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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Stage I-II nodular lymphocyte-predominant Hodgkin lymphoma: a multi-institutional study of adult patients by ILROG

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KEY POINTS

- **Upfront treatment of stage I-II NLPHL with RT/CMT is associated with excellent PFS.**
- **Acknowledging the excellent prognosis, the risk of late effects and potential for transformation should inform management decisions.**

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon histologic variant, and the optimal treatment of stage I-II NLPHL is undefined. We conducted a multicenter retrospective study including patients ≥16 years of age with stage I-II NLPHL diagnosed from 1995 through 2018 who underwent all forms of management, including radiotherapy (RT), combined modality therapy (CMT; RT+chemotherapy [CT]), CT, observation after excision, rituximab and RT, and single-agent rituximab. End points were progression-free survival (PFS), freedom from transformation, and overall survival (OS) without statistical comparison between management groups. We identified 559 patients with median age of 39 years: 72.3% were men, and 54.9% had stage I disease. Median follow-up was 5.5 years (interquartile range, 3.1-10.1). Five-year PFS and OS in the entire cohort were 87.1% and 98.3%, respectively. Primary management was RT alone (n = 257; 46.0%), CMT (n = 184; 32.9%), CT alone (n = 47; 8.4%), observation (n = 37; 6.6%), rituximab and RT (n = 19; 3.4%), and rituximab alone (n = 15; 2.7%). The 5-year PFS rates were 91.1% after RT, 90.5% after CMT, 77.8% after CT, 73.5% after observation, 80.8% after rituximab and RT, and 38.5% after rituximab alone. In the RT cohort, but not the CMT cohort, variant immunoarchitectural pattern and number of sites >2 were associated with worse PFS ($P < .05$). Overall, 21 patients (3.8%) developed large-cell transformation, with a significantly higher transformation rate in those with variant immunoarchitectural pattern ($P = .049$) and number of involved sites >2 ($P = .0006$). OS for patients with stage I-II NLPHL was excellent after all treatments. (*Blood*. 2020;135(26):2365-2374)

Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon subtype of Hodgkin lymphoma representing ~5% of cases.[1] NLPHL most frequently presents as early-stage disease, without B symptoms, and with male predominance.[1,2] In contrast to classic Hodgkin lymphoma, the malignant cells of NLPHL express the CD20 marker and typically lack the expression of CD15 and CD30.[3] An early clinical-pathologic study demonstrated that NLPHL is characterized by an indolent clinical course with excellent overall survival (OS) but with frequent relapses occurring even decades after initial diagnosis.[4]

Most clinical evidence that guides management of early-stage NLPHL arises from studies that used radiation alone or combined-modality therapy (CMT), as patients were often treated according to classic Hodgkin lymphoma protocols.[5-9] Given the excellent prognosis, many groups have investigated de-escalation of treatment. As one example, in a large retrospective series from the German Hodgkin Study Group (GHSG), patients with stage IA NLPHL who received limited radiation alone had a progression-free survival (PFS) rate equivalent to that of patients treated with CMT, leading to the adoption of involved-field radiation therapy (IFRT) as the standard for stage IA NLPHL.[10,11] Further, reports from pediatric cohorts showed reasonable outcomes after surgical excision alone for localized disease.[12,13] In addition, given the excellent OS, it has been proposed that surveillance after initial diagnosis would be a reasonable strategy for adult populations, reserving treatment for those who progress.[14] Despite the CD20$^+$ molecular marker, rituximab alone has not been associated with durable responses.[11,15] These largely single-institution studies highlight the challenge of defining the optimal treatment of stage I-II NLPHL.

Given the low incidence of NLPHL, the conduct of prospective clinical trials is challenging. Thus, we sought to perform a large, multicenter, retrospective study of patients with stage I-II NLPHL treated with any modality from 1995 through 2018.

Materials and methods

Patients

We conducted a multi-institutional, retrospective analysis including data from 18 institutions. Each center obtained institutional review board approval or the equivalent and sent anonymous patient data to a single database. Details of patient characteristics, treatment, follow-up, and outcomes were uniformly collected according to a prospective survey protocol. Inclusion criteria included age ≥16 years, diagnosis of stage I-II and CD20$^+$ disease, managed by observation, systemic therapy, and/or RT at the participating institution from 1995 through 2018. Patients were classified according to GHSG favorable vs unfavorable criteria.[16] Patients with concurrent diagnosis of diffuse large B-cell lymphoma were excluded.

Recorded data included patient age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, immunohistochemistry, immunoarchitectural pattern (IAP) when available,[17] serum laboratory values, erythrocyte sedimentation rate (ESR), stage, number of anatomic sites, bone marrow biopsy status, presence of B symptoms, baseline imaging, management type and dates, and treatment toxicity. Biopsy and resection extent were recorded. RT technique (extended field, IFRT, involved site [ISRT], and involved node [INRT][18]), beam type (photon, electron, or proton), dose, and fractionation were recorded. Chemotherapy (CT) regimen and number of cycles were recorded.

Management, follow-up, and outcomes

Management was according to treating physician and patient preferences. Few patients were treated according to prospective protocols, with the exception of some who were enrolled on a trial utilizing rituximab alone.[15]

Routine follow-up visits and laboratory testing details and frequency were conducted according to physician and institutional practices and were not recorded in this study. Imaging response to treatment, when available, was collected. Metabolic response was assessed with ^{18}F-FDG positron emission tomography-computed tomography (PET-CT) and, when available, scored according to the Deauville 5-point scale.[19] Size response was assessed according to the following criteria: complete response (CR), no residual abnormality; partial response, reduction in diameter by at least 30%; stable disease, no change in lesion diameter; and progressive disease, a 20% increase in diameter or new lesions.[20,21] In patients without response imaging, clinical evaluation was used to assess response.

We recorded each patient's last known vital status. In those who experienced relapse, we collected restaging information, including method of relapse detection (patient symptoms, clinical examination, or surveillance imaging), histology of relapse, stage, location of relapse in reference to the initial site of disease, salvage treatments, and response to salvage treatments.

Treatment-related toxicities

Treatment-related acute and late toxicities were scored according to The Common Terminology Criteria for Adverse Events (CTCAE, version 5). Second cancers, hypothyroidism, cardiac disease, and any other late toxicities were recorded in reference to RT volumes or if secondary to systemic therapy.

End points

PFS after primary and salvage treatment, OS and freedom from transformation to large-cell lymphoma were assessed. PFS was measured from the date of diagnosis to the date of recurrent/progressive lymphoma (including large-cell transformation) or death from any cause. OS was measured from date of diagnosis to date of death. Freedom from transformation was measured from date of diagnosis until biopsy-proven diagnosis of large-cell lymphoma.

Statistical analyses

PFS, OS, and freedom from transformation were measured by the Kaplan-Meier method. There was not a significant competing risk of death in measurements of freedom from transformation. Follow-up was measured by using the reverse Kaplan-Meier approach. Patient and group baseline characteristics were compared by using Fisher's exact test (small count data), χ^2 test (multigroup count data), Mann-Whitney *U* test (continuous data), and analysis of variance (multigroup continuous data). In 260 cases, ESR was missing and was imputed by using linear regression from hemoglobin if available or from the sample mean.[22] When classifying patients as favorable by GHSG criteria, we excluded patients who had mediastinal involvement without size or indication of bulk of disease. Because of the potential for selection bias and the retrospective nature of the study, outcomes of patients after use of different management strategies were not compared. Cox regression was performed with the following R packages: survival and competing-risks regression for stratified and clustered data. To adjust for treatment center, we performed a stratified Cox regression analysis, with clustering by institution. For the univariable and multivariable (MVA) analyses, the following variables had missing data that were imputed using the average for continuous variables or the mode for binary variables: size (n = 113; 20.2%), bone marrow biopsy

status (n = 15; 2.7%), and infradiaphragmatic involvement (n = 4; 0.7%). For the subgroup analyses involving IAP, no imputation was performed, with the number included in the analysis listed. All other variables included in regression analyses did not have missing values. Variables with $P < .05$ on univariable regression analysis were included in MVA. We ensured that the proportional hazards assumption was met by determining the relationship of parameter residuals and survival time, as well as with visualization of log(−log[survival]) plots. All analyses were performed with R (version 3.6; Vienna, Austria).

Results

Patients

There were 559 eligible patients treated at 18 participating institutions from 1995 through 2018. Pathologically diagnosed cases were identified from databases independent of managing medical specialty in 9 institutions (50%), databases of cases managed by both radiation and medical oncology in 3 (16.7%), and databases of cases managed by radiation oncology for 5 (27.8%) or medical oncology alone for 1 (5.6%; supplemental Table 1, available on the *Blood* Web site).

Baseline patient characteristics are shown in Table 1. Median follow-up of the entire cohort was 5.5 years (interquartile range [IQR], 3.1-10.1) and was significantly shorter in patients undergoing observation (Table 1; $P = .02$; excluding observation subgroup, $P = .78$); 134 patients (24.0%) had at least 10 years of follow-up. Patients had a median age of 39 years (range, 16-90 years), male preponderance (72.3%), and good ECOG performance status (0-1, 86.9%). Just over half had stage I NLPHL (54.9%). Few had B symptoms (6.8%) or extranodal involvement (5.7%). The majority of patients underwent staging with PET-CT (71.2%) and bone marrow biopsy (55.6%). Approximately one-third had the IAP described.

Baseline patient and treatment details by management type

Primary management included RT alone in 257 patients (46.0%), CMT in 184 (32.9%), CT alone in 47 (8.4%), observation after biopsy/resection in 37 (6.6%), rituximab and RT in 19 (3.4%), and rituximab alone in 15 (2.7%). As shown in Table 1, there were differences in baseline factors between the different management groups including age ($P = .01$), ECOG performance score ($P = .002$), stage ($P < .0001$), and the percentage of patients with variant IAP ($P = .01$).

We classified patients according to the GHSG clinical criteria, with the majority being favorable (84.6%, Table 1). There was no difference in the percentage of patients who were favorable by GHSG criteria when considering only those without imputed ESR values ($P = .61$). There was a significant difference in the percentage of patients who were favorable by GHSG criteria according to management strategy ($P < .0001$). Nine (1.6%) patients were not classifiable by GHSG criteria, as they had mediastinal involvement without size measurement or documentation of disease bulk.

Focusing on details of patients who underwent treatment, RT techniques used in the RT-alone group included IFRT in 163 patients (63.4%), INRT/ISRT in 66 (25.7%), and EFRT in 28 (10.9%). The median RT dose was 36 Gy (IQR, 30.6-36) in the RT alone group and 30.6 Gy (IQR, 30-35) in the CMT/rituximab and RT groups (supplemental Table 2). The most common CT regimens used in patients receiving CMT were doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine in 149 (ABVD, 81.0%; median, 3 cycles; IQR, 2-4) plus rituximab in a subset (n = 23; 15.4%) followed by cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab in 24 (*R*-CHOP 13.0%; median, 4 cycles; IQR, 3-4). The most common CT regimens used in patients receiving CT alone were ABVD in 32 (68.1%; median 4 cycles; IQR, 4-6) plus rituximab in 6 (18.8%), followed by *R*-CHOP in 10 (21.3% all with stage II NLPHL; median 6 cycles; IQR, 6-6]). In those receiving CT with ABVD, 11 (23.4%) received 6 cycles and 1 (2.1%) received 8 cycles, of whom all except 1 had stage II NLPHL. Additional CT regimens used are summarized in supplemental Table 3. Four patients were scheduled to receive RT after CT but did not, for the following reasons: 1, patient preference (after 4 cycles of ABVD with a CMR); 1, lack of insurance approval (after 3 cycles of ABVD with a CMR); and 2, bleomycin lung toxicity (grade 4 and 5 lung toxicities after 3 and 2 cycles of ABVD, respectively). Nineteen patients (3.4%) received rituximab and RT without CT. All patients selected for rituximab and RT received 4 doses of rituximab with the exception of 1 who received 6 doses and another who received 8. Patients who were selected for rituximab alone received a median of 4 doses (IQR, 4-5).

Thirty-two (86.5%) of the patients who were observed after diagnosis underwent excisional biopsies, and 25 (67.6%) had complete resection without known residual remaining lymphoma. Thirty-two (86.5%) had stage I NLPHL. Thirty-one patients (83.8%) had a staging PET-CT, performed either before or shortly after surgery.

Outcomes and response to management

The 5-year PFS and OS in the entire cohort were 87.1% (95% CI, 83.6%-90.0%) and 98.3% (95% CI, 96.4%-99.2%), respectively (Figure 1). The 5-year PFS rates by management strategy were 91.1% (95% CI, 85.3%-94.7%) with RT, 90.5% (95% CI, 84.8%-94.1%) with CMT, 77.8% (95% CI, 61.3%-88.0%) with CT, 73.5% (95% CI, 50.6%-87.0%) with observation, 80.8% (95% CI, 41.0%-95.1%) with rituximab and RT, and 38.5% (95% CI, 14.0%-62.8%) with rituximab alone (supplemental Figure 1A). The 5-year PFS in patients observed after having a complete resection was 79.1% (95% CI, 52.3%-91.9%). The 5-year OS rates by management strategy were 99.4% (95% CI, 96.1%-99.9%) with RT, 99.4% (95% CI, 95.9%-99.9%) with CMT, 97.9% (95% CI, 85.9%- 99.7%) with CT, 89.8% (95% CI, 64.3%-97.4%) with observation, 100% with rituximab and RT, and 92.3% (95% CI, 56.6%-98.8%) with rituximab alone (supplemental Figure 1B).

The RT and CMT cohorts had sample sizes large enough to perform subset analyses. Figure 2 demonstrates the PFS rates of stage I and II NLPHL in the RT and CMT cohorts. In addition, there was no significant difference in the 5-year PFS of patients classified as favorable vs unfavorable by the GHSG criteria for those receiving RT (91.3% for favorable vs 88.9% for unfavorable; $P = .31$) or CMT (91.1% for favorable vs 91.3% for unfavorable; $P = .35$).

Univariable and multivariable regression analyses of PFS were performed separately in the RT and CMT cohorts, as they were sufficiently large enough for regression analyses. Focusing on

Table 1. Characteristics of patients with stage I-II NLPHL

Parameter	Total (n = 559)	RT (n = 257)	CMT (n = 184)*	CT (n = 47)†	Observation (n = 37)	Rituximab and RT (n = 19)	Rituximab alone (n = 15)	P‡
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Age at diagnosis								
Median (years)	39	42	36	36	43	33	57	.01
IQR	27-52	29-53	25-49	25-48	22-59	21-42	31-72	
Range	16-90	17-90	16-75	17-76	16-81	18-65	16-82	
Sex								
Male	404 (72.3)	187 (72.8)	140 (76.1)	30 (63.8)	24 (64.9)	15 (78.9)	8 (53.3)	.21
Female	155 (27.7)	70 (27.2)	44 (23.9)	17 (36.2)	13 (35.1)	4 (21.1)	7 (46.7)	
ECOG PS								
0-1	486 (86.9)	205 (79.8)	173 (94.0)	44 (93.6)	34 (91.9)	18 (94.7)	12 (80.0)	.002
>1	8 (6.0)	2 (0.8)	2 (1.1)	0 (0.0)	2 (5.4)	0 (0.0)	2 (13.3)	
Unreported	65 (11.6)	50 (19.4)	9 (4.9)	3 (6.4)	1 (2.7)	1 (5.3)	1 (6.7)	
Stage								
Stage I	307 (54.9)	175 (68.1)	77 (41.8)	11 (23.4)	32 (86.5)	9 (47.4)	3 (20.0)	<.0001
Extranodal	12 (2.1)	3 (1.2)	4 (2.2)	2 (4.3)	3 (8.1)	0 (0.0)	0 (0.0)	
B symptoms	13 (2.3)	6 (2.3)	2 (1.1)	4 (8.5)	1 (2.7)	0 (0.0)	0 (0.0)	
Stage II	252 (45.1)	82 (31.9)	107 (58.2)	36 (76.6)	5 (13.5)	10 (52.6)	12 (80.0)	
Extranodal	20 (3.6)	9 (3.5)	8 (4.3)	1 (2.1)	1 (2.7)	0 (0.0)	1 (6.7)	
B symptoms	25 (4.5)	8 (3.1)	11 (6.0)	4 (8.5)	0 (0.0)	1 (5.3)	1 (6.7)	
Spleen	4 (0.7)	2 (0.8)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Disease location								
Above diaphragm	439 (78.5)	206 (80.2)	151 (82.1)	31 (66.0)	25 (67.6)	15 (78.9)	11 (73.3)	.17
Below diaphragm	116 (20.8)	50 (19.5)	32 (17.4)	14 (29.8)	12 (32.4)	4 (21.1)	4 (26.7)	
Unknown	4 (0.7)	1 (0.4)	1 (0.5)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Immunoarchitecture								
A/B Typical	166 (29.7)	86 (33.5)	59 (32.1)	10 (21.3)	6 (16.2)	3 (15.8)	2 (13.3)	.01
C/D/E/F Variant	43 (7.7)	14 (5.4)	17 (9.2)	3 (6.4)	3 (8.1)	1 (5.3)	5 (33.3)	
Unknown	350 (62.6)	157 (61.1)	108 (58.7)	34 (72.3)	28 (75.7)	15 (78.9)	8 (53.3)	
Follow up, years								
Median	5.5	5.4	5.9	5.0	4.1	3.8	6.3	.02
IQR	3.1-10.1	3.0-10.1	3.8-10.8	2.8-8.6	1.9-5.8	2.4-10.9	3.1-7.4	
GHSG clinical criteria								
Favorable	473 (84.6)	234 (91.1)	152 (82.6)	31 (66.0)	35 (94.6)	13 (68.4)	8 (53.3)	<.0001
Unfavorable	77 (13.8)	21 (8.2)	27 (14.7)	14 (29.8)	2 (5.4)	6 (31.6)	7 (46.7)	
Unknown	9 (1.6)	2 (0.8)	5 (2.7)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Treatment dates (range)	1995-2018	1995-2018	1995-2018	1996-2017	2003-2018	2002-2017	2000-2018	

PS, performance score.

*CMT included rituximab (n = 48; 26.1%).

†CT included rituximab (n = 17; 36.2%).

‡*P*-value for between-group comparisons calculated for continuous variables with analysis of variance and categorical variables with χ^2 test (excluding unreported/unknown for ECOG PS, immunoarchitecture and GHSG risk group).

the RT cohort, on univariable analysis, number of involved sites >2 and variant IAP were significantly associated with worse PFS, whereas infradiaphragmatic involvement was associated with improved PFS ($P < .05$; Table 2). Figure 3A demonstrates the PFS rates in patients with 1 to 2 sites vs >2 sites receiving RT ($P = .02$). On MVA, only >2 involved sites and variant IAP remained significantly associated with worse PFS ($P < .05$; Table 2; Figure 3C). There was no significant association between RT dose ($P = .19$) or INRT/ISRT volumes ($P = .39$) and PFS. There was no significant association between variant IAP and OS in those receiving RT ($P = .91$).

Looking at the CMT cohort, increasing age, the presence of B symptoms, and stage II were significantly associated with worse PFS ($P < .05$, Table 2). Figure 3B demonstrates that there was no significant difference in PFS rates in patients with 1 to 2 vs >2 sites of involvement who received CMT (Figure 3B; $P = .81$). On MVA, only the presence of B symptoms remained significantly associated with worse PFS in the CMT cohort ($P = .047$; Table 2; Figure 3D).

OS was excellent regardless of management strategy (supplemental Figure 1B). There were 24 reported deaths with 7 confirmed lymphoma-specific deaths. Nonlymphoma-specific deaths included 2 cardiac events (1 received 6 cycles of ABVD and mediastinal IFRT along with BEACOPP baseline [doxorubicin [Adriamycin], bleomycin, vincristine (Oncovin), cyclophosphamide, procarbazine, etoposide and prednisone] for relapsed NLPHL and the other received mediastinal IFRT alone), 1 from bleomycin lung toxicity, 1 gastrointestinal bleed, 1 secondary to thrombocytopenia possibly due to ITP, 1 from acute myeloid leukemia, 1 from pancreatic cancer, 1 from pneumonia, and 5 noncancer deaths not otherwise specified. Four deaths were of unknown cause.

Response to management by imaging modality

A subset of patients had postmanagement PET-CT (n = 227; 40.6%) or CT (n = 332; 59.4%) performed to assess response within 6 months (supplemental Figure 2). On univariable analysis, failure to achieve a complete metabolic response (no CMR) was associated with an 8 times higher risk of progression (hazard ratio [HR], 8.26; 95% CI, 3.2-21.3; $P = 1.3e-5$), which was a larger effect size than failure to achieve a complete response (no CR) by CT criteria (HR, 2.89; 95% CI, 1.7-4.93; $P = 9e-5$).

Recurrence and salvage treatment

Progressive lymphoma developed in 86 patients (15.4%) at a median of 4.4 years (IQR, 1.7-6.9). Progression events included 9 refractory cases (3 treated with RT, 2 with CMT, and 4 with CT) in which an initial CMR/CR or clinical response to primary treatment was not achieved. The remainder of progression events were relapses that occurred after an initial CMR/CR or clinical response. Median follow-up after progression was 5.8 years (IQR, 3.0-8.4). Seventy patients (81.4%) underwent biopsy at progression and 20 patients had relapse stage III-IV NLPHL at progression. In the majority of patients, progressive lymphoma was detected by surveillance PET-CT or CT (n = 55; 64.0%), with smaller subsets identified by patient symptoms (n = 18; 20.9%), by unknown methods (n = 9; 10.5%), and by clinical examination (n = 4; 4.7%). There was a significantly higher rate of local-only progression (within the initially involved anatomic region) in patients who did not receive RT as part of primary management vs those who received RT (21.6% vs 3.0%, respectively; $P < .0001$; Figure 4A). Patients who underwent observation had a nonsignificantly higher rate of relapse stage III and IV NLPHL (n = 3 of 4; 75%) vs all others (n = 17 of 59; 28.8%; $P = .09$). Five (5.8%) patients did not have restaging information available.

After progressive NLPHL, 7 (10.8%) patients underwent observation, 16 (24.6%) received RT alone or CMT for stage I and II recurrence, 29 (44.6%) received CT (n = 11 with rituximab), 11 (16.9%) received rituximab alone, and 2 (3.1%) underwent autologous stem cell transplant. Five-year PFS after salvage treatment was 85.1% (95% CI, 72.1%-92.4%) and did not differ in patients who underwent initial observation ($P = .71$). The 5-year OS in those without biopsy-proven transformation was 93.1% (95% CI, 82.6%-97.4%; Figure 4B). We did not observe worse OS in those that relapsed within 1 ($P = .37$) or 2 years ($P = .16$) of initial diagnosis.

Transformation

Twenty-one (3.8%) patients underwent transformation to diffuse large B-cell lymphoma or T-cell–rich B-cell lymphoma at a median of 3.6 years (IQR, 2.5-7.8) after primary management. Four lymphoma-specific deaths occurred in patients who experienced transformation, representing more than half of lymphoma-specific deaths. The 5-year freedom from transformation was 96.7% (95% CI; 94.4%-98.1%; Figure 4C). We performed univariable Cox regression and found a significantly increased risk of transformation in those with number of involved sites >2 and variant IAP ($P < .05$; supplemental Table 5).

Median follow-up after transformation was 6.7 years (IQR, 1.5-8.8). With the exception of 1 patient who was lost to follow-up and another who died of progressive lymphoma 3 weeks after diagnosis of transformation, all patients underwent salvage treatment. The 5-year PFS and OS were 62.2% (95% CI, 36.1%-80.1%) and 88.4% (95% CI, 60.2%-97.0%; Figure 4B), respectively, after diagnosis of transformation. The most common salvage treatment was *R*-CHOP (n = 15; 71.4%; median 6 cycles; IQR, 3-6) plus RT in a subset (n = 5). Two others received rituximab-based CT (n = 1; *R*-ABVD, and n = 1 dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin). Two patients underwent autologous stem cell transplantation.

Toxicities

Information regarding treatment-associated toxicities was available for 421 (75.3%) patients. Acute grade 1 to 3 toxicities occurred in 76 (37.6%) patients who received RT alone, 51 (39.2%) after CMT, 27 (59.3%) after CT, 5 after rituximab and RT (26.3%), and 2 after rituximab alone, and all resolved, with the exception of alopecia in a patient who received RT. Grade 4 toxicities were rare but occurred in patients receiving RT (n = 1 laryngeal edema), CMT (n = 1 neutropenia), and CT alone (n = 1 bleomycin lung toxicity and n = 1 thrombocytopenia). One grade 5 toxicity related to bleomycin lung toxicity occurred in a patient who received CT alone.

Late toxicity was uncommon but occurred in patients who received RT (hypothyroidism [n = 8], cardiac disease with mediastinal irradiation [n = 2], and xerostomia [n = 1]), CMT (lung fibrosis [n = 2], hypogammaglobulinemia [n = 1], cardiac disease without mediastinal irradiation [n = 1], and neuropathy

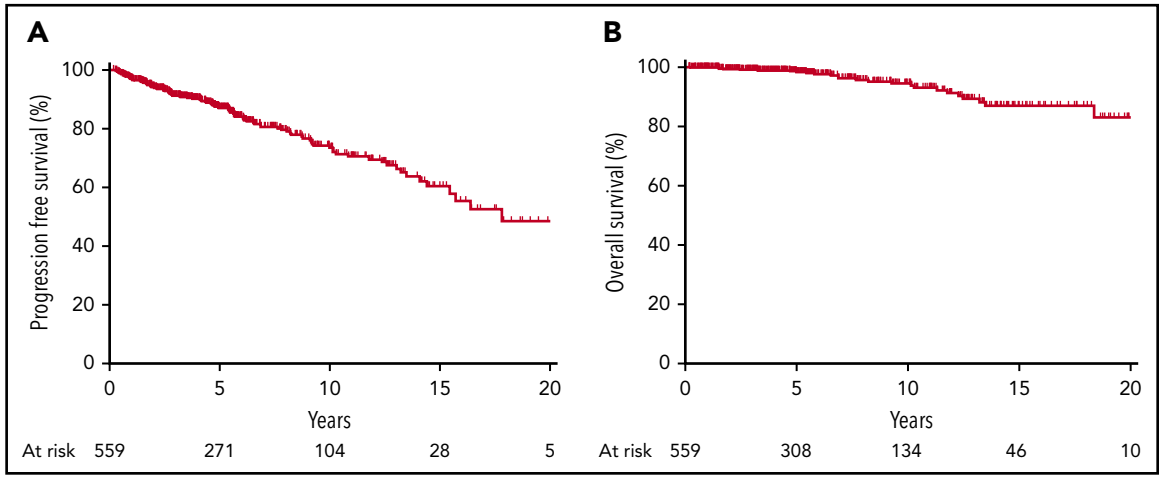

Figure 1. Outcomes for the entire cohort. Kaplan-Meier curves demonstrate PFS (A) and OS (B) of patients with stage I-II NLPHL.

[n = 2]), and CT alone (cardiac disease after anthracycline therapy [n = 3] and pulmonary fibrosis [n = 2]).

Second cancers

Second cancers occurred in 24 (4.3%) patients during follow-up (supplemental Table 6). Four (0.9%) patients who received RT (with or without systemic therapy) developed cancers within the RT treatment volume.

Discussion

In this study, we observed that patients with early-stage NLPHL who received definitive RT-containing therapy had a PFS of greater than 90% at 5 years, and greater than 70% at 10 years. One quarter of the patients in our series had greater than 10 years of follow-up, and there was an ongoing risk of relapse for at least 15 years after diagnosis. After treatment with RT alone, we identified that both the involved sites >2 and variant IAP were associated with worse PFS and may warrant treatment intensification via CMT. Only the presence of B symptoms was a poor prognostic factor for PFS in the CMT cohort after MVA. However, similar to recent reports from the GHSG, non-lymphoma causes of death were greater than lymphoma-specific deaths in our study, and longer follow-up is necessary to further define the second malignancy risk in adult populations.[23] Importantly, OS was excellent after all types of initial management.

Several previous studies have reported excellent outcomes after RT alone for early-stage NLPHL. The GHSG reported a favorable prognosis for patients with stage IA NLPHL who received RT, with no benefit seen from the addition of CT.[5,11] The treatment of stage IIA NLPHL without risk factors is currently controversial: the European Society of Medical Oncology recommends CMT, whereas the National Comprehensive Cancer Network (NCCN) recommends RT alone for many patients.[24,25] In patients with stage II NLPHL, institutions have found worse PFS compared to

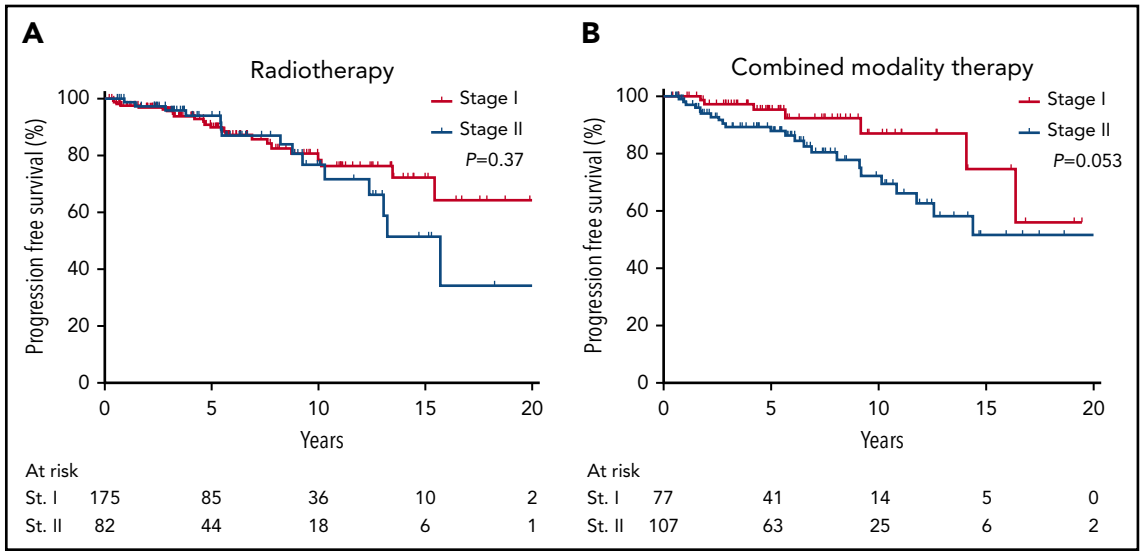

Figure 2. PFS of the RT and CMT cohorts by stage. Kaplan-Meier curves demonstrate the PFS of patients with stages I and II NLPHL receiving RT (A) or CMT (B). Five-year PFS for patients receiving RT was 89.8% (95% CI, 82.8%-94.0%) for stage I and 93.9% (95% CI, 84.4%-97.7%) for stage II. Five-year PFS for patients receiving CMT was 95.3% (95% CI, 86.0%-98.5%) for stage I and 87.9% (95% CI, 79.1%-93.1%) for stage II.

Table 2. Univariate and analysis and MVA for PFS using stratified Cox regression adjusted for treatment center

Variable	RT PFS (38 events)			Combined modality therapy PFS (31 events)	
	Univariate	MVA1	MVA2*	Univariate	MVA
Age (continuous) HR 95% CI *P*	1.01 0.99-1.04 .24	—	—	**1.02** **1.01-1.04** **.009**	1.02 0.99-1.04 .08
Male sex HR 95% CI *P*	1.17 0.59-2.35 .65	—	—	2.07 0.90-4.78 .09	—
B symptoms HR 95% CI *P*	—	—	—	**2.39** **1.25-4.56** **.008**	**1.91** **1.01-3.63** **.047**
Bone marrow biopsy HR 95% CI *P*	0.70 0.41-1.20 .20	—	—	1.02 0.50-2.11 .95	—
Extranodal disease HR 95% CI *P*	1.58 0.53-4.67 .41	—	—	1.00 0.22-4.61 1.00	—
Stage II HR 95% CI *P*	1.35 0.68-2.69 .40	—	—	**2.26** **1.01-5.07** **.048**	2.04 0.85-4.90 .11
Noncontiguous stage II HR 95% CI *P*	0.76 0.18-3.13 .70	—	—	0.76 0.23-2.55 .66	—
Pretreatment size (continuous), cm HR 95% CI *P*	1.06 0.98-1.13 .47	—	—	1.03 0.95-1.11 .47	—
PET staged HR 95% CI *P*	0.98 0.40-2.44 .97	—	—	1.00 0.47-2.12 1.00	—
Number of involved sites >2 HR 95% CI *P*	**2.51** **1.17-5.40** **.02**	**2.66** **1.33-5.32** **.006**	**2.66** **1.23-5.75** **.01**	1.19 0.26-5.40 .43	—
Infradiaphragmatic HR 95% CI *P*	**0.22** **0.06-0.79** **.02**	**0.22** **0.07-0.70** **.01**	0.24 0.04-1.46 .12	0.56 0.20-1.60 .28	—
Variant IAP† HR 95% CI *P*	**2.46** **1.06-5.66** **.04**	—	**2.70** **1.14-6.40** **.02**	0.51 0.05-5.22 .57	—

—, regression did not converge.

*MVA2 performed using the subset with IAP available.

†Subset with IAP available: RT cohort (n = 100; 22 events); CMT cohort (n = 76; 12 events).

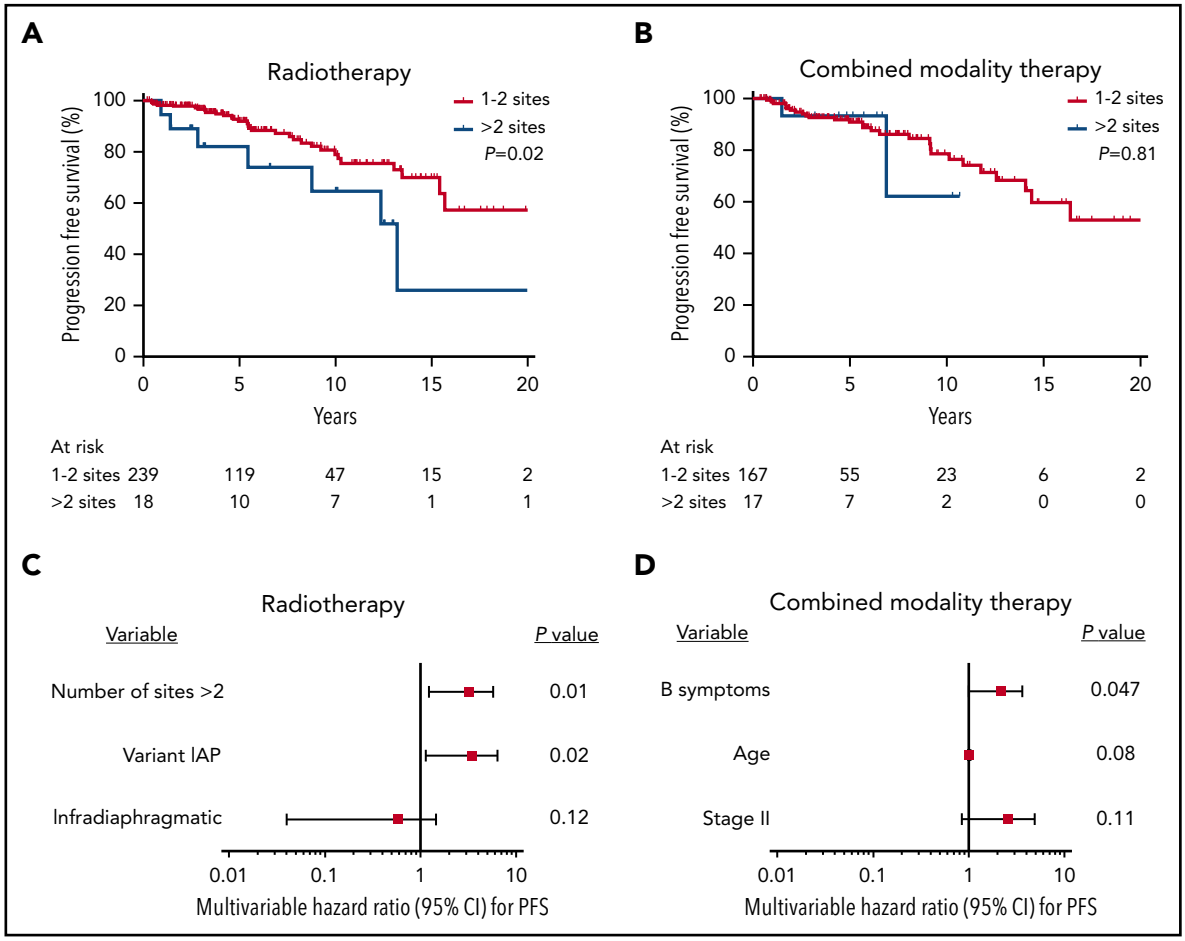

Figure 3. PFS analyses for the RT and CMT cohorts. (A-B) PFS in patients with 1 to 2 sites vs >2 sites of involvement receiving RT ($P = .02$) and CMT ($P = .81$). (C-D) For patients who received RT (C) or CMT (D), a forest plot of the multivariable analysis for PFS, including factors significant in univariable analysis ($P < .05$).

those with stage I.[9,26] Wirth et al[26] reported a large multicenter study of patients receiving RT alone from 1969 through 1995, with freedom from progression of 84% and 73% in patients with stages I and II NLPHL, respectively. Patients with stage II and only 2 sites of disease had a an outcome similar to that of patients with stage I disease. We also found that patients who received RT with >2 sites had a worse PFS. Conversely, there was no difference in PFS in patients who received CMT with >2 sites vs all others, suggesting that treatment intensification may improve outcomes of the subset with >2 sites of involvement.

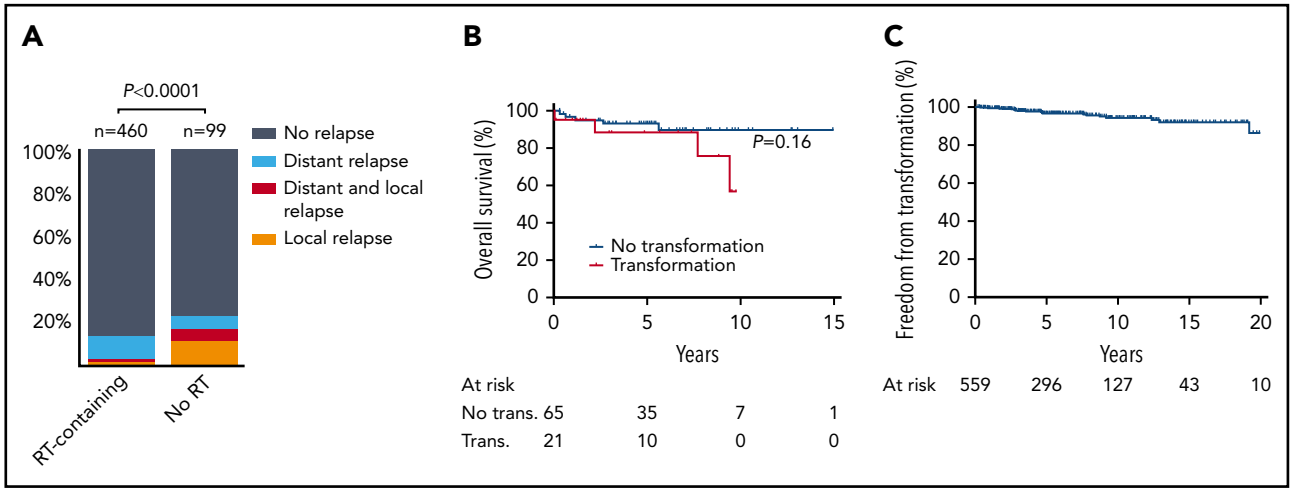

Figure 4. Patterns of failure, transformation rate, and survival after progression. (A) The patterns of failure for patients selected for RT/CMT or other primary managements. (B) OS for patients who progress after primary management, stratified by transformation status. (C) Freedom from transformation to large-cell lymphoma.

Notably, it appears that there is no decrease in local disease control with smaller, more contemporary RT volumes similar to findings by Pinnix et al.[27] We also did not observe worse PFS in patients with infradiaphragmatic involvement, similar to reports by other groups.[28] The small subset of patients in our cohort with stage I NLPHL who received CT had a 5-year PFS of 90.9%, similar to reports by other groups, suggesting CT alone may also achieve excellent disease response.[6,29]

Recently, there has been interest in further de-escalation of upfront treatment of NLPHL, given the high response to salvage treatment at time of relapse. We found that approximately two-thirds of patients with predominantly stage I NLPHL selected for observation, of whom most had complete resection and PET staging, were also free of progressive lymphoma or death at 5 years postresection. A prior prospective pediatric study by Appel et al[12] showed a 5-year event-free survival rate of 77.1% after total resection, which is remarkably similar to our 5-year PFS of 79.1% in those reported as having a complete resection. Borchmann et al[14] recently reported a large single-institution cohort with a 5-year PFS of 65% for early-stage NLPHL. An older French registry study showed a 5-year PFS of 59% in adult patients although they did not specify the proportion with completely resected disease.[30] Both Borchmann et al[14] and Appel et al[12] reported that progressions after active surveillance were most commonly of limited stage (60% and 100%, respectively). In our cohort of patients who were initially observed, 3 of 4 NLPHL relapses with restaging information were of advanced stage. Thus, for adult patients selected for observation, salvage treatment with RT alone may not always be an option.

Previously, the GHSG showed worse PFS for variant IAP vs typical pattern among patients with stage I-IV disease and recently showed a shorter median time to recurrence in those with variant IAP vs typical pattern after treatment with rituximab alone for stage IA NLPHL.[31,32] We similarly found worse PFS in patients with variant IAP in early-stage NLPHL after treatment with RT alone. We did not observe any association between variant IAP and PFS in those receiving CMT, suggesting that the addition of CT may improve outcomes for this subset. Interestingly, we found a nearly 3 times higher risk of transformation in patients with variant IAP (HR, 2.72), further confirming that patients in this subset are at risk of progression to aggressive lymphoma.

Given the excellent survival of patients with early-stage NLPHL, any risk of late effects with a given treatment must be considered. We observed very low rates of late toxicity in patients who received definitive RT or CMT (3.9%). Although we observed very low rates of second cancer (<5% overall, with <1% occurring within RT volumes), our median follow-up was not adequate to capture the late risk of second cancers associated with RT and CT. The GHSG reported long-term outcomes for NLPHL after treatment with RT/CMT/CT, with 10.2% of patients developing a second malignancy within a median observation time of 9.2 years.[23]

Limitations of our study include its retrospective nature; lack of central pathology and imaging review (including lack of Deauville scoring by nuclear medicine specialists); and most important, relatively small subsets of patients selected for non-RT–containing management approaches, with an uneven distribution of prognostic factors between groups limiting any statistical comparisons between management groups. Ultimately, controlled clinical trials are necessary to determine the optimal treatment of early-stage NLPHL, but will be challenging to conduct given the disease incidence and excellent OS.

In conclusion, our data provide further evidence of the efficacy of RT alone for stage I NLPHL. RT alone may also be appropriate for selected patients with stage II disease without risk factors. CMT warrants consideration for patients with unfavorable features, such as variant IAP or stage II disease with 3 or more sites of involvement. Observation appears to be an acceptable alternative for patients with stage I NLPHL who are entirely without evidence of disease after excision, particularly in settings where RT poses a late toxicity risk.

Authorship

Contribution: M.S.B., R.H.A., Y.N., L.S.C., H.T.E., A.W., and R.T.H. conceived of and designed the study, developed the methodology, and supervised the study; and all authors were involved in the acquisition, analysis, and interpretation of the data and the writing, review, and revision of the manuscript.

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Footnotes

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The data are not available for sharing because they contain protected health information.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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Appendix

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