

ONLINE APPENDIX

Title

Primary therapy and survival among patients with nodular lymphocyte-predominant Hodgkin lymphoma: a population-based analysis in the Netherlands, 1993-2016

Short title

Population-based outcomes in NLPHL

Authors and affiliations

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Supplemental methods

Statistical analyses

Overall and age- and sex-specific incidence rates were calculated per 1,000,000 person-years using the annual mid-year population size that was obtained from Statistics Netherlands. All aggregated incidence rates were adjusted for age using the European standard population. Seventy-one patients below age 18 at diagnosis were included in the analyses of aggregated incidence rates. This is compatible with international standards for computing overall incidence rates. Age-specific incidence rates were analyzed for the following age groups: 0-19, 20-39, 40-59, and ≥ 60 years. In addition, age-specific incidence rates were calculated per quinquennial age groupings of 0-4 years to ≥ 85 years. Of note, incidence rates can only be calculated for quinquennial years of age.

The Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables were applied to test for difference between groups.

A generalized linear model (GLM) that assumed a Poisson distribution for the mortality rate was constructed to assess covariates associated with the relative excess risk of mortality during the first ten years after the diagnosis of nodular lymphocyte-predominant Hodgkin lymphoma, with simultaneous adjustment for the following covariates: calendar period of diagnosis, sex, age, stage, and years of follow-up. The ten years of follow-up were split into 2-year time bands. The GLM produces excess mortality ratios (EMRs) with 95% confidence intervals (CIs).

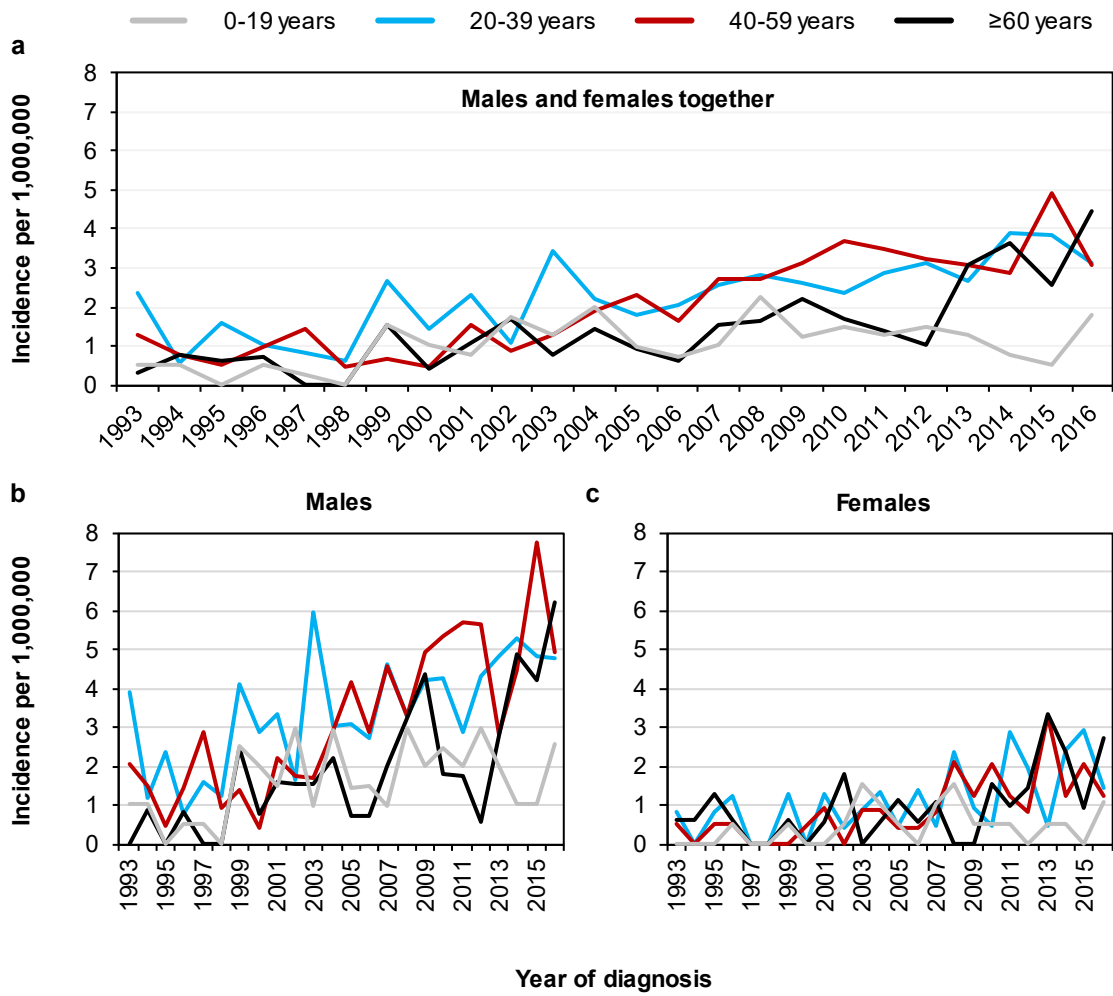
All statistical analyses were performed with STATA Statistical Software Release 14.2 (College Station, TX, U.S.).

Supplemental figure legends

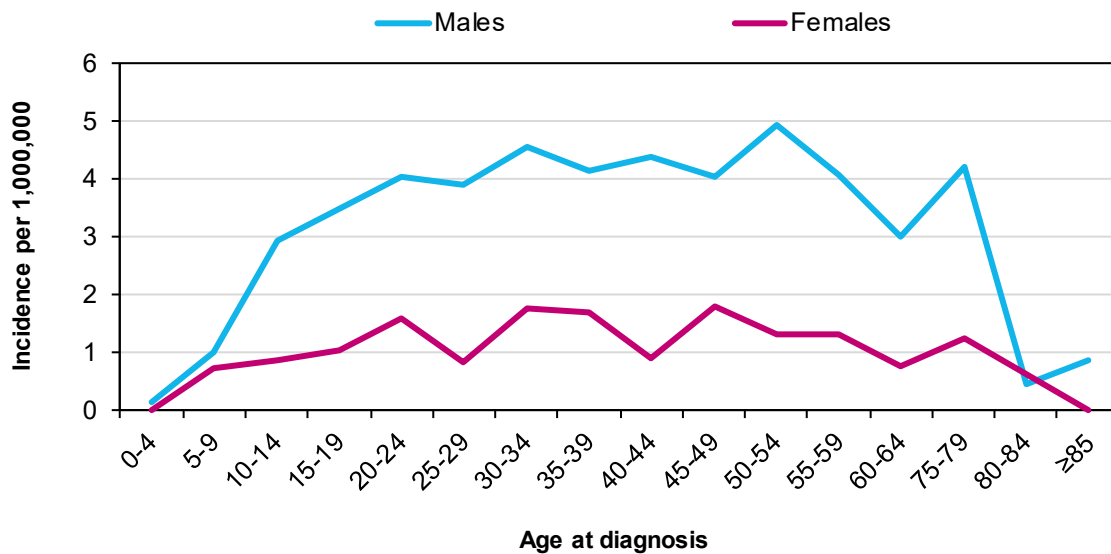
Supplemental Figure 1. Age-specific incidence rates of patients with nodular lymphocyte-predominant Hodgkin lymphoma in the Netherlands, 1993-2016. Incidence rates are presented per 1,000,000 person-years for the following age groups: 0-19, 20-39, 40-59, and ≥ 60 years. Incidence rates are shown for (A) males and females together, (B) males alone, and (C) females alone.

Supplemental Figure 2. Age-specific incidence rates per quinquennial years of age of patients with nodular lymphocyte-predominant Hodgkin lymphoma in the Netherlands, 2003-2016. Incidence rates are presented per 1,000,000 person-years and shown according to sex. The period of 2003-2016 was chosen, as this period in a way represents contemporary clinical practice.

Supplemental Figure 1



Supplemental Figure 2



Supplemental tables

Supplemental Table 1. Patient characteristics

Characteristics	Calendar period						Total		
	1993-2002			2003-2016			No.	(%)	IR ^a
	No.	(%)	IR ^a	No.	(%)	IR ^a			
Total No. of patients	156	-	1.0	531	-	2.2	687	-	1.7
Sex									
Male	123	(79)	1.5	391	(74)	3.3	514	(75)	2.6
Female	33	(21)	0.4	140	(26)	1.2	173	(25)	0.9
Age, years									
Median (range)	34 (4-77)			42 (4-87)			40 (4-87)		
0-17	18	(12)	0.7	53	(10)	1.3	71	(10)	1.0
18-39	80	(51)	1.4	187	(35)	2.8	267	(39)	2.2
40-59	38	(24)	0.9	194	(37)	2.9	232	(34)	2.0
≥60	20	(13)	0.7	97	(18)	1.9	117	(17)	1.4
Ann Arbor stage									
I	95	(61)		239	(45)		334	(49)	
II	34	(22)		143	(27)		177	(26)	
III	17	(11)		102	(19)		119	(17)	
IV	3	(2)		41	(8)		44	(6)	
Unknown	7	(4)		6	(1)		13	(2)	
B symptoms									
No	69	(44)		409	(77)		478	(70)	
Yes	10	(6)		59	(11)		69	(10)	
Unknown	77	(49)		63	(12)		140	(20)	

Abbreviation: IR, incidence rate.

^aIncidence rates are presented per 1,000,000 person-years. The overall and sex-specific incidence rates are standardized as per the European standard population.

Supplemental Table 2. Primary therapy of adult patients with nodular lymphocyte-predominant Hodgkin lymphoma in the Netherlands according to stage at diagnosis, age at diagnosis, and calendar period of diagnosis, 1993-2016

Stage	Age, years	Calendar period	Primary therapy								Total N
			Chemotherapy only		Radiotherapy only		No anti-neoplastic therapy		Rituximab only		
			N	(%)	N	(%)	N	(%)	N	(%)	N
Stage I-II	18-39	1993-2002	9	(13)	50	(75)	8	(12)	0	-	67
		2003-2016	21	(14)	81	(55)	39	(27)	6	(4)	147
		1993-2016	30	(14)	131	(61)	47	(22)	6	(3)	214
	40-59	1993-2002	4	(13)	17	(55)	10	(32)	0	-	31
		2003-2016	19	(15)	67	(54)	37	(30)	0	-	123
		1993-2016	23	(15)	84	(55)	47	(31)	0	-	154
	≥60	1993-2002	2	(14)	8	(57)	4	(29)	0	-	14
		2003-2016	11	(19)	26	(44)	22	(37)	0	-	59
		1993-2016	13	(18)	34	(47)	26	(36)	0	-	73
	All ages	1993-2002	15	(13)	75	(67)	22	(20)	0	-	112
		2003-2016	51	(16)	174	(53)	98	(30)	6	(2)	329
		1993-2016	66	(15)	249	(56)	120	(27)	6	(1)	441
Stage III-IV	18-39	1993-2002	6	(75)	0	-	2	(25)	0	-	8
		2003-2016	30	(79)	2	(5)	6	(16)	0	-	38
		1993-2016	36	(78)	2	(4)	8	(17)	0	-	46
	40-59	1993-2002	5	(83)	0	-	1	(17)	0	-	6
		2003-2016	59	(86)	1	(1)	7	(10)	2	(3)	69
		1993-2016	64	(85)	1	(1)	8	(11)	2	(3)	75
	≥60	1993-2002	5	(100)	0	-	0	-	0	-	5
		2003-2016	20	(56)	1	(3)	13	(36)	2	(6)	36
		1993-2016	25	(61)	1	(2)	13	(32)	2	(5)	41
	All ages	1993-2002	16	(84)	0	-	3	(16)	0	-	19
		2003-2016	109	(76)	4	(3)	26	(18)	4	(3)	143
		1993-2016	125	(77)	4	(2)	29	(18)	4	(2)	162

Supplemental Table 3. Primary therapy of adult patients with nodular lymphocyte-predominant Hodgkin lymphoma in the Netherlands according to stage and age at diagnosis, 2014-2016

Stage	Age, years	Primary therapy												Total N		
		ABVD		BEACOPP		R-CHOP		R-CVP		R-mono		RT only			No therapy	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N
I-II	18-39	6	(18)	0	-	1	(3)	0	-	0	-	21	(64)	5	(15)	33
	40-59	5	(17)	0	-	0	-	0	-	0	-	19	(63)	6	(20)	30
	≥60	2	(8)	0	-	0	-	0	-	0	-	10	(40)	13	(52)	25
	All ages	13	(15)	0	-	1	(1)	0	-	0	-	50	(57)	24	(27)	88
III-IV	18-39	11	(73)	0	-	2	(13)	0	-	0	-	1	(7)	1	(7)	15
	40-59	16	(70)	1	(4)	1	(4)	0	-	2	(9)	0	-	3	(13)	23
	≥60	6	(35)	0	-	2	(12)	2	(12)	1	(6)	0	-	6	(35)	17
	All ages	33	(60)	1	(2)	5	(9)	2	(4)	3	(5)	1	(2)	10	(18)	55

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine, and prednisone; R-mono, rituximab monotherapy; and RT, radiotherapy.

^aOverall, ABVD was combined with rituximab in 26 (57%) of 46 patients

^bRituximab was not added to BEACOPP

Supplemental Table 4. Excess mortality ratio during the first ten years after the diagnosis of nodular lymphocyte-predominant Hodgkin lymphoma

Covariate	P for LRT ^a	EMR ^b	95% CI			P ^b
Period of diagnosis	0.891					
1993-2002		1	(ref)			
2003-2016		1.08	0.33	-	3.52	0.892
Sex	0.477					
Male		1	(ref)			
Female		0.71	0.27	-	1.87	0.491
Age at diagnosis, years	0.005					
18-39		0.15	0.03	-	0.74	0.020
40-59		1	(ref)			
≥60		1.24	0.45	-	3.41	0.674
Stage	<0.001					
I-II		1	(ref)			
III-IV		6.12	2.21	-	16.93	<0.001

Abbreviations: LRT, likelihood ratio test; EMR, excess mortality ratio; and CI, confidence interval.

^aP-values for the likelihood ratio test that compares the model without the specific covariate with the model containing all covariates.

^bAll covariates are simultaneously adjusted.

^cP-values are compared with the reference category.

Supplemental Table 5. The projected 5- and 10-year overall survival among adult patients with nodular lymphocyte-predominant Hodgkin lymphoma in the Netherlands according to primary therapy and stage, 1993-2016

Primary therapy	Time	Stage I-II			Stage III-IV		
		OS	95% CI		OS	95% CI	
CIT	5-year	84%	47%	- 96%	87%	73%	- 94%
	10-year	84%	47%	- 96%			
CT +/- RT	5-year	90%	77%	- 96%	90%	80%	- 95%
	10-year	90%	77%	- 96%	82%	68%	- 90%
CT +/- IT +/- RT	5-year	89%	77%	- 95%	89%	82%	- 94%
	10-year	89%	77%	- 95%	80%	67%	- 88%
R-mono	5-year	100%					
	10-year	100%					
RT alone	5-year	99%	96%	- 100%	100%		
	10-year	99%	96%	- 100%	100%		
No therapy	5-year	93%	87%	- 97%	61%	39%	- 77%
	10-year	80%	69%	- 87%	57%	35%	- 74%

Abbreviations: OS, overall survival; CI, confidence interval; CIT, chemoimmunotherapy; CT, chemotherapy; RT, radiotherapy; and R-mono, rituximab monotherapy.