ORIGINAL PAPERS

Adv Clin Exp Med 2015, **24**, 2, 325–330
DOI: 10.17219/acem/31804

ISSN 1899–5276

Silvana Novelli[1, A–F], Javier Briones[1, A, E–F], Albert Flotats[2, A, E–F], Jorge Sierra[1, E–F]

PET/CT Assessment of Follicular Lymphoma and High Grade B Cell Lymphoma – Good Correlation with Clinical and Histological Features at Diagnosis

[1] Department of Hematology, Hospital of the Holy Cross and Saint Paul, Barcelona, Spain
[2] Nuclear Medicine, Hospital of the Holy Cross and Saint Paul, Barcelona, Spain

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Follicular lymphoma is a common type of non-Hodgkin's lymphoma observed in Western countries. The diagnosis of this disease is based primarily on morphological and immunohistochemical assessment. The proliferative index Ki67 correlates with histological grading and clinical aggressiveness. Currently, positron emission tomography/computed tomography scanning are not applied for standard staging at diagnosis of follicular lymphoma and its use is limited to those patients for whom the identification of residual disease is crucial for therapeutic decisions and only when transformation to a high-grade lymphoma is suspected.
Objectives. Our aim was to assess whether a correlation exists between the maximal standardized uptake value (SUVmax) at the biopsy site as detected *via* positron emission tomography/computed tomography and pathological (Ki67 and FL histological grade) and clinico-biological features (e.g. LDH, beta-2-microglobulin, Ann Arbor stage and FL International Prognostic Index – FLIPI) at diagnosis.
Material and Methods. We retrospectively identified 16 patients during the previous 3.5 years in whom node biopsies were guided, taking into account the SUVmax as detected upon PET/CT scan at diagnosis. The results of these biopsies were diagnostic of follicular lymphoma. We also included 6 patients with high grade B cell lymphoma: 5 diffuse large B cell lymphoma (DLBCL) and 1 FL 3b histological grade. A 2-tailed non-parametric Spearman's correlation analysis of the SUVmax with Ki67, histological grade, LDH and b-2-microglobuline was performed.
Results. The Ki67 ($r = 0.73$) and follicular lymphoma histological grade ($r = 0.75$) at the biopsy displayed a significant correlation with the SUVmax at diagnosis ($p < 0.01$).
Conclusions. Our results suggest that SUV detected by positron emission tomography/computed tomography correlates with histological grade in follicular lymphoma/high grade B cell lymphoma, Ki67 and LDH. Positron emission tomography/computed tomography should be considered for guiding lymph node biopsy when transformation to a high-grade B cell lymphoma is suspected (**Adv Clin Exp Med 2015, 24, 2, 325–330**).

Key words: PET, follicular lymphoma, Ki67, high grade B cell lymphoma.

Follicular lymphoma (FL) is a common type of non-Hodgkin's lymphoma (NHL) observed in western countries. A recent review has indicated that FL was the most common low-grade lymphoma during the past 10 years worldwide [1].

The diagnosis of this disease is based primarily on morphological and immunohistochemical assessment. The World Health Organization (WHO) defines FL as a neoplasm composed of follicle center (germinal center) B cells and classifies the disease as grades 1, 2, 3A, and 3B based on the number of centrocytes and centroblasts in the lymph node [2, 3]. The proliferative index Ki67 correlates with histological grading [4] and clinical aggressiveness. The analytical and clinical features of FL have been summarized in the FL International Prognostic Index (FLIPI) [5]; however, no correlation with novel imaging techniques has been described.

Currently, positron emission tomography/ /computed tomography (PET/CT) scanning is not applied for standard staging at diagnosis of FL, although FL is a fludeoxyglucose (18F) (^{18}F-FDG)--avid disease and more than 90% of patients show PET/CT positivity at presentation [6]. Currently, the use of PET/CT in FL examination is limited to those patients for whom the identification of residual disease is crucial for therapeutic decisions and only when transformation to a high-grade lymphoma is suspected.

The main issues concerning FL treatment are the correct identification of patients with adverse prognosis who might benefit from more intensive treatment and the precise detection of cases in which transformation to a high-grade lymphoma is suspected.

It has been hypothesized that ^{18}F-FDG uptake reflects the proliferative activity of lymphoma cells and therefore is more intense in aggressive types of lymphoma. Some studies have reported a high diagnostic yield for ^{18}F-FDG-PET/CT, especially in patients with FL, while no diagnostic benefit has been observed with small lymphocytic lymphoma [7].

Purpose

Our aim was to assess whether a correlation exists between the maximal standardized uptake value (SUVmax) at the biopsy site as detected *via* PET/CT and pathological (Ki67 and FL histological grade) and clinical-biological features (e.g., LDH, beta-2-microgloblin, Ann Arbor stage and FL International Prognostic Index – FLIPI) at diagnosis. We collected high grade B cell lymphoma data, which served as a control.

Methods

We retrospectively identified 16 patients during the previous 3.5 years in whom node biopsies were guided, taking into account the SUVmax as detected upon PET/CT scan at diagnosis. The results of these biopsies were diagnostic of FL. These PET/CT selected lymph nodes were processed as usual. Immunohistochemistry, Ki67 and histological grade were determined.

Data on clinical presentation, bone marrow infiltration, SUVmax at biopsy site, demographics, Ann Arbor stage, FLIPI results, laboratory parameters and histology, with grading parameters according to the current WHO classification, were collected. Staging with PET/CT was performed following the criteria published [8].

As PET/CT has recently been introduced in our institution, this series is limited. Therefore, we included 6 patients with high grade B cell lymphoma: 5 diffuse large B cell lymphoma (DLBCL) and 1 FL 3b histological grade; this group works as a control of histological high proliferation tumor and strengthens the correlation analysis. The high grade B cell lymphoma patients were also included in the same way as the FL patients. It has been reported that DLBCL and transformed FL (or low-grade lymphoma) display similar SUVs [9, 10]. This study followed the principles in the Declaration of Helsinki.

PET/CT Scan Procedure

The patient fasted for 6 h prior to ^{18}F-FDG PET/ /CT imaging, and blood glucose levels were measured prior to intravenous injection of 259 MBq (7 mCi) of 18F-FDG. Following tracer injection, the patient rested in a comfortable reclined position for 55 min. PET/ /CT imaging was initiated with a planar scout scan, to define the axial range of the study, followed by sequential volumetric CT and PET/CT acquisitions. Scanning was performed from the base of the skull down to the mid-thigh 60 min after ^{18}F-FDG injection using a Gemini TF PET/CT scanner (Philips Healthcare, Eindhoven, The Netherlands). The CT component consisted of a non-breath holding unenhanced 64-detector scan at 120 kVp, 50 mAs, and 5-mm slice width and separation. The PET/CT component consisted of a 3D time-of-flight (TOF) acquisition of 8 overlapping bed positions (2 min/bed position, 50% overlapping). Images were reconstructed with the software supplied using the reconstruction parameters recommended by the manufacturer, which consisted of an ordered subsets expectation maximization (OSEM) algorithm with 3 iterations and 33 subsets with incorporation of TOF information as well as attenuation, detector efficiency and normalization, scatter, and random coincidences to produce fully corrected images.

Standard descriptive analyses were carried out, and non-parametric correlation tests were calculated to assess the relationship between laboratory, pathological and clinical parameters. Two-tailed Spearman's non-parametric correlation analysis was performed between SUVmax and pathologic and clinical features. Correlation was considered relevant when $r > 0$ and statistically significant when $p < 0.05$. The analysis was performed using SPSS ver. 20 for MAC-OS.

Results

The patients' characteristics are summarized in Table 1. Patients were categorized by histological grade to better visualize results.

Table 1. Patient demographics

Feature	Frequency
Age	mean 62.82 years; range (40–82)
Sex (n = 22) male female	 n = 9 (41%) n = 13 (59%)
Stage (n = 22) I II III IV	 n = 1 (4.5%) n = 3 (13.6%) n = 5 (22.7%) n = 13 (59.1%)
FLIPI (n = 17) I II III IV	 n = 3 (13.6%) n = 6 (27.3%) n = 5 (22.7%) n = 3 (13.6%)
Bone marrow infiltration (n = 22) yes no	 n = 5 (22.7%) n = 17 (77.3%)
Other organ involvement small bowel spleen skin bone lungs	 n = 3 n = 2 n = 1 n = 1 n = 1
Histological grade (n = 22) grade 1 grade 2 grade 3a grade 3b/DLBCL	 n = 6 (27.3%) n = 7 (31.8%) n = 3 (13.6%) n = 6 (27.3%)
SUVmax at biopsy site by histological grade grade 1 – SUVmax grade 2 – SUVmax grade 3a – SUVmax grade 3b/DLBCL general	 mean 6.7, range (3.0–14.6) mean 9.3, range (4.3–13.3) mean 12.7 range (5–24) mean 13.55, range (3-40)
Lactate dehydrogenase (n = 22) U/L	mean 361.73, range (135–1349)
B-2 microglobulin (n = 21) mg/L	mean 3.05, range (1.5–5.9)
Ki67 at biopsy site by histological grade grade 1 grade 2 grade 3a grade3b/DLBCL general	 mean 9.67, range (3–20) mean 25.0, range (15–40) mean 51.67, range (45–60) mean 80.83, range (70–95) mean 39.68, range (3–95)

To be more exigent with the study, we performed a 2-tailed non-parametric Spearman's correlation analysis of the SUVmax with Ki67, histological grade (from lymph node biopsy guided by PET/CT), LDH and b-2-microglobuline (from patient at diagnosis). These results are summarized in Table 2.

We found that Ki67 ($r = 0.73$) and FL histological grade ($r = 0.75$) at the biopsy site displayed a significant correlation with the SUVmax in the sampled lymph nodes at diagnosis ($p < 0.01$).

The results for the 1-tailed Spearman's correlation analysis of the SUVmax during lymph node biopsy and the Ki67, histological grade,

Table 2. Spearman's non-parametric correlation

	SUVmax at biopsy site	
Ki67	r = 0.73	p < 0.01
Histological grade	r = 0.75	p < 0.01
LDH	r = 0.50	p = 0.019
FLIPI	r = 0.38	p = 0.138
b-2-microglobulin	r = 0.41	p = 0.064

LDH, b-2-microglobuline and FLIPI were r = 0.73 (p < 0.01), r = 0.75 (p < 0.01), r = 0.50 (p < 0.01), r = 0.41 (p = 0.032) and r = 0.38 (p = 0.069), respectively. A higher number of patients in each group might strengthen these results in the 2-tailed analysis.

Discussion

Currently, CT scanning is considered the standard for FL staging. However, CT only takes into account the size of the lymph nodes but not the metabolic state associated with the disease. Since the introduction of PET/CT, several studies have evaluated the sensitivity of the technique both in Hodgkin's and non-Hodgkin lymphomas [11, 12]. Recently, data obtained from the FOLL5 trial have been published regarding the impact of using PET/CT instead of CT scans for FL staging [13]. PET/CT identified a higher number of nodal areas in 32% of patients and more extranodal sites than CT scans; therefore, the FLIPI was also affected when using PET/CT scanning. In the PRIMA study, the use of PET/CT status at the end of treatment, but not the conventional response, was an independent predictive factor of lymphoma progression [14].

In the present study, we sought to investigate whether a correlation exists between the SUVmax at the biopsy site, as detected *via* PET/CT at diagnosis and pathological and clinical-biological features. This was carried out because PET scanning is a functional imaging technique that allows for the visualization and quantification of glucose metabolism.

FL histological grading depends on the proportion of centrocytes to centroblasts, ranging from grade 1 FL, which is comprised of low numbers of centroblasts (0–5 per high-power field), to grade 3b FL, which is marked by solid sheets of large B cells. FL histological grading has not been assessed with different clinical prognosis, with the exception of 3b in adults. Furthermore, 3b FL exhibits many molecular characteristics similar to DLBCL, possibly explaining the associated divergent prognosis [15]. Therefore, the proper diagnosis of this subgroup of FL is clinically relevant because it affects treatment. In fact, evidence of clonal evolution inside of distinct histological grades has been reported [16]. This observation renders the coexistence of various histological grades in one patient possible. Moreover, this is also true for the transformation of a low-grade lymphoma into a high-grade lymphoma. Clinicians usually have some difficulty in assessing this transformation due to the poor performance status of patients during relapse and in older-aged patients; these difficulties commonly prevent biopsies. Since DLBLC and FL represent almost 50% of our new lymphoma cases, then PET/CT might be useful for proper guidance for biopsy at staging. Its role in the evaluation during and after treatment should be analyzed in large series. On the other hand, we cannot forget that PET/CT also exposes the patient to more radiation, and for this reason its use should be carefully studied.

In our study, we found that SUVmax node biopsy guidance correlated with almost all of the pathological and clinical parameters that are commonly applied.

Due to the transcendence of FL histological grade in the selection of initial treatment, the most relevant finding of our study was the correlation between SUVmax and histological grade. Spearman's coefficient (r = 0.75) revealed a linear dependence between both variables (Fig. 1). This finding may be useful for biopsy guidance.

Moreover, when transformation is suspected, the correlation between SUVmax and Ki67 (r = 0.73) is important, as a higher than expected SUVmax readout in a diagnosed low-grade lymphoma may suggest transformation.

Our results suggest that SUV detected by PET/CT correlated with histological grade in follicular lymphoma/high grade B cell lymphoma, Ki67 and LDH. PET/CT should be considered for guiding lymph node biopsy when transformation to a high-grade B cell lymphoma is suspected. These findings may contribute to further use of PET/CT at diagnosis when suspecting a B cell lymphoma.

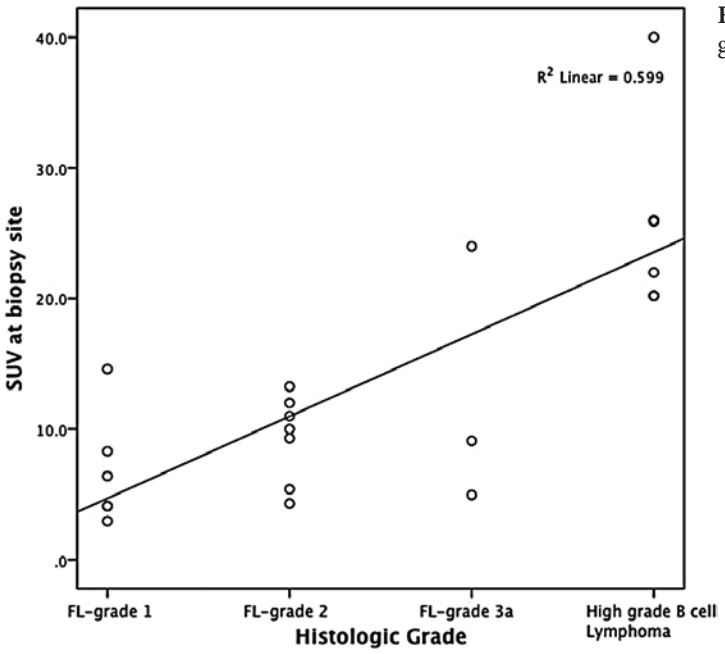

Fig. 1. Spearman's correlation: histological grade and SUVmax at diagnosis

References

[1] **Novelli S, Briones J, Sierra J:** Epidemiology of lymphoid malignancies: last decade update. Springerplus 2013, 2, 70.

[2] **Jaffe ES, Harris NL, Stein H, Campo E, Pileri SA, Swerdlow SH:** Introduction and Overview of the Classification of the Lymphoid Neoplasms. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC 2008, 4th ed., 8, 220–226.

[3] **Klapper W:** Pathobiology and diagnosis of follicular lymphoma. Semin Diagn Pathol 2011, 28, 146–160.

[4] **Miller TP, Grogan TM, Dahlberg S, Spier CM, Braziel RM, Banks PM, Foucar K, Kjeldsberg CR, Levy N, Nathwani BN:** Prognostic significance of the Ki-67-associated proliferative antigen in aggressive non-Hodgkin's lymphomas: a prospective Southwest Oncology Group trial. Blood 1994, 83, 1460–1466.

[5] **Solal-Céligny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, Au WY, Bellei M, Brice P, Caballero D, Coiffier B, Conde-Garcia E, Doyen C, Federico M, Fisher RI, Garcia-Conde JF, Guglielmi C, Hagenbeek A, Haïoun C, LeBlanc M, Lister AT, Lopez-Guillermo A, McLaughlin P, Milpied N, Morel P, Mounier N, Proctor SJ, Rohatiner A, Smith P, Soubeyran P, Tilly H, Vitolo U, Zinzani PL, Zucca E, Montserrat E:** Follicular lymphoma international prognostic index. Blood 2004, 104, 1258–1265.

[6] **Wohrer S, Jaeger U, Kletter K, Becherer A, Hauswirth A, Turetschek K, Raderer M, Hoffmann M:** 18F-fluoro-deoxy- glucose positron emission tomography (18F-FDG-PET/CT) visualizes follicular lymphoma irrespective of grading. Ann Oncol 2006, 17, 780–784.

[7] **Jerusalem G, Beguin Y, Najjar F, Fillet G, Rigo P:** Positron emission tomography (PET/CT) with 18F-fluoro-deoxyglucose (18F-FDG) for the staging of low-grade non-Hodgkin's lymphoma (NHL). Ann Oncol 2001, 12, 825–830

[8] **Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V:** International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol 2007, 25, 579–586.

[9] **Ngeow JY, Quek RH, Ng DC, Hee SW, Tao M, Lim LC, Tan YH, Lim ST:** High SUV uptake on FDG-PET/CT predicts for an aggressive B-cell lymphoma in a prospective study of primary FDG-PET/CT staging in lymphoma. Ann Oncol 2009, 20, 1543–1547.

[10] **Noy A, Schöder H, Gönen M, Weissler M, Ertelt K, Cohler C, Portlock C, Hamlin P, Yeung HW:** The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL). Ann Oncol 2009, 20, 508-512.

[11] **Lapela M, Leskinen S, Minn HR, Lindholm P, Klemi PJ, Söderström KO, Bergman J, Haaparanta M, Ruotsalainen U, Solin O, Joensuu H:** Increased glucose metabolism in untreated non-Hodgkin's lymphoma: a study with positron emission tomography and fluorodeoxyglucose. Blood 1995, 86, 3522–3527.

[12] **Elstrom R, Guan L, Baker G, Nakhoda K, Vergilio J, Zhuang H, Pitsilos S, Bagg A, Downs L, Mehrotra A, Kim S, Alavi A, Schuster SJ:** Utility of FDG-PET/CT scanning in lymphoma by WHO classification. Blood 2003, 101, 3875–3876.

[13] **Luminari S, Biasoli I, Arcaini L, Versari A, Rusconi C, Merli F, Spina M, Ferreri AJ, Zinzani PL, Gallamini A, Mastronardi S, Boccomini C, Gaidano G, D'Arco AM, Di Raimondo F, Carella AM, Santoro A, Musto P, Federico M:** The use of FDG-PET/CT in the initial staging of 142 patients with follicular lymphoma: a retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi. Ann Oncol 2013, 24, 2108–2112.

[14] Trotman J, Fournier M, Lamy T, Seymour JF, Sonet A, Janikova A, Shpilberg O, Gyan E, Tilly H, Estell J, Forsyth C, Decaudin D, Fabiani B, Gabarre J, Salles B, Van Den Neste E, Canioni D, Garin E, Fulham M, Vander Borght T, Salles G: Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol 2011, 29, 3194–3200.

[15] Salaverria I, Siebert R: 2011. Follicular lymphoma grade 3B. Best Pract Res Clin Haematol 2009, 24, 111–119.

[16] Adam P, Schoof J, Hartmann M, Schwarz S, Puppe B, Ott M, Rosenwald A, Ott G, Muller-Hermelink HK: Cell migration patterns and ongoing somatic mutations in the progression of follicular lymphoma. Cytogenet Genome Res 2007, 118, 328–336.

Address for correspondence:

Silvana Novelli
Department of Hematology
Hospital of the Holy Cross and Saint Paul
08041-Barcelona
Spain
Tel.: +34 93 55 65 649
E-mail: snovelli@santpau.cat

Conflict of interest: None declared

Received: 9.06.2014
Revised: 5.11.2014
Accepted: 6.11.2014