Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma; an EORTC cohort study

Elizabeth C. Moser
Evert M. Noordijk
Flora E. van Leeuwen
Joke W Baars
José Thomas
Patrice Carde
Jacobus H. Meerwaldt
Martine van Glabbeke
Hanneke C. Kluin-Nelemans

Background and Objectives. Second cancer has been associated with the treatment of non-Hodgkin's lymphoma (NHL), but few studies have addressed this issue considering specific treatments.

Design and Methods. We estimated risk by standardized incidence ratios (SIR) and absolute excess risk (AER) based on general population rates (European Network of Cancer Registries) in 748 patients (aged 15-82 years) treated for aggressive NHL in four successive EORTC (European Organization for Research on Treatment of Cancer) trials.

Results. All patients received fully-dosed CHOP-like chemotherapy, 65% received involved-field radiotherapy and 14% high-dose treatment. Half of the patients needed salvage treatment and 37% were followed for more than 10 years. The cause of death was NHL in 79% of the patients; 4% died of second cancer with a median survival 8.9 (0.8-20.5) years. Cumulative incidences (death from any cause being a competing event) were 5% and 11% for solid cancer and 1% and 3% for acute myeloid leukemia/myelodysplastic syndrome at 10 and 15 years, respectively. Cancer risk appeared age-related: in young patients high risks were observed for leukemia (SIR 16.7, 95% CI 1.4-93.1, AER 5.0), Hodgkin's lymphoma (SIR 60.1, 95% CI 12.4-175.2, AER 15.7), colorectal cancer (SIR 12.5, 95% CI 2.6-36.5, AER 14.7) and lung cancer (SIR 15.4; 95% CI 4.2-39.4, AER 19.8), while risk in patients older than 45 years matched that in the normal population. The risk of cancer was significantly raised by smoking and salvage treatment.

Interpretation and Conclusions. Half of the patients die of aggressive NHL before living long enough to experience second cancer. Only young patients have a high risk of second cancer during follow-up beyond 10 years.

Key words: long-term sequelae, non-Hodgkin's lymphoma, second cancer.

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From the EORTC Data Centre, Brussels, Belgium (ECM, MvG); Department of Radiotherapy, Leiden University Medical Centre, Leiden, The Netherlands (ECM, EMN); Department of Epidemiology, the Netherlands Cancer Institute, Amsterdam, The Netherlands (FEvL) Department of Medical Oncology, Antoni van Leeuwenhoek ziekenhuis, Amsterdam, The Netherlands e Department of Oncology, U.Z. (JWB); Gasthuisberg, Leuven, Belgium (JT); Department of Hematology, Institute Gustave Roussy, Villejuif, France (PC); Department of Radiotherapy, Medical Spectrum Twente, Enschede, The Netherlands (JHM); Department of Hematology, University Medical Centre Groningen, University of Groningen, The Netherlands (HCK-N).

Correspondence:
Elizabeth C. Moser, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, the Netherlands.
E-mail: e.c.moser@lumc.nl

Nowadays, many patients with malignant lymphoma become long-term survivors. Late, therapy-related sequelae have become an important issue during follow-up. Secondary cancers were the first late sequelae to be noted in survivors of Hodgkin's lymphoma.[1-3] After extended reviews on cancer risk after Hodgkin's disease, reports on patients treated for non-Hodgkin's lymphoma (NHL) have also been published.[4-12] Most studies report a high risk of second cancer (2 to 8-fold increase), mainly due to a high incidence of leukemia, bladder cancer and lung cancer observed after NHL treatment. The magnitude of the risk of second cancer varies substantially in the different studies. Reports on the influence of age at first NHL treatment on second cancer risk are conflicting.[5-12] Cancer risk in elderly NHL patients has never been well defined, as most data available originate from clinical trials enrolling patients up to the age of 60 years. In a large French study, late sequelae were related to first line doxorubicin-based chemotherapy consistently used in patients treated for aggressive NHL, but unfortunately follow-up did not extend much beyond 10 years.[11] Only two studies have reported cancer risk beyond 15 years after NHL treatment.[5,12] Travis *et al*. described a persistently high risk for all cancers over prolonged follow-up periods, while Mudie *et al*. mentioned leukemia and lung cancer in particular. Treatment details (dose, fields) and smoking history were not taken into account in any of the reports.[5-12] Moreover, all different NHL categories were lumped together without central pathology review being part of the selection process. The availability of a large EORTC (European Organization of Research and Treatment of Cancer) database of patients with aggressive NHL, consistently treated with CHOP-like chemotherapy at an age ranging from 15 to 82 years at initial NHL diagnosis, offered the possibility to explore second cancer risk in a well defined population of NHL patients of *all* adult ages. Detailed information on type, dose and fields of first line and salvage treatment but also on smoking history, made it possible to evaluate excess risk according to specific treatments and demographic factors.

Design and Methods

Data collection procedures

A retrospective cohort study was performed in 974 patients with advanced aggressive NHL enrolled in four successive EORTC trials (1980-1999) mainly in the Netherlands, Belgium, France and Italy. The patients' records were reviewed by local investigators (*see appendix A*). For details related to the specifically designed case record forms, see Moser *et al.*[13] All trials were designed for intermediate or high grade NHL, and histology was centrally reviewed in all cases. Approval for the study was obtained from the EORTC Protocol Review Committee and from all local institutions. Informed consent was provided according to the Declaration of Helsinki. We restricted the analyses to those patients treated with at least six cycles of CHOP-like chemotherapy and with a minimal follow-up of 0.5 years after the end of first line treatment.

General population rates

In this study, we used data derived from the EUROCIM database (version 4) registered by the ENCR (European Network of Cancer Registries).[14,15] The crude incidence rates provided by the Eindhoven Cancer Registry up to 1990 and from the Netherlands Cancer Registry for the period of 1990 to 1998 (by 3-year moving averages) were related to the patients treated in the Netherlands (n=291). For the Belgian patients (n=185), the same rates were used for the years 1980-1992, while for the period 1993-1998 the rates provided by the Belgian National Cancer Registry, covering mainly the Flemish region, could be used as the NHL patients originated from institutions in Antwerp, Leuven, Brussels and Tournai. For the French patients (n=143) treated in Rouen, Caen and Paris, we used the crude rates provided by the cancer registries in the Somme, Calvados and La Manche regions (1978-1997) and for the Italian patients (n=129, from Ravenna and Aviano) we used rates from the cancer registries of the regions of Veneto, Parma and Umbria (1978-1997).

Definitions

According to the definitions used in the EUROCIM database, we used diagnoses per tumor-site rather than pathology, based on the ninth edition of the International Classification of Diseases (ICD9 coding).[14,15] Cancers of the bone and soft tissue, upper gastro-intestinal tract, genital tract, nervous system, melanoma or myeloma were not observed in the NHL cohort. In one patient, chronic lymphoid leukemia was diagnosed together with recurrent NHL. This event was excluded from the analyses because of the assumed closely related pathogenesis. Non-melanoma skin cancer (NMSC) and myelodysplastic syndrome (MDS) were registered as events, but no population-based rates were available to estimate excess risk. In the person-years analysis of solid cancer risk all solid cancers, except NMSC, were combined; leukemia risk did not include MDS or lymphocytic leukemia.

Treatment

Most patients (75%) received the CHVmP/BV regimen (consisting of cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin and vincristine) given in all four trials.[16-18] Other first lines regimens were CHVmP (CHVmP/BV without bleomycin and vincristine) in the first and ProMACE-MOPP (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, and procarbazine) in the second trial.[16,17] No relation between cumulative total dose of doxorubicin and complications could be estimated, because information on the doses of salvage treatment was often lacking. In contrast, details on radiotherapy could be retrospectively checked and the cumulative dose per field estimated. According to the study-protocol, radiotherapy consisted of 30 Gy for patients with initially bulky disease (>5 cm) in complete response after first line chemotherapy, and 40 Gy for those with a partial response (in fractions of 1.5-2 Gy). If large fields were needed, a reduction of the field, focusing on the remaining lesion was suggested for the last 4-10 Gy. For extranodal locations the dose was limited to 20-30 Gy. The same dose-levels were often used in the salvage setting.

Statistical analysis

The incidence of second cancer in the study population was compared to the incidences in the Dutch, Belgian, French, and Italian populations. In this tpe of person-years analysis, the ratio of observed and expected numbers per cancer-type was determined.[14,15] The observed/expected ratio is henceforth denoted as the standard incidence ratio (SIR).[19] Expected numbers were computed with the use of age-, sex-, and calendar period-specific incidence rates derived from the EUROCIM database. Absolute excess risk (AER) per 10,000 person-years was calculated as the observed number of cases of secondary cancer in our cohort minus the number expected, divided by number of person-years at risk, multiplied by 10,000, expressing the number of excess cases per 10,000 person-years diagnosed in the study group compared to in the general population. The incidences per person-year were categorized by age in 5-year intervals (running from 15 to 85 years), by sex and by calendar period in 2- to 3-year intervals (running from 1980 to 2001) in both the study and the EUROCIM cohorts. In all patients accumulation of person-time at risk of second cancer began 0.5 years after the end of first line NHL treatment and stopped at the date of diagnosis of a second cancer, date of death, or most recent information on cancer occurrence, whichever came first. When analyzing one specific can-

Table 1. NHL patients and overall treatment characteristics.

Patients' characteristics	*Men n=456*	*Women n=292*	*Total n=748*	*Person-years at risk 5020*
Country				
The Netherlands	181	110	291	2050
Belgium	108	77	185	1237
France	92	51	143	1004
Italy	75	54	129	729
Age				
Younger than 45 years	203	108	291	1882
45 years or older	263	194	457	3138
Ann Arbor stage				
I bulky-II	140	83	223	2022
II-IV	316	209	525	2998
International Prognostic Index				
Low-intermediate	175	93	468	2181
Intermediate	143	109	252	2759
Intermediate-high	69	45	114	290
High	16	14	30	110
History of smoking				
No	205	195	400	1946
Yes	218	83	301	2763
Unknown	33	14	47	311
Follow-up				
5 years or less	206	129	335	972
More than 5 years	250	163	413	4048
More than 10 years	105	115	220	2670
More than 15 years	29	30	59	1768

Table 2. Overall NHL treatment characteristics (including first line and salvage treatment).

Treatment characteristics	*Cumulative dose*	*Men n=456*	*Women n=292*	*Total n=748*	*Person-years at risk 5020*
Chemotherapy containing					
Doxorubicin	up to 400 mg/m^2	456	292	748 (100%)	5020
Cyclophosphamide	up to 5.2 g/ m^2	456	292	748 (100%)	5020
Bleomycin	up to 80 mg	360	230	590 (79%)	3966
MOPP*	–	205	131	336 (45%)	2259
Cisplatin	–	48	37	85 (11%)	512
Salvage chemotherapy	–	244	138	382 (51%)	2870
First line only		212	154	366 (49%)	2150
Salvage	–				
Stem cell transplantation#					
No	–	392	249	641 (86%)	4273
Yes	–	64	43	107 (14%)	747
Radiotherapy fields given	Median				
Neck	38Gy (28-60 Gy)	186	123	309 (41%)	2043
Mediastinum/Axilla	36Gy (28-56Gy)	126	106	232 (31%)	1523
Abdomen/Groins	36Gy (20-42Gy)	166	106	272 (36%)	1888

**MOPP: mechlorethamine, vincristine, prednisone and procarbazine, # stem cell transplantation preceded by high dose chemotherapy, mostly BEAC (carmustine, etoposide, cytarabine, cyclophosphamide); no total body irradiation had been given.*

cer, observed numbers were based on all first dates of diagnosis of the given type of cancer occurring at least 0.5 years after NHL treatment, allowing more than one type of cancer diagnosed per patient in the NHL cohort; the calculation of cancer incidence in the EUROCIM cohort was made correspondingly. Confidence limits were calculated using exact Poisson probabilities of (small) observed numbers.[20,21] The median follow-up, time to occurrence and survival were estimated as a function of time since the start of NHL treatment, and analyzed according to the product-limit method first described by Kaplan and Meier, censoring for death, loss from follow-up and event (whichever came first).[22,23] Cumulative incidences were estimated in the competing risk model with death from any cause as a competing event.[24,25] The Cox proportional-hazards model was used to quantify the effects of different treatments on second cancer risk (all malignancies, except NMSC and NHL) within the patient group, adjusting for confounders, as opposed to the person-years analysis in which risk is compared with that in the general population.[26] Forward stepwise confounder selections, in which the effect of adding one confounder at a time was evaluated, was based on a more than 10% change in the risk estimate of the exposure variable of interest, irrespective of significant values. All factors were categorized and the analyses were stratified by trial (since there was a significant survival difference across trials, see Moser *et al*).[27] Cox's models were fitted using SPSS statistical software (SPSS, Inc Chicago, IL, USA).

Results

Within the four EORTC trials for advanced, aggressive NHL, 864 (91%) patients had been treated in the Netherlands, Belgium, France or Italy. One hundred and twelve patients had a follow-up of less than 0.5 years due to early progression or death. In 748 of the remaining 752 cases, follow-up information was complete until death or January 1st, 2001. The quality of the case record forms was excellent with less than 5% lacking data. The characteristics of the 748 patients are given in Table 1. The mean age was 49 years, with a range from 15 to 82 years. Most patients had stage III or IV disease (71%) and a low to intermediate IPI risk profile (70%). Overall 65% received additional radiotherapy, 49% more than one line of chemotherapy and 14% underwent stem cell transplantation, preceded by high dose chemotherapy; no total body irradiation had been given (Table 2). The median survival was 8.9 years (range 2.1-20.5 years) with 279 (37%) patients followed for more than 10 years. Overall survival at 5 and 15 years was 58% and 41%, respectively. Progression-free survival at 5 and 15 years was 45% and 36%, respectively. The most com-

Table 3. Observed (Obs) and expected (Exp) cases of second cancer (by ICD9 coding) in the NHL cohort by country calculating standardized incidence risks (SIR) and absolute excess risks (AER) per 10,000 person-years of follow-up per cancer type. (*does not include MDS or lymphocytic leukemia).

	The Netherlands (n=291)		*Belgium (n=185)*		*France (n=143)*		*Italy (n=129)*		*Total (n=748)*			
	Obs	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*SIR (95%CI)*	*AER*
Leukemia* **ICD9: 205-208**	0	0.27	0	0.18	1	0.16	0	0.11	1	0.72	1.4 (0.4-7.7)	0.6
Hodgkin's lymphoma **ICD9: 201**	2	0.04	0	0.03	0	0.02	1	0.02	3	0.11	27.3 (5.6-79.7)	5.8
Head & Neck **ICD9: 141-149**	1	1.48	2	0.77	1	0.59	0	0.40	4	3.24	1.2 (0.3-3.2)	1.5
Colorectal **ICD9: 153, 154**	2	2.15	2	1.30	1	1.12	1	1.08	6	5.65	1.1 (0.4-2.3)	0.7
Pancreas **ICD9: 157**	0	0.37	0	0.22	1	0.20	0	0.18	1	0.97	1.0 (0.03-5.7)	0.1
Lung **ICD9: 162**	2	3.19	1	1.48	1	1.60	2	1.64	6	7.91	0.8 (0.3-1.7)	-3.8
Breast **ICD9: 174**	3	1.78	2	1.18	3	0.76	0	0.56	8	4.28	1.9 (0.8-3.7)	7.4
Bladder and urethra **ICD9:188, 189.3-9**	1	0.72	1	0.41	3	0.31	0	0.25	5	1.69	3.0 (1.0-6.9)	6.6
Prostate **ICD9: 185**	2	1.91	1	1.12	1	0.85	0	0.60	4	4.48	0.9 (0.2-2.3)	1.0
Kidney and ureter **ICD9:189.0-2**	1	0.37	0	0.30	1	0.26	0	0.21	2	1.14	1.8 (0.2-6.3)	1.7
Thyroid **ICD9: 193**	1	0.05	0	0.04	0	0.02	0	0.02	1	0.13	7.7 (0.2-42.9)	1.7
Solid cancer **ICD9:140-172, 174-199**	**13**	**16.3**	**8**	**9.8**	**12**	**8.3**	**2**	**4.3**	**37**	**38.8**	**1.0 (0.7-1.3)**	**-3.6**

mon cause of death was NHL (79%), whereas 4% of the patients died of a second cancer. Cumulative incidences for solid cancer were 5% at 10 years and 11% at 15 years, and for MDS/AML were 1% at 10 years and 3% at 15 years (median follow-up 9.4 (0.8-20.5) years). The incidence of solid cancer in the study cohort started to increase after 10-15 years of follow-up without showing any plateau (Figure 1). The median time interval between the end of first line therapy and the diagnosis of secondary cancer was 5.8 (2.4-6.8) years.

Table 3 shows the person-year analyses comparing observed and expected second cancers. A total of 37 solid cancers were observed after NHL treatment (74/10,000 person-years), compared to 38.8 expected tumors (SIR 1.0, 95% CI; 0.7-1.3, AER -3.6). NMSC was observed in 12 patients, half of whom had more than one lesion (24/10,000 person-years). Nine cases of MDS were observed (18/10,000 person-years), and the syndrome progressed in one patient into acute myeloid leukemia, diagnosed 3.1 years after first line NHL treatment (3.3; 95% CI 0.08-18.6, AER 1.4). The risk of leukemia was not elevated (SIR 1.4, 95% 0.1-7.7). Three cases of Hodgkin's lymphoma were diagnosed (median

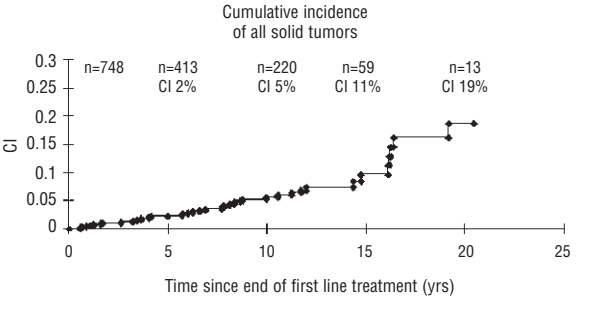

Figure 1. Cumulative incidence of all solid cancers since the end of first line NHL treatment.

Table 4. Standardized incidence risks (SIR) and absolute excess risks (AER) per 10,000 person-years of follow-up (py) per cancer type in patients younger than 45 and in those 45 and older at the time of treatment for NHL.

	Younger than 45 years				*45 years or older*			
	Obs	*Exp*	*SIR (95% CI)*	*AER*	*Obs*	*Exp*	*SIR (95% CI)*	*AER*
Leukemia*	1	0.06	16.7 (1.4-93.1)	5.0	0	0.66	0.0 (0.04-4.9)	-2.1
Hodgkin's lymphoma	3	0.05	60.1 (12.4-175.3)	15.7	0	0.06	0.0 (-1.1-0.5)	-0.2
Head and Neck	1	0.44	2.3 (0.1-12.7)	3.0	3	2.80	1.1 (0.2-3.1)	0.6
Colorectal	3	0.24	12.5 (2.6-36.5)	14.7	3	4.91	0.6 (0.1-1.8)	-6.1
Lung	4	0.26	15.4 (4.2-39.4)	19.8	2	7.60	0.3 (0.1-1.0)	-17.8
Breast	0	0.62	0	-3.3	8	3.66	2.2 (1.0-3.7)	13.8
Bladder	1	0.03	33.3 (0.8-186.4)	5.2	4	1.66	2.4 (0.7-6.2)	7.4
Prostate	1	0.04	25.0 (0.6-139.2)	5.1	3	4.44	0.7 (0.1-2.0)	-4.6
Kidney	0	0.06	0	0.3	2	1.08	1.9 (0.2-6.7)	2.9
Solid cancers	14	3.90	3.6 (2.0-6.0)	20.1	13	34.90	0.4 (0.2-0.6)	-69.9

*(*does not include MDS or lymphoid leukemia).*

Table 5. Observed (Obs) and expected (Exp) cases of solid cancer (except non-melanoma skin cancer) and standardized incidence risks (SIR) and absolute excess risks (AER) analyzed according to smoking history, additional chemotherapy and radiotherapy.

	Obs	*Exp*	*SIR (95% CI)*	*AER per 10.000 py*
Follow-up				
Less than 5 years	12	15.1	0.8 (0.4-1.4)	-31.9
5-15 years	13	16.6	0.6 (0.4-1.3)	-15.8
More than 15 years	12	7.1	1.7 (0.9-3.0)	27.7
Smoking history				
No	16	23.1	0.7 (0.4-1.1)	-36.5
Yes	21	14.1	1.5 (0.9-2.2)	25.0
Additional chemotherapy				
Only first line	16	15.1	1.1 (0.6-1.7)	3.8
Salvage treatment	31	23.7	1.3 (0.9-1.9)	34.0
Additional radiotherapy on mediastinum				
No	17	21.1	0.8 (0.5-1.3)	-11.7
Yes	20	17.7	1.1 (0.7-1.7)	15.0
Additional radiotherapy on abdomen				
No	21	24.1	0.9 (0.5-1.3)	-9.9
Yes	16	14.7	1.1 (0.6-1.8)	6.9

py: patient-years.

interval of 2.8 years), while 0.11 were expected (SIR 27.3, 95% CI 5.6-79.7, AER 5.8). Six cases of lung cancer were observed, while 7.9 were expected (SIR 0.8, 95% CI 0.3-1.5, AER -3.8). Six patients were treated for breast cancer, of whom two had bilateral disease, at a mean interval of 2.3 years (SIR 1.9, 95% 0.8-3.7, AER 7.4). Thyroid cancer was diagnosed in one patient who had received additional radiotherapy to the neck (30 Gy). A significant risk was observed for bladder cancer, with a burden of 6.6 extra cases per 10,000 person-years of follow-up (SIR 3.0, 95% CI 1.0-6.9). Eight out of the nine patients who developed MDS had received additional chemotherapy; in five of them this was followed by stem cell transplantation. The risk of second cancer appeared to be clearly age-related (Table 4): in young patients a significantly higher risk of solid cancer was observed with a burden of 20.1 extra cases per 10,000 person-years of follow-up (SIR 3.6, 95% CI 2.0-6.0). High risks were observed for leukemia, Hodgkin's lymphoma, colorectal cancer and lung cancer. No cases of breast cancer were observed among patients younger than 45 years at the time their NHL was diagnosed, whereas a two-fold increased risk was observed in elderly patients. Trends for an excess risk of solid cancer (Table 5) were seen for patients with a follow-up of more than 15 years, smokers and those who received additional (salvage) chemotherapy. The person-years sub-analyses for site-specific solid cancers were underpowered because of the small number of events. Diagnosis of NHL at a young age, advanced stage NHL, smoking and additional (salvage) chemotherapy appeared to be significant in the multivariate analysis of risk of second cancer (Table 6). In multivariate analysis of the risk of AML/MDS, young age (<45 years) at NHL diagnosis was the only statistically significant factor (hazard ratio 3.8; 95% CI 1.2-5.7). Trends for excess risk were seen for additional high dose treatment with stem cell transplantation (hazard ratio 3.6; 95% CI 0.8-8.7) and salvage chemotherapy (hazard ratio 3.8; 95% CI 0.8-17.7).

Discussion

This is the first report on the incidence of second cancers throughout all age groups of adults treated for aggressive NHL with fully dosed CHOP-like chemotherapy. Cumulative incidences of solid cancer and MDS/AML at 15 years were 11% and 3%, respectively. Although neither excess solid cancer nor excess leukemia risk was observed when all cancers together were taken into account, significantly increased *cancer-specific* risks were observed for bladder cancer and

Table 6. Multivariate analysis of occurrence of second cancer (all types, also including MDS but excluding NHL, lymphocytic leukemia and non-melanoma skin cancer).

Cox proportional hazard model	*Hazard Ratio*	*95% CI lower*	*95% CI upper*
Sex (M vs. F)	1.36	0.64	2.91
Smoking (yes vs. no)	2.11	1.33	4.11
Age (<45 years vs. ≥45 years)	1.91	1.21	4.12
Ann Arbor stage (I-II vs. III-IV)	0.32	0.12	0.84
Performance status (WHO 0-1 vs. >1)	1.51	0.56	4.82
Extranodal disease (0-1 vs. >1 localizations)	1.72	0.72	4.31
Additional (salvage) chemotherapy (yes vs. no)	1.75	1.21	7.70
Additional stem cell transplantation (yes vs. no)	2.21	0.93	15.66
Additional radiotherapy to neck (yes vs. no)	0.85	0.62	3.56
Additional radiotherapy to mediastinum (yes vs. no)	2.45	0.86	6.25
Additional radiotherapy to abdomen (yes vs. no)	2.91	0.97	7.56
Chemotherapy containing bleomycin (yes vs. no)	1.82	0.82	3.75
Chemotherapy containing MOPP (yes vs. no)	0.89	0.76	1.34

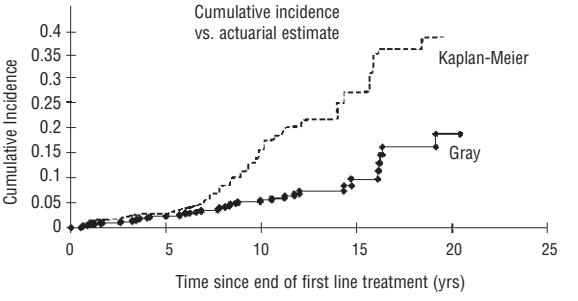

Figure 2. Actuarial incidence of second cancers since the end of first line NHL treatment in the Kaplan-Meier model compared to cumulative incidence according to Gray.

Hodgkin's lymphoma in all adult ages. The risk of second cancer was clearly age-related: in young patients strongly increased risks were observed while the risk in patients aged over 45 when first treated for NHL matched that in the general population.

The statistical methods applied for estimation of late events in patients' cohorts is of key-importance. In a disease with a high percentage of deaths due to recurrences or high age of the patients, any cumulative risk estimated by the Kaplan-Meier method will result in an overestimation of secondary cancers and therefore needs correction in a competing risk model.[24,25] If we had ignored death as a competing risk, the actuarial incidence calculated by the Kaplan-Meier method would have been 15% at 10 years and even 27% at 15 years (Figure 2). Population-based incidence rates are needed for organ-specific cancer risk estimates. Age, sex, environmental and genetic factors influence the risk of cancer. Moreover, cancer incidence varies over time. Therefore, person-years analyses per region, but also per calendar period are needed for optimal excess risk estimation.[19]

Special types of cancers such as angiosarcoma or rare other (bone/soft tissue) tumors related to cancer therapy were not observed, except one case of thyroid cancer. Of note, 10 to 20-year induction periods have been described for these types of second tumor, whereas the median follow-up of the EORTC cohort was 9.4 years.[1,4-6,28-33] Retrospective scoring of smoking history, radiotherapy doses and radiation fields is needed to evaluate factors in cancer risk. These comprehensive data are mandatory, but were not, unfortunately, available in the other large NHL cohort studies.[5-12] In our cohort the role of smoking was evident, but the attribution of involved field radiotherapy was not significant as described by Travis *et al.*, likely due to the small number of events. In the case-control study by Travis *et al.* a relationship was found between the cumulative dose of cyclophosphamide and bladder cancer after NHL treatment.[31] We found a three-fold risk of bladder cancer in our cohort, although rather low doses of cyclophosphamide had been given as first line chemotherapy (up to 8×650 mg/m^2). However, half of the patients received additional chemotherapy as salvage treatment, thereby probably increasing the risk (hazard ratio 1.75; 95% CI 1.2-7.7) because of higher cumulative doses. The role of treatment at young ages has already been emphasized in patients with Hodgkin's lymphoma.[28,29,31,34] In our cohort, no cases of breast cancer were observed among women treated for NHL before the age of 45. We previously described a high cumulative incidence of premature menopause in our report on late non-malignant sequelae. The hormonal changes after alkylating chemotherapy probably protected young patients from breast cancer risk, as they appear to do in young Hodgkin's lymphoma patients.[13,28,34] By contrast, breast cancer risk appeared elevated in postmenopausal NHL patients (13.8 extra cases per 10,000 person-years of follow-up).[35-38] Two (postmenopausal) women had been treated for bilateral breast cancer (aged 47 and 52 at NHL diagnosis). Unfortunately, data on familial predisposition in these women were missing.[39] When considering cancer risk in relation to treatment modalities, it is important to realize that standard treatments have changed and will change over time. Both the dose and field size of radiotherapy have been reduced since the introduction of multi-agent doxorubicin-based chemotherapy. In our cohort, patients were all treated by the involved field principle, aiming to reduce late toxicity. Indeed, an overall low cancer risk was observed.[40,41] As radiation-induced malignancies need time (probably decades) to develop, prolonged follow-up is required to conclude whether reductions in doses and fields of radiotherapy do really lead to a reduction in second tumors.[34,38,42-44] Only a minority of our patients received autologous stem cell transplantation as part of first line or salvage

treatment. Nevertheless, this treatment modality appeared a potential cancer risk factor in multivariate analysis, especially in relation to the risk of AML/MDS. Brown *et al*. described a cumulative 10-year second cancer incidence of 21% (median follow-up of 9.5 years) in a NHL cohort all treated with autologous bone marrow transplantation after conditioning with cyclophosphamide and total body irradiation. The second cancers were mainly AML and MDS.[45] In our cohort second hematologic malignancies were also observed but to a far lesser extent than in this transplantation cohort, probably because of the fact that no total body irradiations had been given and that relatively low doses of cyclophosphamide had been used.[46] The 10-year cumulative incidence rate of solid cancers given by Brown *et al*., with death as a competing risk in transplanted patients, was 10%, but included NMSC as well. In our cohort, the solid cancer risk of 4% increased to 12% if NMSC were included. However, population-based skin cancer incidence rates are scarce and often unreliable, as these lesions are commonly removed without histological confirmation and therefore not registered. We, therefore, left these events out of the analyses. The same holds true for the diagnosis of MDS, which is often based only on cytology, and is severely underreported in cancer registries, if present at all.

In conclusion, data from this large EORTC cohort show that mainly young patients with aggressive NHL treated with CHOP-like chemotherapy are at risk of second cancers, whereas most elderly patients die before living long enough develop a second cancer. Data from older studies must be interpreted with caution because of the statistical models used and the lack of details on both treatment and demographic factors analyzed.

Appendix A - Local investigators in the EORTC trials

P. Carde (Institute Gustave Roussy, Villejuif, France); U.Tirelli. (Centro Di Rifferimento Oncologico, Aviano, Italy); J. Baars (Antoni van Leeuwenhoekziekenhuis, Amsterdam , The Netherlands); J.Thomas (U.Z. Gasthuisberg, Leuven, Belgium); D. Bron (Institut Jules Bordet, Brussels, Belgium); J.C. Kluin-Nelemans (Leiden University Medical Center, Leiden, The Netherlands); W. Schroyens (Universitair Ziekenhuis Antwerpen, Antwerp, Belgium); K.J. Roozendaal (Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands); M. Monconduit (Centre Henri Bequerel, Rouen, France); J.M.M. Raemaekers (St. Radboud University Hospital, Nijmegen, The Netherlands); A.M. Peny (Centre Regional Francois, Baclesse, Caen, France); C.M. Blanc (Hotel-Dieu de Paris, Paris, France); G.J. Creemers (Catherina Ziekenhuis, Eindhoven, The Netherlands); M.B. van 't Veer (Rotterdam Cancer Institute, Rotterdam, The Netherlands); W. Gerrits (Integraal Kankercentrum West, The Netherlands); G.J. Goverde (St. Ignatius Ziekenhuis, Breda., The Netherlands); A. van Hoof (A.Z. St. Jan, Brugge, Belgium); R. Debock (Algemeen Ziekenhuis Middelheim, Antwerp, Belgium); M. Fickers (Atrium Medisch Centrum, Heerlen, The Netherlands); G. Rosti (Ospedale Sta Maria Delle Croci, Ravenna, Italy); H.P. Muller (Streekziekenhuis Gooi-Noord, Blaricum, The Netherlands); H.C. Schouten (Academisch Ziekenhuis Maastricht, Maastricht, The Netherlands); H.N.L.M. Bron (Maaslandziekenhuis,Sittard, The Netherlands); J.J. Keuning (St. Josef Ziekenhuis, Veldhoven, The Netherlands); J. Michel (Centre Hospitalier de Tivoli, Louviere, Belgium): A.C. Tagnon (M.C. De Tournai, Tournai, Belgium).

ECM: performed the update, analyses and wrote the manuscript; EMN, HCK-N: supervised and initiated the project, revised the manuscript; FEvL: monitored the analyses, revised the manuscript; JWB, JT, PC, JHM, MvG: monitored the analyses, revised the manuscript. The authors declare that they have no potential conflicts of interest.

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