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ORIGINAL RESEARCH

Treatment-specific risk of subsequent malignant neoplasms in five-year survivors of diffuse large B-cell lymphoma☆

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Background: The introduction of rituximab significantly improved the prognosis of diffuse large B-cell lymphoma (DLBCL), emphasizing the importance of evaluating the long-term consequences of exposure to radiotherapy, alkylating agents and anthracycline-containing (immuno)chemotherapy among DLBCL survivors.

Methods: Long-term risk of subsequent malignant neoplasms (SMNs) was examined in a multicenter cohort comprising 2373 5-year DLBCL survivors treated at ages 15-61 years in 1989-2012. Observed SMN numbers were compared with expected cancer incidence to estimate standardized incidence ratios (SIRs) and absolute excess risks (AERs/10 000 person-years). Treatment-specific risks were assessed using multivariable Cox regression.

Results: After a median follow-up of 13.8 years, 321 survivors developed one or more SMNs (SIR 1.5, 95% CI 1.3-1.8, AER 51.8). SIRs remained increased for at least 20 years after first-line treatment (SIR ≥20-year follow-up 1.5, 95% CI 1.0-2.2, AER 81.8) and were highest among patients ≤40 years at first DLBCL treatment (SIR 2.7, 95% CI 2.0-3.5). Lung (SIR 2.0, 95% CI 1.5-2.7, AER 13.4) and gastrointestinal cancers (SIR 1.5, 95% CI 1.2-2.0, AER 11.8) accounted for the largest excess risks. Treatment with >4500 mg/m^2 cyclophosphamide/>300 mg/m^2 doxorubicin versus ≤2250 mg/m^2/≤150 mg/m^2, respectively, was associated with increased solid SMN risk (hazard ratio 1.5, 95% CI 1.0-2.2). Survivors who received rituximab had a lower risk of subdiaphragmatic solid SMNs (hazard ratio 0.5, 95% CI 0.3-1.0) compared with survivors who did not receive rituximab.

Conclusion: Five-year DLBCL survivors have an increased risk of SMNs. Risks were higher for survivors ≤40 years at first treatment and survivors treated with >4500 mg/m^2 cyclophosphamide/>300 mg/m^2 doxorubicin, and may be lower for survivors treated in the rituximab era, emphasizing the need for studies with longer follow-up for rituximab-treated patients.

Key words: diffuse large B-cell lymphoma, subsequent neoplasms, alkylating agents, anthracyclines, radiotherapy, survivorship

BACKGROUND

The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) has been the standard treatment of diffuse large B-cell lymphoma (DLBCL) since its introduction in the 1970s.[1,2] In the early 2000s, the monoclonal anti-CD20 antibody rituximab was added to the CHOP regimen, leading to substantial improvement of 5-year

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disease-specific survival.[3,4] Five-year relative survival rates for patients aged <65 years increased from 57% for patients diagnosed between 1989 and 1995 to 78% for patients diagnosed between 2009 and 2016.[5] Consequently, there is a growing number of DLBCL survivors at risk of long-term treatment-related complications, including subsequent malignant neoplasms (SMNs). Most reports on long-term SMN risk after cancer treatment concern Hodgkin's lymphoma (HL) or childhood cancer survivors.[6-10] Due to the historically less favorable prognosis of DLBCL, the burden of solid and hematological SMNs has rarely been studied in DLBCL survivors with long-term follow-up.[11-14] Radiotherapy (RT)[15,16] and several of the drugs used to treat DLBCL, including the alkylating agent cyclophosphamide[17-19] and the anthracycline doxorubicin,[20-22] however, are known carcinogens. Moreover, patients with disease progression or relapse are often treated with high-dose chemotherapy (CT) followed by (autologous) stem-cell transplantation (SCT), which may add to an increased SMN risk.[23] There is no evidence that rituximab increases long-term SMN risk, but most studies that examined this association had short follow-up.[13,14,24] In this study, we investigated the long-term risk of SMNs after treatment with RT and/or (immuno)chemotherapy in a cohort of 5-year DLBCL survivors.

METHODS

Data collection

In the Netherlands, regular surveillance for recurrence of DLBCL (ICD-O-3 morphology codes M9679 to M9684)[25] typically ends 5 years after treatment. After 5 years, survivors who were 15-60 years of age at DLBCL diagnosis are eligible for the survivorship care program recently developed in the Netherlands.[26,27] Eligible survivors in each participating hospital were identified through the population-based Netherlands Cancer Registry (NCR). Patients diagnosed with a primary central nervous system lymphoma are not eligible for survivorship care, therefore, data of these survivors were not abstracted. Data collection to enable recalling 5-year DLBCL survivors (treated 1989-2012) for survivorship care started in 2018. Data from 2538 5-year DLBCL survivors identified in hospitals participating in the Dutch survivorship care program were used to study SMN risk.

For all 5-year DLBCL survivors eligible for follow-up at the survivorship clinics, information on date of DLBCL diagnosis, histology, Ann Arbor stage, smoking status at DLBCL diagnosis, primary and relapse treatment (radiation fields, CT regimens, number of cycles, and receipt of SCT) and date of most recent medical information were collected from the medical records. Information on SMNs (date of diagnosis, location and morphology), vital status and date of death were obtained by record linkage with the NCR, which has nationwide coverage since 1989. Information on SMNs and vital status was complete up to 1 July 2019. This study was declared outside the scope of the Medical Research Involving Human Subject Act by the Institutional Review Board of the Netherlands Cancer Institute (IRBd18008) and the need for individual informed consent was waived, as existing data from medical files and registries were used.

Treatment

DLBCL treatment schemes are stratified according to age, international prognostic index and feasibility of dose-intensified approaches.[28] Patients with Ann Arbor stage I usually received three to four cycles of CHOP(-like) CT, followed by involved field RT, as primary treatment.[29] Patients with advanced stage DLBCL (Ann Arbor stage II/III/IV) usually received primary treatment with six to eight cycles of CHOP(-like) CT with/without RT.[2,30-32] The majority of patients (83.1%) who received RT as part of primary treatment usually received doses between 30 and 40 gray in fractions of 2.0 gray. Rituximab was added to the CHOP regimen in the early 2000s, making R-CHOP immunochemotherapy the new standard treatment.[3,4,32-34]

Statistical analysis

Only 5-year DLBCL survivors were included in the cohort; therefore, to avoid immortal time bias, time at risk started 5 years after first treatment.[35] SMNs diagnosed <5 years after first DLBCL treatment were not taken into account in the analysis; any (subsequent) SMN that occurred ≥5 years after first treatment was included. Time at risk ended at the date of diagnosis of an SMN of interest, date of death, date of last medical information, date of migration or 1 July 2019, whichever occurred first. With the exception of basal cell carcinoma of the skin, which is not registered systematically by the NCR, all invasive SMNs were included in the analyses. In analyses with all SMNs combined, survivors who developed multiple SMNs were only counted once and time at risk ended at the date of diagnosis of the first SMN. In site-specific analyses, survivors who developed multiple SMNs contributed data regarding the SMN of interest, ignoring any preceding SMN at another site.

The incidence of SMNs in the cohort was compared with age-, sex-, calendar year- and site-specific cancer incidence data from the NCR, accounting for person-years of observation in the cohort. Standardized incidence ratios (SIRs) were estimated as the ratio of the observed and expected number of SMNs, whereas absolute excess risks (AERs) were calculated by subtracting the expected from the observed number of SMNs in the cohort and dividing by the number of person-years (expressed per 10 000 person-years). The 95% confidence intervals (95% CI) were calculated using exact Poisson probabilities of observed numbers.[36] *P* values of tests for heterogeneity and trend were calculated using standard methods. Treatment variables were handled as time-varying covariates to account for changes over time. For myelodysplastic syndrome (MDS), population reference rates before 2001 were not available; therefore only 5-year survivors treated from 1996 onwards were included in SIR and AER analyses for MDS. Cumulative incidences of SMNs were estimated with death as a competing risk.[37]

To assess SMN risk associated with cumulative cyclophosphamide and/or doxorubicin doses, the cumulative dose of these agents was estimated using standard doses [milligrams per meter squared (mg/m^2)] per cycle for each used CT regimen (number of cycles $\times$ standard dose $=$ cumulative dose, Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.102248). Cumulative doses were categorized and in case the number of administered CT cycles was incompletely known, survivors were assigned to the dose category that they had definitely received. Cumulative doses of cyclophosphamide and doxorubicin were highly correlated ($r_{spearman} = 0.89$), therefore, in multivariable analyses only one of these agents was considered at a time.

Multivariable Cox regression analysis was used to quantify the effect of different treatments on SMN risks, adjusting for confounders. Survivors with missing information on treatment covariates (3.2%) included in the model were excluded from analyses. The proportional hazards assumption was tested using graphical and residual-based methods. Models were stratified for age at first DLBCL treatment in categories (15-40, 41-50, 51-61 years), because hazards for solid SMNs were non-proportional by age. Interactions between age at first treatment, follow-up time, RT, CT, SCT and smoking were tested using standard methods. A test for trend over categories of dose was carried out by assigning each dose category the value of the median dose within that category, which was then tested as a continuous variable within the multivariable model. All statistical tests were two-sided and a P value <0.05 was considered statistically significant. The lower bound of the confidence interval was rounded downwards towards the nearest integer, while the upper bound of the confidence interval was rounded upwards to the nearest integer. A 95% CI containing 1.0 therefore always indicates a statistically significant result. All analyses were carried out using Stata (version 15.1, StataCorp LLC, College Station, TX).

RESULTS

A total of 165 DLBCL survivors were excluded from analyses: 48 survivors treated with CT or RT for another malignancy before DLBCL diagnosis, 100 survivors with <5 years of follow-up information after first treatment, 15 survivors who did not receive CT or RT, and 2 survivors with unknown primary treatment, leaving a total of 2373 DLBCL survivors eligible for analyses (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.102248).

Median age at first DLBCL treatment was 47.4 years [interquartile range (IQR) 36.8-54.7 years]. Median follow-up was 13.8 years (IQR 9.7-18.5 years), with 18.8% of patients followed $\geq$20 years (Table 1). The majority (62.4%) of patients had stage I or II disease, the median age at end of follow-up was 61.6 years (IQR 51.7-68.6 years) and 80.5% of the patients were alive at the end of follow-up. Most patients (84.1%) received only primary treatment. Treatment (including relapse treatment) consisted of CT alone in

Table 1. Characteristics of 5-year DLBCL survivors

Characteristic	*n*	%
Sex		
Male	1417	59.7
Female	956	40.3
Treatment period[a]		
1989-1997	582	24.5
1998-2005	977	41.2
2006-2012	814	34.3
Age at first treatment of DLBCL, years		
15-40	781	32.9
41-50	683	28.8
51-61	909	38.3
DLBCL Ann Arbor stage		
I	899	37.9
II	581	24.5
III	281	11.8
IV	445	18.8
Unknown	167	7.0
Treatment[b]		
Primary CT only	791	33.3
Primary RT only	56	2.4
Primary CT and RT, no relapse treatment	1148	48.4
Primary and relapse treatment	378	15.9
RT field[c]		
No RT	901	38.0
Supradiaphragmatic RT only	887	37.4
Subdiaphragmatic RT only	355	15.0
Supra- and subdiaphragmatic RT	104	4.4
Other field only or unknown field	126	5.3
Number of alkylating cycles[d]		
0-3	472	19.9
4-6	706	29.8
>6	1146	48.3
Unknown	49	2.1
Rituximab		
No	1256	52.9
Yes, only in primary treatment	885	37.3
Yes, only in relapse treatment	120	5.1
Yes, in primary and relapse treatment	94	4.0
Unknown	18	0.8
Follow-up time, years		
5-9	629	26.5
10-14	723	30.5
15-19	576	24.3
20-24	307	12.9
≥25	138	5.8
Attained age at end of follow-up, years		
20-49	525	22.1
50-59	551	23.2
60-69	816	34.4
≥70	481	20.3
Vital status at end of follow-up		
Alive	1911	80.5
Deceased	462	19.5

Percentages may not total 100 because of rounding.
CT, (immuno)chemotherapy; DLBCL, diffuse large B-cell lymphoma; *n*, number; RT, radiotherapy.
[a]The category 2006-2012 includes six survivors who were diagnosed in 2012 and treated in the beginning of 2013.
[b]For eight survivors who developed a relapse, treatment of relapse was unknown. For these survivors only primary treatment could be categorized. Five out of eight survivors were included in the category 'primary CT only' and three out of eight survivors were included in the category 'primary CT and RT, no relapse treatment'.
[c]The categories 'supradiaphragmatic RT only', 'subdiaphragmatic RT only' and 'supra- and subdiaphragmatic RT' include survivors who may also have received RT to a field other than the trunk, e.g. the lower leg. The category 'other field only or unknown field' includes 27 survivors who received RT to an unknown field and 11 survivors for whom it was unknown if they ever received radiotherapy.
[d]In case the cumulative number of alkylating cycles was incompletely known, survivors were assigned the category of cycles that they had definitely received.

38.4% of the patients, RT alone in 2.5%, and a combination of CT and RT in 59.0%; 46.3% of the patients received rituximab and 14.5% received SCT (Table 1, Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102248). Patients who received rituximab had a median follow-up of 10.9 years (IQR 8.3-13.2 years), whereas patients who never received rituximab had a median follow-up of 17.7 years (IQR 14.7-21.5 years). In more recent treatment periods, fewer survivors had been treated with RT or received relapse treatment, while most survivors were treated with rituximab (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.102248).

SMN rates compared with the general population

During follow-up, 321 patients developed at least one SMN; 285 survivors developed at least one invasive solid SMN and 40 survivors (33 survivors when excluding MDS) developed at least one hematological SMN. The median time between first DLBCL treatment and SMN diagnosis was 11.6 years (IQR 8.0-15.9 years) and the median age at SMN diagnosis was 63.3 years (IQR 56.3-67.6 years). Thirty-six patients developed a third and one patient developed a fourth malignancy. The median interval between the first SMN and the second SMN was 4.0 years (IQR 0.7-5.5 years). DLBCL survivors had a 1.5-fold (95% CI 1.3-1.8-fold) increased SIR for any SMN, corresponding to 51.8 excess SMNs per 10 000 person-years (Table 2). The 25-year cumulative incidence of any solid SMN was 22.5% (95% CI 19.5% to 25.6%; Figure 1).

SIRs were statistically significantly increased for head and neck (2.5, 95% CI 1.4-3.8), esophagus (2.2, 95% CI 1.1-4.0), stomach (3.0, 95% CI 1.5-5.5), anus and anal canal (17.7, 95% CI 7.6-34.9), lung cancer (2.0, 95% CI 1.5-2.7), non-melanoma skin cancer (2.1, 95% CI 1.3-3.0) and bone and soft tissue sarcomas (3.1, 95% CI 1.1-6.9, Table 2). Additionally, acute myeloid leukemia (AML, SIR 7.5, 95% CI 3.5-13.8), MDS (SIR 6.7, 95% CI 2.1-15.6) and HL (SIR 9.6, 95% CI 3.5-21.0) occurred more frequently among 5-year DLBCL survivors than expected. Lung cancer contributed most to the overall AER (13.4/10 000 person-years), representing ∼26% of the excess malignancies in the cohort, followed by gastrointestinal cancers (AER 11.8/10 000 person-years; ∼23% of all excess malignancies).

SMN rates according to sex, age and follow-up compared with the general population

SIRs did not differ much between men and women, except for bladder cancer and unknown primary tumors, which only occurred in male survivors (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.102248).

The SIR for any solid SMN remained increased for at least 20 years after first DLBCL treatment (SIR ≥20 years, 1.5, 95% CI 1.0-2.2, Figure 2, Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.102248). The AER remained stable over time (P_{trend} = 0.2); after ≥20 years of follow-up, DLBCL survivors experienced 72.3 excess solid malignancies per 10 000 person-years. SIRs for lung cancer decreased with longer follow-up (P_{trend} = 0.002), whereas SIRs for gastrointestinal cancer (P_{trend} = 0.01) and female breast cancer (P_{trend} = 0.05) increased with longer follow-up.

SIRs for solid SMNs decreased with older age at first DLBCL treatment (P_{trend} < 0.001) and were highest among survivors aged ≤40 years at first treatment (≤40 years, SIR 2.6, 95% CI 1.9-3.4; >40 years, SIR 1.4, 95% CI 1.1-1.6, $P_{heterogeneity}$ <0.001). The 25-year cumulative incidence of solid SMNs was 15.1% (95% CI 10.7% to 20.2%) for survivors ≤40 years and 26.5% (95% CI 22.6% to 30.5%) for survivors >40 years at first DLBCL treatment (Figure 1). Cumulative incidences for solid and hematological SMNs combined are presented in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.102248.

SMN rates according to treatment compared with the general population

SIRs for solid SMNs were increased among survivors who were treated with CT alone (SIR 1.7, 95% CI 1.4-2.1) and survivors who were treated with a combination of CT and RT (SIR 1.4, 95% CI 1.1-1.7, Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2024.102248). Receipt of relapse treatment did not influence SIRs for solid SMNs (SIR survivors without relapse treatment 1.5, 95% CI 1.2-1.7, SIR survivors with relapse treatment 1.8, 95% CI 1.2-2.4). When analyzing specific SMN sites, we observed increased SIRs for lung cancer among survivors treated with CT alone (SIR 3.2, 95% CI 2.1-4.6), but not among survivors who were treated with a combination of CT and RT (SIR 1.5, 95% CI 0.9-2.2) nor among those treated with RT alone (SIR 1.4, 95% CI 0.1-5.2), although, the latter estimate was based on a small number of survivors. The data showed an increased SIR for female breast cancer among survivors with supradiaphragmatic RT (SIR 1.8, 95% CI 1.0-2.7). SIRs were suggestive of increased risk of gastrointestinal cancers after subdiaphragmatic RT (SIR 1.7, 95% CI 0.9-2.9, Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2024.102248), although not statistically significant. SIRs for solid SMNs (P_{trend} = 0.006) and lung cancer (P_{trend} = 0.01) increased with a higher cumulative cyclophosphamide dose. Compared with incidence rates in the general population, survivors who received rituximab during primary treatment had statistically significantly lower SIRs for any SMN (SIR rituximab 1.2, 95% CI 0.9-1.6, SIR no rituximab 1.7, 95% CI 1.4-2.0), gastrointestinal tract SMNs (SIR rituximab 0.6, 95% CI 0.2-1.2, SIR no rituximab 1.7, 95% CI 1.2-2.4), prostate cancer (SIR rituximab 0.2, 95% CI 0.0-1.0, SIR no rituximab 0.9, 95% CI 0.4-1.6) and HL (SIR rituximab 0.0, 95% CI 0.0-24.9, SIR no rituximab 18.4, 95% CI 6.7-40.1) compared with survivors who did not receive rituximab during primary treatment (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2024.102248). Receipt of rituximab was not correlated with the SIR for lung cancer (SIR rituximab 2.4, 95% CI 1.2-4.0, SIR no rituximab 2.5, 95% CI 1.7-3.6), nor with the SIR

Table 2. Standardized incidence ratios, absolute excess risks and 25-year cumulative incidence of selected invasive subsequent malignancies

	ICD-10 code	*n*	SIR (95% CI)	AER *n* per 10 000 person-years (95% CI)	25-year cumulative incidence (95% CI)
Any cancer[a,b]		316	1.5 (1.3 to 1.8)	51.8 (35.9 to 69.1)	24.6 (21.5 to 27.8)
Any solid cancer	C00-C80	285	1.5 (1.3 to 1.7)	44.4 (29.4 to 60.8)	22.5 (19.5 to 25.6)
Head and neck	C00-C14, C30-C32	20	2.5 (1.4 to 3.8)	5.3 (1.8 to 10.2)	1.7 (0.9 to 3.1)
Mouth	C01-C05	7	3.2 (1.2 to 6.7)	2.1 (0.2 to 5.4)	0.8 (0.2 to 2.2)
Nasal cavity, middle ear, sinuses	C30-31	4	11.7 (3.1 to 30.0)	1.6 (0.3 to 4.4)	0.1 (0.0 to 0.5)
Gastrointestinal tract	C15-C26, C48	75	1.5 (1.2 to 2.0)	11.8 (4.5 to 20.3)	6.1 (4.6 to 8.0)
Esophagus	C15	12	2.2 (1.1 to 4.0)	3.0 (0.3 to 7.0)	1.3 (0.5 to 2.7)
Stomach	C16	11	3.0 (1.5 to 5.5)	3.3 (0.8 to 7.2)	0.8 (0.3 to 1.6)
Colon	C18	23	1.2 (0.7 to 1.8)	1.5 (−2.3 to 6.7)	1.7 (1.0 to 2.8)
Rectum or rectosigmoid junction	C19-C20	6	0.6 (0.2 to 1.3)	−1.9 (−3.7 to 1.3)	0.6 (0.2 to 1.5)
Anus and anal canal	C21	8	17.7 (7.6 to 34.9)	3.4 (1.3 to 6.8)	0.6 (0.2 to 1.2)
Pancreas	C25	6	1.3 (0.4 to 2.8)	0.6 (−1.2 to 3.7)	0.5 (0.1 to 1.1)
Bronchus and lung	C34	59	2.0 (1.5 to 2.7)	13.4 (7.1 to 21.1)	3.5 (2.5 to 4.7)
Melanoma skin cancer	C43	15	1.3 (0.7 to 2.2)	1.7 (−1.3 to 6.0)	1.0 (0.5 to 1.7)
Nonmelanoma skin cancer	C44	30	2.1 (1.3 to 3.0)	6.9 (2.5 to 12.6)	2.8 (1.7 to 4.3)
Bone, joints, cartilage and soft tissue	C40-C41	6	3.1 (1.1 to 6.9)	1.8 (0.1 to 5.0)	0.5 (0.1 to 1.2)
Female breast[c]	C50	37	1.4 (0.9 to 1.9)	11.1 (−1.1 to 26.7)	8.8 (5.5 to 12.9)
Female genital organs[c]	C51-C58	9	1.1 (0.4 to 2.1)	0.6 (−4.8 to 9.5)	2.1 (0.7 to 4.8)
Corpus uteri[c,d]	C54	7	1.8 (0.7 to 3.9)	3.5 (−1.1 to 11.7)	1.9 (0.5 to 4.7)
Male genital organs[e]	C60-C63	26	0.8 (0.5 to 1.3)	−3.7 (−10.6 to 5.5)	3.7 (2.2 to 5.7)
Prostate[e]	C61	22	0.7 (0.4 to 1.2)	−5.8 (−12.0 to 2.8)	3.3 (1.9 to 5.3)
Urinary tract	C64-C68	13	0.6 (0.3 to 1.1)	−3.3 (−6.0 to 0.8)	1.2 (0.5 to 2.3)
Bladder	C67	10	1.6 (0.7 to 3.0)	1.7 (−0.7 to 5.5)	0.9 (0.3 to 1.9)
Thyroid and other endocrine glands	C73-C75	4	3.5 (0.9 to 9.0)	1.3 (−0.1 to 4.1)	0.2 (0.0 to 0.5)
Primary site unknown or ill-defined	C76, C80	9	2.8 (1.2 to 5.4)	2.6 (0.4 to 6.2)	0.5 (0.2 to 1.1)
Hematological malignancies[b]	C81-C96	33	1.8 (1.2 to 2.6)	6.7 (2.0 to 12.7)	2.3 (1.4 to 3.5)
Hodgkin's lymphoma	C81	6	9.6 (3.5 to 21.0)	2.4 (0.7 to 5.6)	0.3 (0.1 to 0.8)
Acute myeloid leukemia	C92	10	7.5 (3.5 to 13.8)	3.8 (1.5 to 7.6)	0.5 (0.2 to 1.0)
Myelodysplastic syndrome[f]	D46	5	6.7 (2.1 to 15.6)	2.8 (0.5 to 7.1)	0.5 (0.1 to 1.2)

Numbers of individual cancers do not add up to number of any cancer due to second or third SMNs. Listed cancers are those of which at least four cases were observed in the cohort. In addition to the specific sites displayed in the table, the following cancers were observed: two cancers of the lip (C00), three oropharyngeal cancers (C01, C09-C10), one hypopharyngeal cancer (C12-C13), three liver cancers (C22), three gallbladder or extrahepatic biliary tract cancers (C23-C24), three larynx cancers (C32), one Kaposi sarcoma (C44), one mesothelioma (C45), one male breast cancer (C50), two vulva cancers (C51), two penile cancers (C60), two testicular cancers (C62), three kidney cancers (C64), one brain tumor (C71), two thyroid cancers (C73), one follicular lymphoma (C82), two Burkitt lymphomas (C83), two small cell B-cell lymphomas (C83), two mature T/NK-cell lymphomas (C84), one malignant immuno-proliferative disease (C88) and four multiple myeloma (C90).

AER, absolute excess risk; CI, confidence interval; ICD-10, International Classification of Diseases, 10th Revision; *n*, number; SIR, standardized incidence ratio; SMN, subsequent malignant neoplasm.

[a]Includes only the first invasive cancer after diffuse large B-cell lymphoma.

[b]Excluding myelodysplastic syndrome.

[c]Only women included in the denominator. For breast cancer, women accumulated 9020.6 person-years in which 27.0 invasive breast cancers were expected. For genital cancer, women accumulated 9133.1 person-years in which 8.4 genital cancers were expected. For cancer of the corpus uteri, women accumulated 9141.1 person-years in which 3.8 corpus uteri cancers were expected.

[d]Includes one corpus uteri sarcoma.

[e]Only men included in the denominator. For genital cancer, men accumulated 13 239.4 person-years in which 30.9 genital cancers were expected. For prostate cancer, men accumulated 13 257.6 person-years in which 29.7 prostate cancers were expected.

[f]Only survivors treated from 1996 onwards included in the denominator. For myelodysplastic syndrome, survivors accumulated 15 381.1 person-years in which 0.8 cases of myelodysplastic syndrome were expected.

for AML (SIR rituximab 9.7, 95% CI 3.5-21.1, SIR no rituximab 11.0, 95% CI 2.2-32.1).

SMN risks within the cohort according to patient and treatment characteristics

Neither supradiaphragmatic nor subdiaphragmatic RT was associated with increased risk of solid SMNs compared with survivors who did not receive supradiaphragmatic or subdiaphragmatic RT, respectively (Table 3). Solid SMN risk increased with a higher cumulative cyclophosphamide dose ($P_{\text{trend over categories}} = 0.015$). Receipt of a cumulative cyclophosphamide dose of >4500 mg/m^2, compared with a dose of ≤2250 mg/m^2, was associated with an increased risk of solid SMNs [hazard ratio (HR) 1.5, 95% CI 1.0-2.2] and lung cancer (HR 2.5, 95% CI 1.1-5.8, Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2024.102248). Solid SMN risk was similar for models including cumulative doxorubicin dose: HR 1.5, 95% CI 1.0-2.2 for survivors who received a doxorubicin dose of >300 mg/m^2 compared with a dose of ≤150 mg/m^2 (Table 3).

Treatment with rituximab was associated with a lower risk of any subdiaphragmatic solid SMN (HR 0.5, 95% CI 0.3-1.0). This association was still present when relapse treatment was added as a separate time-varying covariate to a multivariable model based on primary treatment variables (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2024.102248). Receipt of SCT was associated with increased risk of AML/MDS (HR 6.1, 95% CI 2.3-16.0, Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2024.102248), but not with risk of other malignancies.

Smoking at time of DLBCL diagnosis was an independent risk factor for solid SMNs (HR 2.0, 95% CI 1.5-2.7),

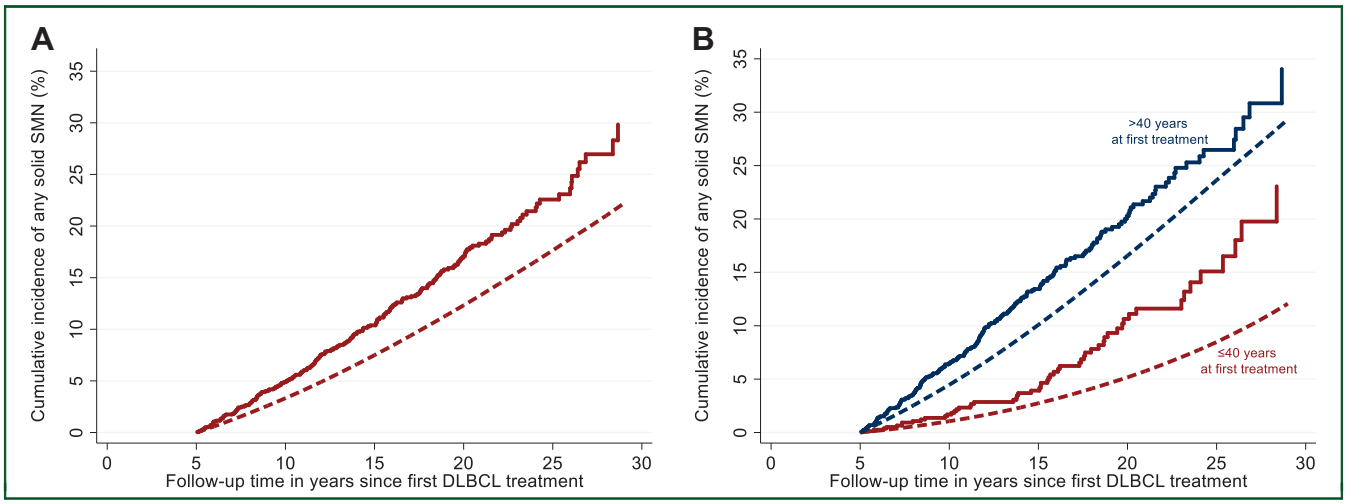

Figure 1. Cumulative incidence of any solid subsequent malignant neoplasm, with death as a competing risk. (A) Overall cumulative incidence of any solid SMN. (B) cumulative incidence of any solid SMN according to age at first DLBCL treatment. Solid lines represent the observed incidence in the cohort, dashed lines represent the expected incidence in the general population. In panel B, red lines represent survivors ≤40 years at first DLBCL treatment and blue lines represent survivors >40 years at first DLBCL treatment.
DLBCL, diffuse large B cell lymphoma; SMN, subsequent malignant neoplasm.

supradiaphragmatic solid SMNs (HR 2.7, 95% CI 1.8-3.9) and lung cancer (HR 8.2, 95% CI 4.1-16.3, Table 3, Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2024.102248). Compared with males, females had a lower risk of subdiaphragmatic solid SMNs (HR 0.6, 95% CI 0.3-0.9). When bladder cancers ($n = 10$, only recorded in male survivors) were excluded from the analyses, the HR no longer differed for females and males (HR 0.7, 95% CI 0.4-1.1).

DISCUSSION

In this study in 5-year DLBCL survivors with detailed treatment data and long-term follow-up, we observed a 1.5-fold higher SMN rate among DLBCL survivors compared with the general population. Increased risks were observed for head and neck, esophagus, stomach, anus and anal canal, and lung cancer, nonmelanoma skin cancer, bone and soft tissue sarcomas, AML, MDS and HL. The 25-year cumulative incidence of any solid SMN was 22.6%. Patients who received rituximab had a lower risk of subdiaphragmatic solid SMNs compared with patients who did not receive rituximab. Solid SMN risk increased with a higher cumulative cyclophosphamide dose.

SIRs observed in our study population were similar to rates reported in a previous study among 2-year survivors of non-Hodgkin's lymphoma,[38] and slightly higher compared with rates reported in a previous study in DLBCL patients.[39] SIRs for solid SMNs were especially increased among survivors aged ≤40 years at first DLBCL treatment, which is consistent with results of previous studies among DLBCL

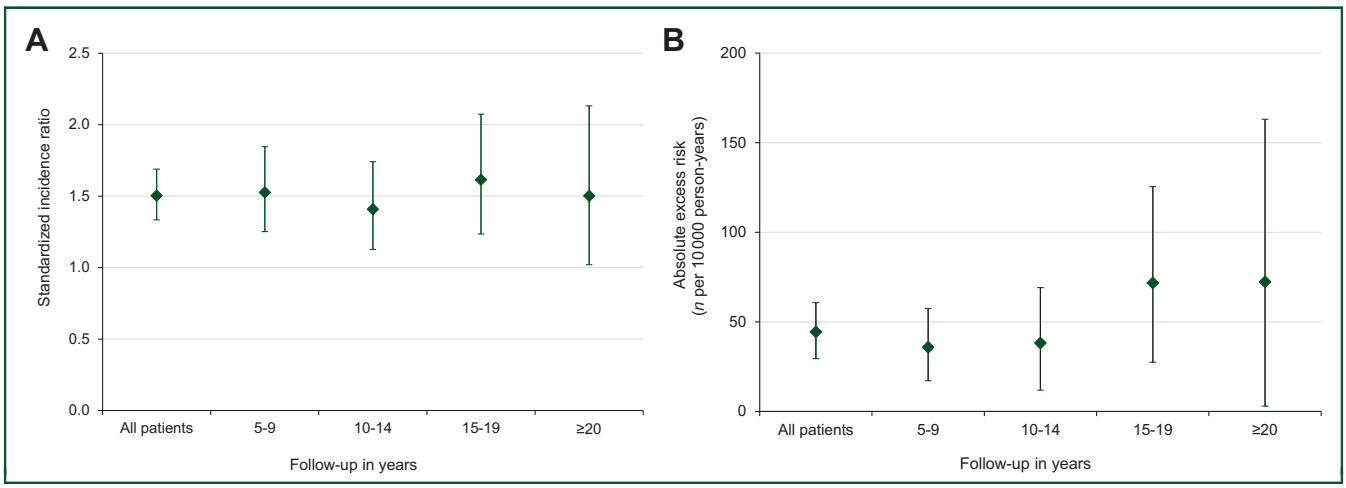

Figure 2. Standardized incidence ratios and absolute excess risks of any solid subsequent malignant neoplasm after DLBCL treatment according to follow-up interval. (A) Standardized incidence ratios of any solid SMN according to follow-up interval. (B) Absolute excess risks of any solid SMN according to follow-up interval. Standardized incidence ratios of the observed and expected number of solid SMNs in the study population and their corresponding 95% confidence intervals (vertical lines) were calculated using exact Poisson probabilities of observed numbers. Absolute excess risk was calculated as the observed number of subsequent malignancies in the cohort minus the number expected and divided by the number of person-years (expressed per 10 000 person-years).
DLBCL, diffuse large B cell lymphoma; *n*, number; SMN, subsequent malignant neoplasm.

Table 3. Patient- and treatment-related risk factors for selected invasive subsequent malignancies during the first 30 years of follow-up, Cox regression analysis

Subsequent malignancy	Any solid SMN (n = 275)		Any supradiaphragmatic solid SMN (n = 145)[a]		Any subdiaphragmatic solid SMN (n = 105)[b]	
	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Sex						
Male	174 (63.3)	1.0 [reference]	80 (55.2)	1.0 [reference]	75 (71.4)	1.0 [reference]
Female	101 (36.7)	0.9 (0.6-1.2)	65 (44.8)	1.3 (0.9-1.8)	30 (28.6)	0.6 (0.3-0.9)
Supradiaphragmatic RT[c]						
No	168 (61.1)	1.0 [reference]	84 (57.9)	1.0 [reference]		
Yes	107 (38.9)	0.8 (0.6-1.1)	61 (42.1)	1.0 (0.7-1.5)		-
Subdiaphragmatic RT						
No	213 (77.5)	1.0 [reference]			75 (71.4)	1.0 [reference]
Yes	62 (22.6)	0.9 (0.6-1.3)		—	30 (28.6)	1.3 (0.8-2.0)
Cyclophosphamide dose, mg/m^2 [d]						
0-2250	45 (16.4)	1.0 [reference]	24 (15.9)	1.0 [reference]	18 (17.1)	1.0 [reference]
2251-4500	88 (32.0)	1.3 (0.8-1.9)	49 (34.5)	1.5 (0.9-2.5)	33 (31.4)	1.2 (0.6-2.2)
>4500	142 (51.6)	1.5 (1.0-2.2)	72 (49.7)	1.5 (0.9-2.5)	54 (51.4)	1.6 (0.9-2.8)
Ever rituximab						
No	214 (77.8)	1.0 [reference]	107 (73.8)	1.0 [reference]	89 (84.8)	1.0 [reference]
Yes	61 (22.2)	0.7 (0.5-1.1)	38 (26.2)	1.0 (0.6-1.5)	16 (15.2)	0.5 (0.3-1.0)
Stem cell transplantation						
No	238 (86.6)	1.0 [reference]				
Yes	37 (13.5)	1.0 (0.6-1.5)		—		—
Smoking at DLBCL diagnosis[e]						
No	115 (41.8)	1.0 [reference]	54 (37.2)	1.0 [reference]	49 (46.7)	1.0 [reference]
Yes	135 (49.1)	2.0 (1.5-2.7)	80 (55.2)	2.7 (1.8-3.9)	44 (41.9)	1.4 (0.9-2.1)
Unknown	25 (9.1)	0.9 (0.6-1.5)	11 (7.6)	0.9 (0.4-1.7)	12 (11.4)	1.1 (0.5-2.1)
Doxorubicin dose, mg/m^2[d,f]						
0-150	47 (17.1)	1.0 [reference]	25 (17.2)	1.0 [reference]	20 (19.1)	1.0 [reference]
151-300	94 (34.2)	1.3 (0.9-1.9)	50 (34.5)	1.4 (0.8-2.3)	36 (34.3)	1.2 (0.6-2.1)
>300	134 (48.7)	1.5 (1.0-2.2)	70 (48.3)	1.6 (0.9-2.6)	49 (46.7)	1.5 (0.8-2.5)

Percentages may not total 100 because of rounding. All analyses were stratified for age at first diffuse large B cell lymphoma treatment in categories. Radiotherapy, cyclophosphamide dose, rituximab and stem cell transplantation were included as time-varying variables. Survivors with incomplete information on included treatment variables were excluded from analyses. Models included the following number of survivors: any solid SMN n = 2297, any supradiaphragmatic solid SMN n = 2304, any subdiaphragmatic solid SMN n = 2304.

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHVmP-BV, cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin, vincristine; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; n, number; RT, radiotherapy; SMN, subsequent malignant neoplasm.

[a]Includes solid cancers of the following sites: head and neck (C00-C14; C30-C32), esophagus (C15.0; C15.1; C15.3-C15.9), trachea (C33), bronchus and lung (C34), thymus (C37), bone, joints, cartilage and soft tissue (C41.0; C41.1; C41.3), skin (C44.0-C44.4), peripheral nerves (C47.0; C47.3), soft tissue (C49.0; C49.3), breast (C50), eye (C69), brain (C70-C71), thyroid (C73), other endocrine glands (C75.0-C75.5), ill-specified locations (C76.0; C76.1).

[b]Includes solid cancers of the following sites: abdominal esophagus (C15.2), stomach (C16), small intestine (C17), colorectal (C18-C20), anus (C21), liver (C22), gallbladder (C23-C24), pancreas (C25), other gastrointestinal (C26), bone, joint, cartilage and soft tissue (C41.4), peripheral nerves (C47.4; C47.5), retroperitoneum (C48), soft tissue (C49.4; C49.5), female genital tract (C51-C58), prostate (C61), kidney and urinary tract (C64-C68), adrenal (C74), ill-specified locations (C76.2; C76.3).

[c]Includes radiotherapy to the head and/or neck

[d]Assuming a cyclophosphamide dose of 750 mg/m^2 and a doxorubicin dose of 50 mg/m^2 per cycle of (R-)CHOP, categories correspond to three or fewer, four to six and more than six cycles of (R-)CHOP (immuno)chemotherapy. See Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.102248 for cumulative cyclophosphamide and doxorubicin doses of other common chemotherapy regimens. In case the cumulative dose of cyclophosphamide or doxorubicin was incompletely known, survivors were assigned the dose category that they had definitely received.

[e]Includes survivors who quit smoking ≤6 months before diffuse large B cell lymphoma diagnosis.

[f]Based on a multivariable Cox regression model including cumulative doxorubicin dose instead of cumulative cyclophosphamide dose.

and other non-Hodgkin's lymphoma survivors.[11,12,40] Even though cancer risk was increased among DLBCL survivors, risks were substantially lower than those observed among HL survivors.[7]

We did not observe an increased risk of solid SMNs after RT. There may be several explanations for this finding. Due to the relatively low absolute number of SMNs, we could only explore rather broad groupings of SMNs in our analyses and had to use a quite coarse categorization of RT fields, which may partly explain the absence of an association between RT and solid SMNs in our study. In addition, compared with HL survivors, DLBCL survivors were exposed to less extensive radiation fields and lower radiation doses. Furthermore, DLBCL survivors had a median age of 47.4 years at first treatment, whereas previous studies have shown that SMN risk (strongly) decreases with higher age at treatment exposure.[7,41-43] Nonetheless, our data were actually suggestive of an elevated risk of female breast cancer after supradiaphragmatic RT and of gastrointestinal cancers after subdiaphragmatic RT.

In our study, 5-year DLBCL survivors who received rituximab had lower risk of subdiaphragmatic solid SMNs compared with survivors who did not receive rituximab. The median follow-up duration for survivors treated with rituximab as part of primary treatment, however, is only 10.9 years and the observed number of subdiaphragmatic solid SMNs is consequently low (n = 8). A previous Dutch study among follicular lymphoma patients also observed slightly

lower SIRs for SMNs in the post-rituximab era (SIR 1.33, 95% CI 1.25-1.42) compared with the pre-rituximab era (SIR 1.53, 95% CI 1.42-1.64).[44] The introduction of rituximab in the early 2000s has led to a better response to treatment and the use of less relapse treatment.[33] However, in the most recent treatment period (2006-2012) in which nearly all survivors in our study population received rituximab, fewer survivors had received relapse treatment or had been treated with RT (supradiaphragmatic and/or subdiaphragmatic), which may have contributed to the overall lower SMN risk among survivors who received rituximab. Previous studies that compared SMN rates among B-cell NHL patients in the pre- and post-rituximab era did not find an association between rituximab exposure and SMN rates,[24,45] except for AML, for which higher rates were observed in the post-rituximab era.[14] With the exception of the incidence of lung cancer and AML, cancer incidence among DLBCL survivors treated with rituximab in our study was not statistically significantly increased compared with incidence rates in the general population. Studies with longer follow-up of DLBCL patients who have received rituximab are needed to determine whether these patients have a higher risk of SMNs compared with the general population.

Solid SMN risk increased with higher cumulative cyclophosphamide dose or doxorubicin dose. Lung cancer risk was increased 2.5-fold among survivors who received >4500 mg/m^2 cyclophosphamide. Cyclophosphamide has previously been associated with increased risks of AML and bladder cancer.[18,19,46,47] Anthracycline exposure has also previously been associated with increased AML risks[20,21] and increased solid SMN risks among childhood cancer survivors.[43] As the majority of the DLBCL survivors were primarily treated with CT regimens which contained both cyclophosphamide and doxorubicin in standard combinations, we were unable to disentangle the separate effects of both agents.

Our study has several potential limitations. Pathology reports for DLBCL and other subsequent lymphomas were not centrally reviewed, therefore, results regarding subsequent HL should be interpreted with caution. Secondly, information on dose intensity of (R-)CHOP {every 14 days [(R-)CHOP14] versus every 21 days [(R-)CHOP21]} and granulocyte colony-stimulating factor (G-CSF) support during DLBCL treatment was not routinely collected. A previous meta-analysis including patients with solid cancer or lymphoma showed that G-CSF support might be associated with a higher risk of developing SMNs.[48] It has also been shown that (R-)CHOP14 is associated with more persistent complications, such as neuropathy, compared with (R-)CHOP21.[49,50] The long-term SMN risk of (R-)CHOP14 versus (R-)CHOP21 has not yet been explored. We used smoking status at DLBCL diagnosis in analyses, as information on smoking habits during follow-up was not systematically reported in the medical files. Cancer survivors may have stopped smoking after their DLBCL diagnosis[51,52] and it would have been interesting to also include duration of smoking. Furthermore, as only SMNs occurring ≥ 5 years after first treatment were included, we were unable to estimate the occurrence of early treatment-related malignancies, and in case a survivor had multiple SMNs, we assumed that the occurrence of a subsequent SMN was independent of the first SMN and treatment of the first SMN was not taken into account in analyses. We also acknowledge that some results are based on a small number of SMNs, therefore the precision of estimates for specific SMNs may be limited. Lastly, our results reflect SMN risk among 5-year survivors mostly treated with (R-)CHOP and are therefore not directly generalizable to patients treated with other CT regimens.

In conclusion, 5-year DLBCL survivors treated from 1989 to 2012 experience $\sim$1.5 times higher rates of SMNs compared with the general population. SIRs were higher for patients $\leq$40 years at DLBCL treatment and largest excess risks were observed for SMNs of the lung and gastrointestinal tract. SMN risks were higher for survivors who received a cumulative cyclophosphamide dose of >4500 mg/m^2 or a cumulative doxorubicin dose of >300 mg/m^2. With the exception of AML, SMN rates appeared lower after the introduction of rituximab. In the Netherlands, the current standard of care for patients with advanced disease entails six cycles of R-CHOP, based on several studies demonstrating that treatment with six cycles of R-CHOP, compared with eight cycles of R-CHOP, is equally effective.[31,50] Studies with long-term follow-up of DLBCL survivors who have received rituximab and six cycles of CHOP are needed to determine whether these survivors have a higher risk of SMNs compared with the general population. The results of our study emphasize the importance of personalized medicine.

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DISCLOSURE

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DATA SHARING

Requests to access anonymized data for academic/non-commercial purposes may be submitted to Michael Schaapveld (m.schaapveld@nki.nl).

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