CT MEASUREMENTS OF PET-POSITIVE SITES

Seventy surveillance scans considered as positive were analyzed. Sites that showed increased FDG uptake were evaluated, including measurement of the length of lymph node (LN) long and short axes and assessment of LN-related morphological parameters, such as central fatty hilum and calcification.

In 15 of 70 surveillance scans, PET was positive but without concordant findings in the CT. In these cases the short and long axes were defined as zero. Thirteen of these scans were FP, 2 scans were TP. In one TP scan, a pathologic hilar uptake was demonstrated, and the radiologist noted difficulty in evaluating hilar lymph nodes by CT without contrast media. The second TP scan demonstrated a temporal lobe uptake only, without lymph node uptake. CT was negative, as may often occur with central nervous system lymphoma on a non-contrast enhanced brain CT. In two additional surveillance scans, the short and long axis parameters were not measurable as pathologic uptakes were in the spleen, thyroid gland and liver with hypodense areas (not focal lesion) in CT. These two scans were TP. At least one lymph node with a long axis diameter > 1.5 cm was demonstrated in 26 of 70 scans (38%). The proportion of PET scans fulfilling this criterion was significantly higher in scans eventually defined to be truly positive (approaching 74%, n=17), compared with its occurrence in FP PET scans (20% only, n=9, $P \leq 0.0001$). Notably, just about a quarter (26%, n= 6) of TP scans represented LNs with a long axis shorter than 1.5 cm. LNs with a short axis larger than 1 cm were found in 23 scans (34%). Again, this finding was predominantly demonstrated in 74% of TP scans, compared with only 13% of FP scans ($P < 0.0001$). The likelihood of a FP scan in images demonstrating LNs with a short axis > 1 cm approached 26%.The ratio between the long and the short axis (defined as "long-short ratio") in FDG-positive LNs ranged between 0.9 and 3.8 (median ratio 1.5), with no significant difference in this ratio between TP versus FP PET scans. LNs fulfilling both CT criteria for relapse, i.e., a long axis > 1.5 cm and a short axis > 1 cm, were demonstrated in 22 scans. The proportion of these "double featured" LNs was higher in TP compared with FP PET scans (73%, n=16 vs. 27%, n=6). The frequency of nodal calcifications in positive PETs was very low; it was reported in three scans only, all considered as FP. Fatty hilum was demonstrated in one case only which was also confirmed as FP.

SURVEILLANCE PET VERSUS COMBINED PET/CT FOR RELAPSE DETECTION

Twenty-five of 70 FU-PET studies (36%) were defined as TP and 45 (64%) as FP. The measurement of either LN long axis > 1.5 cm or short axis > 1.0 cm has significantly improved the prediction of relapse determined by PET, providing an almost twice as high PPV with this combined approach, compared to that obtained with PET only (67% vs. 36%) [Table 1]. With the use of the CT measurement of LN short axis > 1.0 cm, the PPV improved to 74%. Similarly, combined assessment of long axis > 1.5 cm and short axis > 1.0 cm yielded a PPV of 73% [Table

Table 1. Lymph node measurements of PET-positive sites improve PPV of PET results

	PET*	PET*/long axis › 15 mm	PET*/short axis › 10 mm	PET+/short axis ≥ 10 mm	PET*/short axis › 10 mm + long axis › 15 mm	PET*/short axis › 10 mm or long axis › 15 mm	PET*/short axis ≥ 10 mm or long axis ≥ 15 mm
No. of positive results	70	26	23	30	22	27	34
FP	45	9	6	11	6	9	14
TP	25	17	17	19	16	18	20
PPV	36%	65%	74%	63%	73%	67%	59%

PET* = PET-positive

PPV = positive predictive value, FP = false positive, TP = true positive

Table 2. Lymph node measurements of PET-positive sites do not improve PPV of PET results in patients treated with CHOP

	PET*	PET*/long axis › 15 mm	PET*/short axis › 10 mm	PET+/short axis ≥ 10 mm	PET*/short axis › 10 mm + long axis › 15 mm	PET*/short axis › 10 mm or long axis › 15 mm	PET*/short axis ≥ 10 mm or long axis ≥ 15 mm
No. of positive results	17	13	12	12	12	13	13
FP	3	2	2	2	2	2	2
TP	14	11	10	10	10	11	11
PPV	82%	84%	83%	83%	83%	84%	84%

PPV = positive predictive value, FP = false positive, TP = true positive

Table 3. Lymph node measurements of PET-positive sites improve PPV of PET results in patients treated with CHOP+rituximab

	PET*	PET*/long axis › 15 mm	PET*/short axis › 10 mm	PET+/short axis ≥ 10 mm	PET*/short axis › 10 mm + long axis › 15 mm	PET*/short axis › 10 mm or long axis › 15 mm	PET*/short axis ≥ 10 mm or long axis ≥ 15 mm
No. of positive results	53	13	11	18	10	14	21
FP	42	7	4	5	4	7	12
TP	11	6	7	9	6	7	9
PPV	20%	46%	64%	50%	60%	50%	43%

PPV = positive predictive value, FP = false positive, TP = true positive

1]. Two TP surveillance scans were with a long axis < 1.5 and a short axis equal to 1.0 cm. The use of either long axis ≥ 1.5 cm or short axis ≥ 1.0 cm (instead of > 1.5 cm or > 1.0 cm, respectively) in CT measurements provided a PPV for relapse of 59% [Table 1]. Twenty of 25 TP scans were considered positive using these CT criteria. Among the remaining five TP PET/CT scans, one showed pathologic hilar uptakes which were difficult to evaluate by CT without contrast media; one demonstrated a temporal lobe uptake without finding on CT, performed without contrast media; and two revealed pathologic uptake in the spleen, thyroid gland and liver with hypodense areas on CT, which were unmeasurable. Only one of these five TP PET/CT scans demonstrated an uptake in a LN of less than 1 cm x 1.5 cm in diameter.

SUBGROUP ANALYSIS OF PATIENTS TREATED WITH OR WITHOUT RITUXIMAB

Of the 70 positive FU-PETs, 17 were found in patients treated with CHOP only. Of these 17 studies, 14 (82%) were defined as TP and 3 (18%) as FP. The measurement of either LN long axis > 1.5 cm or short axis > 1.0 cm had no additional impact on the prediction of relapse determined by PET [Table 2]. Of the 70 positive FU-PET studies, 53 were observed in patients treated with CHOP-R: 11 (20%) were defined as TP and 42 as FP (80%). The measurement of either LN long axis > 1.5 cm or short axis > 1.0 cm has significantly improved the prediction of relapse determined by PET, providing a PPV of 50% with this combined approach, compared to 20% achieved with PET only [Table 3].

PARAMETERS PREDICTING A TP RESULT

Patient- and disease-related parameters – such as age, gender, International Prognostic Index (IPI) and disease stage at diagnosis – were evaluated for their influence on surveillance PET results. In a univariate analysis, IPI ≥ 2 was associated with a significantly higher rate of TP PETs (64% of TP results vs. 27% of FP results were in patients with IPI ≥ 2, $P = 0.005$); PPV of surveillance PET in patients with IPI ≥ 2 was 57%. The age, gender and disease stage did not affect the prevalence of TP versus FP PET scans. The evaluated treatment-related parameters included exposure to rituximab, and the interval between completion of therapy and appearance of a positive scan. PPV of surveillance PET in patients treated with rituximab was significantly decreased compared to that reported for patients treated with CHOP only (20% vs. 82%, $P < 0.0001$). The period between completion of therapy and PET positivity was not found to have an impact on the likelihood of obtaining a FP or TP result [Table 4]. The significance of imaging-related parameters for technique sensitivity and specificity was evaluated, focusing on the presence of residual FDG uptake in a previously involved site, and occurrence of FDG uptake in a single versus multiple sites. In a univariate analysis, the presence of an uptake in a previously involved site was found to significantly correlate with TP PET, with a PPV approaching 62.5% versus 14% if FDG uptake involved a new site ($P < 0.0001$). The number of FDG-positive sites had no impact on the likelihood of obtaining a TP PET. Details of this analysis are presented in Table 4. Multivariate analysis confirmed IPI ≥ 2, lack of prior rituximab therapy, FDG uptake in a previously involved site, and long or/and short axis measurements ≥ 1.5 and 1.0 cm, respectively, to be independent predictors for TP FU-PET scans (odds ratio 6.89, 6.6, 4.9 and 5.4, $P < 0.05$ for all).

DISCUSSION

FDG-PET, a non-invasive imaging technique visualizing physiological and pathological processes, has been established to be

the most sensitive method evaluating response to therapy in patients with DLBCL [5,14], distinguishing between viable lymphoma infiltrates and necrotic or fibrotic processes [15,16]. The clinical importance of using a surveillance imaging approach in patients with DLBCL is debatable, considering that adoption of currently available strategies has not been shown to prolong overall survival [12]. The new guidelines discourage using routine surveillance PET/CT scans [4,17], which entail unnecessary investigations, radiation exposure, biopsies, expenses, and patient anxiety. Follow-up scans should be prompted by clinical indications only. However, in certain clinical scenarios and specific subpopulations, e.g., high risk patients who are likely to progress soon after completing therapy, surveillance imaging can be considered [6]. The benefit of a surveillance strategy for early detection of relapsed DLBCL depends on the probability of relapse, the sensitivity and specificity of the test, and the clinical value of early detection of relapse. In the current cohort, 78% of relapsed patients presented initially with advanced disease [9]. The integration of PET and CT results, suggested in this study, may potentially increase the specificity of a positive surveillance PET scan, which is of particular importance for a selected population of such high risk patients. Of note, the results of PET/CT imaging performed due to a clinical suspicion of relapse were included in the present analysis. While these scans would be expected to increase the PPV, it was actually found to be low. Many patients and physicians tend to have a low threshold of relapse suspicion, which may lead to unnecessary follow-up PET/CT evaluation. Accordingly, the search for a highly sensitive and specific approach for relapse assessment remains relevant even in the era when routine surveillance PET/CT for all patients with DLBCL who achieved CR is considered unreasonable. Most studies investigating feasibility of surveillance imaging in patients with DLBCL have used CT scanning. The present approach appears to be highly specific (92%) but not sufficiently sensitive (62%) [1]. In contrast, surveillance FDG-PET/CTs, though highly sensitive for detecting relapse, are affected by a high FP rate (30–80%), resulting in relatively low specificity [7,10,18-20]. In consensus with previous studies [9,10], prior exposure to rituximab appeared to contribute to this high FP rate. Therefore, an imaging approach offering high sensitivity along with high specificity and high PPV is required.

The revised response criteria for malignant lymphoma define relapse, assessed by CT according to LN size criteria and progression defined by PET, require existence of FDG uptake in a typical FDG avid *l*ymphoma site [5]. A negative FDG uptake excludes residual post-therapy fibrosis, which may resemble active lymphoma according to CT-defined anatomic criteria, whereas CT findings, particularly LN measurements, may sometimes distinguish between small reactive lymph nodes and lymphoma-related LNs, both of which may present FDG uptake [21]. In other words, residual masses are not always malignant and PET has the unique ability to rule out malignancy independent of the size criteria used in CT response evaluation. A negative PET result excludes lymphoma in CT-positive nodes. On the other hand, the benefits of CT findings are added when size criteria are incorporated in PET analysis, thus excluding PET-positive reactive small lymph nodes.

Table 4. Characteristics of surveillance positive PET scans

	Entire PET+ N=70	TP PET N=25 (36%)	FP PET N=45 (64%)	*P*
Median age	55 (19-81)	59 (19-81)	55 (24-75)	0.15
Gender: male	43 (61.4%)	15 (60%)	28 (62%)	1.00
International Prognostic Index				
0+1	42 (60%)	9 (36%)	33 (73%)	
2+	28 (40%)	16 (64%)	12 (27%)	0.005
Stage				
1+2	24 (34%)	6 (24%)	18 (40%)	
3+4	46 (66%)	19 (76%)	27 (60%)	0.20
Exposure to rituximab				
Yes	53 (76%)	11 (44%)	42 (93%)	
No	17 (24%)	14 (56 %)	3 (7 %)	‹ 0.0001
Time (months) from completion of therapy, average (range)	15 (3–118)	17 (4–118)	15 (3–65)	0.71
Months from end of therapy				
‹ 12 months	28 (40%)	12 (42.9%)	16 (57.1%)	
≥ 12 months	42 (60%)	13 (31%)	29 (69%)	0.32
Involvement of a prior site of disease*				
Yes	24 (36.4%)	15 (62.5%)	9 (37.5%)	
No	42 (63.6%)	6 (14.3%)	36 (85.7%)	‹ 0.0001
More than 1 vs. 1 site				
One site	42 (60%)	12 (48%)	30 (67%)	
More than 1 site	28 (40%)	13 (52%)	15 (33%)	0.15

*In four cases, data regarding the PET uptakes at diagnosis were not available

Lee at al. [13] reported that PET/CT scans demonstrating concordant PET and CT findings were found to significantly improve the PPV of PET/CT scans in detecting recurrent HL. The current study included 70 surveillance FDG-PET/CT scans which were interpreted as positive for relapse. These scans were employed to evaluate whether a combination of PET- and CT-based criteria would reduce the FP rate and improve the PPV of PET scans used to detect DLBCL relapse. We used specific CT morphologic measurements in PET-positive sites, focusing on short and long axis measurements, which fulfill the Cheson criteria [5], and morphologic appearance of lymph node, i.e., calcifications and fatty hilum. The use of LN measurements (long axis ≥ 1.5 cm or short axis ≥ 1.0 cm) in the delineation of PET-positive sites significantly improved the prediction of relapse in patients with DLBCL. With the combination of FDG uptakes and CT lymph node size criteria, five TP cases failed to be defined as positive. Among them, only one case was falsely considered as negative based on the LN size; in two other cases LN measurements were not available for the analysis as the CT demonstrated immeasurable hypodense areas; in the remaining two cases CT did not reveal pathology, most probably because the procedure

was performed without contrast media. Therefore, we assume that the efficacy of the combined PET/CT approach could be improved by using intravenous contrast media.

LN calcifications and fatty hilum are usually considered typical features of benign lymphadenopathy. However, both findings were infrequent, and though not detected in any of the TP scans, appeared in only 9% of the FP scans, suggesting that while their existence supports the presence of a reactive benign process, their absence is insufficient for defining a true relapse. Actually, the low incidence of these findings may be at least partly attributed to the study design, given that surveillance PETs with FDG uptakes in presumably benign LNs were considered negative and were excluded from our analysis.

Even using the proposed integration of PET- and CT-based criteria, and excluding any requirement for repeated short-interval scans to judge the stability or resolution of indeterminate findings, 423 scans were required in order to identify 25 true relapses. Radiation exposure, the remarkably high cost and stressful psychological issues associated with surveillance PET/CTs strategy along with the high FP rate and the unproved prognostic value of this method, raise questions about the feasibility of using this approach in the entire population of patients with DLBCL as compared to a selected high risk cohort only. This suggestion is supported by several retrospective studies, mainly performed in the HL setting, that evaluated the role of surveillance PET/CT scans in high risk patients only [13,22,23]. The PPV of surveillance PET/CT scans was much increased in high risk HL subjects with extranodal disease or positive interim PET compared with that obtained in the entire population: 36% vs. 22% [23]. Moreover, the detection of a radiographic abnormality within 12 months of first remission was associated with improved PPV of PET scans in detecting HL relapse [13]. These findings support the idea of selecting patients for surveillance imaging based on their risk factors for relapse. In line with these data, Petrausch et al. [22] suggested that HL patients with advanced stage disease and those exhibiting residual morphological findings in CT should undergo routine follow-up FDG-PET/CT. Our results support this selective approach, demonstrating a significant proportion of TP scans in patients with less favorable prognostic factors (IPI ≥ 2). This finding is in accordance with a recent publication [24] evaluating the role of surveillance PET/CT in DLBCL. The PPV in patients with IPI < 3 was 56%, compared to 80% in patients with IPI ≥ 3. The authors concluded that surveillance PET/CT is not useful for the majority of DLBCL patients with the possible exception of those with high IPI during the first 18 months after the end of therapy. It should be emphasized that it is not surprising that an IPI score ≥ 2 and the lack of previous treatment with rituximab increased the PPV of scans, as these criteria, a priori, are associated with a higher likelihood of DLBCL relapse in CR; hence, the Bayesian pre-test probability of relapse in these patients would be higher. In our study, an FDG uptake in a site positive at diagnosis was found to be an independent predictor of a TP surveillance PET scan in DLBCL. This observation is in line with findings by Lee and team [13] who determined factors that could significantly improve the PPV of PET scans in detecting recurrent HL, including involvement of a baseline disease site. The data of the current study also correlate with Cheson response criteria, indicating that increased FDG uptake in a previously unaffected site should only be considered as relapsed or progressive disease after confirmation by further evaluation. The likelihood of an abnormal surveillance imaging test to represent a true relapse depends on the probability of relapse in the studied population as well as the sensitivity and specificity of the test [1]. Accordingly, the use of surveillance PET/CT only in a selected high risk population could increase the probability of a TP result.

The correspondence between PET positivity and a CT finding, i.e., short and long axis measurements of positive uptakes and morphologic appearance of these lymph nodes (calcifications and fatty hilum), appears to significantly improve the specificity and PPV of the highly sensitive PET/CT scan. The new Lugano classification incorporates in the revised response criteria the 5-point scale for PET interpretation (1 = no FDG uptake above background, 2 = uptake ≤ mediastinum, 3 = uptake > mediastinum but ≤ liver, 4 = uptake moderately > liver, 5 = uptake markedly higher than liver and/or new lesions, X = new areas of uptake unlikely to be related to lymphoma) [4]. Incorporation of this scale in the combined PET/CT approach might further improve the PPV of PET/CT results and should be assessed accordingly.

Incorporation of CT findings in positive FDG-PET results may further improve PPV of PET/CT not only in the surveillance setting. For instance, a recent prospective evaluation of the predictive value of interim PET in patients with DLBCL treated with R-CHOP [25] confirmed that an interim PET/CT scan has limited prognostic value. The authors of that study concluded that their findings might foster further research by adding clinical, pathologic, or radiologic parameters to the value of an interim PET/CT to better stratify patients with good versus poor prognosis. This will also eventually lead to adapting treatment strategies.

CONCLUSIONS

Although highly sensitive, FDG-PET imaging is not sufficiently specific for detecting DLBCL relapse in asymptomatic patients during CR. Due to the radiation exposure and high costs, it cannot be recommended as a surveillance method for all such patients. The PPV of surveillance PET/CT may be improved if used in selected high risk patients and by combined assessment of PET and CT findings. Combined PET- and CT-based criteria for defining DLBCL relapse should be developed, and the prognostic value of surveillance PET/CT in high risk patients should be further evaluated in large prospective studies.

Correspondence
Dr. N. Lavi
Dept. of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa 31096, Israel
Phone: (972-4) 777-2541
Fax: (972-4)777-2343
email: lavi.noa@gmail.com

References

1. Armitage JO, Loberiza FR. Is there a place for routine imaging for patients in complete remission from aggressive lymphoma? *Ann Oncol* 2006; 17: 883-4.
2. Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol* 2005; 23: 5027-33.
3. Ghielmini M, Vitolo U, Kimby E, et al. ESMO Guidelines consensus conference on malignant lymphoma 2011. Part 1: Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). *Ann Oncol* 2013; 24: 561-76.
4. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Lister TA. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; 32: 3059-68.
5. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; 25: 579-86.
6. NCCN Practice Guidelines in Oncology, Non-Hodgkin's lymphoma. Version 1.2015. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed February 2015.
7. El-Galaly T, Prakash V, Christiansen I, et al. Efficacy of routine surveillance with positron emission tomography/computed tomography in aggressive non-Hodgkin lymphoma in complete remission: status in a single center. *Leuk Lymphoma* 2011; 52: 597-603.
8. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F] fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. *J Clin Oncol* 2009; 27: 1781-7.
9. Avivi I, Zilberlicht A, Dann EJ, et al. Strikingly high false positivity of surveillance FDG-PET/CT scanning among patients with diffuse large cell lymphoma in the rituximab era. *Am J Hematol* 2013; 88: 400-5.
10. Han HS, Escalon MP, Hsiao B, Serafini A, Lossos IS. High incidence of false-positive PET scans in patients with aggressive non-Hodgkin's lymphoma treated with rituximab-containing regimens. *Ann Oncol* 2009; 20: 309-18.
11. Liedtke M, Hamlin PA, Moskowitz CH, Zelenetz AD. Surveillance imaging during remission identifies a group of patients with more favorable aggressive NHL at time of relapse: a retrospective analysis of a uniformly-treated patient population. *Ann Oncol* 2006; 17: 909-13.
12. Goldschmidt N, Or O, Klein M, Savitsky B, Paltiel O. The role of routine imaging procedures in the detection of relapse of patients with Hodgkin lymphoma and aggressive non-Hodgkin lymphoma. *Ann Hematol* 2011; 90: 165-71.
13. Lee AI, Zuckerman DS, Van den Abbeele AD, et al. Surveillance imaging of Hodgkin lymphoma patients in first remission: a clinical and economic analysis. *Cancer* 2010; 116: 3835-42.
14. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999; 17: 1244.
15. Zinzani PL, Chierichetti F, Zompatori M, et al. Advantages of positron emission tomography (PET) with respect to computed tomography in the follow-up of lymphoma patients with abdominal presentation. *Leuk Lymphoma* 2002; 43: 1239-43.
16. Zijlstra JM, Lindauer-van der Werf G, Hoekstra OS, Hooft L, Riphagen, II, Huijgens PC. 18F-fluoro-deoxyglucose positron emission tomography for post-treatment evaluation of malignant lymphoma: a systematic review. *Haematologica* 2006; 91: 522-9.
17. Barrington SF, Mikhaeel NG. When should FDG-PET be used in the modern management of lymphoma? *Br J Haematol* 2014; 164: 315-28.
18. Gallamini A, Kostakoglu L. Positron emission tomography/computed tomography surveillance in patients with lymphoma: a fox hunt? *Haematologica* 2012; 97: 797-9.
19. Hutchings M. Routine follow-up scanning of patients with lymphoma: who, when, how, and why? *Leuk Lymphoma* 2011; 52: 552-3.
20. Petrausch U, Samaras P, Haile SR, et al. Risk-adapted FDG-PET/CT-based follow-up in patients with diffuse large B-cell lymphoma after first-line therapy. *Ann Oncol* 2010; 21: 1694-8.
21. Lewis E, Bernardino ME, Salvador PG, Cabanillas FF, Barnes PA, Thomas JL. Post-therapy CT-detected mass in lymphoma patients: is it viable tissue? *J Comput Assist Tomogr* 1982; 6: 792-5.
22. Petrausch U, Samaras P, Veit-Haibach P, et al. Hodgkin's lymphoma in remission after first-line therapy: which patients need FDG-PET/CT for follow-up? *Ann Oncol* 2010; 21: 1053-7.
23. El-Galaly TC, Mylam KJ, Brown P, et al. Positron emission tomography/computed tomography surveillance in patients with Hodgkin lymphoma in first remission has a low positive predictive value and high costs. *Haematologica* 2012; 97: 931-6.
24. Cheah CY, Hofman MS, Dickinson M, et al. Limited role for surveillance PET-CT scanning in patients with diffuse large B-cell lymphoma in complete metabolic remission following primary therapy. *Br J Cancer* 2013; 109: 312-17.
25. Mamot C, Klingbiel D, Hitz F, et al. Final results of a prospective evaluation of the predictive value of interim positron emission tomography in patients with diffuse large b-cell lymphoma treated with R-CHOP-14 (SAKK 38/07). *J Clin Oncol* 2015; 33: 2523-9.