Supplementary Methods

The following periods were used in our current study as well as in previous studies on our cohort: 1965-1976, 1977-1988, 1989-2000 (Van Eggermond, et al. 2014; Schaapveld, et al. 2015; De Vries, et al. 2018). These periods were indeed primarily based on changes in HL treatment. Most patients were treated in trials or per treatment policies developed by the European Organisation for Research and Treatment of Cancer Lymphoma Group (Carde, et al. 1988; Eghbali, et al. 2005; Raemaekers, et al. 2002; Maraldo, et al. 2015). In the period 1965-1976 primary treatment for early stage patients consisted of mantle field or extended-field radiotherapy with or without vinblastine/procarbazine. Patients usually received 40 Gray (Gy) in fractions of 1.5–2.0 Gy. Radiotherapy was delivered with orthovoltage X-rays in the 1960s and early 1970s. Most patients were treated with megavoltage X-rays as of the late 1970s leading to better coverage of the target volume (Kaplan, 1981). Treatment for advanced stage patients varied substantially and could consist of extensive radiotherapy or of combination chemotherapy with or without radiotherapy. Especially in the 1960s cure rates were still relatively low. In the period 1977-1988, primary chemotherapy for early stage patients no longer consisted of single agents but of combination chemotherapy, usually consisting of mechlorethamine, vincristine, procarbazine and prednisone (MOPP) or MOPP-like regimens. Chemotherapy was combined with intensive radiotherapy regimens still including relatively high radiation doses (30-40 Gy in fractions of 2 Gy) and extensive radiation fields. Consequently, a significant proportion of patients still received both supra- and infradiaphragmatic fields. In the late 1980s anthracycline-containing regimens were introduced in primary setting. These regimens were shown to be more effective and less (gonado)toxic than MOPP-like regimens. Treatment adaptations led to significantly improved cure rates, but also to long-term side effects. The awareness of treatment-associated toxicity led to development of more individualized treatment with, for most patients, less intensive chemo- and radiotherapy regimens. These less intensive regimens were developed in the period 1989-2000. Splenectomy was no longer used as part of the staging procedure. Furthermore, patients were treated with lower doses of procarbazine and received involved-field rather than extended-field radiotherapy.

Supplementary Table 1. Hodgkin lymphoma treatment by treatment period (primary treatment and treatment for relapse combined)

Treatment period	1965–1976 (n=1121)	1977–1988 (n=1588)	1989–2000 (n=2210)
	n (%)	n (%)	n (%)
HL treatment			
Radiotherapy alone	320 (28.6)	422 (26.6)	433 (19.6)
Chemotherapy alone	103 (9.2)	189 (11.9)	396 (17.9)
Radiotherapy and chemotherapy	698 (62.3)	977 (61.5)	1381 (62.5)
Radiotherapy field			
No radiotherapy	103 (9.2)	189 (11.9)	396 (17.9)
Supradiaphragmatic RT	400 (35.7)	590 (37.2)	1016 (46.0)
Infradiaphragmatic RT	47 (4.2)	118 (7.4)	89 (4.0)
Supra- and infradiaphragmatic RT	517 (46.1)	634 (39.9)	549 (24.8)
RT field unknown	54 (4.8)	57 (3.6)	160 (7.2)
Spleen irradiation			
No	908 (81.0)	1125 (70.8)	1529 (69.2)
Yes	159 (14.2)	406 (25.6)	521 (23.6)
RT field unknown	54 (4.8)	57 (3.6)	160 (7.2)
Anthracyclines			
No	972 (86.7)	1097 (69.1)	546 (24.7)
Yes	85 (7.6)	445 (28.0)	1554 (70.3)
CT regimen unknown	64 (5.7)	47 (2.9)	111 (5.0)
Procarbazine			
No	514 (45.9)	547 (34.5)	811 (36.7)
Yes	543 (48.4)	995 (62.7)	1289 (58.3)
CT regimen unknown	64 (5.7)	46 (2.9)	111 (5.0)
Splenectomy			
No	617 (55.0)	1007 (63.4)	2106 (95.3)
Yes	450 (40.1)	485 (30.5)	53 (2.4)
Unknown	54 (4.8)	96 (6.1)	51 (2.3)

Supplementary Table 2. Mortality from causes of death other than Hodgkin lymphoma, solid tumors, and cardiovascular disease by sex, age, treatment, and attained age

	Causes of death other than HL (n=1474)				Solid tumors (n=568)				Cardiovascular disease* (n=363)			
	O	E	SMR (95%CI)	AEM	O	E	SMR (95%CI)	AEM	O	E	SMR (95%CI)	AEM
Sex												
Male	903	188.9	4.8 (4.5-5.1)	133.7	323	61.7	5.2 (4.7-5.8)	48.9	231	43.7	5.3 (4.6-6.0)	35.1
Female	571	102.5	5.6 (5.1-6.0)	109.5	245	50.0	4.9 (4.3-5.6)	45.6	132	14.3	9.2 (7.7-11.0)	27.5
$P_{heterogeneity}$			0.004	0.002			0.437	0.499			0.000	0.054
Age at HL treatment, years												
<25	420	51.2	8.2 (7.4-9.0)	88.0	165	17.4	9.5 (8.1-11.1)	35.2	102	6.9	14.7 (12.0-17.9)	22.7
25–34	473	83.4	5.7 (5.2-6.2)	123.9	197	33.2	5.9 (5.1-6.8)	52.1	107	15.0	7.1 (5.8-8.6)	29.2
35–50	581	156.7	3.7 (3.4-4.0)	185.8	206	61.1	3.4 (2.9-3.8)	63.4	154	36.1	4.3 (3.6-5.0)	51.6
$P_{heterogeneity}$			0.000	0.000			0.000	0.000			0.000	0.000
P_{trend}			0.000	0.000			0.000	0.000			0.000	0.000
HL treatment												
Radiotherapy alone	471	96.3	4.9 (4.5-5.4)	132.1	186	37.7	4.9 (4.2-5.7)	52.3	147	19.5	7.5 (6.4-8.9)	45.0
Chemotherapy alone	108	41.7	2.6 (2.1-3.1)	57.7	38	15.3	2.5 (1.8-3.4)	19.7	14	8.8	1.6 (0.9-2.7)	4.5
Radiotherapy and chemotherapy	895	153.4	5.8 (5.5-6.2)	131.6	344	58.6	5.9 (5.3-6.5)	50.6	202	29.7	6.8 (5.9-7.8)	30.6
$P_{heterogeneity}$			0.000	0.000			0.000	0.000			0.000	0.000
Attained age, years												
<25 years at HL treatment												
<30	50	8.6	5.8 (4.3-7.7)	24.8	5	0.8	6.4 (2.1-15.0)	2.5	5	0.4	12.0 (3.9-28.1)	2.7
30–49	215	22.8	9.4 (8.2-10.8)	89.9	96	6.9	13.9 (11.3-17.0)	41.6	52	3.4	15.5 (11.6-20.3)	22.7
≥50	155	19.8	7.8 (6.6-9.2)	351.9	64	9.7	6.6 (5.1-8.4)	141.4	45	3.1	14.3 (10.4-19.1)	108.9
$P_{heterogeneity}$			0.004	0.000			0.000	0.000			0.819	0.000
P_{trend}			0.382	0.000			0.001	0.000			0.958	0.000
25–34 years at HL treatment												
<50	193	30.4	6.4 (5.5-7.3)	69.2	62	9.1	6.8 (5.2-8.7)	22.5	40	5.1	7.8 (5.6-10.7)	14.8
50–59	143	25.3	5.7 (4.8-6.7)	208.5	70	11.4	6.1 (4.8-7.7)	103.8	34	4.8	7.1 (5.0-10.0)	51.8
≥60	137	27.8	4.9 (4.1-5.8)	476.4	65	12.7	5.1 (3.9-6.5)	228.3	33	5.2	6.4 (4.4-9.0)	121.4
$P_{heterogeneity}$			0.076	0.000			0.266	0.000			0.684	0.000
P_{trend}			0.023	0.000			0.108	0.000			0.384	0.000
35–50 years at HL treatment												
<50	84	18.9	4.5 (3.6-5.5)	75.9	21	6.1	3.5 (2.1-5.3)	17.4	15	4.3	3.5 (1.9-5.7)	12.4

50–59	207	46.3	4.5 (3.9-5.1)	185.1	80	19.5	4.1 (3.3-5.1)	69.7	39	10.9	3.6 (2.5-4.9)	32.3
≥60	290	91.6	3.2 (2.8-3.6)	356.3	105	35.4	3.0 (2.4-3.6)	124.7	100	20.8	4.8 (3.9-5.8)	142.1
$P_{heterogeneity}$			0.000	0.000			0.090	0.000			0.190	0.000
P_{trend}			0.000	0.000			0.117	0.000			0.086	0.000

* Excluding deaths from cerebrovascular disease

O=observed; E=expected; SMR=standardized mortality ratio; 95%CI=95% confidence interval; AEM=absolute excess mortality per 10,000 person-years

Supplementary Table 3. Multivariable Cox regression analyses of potential risk factors for respiratory and digestive disease mortality

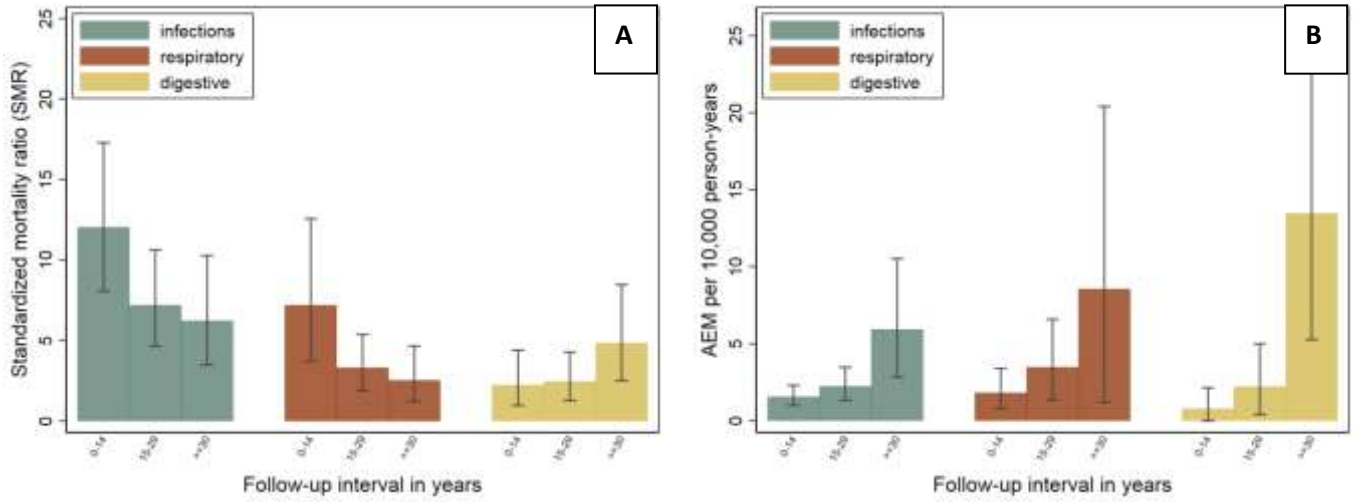
	Respiratory disease* (n=38)		Digestive disease† (n=32)	
	n	HR (95%CI)	n	HR (95%CI)
Sex				
Male	24	1.00 (Ref.)	21	1.00 (Ref.)
Female	14	0.64 (0.33-1.24)	11	0.64 (0.31-1.34)
Age at HL treatment				
<25 years	11	1.00 (Ref.)	10	1.00 (Ref.)
25–34 years	12	1.09 (0.41-2.87)	8	0.42 (0.16-1.08)
35–50 years	15	0.81 (0.28-2.33)	14	0.48 (0.20-1.18)
Supradiaphragmatic RT				
No RT or no supradiaphragmatic RT	2	1.00 (Ref.)		
Yes	36	7.91 (1.85-33.88)		
Infradiaphragmatic RT				
No RT of no infradiaphragmatic RT			11	1.00 (Ref.)
Yes			20	2.41 (1.15-5.06)
Chemotherapy				
Bleomycin				
No	26	1.00 (Ref.)		
Yes	9	0.77 (0.34-1.73)		
Procarbazine				
No	13	1.00 (Ref.)	13	1.00 (Ref.)
Yes	22	2.27 (1.10-4.66)	19	1.54 (0.75-3.14)

* Excluding deaths from pneumonia and influenza

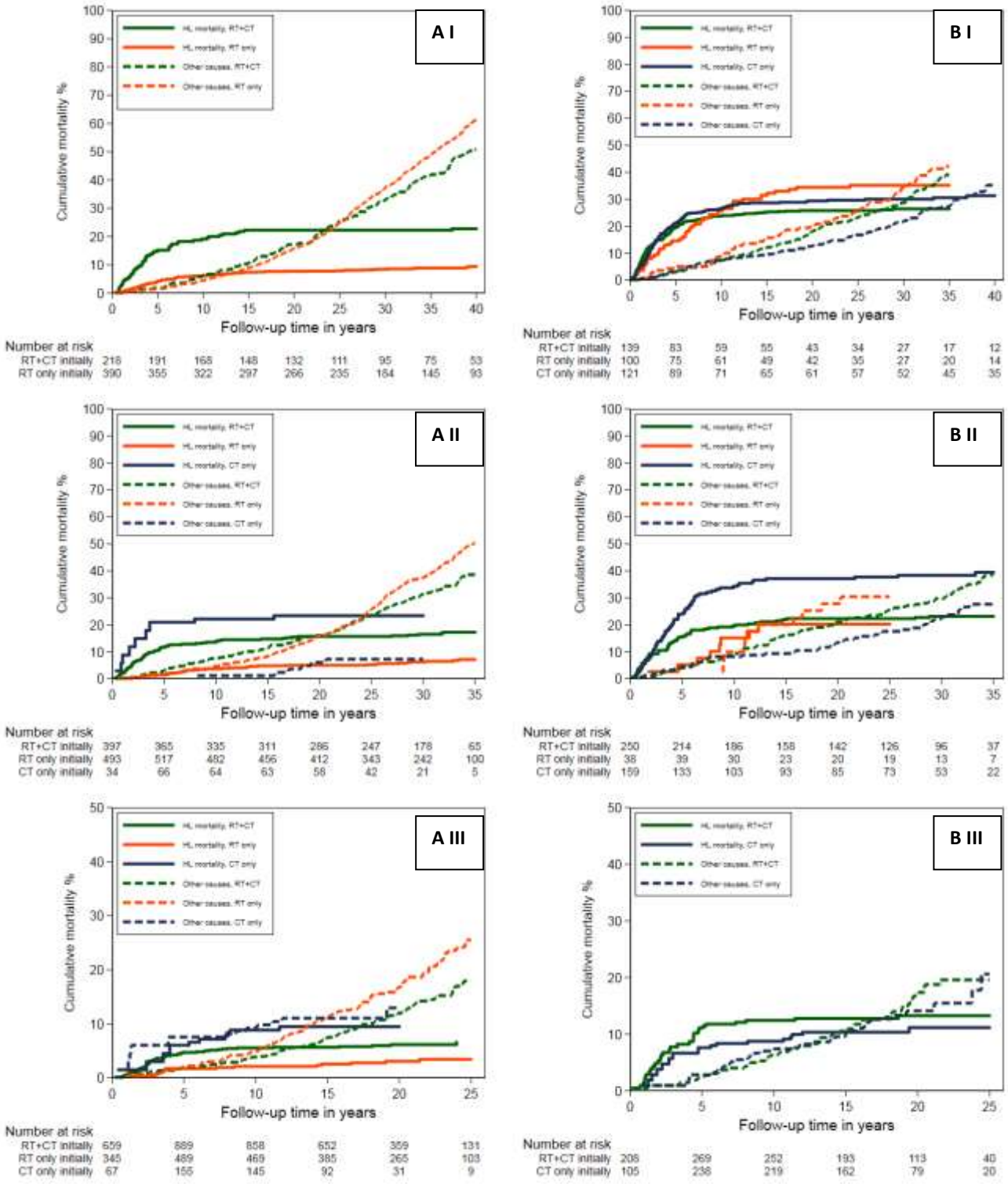
† Non-cancer digestive disease

HL=Hodgkin lymphoma; HR=hazard ratio; 95%CI=95% confidence interval; RT=radiotherapy; CT=chemotherapy

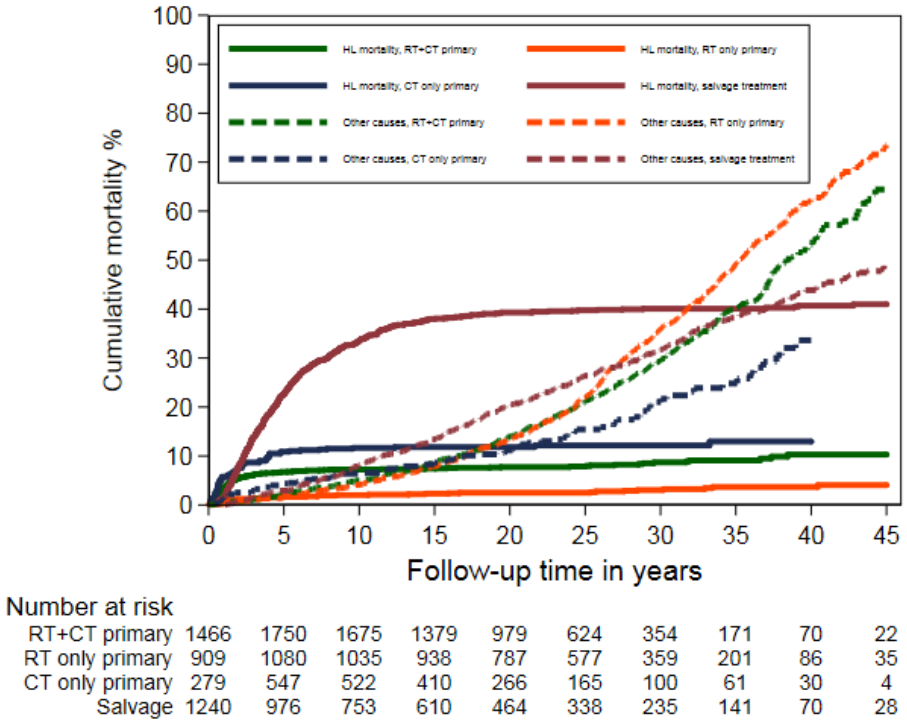
For variables with missing values, the number of cases in each category do not add up to the total number of cases. Missing values for each variable were assigned to a 'missing' category and analyzed as such in the model. Hazard ratios for this category showed no statistical significance and are not presented in this table.



Supplementary Figure 1. Standardized mortality ratios (A) and absolute excess mortality (B) from infectious diseases, respiratory diseases, and digestive diseases by follow-up interval.



Supplementary Figure 2. Cumulative mortality from Hodgkin lymphoma and causes other than Hodgkin lymphoma by stage and initial treatment for patients treated between 1965-1976 (I), 1977-1988 (II), and 1989-2000 (III). The left panels (A) show the cumulative mortality in patients with stage I-II disease, the right panels (B) show the cumulative mortality in patients with stage III-IV disease.



Number at risk

RT+CT primary	1466	1750	1675	1379	979	624	354	171	70	22
RT only primary	909	1080	1035	938	787	577	359	201	86	35
CT only primary	279	547	522	410	266	165	100	61	30	4
Salvage	1240	976	753	610	464	338	235	141	70	28

Supplementary Figure 3. Cumulative mortality from Hodgkin lymphoma and causes other than Hodgkin lymphoma by total treatment received.