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Running Title: Second Primary Malignancies in DLBCL

Second Primary Malignancies in Diffuse Large B-cell Lymphoma Survivors with 40 Years of Follow-Up: Influence of Chemotherapy and Radiotherapy

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Declaration of interests

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.

Abstract:

Purpose: Previous studies have shown an increased risk of second primary malignancies (SPMs) in survivors of diffuse large B-cell lymphoma (DLBCL). As survivors are living longer due to intensification and improvements in therapy, we aimed to characterize SPM patterns in DLBCL patients by treatment modality.

Methods and Materials: Standardized incidence ratio (SIR) and absolute excess risk (AER) of SPMs were assessed in patients with primary DLBCL from 1975 to 2016 in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Subgroup analysis based on, sex, race, age at diagnosis, latency, and treatment modality were then performed. Propensity-score adjusted cumulative incidence curves were generated, stratified by treatment and accounting for death as a competing risk.

Results: In total, 45,946 patients with DLBCL were identified with a mean follow up of 70 months. Overall, 9.2% of patients developed an SPM with an SIR of 1.23 (95% confidence interval [CI] 1.20-1.27). There was no difference in SPM risk between males and females or black and white patients. Patients age <25 were particularly susceptible to development of SPMs, with a risk 2.5 times greater than patients age 50-74. Temporal patterns showed increasing risk of solid malignancies and decreasing risk of hematologic malignancies over time, with bladder cancer posing the greatest AER of any cancer type after 15 years. Patients treated with RT, CT, and CRT all had an increased risk of SPM development compared to the general population. The cumulative incidence of SPMs was lowest in patients treated with RT and highest in CRT. In the modern treatment era the cumulative incidence of SPM for patients treated with CT versus CRT were not significantly different.

Conclusion: In this large population based study, we demonstrate unique SPM risk patterns based on age, latency, and treatment modality that have important implications for treatment and screening of patients diagnosed with DLBCL.

Introduction

An estimated 80,470 people will be diagnosed with non-Hodgkin lymphoma (NHL) in the United States in the year 2022.[1] Survivors of NHL are at increased risk of developing second cancers, known as second primary malignancies (SPMs), and may be at greater risk of developing SPMs than survivors of other cancer types.[2-4] Long-term management of these patients can be challenging, as surveillance strategies are not well defined.

Survivors of diffuse large B-cell lymphoma (DLBCL), the most common subtype of NHL, are susceptible to this increased risk of SPMs.[5, 6] A variety of risk factors have been implicated including radiotherapy (RT), chemotherapy (CT), use of anti-CD20 monoclonal antibodies (i.e. rituximab), immunosuppression, demographics, and genetics.[7-10] With modern treatment advances, survivorship among DLBCL patients has greatly improved. The 5-year disease-specific survival rate has increased from 43% to 63% since 1995.[11] Given these improvements in survival, understanding patient and disease characteristics that predict for increased risk of SPMs has significant clinical implications. Current guidelines and recommendations for SPM screening are limited for DLBCL survivors.[12] Understanding the patterns of SPM development is crucial to guide cancer long-term follow up and surveillance.

In order to update the SPM risk with modern DLBCL treatments and survival outcomes, we utilized the bI·ǘʎƶƴI·f /I·ƴŎŜ Lƴǎǘʎǘǳǘŝǎ {ǳNJǾŝʎfI·ƴŎŝ 9LJʎŘŜϒʎƶfƶƎè I·ƴŘ 9ƴŘ wŜǎǳfǘǎ ό{99wύ LJNJƶƎNJI·ϒǎ ŘI·ǘI·ōI·ǎŜ ǿʎǘK updated diagnosis years from 1975 ς 2016.

Methods and Materials

The SEER 9 Regs Custom Data for Standardized Incidence Ratio (SIR) was used to identify patients who were diagnosed with a first primary DLBCL (lymphoma subtype recode/WHO 2008: 2(a)2.3 Diffuse large B-cell lymphoma[DLBCL]) between 1975-2016. The SEER*Stat Multiple Primary-SIR tool (version 8.3.8) was used to calculate the SIR as well as the absolute excess risk (AER). The SIR compares the number of SPMs in DLBCL survivors with the incidence rates of cancers for a matched U.S. population and is expressed as the ratio of observed (O) to expected (E) events (O/E). The AER gives the absolute number of excess events which occurred per 10,000 person years amongst DLBCL survivors when compared to a matched U.S population. These take into account age, sex, race, patient years at risk, and the year of DLBCL diagnosis. SPM was defined as a second malignancy occurring at least 6 months after the first primary DLBCL diagnosis. Only invasive malignances were included. Non-melanoma skin cancers were excluded. Patients who were recorded to have developed DLBCL as a second malignancy were excluded.

The risk of SPMs was evaluated in DLBCL survivors as a whole as well as stratified by sex, race, stage (including early-stage [stage I-II] and advanced-stage [stage III-IV]), and SPM subtype. Further subgroup analysis was performed to evaluate relationships between SPM risk and age at DLBCL diagnosis, time since DLBCL diagnosis in 5-year increments (latency), and treatment type including radiation therapy alone (RT), chemotherapy alone (CT), and chemotherapy and radiation (CRT). We compared subgroups to test for a heterogenous effect ς for example, whether each subgroup has a similar increased risk relative to their respective endemic populations. Statistical tests and 95% confidence intervals (CI) were based on the assumption that the observed number of SPM was distributed as a Poisson variable. The O/E ratio was deemed statistically significant when the 95% CI did not cross one. When comparing two subgroups, statistical significance was determined on the basis of 95% confidence intervals overlapping or not, which is a conservative assessment of significance when comparing intervals from two different

populations.[13, 14] Information regarding radiation dose, sites to which radiation therapy was directed, and chemotherapy regimens are not available currently in the SEER database and thus could not be included in the analysis.

Additional analysis was performed to compare incidence of SPMs between treatment cohorts following propensity score adjustment. For years with SEER data on Ann-Arbor staging (1983-2015), we estimated the propensity-score among treatment arms using a multinomial logistic regression and calculated matching weights.[15] Balancing covariates included age at diagnosis, race, year of diagnosis, sex, Ann Arbor Staging, and Health Service Area (HSA). Time from DLBCL diagnosis to the earliest of secondary malignancy, death (competing risk), or end of follow-up (censoring) was determined. Cumulative incidence curves of secondary malignancies were generated using the Aalen-Johansen estimator.[16] Differences between arms were tested by bootstrap sampling, recreating the propensity score, and calculating the difference in mean time of secondary malignancies over 30 years. This analytic strategy was used over the Fine and Gray model because (i) the later requires strong proportional hazard and correct mean model specification assumptions and (ii) the sum of cumulative incidence rates can exceed 100% of the data especially when there is long follow-up.[17, 18] Additional stratification by the modern treatment era in which Rituximab and intensity-modulated radiation therapy (IMRT) had become widespread was performed. The year 2001 was chosen to delineate between the pre-rituximab era and the modern treatment era as has previously been used.[5, 7] These analyses were performed in R using the VGAM package to calculate multi-group matching weights (following appendix in citation 15 (Yoshida)) and the survival package to calculate the 30-year mean time of secondary malignancies.[15, 19]

Results

Patient Characteristics

A total of 45,946 DLBCL patients diagnosed between 1975 and 2016 were identified, representing 268,493 patient years at risk. Within our cohort, the mean age at diagnosis was 62 (Table 1) with slightly more male (54%) than female patients, most being of white ethnicity (85%), and a slight majority having early stage disease (53%). The majority of patients were treated with CT (66%), 26% treated with CRT, and 8% with RT.

Incidence of SPM

Overall, 4,247 patients developed a SPM which accounted for 9.2% of the study cohort. Some patients developed more than one SPM, and in total, there were 4,896 SPMs observed. SPM development was significantly higher in the DLBCL cohort compared to the general United States population (O/E 1.23, 95%CI 1.20-1.27, AER 32.05). DLBCL survivors were at increased risk of developing H&N, stomach, colon, anal, hepatobiliary, lung, bone and soft tissue, bladder, kidney, and thyroid cancers as well as HL, NHL (excluding DLBCL), acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and Kaposi sarcoma (Table 2). Of these, Kaposi Sarcoma (O/E 10.83, 95%CI 8.01-14.31), HL (O/E 7.34 [5.78-9.19]), AML (O/E 4.66 [3.95-5.46]), and ALL (O/E 3.33 [1.66-5.95]) had the highest O/E ratio. NHL (AER 6.75), AML (AER 4.20), lung (AER 3.23), H&N (AER 3.14), HL (AER 2.29), and bladder cancers (AER 2.04) demonstrated the highest population level risk. There were decreased rates of prostate cancer and chronic lymphocytic leukemia (CLL).

Risk factors for SPM development

Comparison of baseline demographics showed no difference in SPM development between male (O/E 1.23 [1.19-1.28]) and female (O/E 1.23 [1.18-1.28]) patients or between white (O/E 1.22 [1.19-1.26]) and black (O/E 1.19 [1.04-1.35]) patients. However, patients ǿƙűK ᷊I·ǑŜ ƭI·ōŜƭŜŘ I·ă ά2űKŜ᷊έ ǿŜ᷊Ŝ Ƴ2᷊Ŝ ƭʎ⌊Ŝƭè than white patients to develop SPMs (O/E 1.44 95% CI 1.27-1.40). We also evaluated SPM risk by DLBCL stage at diagnosis. Advanced-stage patients (stage III and IV) had an increased risk of SPM (O/E 1.33, 95% CI 1.27-1.40) compared to early-stage patients (stage I and II) (O/E 1.18, 95% CI 1.13-1.22). Age at diagnosis was also a significant predictor for increased SPM risk. Patients younger than 25 years old at the time of DLBCL diagnosis were three times more likely to develop a SPM than the general population (O/E 2.99, 95% CI 2.29-3.84). The increased risk remained statistically significant for patients 25-49 years old (O/E 1.76, 95% CI 1.64-1.88) and 50-74 years old (O/E 1.18, 1.14-1.23) compared to the general population. The increased SPM risk in patients younger than 25 years old was particularly pronounced when compared to their older counterparts for the development of AML, HL, sarcomas, breast, lung, hepatobiliary, stomach, and thyroid cancer SPMs (Figure 1). O/E ratios and AERs for all SPM types by age of diagnosis are shown in Supplemental Table 1.

SPM risk by treatment modality

We further compared SPM risk by treatment modality and included patients treated with RT alone, CT alone, and CRT. Regardless of treatment type, DLBCL survivors were significantly more likely to develop SPMs compared to their matched counterparts in the general population. This was true for patients treated with RT (O/E 1.15 [1.03-1.28]), CT (O/E 1.25 [1.20-1.30]), and CRT (O/E 1.30 [1.23-1.38]). In all treatment groups, patients were at increased risk of multiple SPM subtypes (Supplemental Table 2). A few notable differences of SPM development between treatment modality were found. There was a significantly increased risk of breast cancer in patients treated with CRT versus CT (O/E 1.32 95%CI 1.12-

1.56 vs. O/E 0.89, 95%CI 0.77-1.01, respectively). Patients treated with CT had a higher risk of developing any leukemia than those who did not receive CT (O/E 2.33, [2.03-2.67] vs. O/E 1.40, [0.98-1.93] respectively). Patients treated with CT alone were less likely than their population-matched counterparts to develop prostate cancer (O/E 0.83, [0.74-0.93]). O/E ratios for malignancies where screening may be performed, stratified by treatment with CT, RT, and CRT are shown in Supplemental Figure 1.

The propensity-score adjusted cumulative incidence of SPMs showed there was a significantly higher incidence of SPMs among patients receiving CRT than patients receiving CT (p=0.001), which in turn was higher than patients receiving RT (p<0.001) (Figure 2). Measured baseline covariates were well balanced between arms (SMD ⟩ 0.12 for all covariates). Associated cumulative incidence of death is shown in Supplemental Figure 2. The cumulative incidence of SPMs in the pre-rituximab era (1983-2000) showed a significantly higher incidence in patients receiving CRT than patients receiving CT (p<0.001) or RT (p<0.001), but no difference between CT and RT (p=0.42) (Figure 3). In the modern treatment era (2001-2015), there was no longer a difference in the cumulative incidence of SPMs between patients treated with CRT versus CT (p=0.355); however, there was a significant difference between CRT and RT (p=0.015) and a trend toward significance between CT and RT (p=0.059). In the modern treatment era, the cumulative incidence of SPMs was numerically higher in all three of the treatment cohorts when compared to the pre-rituximab era.

SPM risk by latency

Temporal patterns of SPM development were analyzed for both solid and hematologic malignancies. The mean interval from DLBCL diagnosis to development of a SPM was 8 years. There was a significantly elevated risk of solid tumor development at all time points (0-4, 5-9, 10-14, 15-19, 20+ years); however,

the increased risk was greatest after the first decade. For leukemia, there was a significantly increased risk in the first decade, which decreased to non-statistically significant levels thereafter.

Solid and hematologic malignancies with notably increased O/E ratios and AERs over time are shown in Figure 4. Sarcomas, H&N cancer, and bladder cancer had the highest O/E ratios of any solid malignancies and had an upward trend over time. Breast cancer had a statistically decreased O/E ratio during the first 5 years, which subsequently increased over time. Within the first 15 years from diagnosis, lung cancer had the highest AER of any solid malignancy, while bladder cancer had the highest AER after 15 years. When evaluating hematologic malignancies, HL had the highest O/E ratio of any SPM followed by AML at all time points. O/E ratios and AERs for all SPMs by latency are shown in Supplemental Table 3.

Discussion

This is the largest population-based study evaluating SPM risk in DLBCL survivors with the longest follow up to date. We identified unique SPM risk patterns based on the age at diagnosis, latency, and importantly treatment modality. We demonstrate first ever cumulative incidence curves stratified by treatment modality in both the pre-rituximab and modern treatment era. These findings have important implications in both treatment and surveillance of these patients.

Age at diagnosis significantly affected the overall risk of SPM development as well as the types of SPMs for which these patients were at risk. Patients diagnosed under 25 years old demonstrated the highest risk of developing a SPM, followed by patients 26-49, and then patients 50-74. Prior studies, including the childhood cancer survivor study, have shown that survivors of childhood cancer are at a 2-6 fold increased risk of developing SPMs.[20-25] Women treated as children and young adults with more historic thoracic RT techniques have previously been shown to have a cumulative incidence of breast cancer between 13-20% by age 40, which later led to the discovery that early breast MRI screening improves

survival in these patients.[12, 26] Furthermore, young patients treated for NHL specifically have been shown to be at a significantly higher risk of hematologic cancers following treatment.[20, 27] This may relate to the fact that children and young adults with cancer are more likely to have genetic predispositions which may be present in up to 10% of pediatric patients based on recent reports using genome-scale germline sequencing of pediatric cancer cohorts.[28-31] Additionally, environmental factors such as smoking and obesity may compound risks from treatment.[32, 33] Regardless of the etiology, it is clear that patients diagnosed with DLBCL at a younger age have increased SPM risk compared to their older counterparts.

The last few decades have seen DLBCL transition toward omission of RT, with increasing frequency of CT only treatment approaches.[7, 34] In some instances, the rationale for this shift in practice patterns is the concern for RT-induced SPM. A previous study utilizing the California Cancer Registry showed an increased risk of SPM in DLBCL patients with use of radiation, however this risk did not persist when only evaluating patients treated since 2001.[7] Studies utilizing the SEER database have been mixed in DLBCL patients, with one study showing no increased risk of SPM development with patients treated with RT and another showing increased risk of specific cancer types in patients treated with RT.[5, 6] In our evaluation, treatment with RT, CT, and CRT were all associated with an increased risk of SPM development compared to the matched general population.

Our propensity-score matched analysis comparing treatment modalities demonstrated the cumulative incidence of SPMs was lowest in patients treated with RT alone, followed by CT, then CRT. Among patients treated in the modern era, the cumulative incidence of SPMs remained lowest in the RT cohort with no statistically significant difference between the CRT and CT cohorts. It is possible that advances in radiation oncology and adoption of involved-site RT with associated improvements in conformality, smaller treatment fields, and lower doses have contributed to a relative decrease in the risk of SPMs

observed in patients who receive RT. These results may help to alleviate concerns regarding SPM risk in patients receiving chemotherapy who could otherwise benefit from the addition of radiation therapy. The notable exception, which has been demonstrated in our data as well as multiple other studies, is the increased risk of breast cancer in patients treated with radiation.[3, 5, 35] The numerically higher cumulative ƛyŎƛŘŜyŎŜ ƻŦ {t a ƛƴ ǇŀǘƛŜƴǘǎ ǘǊŜŀǘŜŘ ŘǳǊƛƴƎ ǘƘŜ ǊƛǘǳȄƛƳŀō ŜǊŀ ŎƻƳǇŀǊŜŘ ǘƻ the pre-rituximab era is likely multifactorial and may be due to changes in treatment practice over time and the addition of rituximab. However, given the relative increase amongst patients in all treatment cohorts we think the most likely explanation is increased detection through improvements in imaging and cancer screening protocols.

Temporal patterns of SPM development varied between solid and hematologic malignancies. SPMs of multiple solid malignancy types including H&N, lung, sarcoma, bladder, and breast cancer increased over time, and is consistent with previous literature evaluating radiation induced SPM.[36, 37] Chemotherapy has also been shown to increase the risk of solid malignancies, and this typically is seen >10 years following exposure.[36] Hematologic malignancies tend to occur a few to several years after treatment with leukemia peaking 5-7 years post treatment,[38] which was also supported by our data. These temporal patterns can help guide various screening recommendations for different malignancy types.

One of the most striking findings in our data was the drastic and significantly delayed risk of development of bladder cancer for DLBCL survivors. It has been well established that cyclophosphamide is a significant risk factor for the development of bladder cancer in a dose dependent manner.[39, 40] A recent systematic review evaluated 285 patients from 121 studies who had received prior cyclophosphamide and later developed urothelial carcinoma. Among these patients, they showed a median latency of ten years from initiation of cyclophosphamide to development of bladder cancer but demonstrated a significant number of patients who developed bladder cancer with a latency >15 years.

[40] In this study, bladder cancer had the highest AER of any cancer type beyond 15 years and accounted for more cases than both breast and lung cancer combined. This highlights the significant risk cyclophosphamide poses in DLBCL survivors, and should be a consideration in limited stage DLBCL patients as radiation can be utilized to decrease the number of cycles of R-CHOP given. Additionally, there are no screening recommendations for DLBCL patients or patients exposed to cyclophosphamide. Some have suggested yearly screening via urinalysis and lower threshold for imaging for patients who develop hematuria and irritative urinary symptoms.[40] While data is extremely limited regarding the utility and cost-effectiveness of these measures, our data highlights the importance of future studies in bladder cancer screening among DLBCL patients.

This study has inherent limitations due to the retrospective nature of database analysis. SEER does not collect or include information on comorbid conditions, specific chemotherapy regimens, RT dose, RT technique, location of treatment, or other cancer risk factors such as smoking. Regarding radiation specifics, both dose and radiation technique have been associated with higher risk of SPM development.[36] We would expect this same association to exist in DLBCL; however, we were unable to explore these associations as this information is unavailable in the SEER database. In addition, while the SEER database has been shown to have an excellent positive predictive value for patients coded as having received RT or CT, it has been shown to have imperfect sensitivity for patients coded as not having received CT or RT. This suggests that some treatment fails to be captured.[41] Finally, we have defined statistical significance as $p < 0.05$ allowing for a false discovery rate higher than 5%. Focused, affirmative follow-up studies would strengthen the conclusion of each finding. Despite the aforementioned shortcomings, the strength of this study lies in the analysis of a very large cohort of patients with sufficient size and statistical power to identify patterns of SPM risk as well the long follow up necessary to fully evaluate SPM risk over time.

Conclusions:

This is the largest study to examine SPM risk in patients treated for DLBCL with over 40 years of follow-up. Patients <25 were found to be particularly susceptible to development of SPMs, with a risk 2.5 times greater than patients 50-74. Temporal patterns showed increasing risk of solid malignancies and decreasing risk of hematologic malignancies over time, with bladder cancer posing the greatest absolute excess risk of any cancer type after 15 years. Patients treated with RT, CT, and CRT all had an increased risk of SPM development compared to the general population. The cumulative incidence of SPMs was lowest in patients treated with RT and highest in CRT. In the modern treatment era, the cumulative incidence of SPMs for patients treated with CT versus CRT were not significantly different. Understanding these risks is essential in the management of DLBCL patients and should inform both treatment and future survivorship guidelines in patients with DLBCL.

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Figure Captions

Figure 1. Observed to expected ratios for various secondary primary malignancies (SPMs) based on the age at DBLCL diagnosis.

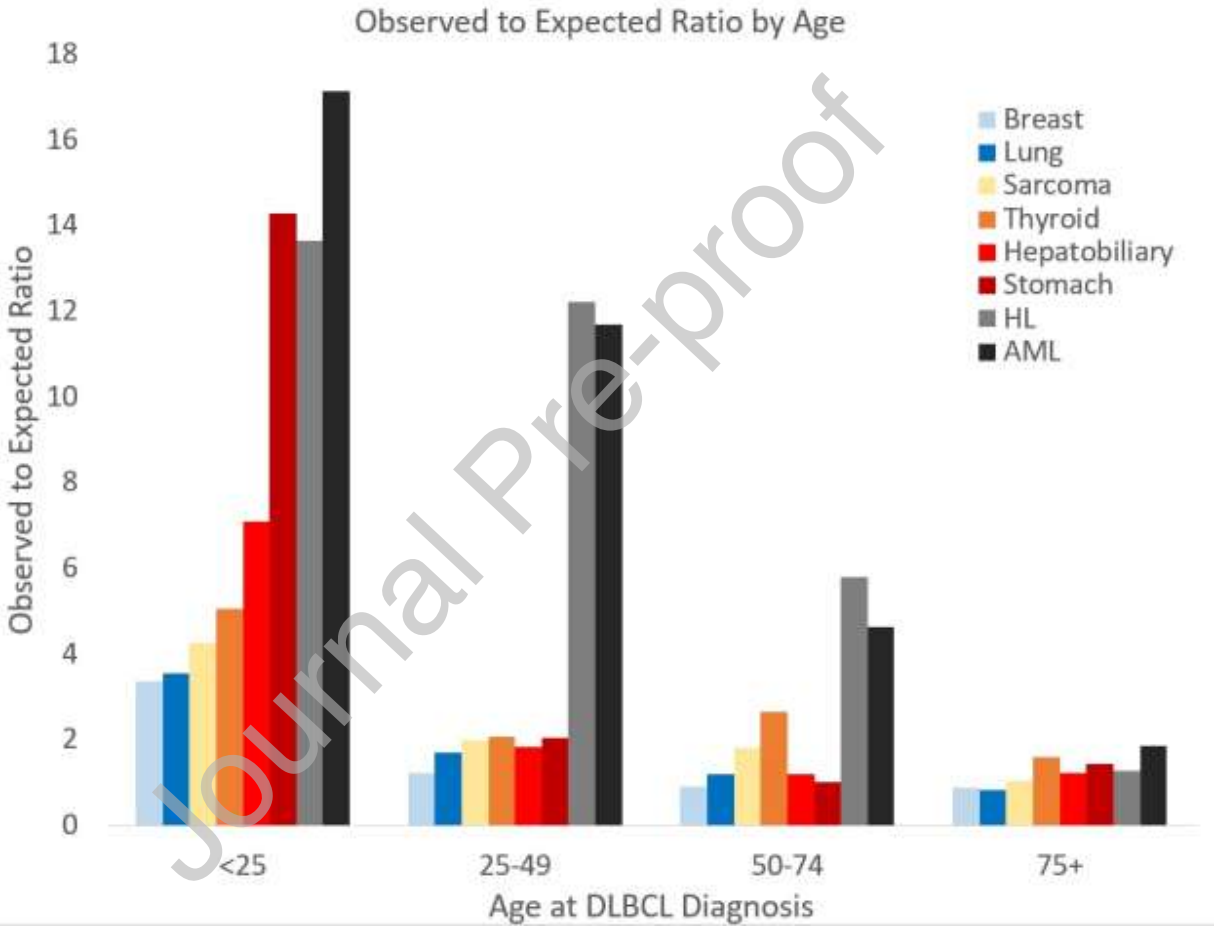

Figure 2. Propensity-score adjusted cumulative incidence of second primary malignancies (SPMs) stratified by treatment modality. The sample size is re-weighted from the propensity score matched weights.

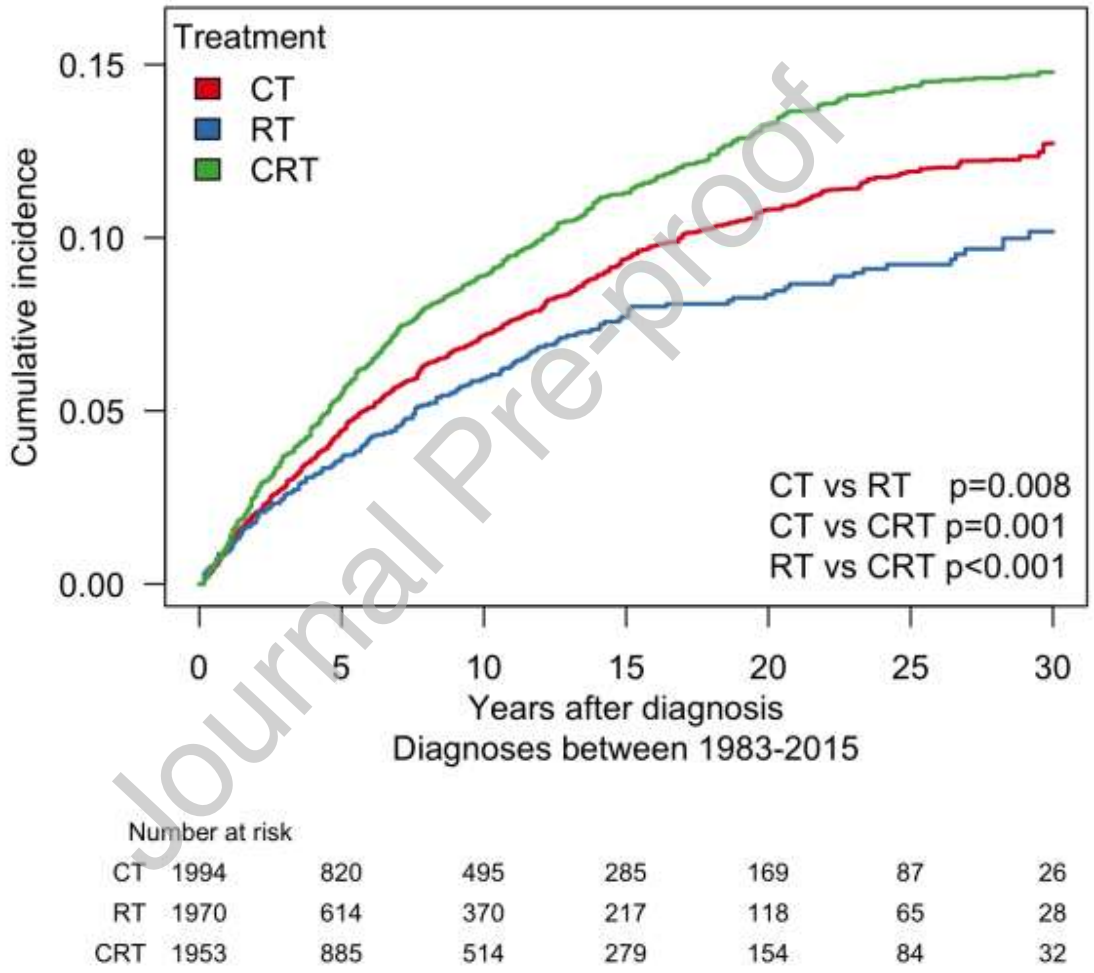

Figure 3. Propensity-score adjusted cumulative incidence of second primary malignancies (SPMs) stratified by treatment modality. Figure 3a demonstrates the cumulative incidence of SPM in the pre-rituximab era (1983-2000) and Figure 3b in the modern treatment era (2001-2015).

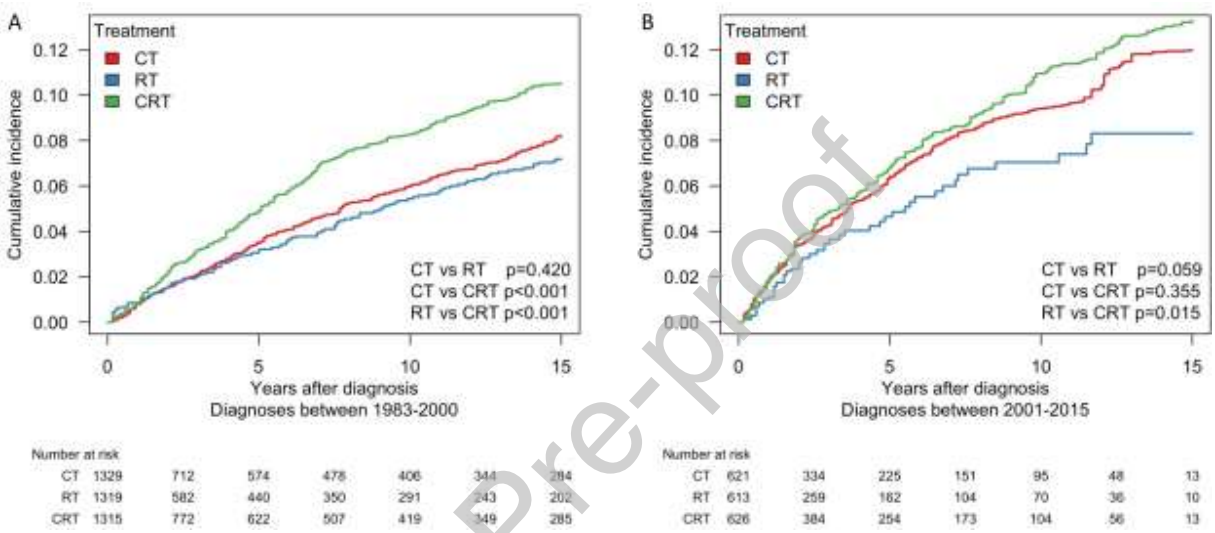

Figure 4. 4A and 4B show O/E ratios and AERs for various solid malignancies. 4C and 4D show O/E ratios and AERs for various hematologic malignancies. Circles indicate O/E ratios in 5 year intervals. Solid circles indicate statistically significant values with $p<0.05$ when compared to the matched general population. Non-Hodgkin lymphoma is excluding DLBCL.

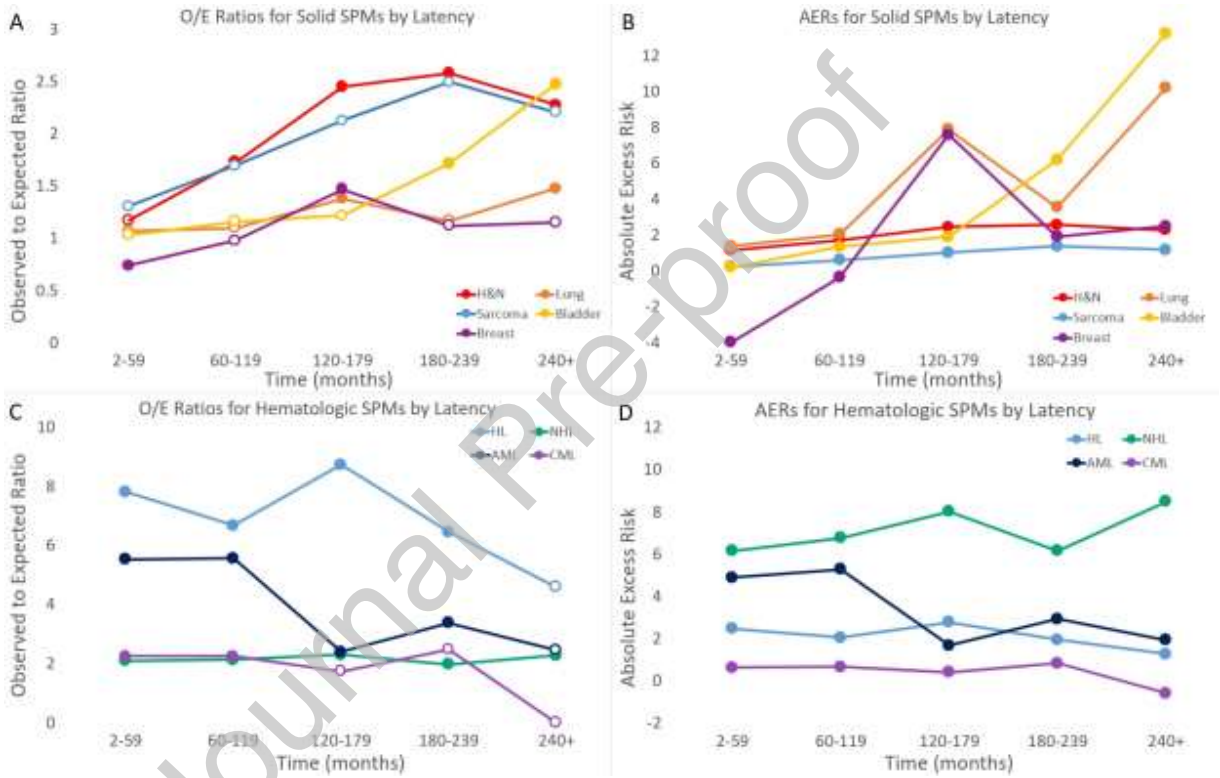

Table 1. Patient Characteristics

	All Patients No. (%)	CT No. (%)	CRT No. (%)	RT No. (%)
Total patients	45,946	25,997	10,017	3,194
Patient years at risk	268,493	140,060	71,295	17,911
Patients with SPM	4,247 (9.2)	2,275 (8.8)	1,071 (10.7)	305 (9.5)
Mean age, DLBCL dx (years)	62.0	61.6	58.2	67.9
Mean age, SPM dx (years)	70.0	70.0	68.8	71.4
Mean follow up (months)	70.1	64.7	85.4	67.3
Sex				
Male	24,876 (54.1)	14,385 (55.3)	5,540 (55.3)	1,535 (48.0)
Female	21,070 (45.9)	11,612 (44.7)	4,477 (44.7)	1,659 (52.0)
Race				
White	38,806 (84.5)	21,833 (84.0)	8,451 (84.4)	2,767 (86.6)
Black	3,169 (6.9)	1,944 (7.5)	578 (5.8)	183 (5.7)
Other	3,808 (8.3)	2,129 (8.2)	961 (9.6)	239 (7.5)
Unknown	163 (0.4)	91 (0.4)	27 (0.3)	5 (0.2)
Stage				
Early stage*	20,990 (53.3)	9,685 (42.2)	6,182 (69.6)	1,692 (78.4)
Advanced stage*	18,386 (46.7)	13,264 (57.8)	2,703 (30.4)	465 (21.6)

Abbreviations: RT, radiotherapy; CT, chemotherapy; CRT, chemoradiation; SPM, second primary malignancy; DLBCL, diffuse large B-cell lymphoma; dx, diagnosis.

*Early stage represents stage I,II DLBCL. Advanced stage represents stage III,IV DLBCL

Table 2. O/E ratio and AER for SPM subtypes in patients with DLBCL

Malignancy/tumor Site	Observed cases (n)	AER*	O/E ratio	95% CI	
				Lower	Upper
All sites	4,896	32.05	1.23†	1.20	1.27
Head and neck	222	3.14	1.68†	1.47	1.92
Esophagus	53	0.28	1.18	0.89	1.55
Stomach	91	0.67	1.27†	1.02	1.56
Colon excluding rectum	372	01.59	1.14†	1.03	1.26
Rectum	96	-0.65	0.84	0.68	1.02
Anus and anal canal	32	0.71	2.77†	1.90	3.92
Hepatobiliary	113	0.92	1.30†	1.07	1.57
Pancreas	119	0.00	1.00	0.83	1.20
Lung	681	3.23	1.16†	1.07	1.25
Sarcoma	42	0.60	1.70†	1.22	2.29
Melanoma	186	0.85	1.15	0.99	1.33
Breast	439	-0.49	0.97	0.88	1.06
Gynecologic	180	0.09	1.01	0.87	1.17
Prostate	632	-1.98	0.92†	0.85	0.99
Bladder	291	2.04	1.25†	1.11	1.40
Kidney and renal pelvis	173	2.03	1.51†	1.29	1.75
Brain	41	0.04	1.03	0.74	1.40
Thyroid	111	2.30	2.46†	2.02	2.96
Hodgkin lymphoma	76	2.29	7.34†	5.78	9.19
Non-Hodgkin lymphoma	363	6.75	2.14†	1.92	2.37
Acute lymphocytic leukemia	11	0.27	3.33†	1.66	5.95
Chronic lymphocytic leukemia	25	-0.97	0.47†	0.31	0.70
Acute myeloid leukemia	153	4.20	4.66†	3.95	5.46
Acute monocytic leukemia	15	0.46	8.40†	4.70	13.86
Chronic myeloid leukemia	31	0.55	2.03†	1.38	2.89
Kaposi sarcoma	49	1.55	10.83†	8.01	14.31

Abbreviations: O/E, observed/expected; AER, absolute excess risk; SPM, second primary malignancy; DLBCL, diffuse large B-cell lymphoma; CI, confidence interval.

* AER indicates the number of cases per 10,000 person-years.

† Indicates $p<0.05$