European Journal of Nuclear Medicine and Molecular Imaging (2024) 51:3311–3321
https://doi.org/10.1007/s00259-024-06765-z

ORIGINAL ARTICLE

End of induction [^{18}F]FDG PET is prognostic for progression-free survival and overall survival in follicular lymphoma patients enrolled in the FOLL12 trial

Luca Guerra · Stephane Chauvie · Federico Fallanca · Fabrizio Bergesio · Luigi Marcheselli · Rexhep Durmo, et al. ***[full author details at the end of the article]***

Received: 27 December 2023 / Accepted: 12 May 2024 / Published online: 25 May 2024

Abstract

Purpose To evaluate the reliability of the Deauville score (DS) in therapy response assessment and to define the prognostic value of the metabolic response of end of induction (EOI) [^{18}F]FDG PET (PET) in follicular lymphoma patients.

Methods Adult patients with untreated grade 1–3a FL/ stage II-IV enrolled in the multicentre, prospective, phase III FOLL12 trial (NCT02063685) were randomized to receive standard immunochemotherapy followed by rituximab maintenance (standard arm) versus standard immunochemotherapy followed by response-adapted post-induction management (experimental arm). Baseline and EOI PET were mandatory for the study. All PET scans were centralized on the WIDEN® platform and classified according to DS in a blind independent central review. DS1–3 was considered negative (CMR), whereas DS4-5 was considered positive (not CMR). The primary endpoint was PFS. The main secondary endpoint was overall survival (OS).

Results Overall, 807 follicular lymphoma patients—52% women, 89% stage III-IV disease, 40% with a high-risk FLIPI-2 score (3–5)—were enrolled in the study; 729 (90.4%) baseline and EOI PET were available for the analysis. EOI PET was positive (DS4–5) in 88/729 (12.1%) cases. Overall inter-reviewer agreement on PET pos/neg result was 0.92, while agreement on positive and negative cases was 0.77 and 0.94, respectively. The median follow-up was 69 months; 247 events were registered in the 5-yr follow-up, with a 5-yr PFS of 67% (95%CI: 63%–70%). The 5-yr PFS rate for PET neg (DS1–3) and PET pos (DS4–5) patients was 71% (95%CI: 67%–75%) and 36% (95%CI: 25%–46%), respectively, with HR 3.49 (95%CI: 2.57–4.72). Five-year PFS was worse as DS increased, with 74% (70%–78%), 58% (48%–67%; HR 1.71; $p = 0.001$)] and 36% (25%–46%; HR 3.88; $p < 0.001$) in DS1–2, DS3 and DS4–5, respectively. EOI PET maintained its prognostic value in both the standard and experimental arms. In the whole population, 5-yr OS was 94% (95%CI: 92%–96%), with 96% (95%CI: 94–97) and 82% (95%CI: 72%–89%) in EOI PET negative (DS1–3) and positive (DS4–5), respectively (HR 4.48; $p < 0.001$). When DS was associated with FLIPI-2, patients with DS3 or DS1–2 with high FLIPI-2 (3–5) experienced worse OS than patients with DS1–2 and low FLIPI-2 (1–2) ($p = 0.003$).

Conclusion This study shows that DS is a reliable prognostic tool to evaluate EOI PET in follicular lymphoma patients, with prognostic value maintained both in the standard and experimental arms, making metabolic imaging a robust tool to assess response in FL. Moreover, although preliminary, this study provides further information on DS3 patients, who are considered as CMR but show a less favourable PFS than DS1–2 patients.

Keywords Follicular lymphoma · Therapy response · [^{18}F]FDG PET/CT · Prognosis · FOLL12 trial

Introduction

Follicular lymphoma (FL) is the most common type of indolent lymphoma [1], characterized by a relatively favourable response to initial therapy, especially after the introduction of rituximab [2–4]. However, FL is associated with a considerable risk of recurrence and transformation into an aggressive disease, with approximately 20% of patients

Trail Registration: https://www.clinicaltrials.gov/study/NCT02063685.

Identifier: NCT02063685.

Retrospectively registered: 21 November 2012.

experiencing relapse within the first two years, a condition that often leads to poor prognosis [5]. Although the Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI2 are currently the consolidated prognostic systems [6], and other prognostic factors have been suggested [7], patients with worse prognosis are not accurately identified at diagnosis [8]. Among available prognostic factors, response to treatment, assessed by 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (PET) scan and the Deauville 5-point scoring system (DS), has been correlated with patients' outcome, and it is currently recommended at the end of induction therapy (EOI) as the standard reference for response assessment [9]. Several retrospective analyses focusing on EOI PET, including the PRIMA trial [8], the FOLL05 trial [10], the GALLIUM trial [11] and a pooled retrospective analysis of three multicentre trials [12], clearly demonstrated that both progression-free survival (PFS) and overall survival (OS) are significantly better in patients achieving complete metabolic response (CMR) in EOI PET. Despite this evidence, some limitations may have hampered the solidity of the above-mentioned studies; in particular, EOI PET scans were evaluated retrospectively, they were not available for the whole population enrolled, and in some cases, response assessment was defined by the local centre without standardized criteria. Hence, this study aimed to evaluate the reliability of DS to assess the response of EOI PET and the prognostic value of EOI PET results in terms of PFS and OS in a large cohort of treatment-naïve FL patients prospectively enrolled in the FOLL12 trial.

Materials and methods

Study population

The FOLL12 trial (NCT02063685) [13] is a multicentre randomized phase III trial that compares standard rituximab-based maintenance therapy versus an EOI PET minimal residual disease (MRD) response-adapted maintenance therapy in patients with Grade 1-3a, advanced stage FL. As per protocol, a baseline (before therapy) and an EOI PET scan were mandatory for all patients enrolled in the study, and the response to treatment was assessed by a blind independent central review (BICR) board according to the standard Deauville criteria [9, 14, 15]. Previously untreated patients aged 18–75 years with a diagnosis of histologically confirmed FL, grade 1, 2, or 3a according to the WHO classification [16], an Ann Arbor stage II-IV, an Eastern Cooperative Oncology Group performance status of 0–2, and a FLIPI2 greater than 0 were enrolled. A baseline PET scan was performed before starting the induction therapy, consisting of six cycles of rituximab in combination either with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or with bendamustine (R-B), as determined by the local investigator. An EOI PET scan was performed after treatment to assess metabolic response. Patients achieving complete metabolic response (CMR) were randomly assigned to either the standard maintenance treatment or the experimental treatment. According to the trial design, patients in the standard arm with complete (DS1–3) or partial response (DS4–5) were followed up with rituximab maintenance therapy, which consisted of one rituximab infusion every eight weeks for two years, whereas patients with less than partial response (DS4–5) were treated with salvage therapy. Patients in the experimental arm with complete response (CR) (DS1–3) were followed up with observation if MRD was negative, or with rituximab treatment (weekly dosage for four weeks) if MRD was positive. Patients with partial response (PR) (DS4–5) underwent radioimmunotherapy (90Y-ibritumomab tiuxetan: 15 MBq/Kg (max dosage 1200 MBq) over 10 min within four hours of rituximab infusion) and rituximab maintenance therapy; patients with less than PR (DS4–5) were treated with salvage therapy. According to the FOLL12 trial protocol, MRD was assessed as previously described by Luminari et al. [13]. For the study, inclusion criteria mandated that baseline and EOI PET scans were available and centrally reviewed. The main study endpoint was progression-free survival (PFS); overall survival (OS), response to therapy according to DS, histological transformation into aggressive lymphoma and the progression of disease within 24 months of follow-up (POD24) were secondary endpoints.

PET scan acquisition and review process

All PET scans were acquired by the local centres following the indications in the FOLL12 clinical trial. After anonymization, PET scans were uploaded by the participating PET sites into the WIDEN® platform (Dixit s.r.l. Torino, Italy), as previously described [17]. Technical review of the scans was performed by a medical physicist at the Cuneo Imaging Corelab (https://doi.org/10.1016/j.ejmp.2023.102836) to ensure the quality of the data and their adherence to the protocol. PET scans with poor-quality images, low statistics, or not considered suitable for diagnostic interpretation for any reason were excluded from the study. Violations concerning the protocol were automatically checked by analysing DICOM headers of PET scans with WIDEN®.

A blind independent central review (BICR) board of six expert nuclear medicine physicians (AF, LG, PS, GS, FF and AV) was instituted to analyse the PET scans (baseline and EOI) according to the BICR modality [17] using the Deauville 5-point scoring system (DS) [15]. Before starting the trial, the review board had decided that the first three concordant reviewers would determine the EOI PET result, with DS1–3 being negative and DS4–5 being positive.

The reviewers had 120 h (5 days) from the receipt of an email alert to review the baseline and EOI PET scans and to upload the review form on WIDEN ®. All six reviewers were then informed that a decision had been reached (but not whether positive or negative) for each scan, which did not undergo any further review. Therefore, not all six reviewers reviewed all the PET scans.

According to the DS, each FDG-avid (or previously avid) lesion was scored DS1 if no residual uptake was evident, DS2 if residual uptake was not higher than mediastinal blood pool (MBP) activity, DS3 if the residual activity was higher than MBP but not higher than normal liver activity, DS4 if the residual activity was higher than liver activity (and SUVmax ≤ 2 SUVmax of the liver) and DS5 if the residual activity was markedly higher than the liver activity (SUVmax of the lesion > 2xSUVmax liver) or if there were new lesions attributable to lymphoma.

Statistics

The concordance between pairs of reviewers with respect to binary reporting for PET positivity was measured with Cohen's kappa [18] for the 15 combinations of the six reviewers. K-values of 0.21–0.40, 0.41–0.60, 0.61–0.80 and 0.81–1.0 indicate fair, moderate, good and very good agreement, respectively. The overall concordance between reviewers concerning binary (positive vs. negative) and discrete reporting was measured using Krippendorf's alpha [19]. The percentages of overall agreement (OA), positive agreement (PA) and negative agreement (NA) were calculated as the ratio of the number of concordant cases plus half of the number of discordant cases divided by the number of cases. PFS was the primary endpoint, whereas OS was a secondary endpoint, and both were calculated according to Cheson et al. [20] from the date of treatment start; the distribution of time-to-event functions was estimated by using the Kaplan–Meier product limit method, with 95% confidence interval (95%CI). Continuous variables are reported as median, range and interquartile range (IQR); categorical variables are reported as absolute and percentage frequencies for the total number of cases; the comparisons of categorical variables between two or more groups were performed using Fisher's exact test or Chi2 test, when appropriate. The comparison of survival functions between two or more groups was performed using the log-rank test and the effect of covariates was estimated by the Cox proportional hazard regression model and reported as hazard ratio (HR) with 95%CI. Proportional risk was checked graphically by scaled Shoenfeld residuals. The cumulative risk of transformation of follicular lymphoma was calculated from the EOI by the Nelson-Aalen estimator, with 95%CI [21].

Results

Overall, 807 follicular lymphoma patients (52% females, 89% stage III-IV disease, 40% with a high-risk FLIPI-2 score [3–5]) were enrolled in the study; 744/807 patients completed the induction therapy and underwent a EOI PET scan. The scans of 729/744 (98%) patients was uploaded for centralized review, while for the remaining 15/744 (2%) patients, EOI PET images were not available at the local recruiting centre for upload as they had been performed at other institutions. Table 1 reports the main characteristics of the study population. According to centralized review process, EOI PET was positive (DS4–5) in 88/729 (12.1%); specifically, DS was 1, 2, 3, 4 and 5 in 361 (49.5%), 168 (23.1%), 112 (15.4%), 49 (6.7%) and 39 (5.3%) patients, respectively. The overall agreement among the reviewers on PET positivity/negativity was 0.92, while agreement on

Table 1 Main clinical characteristics of the patients enrolled in the FOLL12 trial. ULN: upper limit of normal; LodLIN: longest diameter of the largest involved node; FLIPI-2: follicular lymphoma prognostic index-2; R-CHOP: rituximab-cyclophosphamide-doxorubicin-vincristine; R-B: rituximab-bendamustine; LDH: Lactate dehydrogenase (LDH values available in 710 pts)

Factor	n (%)
Age > 60 y	358 (49)
Sex, female	381 (52)
Stage III/IV	647 (89)
Bone marrow involvement	407 (56)
Beta-2 microglobulin > ULN	391 (54)
LodLIN	407 (56)
Haemoglobin < 12 g/dL	110 (15)
LDH > ULN	154 (22)
FLIPI-2 score 3/5	289 (40)
Induction therapy	
R-CHOP	423 (58)
R-B	306 (42)
Maintenance, yes	371 (51)
Deauville score	
1	361 (50)
2	168 (23)
3	112 (15)
4	49 (7)
5	39 (5)
Deauville score grouped into 3:	
1–2	529 (73)
3	112 (15)
4–5	88 (12)
Deauville score grouped into 2:	
1–3	641 (88)
4–5	88 (12)

positive and negative cases was 0.77 and 0.94, respectively. The concordance agreement among all the reviewers on any of the DS values, measured with Krippendorf's alpha, was 0.30. Moreover, the Fleiss' kappa agreement for positivity, with threshold at DS3 (DS 1–2 neg) and DS4 (DS 1–3 neg), was 0.47 (moderate agreement) and 0.62 (good agreement), respectively.

The median follow-up was 69 months (range 1–112 months, in 2022 December), with 247 events registered in the first five years and with a 5-year PFS of 67% (95%CI 63%-70%). The Kaplan–Meier analysis and the relative HR for each DS were evaluated as reported in Fig. 1. According to PET results, the 5-yr PFS rate for PET-negative (DS1–3) and PET-positive (DS4–5) patients was 71% (95%CI: 67%-75%) and 36% (95%CI: 25%-46%), respectively, with HR 3.49 (95%CI: 2.57–4.72). The Kaplan–Meier analysis for PFS for each of the DS (Fig. 1) demonstrates no difference in PFS between DS1 and DS2, whereas there is a worsening for the DS values from 3 to 5. Therefore, dividing the whole population into three groups, the 5-yrs PFS in DS1–2, DS3 and DS4–5 was 74% (95%CI 70%-78%), 58% (95%CI 48%-67%; HR 1.71; p = 0.001) and 36% (25%-46%;

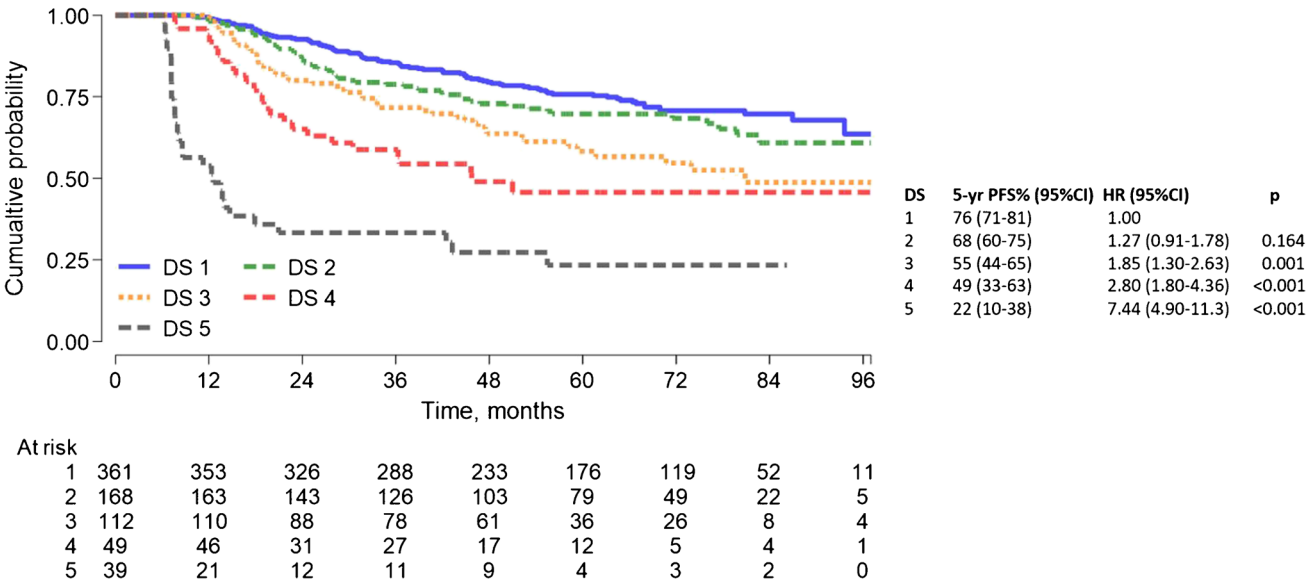

Fig. 1 Kaplan–Meier analysis for PFS and HR for each of the DS in the whole population of 729 pts enrolled in the FOLL12 trial

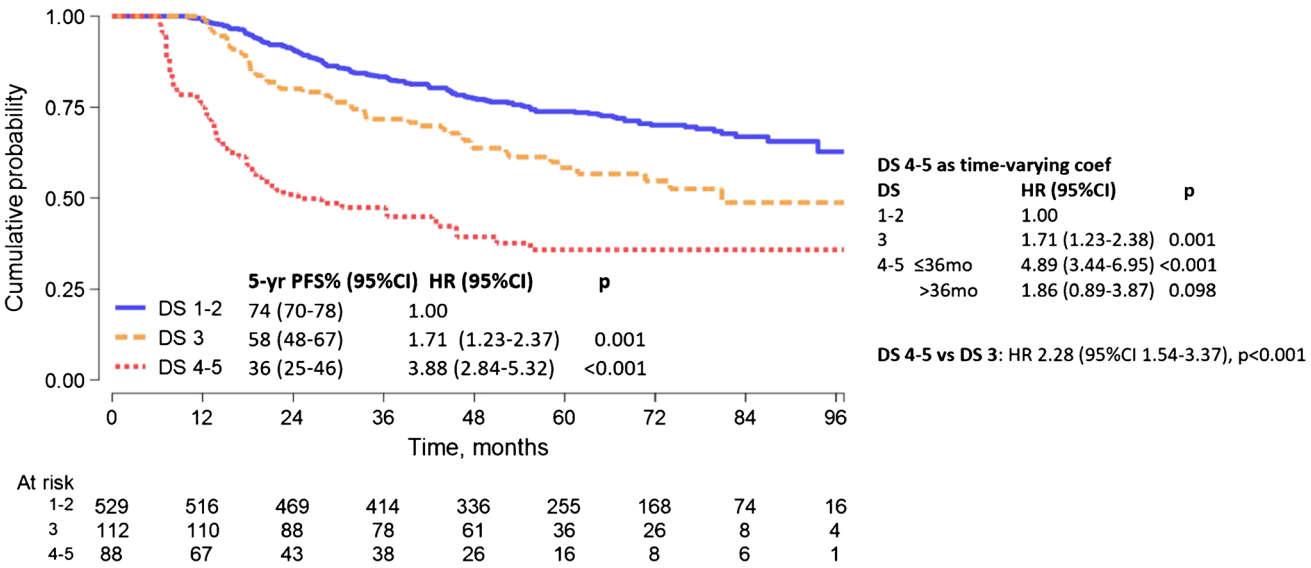

Fig. 2 Kaplan–Meier analysis for PFS and HR according to DS1–2, DS3 and DS 4–5. For DS4–5, HR was also assessed before and after a fixed time point of 36 months of follow-up; DS3 and DS4–5 were also directly compared

HR 3.88; p < 0.001), as reported in Fig. 2. Moreover, HR for DS4–5 maintained its statistical significance only in the first 36 months of follow-up, tending to approach that of DS1–2 afterwards.

To confirm that initial therapy was not a confounder for this analysis, the PFS in patients treated with R-CHOP and R-B therapy was assessed. The 5-yr PFS for R-CHOP and for R-B was 66% (95%CI 61%-70%) and 69% (95%CI 63%-74%, p = 0.833), respectively, with no statistically significant differences even when PSF was expressed as a function of DS group (i.e., DS1–2, DS3 and DS4–5).

PFS analysis was also performed for patients in the standard (374 patients) and the experimental arms (353 patients) of the study. The Kaplan–Meier curves (Fig. 3) show that EOI PET maintained its prognostic value in both arms, confirming the DS3 value as an intermediate risk factor of events in both arms.

Regarding OS, 55 deaths were reported during the follow-up, resulting in a 5-yr OS of 94% (95%CI: 92%-96%), with 96% (95%CI: 94–97) and 82% (95%CI: 72%-89%) in EOI PET-negative and -positive cases, respectively (HR 4.48; p < 0.001) (Fig. 4), with no difference between DS1–2 and DS3 patients. An OS analysis associating DS with FLIPI-2 (Fig. 5) showed that patients with DS3 or DS1–2 with high FLIPI-2 score (3–5) experienced worse OS than did patients with DS1–2 and a low FLIPI-2 score (1–2) (p = 0.003). No statistical difference in terms of PFS or OS was found when comparing low vs high FLIPI-2 in the DS4–5 population.

The ability of EOI metabolic response to predict PFS events at the fixed time point was also tested. Overall, 113 patients experienced a PFS event within the first 24 months of follow-up, including 110 progressions of disease and three deaths in patients without progression. The accuracy of EOI PET in predicting PFS events within 24 months (Table 2) and OS within 48 months (Table 3) was 84.1% and 87.7%, respectively. The risk of transformation into an aggressive lymphoma according to DS was also evaluated. The number of FL transforming into aggressive disease in DS1–2, DS3 and DS4–5 was 10/529 (1.9%), 5/112 (4.5%) and 12/88 (13.6%), respectively (Fig. 6), with a statistically significant increased risk of histological transformation in DS4–5 patients.

Finally, the POD24 was evaluated and correlated to DS (Table 4). A logistic regression analysis showed that there was a close association between the DS value and POD24. Moreover, POD24 (HR 3.04 (95%CI 1.72–5.34), z-score 3.85, p < 0.001, c-Harrell 0.63) and DS4–5 (HR 4.91 (95%CI 2.49–8.64), z-score 5.51, p < 0.001, c-Harrell 0.67) were both correlated with a statistically significant increased risk of death. However, in the Cox analysis, DS4–5 (HR 3.24, 95%CI 1.70–6.18, p < 0.001) was more powerful than POD24 (HR 1.89, 95%CI 0.99–1.59, p = 0.052) in predicting OS.

Discussion

The present study aimed to evaluate the reliability of the DS and the prognostic role of EOI PET after chemo-immunotherapy in patients with high tumor burden follicular lymphoma prospectively enrolled in the FOLL12 trial of Fondazione Italiana Linfomi (FIL). To the best of our

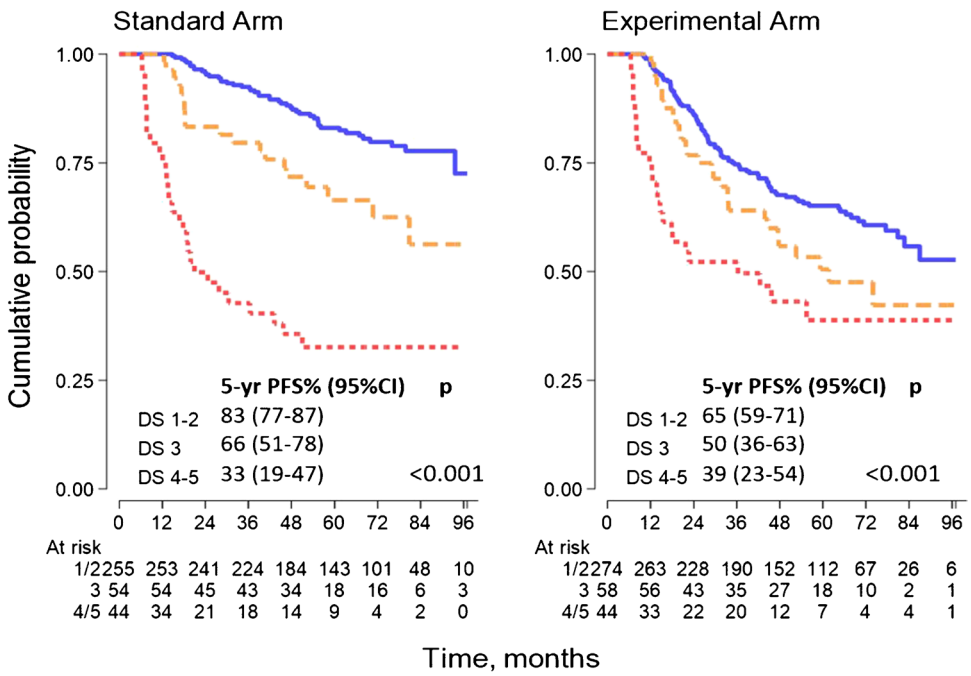

Fig. 3 Kaplan–Meier analysis for PFS in standard and experimental arms of the FOLL12 trial patients according to DS1–2, DS3 and DS4–5

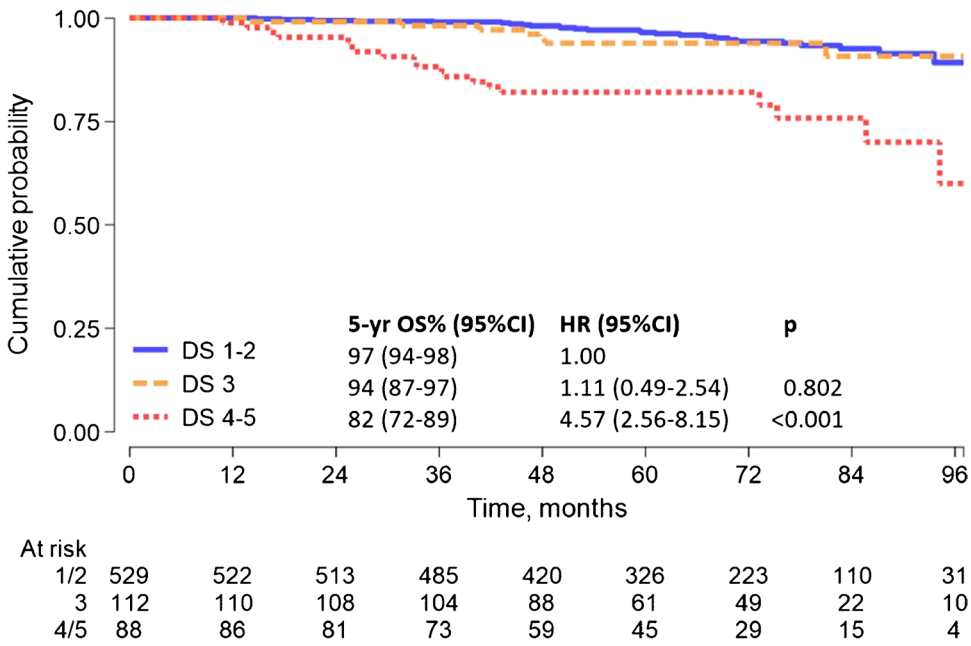

Fig. 4 Kaplan–Meier analysis for OS in DS1–2, DS3 and DS4–5 in the whole population of the FOLL12 trial (n = 729)

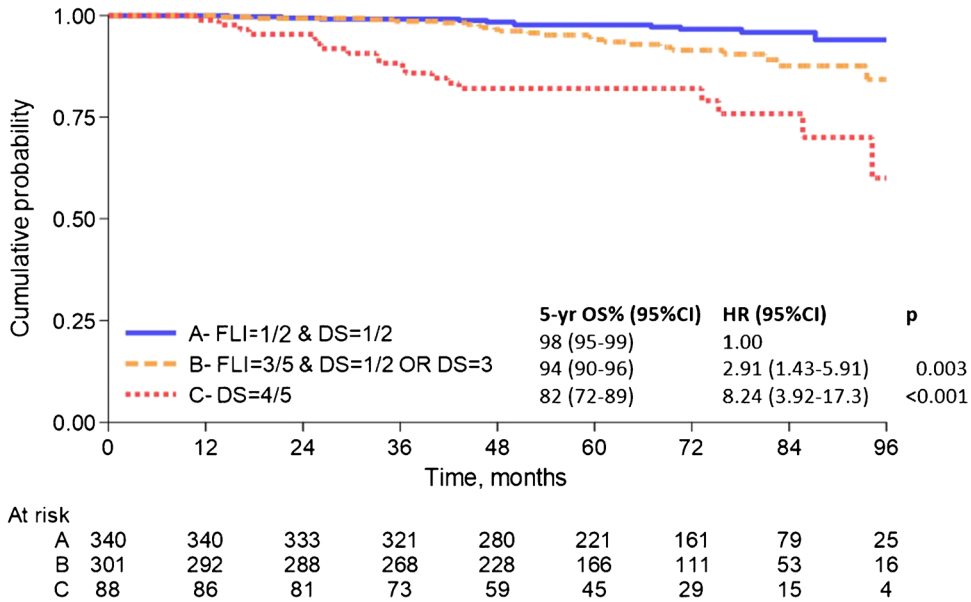

Fig. 5 Kaplan–Meier analysis for OS according to the combination of DS and FLIPI-2 in the whole population (n = 729)

knowledge, this is the first multicentre PET-oriented study that prospectively evaluates the role of EOI PET in follicular lymphoma in a large population of patients. Our results confirm that DS can easily and reliably be used for EOI response assessment, as confirmed by its good accuracy in predicting PFS (84.1%) and OS (87.7%) events, with overall very good inter-reviewer agreement (0.92) as well as good agreement on PET-positive (0.77) and PET-negative (0.94) assessment.

Regarding the prognostic value of EOI PET, our data confirm that EOI PET-positive patients have a worse prognosis compared to EOI PET-negative patients, with a 5-yr PFS of 36% and 71%, respectively, and with three times higher risk of events (HR 3.49; $p < 0.001$). These results align with those already published in previous studies on follicular lymphoma [8, 10, 11, 22]; however, the added value of the present study lies in its design (PET-oriented, prospective, multicentre), in the centralized review of all PET scans according to standardized reading criteria (i.e., Deauville criteria) in a vast patient population, the largest among all the cited studies.

Our data show that any DS higher than DS2 was independently correlated with PFS (Fig. 1). Moreover, the 5-yr PFS of DS3 patients (i.e., CMR patients) was 58% (HR 1.71; $p = 0.001$), significantly lower than that of patients

Table 2 Confusion matrix for PFS events within the first 24 months of follow-up (113 events): PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve-Receiver Operating Characteristic

True status	Predicted status DS 4–5		Total
	Fail	**Not Fail**	
Fail	43	70	113
Not fail	43	557	600
Sensitivity	38.0%		
Specificity	92.8%		
PPV	50.0%		
NPV	88.8%		
Accuracy	84.1%		
AUC-ROC	65.4%		

Table 3 Confusion matrix for OS events within the first 48 months of follow-up (29 events): PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve-Receiver Operating Characteristic

True status	Predicted status DS 4–5		Total
	Fail	**Not Fail**	
Fail	15	14	29
Not fail	59	508	567
Sensitivity	51.7%		
Specificity	89.6%		
PPV	20.3%		
NPV	97.3%		
Accuracy	87.7%		
AUC-ROC	70.7%		

with DS1–2 (74%) (Fig. 2). Although the number of DS3 patients (n = 112) was still too small to consider DS3 a different response category from CMR, these data may suggest to the clinicians that they manage the follow-up of DS3 patients more prudently than that of DS1–2 patients.

It is important to note that the FOLL12 trial demonstrated that in patients with CMR at EOI PET, the rituximab-based maintenance therapy (standard arm) was better in terms of PFS than the PET/MRD-based approach (experimental arm), whereas this finding was not confirmed in non-CMR patients [13]. In particular, patients with DS1–2 in the experimental arm showed a worse PFS compared with those with the same DS in the standard arm (HR 2.36, 95%CI 1.67–3.35, $p < 0.001$); the detrimental effect was less pronounced in DS3 (HR 1.64, 95%CI 0.92–2.94, $p = 0.097$), and no difference was found in DS 4–5 in both arms (HR 0.85, 95%CI 0.50–1.45, $p = 0.552$).

In this secondary analysis, EOI PET maintained the prognostic value both in the standard and the experimental arms of the trial, confirming the reliability of metabolic response to stratify prognosis in FL patients (Fig. 3). Moreover, similarly to the data in the whole population, DS3 correlated with an intermediate risk of events in terms of PFS in both the standard and the experimental arms.

As previously described, while the type of induction therapy (R-CHOP vs R-B) was at the discretion of the local centre, the choice did not influence the prognosis of the patients, as demonstrated by Nizzoli et al. [23]. Accordingly, EOI PET showed similar PFS values in patients undergoing R-CHOP or R-B regimen. These data may suggest the use of metabolic imaging in prospective studies to evaluate new therapeutic approaches in follicular lymphoma patients; however, as new treatments are developed and refined, the metabolic landscape of follicular lymphoma may change, potentially impacting the value of EOI PET

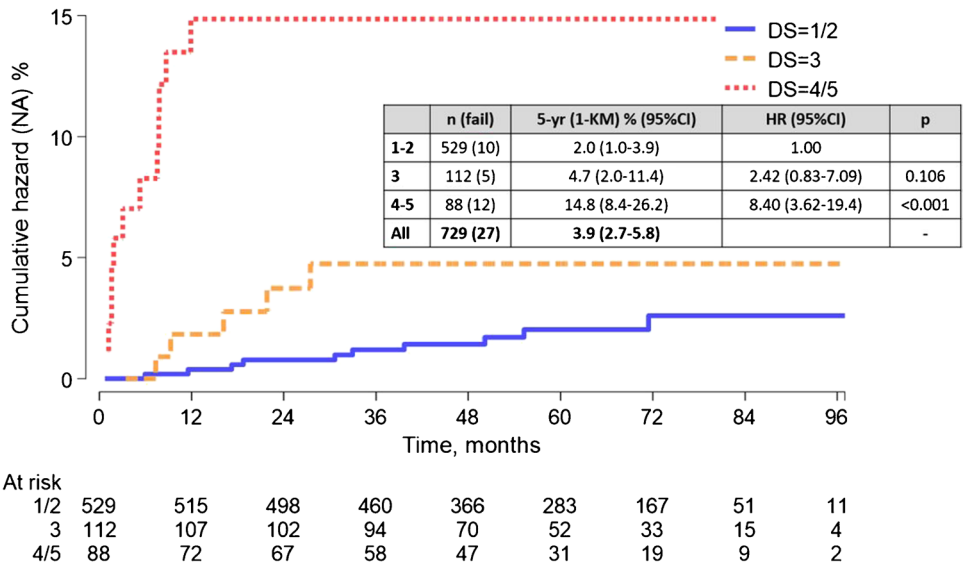

Fig. 6 Nelson-Aalen estimator analysis for histological transformation according to DS patient group

Table 4 Logistic regression analysis correlating DS and POD 24 in the whole population. AUC-ROC 0.735; Linear trend $p < 0.001$

DS	% POD24	OR	95%CI	p
1	7	1		
2	13	2.07	1.12–3.82	0.019
3	19	3.19	1.70–6.00	< 0.001
4	35	7.33	3.56–15.1	< 0.001
5	68	29.00	13.0–64.5	< 0.001

scans in predicting patient outcomes. Another interesting point emerged from the analysis of DS4–5 patients. According to the Kaplan–Meier analysis for PSF (Fig. 2), the risk of events in DS4–5 patients increased significantly in the first 36 months (HR 4.89; $p < 0.001$), then tended to become similar to DS1–2 after that (HR 1.86; $p = 0.098$). In our opinion, these data mimic the prognostic value of POD24, recently validated by Casulo et al. [24], with the advantage that DS4–5 is defined at the end of induction treatment and can consequently anticipate the POD24 information. Indeed, our data demonstrate a close correlation between DS and POD24, with a progressive risk of events for higher DS values, which becomes particularly relevant in DS4–5. Moreover, in the Cox analysis evaluating the correlation between POD24 and DS4–5 and OS, DS4–5 seemed to perform better.

Regarding survival in the whole cohort, the 5-yr OS in EOI PET-negative and EOI PET-positive patients was 96% (95%CI: 94–97%) and 82% (95%CI: 72–89%), respectively, with an HR of 4.48 (95%CI: 2.57–7.81; $p < 0.001$) (Fig. 4), a result very close to that of the GALLIUM study [11]. Differently from the PFS data, DS3 patients did not have a higher risk of death compared to DS1–2 patients, neither when considering the whole population, nor the two arms of the trial. However, by combining FLIPI2 with DS, we identified a new category of patients (DS3 together with DS1–2 with high FLIPI-2) with an intermediate risk of survival (Fig. 5). This finding, although of interest, needs to be explored in a larger cohort of patients, as FLIPI-2 is influenced by various factors, including patient age.

An important issue in FL is the risk of histological transformation into aggressive lymphoma, which is usually correlated with a worse prognosis. Federico M. et al. [25] showed that less than 4% of FL patients treated with rituximab in induction and as maintenance experienced histological transformation at 10 years; this result is very similar to the cumulative incidence of histological transformation in the FOLL12 population (3.9%). Predictive factors of transformation have been previously investigated, such as maximum standardized uptake value (SUVmax), but with contradictory results [26–29]. We found that DS4–5 patients' transformation risk was about 8 times higher than that of patients with DS1–2, with a higher value in the first 12 months (Fig. 6). In their retrospective analysis of the Aristotele consortium database, Alonso-Alvarez S. et al. [30] demonstrated that the cumulative incidence of histological transformation in FL is higher (7.1%) in patients not achieving a CT-based complete response, and it is much higher (34%) in primary refractory FL. Although there are substantial differences between the Aristotele database and the FOLL12 study population, particularly in terms of response assessment, the data of the FOLL12 trial indicate the potential predictive role of EOI PET for histological transformation; this information could help clinicians to better manage patients during follow-up, as EOI PET results are readily available and can help to better predict histological transformation versus relapse of follicular lymphoma.

Currently, there is much interest in investigating other prognosticators in lymphoma patients. It has recently been shown that baseline total metabolic tumor volume (TMTV) calculated from FDG PET/CT is a promising prognostic biomarker in various types of lymphoma, including FL [31, 32], but its value is still not completely clear. In this context, the FOLL12 trial provides an opportunity to investigate the other quantitative prognostic parameters (TMTV, SUV, deltaSUV) in a well-defined, homogeneous, prospectively enrolled patient population with follicular lymphoma.

Limitations of the study

While our study provides valuable insights into the reliability and prognostic role of EOI PET in patients with high tumor burden follicular lymphoma, some limitations should be pointed out. First, the FOLL12 trial included only patients with advanced-stage FL. Therefore, our results may not apply to patients with low tumor burden. Secondly, although the inter-reviewer agreement was very good when categorizing patients as PET-negative or PET-positive, there was a weaker consensus when considering the specific Deauville score (DS) values. However, it is important to note that the weaker agreement derived primarily from variations in DS1 and DS2, which is not of significant concern for the aims of this study, whereas the reliability of DS3 and DS4 was validated by Fleiss kappa analysis. Finally, although a statistically significant increase in the risk of histological transformation in patients with DS4–5 has been highlighted, this observation is based on preliminary data that need to be validated in a larger, more focused population.

Conclusions

The present study confirms the reliability and the prognostic value of EOI PET in advanced stage high tumor burden follicular lymphoma in a prospective PET-oriented

multicentre trial. Prognostic value was maintained both in the standard and the experimental arms, making metabolic imaging a robust tool to assess response in FL. Moreover, although preliminary, this study provides further information on DS3 patients (CMR), who appear to have a less favourable prognosis than do DS1–2 patients. Finally, DS could assume an important role in predicting POD24 and histological transformation into aggressive lymphomas; these data, however, need to be validated in a larger population.

Authors contributions Concept and design of the study: Luca Guerra, Stephane Chauvie, Stefano Luminari, Annibale Versari.

Provision of study materials and PET images: Marco Ladetto, Gerardo Musuraca, Patrizia Tosi, Benedetta Bianchi, Silvia Anna Maria Bolis, Lavinia Monaco, Vincenzo Pavone, Annalisa Chiarenza, Annalisa Arcari, Catello Califano, Alessia Bari, Massimo Massaia, Annarita Conconi, Pellegrino Musto, Donato Mannina, Giovanni Roti, Sara Galimberti, Guido Gini, Flavio Falcinelli, Umberto Vitolo, Sara Valentina Usai, Piero Maria Stefani, Adalberto Ibatici, Anna Marina Liberati, Elsa Pennese, Tommaso Perrone.

Collection and assembly of data: Stefano Luminari, Luca Guerra, Stephane Chauvie, Rexhep Durmo, Fabrizio Bergesio, Federico Fallanca, Lavinia Monaco, Emiliano Barbieri, Simona Peano, Antonella Franceschetto, Luigi Marcheselli, Annibale Versari,

Data analysis and interpretation: Luigi Marcheselli, Luca Guerra, Stephane Chauvie, Stefano Luminari, Annibale Versari, Fabrizio Bergesio.

First manuscript writing: Luca Guerra and Stephane Chauvie contributed equally.

Manuscript revision and discussion: Luca Guerra, Stephane Chauvie, Rexhep Durmo, Stefano Luminari, Annibale Versari, Luigi Marcheselli.

Final approval of the manuscript: all authors.

Funding This study was supported by: Società Italiana di Ematologia (SIE); Associazione Angela Serra per la Ricerca sul Cancro; Ministero della Salute (Direzione Generale della ricerca e dell'Innovazione in sanità), Bando Progetti di Ricerca Giovani Ricercatori — Ricerca Finalizzata 2011–2012.

Data availability Individual participant data that underlie the results reported in this article, after de-identification, can be made available to investigators for research purposes on a case-by-case basis following the time of this publication and by the Fondazione Italiana Linfomi (https://filinf.it/) Data Sharing Policy.

Declarations

Competing interests The authors have no conflicts of interest to disclose related to the subjects, matter or materials discussed in this manuscript.

Ethics approval The FOLL12 trial (NCT02063685; https://classic.clinicaltrials.gov/ct2/show/NCT02063685) is a multicentric clinical trial and it was approved by the institutional review boards at each participating centre. This study involved humans and was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines.

Consent to participate Informed consent was obtained from all individual participants before the enrolment in the study.

Consent to publish Not applicable: the paper does not contain individual person's data in any form.

References

1. Freedman A. Follicular lymphoma: 2012 update on diagnosis and management. Am J Hematol. 2012;87:988–95.
2. Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A, Raposo JC, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol. 2008;26:4579–86.
3. Salles G, Seymour JF, Offner F, López-Guillermo A, Belada D, Xerri L, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet. 2011;377:42–51.
4. Salles G, Mounier N, de Guibert S, Morschhauser F, Doyen C, Rossi J-F, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. Blood. 2008;112:4824–31.
5. Casulo C, Nastoupil L, Fowler NH, Friedberg JW, Flowers CR. Unmet needs in the first-line treatment of follicular lymphoma. Ann Oncol. 2017;28:2094–106.
6. Federico M, Vitolo U, Zinzani PL, Chisesi T, Clò V, Bellesi G, et al. Prognosis of follicular lymphoma: a predictive model based on a retrospective analysis of 987 cases. Intergruppo Italiano Linfomi Blood. 2000;95:783–9.
7. Ladetto M, De Marco F, Benedetti F, Vitolo U, Patti C, Rambaldi A, et al. Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. Blood. 2008;111:4004–13.
8. Trotman J, Fournier M, Lamy T, Seymour JF, Sonet A, Janikova A, et al. 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;29:3194–200.
9. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059–68.
10. Luminari S, Biasoli I, Versari A, Rattotti S, Bottelli C, Rusconi C, et al. The prognostic role of post-induction FDG-PET in patients with follicular lymphoma: a subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi (FIL). Ann Oncol. 2014;25:442–7.
11. Trotman J, Barrington SF, Belada D, Meignan M, MacEwan R, Owen C, et al. Prognostic value of end-of-induction PET response after first-line immunochemotherapy for follicular lymphoma (GALLIUM): secondary analysis of a randomised, phase 3 trial. Lancet Oncol. 2018;19:1530–42.
12. Trotman J, Luminari S, Boussetta S, Versari A, Dupuis J, Tychyj C, et al. Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. Lancet Haematol. 2014;1:e17-27.
13. Luminari S, Manni M, Galimberti S, Versari A, Tucci A, Boccomini C, et al. Response-adapted postinduction strategy in patients with advanced-stage follicular lymphoma: the FOLL12 study. J Clin Oncol. 2021;40:729–39.

14 Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müeller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014;32:3048–58.
15. Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8–9 April 2010. Leuk Lymphoma. 2010;51:2171–80.
16. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–90.
17. Chauvie S, Bergesio F. The strategies to homogenize PET/CT metrics: the case of onco-haematological clinical trials. Biomedicines. 2016;15;4(4):26.
18. Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Meas. 1960;20:37–46.
19. Hayes AF, Krippendorff K. Answering the call for a standard reliability measure for coding data. Commun Methods Meas. 2007;1:77–89.
20. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579–86.
21. Aalen O. Nonparametric inference for a family of counting processes. Ann Stat. 1978;6:701–26.
22. Dupuis J, Berriolo-Riedinger A, Julian A, Brice P, Tychyj-Pinel C, Tilly H, et al. Impact of [(18)F]fluorodeoxyglucose positron emission tomography response evaluation in patients with high-tumor burden follicular lymphoma treated with immunochemotherapy: a prospective study from the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. J Clin Oncol. 2012;30:4317–22.
23. Nizzoli ME, Manni M, Ghiggi C, Pulsoni A, Musuraca G, Merli M, et al. Impact of immunochemotherapy with R-bendamustine or R-CHOP for treatment naïve advanced-stage follicular lymphoma: A subset analysis of the FOLL12 trial by Fondazione Italiana Linfomi. Hematol Oncol. 2023;41:655–62.
24. Casulo C, Dixon JG, Le-Rademacher J, Hoster E, Hochster HS, Hiddemann W, et al. Validation of POD24 as a robust early clinical end point of poor survival in FL from 5225 patients on 13 clinical trials. Blood. 2022;139:1684–93.
25. Federico M, Caballero Barrigón MD, Marcheselli L, Tarantino V, Manni M, Sarkozy C, et al. Rituximab and the risk of transformation of follicular lymphoma: a retrospective pooled analysis. Lancet Haematol. 2018;5:e359–67.
26. Noy A, Schöder H, Gönen M, Weissler M, Ertelt K, Cohler C, et al. 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;20:508–12.
27. Wondergem MJ, Rizvi SNF, Jauw Y, Hoekstra OS, Hoetjes N, van de Ven PM, et al. 18F-FDG or 3'-deoxy-3'-18F-fluorothymidine to detect transformation of follicular lymphoma. J Nucl Med. 2015;56:216–21.
28. Karam M, Feustel PJ, Vera CD, Nazeer T. Features of large cell transformation of indolent lymphomas as observed on sequential PET/CT. Nucl Med Commun. 2011;32:177–85.
29. Mir F, Barrington SF, Brown H, Nielsen T, Sahin D, Meignan M, et al. Baseline SUVmax did not predict histological transformation in follicular lymphoma in the phase 3 GALLIUM study. Blood. 2020;135:1214–8.
30. Alonso-Álvarez S, Manni M, Montoto S, Sarkozy C, Morschhauser F, Wondergem MJ, et al. Primary refractory follicular lymphoma: a poor outcome entity with high risk of transformation to aggressive B cell lymphoma. Eur J Cancer. 2021;157:132–9.
31. Cottereau AS, Rebaud L, Trotman J, Feugier P, Nastoupil LJ, Bachy E, Flinn IW, Haioun C, Ysebaert L, Bartlett NL, Tilly H, Casasnovas O, Ricci R, Portugues C, Buvat I, Meignan M, Morschhauser F. Metabolic tumor volume predicts outcome in patients with advanced stage follicular lymphoma from the RELEVANCE trial. Ann Oncol. 2024;35:130–7.
32. Meignan M, Cottereau AS, Versari A, Chartier L, Dupuis J, Boussetta S, et al. Baseline Metabolic Tumor Volume Predicts Outcome in High–Tumor-Burden Follicular Lymphoma: A Pooled Analysis of Three Multicenter Studies. J Clin Oncol. 2016;34:3618–26.

Authors and Affiliations

Luca Guerra[1,2] · Stephane Chauvie[3] · Federico Fallanca[4] · Fabrizio Bergesio[3] · Luigi Marcheselli[5] · Rexhep Durmo[6] · Simona Peano[7] · Antonella Franceschetto[8] · Lavinia Monaco[1] · Emiliano Barbieri[9] · Marco Ladetto[10] · Gerardo Musuraca[11] · Patrizia Tosi[12] · Benedetta Bianchi[13] · Silvia Anna Maria Bolis[14] · Vincenzo Pavone[15] · Annalisa Chiarenza[16] · Annalisa Arcari[17] · Catello Califano[18] · Alessia Bari[19] · Massimo Massaia[20] · Annarita Conconi[21] · Pellegrino Musto[22] · Donato Mannina[23] · Giovanni Roti[24] · Sara Galimberti[25] · Guido Gini[26] · Flavio Falcinelli[27] · Umberto Vitolo[28] · Sara Veronica Usai[29] · Piero Maria Stefani[30] · Adalberto Ibatici[31] · Anna Marina Liberati[32] · Elsa Pennese[33] · Tommasina Perrone[34] · Annibale Versari[6] · Stefano Luminari[35,36] · on behalf of Fondazione Italiana Linfomi (FIL)

✉ Luca Guerra
luca.guerra@unimib.it

[1] Nuclear Medicine, Fondazione IRCCS San Gerardo Dei Tintori, Monza, Italy

[2] University of Milano Bicocca, Milan, Italy

[3] Medical Physics, Ospedale Santa Croce E Carle, Cuneo, Italy

[4] Nuclear Medicine, IRCCS Ospedale San Raffaele, Milan, Italy

[5] Fondazione Italiana Linfomi, Modena, Italy

[6] Nuclear Medicine, Azienda USL–IRCCS di Reggio Emilia, Reggio Emilia, Italy

[7] Nuclear Medicine Azienda Ospedaliera S. Croce E Carle, Cuneo, Italy

[8] Nuclear Medicine, Azienda Ospedaliero-Universitaria Di Modena, Modena, Italy

[9] Clinical and Experimental Medicine PhD Program, University of Modena E Reggio Emilia, Modena, Italy

[10] Hematology Unit, Azienda Ospedaliera Di Alessandria, Alessandria, Italy

[11] Hematology and HSC Transplantation, IRCCS Istituto Romagnolo Per Lo Studio Dei Tumori Dino Amadori, Meldola, Italy

[12] Hematology Unit, AUSL Della Romagna, Rimini, Italy

[13] Hematology Unit, Ospedale Di Circolo E Fondazione Macchi ASST Sette Laghi, Varese, Italy

[14] Hematology Unit, Fondazione IRCCS San Gerardo Dei Tintori, Monza, Italy

[15] Hematology and Bone Marrow Transplantation, Ospedale C. Panico, Tricase, Italy

[16] Hematology and Bone Marrow Transplantation, AOU Policlinico S. Marco, Catania, Italy

[17] Hematology Unit, Ospedale Guglielmo da Saliceto, Piacenza, Italy

[18] Hematology Unit, Ospedale Andrea Tortora, Pagani, Italy

[19] Oncology Unit, Azienda Ospedaliero-Universitaria Policlinico, Modena, University of Modena and Reggio Emilia, Modena, Italy

[20] Hematology Unit, Ospedale Santa Croce E Carle, Cuneo, Italy

[21] Hematology Unit, Ospedale Degli Infermi, Biella, Italy

[22] Hematology and Stem Cells Transplantation, IRCCS CROB, Rionero in Vulture, Italy

[23] Hematology Unit, Azienda Ospedaliera Papardo, Messina, Italy

[24] Hematology Unit, Azienda Ospedaliero-Universitaria Di Parma, Parma, Italy

[25] Hematology Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

[26] Hematology Unit, Azienda Ospedaliero-Universitaria Delle Marche, Ancona, Italy

[27] Hematology and Bone Marrow Transplantation, Azienda Ospedaliera Di Perugia, Perugia, Italy

[28] Hematology Unit, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy

[29] Hematology and Bone Marrow Transplantation, Ospedale Brotzu, Cagliari, Italy

[30] Hematology Unit, General Hospital Ca' Foncello, Treviso, Italy

[31] Ematologia E Terapie Cellulari, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[32] Università Degli Studi Di Perugia, A.O. Terni, Terni, Italy

[33] Hematology Unit, ASL Pescara, Pescara, Italy

[34] Hematology and Stem Cells Transplantation, AOUC Policlinico, Bari, Italy

[35] Hematology Unit, Azienda USL–IRCCS di Reggio Emilia, Reggio Emilia, Italy

[36] Department Chimomo, Università Di Modena and Reggio Emilia, Modena, Italy