RESEARCH LETTER

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TO THE EDITOR:

Disease site number was not prognostic in a low-risk Hodgkin lymphoma combined modality trial: revisiting PHC HOD90

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In 2007, the Pediatric Hodgkin Consortium (PHC) published the results of a trial using combined modality therapy with vinblastine, doxorubicin, methotrexate, and prednisone (VAMP) and involved-field radiation (IFRT) for pediatric patients with low-risk Hodgkin lymphoma (HL) between 1990 and 2000.[1] This trial (HOD90) included both patients with classical HL (cHL) and those with nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL). Analysis of event-free survival (EFS) rate was performed based on the number of sites of disease at diagnosis. This revealed an inferior 10-year EFS rate of 80% for patients with ≥3 sites of disease compared with a 10-year EFS rate of 92.7% for patients with <3 sites of disease.[1] These data formed the basis for risk stratification in subsequent PHC trials, which incorporated a restriction of <3 sites of disease for patients at low risk.[2] However, evolution in our understanding of the biology of NLPHL and increasing use of targeted therapies has led to the exclusion of patients with NLPHL from contemporary frontline clinical trials for cHL.[3] Given the superior outcomes for patients with NLPHL compared with those with cHL on HOD90 (10-year EFS of 100% for the NLPHL cohort vs 85.4% for those with cHL)[1] and the preponderance of patients with NLPHL with 1 or 2 sites of disease,[1] we hypothesized that the number of sites may be less predictive of the outcome among patients with cHL who otherwise met the criteria for low-risk disease. We performed an analysis of HOD90 trial data to assess for the prognostic significance of the number of sites of disease in cHL.

Details of the study population and treatment regimen have been reported previously.[1] This study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review boards of each participating institution. Notably, between 30 September 1990 and July 1998, patients with Ann Arbor stage IB and IIB disease were eligible; an amendment in July 1998 modified the eligibility criteria to exclude patients with systemic symptoms. All patients received IFRT: 15 Gy among those patients who achieved a complete response and 25.5 Gy among those who achieved a partial response to 2 cycles of VAMP chemotherapy. Two additional VAMP cycles followed IFRT. Data were reanalyzed to assess for a potential association between the number of sites of disease and EFS and overall survival (OS) of 77 patients with cHL included in the original HOD90 publication. A total of 33 patients with NLPHL were excluded. As described in the original report, EFS was based on enrollment date to first event or last follow-up examination. Events encompassed relapse, progression, second malignancy, or death. OS was based on the enrollment date to death from any cause or last follow-up examination. Cox regression models were fitted to assess the association between the number of disease sites and the 5-year EFS/OS. Log rank tests were performed to examine potential differences in the 5-year EFS/OS among patients with differing numbers of disease sites.

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The study protocol and data are available on reasonable request from the corresponding author, Angela M. Feraco (angela_feraco@dfci.harvard.edu), with a carbon copy to Yiwang Zhou (yiwang_zhou@stjude.org).

Table 1. Summary of the number of patients and the number and percentage of 5-year EFS/OS events in each stratum of disease sites

Disease sites	Patients	EFS events	OS events
1	17	2 (11.8)	0 (0)
2	33	0 (0)	0 (0)
3	18	4 (22.2)	1 (5.6)
4	7	2 (28.6)	0 (0)
5	1	0 (0)	0 (0)
6	1	0 (0)	0 (0)
Overall	77	8 (10.4)	1 (1.3)

Table 1 summarizes the number of patients and describes events based on the number of disease sites (range, 1-6). The majority of the 77 patients with cHL had 1 to 3 sites of disease (n = 68; 88.3%). Five had systemic symptoms. Importantly, there were 17 patients with cHL with 1 disease site, whereas in the original analysis, there were 34 patients with 1 disease site. Within the 5-year timeframe, there were 8 total events. Among 17 patients with 1 site of disease, 2 experienced events (11.8%), whereas among patients with 4 disease sites, 2 of 7 (28.6%) experienced an event. Four of 18 patients with 3 disease sites experienced an event (22.2%), and 2 of these 4 patients had stage IIB disease. One patient, who had 3 sites of disease at diagnosis and developed progressive disease during treatment, subsequently died. There were no events in the 2 patients with 5 or 6 sites of disease. The 5-year EFS and OS rates for these 77 patients were 89.6% (95% confidence interval [CI], 83.0%-96.7%) and 98.7% (95% CI, 96.2%-100%), respectively. Results obtained from the Cox regressions show that disease site number is not significantly associated with either 5-year EFS or OS for these patients with cHL (Table 2). When the number of disease sites was treated as a continuous variable, the estimated hazard ratio (HR) of disease sites for the 5-year EFS was 1.48 (95% CI, 0.86-2.56; $P = .160$), and the estimated HR of disease sites for the 5-year OS was 1.68 (95% CI, 0.38-7.43; $P = .493$). When the 5 patients with systemic symptoms were excluded, the estimated HR of disease sites for the 5-year EFS was 1.38 (95% CI, 0.73-2.63; $P = .323$), and the estimated HR of disease sites for the 5-year OS was 1.65 (95% CI, 0.38-7.14; $P = .501$). Pairwise log rank tests for the 6 strata of disease sites show no significant differences in the 5-year OS. The log rank test comparing the 5-year EFS for patients with 1 vs 2 sites of disease had a P value of .045; for patients with 2 vs 3 sites of disease, it had a P value of .005; and for patients with 2 vs 4 sites of disease, it had a P value of .001. No other significant differences were detected in the log rank tests of the 5-year EFS.

Table 2. Summary of results obtained from the Cox regression models, in which 5-year EFS/OS was treated as the outcome variable and the number of sites was taken as a continuous covariable

Cohort	Outcome	HR	95% CI	*P* value
Cohort 1 (n = 77)	EFS	1.48	(0.86-2.56)	.160
	OS	1.68	(0.38-7.43)	.493
Cohort 2 (n = 72)	EFS	1.38	(0.73-2.63)	.323
	OS	1.65	(0.38-7.14)	.501

The P values were obtained based on Wald tests.
Cohort 1: all 77 patients with cHL; cohort 2: 72 patients with cHL, with 5 excluded because of systemic symptoms.

Overall, the results suggest that the number of Ann Arbor disease sites was not strongly predictive of EFS or OS in this modest sample of uniformly treated patients with low-risk cHL. In this analysis, identified significant differences in the 5-year EFS between certain subgroups of disease site numbers appear to be driven by the absence of events in patients with 2 disease sites and the inclusion of a small number of patients with stage IIB disease. The relatively small sample size of this study may result in insufficient statistical power to make definitive conclusions. Thus, caution should be exercised in interpreting this data, given the small numbers and therefore potential imprecision in event estimates. Notably, the European Organization for Research and Treatment of Cancer, the German Hodgkin Study Group, and the National Comprehensive Cancer Network (NCCN) incorporate the number of nodal sites in their risk stratification schemas.[4] However, the European Organization for Research and Treatment of Cancer enumerates 5 major supradiaphragmatic nodal areas,[5] the German Hodgkin Study Group 11 nodal areas,[6] and the NCCN uses Ann Arbor nodal sites.[7] The original HOD90 analysis that found ≥3 sites of involvement to be unfavorable[1] used the NCCN/Ann Arbor basis for defining nodal sites yet identified a lower extent of nodal involvement as unfavorable than did the NCCN, which defines >3 Ann Arbor nodal sites as an unfavorable feature.[7] Additionally, our current targets for 5-year EFS rates among patients with low-risk cHL are somewhat higher than those achieved in HOD90.[8] However, because compelling data that the number of Ann Arbor nodal sites portends inferior outcome among patients with otherwise low-risk cHL are absent, these data formed the basis to remove disease site number as a criterion for risk stratification in cHOD17 (NCT03755804), the current PHC cHL frontline trial. Given our understanding of NLPHL as a biologically distinct entity, reanalyses of clinical trial data that restrict the evaluable sample to patients with cHL may refine our understanding of meaningful prognostic factors in this disease. In this instance, exclusion of patients with NLPHL from the evaluable sample reversed a previous conclusion from the HOD90 study. Removal of the requirement to have <3 Ann Arbor sites of disease may allow for appropriate therapy reduction for patients with otherwise low-risk classical HL.

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