

Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study

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A B S T R A C T

Purpose

Twenty percent of patients with follicular lymphoma (FL) experience progression of disease (POD) within 2 years of initial chemoimmunotherapy. We analyzed data from the National LymphoCare Study to identify whether prognostic FL factors are associated with early POD and whether patients with early POD are at high risk for death.

Patients and Methods

In total, 588 patients with stage 2 to 4 FL received first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Two groups were defined: patients with early POD 2 years or less after diagnosis and those without POD within 2 years, the reference group. An independent validation set, 147 patients with FL who received first-line R-CHOP, was analyzed for reproducibility.

Results

Of 588 patients, 19% (n = 110) had early POD, 71% (n = 420) were in the reference group, 8% (n = 46) were lost to follow-up, and 2% (n = 12) died without POD less than 2 years after diagnosis. Five-year overall survival was lower in the early-POD group than in the reference group (50% v 90%). This trend was maintained after we adjusted for FL International Prognostic Index (hazard ratio, 6.44; 95% CI, 4.33 to 9.58). Results were similar for the validation set (FL International Prognostic Index–adjusted hazard ratio, 19.8).

Conclusion

In patients with FL who received first-line R-CHOP, POD within 2 years after diagnosis was associated with poor outcomes and should be further validated as a standard end point of chemoimmunotherapy trials of untreated FL. This high-risk FL population warrants further study in directed prospective clinical trials.

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INTRODUCTION

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma in the United States and Europe, with approximately 15,000 cases diagnosed in the United States per year.¹ Over the past several decades, substantial advances have been made in the event-free survival, progression-free survival (PFS), and overall survival (OS) of patients with FL.²⁻⁵ These survival improvements are mostly attributed to progress in the delivery of effective antilymphoma therapies and improvements in supportive care.^{2,3,5}

Despite the improved effectiveness of chemoimmunotherapy regimens, including rituximab

with cyclophosphamide, vincristine, and prednisone (R-CVP)⁶; rituximab with mitoxantrone, chlorambucil, and prednisolone (R-MCP)⁷; rituximab with fludarabine and mitoxantrone (R-FM)⁸; bendamustine and rituximab (BR)^{9,10}; and rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)¹¹; approximately 20% of patients with FL experience progression of disease (POD) within 2 years of first-line therapy.^{8,10-12} This remains the case despite the benefit of additional rituximab in the form of maintenance, as shown in the PRIMA (Primary Rituximab and Maintenance) study.¹² The remarkably consistent frequency of early relapse across studies is suggestive of a group of patients with different disease

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biology who are uniquely at risk and who may benefit from alternate therapies, either up front or at the time of relapse. Currently, the clinical significance of early POD in FL is unknown, and the impact of early POD on subsequent OS has not been explored.

Given the heterogeneity of FL, clinical indices of risk have been created to identify patients with more aggressive disease and shorter responses to treatment. These include the Follicular Lymphoma International Prognostic Index (FLIPI) and the FLIPI 2 scores.¹³⁻¹⁵ Beyond the clinical realm, biologic predictors of risk in FL involve mutations in key genes, modification of histones,¹⁶ and changes in the FL tumoral microenvironment.¹⁷ However, these biologic contributors of FL risk have not been incorporated into clinical use.

To our knowledge, stratification of risk in the setting of disease progression and its influence on subsequent patient survival has not been previously validated in FL. Depth and duration of response to previous treatments have been proposed as prognostic indicators without widespread acceptance,¹⁸⁻²⁰ though these benchmarks may be less relevant in the current era of rituximab and targeted therapies. Moreover, the timing of POD and the quality of response in FL may be underappreciated as prognostic factors, because FL is commonly viewed as a disease with a relapsing and remitting course in which patients experience benefits of sequential therapies at relapse, without direct dependence on the outcomes of previous regimens. We sought to understand whether time to progression after diagnosis in patients who received first-line chemoimmunotherapy may be a factor affecting survival outcomes in FL. We analyzed data from the National LymphoCare Study (NLCS) to identify patients with FL who are at high risk for death after treatment with R-CHOP to determine whether early POD is predictive of inferior OS in this disease, and we validated our findings in an independent cohort.

PATIENTS AND METHODS

Patients

Details regarding development and operation of the NLCS have been published elsewhere.²¹ Patients provided written, informed consent before

participating, and the protocol was approved by an institutional review board. Consecutive patients with newly diagnosed FL (within 6 months after diagnosis) from March 2004 to March 2007 at participating sites were recruited. No central pathology review was performed; the local pathology report defined the diagnosis of FL after investigators were trained regarding WHO definitions for the classification of FL.

We focused on patients from the NLCS who were treated with front-line R-CHOP. Therapeutic decisions were made entirely by the treating physician with no influence from the NCLS. For this analysis, we selected only patients with stage II, III, or IV FL in the NLCS. Patients were not permitted to have mixed or transformed histology, they could not have undergone watchful waiting or other forms of treatment, and they could not have had POD before starting first-line R-CHOP. Patients treated with R-CHOP were grouped into two categories: those with POD within 24 months of diagnosis, that is, early progressors or early POD, and those without POD within 24 months of diagnosis, the reference group (Fig 1, CONSORT diagram). The 24-month cutoff point was selected on the basis of published data showing that approximately 20% of patients with FL experience POD within 24 months of chemotherapy and maintenance rituximab treatment. Another reason was to capture most events (see the Appendix, online only, for further details of choice of cut point and exploratory analysis with other time points).^{8,10-12}

We identified an independent validation set of patients with FL at the University of Iowa and Mayo Clinic Molecular Epidemiology Resource.²² One hundred forty-seven patients treated with first-line R-CHOP were identified. As in the NLCS cohort, only patients with stage II, III, or IV FL were included. Patients were not permitted to have mixed or transformed histologic results, and they could not have undergone watchful waiting or other forms of treatment. Associations between early progression and OS were assessed for this validation set by using the same methodology as that applied to the NLCS data.

Statistical Methods

The Kaplan-Meier method was applied to estimate survival probability and generate survival curves. Unadjusted and FLIPI-adjusted Cox models in which missing FLIPI data were included as a category in the model were used to evaluate the association between early POD and OS from a risk-defining event, that is, survival from time of POD for early progressors or from 2 years after diagnosis for the reference group. OS from diagnosis was also evaluated as a sensitivity analysis. (See the Appendix for further discussion of the choice of OS end point and for sensitivity analysis results.) This same method was used to explore whether the relationship between early progression and OS from a risk-defining event existed for other regimens (R-CVP and R-fludarabine

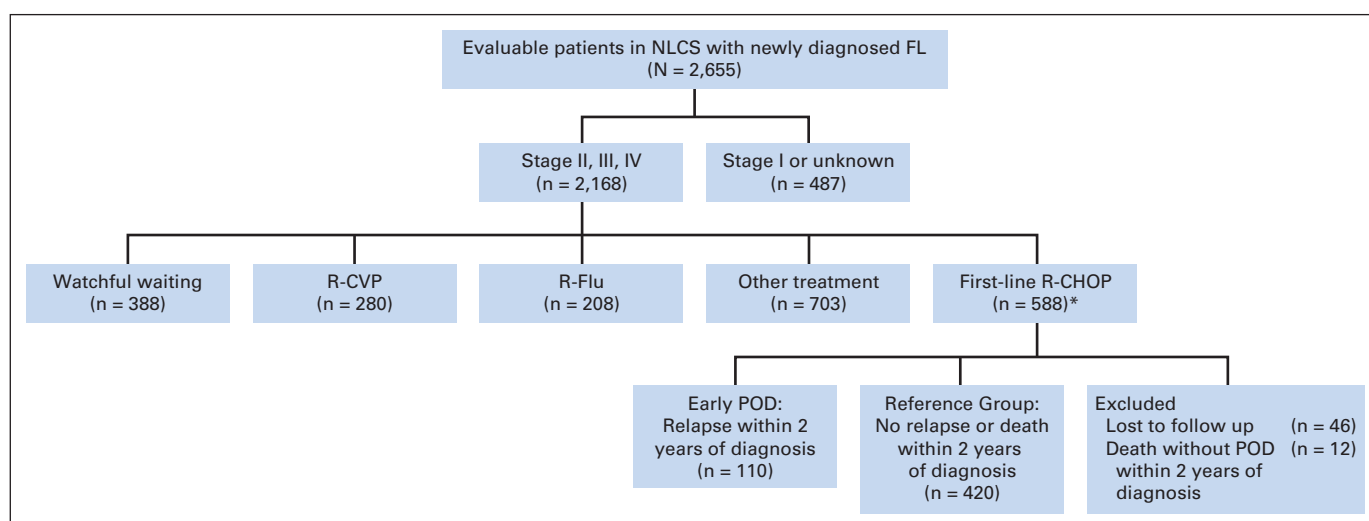


Fig 1. CONSORT diagram for participant selection. One patient who experienced progression of disease (POD) before receiving rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was excluded. FL, follicular lymphoma; NLCS, National LymphoCare Study; R-CVP, rituximab with cyclophosphamide, vincristine, and prednisone; R-Flu, rituximab with fludarabine.

Table 1. Characteristics of Patients From the NLCS and Validation Sets From the University of Iowa and the Mayo Clinic Molecular Epidemiology Resource

Characteristic	NLCS (n = 1,075)						R-CHOP Validation Set Iowa and Mayo Clinic (n = 147)	
	R-CHOP (n = 588)		R-CVP (n = 280)		R-Flu (n = 207)		No.	%
	No.	%	No.	%	No.	%		
Age, years								
≤ 60	333	57	113	40	115	56	81	55
61-70	166	28	66	24	42	20	37	31
71-80	78	13	70	25	42	20	14	10
> 80	11	2	31	11	8	4	6	4
Sex								
Female	271	46	156	56	111	54	48	47
Male	317	54	124	44	96	46	92	56
Race								
White	540	92	249	89	177	86	142	97
African American	16	3	10	4	14	7	0	0
Hispanic	24	4	16	6	14	7	0	0
Other	8	1	5	2	2	1	5	3
Follicular histologic grade								
1 or 2	322	62	228	89	160	86	67	46
3	200	38	28	11	26	14	80	54
Missing	66	—	24	—	21	—	0	0
FLIPI score								
Good, 0 to 1	110	23	54	22	37	23	40	27
Intermediate, 2	162	33	61	25	64	40	46	31
Poor, 3 to 5	213	44	126	52	61	38	61	42
Missing	103	—	39	—	45	—	0	0

Abbreviations: FLIPI, Follicular Lymphoma International Prognostic Index; NLCS, National LymphoCare Study; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine, and prednisone; R-Flu, rituximab with fludarabine.

[R-Flu]). Epanechnikov kernel smoothed estimated hazard rates of POD over time are provided.²³ To identify factors associated with early POD, logistic regression analysis was performed with backwards selection (removing factors when $P > .05$). Univariable associations between factors and POD were calculated by using the Pearson χ^2 test. Sensitivity analysis of OS modeling was also performed for validation.

RESULTS

Patient Characteristics of the NLCS Cohort

Patient characteristics from the NLCS cohort are noted in [Table 1](#). A total of 588 patients treated with first-line R-CHOP. Forty-six percent of patients were female. Sixty-two percent of patients had grade 1 or 2 FL; 44% had high-risk FLIPI scores.

Of the 588 patients, 110 (19%) had a relapse of lymphoma within 24 months of diagnosis, that is, early POD. Estimated hazard curves ([Fig 2](#)) showed that peak risk of POD occurred within the first 24 months after diagnosis. Of the remaining 478 patients, 420 (76%) had no relapse or death during the first 24 months after diagnosis—this was the reference group. Forty-six patients were lost to follow-up. Twelve died without POD within 24 months of diagnosis.

For the 110 patients with early POD, median age was 58 years (range, 31 to 88 years), and 65% of patients were male ([Table 2](#)). Sixty-six percent of patients had low-grade histology (grade 1 or 2). Patients in the early-POD group were more likely to have high-risk FLIPI scores than the reference group ($P = .007$). In the logistic regression analysis, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), B symptoms, male sex, elevated lactate de-

hydrogenase level, stage 3 or 4 disease, and African-American or other race were significantly associated with early POD ($P < .05$). Grade 3 FL histologic findings were not associated with early POD ($P = .33$).

POD and Subsequent Survival of the NLCS Cohort

Median follow-up time for the entire cohort of 588 patients was 7 years. Of 110 patients with early POD, 57 died during study follow-up. OS from a risk-defining event at 2 years in the early-POD group was 68%, and at 5 years it was 50% compared with 97% and 90%, respectively, for patients without early POD ([Fig 3A](#)).

In unadjusted Cox regression analysis, early POD was associated with markedly reduced OS with a hazard ratio (HR) of 7.17 (95% CI, 4.83 to 10.65) compared with the reference group. Even after we adjusted for the FLIPI score, early POD was associated with an elevated risk of death with an HR of 6.44 (95% CI, 4.33 to 9.58). Exploratory analyses of patients receiving initial therapy with R-CVP ($n = 237$) and R-Flu ($n = 184$) demonstrated similar patterns in the peak hazard of progression ([Fig 2](#)), which were significantly worse OS for patients who experienced early POD in unadjusted and adjusted Cox regression models ([Table 3](#)).

To further characterize the effect of early POD, OS from time of POD was evaluated for patients whose disease progressed early versus patients whose disease progressed more than 2 years after diagnosis. Patients with early progression had inferior subsequent OS compared with those whose progression occurred after 2 years (HR, 1.89; 95% CI, 1.18 to 3.03; $P = .008$).

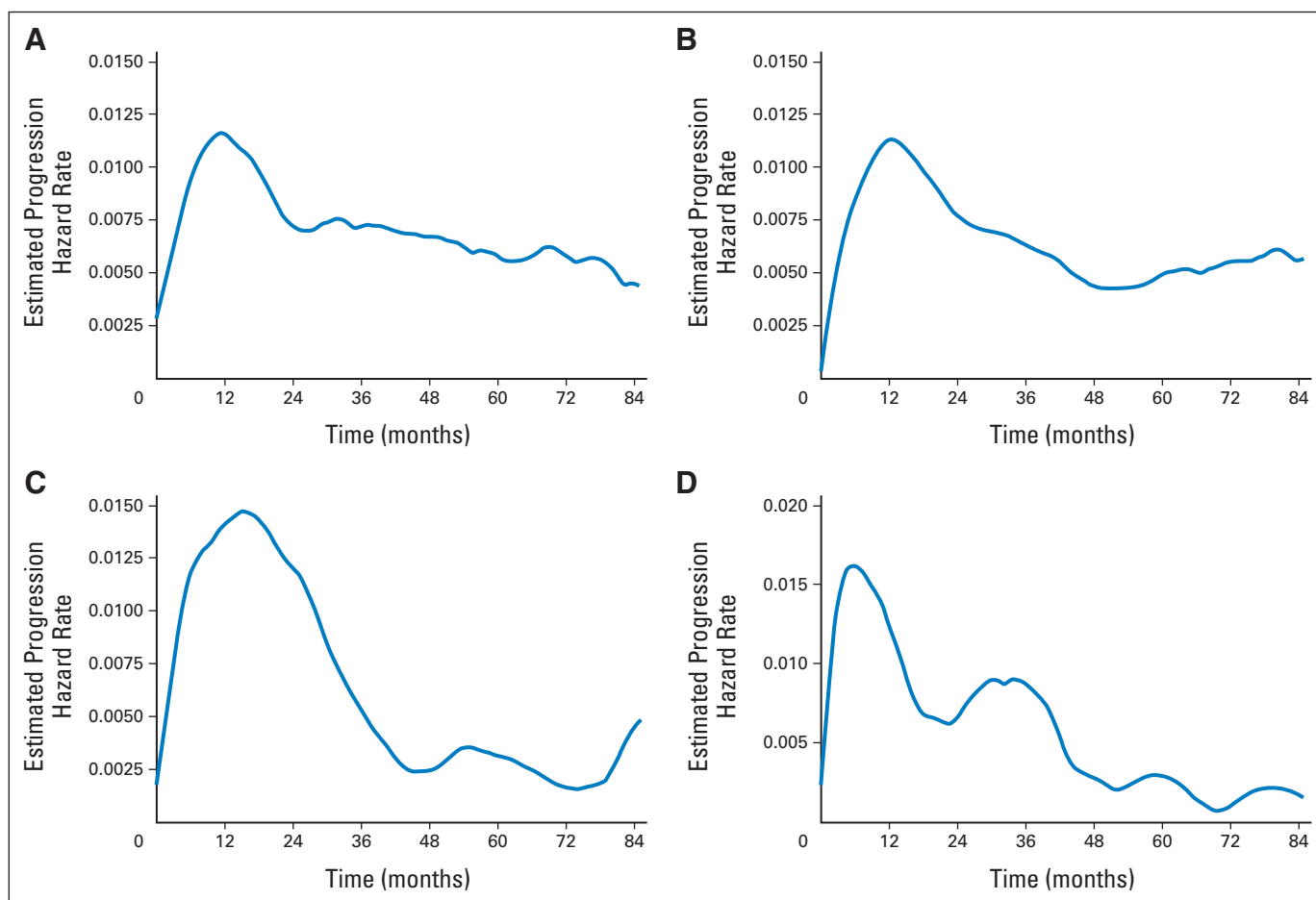


Fig 2. Estimated hazard of progression for the (A-C) National LymphoCare Study and (D) University of Iowa and Mayo Clinic Molecular Epidemiology Resource validation cohorts. (A) Rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP); (B) rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); (C) rituximab with fludarabine (R-Flu); (D) validation set (R-CHOP).

Factors Associated With OS in the NCLS Cohort

For patients experiencing early POD, Cox regression with backwards selection (factors removed when $P > .05$) showed that clinical factors predictive of inferior subsequent OS were age, ECOG PS, nodal sites, and disease stage. For the reference group, clinical factors significantly predictive of OS were age and extranodal sites. In the Cox regression with these factors and early POD, only early POD, age, and ECOG PS remained significant.

Patient Characteristics of the Validation Cohort

Characteristics of patients in the validation cohort are shown in Table 1. Median age was 59 years (range, 28 to 86 years). Most patients were male (56%). Patient demographics and FLIPI scores were similar to those of patients from NLCS. However, the validation set had more patients with grade 3 disease (54%) than the NLCS group (38%); ($P < .001$).

After a median follow-up of 5.5 years, 26% of patients had early POD. Seventy-one percent did not have early POD. In five patients (3%), follow-up was less than 24 months. None died without previous POD within 24 months of diagnosis.

POD and Survival Validation Cohort

Similar to the NLCS group, patients in the validation set with early POD after R-CHOP had poor outcomes. In the early-POD

group, the 2-year OS rate was 64% (95% CI, 49% to 83%), and the 5-year OS rate was 34% (95% CI, 19% to 60%). In comparison, the 2-year OS rate in the reference group was 98% (95% CI, 95% to 100%), and the 5-year OS rate was 94% (95% CI, 88% to 100%; Fig 3B). Results from the Cox model confirmed that patients treated with R-CHOP who experienced early progression after diagnosis had an increased risk of death, with an unadjusted HR of 20.0 (95% CI, 6.8 to 59.0). Similar results were obtained after we adjusted for FLIPI score (HR, 19.8; 95% CI, 6.7 to 58.8).

Exploratory Analyses

Additional analyses (in the Appendix) were performed to explore other definitions of early POD. We evaluated the significance of early relapse within 1 and 3 years of diagnosis after R-CHOP. For both alternate definitions of early relapse, early POD was significantly associated with worsened OS (Appendix Table A2, online only).

DISCUSSION

Patients with FL treated with R-CHOP who developed POD within 2 years of diagnosis had a substantially increased risk of death within 5 years after diagnosis, and OS significantly worse than that of patients

Characteristic	Early POD (n = 110)		Reference (n = 420)	
	No.	%	No.	%
Age, years				
Median	58		58	
Range	31-88		22-84	
Sex				
Female	38	35	200	48
Male	72	65	220	52
Follicular histologic grade				
1 or 2	63	66	227	60
3	33	34	150	40
Missing	14		43	
FLIPI score				
Good, 0 to 1	10	12	92	26
Intermediate, 2	29	34	119	34
Poor, 3 to 5	47	55	140	40
Missing	24		69	

Abbreviations: FLIPI, Follicular Lymphoma International Prognostic Index; NLCS, National LymphoCare Study; POD, progression of disease.

without POD within 2 years after diagnosis. This finding was confirmed in a second independent cohort and in patients treated with other chemoimmunotherapy regimens. Because expected median survival for patients with FL treated in the modern era with front-line chemoimmunotherapy now exceeds 18 years, POD within 2 years of diagnosis in patients treated with front-line chemoimmunotherapy identifies a population of patients with FL who have remarkably poor outcomes.⁵ Early progression after diagnosis in patients treated with other chemoimmunotherapy regimens also indicated a significantly increased risk of death. To our knowledge, this is the first study to establish that early relapse after diagnosis in patients who received chemoimmunotherapy is predictive of poor survival in FL with validation in an independent cohort of patients.

The observation that 20% of patients with FL relapse within 2 years of treatment has been made in many studies of several chemoimmunotherapy regimens and is not altered with the addition of maintenance rituximab.^{6-8,10-12,25} Validated tools for risk assessment and prognostication in newly diagnosed FL incorporate clinical and laboratory features applicable to use in the front-line setting.^{13,15} Risk stratification at relapse requires more empiricism and is not guided by any particular feature, though, in practice, number of previous treatments, depth of response, patient age, and PS may be considered.¹⁶ Given our findings, early relapse after diagnosis in patients treated with first-line chemoimmunotherapy is a powerful prognostic indicator of outcome and should be used to stratify the risk of patients in studies of relapsed FL.

We chose the 2-year postdiagnosis time point as an important end point given how consistently and reproducibly 20% of patients experienced POD by this time after treatment with chemoimmunotherapy across many studies. This is supported by our estimated hazard curves (Fig 2) demonstrating that peak risk of POD in patients treated with R-CHOP occurred within the first 2 years after diagnosis. Moreover we demonstrated the significance of this time point by means of validation in an independent patient cohort. The clinical implications of early POD after chemoimmunotherapy are highly relevant to future clinical-trial design for relapsed FL to improve patient survival. Although novel front-line therapies are being examined for patients with FL, chemoimmunotherapy remains the standard of care. R-CHOP, in particular, is one of the most effective treatments currently in use, and it is equivalent to other regimens.⁹ The effect of early POD with novel non-chemotherapy-containing regimens will require validation in future studies.

Aggressive salvage therapies or autologous stem-cell transplantation (ASCT) may potentially abrogate the negative prognostic effect of early relapse because the salvage chemotherapy followed by ASCT has an established role in relapsed FL.²⁶⁻²⁸ Both prospective and retrospective studies have demonstrated high response rates and suggested long-term survival.^{27,28} Of interest, only eight patients in the early-POD group were

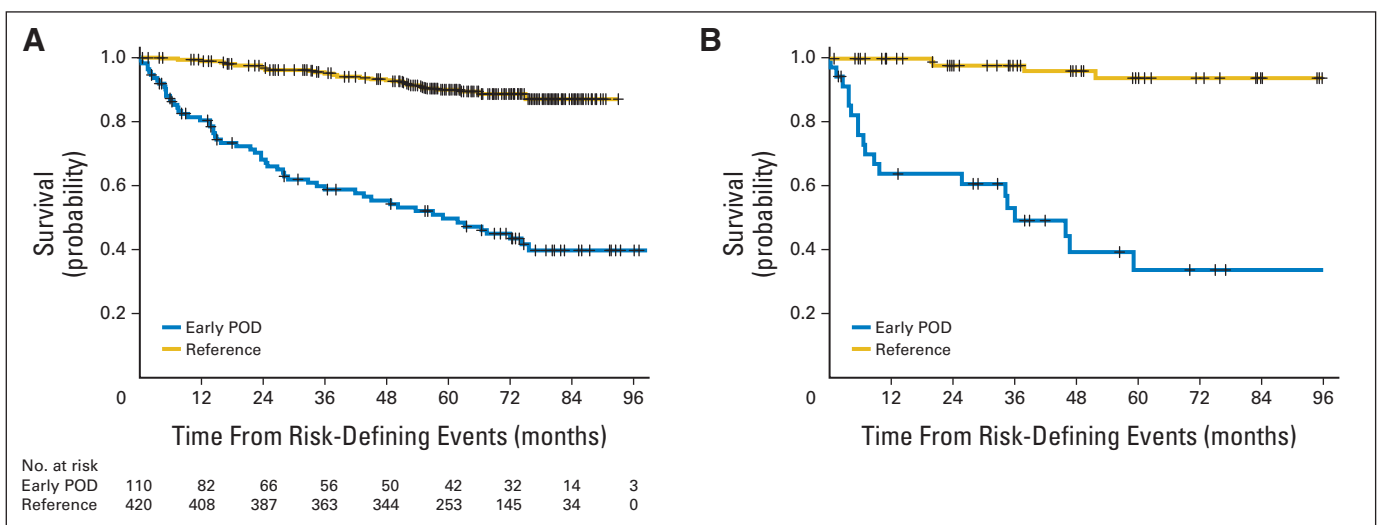


Fig 3. (A) Overall survival (OS) from a risk-defining event after diagnosis in patients who received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the National LymphoCare Study group. Patients with early progression of disease (POD) had poor survival. Two-year OS was 68% (95% CI, 58.2% to 76.3%). Five-year OS was 50% (95% CI, 39.4% to 59.2%). OS in the reference group was 97% (95% CI, 94.6% to 98.1%) at 2 years and 90% (95% CI, 86.2% to 92.4%) at 5 years. (B) Patients in the validation set who received R-CHOP with early POD also had inferior OS.

Table 3. Overall Survival for Patients With Early POD Versus the Reference Group

Group	R-CHOP				R-CVP				R-Flu			
	Total No.	No. of Deaths	HR	95% CI	Total No.	No. of Deaths	HR	95% CI	Total No.	No. of Deaths	HR	95% CI
Reference	420	44			184	34			131	17		
Early POD	110	57										
FLIPI adjusted	110	57	6.44	4.33 to 9.58	53	31	3.66	2.20 to 6.09	53	27	4.86	2.60 to 9.10
Unadjusted	420	44	7.17	4.83 to 10.65	53	31	4.91	3.00 to 8.01	53	27	5.87	3.17 to 10.87

NOTE. Early POD after other chemoimmunotherapy regimens was similarly predictive of poor overall survival.

Abbreviations: FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; POD, progression of disease; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine, and prednisone; R-Flu, rituximab with fludarabine.

treated with ASCT. Hence, we were unable to establish whether ASCT consolidation or other alternate treatments at relapse mitigate the risk of death after R-CHOP in early progressors. However, given their poor prognosis, consideration of early-POD patients for aggressive second-line treatments, including possibly ASCT, seems reasonable. This was suggested by investigators from the Groupe d'Etudes des Lymphomes de l'Adulte (GELA)/Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang (GOELAMS) FL2000 study who evaluated ASCT in the first relapse of FL.²⁹

Rational design of clinical trials aimed at changing the outcome of this particular group of patients at relapse is needed to incorporate appropriate treatment strategies into clinical practice. At present, determining changes in OS remains the gold standard in clinical trial endpoints.^{30,31} Yet, in the context of an illness with a long natural history like FL, and with the advent of novel treatments aimed at extending survival, OS assessments seem increasingly elusive. On the basis of our results, we believe that 2-year PFS should be further validated in the context of randomized clinical trials as a potential surrogate end point and an alternative to PFS or OS as a primary end point in patients with FL treated with first-line chemoimmunotherapy. Secondary analyses of data from clinical trials have been performed to establish surrogate end points for other cancers,^{32,33} and similar approaches are underway in FL in which 2-year PFS could be compared with alternative early end points. Similar attention is emerging regarding 2-year event-free survival as an end point in diffuse large B-cell lymphoma.^{33a} Understanding that early relapse is predictive of poor survival fills a knowledge gap that can aid clinicians in discussions of prognosis and in selection of subsequent treatments.¹⁶ Intuition suggests that patients with FL who experience POD earlier than the median time may be expected to have worse disease. Our findings show the degree to which this is the case. These findings also suggest that developing strategies that affect the early-POD group can provide meaningful clinical benefit for patients with FL.

A biologic rationale to explain this heterogeneity in patient outcomes would provide meaningful insights that can influence the next generation of treatments for patients with FL. Investigators in a landmark study using gene-expression profiling established that the microenvironment in FL has significant prognostic importance and influences survival. The immune response 1 gene signature was characterized by a high expression of genes from non-neoplastic cells, such as macrophages and T cells, in the tumoral microenvironment, and it was associated with a favorable prognosis. In contrast, the immune response 2 signature comprised genes expressed by dendritic cells and macrophages and had worse outcomes.¹⁷ Moreover, other genetic

alterations, such as chromosomal gains and losses or rearrangements of *P53* or *MYC*, have been implicated in poor outcomes in FL.^{34,35} Understanding whether patients with early POD in FL are enriched with some of these biologic features is a critical next step in changing survival for this group of patients through rationally targeted approaches, but this was not possible in our clinical database.

Our current study has other limitations. Histologic results were not centrally reviewed in the NLCS. We believe this is not likely to affect our conclusions because previous data suggested a high rate of accuracy in community diagnosis of FL.³⁶ In the NLCS, disease progression was determined by the treating physician radiographically and clinically; this approach may be viewed as a surrogate for true time to relapse. Registry data reflect treatment decisions made by the treating physician. As a result, they may be biased by patient selection and other confounding factors, and they do not provide a biologic basis to explain why these patients have poor outcomes. However, to address some of these limitations, we validated our findings in an independent cohort with histologic findings reviewed by expert hematopathologists and found equivalent results.

In summary, POD within 2 years of diagnosis in patients treated with R-CHOP defines a unique subgroup of patients with FL who are at a substantially greater risk of death compared with patients treated with R-CHOP without early POD. Understanding the mechanisms responsible for this by means of targeted sequencing or gene-expression profiling would be important to improving the outcome of this group. This newly defined high-risk group of patients represents a distinct population in whom further study is warranted in both directed prospective clinical trials of FL biology and treatment. Moreover, we propose that 2-year PFS may be a practical and meaningful clinical end point for trials involving a chemoimmunotherapy backbone in FL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study

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Appendix

Sensitivity Analysis of Overall Survival Modeling

Particular challenges are posed in comparing groups that are not known at baseline. In our case, we cannot classify patients until they have either experienced early progression of disease (POD) or survived without POD until 2 years after diagnosis. If a traditional Cox model with an end point of overall survival from diagnosis is used, the reference group would by definition have a 2-year survival benefit built in to their survival duration; this would introduce immortal time bias. One method for handling this type of time-varying group membership is to use a landmark approach in which patients who have not yet experienced an event are classified according to their group membership at a fixed point in time. This method works well when group membership is known relatively early, for example, in comparing treatments that are started within 3 months of diagnosis, and when few events have occurred before that time point. In our case, where group membership was not known until 2 years after diagnosis, and where 40% of deaths in the early-POD group occurred before the 2-year landmark, landmark analysis from the 2-year postdiagnostic mark would be misleading. The recommended alternative in this situation would be the Cox proportional hazards model with early-POD status as a time-varying covariate, where patient survival would contribute to the early-POD group from the time early POD occurs onward (results shown in [Table A1](#)). Because this approach gives a more theoretical result that can be difficult to conceptualize (eg, it is not possible to visualize with traditional Kaplan-Meier plots), we selected the slightly more conservative end point of OS from risk-defining event for our primary analysis. The clock for the reference group starts furthest from diagnosis, serving to reduce the estimated effect of early POD using this end point.

Exploration of Alternative Definitions of High Risk

We empirically chose the 24-month time point to define patients at high risk to capture the window when the peak risk of progression was observed. We also investigated whether POD within other time windows may meaningfully separate patients by high and low risk. Early POD was associated with similarly worse OS regardless of cutoff point selected ([Table A2](#)). However, selection of the 2-year cutoff point allowed us to identify substantially more patients at high risk than did the 1-year cutoff point ([Table A3](#)) without requiring the additional year of follow-up for the 3-year cutoff point.

Table A1. HRs for Overall Survival From Diagnosis in Patients with Early POD Compared With Those With No Early POD

Early POD	Overall Survival			
	Unadjusted		FLIPI Adjusted	
	HR	95% CI	HR	95% CI
R-CHOP	8.94	6.11 to 13.09	8.07	5.51 to 11.83
R-CVP	5.45	3.45 to 8.61	4.20	2.62 to 6.73
R-Flu	8.17	4.60 to 14.51	6.48	3.60 to 11.67

NOTE. Cox proportional hazards estimates were performed with risk status as a time-varying covariate. Analysis included patients with less than 2 years of follow-up without POD or death before progression contributing to the no-early-POD group.

Abbreviations: FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; POD, progression to disease; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine, and prednisone; R-Flu, rituximab with fludarabine.

Table A2. Overall Survival From a Risk-Defining Event for POD Within 1 Year and 3 Years

Early POD	Overall Survival			
	≤ 1 Year		≤ 3 Years	
	HR	95% CI	HR	95% CI
R-CHOP	8.19	5.43 to 12.34	6.66	4.34 to 10.22
R-CVP	4.86	2.86 to 8.25	5.03	2.97 to 8.51
R-Flu	7.08	3.86 to 12.99	6.23	3.19 to 12.16

NOTE. Data are unadjusted Cox proportional hazards estimates for overall survival from the time of a risk-defining event, that is, POD for early POD or 1 year or 3 years for corresponding reference groups.

Abbreviations: HR, hazard ratio; POD, progression of disease R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine, and prednisone; R-Flu, rituximab with fludarabine-containing regimen.

Relapse After R-CHOP in FL Confers High Risk of Death

Table A3. No. of Patients Classified as Having Early POD Within 1, 2, or 3 Years

	POD								
	R-CHOP			R-CVP			R-Flu		
	≤ 1 Year	≤ 2 Years	≤ 3 Years	≤ 1 Year	≤ 2 Years	≤ 3 Years	≤ 1 Year	≤ 2 Years	≤ 3 Years
Reference	497	420	364	230	184	157	170	131	113
Early POD	58	110	144	30	53	68	27	53	65

Abbreviations: POD, progression of disease; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine, and prednisone; R-Flu, rituximab with fludarabine.