

Pre-treatment maximum standardized uptake value predicts outcome after frontline therapy in patients with advanced stage follicular lymphoma



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ABSTRACT

The impact of pre-treatment maximum standardized uptake value (SUV_{max}) on the outcome of follicular lymphoma (FL) following specific frontline regimens has not been explored. We performed a retrospective analysis of 346 patients with advanced stage follicular lymphoma (FL) without histological evidence of transformation, and analyzed the impact of SUV_{max} on outcome after frontline therapy. Fifty-two (15%) patients had a SUV_{max} >18, and a large lymph node ≥6 cm was the only factor associating with SUV_{max} >18 on multivariate analysis (odds ratio 2.7, 95% confidence interval [CI]: 1.3-5.3, *P*=0.006). The complete response rate was significantly lower among patients treated with non-anthracycline-based regimens if SUV_{max} was >18 (45% vs. 92%, *P*<0.001), but not among patients treated with R-CHOP (*P*=1). SUV_{max} >18 was associated with significantly shorter progression-free survival among patients treated with non-anthracycline-based regimens (77 months vs. not reached, *P*=0.02), but not among patients treated with R-CHOP (*P*=0.73). SUV_{max} >18 associated with shorter overall survival (OS) both in patients treated with R-CHOP (8-year OS 70% vs. 90%, *P*=0.02) and non-anthracycline-based frontline regimens (8-year OS 50% vs. 85%, *P*=0.001). In conclusion, pre-treatment PET scan has prognostic and predictive value in patients with advanced stage FL receiving frontline treatment.

Introduction

Despite its indolent biology, follicular lymphoma (FL) can be fluorodeoxyglucose (FDG) avid on positron emission tomography (PET). A wide range of inter- and intra-patient degree of FDG avidity has been reported, with a maximum standardized uptake (SUV_{max}) value ranging between 3 and 40.¹⁻⁴ PET scan is more sensitive and specific than standard computed tomography (CT) scan in identifying nodal and extra-nodal disease, altering stage assignment in 10-31% of patients with FL, and determining a treatment plan revision based on upstaging (I-II to III-IV) in 34-45% of cases.⁵⁻¹⁰ PET-based imaging is also an effective tool for early detection of FL transformation, incremental threshold of SUV_{max} values associating with increasing test specificity.¹¹⁻¹⁴ False positivity is still possible, though, and histological confirmation through tissue biopsy is recommended.^{15,16}

Despite its beneficial effect on staging reassignment and histological classification, the prognostic role of PET-based imaging at time of diagnosis remains unclear, with conflicting data published in the literature with regards to its impact on the Follicular Lymphoma International Prognostic Index (FLIPI) determination.^{6,8,17} In addition, while multiple studies have investigated the association between a post-treatment PET scan and the risk of relapse, limited data are available regarding the predictive role of pre-treatment PET data in the frontline setting.¹⁸⁻²² We provide a

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retrospective analysis of 346 patients with advanced stage FL, in whom a PET-CT scan was performed prior to initiation of therapy, and analyze the impact of SUV_{max} on the quality of response and outcomes after frontline therapy.

Methods

Patient selection

This is a retrospective analysis of patients with stage III or IV FL, grades I, II, or IIIA, receiving frontline treatment at the MD Anderson Cancer Center (MDACC) between August, 2001 and April, 2014, and who had a pre-treatment PET-CT scan performed. Patients with histological diagnosis of FL grade IIIB or concurrent diffuse large B-cell lymphoma (DLBCL) were excluded.

The clinical and laboratory features were confirmed by review of the medical records. Frontline therapy was administered according to the previously described schedule.²³⁻²⁷ The FLIPI and FLIPI-2 scores were calculated as previously described.^{28,29} Lugano classification was used to define complete response.^{30,31} The study was approved by the Institutional Review Board of the MDACC and conducted in accordance with our institutional guidelines and the principles of the Declaration of Helsinki.

PET scan and SUV_{max} threshold selection

Baseline PET-CT scans were obtained at MDACC before initiation of frontline therapy. After patients had fasted for at least 4-6 hours, blood glucose was measured and confirmed to be <140 mg/dL (<200 mg/dL for patients with diabetes) before injection of 333-407 MBq (9-11 mCi) of [¹⁸F]FDG. Emission scans were acquired at 2-3 minutes per field of view in the three-dimensional mode after a 60-minute uptake time (± 10 minutes). CT non-contrast images were acquired in helical mode with 3.75-mm slices from the skull base through the mid thigh. Commercially available iterative algorithms were used for image reconstruction. PET images were collected and transferred to commercially available software (MIMVista version 6.4.9; MIMVista Corporation, Cleveland, OH). SUV_{max} was calculated as previously described.³² All reports of pre-treatment scans and of scans performed to assess response to frontline therapy were reviewed by an oncologist with expertise in lymphoma.

Analyzing multiple single unit increments of SUV_{max} among all 346 patients included in the study, 18 showed the strongest association with progression-free survival (PFS) (hazard ratio [HR] 1.5, 95% confidence interval [CI]: 0.95-2.3, $P=0.08$), and was selected as cut-off for further analysis (*Online Supplementary Table S1*).

Statistical methods

Association with categorical variables was evaluated using χ^2 or Fisher exact tests, or the Mann-Whitney test, as appropriate, and logistic regression was used for multivariate analysis. Only factors significant (P -value <0.05) on univariate analysis were included in multivariate models. PFS was defined as the time from the start of therapy to progression of disease, death, or last follow-up (whichever occurred first). Overall survival (OS) was defined as the time from the start of therapy to death or last follow-up. PFS and OS were calculated for all patients in the study and for subgroups of patients using Kaplan-Meier estimates and were compared between subgroups using the log-rank test. Multivariable Cox regression analysis was performed to assess the associations between patient characteristics and PFS or OS. A P -value of <0.05 (two-tailed) was considered statistically significant. Statistical analyses were completed using SPSS 21.

Results

Patient baseline characteristics

Three-hundred and forty-six patients were included in the study, median SUV_{max} was 11 (range: 1.5-42), and 52 (15%) patients had a $SUV_{max} >18$. All 52 patients with $SUV_{max} >18$ had a biopsy of the most FDG-avid lymph node, and no histological evidence of transformation was observed. Baseline characteristics are shown in Table 1. On univariate analysis, factors associated with $SUV_{max} >18$ were male sex (67% vs. 52%, $P=0.05$), elevated β_2 -microglobulin (65% vs. 47%, $P=0.02$), elevated lactate dehydrogenase (LDH) (37% vs. 13%, $P<0.001$), presence of B symptoms (35% vs. 14%, $P=0.01$), and a large lymph node >6 cm (64% vs. 30%, $P<0.001$) (Table 1). On multivariate analysis, a large lymph node ≥ 6 cm was the only factor maintaining its association with $SUV_{max} >18$ (odds ratio [OR] 2.7, 95% CI: 1.3-5.3, $P=0.006$) (Table 2).

Response to frontline therapy: complete response (CR)

One-hundred and fifty-one (44%) patients were treated with frontline rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), and 195 (56%) with other therapies, including rituximab and bendamustine (BR) in 55 (16%) patients, rituximab and lenalidomide (R²) in 63 (18%), rituximab, fludarabine, mitoxantrone, and dexamethasone (R-FND) in 24 (7%), and single agent rituximab in 53 (15%) patients. Two-hundred and thirty-two (65%) patients received maintenance rituximab and 114 (33%) were observed after completion of frontline therapy. While no differences in the use of maintenance therapy were observed between the two groups (75% vs. 67%, $P=0.20$), a significantly higher proportion of patients with baseline pre-treatment $SUV_{max} >18$ were treated with R-CHOP versus non-anthracycline-based regimens (75% vs. 38%, $P<0.001$), so subsequent results were stratified by treatment arm.

Among 342 patients evaluable for response, 305 (89%) achieved CR; the CR rate was 91% for patients with $SUV_{max} <18$ and 80% for patients with $SUV_{max} >18$ ($P=0.03$). No association between SUV_{max} and CR rate was observed among patients treated with R-CHOP (89% for $SUV_{max} >18$ vs. 88% for $SUV_{max} <18$, $P=1$). However, $SUV_{max} >18$ significantly associated with a lower CR rate among patients treated with other frontline regimens (45% for $SUV_{max} >18$ vs. 92% for $SUV_{max} <18$) ($P<0.001$) (Figure 1). After excluding patients treated with single agent rituximab a trend for a lower CR rate among patients treated with other frontline regimens and $SUV_{max} >18$ was observed (80% vs. 94%, $P=0.17$); of interest, in this group, only five patients with $SUV_{max} >18$ were evaluable for response, likely limiting achievement of statistical significance.

Progression-free survival (PFS) and PFS24

After a median follow-up of 94 months (95% CI: 88-100 months), median PFS was not reached, and a trend for decreased PFS was observed in patients with baseline $SUV_{max} >18$ compared to patients with baseline <18 (114 months vs. not reached, $P=0.08$). Baseline ≥ 18 did not associate with shorter median PFS among patients treated with frontline R-CHOP (114 months vs. 144 months, $P=0.73$), but it did associate with significantly shorter PFS among patients treated with other frontline regimens (77 months vs. not reached, $P=0.02$) (Figure 2). After excluding

patients treated with single agent rituximab, a trend for shorter PFS among patients treated with other frontline regimens and baseline $SUV_{max} > 18$ was observed (77 months vs. not reached, $P=0.17$); of interest, in this group, only seven patients with baseline $SUV_{max} > 18$ were evalu-

able for survival, likely limiting achievement of statistical significance.

Use of maintenance rituximab associated with a significantly longer PFS (not reached vs. 84 months, $P<0.001$); the association between use of maintenance rituximab

Table 1. Patient baseline characteristics and association with pre-treatment maximum standardized uptake value (SUV_{max}) > 18 .

| | All patients (N=346) | Number (percentage) | | P |
|----------------------|-------------------------|-----------------------------|----------------------------|--------|
| | | $SUV_{max} < 18$ (N=294) | $SUV_{max} > 18$ (N=52) | |
| Age | | | | |
| < 60 years | 199 (57) | 168 (57) | 31 (60) | 0.76 |
| ≥ 60 years | 147 (43) | 126 (43) | 21 (40) | |
| Female | 157 (45) | 140 (48) | 17 (33) | 0.05 |
| Male | 189 (55) | 154 (52) | 35 (67) | |
| Hemoglobin | | | | |
| ≥ 12 g/dL | 286 (83) | 245 (83) | 41 (79) | 0.43 |
| < 12 g/dL | 60 (17) | 49 (17) | 11 (21) | |
| β2-microglobulin | | | | |
| ≤ ULN | 165 (51) | 148 (53) | 17 (35) | 0.02 |
| > ULN | 161 (49) | 129 (47) | 32 (65) | |
| LDH | | | | |
| ≤ ULN | 288 (84) | 255 (87) | 33 (63) | <0.001 |
| > ULN | 56 (16) | 37 (13) | 19 (37) | |
| Grade | | | | |
| 1-2 | 339 (99.5) | 288 (99) | 51 (100) | 1 |
| 3A | 3 (0.5) | 3 (1) | 0 (0) | |
| Ki-67 | | | | |
| < 40% | 173 (86) | 147 (87) | 26 (79) | 0.28 |
| ≥ 40% | 29 (14) | 22 (13) | 7 (21) | |
| Bone marrow | | | | |
| not involved | 159 (47) | 134 (46) | 25 (50) | 0.65 |
| involved | 182 (53) | 157 (54) | 25 (50) | |
| B-symptoms | | | | |
| absent | 286 (83) | 252 (86) | 34 (65) | 0.001 |
| present | 60 (17) | 42 (14) | 18 (35) | |
| Ann Arbor Stage | | | | |
| III | 102 (29) | 87 (30) | 15 (29) | 1 |
| IV | 244 (71) | 207 (70) | 37 (71) | |
| Involved nodal areas | | | | |
| < 5 | 139 (42) | 114 (40) | 25 (50) | 0.22 |
| ≥ 5 | 193 (58) | 168 (60) | 25 (50) | |
| Largest lymph node | | | | |
| < 6 cm | 179 (64) | 163 (70) | 16 (36) | <0.001 |
| ≥ 6 cm | 99 (36) | 71 (30) | 28 (64) | |
| Extra-nodal disease | | | | |
| absent | 203 (59) | 175 (60) | 28 (54) | 0.27 |
| present | 143 (41) | 119 (40) | 24 (46) | |
| FLIPI score | | | | |
| low | 67 (19) | 56 (19) | 11 (21) | 0.11 |
| Intermediate | 137 (40) | 123 (42) | 14 (27) | |
| high | 142 (41) | 115 (39) | 27 (52) | |
| FLIPI-2 score | | | | |
| low | 29 (8) | 26 (9) | 3 (6) | 0.16 |
| Intermediate | 186 (54) | 163 (55) | 23 (44) | |
| high | 131 (38) | 105 (36) | 26 (50) | |

LDH: lactate dehydrogenase; ULN: upper limit of normal; FLIPI: follicular lymphoma international prognostic index; SUV_{max} : maximum standardized uptake value.

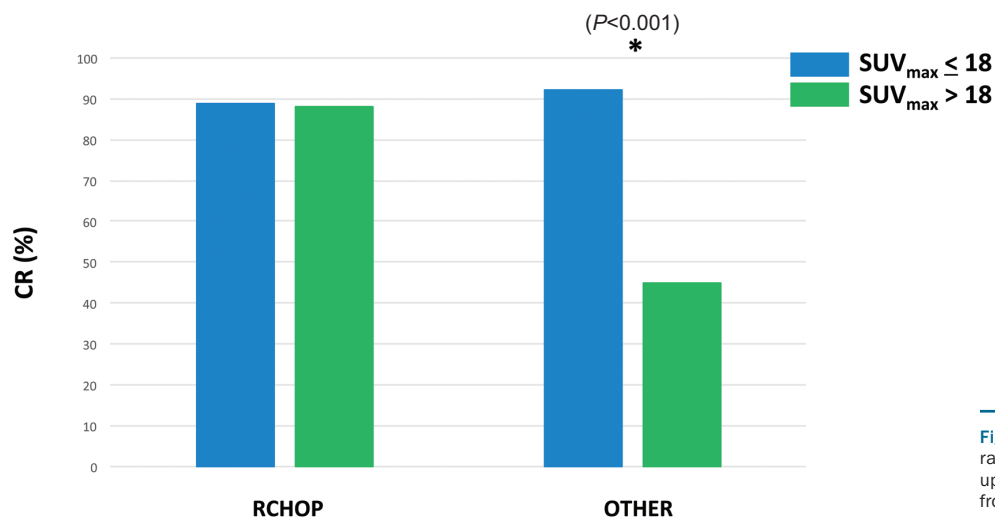


Figure 1. Complete response (CR) rates by maximum standardized uptake (SUV_{max}) values according to frontline regimens.

and prolonged PFS was maintained also after adjusting for pre-treatment SUV_{max} >18 (HR 2, 95% CI: 1.3-2.9, $P < 0.001$). Further subgroup analysis, to assess the effect of maintenance rituximab after specific regimens according to pre-treatment SUV_{max} >18 could not be performed, because of small population samples.

Excluding 11 patients who did not progress and were lost to follow-up within 24 months, 67 (20%) patients had a PFS of less than 24 months: PFS <24 months was observed in 51 (18%) patients with baseline SUV_{max} <18, and 16 (34%) of patients with baseline SUV_{max} >18 ($P = 0.02$). SUV_{max} >18 did not associate with a significantly higher rate of PFS <24 months among patients treated with R-CHOP (32% vs. 24%, $P = 0.39$), but it did associate with a higher rate of PFS <24 months among patients treated with other regimens (40% vs. 14%, $P = 0.05$). After excluding patients treated with single agent rituximab, a trend for higher PFS24 rate among patients treated with other frontline regimens and SUV_{max} >18 was observed (20% vs. 11%, $P = 0.45$); of interest, only five patients with SUV_{max} >18 were evaluable for PFS24, likely limiting achievement of statistical significance.

Overall survival (OS) and risk of transformation

After a median follow-up of 94 months (95% CI: 88-100 months), median OS has not been reached, and it was significantly shorter among patients with SUV_{max} >18 (8-year OS 65% vs. 89%, $P = 0.001$). SUV_{max} >18 associated with shorter OS both in patients treated with frontline R-CHOP (8-year OS 70% vs. 90%, $P = 0.02$) and in patients treated with other frontline regimens (8-year OS 50% vs. 85%, $P = 0.001$) (Figure 3). A trend for longer OS was observed among patients with SUV_{max} >18 when comparing treatment with frontline R-CHOP to other frontline treatments (8-year OS 70% vs. 50%, $P = 0.15$). The association between SUV_{max} >18 and OS was maintained also on multivariate analysis including either FLIPI score (HR 2.6, 95% CI: 1.5-4.6, $P = 0.001$) or FLIPI-2 score (HR 2.2, 95% CI: 1.3-3.9, $P = 0.006$).

At the most recent follow-up, 18 (5%) patients have progressed with histological evidence of transformation to large B-cell lymphoma, after a median time of 23 months (range: 5-139 months). Twelve transformations (4%) occurred among patients with baseline SUV_{max} <18, and

six (11%) among patients with baseline SUV_{max} >18 ($P = 0.04$). Of these 18 patients, 11 had received frontline R-CHOP (of whom six had baseline SUV_{max} >18) and seven other frontline regimens (none of whom had baseline SUV_{max} >18). After excluding patients treated with single agent rituximab, a statistically significant shorter OS among patients treated with other frontline regimens and SUV_{max} >18 was observed (86 months vs. not reached, $P = 0.05$).

Discussion

Recent guidelines recommend the use of PET-CT in FL for initial staging, evaluation of potential transformation, and at time of response assessment.^{31,33} However, the impact of baseline PET-based imaging on the outcome following specific frontline treatment has not been previously explored.

In our analysis, an SUV_{max} cut-off of 18 was identified as clinically significant, showing the strongest association with PFS. SUV_{max} cut-offs of 10, 14 and 17 have been proposed in previous retrospective studies to identify patients with FL at higher risk of transformation to DLBCL,^{11,12,14} with OR for transformation of 1.25 for each increase in unit of SUV_{max}.¹⁰ To this regard, patients with histological evidence of FL grade IIIB or DLBCL were excluded from this study. Although tumor heterogeneity may have caused a false-negative result, elevated SUV_{max} in the absence of histological evidence of transformation may reflect a more aggressive biology, associating with a worse outcome, as already shown in other forms of low grade B-cell lymphomas.³⁴ It is interesting to note that in our study the only factor significantly associated with SUV_{max} >18 was the lymph node size ≥ 6 cm and that more transformations occurred in patients with pre-treatment SUV_{max} >18 (11% vs. 4%, $P = 0.04$). While a core needle biopsy of a large lymph node may miss a diagnosis of DLBCL, the large tumor size may also simply be a surrogate marker of accelerated biology in the absence of transformation. Prospective studies, employing excisional biopsy, as opposed to core biopsy, may shed light on this question.

In our study, patients with SUV_{max} >18 were more frequently treated with R-CHOP, compared to other thera-

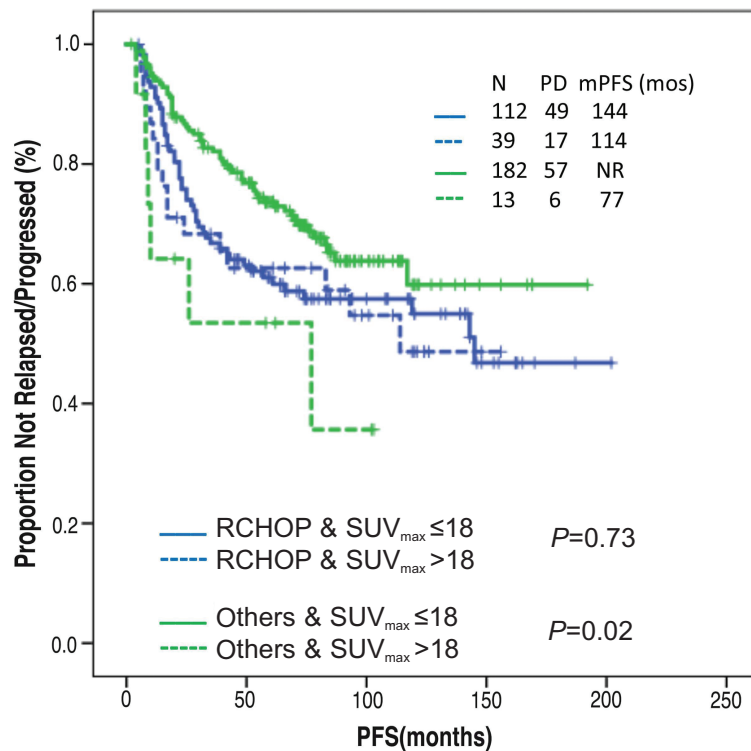


Figure 2. Association between progression-free survival (PFS) and maximum standardized uptake (SUV_{max}) separated by frontline treatment arm.

Table 2. Multivariate analysis of baseline characteristics associated with pre-treatment maximum standardized uptake value (SUV_{max}) >18

| | Total (N=263) | Number (percentage) OR [95% CI] | P-multi |
|--------------------|---------------|------------------------------------|---------|
| Female | 123 | 1.9 [0.9-3.8] | 0.08 |
| Male | 140 | | |
| β2-microglobulin | | | |
| ≤ ULN | 135 | 1.3 [0.6-2.7] | 0.56 |
| > ULN | 128 | | |
| LDH | | | |
| ≤ ULN | 218 | 2 [0.9-4.1] | 0.08 |
| > ULN | 45 | | |
| B-symptoms | | | |
| absent | 214 | | |
| present | 49 | 1.5 [0.7-3.1] | 0.26 |
| Largest lymph node | | | |
| < 6 cm | 169 | 2.7 [1.3-5.3] | 0.006 |
| ≥ 6 cm | 94 | | |

Overall, 263 of 346 patients had no missing values for all five variables, and were included in the model: 42 with SUV_{max} >18 and 221 with SUV_{max} ≤18. LDH: lactate dehydrogenase; ULN: upper limit of normal; SUV_{max}: maximum standardized uptake value.

pies (including BR, R-FND, R² and single agent rituximab). Abou-Nassar et al. had previously reported similar findings, likely reflecting the treating physician's concern for occult transformation, and subsequent need for anthracycline-based therapy.¹⁷ We acknowledge as a potential bias of our study that patients with SUV_{max} >18 treated with other therapies may have not been fit for R-CHOP, based on variables not analyzed in this study, such as comorbidities, reflecting a clinician's therapeutic bias, and therefore more likely to experience a dismal outcome.

Of interest, in our study, the association between SUV_{max} >18 and lower CR rate, observed for the whole popula-

tion, was lost among patients treated with R-CHOP. In the rituximab era, the use of anthracycline-based regimens, such as R-CHOP, has significantly improved the outcome of patients with previously untreated transformed FL, resulting in response rates and survival similar to what has been observed in de novo DLBCL.³⁵⁻³⁸ Our results indicate that patients with more aggressive forms of FL, as suggested by pre-treatment SUV_{max} >18, may benefit from anthracycline-based therapies as the CR rates were significantly lower with alternative regimens. This is further supported by the fact that in our analysis the lower PFS associated with SUV_{max} >18 (including high rates of progressions

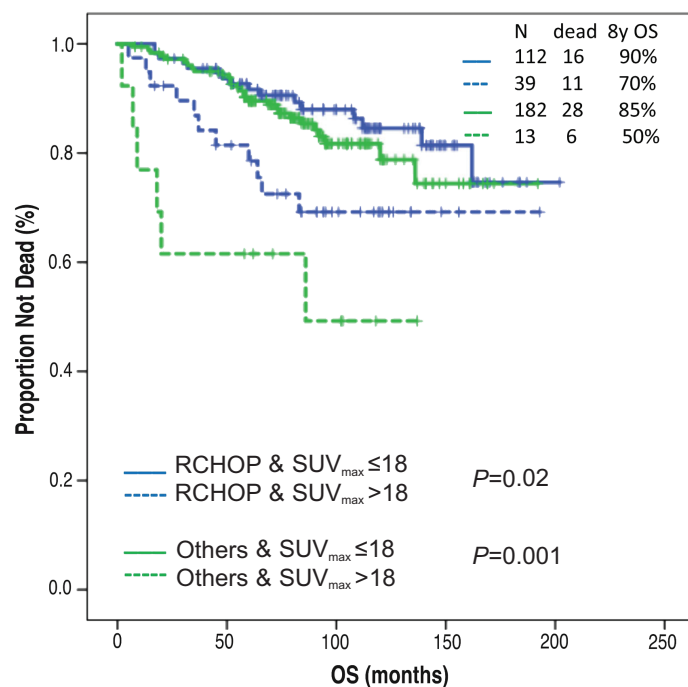


Figure 3. Association between overall survival (OS) and maximum standardized uptake (SUV_{max}) separated by frontline treatment arm.

within 24 months from treatment initiation) was overcome by the use of frontline R-CHOP. These novel and clinically relevant findings highlight the need to examine the impact of pre-treatment SUV_{max} on outcomes in recently completed randomized phase 3 trials in FL comparing different frontline regimens such as R-CHOP, BR, and/or R².^{24,25,39} It is important to note that, as only three patients with FL grade IIIA were included in this study, these results can apply only to patients with grades I-II FL.

Finally, despite the beneficial effect of R-CHOP on CR rate and PFS of patients with SUV_{max} >18, subsequent transformations were still observed among patients treated with this regimen. However, this was not unexpected as not all patients with occult or histologically proven transformed FL achieve durable remissions with R-CHOP. Recurrent disease with transformation after R-CHOP can be salvaged with high-dose chemotherapy with autologous stem cell transplantation and/or chimeric antigen receptor T-cell therapy.⁴⁰⁻⁴⁴ While patients with transformation at the time of relapse who are anthracycline-naïve can be salvaged with R-CHOP, the superior OS observed in patients treated with frontline R-CHOP compared with other regimens within the sub-group of patients with SUV_{max} >18 (8-year OS 70% vs. 50%, $P=0.15$) raises the possibility that upfront treatment with anthracycline-based regimen may lead to better outcomes in such patients. On the other hand, relapses occurring in patients with high SUV_{max} after frontline R-CHOP may have a more aggressive biology, including transformation,

explaining the difference in OS according to SUV_{max} observed in patients treated with this regimen.

We acknowledge that there are some limitations due to the retrospective nature of this study and the well-known variability and limited reproducibility of SUV measurements.⁴⁵ For example, consistent criteria may not have been used to select patients in whom to perform a tissue biopsy for exclusion of transformation, and therefore patients with concurrent undiagnosed FL grade IIIB and/or DLBCL may have been included in the study. There was also likely variability in dose-intensity of the chemotherapy between patients. The total metabolic tumor volume (TMTV) was not calculated in this analysis, and the latter has been shown to predict the outcome after frontline therapy in patients with high-burden FL.⁴⁶ Upon further validation, TMTV and other PET-based functional parameters, such as total lesion glycolysis, may in the future provide a more standardized approach to assess the prognostic value of pre-treatment PET in patients with FL.

Nevertheless, the significant decrease in the CR rate, PFS, and OS observed in patients with SUV_{max} >18 in our study suggest that a pre-treatment PET scan has a prognostic and predictive value in patients with advanced stage FL receiving frontline treatment and prospective randomized trials are warranted to investigate this further.

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