

Resection Alone in 58 Children With Limited Stage, Lymphocyte-predominant Hodgkin Lymphoma—Experience From the European Network Group on Pediatric Hodgkin Lymphoma

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BACKGROUND. Lymphocyte-predominant Hodgkin lymphoma (LPHL) is a rare, CD20-positive, good prognostic lymphoma in children. Patients with early-stage LPHL who underwent successful surgical lymph node resection alone have been reported. To clarify the optimum treatment strategy in children, European study groups were asked to report their experience of surgery alone used in the treatment of pediatric LPHL.

METHODS. Data from 58 patients were collected by the French Society for Pediatric Cancers, the German-Austrian Pediatric Study Group/German Society of Pediatric Oncology and Hematology (Germany), and the Children's Cancer and Leukaemia Group (United Kingdom). In total, there were 50 boys and 8 girls, and the median age was 11 years (age range, 4-17 years). Fifty-four patients had stage IA disease, 2 patients had stage IIA disease, and 2 patients had stage IIIA disease.

RESULTS. With a median follow-up of 43 months (range, 2-202 months), the overall survival rate was 100%, and the progression-free survival (PFS) rate was 57%. Fifty-one of 58 patients achieved complete remission (CR) after surgery. In the CR group, the overall PFS rate was 67% (95% confidence interval, 51-82%). All seven patients who had residual disease after initial surgery developed recurrences ($P = .003$). Among 18 patients with stage IA LPHL who developed recurrent disease, 11 patients had local recurrences, and 7 patients recurred in stage IIA. One patient with stage IIIA disease presented with high-grade B-cell non-Hodgkin lymphoma at 10 years of follow-up.

CONCLUSIONS. When complete resection was achieved, a substantial proportion of patients with surgically treated, early-stage LPHL experienced long-term remission and actually may have been cured. *Cancer* 2007;110:179-85. © 2007 American Cancer Society.

KEYWORDS: Hodgkin lymphoma, surgery alone, lymphocyte predominant, Hodgkin lymphoma, children.

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Lymphocyte-predominant Hodgkin lymphoma (LPHL), or Poppema-Lennert paragranuloma, is a rare subtype of CD-20-positive Hodgkin lymphoma that was recognized as a distinct entity in the new classifications proposed by the International Lymphoma Study Group in 1994 and by the World Health Organization in 2001.^{1,2} LPHL is characterized by the presence of lymphocytic and histiocytic (L&H) cells with polylobular nuclei within nodules composed of small, mature B lymphocytes. Reed-Sternberg cells are few or absent. The L&H cells frequently are negative on immunostaining for CD15, CD30, and the Epstein-Barr virus (EBV) genome but positive for B-cell antigens (CD20, CD79a, and CD75), leukocyte (CD45), and epithelial membrane antigen (EMA).^{3,4} Bcl6 activation and expansion of a single clone originating from a germinal center B-cell commonly is described.⁵⁻⁸

Patients typically present with early stage disease, mainly stage IA, with peripheral lymph node involvement (ie, cervical, axillary, and inguinal involvement rather than mediastinal involvement, which rarely is observed). There is a striking male predominance. The prognosis is favorable with an indolent course of disease, and the rare patient deaths are related to secondary (treatment-related) malignancies or transformation to aggressive B-cell lymphoma⁹⁻¹⁴ or classic Hodgkin lymphoma (HL). In the past, patients with LPHL often have been treated with chemotherapy and radiotherapy according to standard, classic HL protocols.¹⁵⁻¹⁷ Patients with early-stage disease who were treated with radiotherapy alone usually received extended-field radiation,¹⁸⁻²⁰ chemotherapy alone,²¹ or, more recently in adults, monoclonal antibody therapy with rituximab.²¹⁻²³ With these modalities, long-term, progression-free survival (PFS) rates between 80% and 95% and overall survival (OS) rates between 83% and 100% have been reported, although patients may develop delayed recurrences.

Occasionally, patients with early-stage LPHL have been treated with surgery alone. In 1983, Miettinen et al. reported an overall survival rate of 93% at 5 years in 31 adult patients with retrospectively diagnosed LPHL who remained untreated except for lymph node excision, because their original histology was reported as benign.²⁴ In 1984, Hansmann et al. reported on 24 patients with LPHL who underwent surgery only for various reasons. Nine of those patients achieved long-term remission.²⁵ These reports suggest that surgery alone may be an option in early-stage LPHL. In children, only 19 cases have been published to date.^{26,27} The decision to use surgery alone in these patients with early-stage disease

was made on an individual basis by the treating physicians in consultation with the parents in an effort to limit treatment toxicity while maintaining a successful outcome. In view of published reports described above, we in the European Network Group on Pediatric Hodgkin Lymphoma (EuroNet-PHL), a pan-European group that works on pediatric HL (encompassing the United Kingdom Children's Cancer Study Group, now the Children's Cancer and Leukaemia Group [CCLG], the French Society for Pediatric Cancers [SFCE], and the German-Austrian Pediatric Study Group/German Society of Pediatric Oncology and Hematology [DAL/GPOH]), report our joint experience of treating children with LPHL with surgery alone. Our collective datasets were used to try to answer 2 questions: 1) Can a significant proportion of patients with early-stage LPHL be cured by surgery alone?; and 2) Is a watch-and-wait strategy after surgery alone a safe option in those who have obtained complete remission (CR)? In particular, what is the risk of a significant upstaging at recurrence (ie, stage >II or B-symptoms) and/or of a histologic transformation into a more aggressive B-cell lymphoma?

MATERIALS AND METHODS

The European study groups that participated in the EuroNet-PHL intergroup were asked to report their experience of surgery alone used in the treatment of early-stage, pediatric LPHL. Surgery as the single treatment modality has been used since 1989/1990 by the SFCE (France) and the DAL/GPOH (Germany, Austria, Sweden, Norway, and Switzerland) and, more recently, by the CCLG (United Kingdom). To our knowledge, the approach has not been used to date in Italy, Poland, Spain, the Czech Republic, or Slovakia. Individual data from 58 patients were collected by using a common case report form. The contributing centers and physicians are listed on Table 1. Consent from patients and parents was obtained according to each country's guidelines on ethics. The series of 13 patients published by Pellegrino et al. was updated and has been included.²⁶ Fifty-five of 58 patients had their tumor histology confirmed in a pathology review by specialist hematopathologists in their respective countries.

Statistical Analysis

OS was measured from the date of diagnosis to the date of the last visit or death. PFS was measured from the date of diagnosis to the date of recurrence, disease progression, death, second malignancy, or last follow-up. The probability estimates of PFS or

TABLE 1
Participating Centers

Germany	Norway
Department of Pediatric Hematology/Oncology, University of Greifswald, Greifswald (J. Beck)	Department of Pediatric Hematology/Oncology, University of Oslo, Oslo (M. Hellebostad)
Department of Pediatric Hematology/Oncology, University of Luebeck, Luebeck (P. Bucsky)	Sweden
Department of Pediatric Hematology/Oncology University of Halle, Halle (S. Burdach)	Department of Pediatric Hematology/Oncology, University of Linköping, Linköping (M. Behrendtz)
Department of Pediatric Oncology/Hematology, University of Heidelberg, Heidelberg (K.-M. Debatin and A. Kulozik)	French Society for Pediatric Cancers (France)
Department of Pediatrics, HELIOS Clinic, Berlin-Buch (W. Doerffel)	Pediatric Hematology Service, American Hospital, Reims (C. Behar)
Department of Pediatric Hematology/Oncology, University of Berlin, Berlin (G. Henze)	Pediatric Oncology Unit, Timone Children's Hospital, Marseille (C. Coze)
Cnopf'sche Pediatric Clinic, Diakonie Neuendettelsau, Nurnberg (A. Jobke)	Pediatric Day Hospital, Jeanne of Flanders Regional University Hospital, Lille (A. Lambilliotte)
Department of Pediatric Hematology/Oncology, University of Muenster, Muenster (H. Juergens)	Department of Pediatric Hematology/Oncology, Armand Trousseau AP-HP, Paris (J. Landman-Parker)
Department of Pediatrics, SLK Clinic, Heilbronn (W. Kachel); Department of Pediatrics, Stadt Clinic, Braunschweig (H. G. Koch)	Pediatric Hematology Service, Saint-Louis AP-HP, Paris (T. Leblanc)
Department of Pediatric Hematology/Oncology, University of Goettingen, Goettingen (M. Lakomek)	Pediatric Service, Curie Institute, Paris (H. Pacquement)
Department of Pediatric Hematology/Oncology, University of Magdeburg, Magdeburg (U. Mittler)	Pellegrin Group, Children's Hospital, Bordeaux (Y. Perel)
Department of Pediatric Hematology/Oncology, University of Freiburg, Freiburg (C. Niemeyer)	Pediatric Service, Gustave Roussy Institute, Villejuif (O. Oberlin)
Department of Pediatric Hematology/Oncology, University of Tuebingen, Tuebingen (D. Niethammer and R. Handgretinger)	Pediatric Hematology/Oncology Service, Nord Regional University Hospital, Amiens (B. Pautard)
Department of Pediatric Hematology/Oncology, University of Hamburg, Hamburg (R. Schneppenheim)	Pediatric Oncology/Hematology Service, Feliz Guyon Central Departmental Hospital, Saint-Denis de la Reunion (Y. Reguerre)
Department of Pediatrics, Stadt Clinic, Bremen (H.-J. Spaar)	Hematology/Oncology Service, Children's Hospital, Toulouse (A. Robert)
Switzerland	Pediatric Medicine Service 1, Children's Hospital, Vandoeuvre (C. Schmitt)
Canton Hospital, Aarau (P. Imbach)	Pediatric and General Medicine Service, Charles Nicolle Hospital, Rouen (J. P. Vannier)
University Children's Hospital, Bern (K. Leibundgut)	Children's Cancer and Leukaemia Group (United Kingdom)
Austria	John Radcliffe Hospital, Headington, Oxford (G. W. Hall)
Department of Pediatric Hematology/Oncology, University of Graz, Graz (C. Urban)	Pediatric Oncology, Great Ormond Street Hospital, London (G. Levitt)
	Department of Pediatric and Adolescent Oncology, University College Hospital, London (A. Shankar)
	Pediatric Oncology, University College Hospital, London (S. Stoneham)
	Royal Hospital for Sick Children, Edinburgh, (W. H. Wallace).

OS were calculated by using the Kaplan-Meier method.

RESULTS

Clinical Characteristics of the 58 Patients

Age at diagnosis for the 58 patients ranged from 4 years to 17 years (median age, 11 years) (Table 2). There was a strong predominance of males (50 boys, 8 girls). Patients presented with stage IA disease (n = 54 patients), stage IIA disease (n = 2 patients), or stage IIIA disease (n = 2 patients). Lymph node involvement at presentation generally included mainly supradiaphragmatic lymph nodes (n = 46 patients); mainly cervical lymph nodes (n = 40 patients); and, less often, subdiaphragmatic (mainly inguinal) lymph nodes (n = 11 patients). Computed tomography (CT) and magnetic resonance imaging (MRI) studies were obtained from 80% of patients. No mediastinal involvement was reported. None of the patients had systemic B symptoms. All children

underwent surgical adenectomy only and received no further treatment based on physician and parental decision. Evaluation after surgery was heterogeneous based mainly on clinical evaluation or CT/MRI studies. In only 10 of the most recent patients was a flurodeoxyglucose-positron emission tomography (FDG-PET) scan used to confirm CR. In 6 patients, additional surgery after the diagnostic biopsy was necessary to achieve a complete resection. No complications of surgery were reported.

Outcome

With a median follow-up of 43 months (range, 2-202 months), all 58 patients remained alive. Fifty-one patients achieved CR after surgery alone. Involved lymph nodes in 7 patients were not completely resected (4 patients with stage IA disease, 1 patient with stage IIA disease, and 2 patients with stage IIIA disease) (Fig 1). Twenty-one of 58 children developed recurrences from 4 months to 120 months after diag-

TABLE 2
Clinical Characteristics of the 58 Patients With Lymphocyte-predominant Hodgkin Lymphoma

Characteristic	No. of patients
Mean age at diagnosis [range], y	11 [4-17]
No. of boys (%)	50/58 (86)
Stage	
IA	54
IIA	2
IIIA	2
No. with supradiaphragmatic disease	46
Involved sites	
Cervical	40
Supraclavicular	2
Axillary	4
Cubital	3
No. with infradiaphragmatic disease	14
Involved sites	
Inguinal	11
Femoral	1
Spleen	1
Intra-abdominal	1
Complete resection after surgery	51
Follow-up, mo	
Median	43
Range	2-202
Overall survival rate, %	100
PFS rate [95% CI], %	
All patients	57 at 50 mo [42-73]
Patients with CR after surgery, n=51	67 at 26 mo [51-82]

PFS indicates progression-free survival; CR, complete response; 95% CI, 95% confidence interval.

nosis (median, 11 months). In the CR group, 14 recurrences were observed that occurred early, all within 26 months. Histologic confirmation of recurrence was obtained by lymph node biopsy. The overall PFS survival estimate at 50 months was 57% (95% confidence interval [95% CI], 42-73%), and the PFS estimate for the group of 51 patients who achieved CR after surgery was 67% at 26 months (95% CI, 51-82%). In the group of 7 patients who had clinical residual disease, all 7 patients developed recurrences at a median of 17 months (log-rank test: $P < .011$). One of those patients (initial stage IIIA disease) had a recurrence with a B-cell lymphoma 10 years after initial diagnosis.

The modalities used for restaging were identical to those used at initial presentation and diagnosis. Among the 18 patients with stage IA disease who developed a recurrence, 11 patients had local recurrences, and 7 recurrences represented a higher disease stage (ie, stage IIA). In this group, the rate of significant upstaging, which was defined as B-symptoms or recurrence stage >IIA, was 0% (95% CI, 0-18.5%). Clinical characteristics, treatments, and outcomes of the patients with recurrent LPHL are

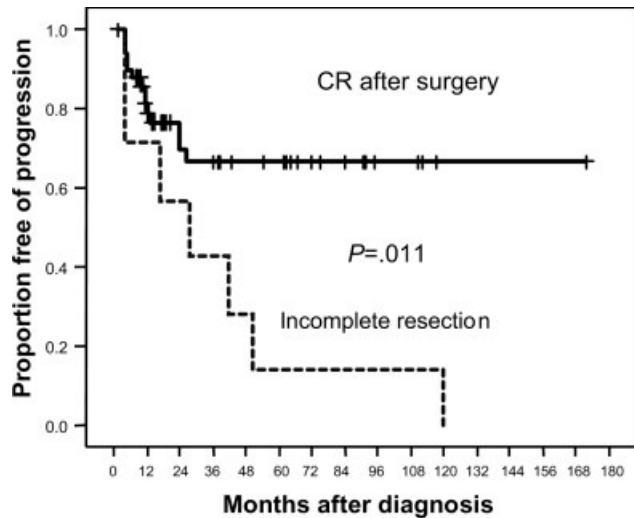


FIGURE 1. Progression-free survival after surgery alone. Solid line, complete response (CR) after surgery (14 of 51 events); dashed line, incomplete resection (7 of 7 events; log-rank test; $P < .011$).

detailed in Table 3 (the patient with non-Hodgkin lymphoma is not included). It is noteworthy that, as of the time of the current report, 17 of 20 patients were in second CR, and 4 of 20 patients had undergone second surgery. Overall, only 5 patients received radiation therapy. PFS for these patients is reported on Figure 2. The 2 patients who had second recurrences relapse were not in CR after their first and second treatments (1 patient stage III). At a median follow-up of 52 months, the PFS rate for the patients with recurrent disease was 80%.

DISCUSSION

Our study combines the experience of 3 major European pediatric Hodgkin lymphoma study groups on surgery alone in early-stage LPHL. The 58 patients reported here form the largest series of patients using the surgery-alone approach in children with LPHL.

The global prognosis for patients with LPHL is excellent, as demonstrated in previous studies, with an OS rate of $\approx 95\%$ and a PFS rate between 85% and 94%.¹⁵⁻¹⁸ Our study confirmed these results, with a 100% OS rate at a median follow-up of 4 years. Although long-term analyses in adults have reported recurrences up to 10 years after radiotherapy or combined-modality treatment,¹⁵⁻¹⁸ most of the deaths reported in patients with LPHL are related to treatment and/or the development of subsequent malignancies, including lymphoma, rather than to progression of the original disease. Adverse acute and long-term consequences of treatment clearly are dependent on the modality used in up-front treat-

TABLE 3
Clinical Characteristics of the Patients With Recurrent Lymphocyte-predominant Hodgkin Lymphoma After Surgery Alone

Patient	CR*	PFS, mo	Stage	Lymph node involvement			Recurrence stage	Second treatment	P2FS, mo	Second recurrence	Last status
				At staging	At recurrence	Recurrence stage					
2	1	4	I	R cervical	R cervical	I	Endoxan	62		CR2	
3	0	42	III	R axilla and elbow, abdomen	R axilla and elbow, abdomen	III	4 MOPP/ABVP	49	Yes	CR3 after Mabthera	
4	1	4	I	Cervical	L cervical	I	Second surgery	62		CR2	
7	1	26	I	R axilla	7 Lymph nodes in axillary G	II	4 VBVP and 20 Gy IF	52		CR2	
8	1	11	I	L cervical	3 Lymph nodes and R cervical	II	2 MOPP, 2 ABVP, and 20 Gy IF	89		CR2	
9	0	50	I	L cervical	L cervical	I	Second surgery	43	Yes	CR3 after 4 VBVP	
11	0	4	I	L cervical	L and R cervical	II	4 VBVP and 20 Gy IF	81		CR2	
18	1	5	I	L cervical	L cervical	I	4 VBVP and 20 Gy IF	17		CR2	
22	1	4	I	L cervical	L cervical	I	Second surgery	9		CR2	
23	1	11	I	R cervical	R cervical	I	Second surgery	5		CR2	
25	1	10	I	L cervical	L cervical	I	3 CVP	5		CR2	
39	1	5	I	R cervical	R and L cervical, jugular	II	2 OEPA	73		CR2	
40	1	13	I	L cervical	L and R axilla, jugular	II	2 OEPA	59		CR2	
41	0	4	I	L femoral	L femoral, L inguinal	II	2 OEPA	27		CR2	
42	1	12	I	R cervical	R and L cervical	II	2 OEPA	27		CR2	
47	1	24	I	L axilla	L axilla	I	2 OEPA and 25 Gy IF	88		CR2	
50	1	24	I	R inguinal	R inguinal	I	2 OEPA	75		CR2	
53	0	28	I	R upper neck	R upper neck	I	2 OEPA	0		First recurrence	
54	1	6	I	L elbow	L elbow	I	2 OEPA	6		CR2	
55	0	17	II	L and R upper neck, L supraclavicular	L and R upper neck, L supraclavicular	II	2 OEPA	5		CR2	

CR indicates complete remission; PFS, progression-free survival; P2FS, PFS after first recurrence; R, right; L, left; MOPP/ABVP, nitrogen mustard, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, etoposide, prednisone; VBVP, vinblastine, bleomycin, etoposide, prednisone; Gy, grays; OEPA, vincristine, etoposide, prednisone, doxorubicin.

* CR: 0, indicates no first CR; 1, complete CR.

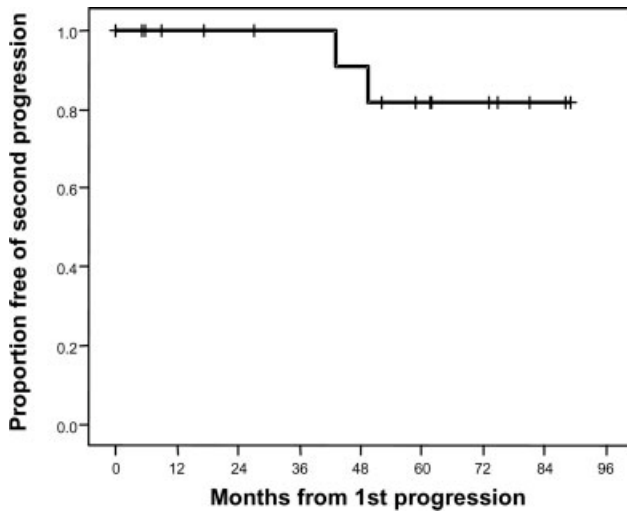


FIGURE 2. Progression-free survival after first progression.

ment (anthracyclines, alkylating agents, or radiation), especially in children. Because significant proportions of patients have stage I disease with involvement of 1 or 2 contiguous lymph nodes, surgical resection alone seems an acceptable option considering the benign natural history of the disease reported since the early 1980s.²⁴ In our retrospective study, substantial proportions of surgically treated patients with stage IA LPHL have experienced long-term remission. This result needs to be confirmed by long-term analyses and prospective studies. However, patients with incomplete resection have a high probability of early recurrence, although most recurrences occur in the initially involved site without upstaging. Now that PET and CT/MRI studies are easier to obtain, better evaluation of remission after surgery is possible, and this should help develop a risk-adapted approach to management.^{28,29} Alternative modalities to surgery alone may include radiotherapy alone with extended or involved fields (from 36 grays [Gy] to 40 Gy), like what is used in adults,^{18,19} although this approach may not be desirable in growing children. Combined-modality treatment (4 to 6 cycles of chemotherapy with or without radiotherapy) has been reported in adults with excellent results.^{16,17} Currently in pediatric oncology groups, patients who have early-stage LPHL receive the same modalities as patients who have classic Hodgkin lymphoma or are treated with 2 to 3 cycles of chemotherapy; however, to date, little has been published regarding long-term outcomes with reduced-intensity treatments.^{26,27,30,31} Rituximab alone or used with chemotherapy has been evaluated in Phase II studies and in patients with recurrent disease but not as first-line therapy.^{22,23}

Our current results suggest that a significant proportion of patients with stage I LPHL and limited disease may be cured by surgical resection alone, thus avoiding acute or long-term toxicity related to chemotherapy or radiotherapy. We emphasize the need for a prospective study to identify which patients may benefit from this approach. The EuroNet-PHL group is launching a Europe-wide study (EuroNetPHL-LP1) in 2007 for children with early-stage LPHL to define a risk-adapted strategy and to confirm these retrospective results.

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