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ORIGINAL REPORT

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

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ABSTRACT

Purpose
The utility of [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET-CT) in assessing response at the end of induction therapy is well documented in Hodgkin's and diffuse large B-cell lymphomas, but its role in follicular lymphoma (FL) remains undetermined. We investigated the prognostic significance of PET-CT performed after first-line therapy in patients with FL treated in the prospective Primary Rituximab and Maintenance (PRIMA) study.

Patients and Methods
Results of PET-CT scans performed after induction immunochemotherapy were recorded retrospectively. Patients went on to either observation or rituximab maintenance per protocol independent of the PET-CT result. Patient characteristics and outcomes were then evaluated.

Results
Of 122 PET-CT scans performed at the end of the induction immunochemotherapy, 32 (26%) were reported as positive by the local investigator. Initial demographic or disease characteristics did not differ between PET-CT–positive (PET-positive) and PET-CT–negative (PET-negative) patients. PET status correlated with conventional response criteria ($P < .001$). Patients remaining PET positive had a significantly ($P < .001$) inferior progression-free survival at 42 months of 32.9% (95% CI, 17.2% to 49.5%) compared with 70.7% (95% CI, 59.3% to 79.4%) in those who became PET negative. PET status, but not conventional response (complete response or complete response unconfirmed *v* partial response) according to IWC 1999, was an independent predictive factor for lymphoma progression. The risk of death was also increased in PET-positive patients (hazard ratio 7.0; $P = .0011$).

Conclusion
[^{18}F]FDG PET-CT status at the end of immunochemotherapy induction in patients with FL is strongly predictive of outcome and should be considered a meaningful clinical end point in future studies.

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INTRODUCTION

Disseminated follicular lymphoma (FL) is a common, incurable lymphoma with heterogeneous clinical behavior. Although initially sensitive to combined rituximab-chemotherapy, FL is characterized by recurrent relapses and risk of histologic transformation. Reliable prognostic markers for the individual patient are lacking. The Follicular Lymphoma International Prognostic Index (FLIPI) and later the FLIPI2 index, although discriminating, fail to identify a significant proportion of patients with a particularly poor outcome.[1-3] Molecular methods (eg, *BCL2-IGH* molecular response monitoring) and immune response profiles either lack ease of clinical application or fail to provide sufficient prognostic power, and other biomarkers lack adequate validation in the immunochemotherapy setting.[4]

Optimal management of patients with FL should also consider the quality of response achieved at the end of first-line treatment. However, conventional response assessment that uses the 1999 International Standardized Response Criteria has acknowledged limitations.[5] Although there are progression-free survival (PFS) benefits to achieving a complete response (CR) or complete response unconfirmed (CRu) versus partial response (PR) in FL, there is no consensus on whether depth of conventional response

has an impact on overall survival (OS).[6] Only recently has achievement of a computed tomography (CT) –based CR after first-line chemotherapy without rituximab been correlated with improved OS.[7]

Positron emission tomography CT (PET-CT) that uses [^{18}F]fluorodeoxyglucose (FDG) is a powerful post-therapy prognostic tool in Hodgkin's and diffuse large B-cell lymphomas. Recent International Harmonization Project (IHP) recommendations for standardization of PET-CT imaging and response criteria were developed from data acquired in these diseases,[8-10] for which post-treatment PET-CT is now a standard response evaluation tool. However, the limited impact of post-treatment response-adapted therapy has driven the evaluation of standardized interim PET-CT response-adapted protocols in current trials. Contrary to the enthusiasm surrounding these histologies, there has been some skepticism of the role of PET-CT in FL, perhaps based on the heterogeneous glucose avidity of lesions,[11,12] and the chronic, incurable nature of this lymphoma. Small series have reported that a positive PET scan in 13% to 25% of patients after therapy is significantly associated with an inferior PFS. Patient populations in these single-institution studies were often mixed, and later-generation PET-CT devices were not universally used.[13-18] Therefore, the IHP-revised response criteria remain unvalidated in FL.

One of the challenges facing response assessment to first-line therapy is the prolonged OS of patients with FL. Estimates of median OS are being redefined in the rituximab era, but likely exceed 10 years.[19,20] Thus, most front-line studies use PFS as an accepted primary end point. The Primary Rituximab and Maintenance (PRIMA) study—the largest randomized study conducted in FL—demonstrated an improved PFS in patients with high tumor burden receiving rituximab in both the first-line and maintenance settings.[21] We used prospectively collected PRIMA clinical data as a platform for an exploratory analysis of [^{18}F]FDG PET-CT scanning in FL. We present the first large-scale evidence that postinduction PET-CT is a strong independent predictor of PFS after first-line immunochemotherapy in FL.

PATIENTS AND METHODS

Study Design

Details of the PRIMA study design have been published elsewhere.[21] In brief, patients with untreated high-tumor-burden FL received either six cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or eight cycles of rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP), with both treatment arms receiving eight induction doses of rituximab, followed by conventional response assessment using the 1999 International Standardized Response Criteria for non-Hodgkin's lymphoma (NHL).[5] Patients achieving PR, CRu, or CR after induction were eligible for random assignment to rituximab maintenance (375 mg/m^2 every 8 weeks for 24 months) or observation. Patients were enrolled between 2004 and 2007, and 1,018 of 1,217 were randomly assigned. After 36 months median follow-up from random assignment, there was a significant ($P < .001$) improvement in the primary end point of PFS for rituximab maintenance (3-year PFS rates of 75% in the maintenance arm *v* 58% in the observation arm).[21] The PRIMA database was interrogated and investigators were surveyed to identify [^{18}F]FDG PET-CT scans performed for staging or response assessment in study participants. Single-modality PET scans were excluded.

PET-CT Scans

PET-CT scans performed at diagnosis and up to 3 months after the last cycle of induction therapy were included in the analyses. Diagnostic PET scans were performed between diagnosis and induction therapy. Postinduction PET scans were those performed between the last chemotherapy (sixth cycle of R-CHOP or eighth cycle of R-CVP), and up to 3 months after the eighth induction rituximab infusion for all patients. A positive or negative PET scan was defined by the local investigator's interpretation of the nuclear medicine physician's scan report.

Statistics

Comparisons of patient characteristics between different patient groups were performed by using χ^2 or Fisher's tests. The primary end point of this study was PFS, defined as time from PRIMA registration to progression, relapse (on the basis of investigator assessment), or death from any cause. OS was defined as time from study registration to death or last follow-up. Responding patients and patients lost to follow-up were censored at last tumor assessment date. Clinical cutoff was identical to that used for the whole study report,[21] with median follow-up 42 months after study registration (36 months after random assignment). Survival functions were estimated by the Kaplan-Meier method and compared by log-rank test. Univariate Cox regression analysis was performed to adjust for the impact of postinduction PET with known prognostic factors: age; bulky disease (largest tumor mass > 7 cm); lactate dehydrogenase (LDH); FLIPI score of 0 to 1, 2, ≥ 3; induction treatment; random assignment or not; randomization group; and conventional response category. Potential interactions between risk factors and postinduction PET were included in the model. Multivariate Cox model regression was fitted with bulk, LDH (or FLIPI) categories, induction treatment, and conventional response category. Differences between the results of comparative tests were considered significant if the two-sided *P* value was less than .05. All statistical analyses were performed by using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

There were 242 PET scans performed on 160 patients at 40 sites, representing 160 (13%) of 1,217 patients in the PRIMA population. Baseline patient characteristics were comparable with those of the general PRIMA population (Appendix Table A1, online only).

Diagnosis and Postinduction PET Scans

In all, 120 patients had scans at diagnosis, a median 17 days (range, −368 to +7 days) before day 1 of cycle 1, and 119 (99%) of 120 were positive. The report of the sole negative PET scan cited a poor signal-to-noise ratio due to obesity, and this patient had no subsequent PET scan.

Postinduction PET was performed on 122 patients at a median of 64 days (range, 9 to 124 days) after the last rituximab-chemotherapy course and a median of 27 days after the last single-agent rituximab infusion. Again, patient baseline clinical characteristics were comparable with those of the general PRIMA population (Appendix Table A1). Eighty-four patients had both pre- and postinduction PET scans. Central pathology review performed in 113 (92.6%) of 122 patients confirmed definite FL in 104 (92.0%) of 113 and probable FL in six (4.6%) of 113. There was greater use of R-CHOP therapy (84% *v* 76%) but no difference in conventional response rates for patients undergoing postinduction PET compared with patients in the general PRIMA population (CR, 40% *v* 38%; CRu, 32% *v* 30%), indicating no apparent response-based selection bias by local investigators in performing postinduction PET. Given the high sensitivity (99%) of PET scans at diagnosis, outcome analysis was performed on all 122 patients, regardless of whether they had undergone a baseline PET scan.

Conventional and PET-Based Response Assessment

With the use of conventional response criteria, there was a 93.4% overall response rate: CR was achieved in 49 patients (40.2%), CRu in 39 (32.0%), PR in 26 (21.3%), stable disease (SD) in three (2.5%), and progressive disease (PD) in five (4.1%).

There were 34 positive postinduction PET scans. Two with FDG uptake due to known nonlymphoma causes (one focal infection and one colonic polyp) were reclassified as negative by the local investigator. Positive postinduction PET scans ascribed to lymphoma occurred in 32 (26%) of 122 patients (Table 1). There was a modest trend toward increased incidence of PET-positive results in patients with increased LDH or bulky disease, but PET-positive and PET-negative patients were not significantly different for baseline prognostic variables. The PET-positive frequency was not statistically different in 25 (24%) of 103 patients treated with R-CHOP and seven (37%) of 19 patients treated with R-CVP.

There was a significant correlation between conventional response assessment (CR/CRu *v* PR *v* SD/PD) and postinduction PET ($P < .001$). The incidence of positive postinduction PET scans increased across the categories of lesser conventional responses occurring in four (8%) of 49 CR, 12 (31%) of 39 CRu, 10 (38%) of 26 PR, two (67%) of three SD, and four (80%) of five PD. Table 2 lists the concordance/discordance between the 1999[5] and the revised 2007 response criteria[9] in the 122 patients studied. Of the 90 PET-negative patients, 72 (80%) were in CR/CRu according to 1999 criteria, but so were 16 (50%) of the 32 PET-positive patients.

Conventional and Postinduction PET Response and PFS

Median follow-up from study registration was 42 months (range, 6 to 57 months). By using conventional response criteria, the PFS rate at 42 months for patients in CR/CRu was 66.9% (95% CI, 55.4% to 76.1%); PR, 55.0% (95% CI, 33.4% to 72.2%); and SD/PD, 0% ($P < .001$; Fig 1). The substantial prognostic impact of conventional response assessment was due to a significant difference between SD/PD and CR/CRu (hazard ratio [HR], 9.8; $P < .001$) and between SD/PD and PR (HR, 6.7; $P < .001$). There was no significant difference in PFS comparing PR and CR/CRu (HR, 1.5; $P = .27$).

Patients who remained PET positive at the end of treatment had a significantly inferior 42-month PFS rate of 32.9% (95% CI, 17.2% to 49.5%) compared with 70.7% (95% CI, 59.3% to 79.4%; $P < .001$) in those who became PET negative. The HR for progression was 3.3 (95% CI, 1.9 to 5.9; Figure 2), and the median PFS was 20.5 months (95% CI, 12.3 to 35.1 months) for PET-positive patients versus not reached (95% CI, 51.7 to not reached) for PET-negative patients. In the largest subgroup (n = 103) of patients treated with R-CHOP, the 42-month actuarial PFS rates in the PET-positive (n = 25) and PET-negative (n = 78) groups were 39.6% versus 73.7%, respectively (HR, 3.3; $P < .001$). In patients receiving R-CVP (n = 19), the actuarial PFS rates at 42 months were 0.0% versus 50.0%, respectively (HR, 3.1;

Table 1. Baseline Characteristics of PRIMA Patients With PET-Positive and PET-Negative Results Post Induction

Characteristic	Patients With PET-Positive Results Post Induction (n = 32) n/N	%	Patients With PET-Negative Results Post Induction (n = 90) n/N	%
Male sex	22	69	45	50
Age				
> 60 years	12	38	38	42
Median	56		58	
Range	28-82		26-79	
Hemoglobin < 12 g/dL	7	22	19	21
Ann Arbor stage III to IV	29	91	79	88
ECOG PS				
1	12	38	34	38
2	2	6	4	4
B symptoms	11	34	29	32
LDH > ULN	13/31	42	24	27
FLIPI				
2	11/31	34	36	40
≥ 3	14/31	45	33	37
β_2-microglobulin ≥ 3 mg/L	10/28	36	23/79	29
Bulky disease (≥ 7 cm)	19/31	61	39/88	44
Bone marrow involvement	17/31	55	51	57
R-CHOP received as induction	25	78	78	87
R-CVP received as induction	7	22	12	13

NOTE. n/N, number of patients with given characteristic/number of evaluable patients. N not reported if equal to n.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index[1]; LDH, lactate dehydrogenase; PET, positron emission tomography; PRIMA, Primary Rituximab and Maintenance study; PS, performance status; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; ULN, upper limit of normal.

Table 2. Response Evaluation in Accordance With 1999 IWC and 2007 Revised Response Criteria

1999 IWC Response to Induction Regimen	Revised Response Criteria (IWC plus PET) CR	PR	SD	PD	Total
CR	45	4	0	0	49
CRu	27	12	0	0	39
PR	16	10	0	0	26
SD	1*	0	2	0	3
PD	1†	0	0	4	5
Total	90	26	2	4	122

Abbreviations: CR, complete response; CRu, complete response unconfirmed; IWC, International Workshop Criteria; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

*This patient with SD experienced disease progression at month 32.

†This patient had PD defined by the investigator as a new, unbiopsied prepancreatic lesion at the end of induction, which has remained unchanged 3 years later.

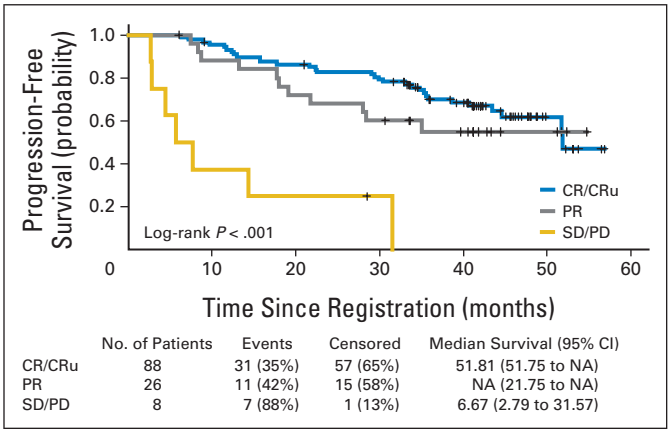
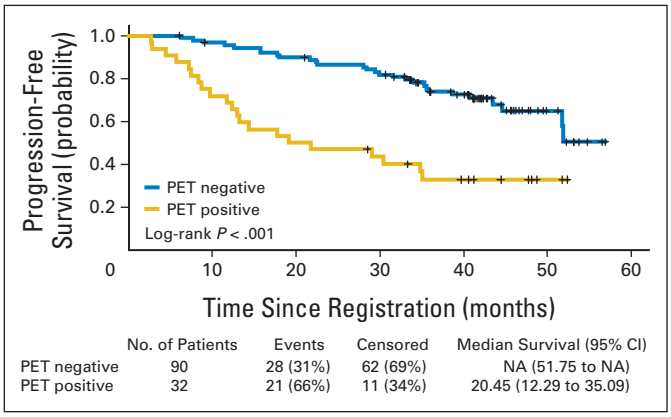


Fig 1. Prognostic impact of conventional response assessment on progression-free survival (PFS) in 122 patients. The overall log-rank *P* value (complete response/complete response unconfirmed [CR/CRu] *v* partial response [PR] *v* stable disease/progressive disease [SD/PD]) was less than .001, but PFS of CR/CRu patients (n = 88) versus PR patients (n = 26) was not significantly different (only eight patients with SD/PD). N/A, not applicable.



	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	28 (31%)	62 (69%)	NA (51.75 to NA)
PET positive	32	21 (66%)	11 (34%)	20.45 (12.29 to 35.09)

Fig 2. Prognostic impact of postinduction positron emission tomography–computed tomography (PET-CT) on progression-free survival (PFS) in 122 patients. PET negative designates patients (n = 90) with a negative PET-CT after induction therapy, and PET positive designates those (n = 32) with a positive PET-CT. Log-rank $P < .001$. N/A, not applicable.

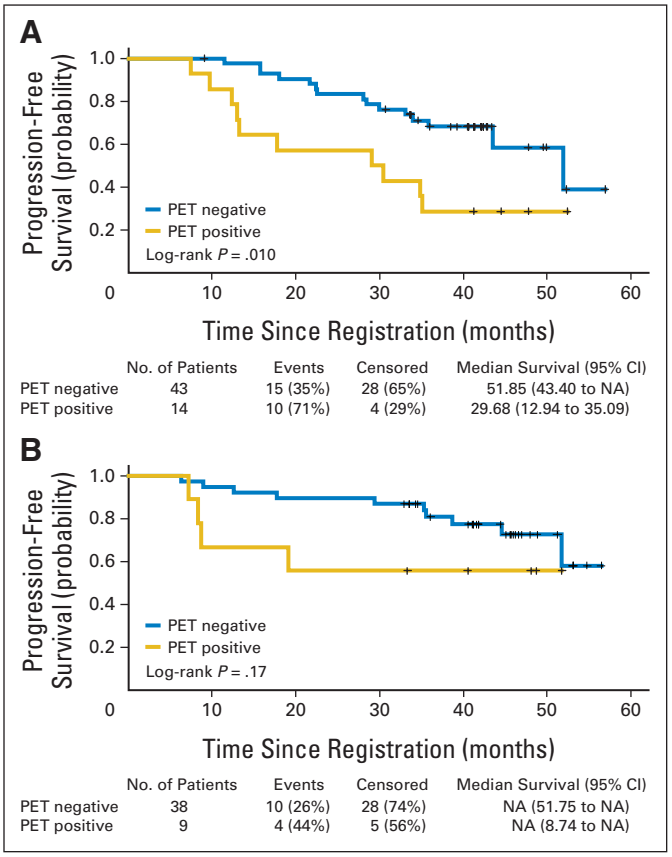
$P = .05$). Similar results (not shown) were obtained when excluding three patients for whom a diagnosis of FL was not confirmed on central pathology review.

Of the 122 patients who underwent postinduction PET, 18 patients (15%) did not undergo random assignment, a proportion that did not differ from those not randomly assigned in the whole PRIMA study (16%), again indicating a lack of apparent selection bias in PET evaluation. These patients who were not randomly assigned included eight with SD/PD (six of eight were PET positive) who were ineligible per protocol for random assignment; nine with protocol violations, including two patients in PR who received radiotherapy; and one with persisting treatment toxicity (three of nine were PET positive). Postinduction PET positivity was not recorded as a reason for not randomly assigning any patient and remained a significant predictor of inferior PFS ($P = .027$) in patients who were not randomly assigned.

In the 104 randomly assigned patients, postinduction PET positivity remained a highly significant predictor of disease progression, with a 42-month PFS rate of 38.3% in PET-positive versus 72.6% in PET-negative patients (HR, 2.8; $P = .002$). The effect of rituximab maintenance on PFS was similar to that observed in the principal PRIMA study but was not statistically significant because of a limited number of patients in this series (73.2% for rituximab maintenance *v* 57.8% for the observation arm; HR, 0.59; $P = .11$).

The impact of PET status in the two randomly assigned arms was analyzed separately. For patients undergoing observation, postinduction PET positivity (14 of 57) remained predictive of inferior PFS (42-month rates of 28.6% v 68.2%; HR, 2.8; P = .01) with actuarial median PFS of 29.7 versus 51.8 months, respectively (Fig 3A). In patients receiving rituximab maintenance, a nonsignificant inferior PFS was observed in nine of 47 PET-positive patients (55.6% *v* 77.4%; HR, 2.2; $P = .18$), but the median PFS has not been reached in either the PET-positive or PET-negative group (Fig 3B).

In seeking to evaluate possible selection bias, the PFS of the 84 patients having both pre- and postinduction PET scans was also analyzed. Again, PET-positive patients had an inferior 42-month PFS of 27.3% versus 69.8% for PET-negative patients (HR, = 4.0; $P < .001$).



	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	43	15 (35%)	28 (65%)	51.85 (43.40 to NA)
PET positive	14	10 (71%)	4 (29%)	29.68 (12.94 to 35.09)

	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	38	10 (26%)	28 (74%)	NA (51.75 to NA)
PET positive	9	4 (44%)	5 (56%)	NA (8.74 to NA)

Fig 3. Impact of postinduction positron emission tomography–computed tomography (PET-CT) on progression-free survival (PFS) in 104 randomly assigned patients. (A) Observation arm (n = 57). PET negative designates patients (n = 43) with a negative PET-CT after induction therapy, and PET positive designates those (n = 14) with a positive PET-CT. Log-rank $P = .010$. (B) Rituximab maintenance arm (n = 47). PET negative designates patients (n = 38) with a negative PET-CT after induction therapy, and PET positive designates those (n = 9) with a positive PET-CT. Log-rank $P = .17$. N/A, not applicable.

Prognostic Significance of Postinduction PET Status and Conventional Response Category

On a proportional hazard regression analysis that used postinduction PET and conventional response category (CR/CRu *v* PR *v* SD/PD) as covariates, both conventional response (overall $P < .001$) and PET positivity (HR, 2.7; $P = .0013$) were significant predictors of inferior PFS. However, only SD/PD versus CR/CRu (HR, 6.5; $P < .001$) and SD/PD versus PR (HR, 5.5; $P < .001$) were significant, whereas PR versus CR/CRu was not (HR, 1.2; $P = .7$).

Analysis of PET in conventional response subgroups demonstrated a significant impact of PET status in both the CR/CRu (HR, 2.6; $P = .017$) and PR (HR, 3.9; $P = .03$) groups but not in the SD/PD group (HR, 2.8; $P = .36$). Conversely, CR/CRu versus PR was no longer significant in either the PET-positive (HR, 1.4; $P = .5$) or PET-negative (HR, 1.0; $P = .98$) subgroups (Appendix Figs A1A and A1B, online only).

Postinduction PET Compared With Other Prognostic Factors

Multivariate Cox analyses were performed with PET-based and conventional response assessments as well as induction treatment (R-CVP *v* R-CHOP), LDH, and bulky disease. In this model, only PET-positive status postinduction remained a significant predictor of inferior PFS (HR,

3.6; 95% CI, 2.0 to 6.6; $P < .001$) together with conventional response (overall $P < .001$). When considering each individual category of conventional response in this model, only SD/PD versus CR/CRu (HR, 10.8; $P < .001$) and SD/PD versus PR (HR, 7.6; $P < .001$) were significant whereas PR versus CR/CRu was not significant (HR, 1.4; $P = .33$; Appendix Table A2, online only). Similar results were obtained when the model included the different FLIPI categories together with induction treatment and bulk, with FLIPI status not significantly predictive of outcome.

In evaluating similar multivariate Cox models in the 104 randomly assigned patients (only patients in PR or CR/CRu), only postinduction PET positivity (HR, 3.1; $P = .001$) and marginally R-CVP (HR, 2.2; $P = .05$) were predictive of inferior PFS (Appendix Table A2).

OS

At the time of analysis, 10 patients had died: three in the PET-negative group (two from unrelated causes) and seven in the PET-positive group (all from lymphoma). Postinduction PET-positive patients had a significantly inferior OS: 42-month rate of 78.5% (95% CI, 57.6% to 89.9%) compared with 96.5% (95% CI, 89.7% to 98.9%) for PET-negative patients (log-rank $P = .0011$; HR, 7.0; 95% CI, 1.8 to 27.0; Figure 4). Similar results were obtained when considering only randomly assigned patients (HR, 7.0; $P = .0013$) and excluding patients without confirmed FL on central pathology review (HR, 7.3; $P < .001$).

DISCUSSION

This study indicates that postinduction PET assessment represents a strong and independent predictor of progression and death in patients with FL treated with immunochemotherapy. Furthermore, the predictive power of PET response status persists regardless of whether the patient has achieved a conventionally assessed CR/CRu or PR. These data support PET evaluation as an important therapeutic end point in clinical trials for patients with FL.

As reported previously,[13,22-28] and confirmed here, FL is almost always glucose avid, an essential basis for post-treatment PET evaluation. Scans in this study were reported by more than 40 individual PET physicians, who likely were using the visual assessment practices common in clinical practice over the study period (2004 to 2007). This analysis was unplanned and retrospective, without independent scan review. Nonetheless, the PET data are compared with those of prospective, independently verified, conventional response assessments of the homogeneously treated PRIMA patient population. Positive selection bias was deemed unlikely by demonstrating baseline patient characteristics comparable with those of the general PRIMA population and a comparable PFS in 84 patients having both diagnostic and post-treatment scans.

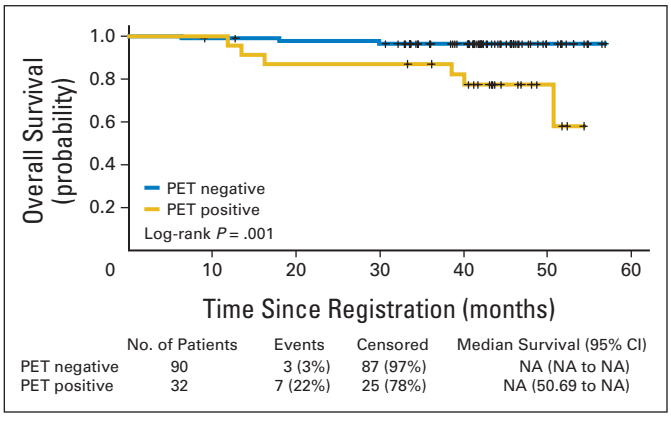


Fig 4. Prognostic impact of postinduction positron emission tomography–computed tomography (PET-CT) on overall survival (OS) in 122 patients. PET negative designates patients (n = 90) with a negative PET-CT after induction therapy, and PET positive designates those (n = 32) with a positive PET-CT. Log-rank $P = .001$. N/A, not applicable.

These results suggest that the incorporation of PET response assessment using the 2007 revised response criteria[9] is appropriate for FL. Within the context of a 94% overall conventional response rate, PET is capable of discriminating within these responders, among whom more than 38% of patients with PR and 18% of patients with CR/CRu remain PET positive. Conversely, 20% of PET-negative patients were not considered to have reached CR/CRu when 1999 response criteria were used. The improved predictive power of postinduction PET over standard response evaluation likely reflects PET's capacity as a biomarker, identifying residual disease activity in small nodes and confirming or excluding active disease in areas of persisting radiologic abnormality. Although PET remains highly predictive of outcomes in conventionally assessed patients, the converse is not true: in both PET-positive and PET-negative patients, further classification as either CR/CRu or PR was not prognostically significant. These results suggest that performed on its own, conventional response assessment may be misleading, creating false optimism for some patients in CR/CRu and unwarranted pessimism for many in PR. The results support moving away from response criteria that are based solely on tumor volume, as recommended in the 2007 IWC.[9]

The results of multivariate analysis also discount confounding factors (increased LDH, tumor bulk, or high FLIPI score) that could have contributed to a higher proportion of postinduction PET-positive patients, demonstrating that PET independently reflects the degree of lymphoma sensitivity to rituximab plus chemotherapy. Furthermore, within the limits of small numbers of patients, FLIPI and induction treatment, which were of prognostic significance in the whole PRIMA study population, appear to be overridden by PET results. Of note, although slightly more patients were PET positive after R-CVP induction, PET's prognostic value was independent of the chemotherapy administered.

A negative postinduction PET in almost 75% of the patients after induction rituximab-chemotherapy predicts a prolonged PFS. The 77% 42-month PFS of PET-negative patients receiving rituximab maintenance is encouraging and suggests that the current PRIMA-derived standard of 2 years of rituximab maintenance is appropriate for PET-negative patients. Conversely, persistent glucose avidity in about 25% of the patients confers a markedly inferior PFS. Despite anthracycline use, the median PFS of 22 months in PET-positive patients after R-CHOP identifies a population for whom FL cannot be characterized as an indolent disease. The limited population precluded statistical evaluation of the impact of rituximab maintenance for PET-positive patients; however, the median PFS was not reached in the maintenance arm compared with 2.5 years in the observation arm.

With the limitations of an exploratory, retrospective analysis, postinduction PET in this PRIMA substudy highlights the heterogeneous biology and clinical outcome of patients with FL. The considerably inferior PFS in patients remaining PET positive after therapy heralds a higher risk of death, findings that require prospective validation by using standardized PET evaluation criteria, with consensus on the definition of PET positivity and PET negativity.[8,29] If current and future studies confirm that postinduction PET identifies a poor prognosis population at an early time

point in their disease, we are provided with a meaningful clinical end point for study of response-adapted strategies. In an era of promising alternative chemotherapies, emerging antibodies, biotherapies, and potential for treatment intensification, assessment of such strategies would be timely. Determining whether persistently PET-positive patients can be converted to a complete metabolic response, with improved survival, represents a future challenge for clinical research in FL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: John Francis Seymour, Roche (C) **Consultant or Advisory Role:** John Francis Seymour, Roche (C); Ofer Shpilberg, Roche (C); Emmanuel Gyan, Janssen-Cilag (C), Celgene (C); Gilles Salles, Roche (C) **Stock Ownership:** None **Honoraria:** John Francis Seymour, Roche; Ofer Shpilberg, Roche; Hervé Tilly, Roche; Gilles Salles, Roche **Research Funding:** Ofer Shpilberg, Roche; Emmanuel Gyan, Janssen-Cilag, Amgen, Celgene; Gilles Salles, Roche **Expert Testimony:** None **Other Remuneration:** John Francis Seymour, Roche

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