Extranodal presentation in limited-stage diffuse large B-cell lymphoma as a prognostic marker in three SWOG trials S0014, S0313 and S1001

Several recent trials have changed the standard-of-care for patients with limited stage (LS) diffuse large B-cell lymphoma (DLBCL) by minimizing the number of chemoimmunotherapy cycles and/or eliminating the need for radiotherapy without compromising long-term outcomes.[1,2] However, there may be patient subsets where an abbreviated-treatment approach is insufficient. With this in mind, Bobillo *et al.*, retrospectively reviewed LS DLBCL patients treated at a single institution with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) for four to six cycles with or without radiotherapy.[3] This group reported that an extranodal presentation had shorter progression-free (PFS) and overall survival (OS) compared with nodal presentation. In these patients, consolidative radiotherapy prolonged survival in patients with extranodal disease, especially those with a positive positron emission tomography (PET) scan at the end of chemoimmunotherapy. In response, we analyzed similar patients treated on three consecutive SWOG studies (S0014, S0313, S1001; clinicaltrails gov. Identifier: NCT00005089, NCT00070018, NCT01359592).[2,4,5]

From April 2000 to June 2016, 234 eligible patients with non-bulky (exception of 2 patients) LS DLBCL were accrued to S0014 (n=60), S0313 (n=43), or S1001 (n=131).[2,4,5] Bulky disease was defined as any tumor mass >10 cm (greatest diameter) and/or a mediastinal mass ≥ one third of the maximum chest diameter. Tumor bulk was measured prior to initial biopsy from available commuted tomography scans. Reasons for exclusion are detailed in the *Online Supplementary Figure S1*. Enrolled patients received therapy with RCHOP (rituximab, cyclophos-phamide, doxorubicin, vincristine, prednisone) for three cycles (RCHOP3) + involved field radiotherapy (IFRT; 26%); RCHOP3 + IFRT + ibritumomab tiuxetan (24%); or RCHOP alone for three to four cycles (51%; *Online Supplementary Figure S1*). For patients enrolled in S1001, an interim PET (iPET) scan was performed after RCHOP3 and considered negative if the Deauville Score was ≤3.[2] Nodal disease was defined as lymphoma limited to lymph nodes, spleen, or tonsils. Extranodal disease included lymphoma in all other locations. Fisher's exact test for categorical variables and Wilcoxon sum rank test for continuous variables were used to compare the distribution of the characteristics and treatments received at 2-sided α of 0.05. PFS was calculated from date of registration until progression, relapse, or death. OS was calculated from date of registration until death. PFS and OS estimates were calculated using the Kaplan-Meier method.

Median follow-up is 7 years (range, 1.1–15.8). Median age was 62 years (range, 18–85). Of the 234 patients, 104 (44%) had extranodal disease. The most common sites of extranodal disease were head and neck (n=46; nasopharynx n=14 [6 were localized to the nose or nasal cavity and the remaining covered larger areas of the nasopharynx, excluding the tonsils]; oral cavity n=17; orbit n=2; parotid n=4; sinus n=7; submandibular gland n=1; and vocal cord n=1]), bone (n=13), skin/soft tissue/muscle (n=12), gastrointestinal tract (n=11), thyroid (n=9), and breast (n=6). Baseline clinical characteristics (age, stage, lactate dehydrogenase [LDH], sm-IPI) and treatments received between extranodal and nodal disease presentations were not statistically different (Table 1). For all patients, estimated 10-year PFS and OS were 71% (95% confidence interval [CI]: 64-77%) and 77% (95% CI: 69-83%), respectively. For patients with extranodal *versus* nodal disease, there was no difference in the estimated 10-year PFS (68% *vs.* 74%; 2-sided log-rank *P*=0.51, Figure 1A) or 10-year OS (77% *vs.* 77%; 2-sided log-rank *P*=0.65; Figure 1B). Of the 135 patients with stage I disease, there was no difference in the estimated 10-year PFS (70% *vs.* 73%; 2-sided log-rank *P*=0.79) or 10-year OS (73% *vs.* 81%; 2-sided log-rank *P*=0.88) when comparing patients with extranodal *versus* nodal disease (*Online Supplementary Figure S2*). For the 46 patients with extranodal disease of the head and neck, estimated 10-year PFS and OS were 57% (95% CI: 38-71%) and 75% (95% CI: 58-86%). Among the different subgroups of patients with disease classified as extranodal disease of the head and neck (nasopharynx, oral cavity, sinus, or other) there were no significant differences in estimated 10-year PFS or OS (2-sided log-rank *P* values of 0.84 and 0.71, respectively). For 10-year PFS and OS for the other sites of extranodal presentation, see the *Online Supplementary Table S1*. Among patients with extranodal disease who received IFRT (n=54) *versus* those who did not (n=50), there was no difference in the estimated 5-year PFS (83% *vs.* 87%; 2-sided log-rank *P*=0.52) or 5-year OS (85% *vs.* 92%; 2-sided log-rank *P*=0.28; Figure 2). Specifically for the patients presenting with head and neck extranodal disease, there is no difference in 5-year PFS or OS for patients who received IFRT compared those who did not receive IFRT after completion of chemotherapy (2-sided log-rank *P* values of 0.35 and 0.43,

Table 1. Baseline patient characteristics.

	Total, N (%)	Nodal, N (%)	Extranodal, N (%)	2-sided *P* value*
Number of patients	234	130 (56)	104 (44)	
SWOG Study S0014 S0313 S1001	 60 (26) 43 (18) 131 (56)	 33 (26) 21 (16) 76 (58)	 27 (26) 22 (21) 55 (53)	
Age in years, median (range)	62 (18-85)	62 (23-85)	64 (18-85)	0.69†
Male	124 (53)	67 (52)	57 (54)	0.69
Zubrod Performance Status 0-1 2	 227 (97) 7 (3)	 128 (98) 2 (2)	 99 (95) 5 (5)	0.25
Disease Stage I II No evidence of disease	 135 (58) 95 (41) 4 (2)	 76 (58) 51 (39) 3 (2)	 59 (57) 44 (42) 1 (1)	0.75
Bulky**	2 (0.8)	0 (0)	2 (2)	0.20
B symptoms	46 (20)	25 (19)	21(20)	0.87
Elevated LDH	47 (20)	22 (17)	25 (24)	0.19
SM-IPI score 0 1 2 3 4	 36 (15) 123 (53) 60 (26) 14 (6) 1 (0.4)	 24 (18) 70 (54) 28 (22) 8 (6) 0 (0)	 12 (11) 53 (51) 32 (31) 6 (6) 1 (1)	0.26
Treatment R-CHOP R-CHOP + RT R-CHOP + RT + 90Y-IT	 119 (51) 60 (26) 55 (24)	 69 (53) 33 (25) 28 (22)	 50 (48) 27 (26) 27 (26)	0.68
IFRT dose, cGy¥ median (range)	4140 (400-5,400)	4140 (3,780-5,400)	4140 (400-5,000)	.38†
Complete surgical excision before treatment	12 (5)	10 (8)	2 (2)	.07

Cgy: centi-gray; IFRT: involved-field radiotherapy; LDH: lactate dehydrogenase; NED: no evidence of disease; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SM-IPI: stage-modified international prognostic index; 90Y-IT: ibritumomab tiuxetan.** Bulky disease: any mass ≥10 cm in diameter or a mediastinal mass >1/3 chest diameter. * Fisher's exact *P* values calculated exclude missing or unclassifiable/unevaluable values. † Wilcoxon sum rank test. ¥ 107 patients reported total RT dose (51 had extranodal disease).

respectively). Of 55 patients with extranodal disease treated on S1001, five (9%) patients had a positive iPET, 47 (85.5%) patients had a negative iPET, and three (5.5%) patients did not have an iPET. In the five patients with extranodal disease and a positive iPET, all received IFRT and one progressed. Among 123 patients on S1001 who had available measurement of the largest lymph node or mass diameter, the median of the largest diameter was 3.5 cm (range, 1.0–9.7 cm). There was no difference in 5-year PFS or OS for patients with the largest diameter above the median compared those with the largest diameter below the median (2-sided log-rank *P* values of 0.36 and 0.61), respectively. There were 50 patient deaths. Of these, the cause of death was lymphoma in 16 (32%), second cancer in six (12%), other in 15 (30%), and unknown in 13 (26%).

Patients with LS DLBCL treated on three SWOG studies (S0014, S0313, and S1001) had excellent and prolonged PFS and OS regardless of extranodal *versus* nodal presentation or receipt of consolidative radiotherapy. As seen in previous studies, there was a continuous rate of relapse without plateau of the PFS curves.[6] The most common known cause of death was lymphoma, which supports the need for long term follow-up.

Our results contrast with those from Bobillo *et al.*[3] and do not support extranodal disease as an adverse prognostic factor for patients with LS DLBCL. There are several differences between the two patient populations. The SWOG population included 41% stage II disease, while the

Bobillo dataset was exclusively stage I disease. An analysis of the 135 patients with stage I disease in our dataset showed no difference in the estimated 10-year PFS or OS when comparing extranodal *versus* nodal presentations. The most common sites of extranodal disease presentation were different between the two analyses. In the SWOG dataset, the most common extranodal sites were head and neck (44%), bone (13%), skin/muscle/soft tissue (12%), and gastro-intestinal tract. Although the estimated rates of 10-year OS within the subgroups of extranodal disease were similar, ranging from 63-100%, patient numbers in each subgroup were too small to make definitive conclusions about risk based on disease site. As the most common site of extranodal disease in the SWOG dataset was head and neck and this group was amongst the lowest estimated 10-year PFS and OS (*Online Supplementary Table S1*), we compared outcomes between extranodal and nodal disease in this subset and found no significant difference in survival. Another group found that extranodal presentation of limited stage DLBCL in the head and neck benefitted from radiation, however when we compared outcomes between patients in this subgroup who received and did not receive IFRT, we found no difference in survival.[7] In the Bobillo dataset, the most common extranodal sites were GI tract (27%), bone (21%), head and neck (15%), and testis (9%). An additional difference between the two studies was that patients with testicular involvement did not enroll on the SWOG studies. As testicular lymphoma carries a particularly high risk of relapse, Bobillo *et al*. performed a survival subanalysis excluding patients with testicular involvement.[8,9] They found no difference from their original results. Analysis of a larger population of LS DLBCL could have the statistical power necessary to determine whether a specific extranodal site of disease contributes to risk for relapse.

Patients in the SWOG dataset generally received fewer cycles of RCHOP (maximum 4 cycles *vs.* 36% receiving 6 cycles) and had a higher median radiation dose (4,140 cGy

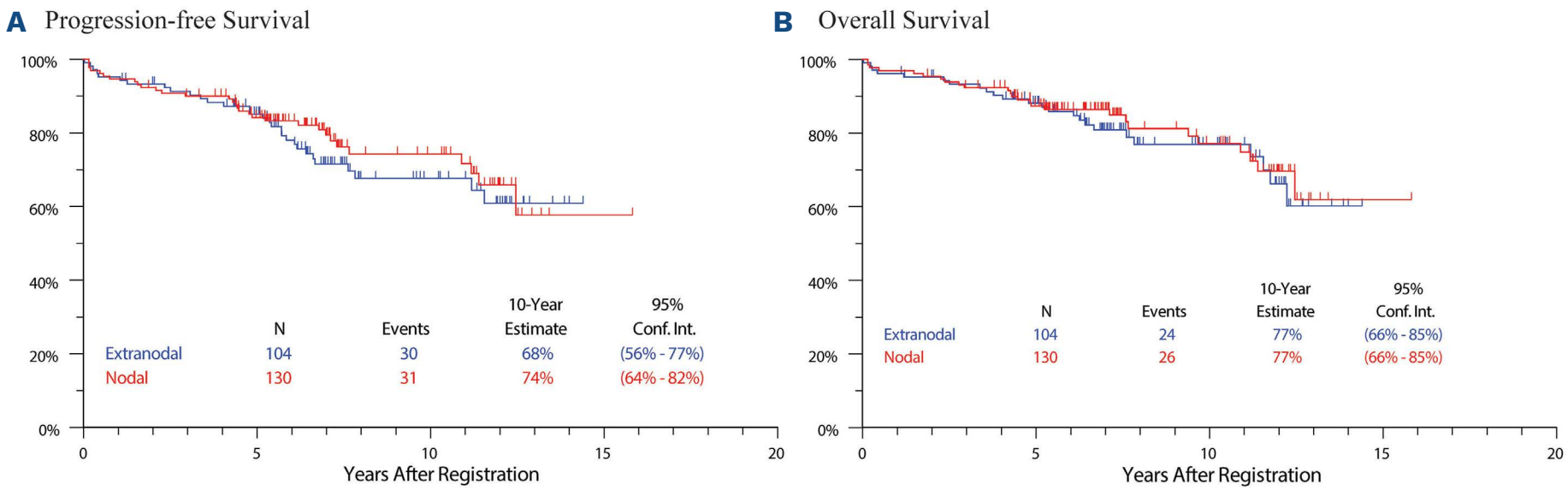

Figure 1. Estimated 10-year survival is not statistically different between patients presenting with nodal versus extranodal presentation of limited stage diffuse large B-cell lymphoma. (A) Estimated 10-year progression-free survival. (B) Estimated 10-year overall survival. Conf.Int.: confidence interval.

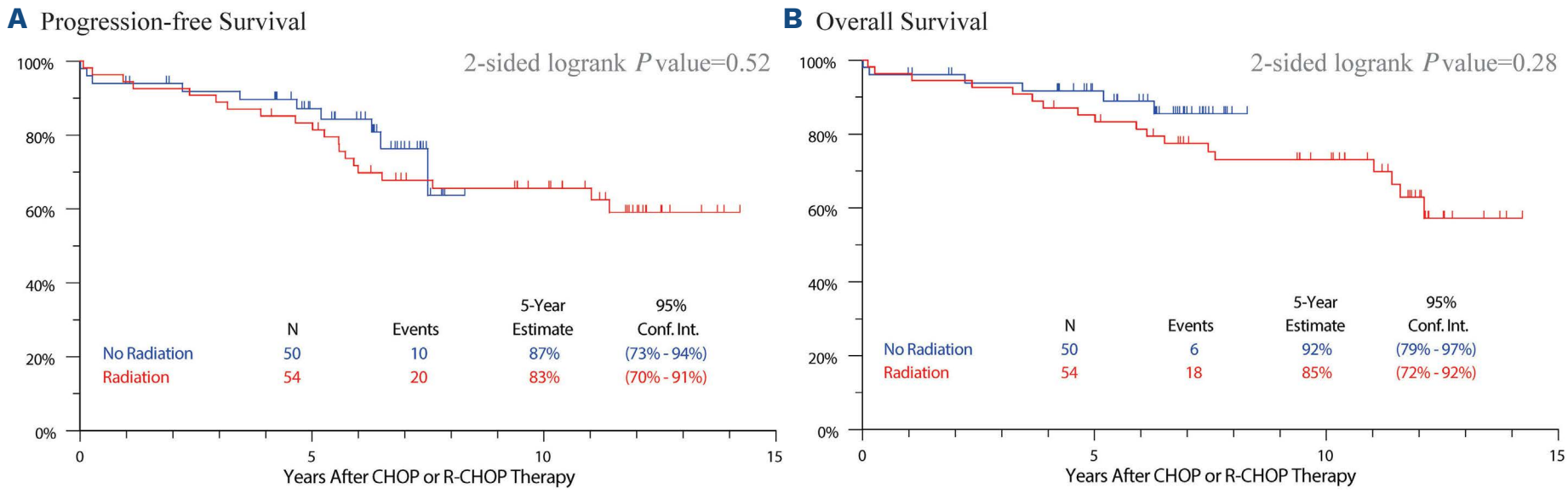

Figure 2. Estimated 5-year survival was not statistically different in the 104 patients with limited stage diffuse large B-cell lymphoma who were treated with or without radiation. (A) Estimated 5-year progression-free survival. (B) Estimated 5-year overall survival. RCHOP: rituximab, cyclophos-phamide, doxorubicin, vincristine, prednisone.

vs. 3,060 cGy) when compared to patients in the Bobillo dataset. It is unclear whether differences in therapy could be the reason for the contrasting results.
Finally, there were too few patients with extranodal disease treated on the S1001 study that had a positive iPET to make a recommendation for PET-adapted IFRT.
Unlike the Bobillo study, the SWOG experience was prospective and enrolled patients across the National Clinical Trials Network. Although patients enrolled on clinical trials may be biased toward more favorable characteristics, this may be less of an issue with limited stage presentations of DLBCL.[2] A strength of our study is that patients were enrolled throughout the National Clinical Trials Network including community sites, which reflects a "real-world" setting.[10] Based upon our analysis, patients with extranodal presentations of LS DLBCL should be approached like those with nodal presentations, with a risk-adapted approach rather than uniform IFRT. Our results support the NCCN guidelines in this setting. Future trials are needed to determine if subsets of patients may benefit from response adaptation.

Authors

Deborah M. Stephens,[1] Hongli Li,[2] Louis S. Constine,[3] Thomas J. Fitzgerald,[4] John P. Leonard,[5] Brad S. Kahl,[6] Joo Y. Song,[7] Michael L. LeBlanc,[2] Sonali M. Smith,[8] Daniel O. Persky[9] and Jonathan W. Friedberg[10]

[1]Division of Hematology, University of Utah, Salt Lake City, UT; [2]SWOG Statistics and Data Management Center, Fred Hutchinson Cancer Research Center, Seattle, WA; [3]Departments of Radiation Oncology and Pediatrics, University of Rochester, Rochester, NY; [4]Imaging and Radiation Oncology Core (IROC), Lincoln, RI; [5]Division of Hematology and Medical Oncology, Weill Cornell Medical Center, New York, NY; [6]Department of Medicine, Washington University School of Medicine, St. Louis, MO; [7]Department of Pathology, City of Hope, Duarte, CA; [8]Section of Hematology/Oncology, University of Chicago, Chicago, IL; [9]Division of Hematology/Oncology, University of Arizona, Tucson, AZ and [10]Division of Hematology/Oncology, University of Rochester, Rochester, NY, USA

Correspondence:
D. M. STEPHENS - Deborah.stephens@hci.utah.edu

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Contributions

DMS, HL, SMS, JWF, and DOP designed the research, collected and analyzed data, drafted the original manuscript, revised the manuscript, and approved the final draft. LSC, TJF, JPL, BSK, JYS, and MLL collected and analyzed data, revised the manuscript, and approved the final draft.

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Data-sharing statement

Original data and protocols can be obtained by emailing the corresponding author.

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