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Identification of potential surrogate end points in randomized clinical trials of aggressive and indolent non-Hodgkin's lymphoma: correlation of complete response, time-to-event and overall survival end points

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Background: The correlation between efficacy end points in randomized controlled trials (RCTs) of systemic therapy for non-Hodgkin's lymphoma (NHL) was investigated to identify an appropriate surrogate end point for overall survival (OS).

Methods: RCTs of previously untreated NHL published from 1990 to 2009 were identified. Associations between absolute differences in efficacy end points were determined using nonparametric Spearman's rank correlation coefficients (r_s).

Results: Thirty-eight RCTs representing 85 treatment arms for aggressive NHL and 20 RCTs representing 42 arms for indolent NHL were included. For aggressive NHL, differences in 3-year progression-free survival (PFS)/event-free survival (EFS) were high correlated with differences in 5-year OS {r_s of 0.90 [95% confidence interval (CI) 0.73–0.96]} and linear regression determined that a 10% improvement in 3-year EFS or PFS would predict for a 7% ± 1% improvement in 5-year OS. For indolent histology disease, differences in complete response were strongly correlated with differences in 3-year EFS [r_s 0.86 (95% CI 0.35–0.97)], but there was no correlation between 3-year time-to-event end points and 5-year OS.

Conclusions: Improvements in 3-year EFS/PFS are highly correlated with improvements in 5-year OS in aggressive NHL and should be explored as a candidate surrogate end point. Definition of these relationships may inform future clinical trial design and interpretation of interim trial data.

Key words: clinical trials, non-Hodgkin's lymphoma, surrogate end points

introduction

Selection of efficacy end points for randomized controlled trials (RCTs) of non-Hodgkin's lymphoma (NHL) depends largely on histology and treatment goals. In untreated aggressive histology lymphomas, primary treatment with chemotherapy is undertaken with curative intent, so the development of new treatments to increase the rate of overall survival (OS) remains an important goal for this patient population. In contrast, indolent histology lymphomas have a very long natural history and are generally incurable, and systemic treatment is generally directed at improving symptoms and prolonging progression-free survival (PFS).

Although OS is an unambiguous measure of efficacy in clinical trials, its use as a primary end point requires a long duration of follow-up and may prolong the process of identifying novel and potentially beneficial therapy. Surrogate end points for OS have been explored in breast [1, 2], lung [3], and rectal cancers [4] but only have been validated in colon cancer [5–7]. Nonetheless, there is emerging acceptance of such end points by the oncology community and by regulatory agencies [8–10].

While there is great interest in developing validated surrogate end points for OS, there is no consensus on the necessary validation process [5,11–14]. Prentice et al. proposed that the surrogate marker should correlate with the true end point and capture the net effect of the treatment on the true end point [11, 12]. More recently, Buyse et al. [13] stated that the surrogate should be predictive of the final end point using both trial- and individual-level data. Additionally, Begg and Leung [14] argued that significant differences observed for the candidate surrogate end point in trials should be concordant with results for the true end point.

Surrogate end points have yet to be explored in the trials of NHL. Time-to-event end points including event-free survival (EFS) or PFS permit earlier reporting of results, but their ability

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to predict OS is unknown. The purpose of this study is to describe reporting of primary and secondary end points in RCTs of NHL and to determine the correlations between response, intermediate time-to-event, and survival end points in the treatment of NHL with the goal of identifying a surrogate end point for OS.

methods

trial selection

RCTs were eligible for inclusion if they enrolled previously untreated aggressive NHL with at least 100 patients per arm or untreated indolent NHL with at least 75 patients per arm. Studies were excluded if they primarily investigated the effect of autologous stem-cell transplantation (ASCT), maintenance, or local therapies (i.e. surgery, radiation); exclusively enrolled T cell, mantle cell, HIV-associated Burkitt, primary central nervous system, or small-cell lymphocytic lymphomas (including chronic lymphocytic leukemia); and those reporting pooled data from multiple trials.

literature search. A systematic literature search was conducted to identify RCTs using Medline, EMBASE (Exerpta Medica Database), and the Cochrane Central Register of Controlled Trials databases from 1 January 1990 to 1 May 2009. Search strategy included MeSH headings and keywords such as 'Lymphoma, Non-Hodgkin's', 'non-Hodgkin' or 'NHL'; 'Antineoplastic Agents', 'Antineoplastic Combined Chemotherapy Protocols' or 'chemotherapy'; and 'Randomized Controlled Clinical Trial' or 'Phase III Clinical Trial'. A manual search was also carried out for abstracts in the published proceedings of the annual meetings of the American Society of Clinical Oncology, American Society of Hematology, and the triennial International Conference on Malignant Lymphoma in Lugano from 2004 to 2009. Abstracts from all identified RCTs were manually reviewed for eligibility based on inclusion and exclusion criteria. RCTs were subgrouped for analysis by disease histology (i.e. aggressive or indolent).

data collection. For each eligible published RCT, data were extracted regarding study design, sample size, enrollment dates, experimental arms, and response rates (RRs). The standard chemotherapy arm and primary end point in each trial were determined by consensus of two investigators (LL and MC). Data on EFS, PFS, and OS were determined for all treatment arms using published data or survival curves. Reported time-to-event end points reflect the original terminology used by authors in the RCT. For our analysis, time-to-event end points were defined as PFS or EFS according to established (i.e. per-protocol) definitions in the International Working Group Revised Response Criteria for Lymphoma [15]. Results of each trial for PFS, EFS or OS were considered significant based on the per-protocol analysis with a P-value ≤ 0.05. RCTs were categorized as 'positive' if the specified primary end point was met. If a RCT was reported on multiple occasions, data were collated from all abstracts and the most recent data were used in the event of discrepancies.

statistical analysis

Descriptive statistics were used to summarize trial characteristics and end point selection. To evaluate changes in primary end point selection over time, studies were dichotomized into an earlier or later time period based on the year of study initiation and the frequency of time-to-event end points was examined using the Cochran–Armitage test for trend. In addition, trials were evaluated based on whether rituximab was included in at least one of the treatment arms, and differences in primary end point selection were determined using Fisher's exact test. For each trial, the absolute differences in end points [complete response (CR), EFS, PFS, and OS] were calculated as the estimate in the experimental arm minus the estimate in the standard arm. For multiarm and factorial-design studies, only one randomly chosen experimental arm (or factorial group) was used to ensure that the absolute differences of the same end point were considered independent.

The nonparametric Spearman's rank correlation coefficient (r_s) was used as a measure of correlation between the differences in (i) CR and intermediate time-to-event end points (3-year EFS/PFS or OS) and (ii) potential surrogate end points (CR, 3 year EFS/PFS) and 5-year OS. In this analysis, PFS and EFS were considered together as an intermediate time-to-event end point since the per-protocol definition of EFS always included progression and death as events; however, a separate analysis was also presented where possible. Correlation coefficients were compared using the normal approximation to the z-transformation of r_s and its standard deviation. For strongly correlated end points, linear regression analysis was carried out to obtain slope, which served as a conversion factor between end points and determined the proportion of variability explained (R^2). Furthermore, concordance of strongly correlated end points was assessed by determining the proportion of trials in which the set of end points led to the same conclusion based on statistical significance testing ($P < 0.05$).

results

A total of 58 RCTs conducted from 1978 to 2005 were identified: 38 in aggressive histology and 20 in indolent histology lymphomas (Table 1). The aggressive lymphoma RCTs included 85 treatment arms representing 16 103 patients and had a median follow-up of 55 months (range 20–108). The indolent lymphoma RCTs included 42 treatment arms and 5128 patients, with a median follow-up of 52 months (range 29–144).

end point selection and reporting

Regardless of lymphoma histology, almost all trials reported OS (94% for aggressive, 95% for indolent), most trials included RR (97% for aggressive, 75% for indolent), but only approximately one-third of the trials reported at least one other time-to-event end point (Table 1).

Seven different primary end points were reported, reflecting heterogeneity in reporting terminology (Table 2). OS and RR were unambiguously defined as demonstrated by their consistent frequency of use as primary end points regardless of reported or per-protocol definitions for both histologies of lymphoma (Table 2). Discrepancies between reported and per-protocol end point definitions arose from the use of 'event' or 'failure', which affected time-to-event end points, such as PFS, EFS, time-to-failure (TTF), failure-free survival (FFS), and disease-free survival. For example if failure was defined as progression or death, FFS would be classified as PFS by the per-protocol definition, whereas inclusion nonprogression events suggested that this term was being used synonymously with EFS.

For aggressive lymphoma RCTs, the most commonly reported primary end point was OS followed by EFS. For indolent lymphoma RCTs, choice of primary end point was more heterogeneous, but use of either TTF or RR was most common (Table 2). Trend in the selection of primary end points was evaluated by comparing RCTs initiated before 1990 to those initiated following 1991 (Figure 1A) and by comparing RCTs based on the presence of rituximab in at least one treatment arm (Figure 1B). In the more recent time period, use

Table 1. Characteristics of included phase III trials

Characteristic	Aggressive histology ($N = 38$), n (%)	Indolent histology ($N = 20$), n (%)
Sample size		
Median	382	244
Range	177–1222	131–428
Time period of study		
Before 1990	16 (42)	7 (35)
1991–2005	22 (58)	13 (65)
Accrual duration (years)		
Median	4	5
Range	1–10	2–9
Follow-up duration (months)		
Median	55	53
Range	20–108	29–144
Design		
Two-arm	25 (66)	12 (60)
Three-arm	1 (3)	2 (10)
Four-arm	1 (3)	0
Two-arm, Two-stage	5 (13)	6 (30)
2 × 2 factorial	6 (16)	0
Number of comparisons per trial		
1	33 (87)	18 (90)
2	2 (5)	2 (10)
3	3 (8)	0
Frequency of reported end point[a]		
OS	36 (94)	19 (95)
EFS	10 (26)	6 (30)
PFS	12 (32)	6 (30)
DFS/RFS	15 (39)	4 (20)
FFS	8 (21)	2 (10)
TTF	4 (10)	10 (50)
TTP	2 (5)	4 (20)
RR	37 (97)	15 (75)
Outcomes		
Positive	12 (32)	11 (55)
Negative	26 (68)	9 (45)

[a]Includes primary and secondary end points, with percentages presented as a ratio of total number of randomized clinical trials.

OS, overall survival; EFS, event-free survival; PFS, progression-free survival; DFS, disease-free survival; RFS, relapse-free survival; FFS, failure-free survival; TTF, time-to-failure; TTP, time-to-progression; RR, response rate.

of OS decreased in both indolent (28% versus 0%, $P = 0.042$) and aggressive NHL trials (81% versus 36%, $P = 0.006$). In the latter histologic subgroup, use of EFS became more common (0% versus 36%, $P = 0.007$). In aggressive NHL, RCTs evaluating rituximab were significantly less likely to use OS as the primary end point than RCTs without rituximab (14% versus 64%, $P = 0.013$), but there was no such difference noted for indolent histology NHL.

correlation between response and intermediate time-to-event end points

For aggressive NHL, differences in CR rates strongly correlated with differences in 3-year EFS/PFS with an r_s of 0.70 [95% confidence interval (CI) 0.42–0.86] (Table 3). The r_s between differences in CR rate and differences in 3-year EFS and 3-year PFS were 0.88 (95% CI 0.57–0.97) and 0.63 (95% CI 0.21–0.84), respectively. There was a moderate correlation between differences in CR rate and differences in 3-year OS with a r_s of 0.58 (95% CI 0.29–0.77).

For indolent NHL, differences in CR rate also strongly correlated with differences in 3-year EFS/PFS with a r_s of 0.77 (95% CI 0.41–0.92). While differences in CR rate correlated strongly with differences in 3-year EFS when considered alone with a r_s of 0.86 (95% CI 0.35–0.97), there was no correlation between differences in CR rate and differences in 3-year PFS or 3-year OS.

correlation between potential surrogate and OS end points

There was no relationship between difference in CR and difference in 5-year OS in either aggressive or indolent NHL (Table 3). However, in aggressive NHL, differences in 3-year PFS/EFS were highly correlated with differences in 5-year OS with a r_s of 0.90 (95% CI 0.73–0.96), and similarly strong correlations were noted when differences in 3-year PFS and 3-year EFS were separately correlated with 5-year OS. In contrast, there was no correlation between differences in these intermediate time-to-event end points and differences in 5-year OS in indolent NHL (Table 3).

In an exploratory analysis, we determined the correlation between 3-year PFS or EFS with 5-year OS within individual arms of the randomized trials (supplemental Data available at *Annals of Oncology* online). Similarly, these two end points were strongly correlated in aggressive NHL with a $r_s = 0.85$ (95% CI 0.71–0.92, $P < 0.001$) (supplemental Figure S1, available at *Annals of Oncology* online) but only moderately correlated in indolent NHL with a $r_s = 0.56$ (95% CI 0.2–0.78, $P = 0.004$) (supplemental Figure S2, available at *Annals of Oncology* online).

linear regression analysis

For strongly correlated end points, linear regression was carried out through the origin. In aggressive NHL, the regression of differences in CR and 3-year EFS yielded a slope of 0.9 ± 0.1 [±1 standard error (SE) of the estimate] with a R^2 of 0.78 (Figure 2). The regression of differences in 3-year EFS/PFS and 5-year OS yielded a slope of 0.7 ± 0.1 (±1 SE of the estimate) with a R^2 of 0.66 for aggressive histology NHL (Figure 3). In indolent NHL, the regression of differences in CR and 3-year EFS yielded a slope of 0.9 with a large SE (0.3) due to the smaller number of trials.

These findings suggest that in aggressive NHL, a 10% improvement in CR is estimated to correspond with a 9% ± 1% improvement in 3-year EFS and that a 10% improvement in 3-year EFS or PFS would predict for a 7% ± 1% improvement in 5-year OS. In indolent NHL, a 10% improvement in CR is estimated to predict a 9% ± 3% benefit in 3-year EFS.

concordance of trial results for correlated end points

For aggressive NHL, 26 trials had paired results where differences in 3-year EFS/PFS and 5-year OS between treatment

Table 2. Frequency and reporting of primary end points in lymphoma randomized clinical trials[a]

Primary end point	Aggressive ($N = 38$)		Indolent ($N = 20$)	
	Reported, *n* (%)	Per-protocol, *n* (%)	Reported, *n* (%)	Per-protocol, *n* (%)
OS	21 (55)	21 (55)	2 (10)	2 (10)
EFS	8 (21)	12 (32)	2 (10)	5 (25)
PFS	0	0	3 (15)	5 (25)
DFS	0	1 (3)	0	0
FFS	4 (10)	0	0	0
TTF	1 (3)	0	5 (25)	0
RR	2 (5)	2 (5)	5 (25)	5 (25)
CR	2 (5)	2 (5)	3 (15)	3 (15)

[a]Primary end point based at time of study initiation. 'Reported' refers to the original terminology used by study authors, whereas 'per-protocol' refers to classification of the end point according to International Working Group guidelines based on its definition within the protocol [15].
OS, overall survival; EFS, Event-Free Survival; PFS, Progression-Free Survival; DFS, Disease-Free Survival; FFS, Failure-Free Survival; TTF, Time-to-Failure; RR, Response Rate; CR, Complete Response.

arms were assessed for statistical significance. Concordant results were present in 23 trials (15 had no difference between arms for either end points and 8 had significant differences for both end points, Table 4). The three discordant trials all showed a significant difference in the 3-year time-to-event end point, but no difference in 5-year OS.

Of the 14 indolent lymphoma trials that had paired results for CR and 3-year EFS/PFS, eight had concordant conclusions (five reported statistically significant differences for both end points and two trials reported no difference at either end points, Table 4). Among the six trials with discordant results, five had no difference in CR but did have a significant difference in 3-year EFS/PFS, while only one trial had a difference in CR but no difference in 3-year EFS/PFS.

discussion

Despite the lack of validated surrogate end points in NHL, our review reveals that time-to-event end points are increasingly used in place of OS as the primary end point in recent phase III clinical trials. There was a trend toward increasing use of EFS and TTF, respectively, in RCTs of aggressive and indolent histology disease. Improvements in CR strongly predicted for improvements in 3-year EFS in both aggressive and indolent histology lymphomas but were not predictive of OS. In aggressive histology lymphoma, 3-year PFS/EFS were strongly correlated with 5-year OS, and statistically significant differences in PFS/EFS observed at 3 years predicted for differences in OS after 5 years of follow-up. However, considerable inconsistency exists both in the reporting and definition of failure or event end points. Our results suggest that 3-year PFS should be further explored as a candidate surrogate end point in RCTs of aggressive NHL using individual patient data.

A validated surrogate end point for 5-year OS offers potential advantages for conducting clinical trials more efficiently and expediting development of new treatments. In contrast to OS, however, time-to-event end points are poorly defined and may suffer from bias in ascertainment [16–18]. For example EFS is a composite end point consisting of objective measures, such as death and progression, in addition to more subjective components (i.e. investigator decision to initiate new treatment). Guidelines for the harmonization of response assessment in clinical trials of lymphoma provide a clear definition and methodology for assessing progression but do not address the definition and assessment of nonprogression events [15, 19]. Consequently, PFS may be a better candidate surrogate since the specificity of included 'events' has implications for the power of a trial, the likelihood of a significant result, and ability to conduct cross-trial comparisons [18].

Recognizing that the majority of RCTs were initiated before the publication of guidelines to harmonize end points [15, 19], PFS and EFS were combined in our analysis. For both histologic subgroups of lymphoma, initial CR predicted for lack of events at 3 years, but the correlation with OS at either 3 or 5 years was not strong, implying that attainment of CR does not provide information about longer term outcomes. While CR and 3-year EFS were strongly correlated, this may be partially attributed to the actual definition of event, which encompassed lack of response or absence of CR in some trials. In indolent lymphoma, a similar relationship between higher CR rates and improved EFS/PFS has been demonstrated in individual trials of rituximab-based treatment [20–22] but was not consistently seen in trials evaluating cytotoxic chemotherapy [23–25]. However, attainment of CR did not predict for improved OS, which was likely due to the availability of effective treatments for relapsed or refractory disease and the relatively short duration of follow-up of 5 years, which may be inadequate for evaluation of OS given the long natural history of indolent lymphomas.

For aggressive NHL, the strong relationship between CR and EFS/PFS is not surprising. Achievement of CR may be associated with lower relapse rates [26] and failure to achieve CR is an indication for high-dose chemotherapy and ASCT for young fit patients. The correlation between CR and OS was moderate at 3 years but was not apparent at 5 years of follow-up. This dissociation between CR and OS at 5 years may reflect the cumulative impact of relapse over time [27, 28]. In contrast, a significant number of deaths within the first 3 years are likely

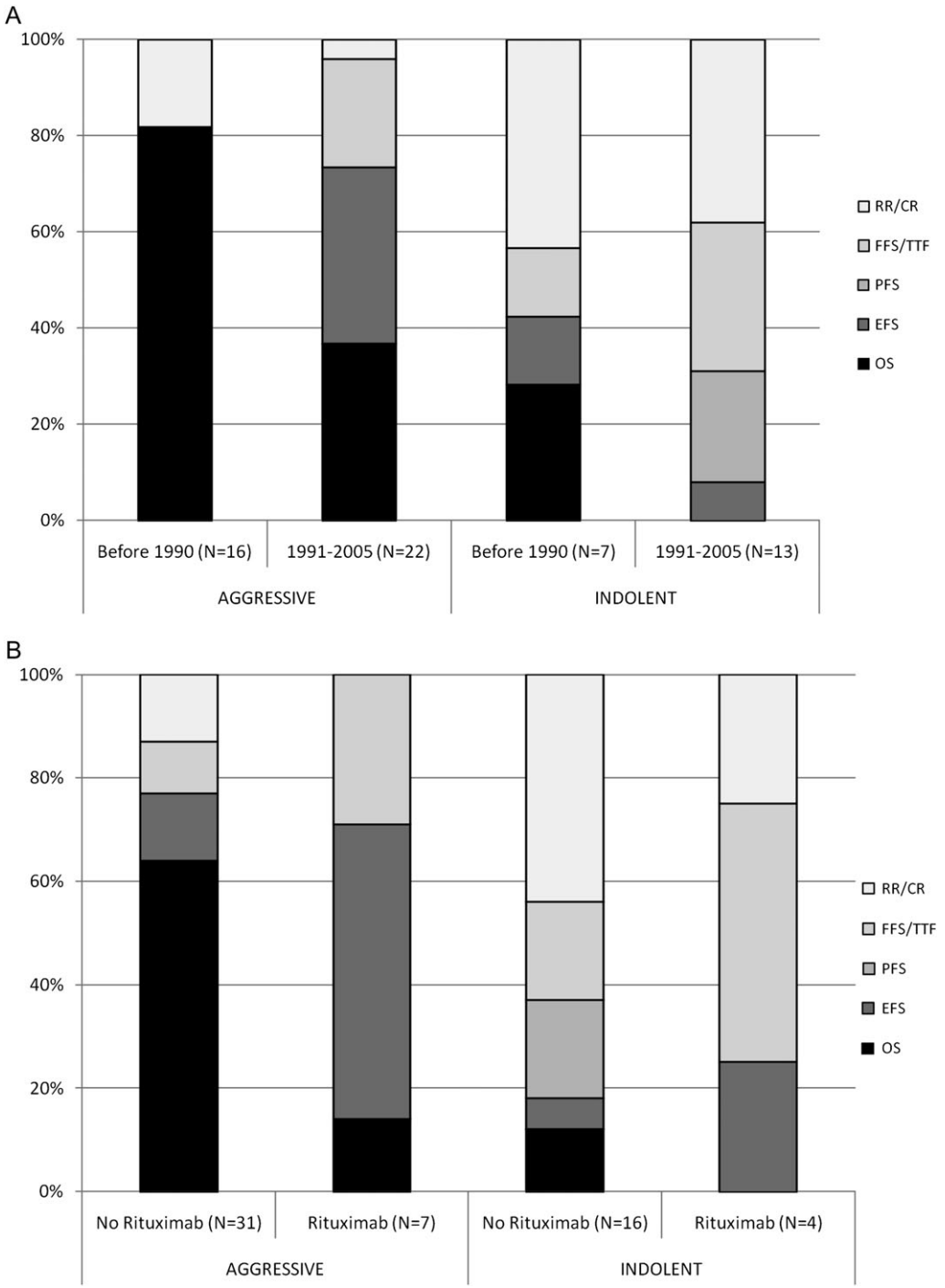

Figure 1. Trends in selection of primary end points according to (A) time period and (B) presence or absence of rituximab in at least one treatment arm of the trial. RR/CR, response rate or complete response; FFS, failure-free survival/TTF, time-to-failure; PFS, progression-free survival; EFS, event-free survival; OS, overall survival.

attributed to those without initial CR (i.e. those with refractory or residual disease). Although these patients may be offered ASCT, they tend to have worse outcomes [29], so the potentially confounding effect of ASCT on 3-year survival is minimal.

It is striking that a 3-year time-to-event end point such as PFS may be predictive of 5-year OS in aggressive histology lymphoma, considering the diversity of treatments investigated in the trials that we evaluated. The correlation between PFS and OS in aggressive but not indolent NHL is consistent with the observation that the relationship between these two end points is influenced by expected survival post-progression (SPP) time [30]. A significant difference in PFS is more likely to predict for significant OS difference in a disease with a shorter expected SPP such as aggressive lymphoma where median survival following relapse is 9 months [27] compared with follicular

Table 3. Correlation between CR, time-to-event, and OS end points

	Aggressive			Indolent		
	Nonparametric Spearman rank coefficient	95% CI	*P*-value	Nonparametric Spearman rank coefficient	95% CI	*P*-value
CR and 3-year time-to-event and OS end points						
CR and 3-year EFS	0.88	0.57–0.97	0.0003	0.86	0.35 to 0.97	0.0059
CR and 3-year PFS	0.63	0.21–0.84	0.005	0.41	−0.52 to 0.88	0.35
CR and 3-year PFS/EFS	0.70	0.42–0.86	<0.0001	0.77	0.41–0.92	0.0007
CR and 3-year OS	0.58	0.29–0.77	0.004	0.41	−0.1 to 0.74	0.098
Potential surrogate end points and 5-year OS						
CR and 5-year OS	0.50	0.23–0.74	0.01	0.21	−0.34 to 0.5	0.44
3-year EFS or PFS and 5-year OS	0.90	0.73–0.96	<0.0001	0.26	−0.38 to 0.72	0.41

CI, confidence interval; CR, complete response; EFS, Event-Free Survival; PFS, Progression-Free Survival; OS, overall survival.

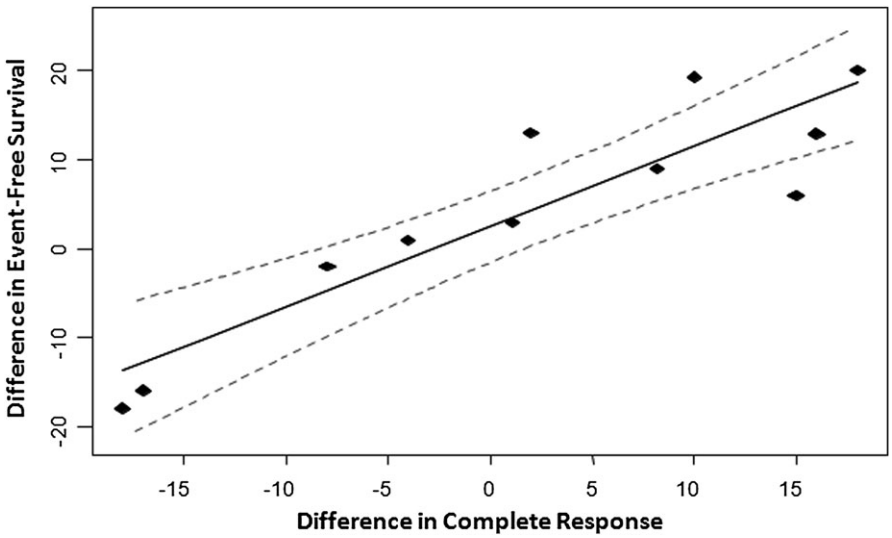

Figure 2. Correlation between differences in complete response rates and differences in 3-year event-free survival in aggressive non-Hodgkin's lymphoma. Solid line represents the linear regression with 95% confidence intervals indicated by the dashed lines.

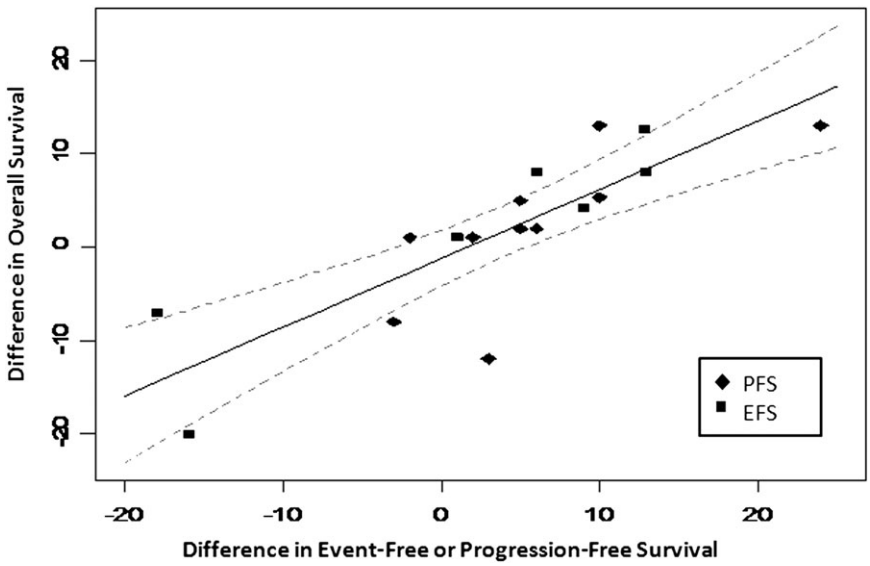

Figure 3. Correlation between differences in 3-year event or progression-free survival and 5-year overall survival in aggressive non-Hodgkin's lymphoma. Solid line represents the linear regression with 95% confidence intervals indicated by the dashed line.

Table 4. Concordance of randomized clinical trial outcomes

Treatment[a]	*N*	Primary end point (per-protocol)	Significant difference in CR	Significant difference in EFS/PFS	Significant difference in OS	Superior arm
Aggressive histology lymphoma						
Dose-escalated CHOEP-21 versus CHOEP-21 [33]	389	EFS	No	No	No	No difference
R-CHOP-14 versus CHOP-14 for 6 versus 8 cycles [34]	1222	EFS	Yes	Yes	Yes	R-CHOP-14 for 6 cycles
CEOP-14 versus CEOP-21, ±R [35]	217	OS	No	n/a	No	No difference
Escalated R-CEOP versus escalated CEOP [36]	204	DFS	No	n/a	No	No difference
Intensified CHOP-14 for 6 cycles versus standard CHOP-21 for 8 cycles [37]	477	OS	No	No	No	No difference
Mini-COEP versus P-VEBEC [38]	232	OS	No	No	No	No difference
R-CHOP versus CHOP, then R-maintenance versus nothing [39]	632	EFS	n/a	Yes	No	R-CHOP
R-CHOP-like versus CHOP-like chemotherapy [34]	824	EFS	Yes	Yes	Yes	R-CHOP like
PMitCEBO versus CHOP, ±GCSF [40]	784	EFS	Yes	No	No	No difference
Flexible versus fixed dosing of anthracycline in ProMECE-CytaBOM or ProMI-CytaBOM [41]	356	EFS	No	n/a	No	No difference
ProMECE-CytaBOM versus ProMI-CytaBOM, then maintenance chemotherapy [42]	249	OS	No	No	No	No difference
R-CHOP-14 versus CHOP-14 [43]	243	EFS	n/a	n/a	Yes	R-CHOP
CIOP versus CHOP [44]	211	OS	Yes	Yes	Yes	CHOP
Pirarubicin-COP versus CHOP (2/3 dose) versus pirarubicin-COPE [45]	443	OS	No	No	No	No difference
VEPA-B/FEPP-AB/M-FEPA every 10 weeks for 3 cycles versus VEPA-B/FEPP-B/M-FEPA every 14 weeks for 4 cycles [46]	447	OS	No	n/a	No	No difference
CHOP-14 versus CHOP-21, ±etoposide [47]	689	EFS	n/a	Yes	No	CHOP-14
ACVBP versus CHOP [26]	635	EFS	No	Yes	Yes	ACVBP
CHOEP versus CHOP, every 14 versus 21 days [48]	710	EFS	n/a	Yes	No	CHOEP
CNOP versus CHOP, ±GCSF [49]	458	EFS	Yes	Yes	Yes	CHOP
R-CHOP versus CHOP [50]	399	EFS	Yes	Yes	Yes	R-CHOP
CNOP versus CEOP [51]	249	OS	No	No	No	No difference
PMitCEBO versus PAdriaCEBO [52]	473	OS	No	n/a	Yes	PMitCEBO
CHOP + IFN versus CHOP [53]	435	RR	No	n/a	No	No difference

Table 4. (*Continued*)

Treatment[a]	*N*	Primary end point (per-protocol)	Significant difference in CR	Significant difference in EFS/PFS	Significant difference in OS	Superior arm
PACEBOM versus CHOP [54]	459	OS	No	n/a	No	No difference
MACOP-B versus CHOP [55]	374	OS	No	No	No	No difference
CAPOMEt versus CHOP-MTX [56]	281	OS	No	n/a	No	No difference
MECOP-B versus MACOP-B [57]	211	OS	No	n/a	No	No difference
Alternating B-CHOP-M and PEEC-M versus B-CHOP-M [58]	325	OS	No	n/a	No	No difference
CTVmP versus CVmP [59]	453	OS	Yes	Yes	Yes	CTVmP
MACOP-B over CHOP [60]	236	CR	No	Yes	Yes	MACOP-B
ProMACE-MOPP versus MACOP-B [61]	221	OS	No	No	No	No difference
ProMECE-CytaBOM versus MACOP-B [62]	210	OS	No	No	No	No difference
m-BACOD versus CHOP versus ProMACE-CytaBOM versus MACOP-B [63]	899	OS	No	No	No	No difference
ProMACE-MOPP versus CHVmP-VB [64]	430	OS	n/a	No	No	No difference
Escalated BACOP versus BACOP [65]	238	OS	No	No	No	No difference
m-BACOD versus CHOP [66]	325	OS	No	No	No	No difference
F-MACHOP versus MACOP-B [67]	286	CR	No	n/a	No	No difference
Low-dose bleomycin + CHOP versus CHOP, then low versus high-dose MTX [68]	177	RR	No	No	No	No difference
Indolent histology lymphoma						
R-CVP versus CVP [21]	321	EFS	Yes	Yes	Yes	R-CVP
R-CHVP + IFN versus CHVP-IFN [22]	360	EFS	Yes	Yes	No	R-CHVP + IFN
R-MCP versus MCP [20]	358	RR	Yes	Yes	Yes	R-MCP
CID versus CD [69]	200	EFS	No	Yes	No	CID
MCP versus CHOP [25]	277	CR	No	n/a	No	No difference
F versus CVP [23]	381	PFS	Yes	No	No	No difference
FMD versus CMD [70]	400	PFS	No	n/a	n/a	CMD
R-CHOP versus CHOP [71]	428	EFS	No	Yes	Yes	R-CHOP
CHOP + bleomycin versus cyclophosphamide [72]	228	OS	No	No	No	No difference
COPA + IFN versus COPA [73]	291	PFS	No	Yes		COPA + IFN
PmM versus COP, then IFN-maintenance versus observation [74]	246	RR	Yes	n/a	n/a	Not available
CHOP versus chlorambucil + prednisone [24]	259	RR	n/a	Yes	No	No difference
CHVP + IFN versus CHVP [75]	242	PFS	No	Yes	Yes	CHVP + IFN
BOP versus COP [76]	164	CR	No	n/a	No	No difference

Table 4. (*Continued*)

Treatment[a]	*N*	Primary end point (per-protocol)	Significant difference in CR	Significant difference in EFS/PFS	Significant difference in OS	Superior arm
Cladribine versus CVP versus cladribine + C [77]	197	PFS	Yes	Yes	n/a	Cladribine
FM versus mini-CHVdP [78]	155	CR	Yes	Yes	No	FM
FND versus alternating triple therapy (CHOD-bleomycin, ESHAP, and NOPP) [79]	142	RR	No	Yes	No	No difference
CHVmP + IFN versus F [80]	131	EFS	No	n/a	n/a	CHVP + IFN[b]
CVP + IFN versus CVP, then IFN-maintenance versus observation [81]	155	RR	n/a	Yes	No	No difference
IFN versus prednimustine versus observation [59]	193	OS	No	No	No	No difference

[a]Bolded items represent the two comparator arms used for analysis in the following format: experimental versus standard arm.
[b]Conclusion based on 2-year follow-up data.
RR, response rate; CR, complete response; EFS, Event-Free Survival; PFS, Progression-Free Survival; OS, overall survival; n/a, not applicable; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CEOP, cyclophosphamide, epirubicin, vincristine, prednisone; R, rituximab; 14, cycle given every 14 days; 21, cycle given every 21 days; P-VEBEC, prednisone, vinblastine, epirubicin, bleomycin, etoposide, cyclophosphamide; PMitCEBO, prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine; ProMECE-CytaBOM, prednisone, cyclophosphamide, etoposide, epidoxorubicin, cytarabine, bleomycin, vincristine, methotrexate with leucovorin; ProMICE-CytaBOM, prednisone, cyclophosphamide, etoposide, idarubicin, cytarabine, bleomycin, vincristine, methotrexate with leucovorin; CIOP, cyclophosphamide, idarubicin, vincristine, prednisone; COP or CVP, cyclophosphamide, vincristine, prednisolone (or prednisone); COPE, cyclophosphamide, vincristine, prednisolone, etoposide; VEPA-B/FEPP-AB/M-FEPA and VEPA-B/FEPP-B/M-FEPA both contain vincristine, cyclophosphamide, prednisolone, doxorubicin, bleomycin, etoposide, procarbazine, methotrexate, leucovorin, vindesine (at differing doses and schedules of administration); ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; CNOP, cyclophosphamide, mitoxantrone, vincristine, prednisone; PAdriaCEBO, prednisolone, adriamycin, cyclophosphamide, etoposide, bleomycin, vincristine; IFN, interferon; GCSF, granulocyte colony stimulating factor; MTX, methotrexate; PACEBOM, prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, methotrexate; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; CAPOMEt, weekly alternating cyclophosphamide and doxorubicin, vincristine and prednisolone, methotrexate with leucovorin and etoposide; MECOP-B, methotrexate, epirubicin, cyclophosphamide, vincristine, prednisolone, and bleomycin; B-CHOP-M, bleomycin, cyclophosphamide, doxorubicin, vincristine, prednisolone and methotrexate; PEEC-M, methylprednisolone, vindesine, etoposide, chlorambucil and methotrexate; CVmP, cyclophosphamide, teniposide, prednisone; CTVmP, cyclophosphamide, pirarubicin, teniposide, prednisone; ProMACE-MOPP, procarbazine, methotrexate with leucovorin, doxorubicin, cyclophosphamide, and etoposide; m-BACOD, low-dose methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; ProMACE-CytaBOM, prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue; CHVmP-VB, cyclophosphamide, doxorubicin, teniposide, prednisone and vincristine, bleomycin; BACOP, bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone; m-BACOD, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone, methotrexate with leucovorin; F-MACHOP, 5-fluorouracil, methotrexate with leucovorin, cytarabine, cyclophosphamide, doxorubicin, vincristine, prednisone; CHVP, cyclophosphamide, doxorubicin, etoposide, prednisolone; MCP, mitoxantrone; chlorambucil, prednisolone; CID, chlorambucil, idarubicin, dexamethasone; CD, chlorambucil, dexamethasone; F, fludarabine; CMD, chlorambucil, mitoxantrone, dexamethasone; FMD, fludarabine, mitoxantrone, dexamethasone; COPA, cyclophosphamide, doxorubicin, vincristine and prednisone every 28 days; PmM, prednimustine, mitoxantrone; BOP, bendamustine, vincristine, prednisone; FM, fludarabine, mitoxantrone; CHVdP, cyclophosphamide, doxorubicin, vindesine, prednisone; FND, fludarabine, mitoxantrone, dexamethasone; CHOD, cyclophosphamide, doxorubicin, vincristine, dexamethasone, bleomycin; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; NOPP, mitoxantrone, vincristine, procarbazine, prednisone.

lymphoma where median OS is not reached even after 6 years of follow-up [31].

Our literature-based analysis is the first to examine end points in RCTs of untreated aggressive and indolent lymphoma spanning a 25-year period. One previous meta-analysis of follicular lymphoma trials reported a correlation between higher CR rate and reduction in hazard rate for PFS [32]. However, that analysis included single-arm phase II trials and effectively compared overall rates of CR and PFS associated with individual treatment arms. By including only RCTs, we were able to compare the actual impact of different treatments on these end points.

This study does have some limitations. First, our analysis was conducted using published trial-level data. To confirm the validity of 3-year PFS as a surrogate for 5-year OS in aggressive lymphoma, it is necessary to assess their correlation using individual patient data. Second, as the total number of trials included for each histologic subgroup of lymphoma was small,

the power to evaluate these relationships was limited by the actual reporting of the published studies. To test for correlations, a complete set of data for both the candidate surrogate and true end points is required [14] and only half of all trials had quantitative estimates for both PFS/EFS and OS. While hazard ratios would have provided a better comparison of the overall effect of treatment on survival over time, these were reported in <20% of all trials. Furthermore, in contrast to trials of metastatic cancer [3, 7], median time-to-event was often not reached in trials of primary chemotherapy for NHL thereby rendering it difficult to evaluate the relationship between time-to-progression and median OS end points, either at the trial level as differences between treatment arms or to determine the correlation between these two end points within individual treatment arms. Finally, since we only included RCTs of untreated NHL in this study, estimates of these relationships are not applicable to RCTs of relapsed or refractory disease or of maintenance strategies.

In this study, we determined correlations as well as estimated relationships between different end points in RCTs of untreated aggressive and indolent NHL. Definition of these relationships may improve the design of clinical trials in lymphoma. Estimates between response and efficacy end points may be helpful for designing randomized phase III RCTs based on randomized phase II data. Our findings suggest that 3-year PFS may be an appropriate surrogate end point for 5-year OS in clinical trials of aggressive NHL and provides the preliminary evidence necessary to further evaluate the strength of this relationship using a meta-analysis with individualized patient data. Use of PFS rather than OS would lead to considerable lead time advantage in the evaluation of clinical trials for aggressive lymphoma, but acceptance of PFS as a surrogate end point is required in order to expedite approval of novel agents.

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disclosure

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