

The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: a retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi

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Background: The role of [¹⁸F] fluorodeoxyglucose (FDG)-positron emission tomography (PET) in follicular lymphoma (FL) staging is not yet determined.

Patients and methods: The aim of the present study was to investigate the role of PET in the initial staging of FL patients enrolled in the FOLL05-phase-III trial that compared first-line regimens (R-CVP, R-CHOP and R-FM). Patients should have undergone conventional staging and have available PET baseline to be included.

Results: A total of 142 patients were analysed. PET identified a higher number of nodal areas in 32% (46 of 142) of patients and more extranodal (EN) sites than computed tomography (CT) scan. Also, the Follicular Lymphoma International Prognostic Index (FLIPI) score increased in 18% (26 of 142) and decreased in 6% (9 of 142) of patients. Overall, the impact of PET on modifying the stage was highest in patients with limited stage. Actually, 62% (15 of 24) of cases with limited disease were upstaged with PET.

Conclusions: The inclusion of PET among staging procedures makes the evaluation of patients with FL more accurate and has the potential to modify therapy decision and prognosis in a moderate proportion of patients. Further prospective clinical trials on FL should incorporate PET at different moments, and the therapeutic criteria to start therapy should be re-visited in the views of this new tool.

Key words: follicular lymphoma, FDG-PET, staging, CT scan

Introduction

Follicular lymphoma (FL) accounts for about 10%–20% of lymphomas in western countries and is the most frequent of indolent lymphomas. Although patients with FL achieve excellent response with initial treatment, most of them relapse

with median progression-free survival of 60 months and a variable clinical course [1].

[¹⁸F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) recently emerged as a powerful functional imaging tool in staging and response assessment in Hodgkin's lymphoma and diffuse large B-cell lymphoma [2, 3]. FL is a [¹⁸F]-FDG avid disease; more than 90% of patients show a PET positive at presentation and sensitivity of staging PET is usually >95% [4–7]. Despite this, the literature concerning the role of PET in FL staging is scarce, and this tool is not recommended as a routine procedure [3]. In a retrospective

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analysis on 22 patients, PET was able to detect more nodal and extranodal (EN) lesions than computed tomography (CT) scan [8]. Moreover, the use of PET can result in a modification of initial staging in up to one-third of patients [9–12]. Recent data from a large multicentre clinical trial in advanced FL patients (PRIMA trial) showed that the PET status at the end of immunochemotherapy is strongly predictive of outcome [13, 14]. Furthermore, the potential modification of initial stage by PET could be associated with both a change in therapeutic choice and overall prognosis.

In 2005, the Fondazione Italiana Linfomi (FIL) started the FOLL05 prospective, randomized trial (NCT00774826) that compared three chemoimmunotherapy regimens (R-CVP, R-CHOP and R-FM) as first-line treatment for patients with stage II/IV FL [15]. Although PET was not included among diagnostic procedures, several patients underwent PET scan for initial staging. Taking this into consideration, we investigated the role of PET in the initial staging of patients with FL by comparing PET-based staging with the conventional CT-based Ann Arbor staging.

patients and methods

inclusion and exclusion criteria

The study was designed as a retrospective analysis on patients with FL who were enrolled in the FOLL05 phase III trial (NCT00774826), which compared three chemoimmunotherapy regimens as first-line treatment (R-CVP, R-CHOP and R-FM regimens). As this study is based on an unplanned analysis of the FOLL05, a specific protocol was approved by ethics committee and patients were required to sign an informed consent form.

In order to be considered for the current study, patients were required to be randomly assigned in the FOLL05 trial, who are between 18 and 75 years, have Ann Arbor stage II–IV, and have active disease [16]. For the purposes of the present study, patients should also have available data on baseline CT scan (B-CT) with iodine contrast medium for neck, thorax and abdomen, and on baseline total-body PET/CT scan (B-PET). B-PET was allowed if available by the FOLL05 procedures but not mandatory. Most of the patients did not undergo a baseline PET because of reimbursement issues and logistic reasons. Both B-CT and B-PET were to be carried out before treatment start, time between the B-PET and B-CT should not exceed 3 months, no surgical procedures were allowed during the period elapsed between the two examinations and explored regions should be comparable regarding extension. Finally, all patients were also required to have available details on clinical presentation, treatment and follow-up.

data collection and analysis plan

Patients were identified with the original Id number of the FOLL05. Data on clinical presentation, treatment and follow-up were retrieved from the existing dataset of the randomized protocol: histology with grading according to the current REAL-WHO classification, demographics, Ann Arbor stage, bone marrow (BM) biopsy and laboratory parameters.

For specific study purposes, data were collected on each B-PET or B-CT scan based on the original report of the examination. B-CT and B-PET were reviewed by SL, AV and MQ and discussed with the nuclear physician. We considered as positive all lesions that were described as positive in the local report. PET analysis was based on a qualitative assessment of PET results and no data were available on functional findings.

For staging assessment, disease extension at baseline was estimated independently for both PET and CT. The conventional and reference stage

was defined with CT and BM only [17]. For each examination, nodal sites were classified and counted accordingly to the Follicular Lymphoma International Prognostic Index (FLIPI) schema [18]. Nodal sites were considered positive if their maximum transverse diameters were >1.5 cm at CT or if they were positive at PET scan. EN sites were considered positive at CT in the case of nodular involvement or case of organ enlargement not otherwise justified. EN involvement at PET scan was considered for sites showing avidity for FDG. EN sites were counted on an organ basis. BM involvement was established on the basis of the local pathology report of BM biopsy.

statistical analysis

Statistical analysis was carried out with SPSS software (Chicago, IL) and Stata. Standard descriptive analyses were carried out. In order to evaluate the agreement between CT and PET results regarding the number of nodal sites, the number of EN sites, Ann Arbor Staging and FLIPI score, Cohen's kappa statistic was used. The level of agreement was defined by Koch–Landis scale [19].

results

One hundred and ninety-nine outpatients were initially identified for this study. Subsequently, 57 patients were excluded due to violation of the inclusion criteria. The remaining 142 patients fulfilled the eligibility criteria and were considered for this study. Using the original FOLL05 data, the two groups were well balanced regarding stage and FLIPI score (data not shown).

The median age was 57 years (range 33–74). Patients' characteristics at diagnosis are shown in Table 1. FDG avidity

Table 1. Patients' characteristics

feature	n = 142 (%)
Gender	
Male	69 (49)
Female	73 (51)
Ann Arbor stage (CT + BM)	
I–II	25 (18)
III	37 (26)
IV	80 (56)
Bulky disease	
No	82 (58)
Yes	57 (40)
Missing	3 (2)
BM infiltration	
No	72 (51)
Yes	70 (49)
β 2-microglobulin	
\leq 1 unl	68 (48)
>1 unl	73 (51)
Missing	1 (1)
FLIPI	
0–1	45 (32)
2	53 (37)
3–5	44 (31)

FLIPI, Follicular Lymphoma International Prognostic Index; BM, bone marrow; CT, computed tomography; UNL, upper normal limit.

was demonstrated in 98% (139 of 142) of patients. These FDG-negative cases were related to low-grade FL.

nodal areas

PET allowed the identification of more nodal areas than CT scan in 32% (46 of 142) of the patients. In fact, 39%, 39% and 22% of cases presented with <4, 4-7 and >7 nodal areas, respectively, at CT scan. Using PET, 28%, 37% and 35% of cases presented with <4, 4-7 and >7 nodal areas, respectively. PET identified a lower number of nodal areas in only 15 (11%) patients. The agreement between PET and CT scan was considered fair ($\kappa = 0.37$, Table 2).

FLIPI score

Using PET, the FLIPI score was increased in 26 (18%) patients and decreased in 9 (6%). In fact, 32%, 37% and 31% of patients were classified by CT with a score of 0-1, 2 and 3-5, respectively. Using PET, 25%, 40% and 35% of cases were classified with a score of 0-1, 2 and 3-5, respectively. The agreement between PET and CT scan for FLIPI was considered substantial ($\kappa = 0.62$, Table 2).

staging

Initial PET had an impact on Ann Arbor staging. A proportion of 17% (24 of 139) and 83% (115 of 139) of FDG avidly

patients were classified by CT as stage II and III-IV, respectively. On the other hand, 10% (14 of 139) and 90% (125 of 139) of patients were classified by PET as stage II and III-IV, respectively. Fifteen (11%) patients were up-staged with PET, while only five (1%) were down-staged. Moreover, 15 (62%) of the 24 patients previously classified as stage II were classified by PET as having stage III-IV (Table 3).

The agreement between PET and CT scan for staging purposes was considered fair when the information on histology of BM was not taken into account, and it improved to moderate ($\kappa = 0.62$) when this information was considered (Table 3).

extranodal sites

Overall, CT scans allowed the identification of 60 extranodal sites (ENSs) in 47 patients, 2 or more were described in 12 patients; the most frequent were spleen, liver and gastrointestinal (GI) tract. PET allowed the identification of 97 ENSs in 67 patients and 2 or more ENSs were found in 21 patients; the most frequent were bone, spleen and GI tract (Table 4). PET detected bone lesions in 34 patients. In these 34 patients, BM involvement was detected in 71% of the patients (24 of 34). In the group of 108 patients without PET detected bone lesions, BM involvement was detected in 43% (46 of 108). Overall PET and BMB were concordant in 85 of 142 cases with a fair concordance ($\kappa = 0.2$).

Table 2. Number of nodal areas and FLIPI score

		Nodal areas				Total		FLIPI score				Total
		CT scan						CT scan				
		<4	4-7	>7			0-1	2	3-5			
PET scan	<4	30	10	0	40	PET scan	0-1	29	4	2	35	
	4-7	23	25	5	53		2	15	39	3	57	
	>7	3	20	26	49		3-5	1	10	39	50	
	Total	56	55	31	142		Total	45	53	44	142	
κ		0.37					0.62					
Agreement		57%					75%					

FLIPI, Follicular Lymphoma International Prognostic Index; PET, positron emission tomography; CT, computed tomography.

Table 3. Ann Arbor stage without bone marrow histopathology and with bone marrow histopathology (n = 139 patients with baseline-positive positron emission tomography)

		Without BM histopathology					Total		With BM histopathology					Total
		CT scan							CT scan					
		I	II	III	IV			I	II	III	IV			
PET scan	I	0	1	3	0	4	PET Scan	I	0	1	1	0	2	
	II	0	11	3	1	15		II	0	8	3	1	12	
	III	1	9	57	5	72		III	1	8	27	3	39	
	IV	0	10	21	17	48		IV	0	6	6	74	86	
	Total	1	31	84	23	139		Total	1	23	37	78	139	
κ		0.36						0.62						
Agreement		61%						78%						

BM, bone marrow; PET, positron emission tomography.

Table 4. Extranodal (EN) sites identified by computed tomography (CT) scan and positron emission tomography, PET

	CT (n=60)	PET (n=97)	K
Spleen	31	26	0.49
Bone	3	34	0.07
Liver	8	2	0.18
Skin and soft tissues	5	12	0.44
Gastrointestinal (GI) tract	2	9	0.35
Others	11*	14*	NA

*Others in CT include tonsil, gall bladder, thyroid, pleura, adrenal, lung, peritoneum, ocular adnexal, parotid, nasopharynx, gluteal muscle (each $n = 1$).

Others in PET include pleura ($n = 3$), lung ($n = 2$), parotid ($n = 2$), ocular adnexal, nasopharynx, glands, laryngeal, adrenal, utero and thyroid (each $n = 1$).

NA, not applicable.

discussion

Emerging data regarding the role of PET in the management of FL patients were recently published [6, 8, 13, 14, 20]. However, the literature regarding the role of PET in staging of FL patients is scarce. In the present study, we sought to investigate if there is an impact of PET on staging in a retrospective analysis of patients included in the FOLL05 multicentre randomized clinical trial conducted in 60 centres in Italy. To our knowledge, it is one of the largest multicentre cohorts of FL patients that addressed this issue. The main findings of this analysis were that PET can detect more nodal and EN sites than CT scan, yielding a moderate stage migration. PET was also able to modify FLIPI, but the prognostic impact and clinical relevance of these findings are not yet clear.

Overall, the impact of PET on modifying the stage was highest in patients with limited stage. Actually, in our series 62% of cases with limited disease were upstaged with PET. Regarding patients with advanced stage, although PET was able to identify more sites than CT scan, the impact in modifying staging was less apparent and in most cases neutralized by the information of BM biopsy. Upstaging of localized disease could have relevant therapeutic and clinical implications. Currently, a therapeutic approach for limited stage FL patients is involved-field radiation therapy which yields long-term freedom from progression in half of the patients, with most relapses occurring outside the irradiated volume [21]. Although our findings must be validated by other studies specifically focused on limited stage FL, they are clear enough to recommend more accurate staging procedures, including PET at least in patients for whom involved field radiation therapy are an option.

In addition to stage migration, the high accuracy of PET in describing nodal sites may have implications regarding prognostic assessment. The number of nodal sites is one of the prognostic factors of the FLIPI score, which has been available for more than 5 years and is currently an important tool for treatment planning in FL [18]. Based on our results, the agreement between the FLIPI calculated with CT and PET was substantial and 75% of patients were allocated to the same risk

group by the two techniques. Whether the outcome of the remaining 25% of the patients is better foreseen by PET or not deserves further investigation. FLIPI-2 is another validated tool to assess prognosis of patients with FL and that do not include the number of nodal sites and is not affected by PET results [22].

PET was also able to detect more EN sites than CT, particularly bones. Also, the concordance of PET and CT for different organs was only moderate for spleen, skin and soft tissue, and only fair and slight for others. If we take into consideration the GELF criteria for starting treatment, the information of PET regarding EN sites could change the approach in a small group of patients. This point should be considered carefully because we cannot exclude the possibility that some unusual sites may represent, in fact, false-positive EN sites. Moreover, PET was not useful in detecting BM infiltration and no data are currently available to omit BM biopsy among initial staging procedures in all patients with FL.

We are aware that one limitation of the present study was its retrospective nature. Nevertheless, a selection bias is unlikely because although PET was not mandatory among the staging procedures of the FOLL05 clinical trial, it was recommended in all centres where the facility was available. Also, the clinical information was prospectively collected, except for the PET results. Another aspect that should be raised is the use of routine visual assessment practices for PET interpretation. Observer variation in the interpretation of imaging studies can be substantial, and the reasons might differ depending on each method. One could argue that disagreement between CT and PET could not be only explained by the fact that PET detects more sites than CT but it is also related, at least in multicentric retrospective studies like this one, to a lack of standardization of CT reporting.

Finally, our analysis was based on a qualitative "anatomic" assessment of PET results and no data were available on functional findings. As observed in diffuse large B cell lymphomas, the rate of metabolic activity of disease measured by SUV and SUV max seems to add important information mainly in terms of prognosis [23]. The baseline SUV has not been extensively studied in FL patients so far, but it is likely that in terms of SUV, assessment requires accurate and standardized procedures and requires well-designed prospective studies.

In conclusion, based on our results, the inclusion of PET among staging procedures makes the evaluation of patients with FL more accurate and has the potential to modify therapy decision and prognosis in a moderate proportion of patients. Further prospective clinical trials on FL should incorporate PET at different moments, and the therapeutic criteria to start therapy should be re-visited in the views of this new tool. Taken together, the results of our study support the claim for the need of a consensus to include PET scanning among staging procedures in FL.

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disclosure

The authors have declared no conflicts of interest.

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