



The relationship among primary anatomic subsite and risk and distribution of second malignant neoplasms in patients with stage I/II diffuse large B-cell lymphoma: An analysis of the surveillance, epidemiology, and end results database

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Abbreviations

DLBCL: diffuse large B-cell lymphoma
SEER: surveillance
SMNs: secondary malignant neoplasms
SIR: standardized incidence ratio
GI tract: gastrointestinal tract
AER: absolute excess risk
CI: confidence interval
O/E: observed-to-expected
HR: hazard ratio
OS: overall survival

ABSTRACT

Background: Recent studies have reported that diffuse large B-cell lymphoma (DLBCL) involving different primary extranodal sites have distinct clinicopathological characteristics and prognosis. However, the risk of secondary malignant neoplasms (SMNs) in DLBCL survivors with different primary extranodal sites are unknown.

Methods: A total of 40,714 patients diagnosed with stage I/II DLBCL were included from the Surveillance, Epidemiology, and End Results (SEER) database from 1983 to 2015. The standardized incidence ratio (SIR) and absolute excess risk (AER) were used to assess the risk of SMNs.

Results: The results show that the risk of SMN was significantly higher in extranodal DLBCL than in the US general population (SIR, 1.18; 95% CI, 1.11–1.26), and the risk of developing SMN remains significantly elevated with increased latency. Moreover, there were multiple site-specific risk patterns. There was a 22%, 44%, 66%, 123% and 151% increased risk of SMN 10 years after primary gastrointestinal tract, head/neck, skeletal, lung and liver/pancreas DLBCL diagnosis, respectively. There was a significant decrease risk of SMN with increasing age at diagnosis for primary gastrointestinal tract and skeletal DLBCL. In addition, DLBCL patients with primary sites in the gastrointestinal tract, thyroid and liver/pancreas had the highest incidences of secondary stomach cancer, second thyroid cancer, and second hepatobiliary cancer, respectively, which indicated that the initial site of DLBCL may predict the type of SMN.

Conclusions: The strategies for cancer surveillance after extranodal DLBCL diagnosis may need to be individualized according to the subsite of extranodal DLBCL.

Background

Diffuse large B-cell lymphomas (DLBCL), comprising approximately 30% of all non-Hodgkin lymphoma (NHL) cases, are the most common NHL types. DLBCL can be separated into distinct categories with 5-year survival rates ranging from 30% to 80%, based on clinical features, pathology, and gene expression signature [1]. The overall survival (OS) of DLBCL has improved significantly since the introduction of rituximab in 2006 [2]. But increased survival correlates with late influence, including the progress of a second malignant neoplasm (SMN) and long-term toxicities [3].

Regarding all cancer cases, about 1 in 6 is a subsequent or second tumor [4]. Age, lifestyle behaviors/exposures, genetic factors, and treat-

ment exposures (radiotherapy, alkylating agent) are essential inducers for the second tumor. However, little is known about the risk of SMN in DLBCL, particularly extranodal DLBCL. There is mounting evidence that primary extranodal sites reflect distinct clinicopathological characteristics and prognostic implications, and require specific therapy [5,6]. Hence, we hypothesized that there might be a difference in the risk of SMN depending on the site of involvement in patients with DLBCL. Because multiple sites are involved in the late stages of DLBCL, the initial site involved cannot be accurately defined. In order to avoid the interaction and confusion of multiple external sites, we only included the patients in stage I/II to focus on assessing the difference in the extranodal site of origin.

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Table 1
Patient characteristics.

Primary site	Total no.	Males(%)	Era of diagnosis (2006–2015) (%)	Age 15–39(%)	Age		Race		
					40–60(%)	>60(%)	White(%)	Black(%)	Other(%)
Lymph Node	21,747	11,378(52.32)	10,035(46.14)	3026(13.91)	6005(27.61)	12,716(58.47)	18,646(85.74)	1481(6.81)	1620(7.45)
Extranodal	18,967	10,028(52.87)	8733(46.04)	1722(9.08)	5070(26.73)	12,175(64.19)	15,851(83.57)	1249(6.59)	1867(9.84)
Skin and soft tissue	2130	1133(53.19)	934(43.85)	164(7.7)	542(25.45)	1424(66.85)	1880(88.26)	136(6.38)	114(5.35)
Gastrointestinal tract	6507	3874(59.54)	2704(41.56)	494(7.59)	1636(25.14)	4377(67.27)	5339(82.05)	420(6.45)	748(11.5)
Head/Neck	4377	2437(55.68)	2129(48.64)	407(9.3)	1257(28.72)	2713(61.98)	3508(80.15)	311(7.11)	558(12.75)
Kidney	207	132(63.77)	102(49.28)	13(6.28)	52(25.12)	142(68.6)	174(84.06)	16(7.73)	17(8.21)
Skeletal tissue	1255	694(55.3)	655(52.19)	297(23.67)	327(26.06)	631(50.28)	1092(87.01)	97(7.73)	66(5.26)
Lung	676	353(52.22)	321(47.49)	98(14.5)	169(25)	409(60.5)	592(87.57)	54(7.99)	30(4.44)
Uterus/uterine appendages	205	0(0)	98(47.8)	50(24.39)	92(44.88)	63(30.73)	164(80)	21(10.24)	20(9.76)
Thyroid	921	275(29.86)	387(42.02)	38(4.13)	246(26.71)	637(69.16)	837(90.88)	18(1.95)	66(7.17)
Liver/pancreas	665	411(61.8)	355(53.38)	36(5.41)	197(29.62)	432(64.96)	559(84.06)	61(9.17)	45(6.77)
Breast tissue	624	18(2.88)	312(50)	46(7.37)	158(25.32)	420(67.31)	491(78.69)	39(6.25)	94(15.06)
Other	1400	701(50.07)	736(52.57)	79(5.64)	394(28.14)	927(66.21)	1215(86.79)	76(5.43)	109(7.79)

In addition, it is unknown whether second cancers alter the disease course of DLBCL once they occur. Due to concerns about the toxicity or competing risks associated with lymphoma and its treatment, such patients may encounter obstacles in receiving appropriate cancer treatment. However, the outcomes of patients with DLBCL who develop SMNs have not been studied. This study was designed to evaluate the risk of SMN in patients with stage I/II DLBCL characterized by different primary extranodal sites, and comparing OS between patients with and without SMNs by analyzing records in the United States (US) Surveillance, Epidemiology, and End Results (SEER) database.

Material and methods

SEER patient selection

The SEER database gathers and reports demographics, morphology, primary tumor site, treatment information, and survival data of patients with tumors. It covers up to 28% of the population in the US, including 67% Pacific/Hawaiian Islander, 50% Asian, 44% Alaskan/American Indian Native, 38% Hispanic, and 26% black.

We collected information on DLBCL patients diagnosed between 1983 and 2015 from the registries of the SEER program of the US National Cancer Institute. Eligible patients were those diagnosed with lymphoma per the International Classification of Diseases for Oncology, third edition, ICD-O-3 histology code 9680 (DLBCL, not otherwise specified). Patients with the following features were excluded: 1. DLBCL was not primary malignancy; 2. diagnosis was made only by death certificate or autopsy; 3. They were diagnosed before 1983. The choice of this cut-off was motivated by the SEER database has only been recorded on the Ann Arbor Stage since 1983; 4. age at diagnosis was ≤ 14 years; 5. the primary site of lymphoma was unknown or was the central nervous system, testicular and mediastinal. Patients with primary CNS lymphoma, primary testicular lymphoma and primary mediastinal lymphoma were excluded, because the outcomes and characteristics of those cases are different, and require specific therapy; 6. those who survived for less than a month and unknown cause of death were excluded in survival analysis, because their survival time were recorded as 0 in SEER database.

Definition of variables from SEER

Year of diagnosis, age, sex, race, the primary site of involvement, clinical stage, survival time, outcome, the cause of death, the total number of *in situ*/malignant tumors, and sequence numbers for patients were collected. Age at the time of diagnosis was divided into 3 groups: 1) adolescent and young adults (AYAs): 15–39 years; 2) adults: 40–60 years; 3) the elder: >60 years, in conformity with the National Comprehensive

Cancer Network guidelines and the National Cancer Institute Progress Review Group on AYA Oncology. The era of diagnosis was divided into 2 groups: 1983–2005 and 2006–2015. Because rituximab was approved for the treatment of DLBCL in 2006 by the US FDA (Food and Drug Administration), and in view of differences in DLBCL treatment regimens with/without rituximab. Based on the ICD-O-3 topography code reported by SEER, primary sites were divided into 12 groups: Lymph Node; Skin/soft tissue; Gastrointestinal tract; Head/Neck; Kidney; Skeletal tissue; Lung; Uterus/uterine appendages; Thyroid; Liver/pancreas; Breast tissue; and other(i.e., blood, peritoneum, eye and adrenal gland).

Definition of SMN

The SMN was defined as the first subsequent primary cancer which occurs at least 2 months after the first cancer diagnosis [7–9]. The primary cancers were defined as two or more cancers which exist at the same site but in different histological findings or at different sites according to the International Agency for Research on Cancer [10]. Therefore, the person-year at risk for each person should start from the 2 months of follow-up to whichever coming first: the SMN diagnosis, the last known vital status, death, or the end of the study period for follow-up.

Statistical analysis

The standardized incidence ratio (SIR) was calculated as follows: observed malignancies/expected malignancies. The expected numbers of second cancers could be calculated by multiplying the accumulated person-years at risk with sex-, age-, race group-, and calendar year-specific SEER cancer incidence rates (available at <http://seer.cancer.gov>) [11]. The absolute excess risk (AER) was computed as the excess cancers per 10,000 persons per year as follows: ([observed - expected count] X 10,000)/person-years at risk. The SIR and AER were calculated via the multiple primary SIR session of the SEER*Stat software (version 8.3.4). We used the Poisson exact methods for SIR to compute the 95% confidence intervals (CIs) and corresponding P values, and $P < 0.05$ are defined as significant differences for SIR.

Chi-square and correlation tests were applied to investigate the differences between respective, continuous, and discrete epidemiological, pathological, and clinical characteristics. In order to determine how distinct variable levels were associated with survival relatively, as well as individually, hazard ratios (HR) and 95% confidence intervals (CI) were calculated through the univariable and multivariable Cox proportional hazards regression models. SPSS statistical software was used to perform Other analyses.

Table 2

Cancer site-specific standardized incidence ratios (O/E Ratios and 95% CIs) for second malignant neoplasm by site of first primary cancer.

	Lymph Node	Extranodal	Skin/soft tissue	Gastrointestinal tract
Solid Tumor				
Oral Cavity and Pharynx	1.98* (1.06–3.39)	3.52 (2.12–5.50)	1.38(0.38–3.52)	1.88*(1.05–3.1)
Esophagus	1.49(0.85–2.42)	2.50* (1.00–5.14)	1.37(0.17–4.97)	1.21(0.39–2.83)
Stomach	1.15(0.69–1.8)	2.29* (1.10–4.22)	1.39(0.29–4.05)	2.96*(1.09–6.44)
Colorectal	0.98(0.80–1.19)	1.13(0.93–1.37)	1.11(0.62–1.83)	0.93(0.66–1.28)
Hepatobiliary	0.93(0.56–1.46)	1.16(0.73–1.76)	0.74(0.09–2.67)	1.13(0.52–2.15)
Pancreas	1.03(0.69–1.48)	0.88(0.56–1.32)	1.08(0.29–2.76)	1.02(0.51–1.83)
Lung and Bronchus	1.43* (1.08–1.85)	1.43* (1.06–1.88)	0.49* (0.23–0.94)	1.64* (1.07–2.40)
Melanoma of the Skin	1.38*(1.04–1.80)	1.15(0.81–1.58)	1.17(0.43–2.56)	0.53(0.21–1.09)
Other Non-Epithelial Skin	1.37(0.50–2.98)	4.43* (1.44–10.35)	–	2.39(0.65–6.12)
Breast	1.50* (1.10–1.98)	0.98(0.80–1.20)	0.97(0.50–1.70)	1.01(0.69–1.41)
Corpus and Uterus, NOS	1.10(0.71–1.63)	1.16(0.73–1.74)	1.18(0.24–3.44)	1.05(0.42–2.16)
Ovary	0.76(0.35–1.45)	0.85(0.39–1.62)	–	0.55(0.07–1.99)
Prostate	0.83* (0.70–0.98)	1.02(0.86–1.20)	1.00(0.63–1.49)	1.14(0.90–1.43)
Urinary Bladder	1.17(0.9–1.49)	1.79* (1.18–2.61)	1.20(0.55–2.28)	2.23* (1.22–3.74)
Kidney and Renal Pelvis	4.28* (2.14–7.67)	3.14* (1.26–6.48)	2.18(0.94–4.30)	1.11(0.55–1.99)
Thyroid	4.10*(1.12–10.49)	12.64*(6.06–23.25)	27.73* (5.72–81.03)	1.32(0.36–3.38)
All Solid Tumors	1.27*(1.14–1.42)	1.30* (1.15–1.46)	1.01(0.83–1.21)	1.27*(1.05–1.53)
Hematologic Malignancies				
Hodgkin Lymphoma	11.29*(5.41–20.76)	10.85*(3.98–23.61)	3.30(0.08–18.37)	3.8(0.78–11.10)
Myeloma	0.58(0.25–1.14)	0.64(0.27–1.25)	–	0.57(0.12–1.67)
All Leukemia	3.44*(2.35–4.86)	1.21(0.82–1.72)	0.80(0.17–2.35)	1.41(0.79–2.32)
Lymphocytic Leukemia	0.28* (0.08–0.71)	0.54(0.22–1.12)	0.52(0.01–2.91)	0.75(0.21–1.93)
Myeloid and Monocytic Leukemia	7.75*(5.27–11.01)	2.69*(1.29–4.99)	1.25(0.15–4.52)	1.94(0.89–3.68)
All Hematologic Malignancies	2.16*(1.66–2.78)	1.85* (1.36–2.45)	2.05* (1.30–3.07)	1.23(0.87–1.68)
Kaposi Sarcoma	34.75*(11.28–81.09)	36.98*(10.08–94.69)	–	2.88(0.07–16.02)
Miscellaneous	1.2(0.77–1.77)	0.75(0.42–1.24)	0.72(0.09–2.61)	0.84(0.34–1.72)
All Sites	1.16*(1.09–1.23)	1.18*(1.11–1.26)	1.09(0.91–1.29)	1.16*(1.05–1.27)
All Sites excluding Non-Melanoma Skin	1.15*(1.09–1.22)	1.18*(1.11–1.26)	1.09(0.92–1.30)	1.15*(1.04–1.27)

* P<0.05.

Table 2a

Cancer site-specific standardized incidence ratios (O/E Ratios and 95% CIs) for second malignant neoplasm by site of first primary cancer.

	Head/Neck	Kidney	Skeletal tissue	Lung
Solid Tumor				
Oral Cavity and Pharynx	5.07* (1.38–12.97)	–	1.54(0.19–5.58)	4.61(0.56–16.67)
Esophagus	0.61(0.02–3.40)	–	1.62(0.04–9.03)	–
Stomach	1.02(0.21–2.98)	–	2.27(0.27–8.19)	3.00(0.08–16.73)
Colorectal	2.43*(1.39–3.95)	–	0.90(0.29–2.10)	0.87(0.11–3.16)
Hepatobiliary	2.07(0.83–4.26)	–	0.89(0.02–4.94)	–
Pancreas	1.11(0.36–2.60)	–	0.64(0.02–3.57)	–
Lung and Bronchus	0.94(0.57–1.45)	–	1.06(0.46–2.09)	2.29(0.92–4.72)
Melanoma of the Skin	7.48* (2.04–19.14)	–	0.42(0.01–2.34)	–
Other Non-Epithelial Skin	2.95(0.36–10.66)	–	–	–
Breast	1.03(0.58–1.70)	2.09(0.25–7.55)	1.07(0.39–2.33)	0.63(0.08–2.29)
Corpus and Uterus, NOS	2.36(0.95–4.87)	–	1.73(0.21–6.25)	–
Ovary	1.86(0.38–5.44)	–	3.36(0.41–12.16)	–
Prostate	0.94(0.60–1.39)	2.03(0.42–5.92)	1.05(0.50–1.92)	0.82(0.10–2.97)
Urinary Bladder	0.70(0.26–1.51)	2.16(0.05–12.04)	1.30(0.36–3.43)	0.89(0.02–4.96)
Kidney and Renal Pelvis	7.13* (1.47–20.85)	–	14.39* (1.74–51.99)	15.70* (1.90–56.71)
Thyroid	2.15(0.44–6.27)	–	4.39(0.91–12.83)	–
All Solid Tumors	1.31* (1.12–1.53)	0.96(0.39–1.98)	1.74* (1.13–2.57)	2.30* (1.05–4.37)
Hematologic Malignancies				
Hodgkin Lymphoma	25.76* (3.12–93.07)	–	5.89(0.15–32.79)	68.87* (1.72–378.17)
Myeloma	0.47(0.01–2.62)	8.19(0.21–45.63)	–	6.71(0.81–24.24)
All Leukemia	1.39(0.51–3.02)	–	0.63(0.02–3.51)	4.77(0.98–13.94)
Lymphocytic Leukemia	0.47(0.01–2.60)	–	–	–
Myeloid and Monocytic Leukemia	5.64* (1.54–14.45)	–	1.47(0.04–8.17)	19.12* (2.32–69.08)
All Hematologic Malignancies	2.87* (1.57–4.82)	2.74(0.33–9.89)	1.24(0.45–2.70)	9.24*(1.12–33.38)
Kaposi Sarcoma	47.07*(1.19–262.27)	–	–	469.36*(56.84–1695.48)
Miscellaneous	0.58(0.07–2.10)	–	–	–
All Sites	1.37* (1.19–1.58)	1.10(0.50–2.08)	1.27(0.99–1.62)	1.66*(1.15–2.32)
All Sites excluding Non-Melanoma Skin	1.36* (1.18–1.57)	1.10(0.50–2.09)	1.28(0.99–1.62)	1.67*(1.16–2.33)

* P<0.05.

Results

Patient characteristics

A total of 40,714 patients diagnosed with stage I/II DLBCL were included from the SEER database from 1983 to 2015. Among them, 18,967

(46.59%) patients' primary sites were extranodal, with the gastrointestinal tract (GI tract), head/neck and skin/soft tissue the most common extranodal sites of involvement. Patient characteristics are outlined in [Table 1](#). Briefly, age distribution in nodal DLBCL was as follows: 15–39 years (AYAs) 13.91%, 40–60 years (adults) 27.61%, and >60 years (the elderly) 58.47%. The elderly group comprised the largest propor-

Table 2b
Cancer site-specific standardized incidence ratios (O/E Ratios and 95% CIs) for second malignant neoplasm by site of first primary cancer.

	Uterus/uterine appendages	Thyroid	Liver/pancreas	Breast tissue	Other
Solid Tumor					
Oral Cavity and Pharynx	–	–	5.82* (1.20–17.01)	–	1.45(0.04–8.09)
Esophagus	–	15.05* (3.1–43.98)	–	–	–
Stomach	–	–	–	–	–
Colorectal	1.44(0.04–8.02)	1.35(0.67–2.42)	2.01(0.65–4.69)	0.70(0.09–2.54)	1.23(0.33–3.15)
Hepatobiliary	–	–	16.07* (1.95–58.04)	–	–
Pancreas	–	–	2.90(0.35–10.49)	–	–
Lung and Bronchus	7.41* (1.53–21.66)	0.98(0.47–1.80)	1.70(0.62–3.71)	1.19(0.32–3.05)	0.82(0.22–2.11)
Melanoma of the Skin	–	1.65(0.45–4.21)	2.08(0.25–7.51)	–	2.19(0.45–6.39)
Other Non-Epithelial Skin	–	–	–	–	–
Breast	–	1.27(0.71–2.10)	1.19(0.25–3.48)	1.11(0.45–2.29)	–
Corpus and Uterus, NOS	–	0.82(0.10–2.96)	–	–	2.26(0.27–8.16)
Ovary	–	0.75(0.02–4.17)	–	1.49(0.04–8.33)	–
Prostate	–	0.70(0.23–1.64)	0.74(0.15–2.17)	2.97(0.08–16.54)	0.19(0–1.08)
Urinary Bladder	–	0.60(0.07–2.18)	1.37(0.17–4.95)	–	5.79* (1.19–16.91)
Kidney and Renal Pelvis	6.14(0.16–34.19)	0.57(0.01–3.19)	–	13.30* (1.61–48.05)	1.09(0.03–6.09)
Thyroid	–	35.69* (4.32–128.91)	4.18(0.11–23.26)	2.31(0.06–12.87)	–
All Solid Tumors	1.09(0.44–2.24)	0.96(0.72–1.24)	2.84* (1.51–4.86)	1.01(0.62–1.54)	0.78(0.49–1.18)
Hematologic Malignancies					
Hodgkin Lymphoma	–	7.06(0.18–39.32)	–	–	–
Myeloma	–	1.05(0.03–5.87)	–	–	–
All Leukemia	–	1.00(0.12–3.61)	–	–	1.06(0.03–5.89)
Lymphocytic Leukemia	–	–	–	–	2.07(0.05–11.51)
Myeloid and Monocytic Leukemia	–	2.32(0.28–8.37)	–	–	–
All Hematologic Malignancies	1.83(0.05–10.18)	2.98* (1.09–6.49)	–	1.97(0.54–5.04)	1.04(0.22–3.05)
Kaposi Sarcoma	–	–	130.80* (2.63–578.34)	–	–
Miscellaneous	–	1.76(0.36–5.13)	–	1.69(0.04–9.44)	–
All Sites	1.12(0.48–2.21)	0.99(0.77–1.26)	1.47* (1.02–2.06)	1.10(0.72–1.61)	0.78(0.51–1.16)
All Sites excluding Non-Melanoma Skin	1.13(0.49–2.22)	0.99(0.77–1.26)	1.48* (1.03–2.07)	1.11(0.72–1.62)	0.79(0.51–1.16)

* $P < 0.05$.

tion in patients with DLBCL involving extranodal sites, except for the uterus/uterine appendages sites where the adults group was prevalent (44.88%). Male patients made up 52.32% of the nodal DLBCL patients and also a large proportion of most extranodal DLBCL sites, except for the uterus/uterine appendages sites (0%), thyroid sites (29.86%), and breast tissue sites (2.88%).

Features of patients with SMN

Overall, 2090 (9.61%) SMN were diagnosed in 21,747 patients with nodal DLBCL, and 2070 (10.91%) SMN were diagnosed in 18,967 patients with extranodal DLBCL. Among nodal and extranodal DLBCL patients who subsequently developed SMNs, the median time between the first DLBCL and SMN was the same, with a difference of 68 months. In extranodal DLBCL patients with 11 different primary extranodal sites, the shortest median latency between first DLBCL diagnosis and SMN diagnosis was observed in the lung sites, with a difference of 38 months. The clinical characteristics of the patients who developed SMNs are summarized in Tables S1.

Overall risk of SMN for DLBCL patients compared with the US general population

The risk of SMN among patients with nodal DLBCL (SIR, 1.16; 95% CI, 1.09–1.23, Table 2) and extranodal DLBCL (SIR, 1.18; 95% CI, 1.11–1.26, Table 2) was similar and higher than the risk in the US general population, resulting in 20.84 and 27.82 excess cancers per 10,000 person-years (PYs), respectively.

In DLBCL patients with 11 different primary extranodal sites, only four sites had significantly higher risks of SMNs than the US general population, including the GI tract, head/neck, lung and liver/pancreas. The highest SIR of SMN was observed in the lung sites (SIR, 1.66; 95% CI, 1.15–2.32; Table 2), and it explicitly associated with an increased incidence of Hodgkin lymphoma (SIR, 68.87; 95% CI, 1.72–378.17) and kidney/renal pelvis cancer (SIR, 15.70; 95% CI, 1.90–56.71).

Latency and risk

In patients with nodal DLBCL, there was a gradually increasing SIR of SMN during the follow-up period, remaining high for 10+ years after the diagnosis of nodal DLBCL (Table 3). After 10+ years of follow-up, nodal DLBCL patients had developed 42.53 excess cancers per 10,000 PYs.

Similarly, extranodal DLBCL has the highest risk of SMNs more than 10 years after diagnosis (<1 year: SIR=1.01; 1–5 year: SIR=1.14; 5–10 year: SIR=1.16; ≥10 year: SIR=1.32; $P < 0.05$), underscoring the persistent increased locoregional risk. There was a 22%, 44%, 66%, 123% and 151% increased risk of SMN 10 years after primary GI tract DLBCL (SIR, 1.22; 95% CI, 1.02–1.45), primary head/neck DLBCL (SIR, 1.44; 95% CI, 1.05–1.91), primary skeletal tissue DLBCL (SIR, 1.66; 95% CI, 1.09–2.41), primary lung DLBCL (SIR, 2.23; 95% CI, 1.07–4.09) and primary liver/pancreas DLBCL diagnosis (SIR, 2.51; 95% CI, 1.34–4.3), respectively.

Sex-specific risk

We observed that women had a slightly increased risk of developing SMNs in nodal DLBCL (SIR for a woman, 1.23; 95% CI, 1.13–1.35; SIR for a man, 1.10; 95% CI, 1.02–1.19, Table 3). However, for the extranodal DLBCL survivors, man accounted for a significant proportion of the increased risk of secondary malignancies (SIR for a woman, 1.16; 95% CI, 1.05–1.27; SIR for a man, 1.20; 95% CI, 1.10–1.30), especially those with primary sites in the GI tract (SIR for a woman, 1.15; 95% CI, 0.96–1.35; SIR for a man, 1.16; 95% CI, 1.03–1.31) and lung (SIR for a woman, 1.48; 95% CI, 0.86–2.37; SIR for a man, 1.89; 95% CI, 1.10–3.02).

Age-specific risk

We divided patients with nodal DLBCL into 3 groups according to age at the time of diagnosis. We demonstrated that the risk of SMN was

Table 3
Standardized Incidence (O/E Ratios and 95% CIs) Values for Development of Second Malignant Neoplasm (SMN) According to Patient Characteristics by site Group.

Site group	Sex		Age,y		
	Male	Female	15–39	40–60	>60
Lymph Node	1.10* (1.02–1.19)	1.23* (1.13–1.35)	2.34* (1.91–2.85)	1.22* (1.09–1.36)	1.05(0.97–1.13)
Extranodal	1.20* (1.10–1.30)	1.16* (1.05–1.27)	1.91* (1.34–2.64)	1.34* (1.19–1.51)	1.10* (1.02–1.19)
Skin and soft tissue	1.09(0.87–1.35)	1.09(0.81–1.44)	0.34(0.01–1.88)	1.19(0.85–1.62)	1.08(0.87–1.32)
Gastrointestinal tract	1.16* (1.03–1.31)	1.15(0.96–1.35)	2.02* (1.05–3.54)	1.15(0.92–1.41)	1.13* (1.01–1.27)
Head/Neck	1.38* (1.14–1.65)	1.36* (1.07–1.71)	2.30(0.84–5.00)	1.67* (1.26–2.19)	1.26* (1.06–1.49)
Kidney	1.24(0.46–2.7)	0.89(0.18–2.59)	–	0.62(0.08–2.25)	1.40(0.56–2.89)
Skeletal tissue	1.36(0.99–1.82)	1.14(0.72–1.71)	3.39* (1.63–6.24)	1.49(0.96–2.20)	0.97(0.67–1.37)
Lung	1.89* (1.10–3.02)	1.48(0.86–2.37)	1.88(0.05–10.48)	3.08* (1.64–5.27)	1.27(0.78–1.96)
Uterus/uterine appendages	–	1.12(0.48–2.21)	–	1.51(0.55–3.29)	0.87(0.11–3.15)
Thyroid	0.85(0.52–1.31)	1.07(0.78–1.42)	–	0.91(0.50–1.52)	1.03(0.77–1.34)
Liver/pancreas	1.55(0.97–2.35)	1.35(0.7–2.36)	4.24 (0.51–15.30)	2.54* (1.31–4.43)	1.12(0.69–1.73)
Breast tissue	0.95(0.02–5.28)	1.11(0.72–1.64)	2.14(0.26–7.72)	2.04* (1.02–3.65)	0.75(0.40–1.29)
Other	0.84(0.47–1.38)	0.72(0.34–1.32)	1.89(0.23–6.84)	1.2(0.58–2.21)	0.58* (0.31–0.99)

* P<0.05. O/E:observed/expected; CI: confidence interval.

Table 3a
Standardized Incidence (O/E Ratios and 95% CIs) Values for Development of Second Malignant Neoplasm (SMN) According to Patient Characteristics by site Group.

Site group	Latency periods, m				Era of diagnosis	
	2–12	13–60	61–120	120+	1983–2005	2006–2015
Lymph Node	0.97(0.78–1.19)	1.15* (1.04–1.27)	1.07(0.94–1.20)	1.31* (1.18–1.45)	1.12* (1.05–1.20)	1.31* (1.14–1.50)
Extranodal	1.01(0.81–1.25)	1.14* (1.02–1.27)	1.16* (1.02–1.30)	1.32* (1.17–1.47)	1.14* (1.07–1.23)	1.36* (1.18–1.57)
Skin and soft tissue	1.39(0.81–2.22)	1.19(0.88–1.57)	0.99(0.68–1.39)	0.97(0.67–1.34)	0.97(0.79–1.18)	1.68* (1.16–2.35)
Gastrointestinal tract	0.65* (0.4–0.99)	1.11(0.93–1.32)	1.30* (1.09–1.55)	1.22* (1.02–1.45)	1.14* (1.02–1.27)	1.25(0.96–1.60)
Head/Neck	1.33(0.82–2.03)	1.38* (1.09–1.73)	1.33(0.99–1.74)	1.44* (1.05–1.91)	1.33* (1.13–1.56)	1.56* (1.12–2.11)
Kidney	2.3(0.28–8.31)	0.38(0.01–2.12)	1.35(0.28–3.94)	1.21(0.25–3.53)	1.10(0.44–2.27)	1.07(0.13–3.888)
Skeletal tissue	1.23(0.45–2.68)	1.04(0.62–1.64)	1.13(0.65–1.83)	1.66* (1.09–2.41)	1.25(0.94–1.64)	1.35(0.74–2.27)
Lung	2.42(0.89–5.27)	1.48(0.77–2.59)	1.10(0.41–2.40)	2.23* (1.07–4.09)	1.35(0.84–2.07)	2.63* (1.40–4.50)
Uterus/uterine appendages	1.98(0.05–11.06)	0.57(0.01–3.19)	0.57(0.01–3.16)	1.60(0.52–3.74)	1.02(0.37–2.22)	1.60(0.19–5.77)
Thyroid	0.57(0.12–1.66)	0.89(0.54–1.39)	0.85(0.49–1.35)	1.34(0.89–1.93)	1.04(0.80–1.34)	0.60(0.19–1.40)
Liver/pancreas	0.36(0.01–1.99)	1.82* (1.04–2.95)	0.64(0.17–1.63)	2.51* (1.34–4.3)	1.34(0.86–1.99)	1.95(0.94–3.59)
Breast tissue	2.08(0.76–4.52)	0.32(0.07–0.93)	1.44(0.66–2.72)	1.59(0.69–3.14)	1.26(0.79–1.90)	0.66(0.18–1.68)
Other	0.26(0.01–1.47)	0.87(0.41–1.59)	0.35(0.07–1.03)	1.38(0.69–2.46)	0.78(0.47–1.22)	0.8(0.29–1.74)

* P<0.05. O/E:observed/expected; CI: confidence interval.

higher in AYA population (SIR, 2.34; 95% CI, 1.91–2.85, Table 3) versus the adults (SIR, 1.22; 95% CI, 1.09–1.36) and the elderly (SIR, 1.05; 95% CI, 0.97–1.13).

In extranodal DLBCL patients, the AYA population also had the highest risk of SMN (SIR, 1.91; 95% CI, 1.34–2.64), especially those with primary sites in the GI tract (SIR, 2.02; 95% CI, 1.05–3.54) and skeletal tissue (SIR, 3.39; 95% CI, 1.63–6.24). In contrast, there is an increased risk of SMN in adults group with primary sites in the head/neck (SIR, 1.67; 95% CI, 1.26–2.19), lung (SIR, 3.08; 95% CI, 1.64–5.27), liver/pancreas (SIR, 2.54; 95% CI, 1.31–4.43) and breast tissue (SIR, 2.04; 95% CI, 1.02–3.65). No changes in the risk of SMN associated with age were observed in extranodal DLBCL patients with the other primary sites.

Rituximab-containing therapeutics and risk

In patients with nodal DLBCL, there was a slightly increased risk of SMN after the introduction of rituximab-containing therapeutics (2006–2015: SIR, 1.31; 95% CI, 1.14–1.50; 1973–2005: SIR, 1.12; 95% CI, 1.05–1.20, Table 3).

In patients with extranodal DLBCL, the risk of SMN increased after the introduction of rituximab (2006–2015: SIR, 1.36; 95% CI, 1.18–1.57; 1973–2005: SIR, 1.14; 95% CI, 1.07–1.23). Particularly, patients with primary site in the skin and soft tissue (2006–2015: SIR, 1.68; 95% CI, 1.16–2.35; 1973–2005: SIR, 0.97; 95% CI, 0.79–1.18), head/neck (2006–2015: SIR, 1.56; 95% CI, 1.12–2.11; 1973–2005: SIR, 1.33; 95% CI, 1.13–1.56), and lung (2006–2015: SIR, 2.63; 95% CI, 1.40–4.50; 1973–2005: SIR, 1.35; 95% CI, 0.84–2.07) had a higher risk of SMN after the introduction of rituximab. In contrast, the risk of SMN in pa-

tients with primary sites in the GI tract declined significantly after the introduction of rituximab (2006–2015: SIR, 1.25; 95% CI, 0.96–1.60; 1973–2005: SIR, 1.14; 95% CI, 1.02–1.27). There was no significant change in the risk of SMN after the introduction of rituximab in DLBCL patients with the other primary sites.

Distribution of SMN by the primary anatomic subsite of DLBCL

The risk of second solid tumors among extranodal DLBCL with primary sites in the GI tract (SIR, 1.27; 95% CI, 1.05–1.53, Table 2), head/neck (SIR, 1.31; 95% CI, 1.12–1.53), skeletal tissue (SIR, 1.74; 95% CI, 1.13–2.57), lung (SIR, 2.30; 95% CI, 1.05–4.37) and liver/pancreas (SIR, 2.84; 95% CI, 1.51–4.86) were significantly increased statistically. Significantly increased incidences were observed for secondary kidney and renal pelvis cancers (SIR, 3.14; 95% CI, 1.26–6.48) and second thyroid cancers (SIR, 12.64; 95% CI, 6.06–23.25) within 1 year post extranodal DLBCL diagnosis, while significantly increased incidences for second oral cavity and pharynx cancers (SIR, 3.52; 95% CI, 2.12–5.50), second esophagus cancers(SIR, 2.50; 95% CI, 1.00–5.14), second stomach cancers (SIR, 2.29; 95% CI, 1.10–4.22), second lung and bronchus cancers (SIR, 1.43; 95% CI, 1.06–1.88), and second urinary bladder cancers (SIR, 1.79; 95% CI, 1.18–2.61) were noticed more than 10 years post extranodal DLBCL diagnosis. The extranodal DLBCL patients with primary sites in the GI tract, thyroid and liver/pancreas had the highest incidences of secondary stomach cancer (SIR, 2.96; 95% CI, 1.09–6.44), second thyroid cancer (SIR, 35.69; 95% CI, 4.32–128.91), and second hepatobiliary cancer (SIR, 16.07; 95% CI, 1.95–58.04), respectively.

Table 4
Univariate and Multivariate Analysis of Prognostic Factors for Overall Survival in Diffuse Large B-Cell Lymphoma Patients from the SEER Database.

Variable	Univariate analysis HR (95% CI)	P	Multivariate analysis HR (95% CI)	P
Age,y				
15–39	1	Ref.	1	Ref.
40–60	1.661(1.546–1.785)	0.000	1.725(1.605–1.854)	0.000
>60	5.066(4.743–5.412)	0.000	5.432(5.081–5.807)	0.000
Sex				
Male	1	Ref.	1	Ref.
Female	1.040(1.010–1.070)	0.008	0.909(0.883–0.936)	0.000
Race				
White	1	Ref.	1	Ref.
Black	0.916(0.862–0.974)	0.005	1.227(1.154–1.304)	0.000
Other	0.884(0.837–0.933)	0.000	0.915(0.867–0.967)	0.002
Era of diagnosis				
1983–2005	1	Ref.	1	Ref.
2006–2015	0.746(0.721–0.771)	0.000	0.704(0.680–0.728)	0.000
SMN				
No	1	Ref.	1	Ref.
Yes	0.861(0.825–0.899)	0.000	0.709(0.679–0.740)	0.000
Site				
Lymph Node	1	Ref.	1	Ref.
Skin and soft tissue	1.084(1.018–1.155)	0.012	0.961(0.903–1.024)	0.221
Gastrointestinal tract	1.227(1.180–1.276)	0.000	1.057(1.016–1.100)	0.006
Head/Neck	0.983(0.936–1.032)	0.484	0.925(0.880–0.971)	0.002
Kidney	1.168(0.953–1.431)	0.135	1.054(0.860–1.291)	0.613
Skeletal tissue	0.665(0.603–0.734)	0.000	0.750(0.680–0.827)	0.000
Lung	1.471(1.323–1.636)	0.000	1.426(1.282–1.586)	0.000
Uterus/uterine appendages	0.461(0.350–0.606)	0.000	0.665(0.504–0.876)	0.004
Thyroid	0.888 (0.805–0.980)	0.018	0.749(0.678–0.826)	0.000
Liver/pancreas	1.443(1.288–1.617)	0.000	1.333(1.189–1.493)	0.000
Breast tissue	1.047(0.932–1.176)	0.438	0.964(0.858–1.084)	0.542
Other	1.077(0.992–1.169)	0.076	0.987(0.910–1.071)	0.759

HR, hazard ratio; CI, confidence interval.

The increased SIR of secondary hematologic tumors was pronounced within 1–5 years after the diagnosis of extranodal DLBCL, with primary sites in the skin/soft tissue (SIR, 2.05; 95% CI, 1.30–3.07), head/neck (SIR, 2.87; 95% CI, 1.57–4.82), lung (SIR, 9.24; 95% CI, 1.12–33.38), and thyroid (SIR, 2.98; 95% CI, 1.09–6.49). The most common second hematologic cancers were: Hodgkin lymphoma in survivors with primary sites in the head/neck (SIR, 25.76; 95% CI, 3.12–93.07) and lung (SIR, 68.87; 95% CI, 1.72–378.17); myeloid and monocytic leukemia with primary sites in the head/neck (SIR, 5.64; 95% CI, 1.54–14.45) and lung (SIR, 19.12; 95% CI, 2.32–69.08).

Survival analysis

We performed a survival analysis to estimate the independent effect of the individual extranodal primary sites on the prognosis, and the results are shown in Table 4. Per multivariate analysis, the average prognosis estimates derived from the whole patients with various extranodal DLBCL failed to show any statistically significant difference when compared to patients with nodal DLBCL (Table S2). However, when referring to detailed extranodal sites, we observed that head and neck sites ($p < 0.001$, HR: 0.925, CI: 0.880–0.971), skeletal tissue sites ($p < 0.001$, HR: 0.750, CI: 0.680–0.827), uterus/uterine appendages sites ($p = 0.004$, HR: 0.665, CI: 0.504–0.876), and thyroid sites ($p < 0.001$, HR: 0.749, CI: 0.678–0.826) were associated with better prognosis, while GI tract sites ($p = 0.006$, HR: 1.057, CI: 1.016–1.100), lung sites ($p < 0.001$, HR: 1.426, CI: 1.282–1.586), and liver/pancreas ($p < 0.001$, HR: 1.333, CI: 1.189–1.493) were linked to worse prognosis, compared to primary lymph node sites. All the comparisons above were implemented after the multivariate adjustment for age at the time of diagnosis, sex, race, the era of diagnosis, and the ann arbor stage.

Both the univariate model and multivariate adjustment showed that patients with SMN did not have worse survival rate than those without SMN ($p < 0.001$, HR: 0.709, CI: 0.679–0.740), which applied to both

nodal and extranodal DLBCL patients (Table 4). Compared with patients without SMN, patients with SMN demonstrated significantly greater cumulative survival incidence for 5 years among both nodal and extranodal DLBCL (Fig. 1A-1B).

Discussion

As far as we know, this is the first large-population based study which assesses different risk and the distribution of SMN based on primary anatomic subsite involved in DLBCL. We have demonstrated that patients with extranodal DLBCL had a more than 18% increased risk of secondary cancers than the US general population, which was similar to patients with nodal DLBCL who had a more than 16% increased risk of secondary cancers than the US general population, and moreover, the risk of SMN was significantly elevated over time. The risk of SMN significantly differs according to the location of DLBCL, age, sex, latency and the era of diagnosis. The extranodal DLBCL patients with primary sites in lung had the highest risk of developing secondary solid tumors more than 10 years and secondary hematologic cancers within 1–5 years after primary lung DLBCL diagnosis, with Hodgkin lymphoma being the most common type of SMN.

Our data indicate that primary lung DLBCL has the highest risk of developing SMN. This increased risk could be attributed to treatment-related factors, including the use of radiation [12–14]. We report that the risk of SMN increased significantly with a prolonged latency per our findings, which supports the hypothesis that treatment-related factors is the potential cause of increased risk for SMN in the future. Another important cause is that many previous articles have indicated that the pathogenesis of primary lung DLBCL is associated with underlying immunosuppression and autoimmune disease [15–17]. The humoral and cell-mediated immune impaired may create an environment that allows the occurrence and development of SMNs among individuals with primary lung DLBCL [18]. In addition, primary lung DLBCL is associated

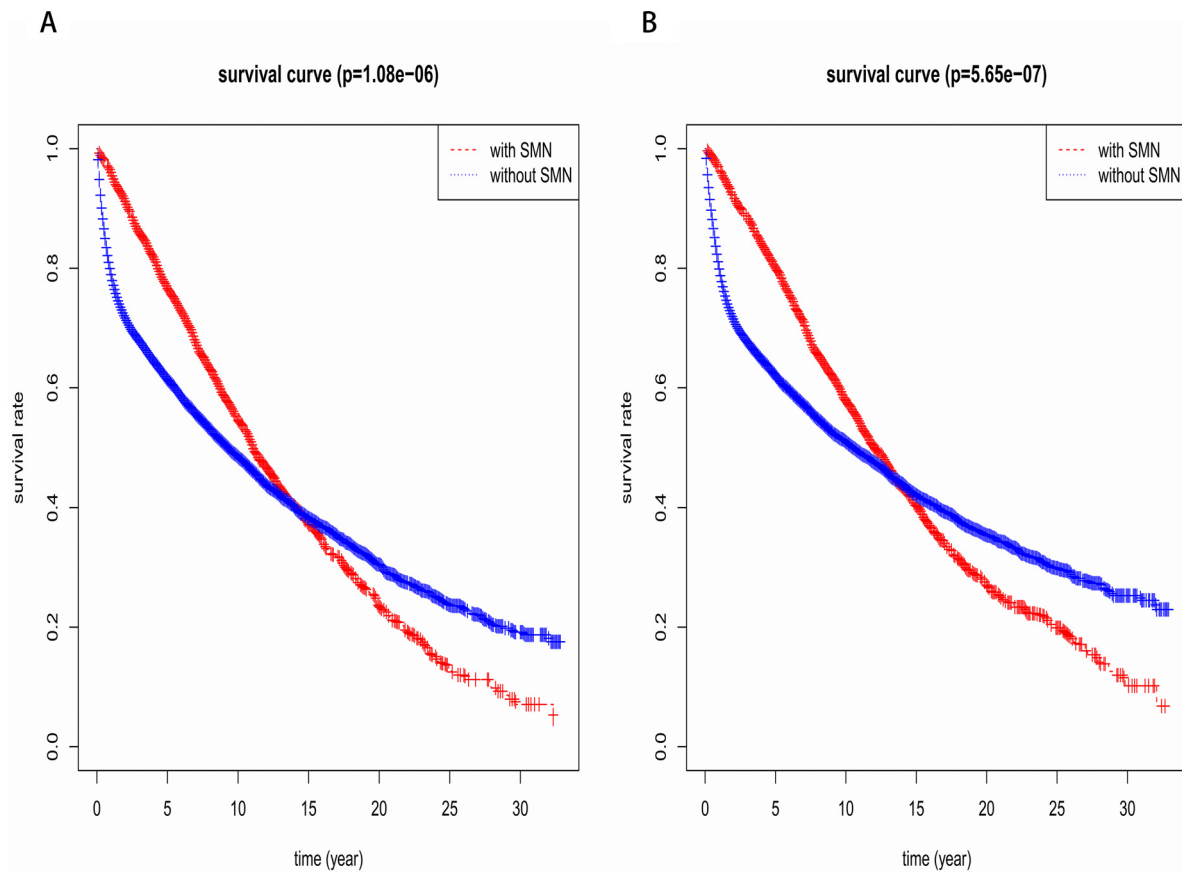


Fig. 1. Kaplan-Meier for OS in groups with SMN and groups without SMN in extranodal DLBCL patients(A) and in nodal DLBCL patients(B).

with a potential reactivation /chronic persistent viral infection (e.g. EBV positivity) [19], which play a key role in the development of cancer [20]. Furthermore, patients with primary lung DLBCL often carry BCL2 translocations, P53 alterations or MYC aberration, which are all factors related to the occurrence of SMNs [16]. So it is important that physicians should keep this risk in mind, and focus on the screening of SMN after primary lung DLBCL diagnosis.

We have also shown in this investigation that compared with the adult and elderly groups, the AYA population with nodal DLBCL and extranodal DLBCL originating from gastrointestinal tract and skeletal tissue exhibited the highest risk of developing SMN, which is consistent with previous reports [4,21,22]. It is possible that young cancer survivors completed cancer treatment at an early age, and the risk associated with treatment is the underlying cause of higher risk for SMN development in the future [21,23]. Another important cause is that younger cancer survivors have a longer survival time, which results in more opportunities to develop a second cancer. In addition, increasing evidence shows that young patients tend to have genetic predispositions that are associated with cancer susceptibility [24,25]. The increasing risk of SMN in the AYA population may also be affected by cancer predisposition syndromes. [25]. Thus, when AYA patients transit from pediatric to adult oncology, physicians should be informed of the need to keep an eye on the presence of SMN.

We have observed that nodal DLBCL and extranodal DLBCL with primary sites in the skin and soft tissue, head/neck and lung DLBCL have a higher risk of developing SMN in the period 2006–2015 comparing with the period of 1983–2005. The potential explanations for this finding are that the significantly increased survival rate after the introduction of rituximab-containing therapeutics in the period 2006–2015 resulted in more opportunities to develop SMNs, a fact supported by previous re-

ports [26,27]. Indeed, rituximab therapy did not improve the prognosis of primary kidney DLBCL patients significantly due to a high rate of central nervous system relapse and acute kidney injury [28,29]. We found that there was no difference in the risk of SMN in primary kidney DLBCL patients diagnosed in the rituximab era or pre-rituximab era, which further indicated that improved survival rate after the introduction of rituximab was an essential cause of SMN occurrence. In addition, compared with the period of 1983–2005, the period 2006–2015 has more advanced imaging technology, more accurate laboratory examination results, as well as a more standardized follow-up policy and screening guidelines for cancer patients, which may lead that more SMNs were found in DLBCL patients.

Patients diagnosed with the primary gastrointestinal tract, thyroid and liver/pancreas DLBCL during our investigation had the highest incidence of secondary stomach cancer, secondary thyroid cancer and secondary hepatobiliary cancer, respectively. The characteristics of these SMNs reflected the original sites, which may mirror the field effect and long-term risk of recurrence related to the original disease. Previous studies have also reported a similar phenomenon [30–32]. In a large population-based study of patients diagnosed initially with colorectal extramammary Paget cancer, an increased risk was only observed for secondary colorectal malignancies [33]. It is probable that embryo-associated tissues that potentially react to carcinogens and environmental exposures analogously and might be similarly subject to abnormal epigenetic alterations are the bases of the increased risk. Conversely, such epigenetic alterations could make these tissues more prone to cancer development [31]. It is also plausible that the SMN may be affected by the same genetic predisposition as the initial primary cancer, such as familial cancer syndromes [34]. However, the data of genetic information is not available in the SEER database applied, we could not evaluate

the relationship between genetic predisposition and the distinct clinico-pathological characteristics and prognosis of SMN in our analysis.

In the survival analysis, we found that DLBCL patients with SMN did not have worse survival rate than those without SMN after multivariate adjustment. A previous study reported that waldenström macroglobulinemia (WM) patients with second prostate or lung cancer had better outcomes than controls [35]. Another large retrospective study also shown that OS and cancer specific survival did not differ among chronic lymphocytic leukemia (CLL) with second ovary (HR for OS, 1.04; 95% CI, 0.78 to 1.38; $P = 0.81$) or pancreas cancer (HR for OS, 0.97; 95% CI, 0.81 to 1.18; $P = 0.78$) and controls [36]. The reasons might be that: (1) Because of improved therapies, patients now survived longer. Increased survival correlates with late influence which includes the development of a SMN, while patients with poor prognosis fail to develop SMN due to the short survival period [26,37]. (2) Patients with SMN may benefit from aggressive screening strategies and early detection, and early detection could decrease mortality. For example, during DLBCL staging or follow-up, small pulmonary nodules by screening CT could be accidentally diagnosed which may contribute to the high proportion of early-stage pulmonary cancer [38]. (3) Patients with SMN may be more likely to receive active treatment than those without SMN. A recent study found that patients who were previously diagnosed with solid or hematological malignancies and who had received chemotherapy or had been seen by a hematologist/oncologist within one year before the diagnosis were more likely to receive active treatment [39]. (4) Previous DLBCL diseases or DLBCL-specific treatment may have already altered the immune microenvironment. It is well known that complex immune interactions occur between the host, immune system and tumor especially in some tumor types (for example, melanoma [40] and renal cell carcinoma [41]), which may be related to this phenomenon. Multicenter studies with thorough individual data are urgently required to further explore the potential explanations for our observed consequences.

Some limitations, based on the information available in the SEER database, should be taken into account when interpreting our findings. First, no information on the baseline performance status, B-symptoms, bulky disease, and lactate dehydrogenase levels was available. Therefore, we could not adjust the bias from their distinct distribution in extranodal or nodal lymphomas and could not assess the possibility of unfavorable risk factors in patients. Nevertheless, we made adjustments for all available patient and tumor characteristics. Second, information regarding therapy is limited. In SEER, there is no information on chemotherapy, which is an essential modality for DLBCL treatment. We partially addressed this issue by separating the era of diagnosis into pre-rituximab and rituximab use. Third, information on staging modalities is limited. Adequate staging is the cornerstone of treatment selection to achieve the best prognosis for patients. FDG-PET can more accurately evaluate the stage than conventional CT, but this technique is not recorded in the database. Fourth, information on smoking, family history, and HIV status that could affect the risk of SMNs, DLBCL, and extranodal involvement was not available.

Conclusions

To conclude, our study demonstrates that patients with extranodal DLBCL have an increased risk of SMN than the US general population, and provide evidence that the risk of SMN significantly differs according to the location of DLBCL, age, sex, latency and the era of diagnosis. In addition, different anatomical sites tend to develop different types of second tumors, reflecting that the SMN may be affected by the field effect and long-term risk of recurrence related to the original sites. Although the precise mechanisms underlying this pattern of increased risk are unclear, these results suggest that strategies for cancer surveillance after extranodal DLBCL diagnosis may need to be individualized according to the subsite of extranodal DLBCL.

Declarations

Ethics approval and consent to participate

This study was fully compliance with the publication guidelines provided by SEER. The data were obtained from SEER, so the approval of ethics committee was not needed.

Availability of data and materials

The data were obtained from the SEER database (<https://seer.cancer.gov/seerstat/>), which is freely accessible to the public.

Competing interests

The authors declare no conflict of interest.

Consent for publication

Not applicable.

Authors' contributions

XJ Yin and AS Xu collected and analyzed the data, wrote the paper; ZL Huang, FJ Fan, YJ Wang, L Chen and GH Cui research literature, edit the paper and revise the paper; CY Sun and Y Hu conceived and designed this study, analyzed the data, wrote the paper; and all authors reviewed the paper, and approved the final manuscript.

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Table S1. Patient with SMN characteristics.

Table S2. Univariate and Multivariate Analysis of Prognostic Factors for Overall Survival in nodal and extranodal DLBCL.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Xuejiao Yin: Conceptualization, Methodology, Software, Data curation, Formal analysis, Writing – original draft, Visualization. **Aoshuang Xu:** Visualization, Investigation, Validation. **Zhenli Huang:** Visualization, Investigation, Validation. **Fengjuan Fan:** Visualization, Investigation, Validation. **Yajun Wang:** Visualization, Investigation, Validation. **Lei Chen:** Validation. **Guohui Cui:** Supervision. **Yu Hu:** Supervision. **Chunyan Sun:** Writing – review & editing, Project administration, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2021.101106.

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