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Treatment Modalities and Survival Outcomes for Sinonasal Diffuse Large B-Cell Lymphoma

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Abstract

Objectives: This study utilizes a large population national database to comprehensively analyze prognosticators and overall survival (OS) outcomes of varying treatment modalities in a large cohort of sinonasal diffuse large B-cell lymphoma (SN-DLBCL) patients.

Study Design: Retrospective database study.

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Methods: The National Cancer Database was queried for all SN-DLBCL cases diagnosed from 2004–2015. Kaplan-Meier log-rank test determined differences in OS based on clinical covariates. Cox proportional-hazards analysis was used to determine clinical and sociodemographic covariates predictive of mortality.

Results: A total of 2,073 SN-DLBCL patients were included, consisting of 48% female with a mean age of 66.0 ± 16.2 years. Overall, 82% of patients were Caucasian, 74% had early-stage disease, and 49% had primary tumors in the paranasal sinuses. Early-stage patients were more likely to receive multi-agent chemoradiotherapy compared to multi-agent chemotherapy alone ($p<0.001$). Multivariable cox proportional-hazards analysis revealed chemoradiotherapy to confer significantly greater OS improvements than chemotherapy alone (HR: 0.61; $p<0.001$). However, subset analysis of late-stage patients demonstrated no significant differences in OS between these treatment modalities ($p=0.245$). On multivariable analysis of chemotherapy patients treated post-2012, immunotherapy (HR=0.51; $p=0.024$) demonstrated significant OS benefits. However, subset analysis showed no significant advantage in OS with administering immunotherapy for late-stage patients ($p=0.326$). Lastly, for all patients treated post-2012, those receiving immunotherapy had significantly improved OS compared to those not receiving immunotherapy ($p<0.001$).

Conclusions: Treatment protocol selection differs between early- and late-stage SN-DLBCL patients. Early-stage patients receiving chemotherapy may benefit from immunotherapy as part of their treatment paradigm.

Keywords

Sinonasal; B-cell lymphoma; Treatment; overall survival; NCDB; chemoradiotherapy; immunotherapy

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma (NHL), representing 30% of all malignant lymphomas.[1–3] Approximately one-third of all NHL cases are extranodal.[4,5] Of those that originate from within the sinonasal tract, DLBCL comprises the majority of cases.[6] Patients with sinonasal-DLBCL (SN-DLBCL) present with progressive lymphoid tissue enlargement and a variety of possible clinical manifestations, including B symptoms (i.e., fever, night sweats, weight loss > 10% over 6 months).[7,8] As with many head and neck malignancies, SN-DLBCL is associated with human immunodeficiency virus (HIV).[9] Although SN-DLBCL is less aggressive and associated with a better prognosis compared to other sinonasal lymphomas,[6,10] 5-year overall survival (OS) rates are still guarded at around 50–75%, with the immunoblastic phenotype portending the worst overall prognosis.[6,11–13]

The treatment of SN-DLBCL predominantly involves the single- or multi-modality use of chemotherapy or radiotherapy.[14] Surgery is typically employed for excisional biopsies and rarely considered a primary treatment option.[6,15] The National Cancer Comprehensive Network (NCCN) guidelines recommend rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) multimodal chemotherapy with or without involved site radiation therapy depending on the number of R-CHOP cycles in stage

I-II disease. Prior large-population national database studies using the Surveillance, Epidemiology, and End Results (SEER) database have identified radiotherapy and chemotherapy as independent predictors for improved OS.[11,12] In Ann Arbor stage III-IV disease, NCCN recommends R-CHOP-21 as initial therapy. However, other therapies (*e.g.,* da-EPOCH-R, mini-CHOP, R-CVP, clinical trials) may be utilized based on an individual's age, stage, histological subtype and performance status.[16] Due to the rare presentation of SN-DLBCL, there exists a paucity of data comparing varying treatment modalities within early- and late-stage disease patient cohorts. Therefore, this study uses the NCDB to determine OS outcomes of varying treatments important for early- and late-stage disease SN-DLBCL patients, along with determining clinical and sociodemographic prognosticators of OS.

Methods

This investigation did not require UC Irvine Institutional Review Board approval because of the unrestricted and available use of this deidentified database. The Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society mutually facilitate data collection from >1500 CoC-accredited institutions through the NCDB. Unlike SEER, which was primarily designed as an epidemiological tool to study cancer incidence, the NCDB is a surveillance tool that captures more cancer cases and offers several unique clinical variables, such as systemic adjuvant therapies, margin status, surgical approach, and hospital characteristics.[17] Fundamentally, these databases do not differ greatly in terms of demographic and survival outcomes for head and neck malignancies, but mainly differ in how the populations are sampled (NCDB, hospital-based, versus SEER, population-based) and the breath of information provided.[18] The NCDB represents a large proportion of newly diagnosed neoplasms, and specifically >80% of lymphomas, annually in the United States.[19] A systematic query from the 2004–2015 NCDB was performed using the *International Classification of Disease for Oncology, Third Edition* primary site codes for the nasal cavity (C30.0), paranasal sinuses (C31.0–31.3; C31.8–31.9), and nasopharynx (C11.0–11.3; C11.8–11.9) with SN-DLBCL histology/behavior codes (9680/3). Patients were excluded if they met any of the following criterion: 1) presented with >1 primary malignancy, 2) sought treatment outside the reporting CoC-accredited institution, 3) received palliative treatment, 4) received any other type of non-cancer-related or unspecified treatment, or 5) had unknown follow-up.

Our analysis included the following clinical and sociodemographic covariates: age, sex, race, diagnosis year, tumor primary site, Charlson Comorbidity Index (CCI), Ann Arbor stage, presence of B-symptoms, HIV status, insurance type, and facility type. Moreover, we analyzed the therapeutic effect of the following treatments: surgery (excluding excisional biopsy), radiotherapy, chemotherapy, and immunotherapy. Multi-agent chemotherapy (MAC) was defined as per the NCDB data dictionary. All analyses involving immunotherapy were performed on a subset of our cohort where diagnoses were made post-2012 when the NCDB had started defining rituximab as immunotherapy.

Statistical analyses were executed using R (version 4.0.2; The R Foundation for Statistical Computing) and RStudio (version 1.2.1335), with a $p<0.05$ considered statistically

significant. Significant differences in continuous and categorical covariates were assessed with independent t-test and chi-square test, respectively. Clinical and sociodemographic factors were correlated with OS via univariate and multivariable Cox proportional-hazards analysis. Covariates with p-values <0.10 on univariate regressions were included in the multivariable Cox proportional-hazards models. Kaplan-Meier log-rank test was used to compare OS amongst various clinical covariates and treatment protocols.

Results

The cohort consisted of 2,073 patients with histologically confirmed SN-DLBCL diagnosed between 2004 through 2015. The cohort's mean age was 66.0 ± 16.2 years, where males presented at significantly younger ages (63.3 ± 16.3 years) than females (68.9 ± 15.5 years) (p<0.001). There were no significant differences in presenting age between early-stage (66.4 ± 15.9) and late-stage (64.6 ± 16.2) patients. Many patients were male (52%), of Caucasian race (82%), had primary tumors in the paranasal sinuses (49%), and had early-stage SN-DLBCL (74%) (Table 1). Early-stage (Ann Arbor stages I-II) patients were more likely to receive multi-agent chemoradiotherapy (MAC-RT) than MAC compared to late-stage (Ann Arbor stages III-IV) patients (p<0.001).

The OS of the cohort at 1-, 2-, 5-, and 10-years was 87.5%, 81.7%, 69.9%, and 51.2%, respectively, with a median survival time of 10.5 years (95% CI: 9.4–11.1) (Table 2). The mean follow-up for the cohort was 50.3 ± 41.2 months. The 5- and 10-year OS rates for MAC and MAC-RT were 60.2% and 42.7%, and 78.5% and 57.1%, respectively (Table 2).

MAC-RT had significantly improved OS compared to MAC for all patients (p<0.001) and early-stage patients (p<0.001) (Figure 1A), but there were no significant differences in late-stage patients (p=0.245) (Figure 1B). The 5-year OS stratified by primary site were 63.0%, 65.0%, and 61.5% for the nasal cavity, paranasal sinuses, and nasopharynx, respectively. Kaplan-Meier log-rank test demonstrated no significant differences in OS based on primary site tumor location (p=0.259) (Figure S1A). The 5-year OS rates for Ann Arbor stages I, II, III, and IV were 67.5%, 65.7%, 53.4%, and 49.6%, respectively (Table 2). Kaplan-Meier log-rank test demonstrated that early-stage patients to have significantly higher OS than late-stage patients (p<0.001, Figure S1B). Moreover, patients with B symptoms (p<0.001) (Figure S1C), government insurance (p<0.001) (Figure 2A), or those treated at non-academic facilities (p<0.001) (Figure 2B) had significantly worse OS.

On univariate analysis, radiotherapy use (HR=0.62; p<0.001), chemotherapy use (HR=0.46; p<0.001), and immunotherapy use (HR=0.77; p=0.007) were all significantly associated with improved OS, while surgery (HR=0.89; p=0.261) was not associated with OS. For the entire cohort, factors predictive of OS on univariate and multivariable Cox proportional-hazards analysis are demonstrated in Table 3. On multivariable analysis, age ≥65 years (HR=2.20; p<0.001), government insurance (HR=2.08; p<0.001), CCI ≥2 (HR=2.60; p<0.001), presence of B symptoms (HR=1.59; p=0.003), positive HIV status (HR=2.06; p=0.01), and Ann Arbor Stage IV (HR=1.91; p<0.001) were found to be independent predictors of worse OS, while receiving treatment at an academic facility

(HR=0.70; p=0.007) and undergoing multi-agent chemoradiotherapy (HR=0.61; p<0.001) were independent predictors of improved OS (Table 3).

For patients treated post-2012 who received chemotherapy, multivariable analysis demonstrated that age ≥65 years (HR=2.69; p=0.010) and Ann Arbor Stage IV (HR=2.07; p=0.024) were independent predictors of worse OS, while receiving immunotherapy (HR=0.51; p=0.024) and radiotherapy (HR=0.35; p<0.001) were independent predictors of improved OS (Table 4). Among the entire cohort treated post-2012, patients receiving immunotherapy had significantly improved OS compared to patients not receiving immunotherapy (p<0.001) (Figure 3). However, on multivariable analysis, MAC-RT with immunotherapy was not associated with improved OS compared to MAC-RT alone (Table S1). Lastly, for early-stage patients treated post-2012 (n=339) receiving multi-agent chemotherapy, multivariable analysis demonstrated that adding radiotherapy (HR=0.21; p<0.001) and immunotherapy (HR=0.38; p=0.009) conferred significantly improved OS, while this was not demonstrated in late-stage patients (p=0.33).

Discussion

In this study, we utilized a large-population national database to evaluate SN-DLBCL presentation, assess survival outcomes based on clinical, sociodemographic, and therapeutic factors, and uncover independent prognosticators of patient survival. We observed that early-stage patients were more likely to receive MAC-RT, which conferred improved survival outcomes compared to MAC alone. Moreover, we demonstrated several clinical and sociodemographic predictors of increased mortality, including older age, government insurance, higher C/D Comorbidity index, presence of B symptoms, HIV status, and Ann Arbor Stage IV. Conversely, treatment at an academic facility and receipt of MAC-RT were found to be independent predictors of improved OS. Lastly, we demonstrated that supplementing multi-agent chemotherapy with immunotherapy was associated with improved OS for early-stage patients.

Prior population-based database studies have investigated the use of MAC-RT for early-stage DLBCL patients. Vargo and colleagues demonstrated that, for early-stage DLBCL, multi-agent chemoradiotherapy conferred improved OS compared to chemotherapy alone.[20] Additionally, Peng *et al.* similarly demonstrated that for early-stage head and neck DLBCL, chemoradiotherapy resulted in improved OS compared to chemotherapy alone; however no additional OS benefits were seen for patients who also received immunotherapy as part of their treatment.[21] Moreover, Chung *et al.* demonstrated that early-stage patients responding well to multi-agent chemotherapy may not need consolidative radiotherapy, with tumor size influencing treatment decision.[22] However, a separate study analyzing all anatomical locations of early-stage DLBCL observed that compared to no radiotherapy, multi-agent chemotherapy followed by radiotherapy improved OS, especially in older patients.[23] Our study results closely align with these studies and others that propose multi-agent chemoradiotherapy to be the mainstay of treatment for early-stage SN-DLBCL patients. Additionally, we provide data that suggests immunotherapy may augment current treatment paradigms that already include multi-agent chemoradiotherapy. This was suggested in a recent retrospective analysis of SN-DLBCL patients where addition of rituximab to CHOP

(cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like chemotherapy conferred improved progression-free survival and OS.[24] Future research is warranted to understand which early-stage patients respond to immunotherapy, and novel strategies are needed to improve the efficacy in late-stage patients.

The role of multi-agent chemoradiotherapy is currently not well understood for patients with late-stage DLBCL. For late-stage DLBCL patients who attain complete response to MAC, Shi *et al.* demonstrated that MAC-RT resulted in significantly improved local control and progression-free survival (PFS), but not OS.[25] Additionally, a meta-analysis comparing multi-agent chemotherapy with and without consolidative radiotherapy for late-stage patients reported a benefit in PFS, but not OS.[26] Our study demonstrated that, for late-stage SN-DLBCL patients, multi-agent chemoradiotherapy did not significantly improve OS compared to multi-agent chemotherapy alone. However, as demonstrated in these other studies, radiotherapy following MAC may improve other cancer-specific outcome measures such as local control and PFS for SN-DLBCL, which we were not able to assess due to a limitation in NCDB reporting. Lastly, for late-stage DLBCL patients, previous studies have suggested that autologous stem cell transplantation may improve OS and PFS outcomes in the setting of relapsed disease,[27–29] yet some controversies remain in terms of treatment timing.[30] In our study, only ten late-stage patients had received some form of hematologic transplant, and therefore, analysis of this treatment effect was not possible. As a result, future studies are warranted to investigate the most optimum combinations of multi-agent chemotherapy with or without autologous stem cell transplantation for late-stage DLBCL patients.

There are important pre-treatment clinical factors that can affect OS outcomes in DLBCL. According to prior investigations, these factors may include older age, presence of B symptoms, worse physical health status, high International Prognostic Index (IPI), high Eastern Cooperative Oncology Group score, increased lactate dehydrogenase levels, and late-stage disease.[7,11,20,21,31] Our study confirms these previous findings, as we found older age, higher CCI, presence of B symptoms, and positive HIV status to be predictors of mortality in SN-DLBCL. Additionally, another factor that may influence DLBCL OS outcomes is time from diagnosis to therapy (DTI). In a pooled analysis, Maurer and colleagues analyzed a large cohort of DLBCL patients and observed that a DTI ≥15 days was associated with improved OS.[32] On univariate analysis, we observed a DTI ≥15 days to not be associated with improved OS (HR=0.99, p=0.32). This was more in-line with a study of acute myeloid leukemia patients by Sekeres et al., where delayed time to treatment did not affect OS in older patients.[33] Given the potential discrepancies in the literature regarding the influence of DTI with OS, further studies are warranted to investigate the relationship between DTI and disease severity or OS outcomes, which can also be influenced by sociodemographic factors in the at-risk population.

Other studies have observed that various sociodemographic factors influence OS outcomes for DLBCL patients. Two previous studies suggested that treatment at academic centers was associated with improved OS for DLBCL patients compared to treatment at non-academic facilities.[34,35] This effect remained significant when patients were adjusted for International Prognostic Index (IPI) scoring, a common measure used to guide prognosis

of lymphomas.[34] Additionally, insurance status has been shown to affect OS for DLBCL patients, with non-private insurance patients having worse OS outcomes.[36] Moreover, it has been observed that residing in rural or urban populations [31] and having lower income[20,35] are associated with worse OS outcomes. Our study validated these previous findings, suggesting that sociodemographic factors, including insurance and facility type need to be taken into consideration when estimating SN-DLBCL prognosis. The link between non-private insurance and DLBCL OS has been previously hypothesized to stem from a presentation at late-stage disease with worse physical health.[36] However, we found early- and late-stage disease SN-DLBCL patients to have comparable presentations regardless of insurance status, suggesting more multifaceted and unexplored reasons for insurance-related health disparities. Further investigations are warranted to help explain the influence of sociodemographic factors on OS outcomes for DLBCL patients.

This study, although carefully analyzed and interpreted, has a few important limitations that need to be given consideration. First, the IPI is a common metric to use for lymphoma prognosis, especially DLBCL;[37] however, the majority of our cohort did not have this information reported. Similarly, tumor size, which may also influence OS and treatment type, was missing for most of the cohort. Second, survival analysis from the NCDB is limited to OS, therefore, important measures such as local recurrence, metastasis-free survival, and PFS were not able to be analyzed across treatment protocols and disease severity.[19] Third, information regarding patient response to therapy or relapse/remission from therapy is not recorded in the database. As a result, we were not able to delineate multi-agent chemotherapy responders versus non-responders, which has been shown to influence treatment outcomes and subsequent course of therapy for DLBCL.[25,26] Fourth, the number of administered cycles (and specific agents) of the chemotherapy or immunotherapy treatment protocol was not defined, along with the dosage, timing, and use of salvage therapy which have all been shown to affect treatment-related outcomes such as OS and PFS.[38] Lastly, as with any retrospective study, selection bias may be an inherent factor in our results. However, despite these limitations, this study adds to the current SN-DLBCL literature by comprehensively analyzing the varying clinical and sociodemographic factors between early- and late-stage disease patients that influence treatment selection and OS outcomes for SN-DLBCL.

Conclusion

This study uses a large-population database to analyze presentations and SN-DLBCL OS outcomes based on Ann Arbor stage and treatment protocols consisting of multi-agent chemotherapy ± radiotherapy ± immunotherapy. It was observed that OS outcomes were influenced by clinical factors such as age, overall physical health, B symptoms, HIV status, and sociodemographic factors such as treatment facility type and insurance. Future clinical trials are necessary to determine proper treatment protocols involving immunotherapy based on disease severity and treatment response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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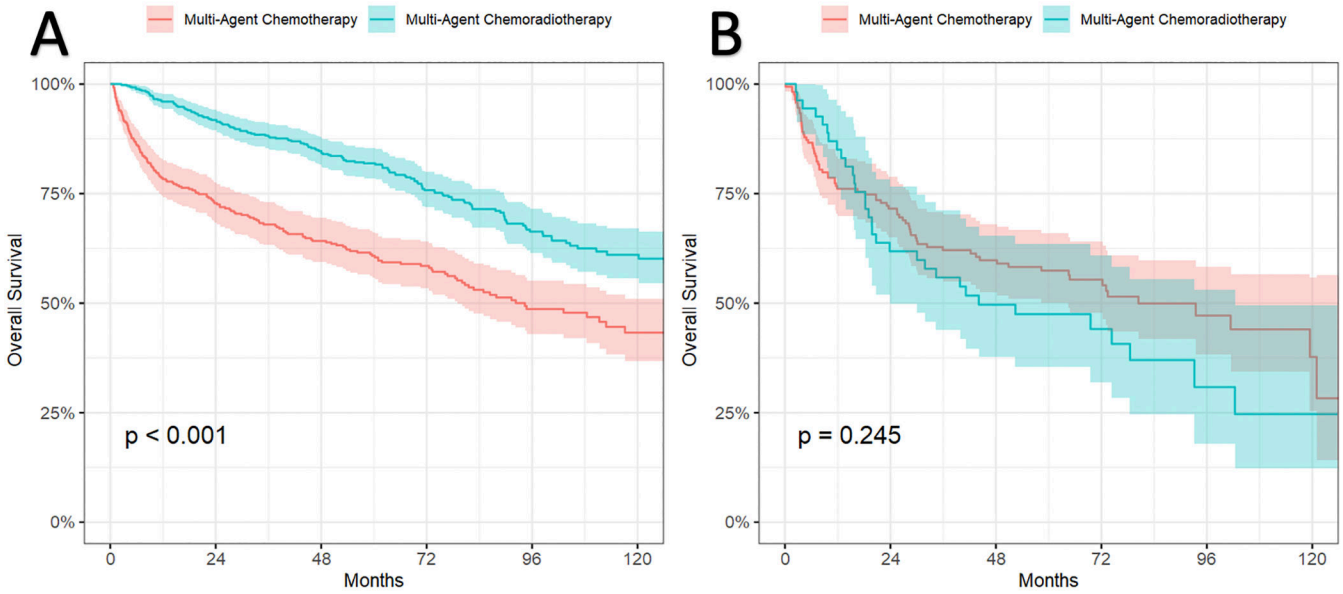

Figure 1:

Kaplan-Meier curves of overall survival for multi-agent chemotherapy vs multi-agent chemoradiotherapy stratified by A) early-stage and B) late-stage patients.

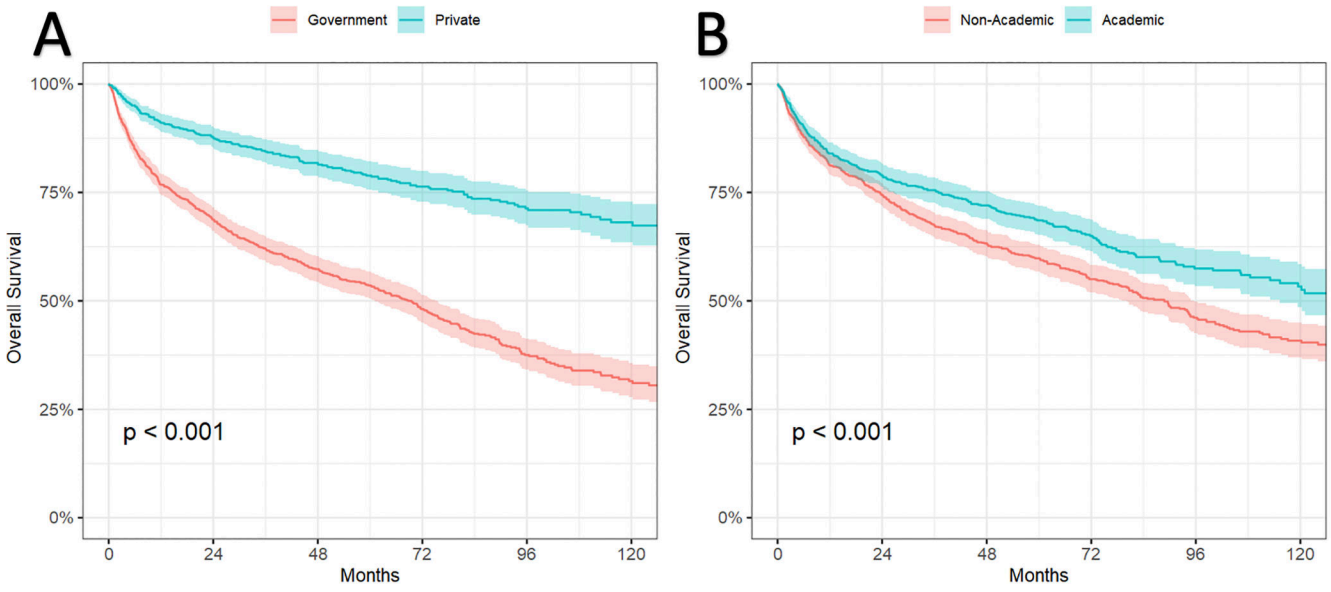

Figure 2:
Kaplan-Meier curves of overall survival for entire cohort stratified by A) insurance and B) facility type.

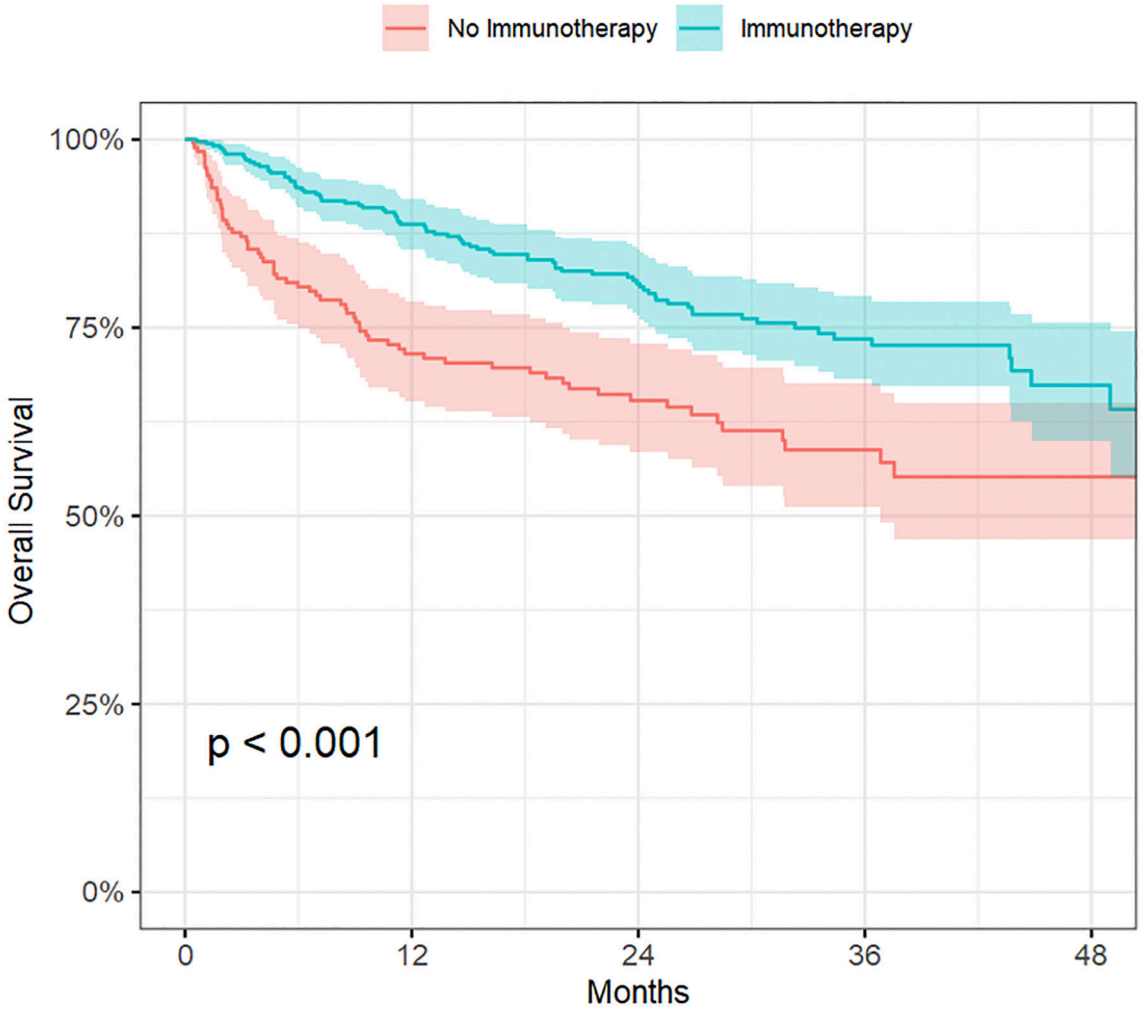

Figure 3:
Kaplan-Meier curve of overall survival for patients treated post-2012 with immunotherapy.

Table 1:

Clinical characteristics of patients with sinonasal diffuse large B-cell lymphomas.

Characteristic	Value
Mean Age, years (SD)	66.0 ± 16.2
Male	63.3 ± 16.3
Female	68.9 ± 15.5
Sex, no. (%)	
Male	1069 (51.6)
Female	1004 (48.4)
Race, no. (%)	
Caucasian	1692 (81.6)
African American	213 (10.3)
Asian	122 (5.9)
Primary Site, no. (%)	
Nasopharynx	635 (30.6)
Paranasal Sinuses	1017 (49.1)
Nasal Cavity	421 (20.3)
Charleson/Deyo Comorbidity Score, no. (%)	
0	1650 (79.6)
1	281 (13.6)
≥2	142 (6.8)
Ann Arbor Stage, no. (%)	
I	1039 (50.1)
II	490 (23.6)
III	86 (4.1)
IV	310 (15.0)
B Symptoms Present, no. (%)	
Yes	276 (13.3)
No	1590 (76.7)
HIV Status, no. (%)	
Present	78 (3.8)
Absent	1184 (57.1)
Insurance Status, no. (%)	
Private	758 (36.6)
Government	1214 (58.6)
Facility Type, no. (%)	
Academic	899 (43.4)
Non-Academic	1174 (56.6)
Treatment, no. (%)	
Surgery	284 (13.7)

Characteristic	Value
Radiotherapy	984 (47.7)
Chemotherapy	1735 (83.7)

Table 2:

Overall Survival Analysis

Median Survival (y)	OS (95% CI)			
Overall	10.5 (9.4–11.1)			
Percent Survival (%)				
At 1 year	87.5% (85.9–89.2)			
At 2 years	81.7% (79.8–83.6)			
At 5 years	69.9% (67.5–72.4)			
At 10 years	51.2% (47.7–54.9)			
	% OS (95% CI)			
By Primary Site (y)	1	2	5	10
Nasal Cavity (n=421)	84.8% (81.4–88.4)	79.8% (75.9–83.9)	63.0% (57.9–68.4)	44.5% (37.9–52.3)
Paranasal Sinuses (n=1017)	84.3% (82.1–86.6)	78.2% (75.7–80.9)	65.0% (61.8–68.3)	46.8% (42.6–51.5)
Nasopharynx (n=635)	77.8% (74.6–81.2)	71.1% (67.5–74.8)	61.5% (57.5–65.7)	44.9% (39.6–50.9)
By Ann Arbor Stage (y)				
I (n=1039)	86.5% (84.5–88.7)	81.2% (78.8–83.7)	67.5% (64.3–70.7)	49.3% (45.2–53.9)
II (n=490)	81.0% (77.6–84.6)	74.8% (71.0–78.9)	65.7% (61.3–70.3)	46.1% (39.7–53.6)
III (n=86)	79.0% (70.6–88.4)	68.5% (58.9–79.6)	53.4% (42.5–66.9)	31.8% (18.7–54.1)
IV (n=310)	71.6% (66.6–76.9)	64.2% (58.9–70.0)	49.6% (43.8–56.1)	37.1% (29.3–47.0)
By Treatment All Years (y)				
MAC (n=596)	78.3% (75.0–81.7)	72.9% (69.4–76.7)	60.2% (56.2–64.5)	42.7% (37.2–49.1)
MAC-RT (n=615)	94.6% (92.8–96.4)	88.7% (86.2–91.3)	78.5% (75.2–82.0)	57.1% (52.0–62.7)

OS: Overall Survival; MAC: Multi-Agent Chemotherapy; RT: Radiotherapy

Table 3:

Multivariable analysis of clinical and demographic/socioeconomic factors of sinonasal diffuse large B-cell lymphoma patients on overall survival.

	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age, y				
<65	1 [Reference]		1 [Reference]	
≥65	3.106 (2.639–3.655)	<0.001*	2.199 (1.520–3.181)	<0.001*
Sex				
Male	1 [Reference]		1 [Reference]	
Female	1.123 (0.980–1.288)	0.094	0.944 (0.732–1.218)	0.656
Race				
White	1 [Reference]		1 [Reference]	
Black	0.955 (0.753–1.210)	0.700	~	~
Asian	1.128 (0.844–1.507)	0.416	~	~
Insurance				
Private	1 [Reference]		1 [Reference]	
Government	2.878 (2.431–3.408)	<0.001*	2.079 (1.442–2.999)	<0.001*
Facility Type				
Non-Academic	1 [Reference]		1 [Reference]	
Academic	0.731 (0.635–0.843)	<0.001*	0.694 (0.533–0.903)	0.007*
Charlson Comorbidity Index				
0	1 [Reference]		1 [Reference]	
1	1.501 (1.241–1.816)	<0.001*	1.475 (1.040–2.090)	0.029*
≥2	3.142 (2.541–3.884)	<0.001*	2.603 (1.767–3.836)	<0.001*
B Symptoms				
No	1 [Reference]		1 [Reference]	
Yes	1.377 (1.140–1.664)	<0.001*	1.594 (1.172–2.169)	0.003*
HIV Status				
Absent	1 [Reference]		1 [Reference]	
Present	1.550 (1.117–2.150)	0.009*	2.059 (1.155–3.672)	0.014*
Primary Site				
Nasopharynx	1 [Reference]		1 [Reference]	
Paranasal Sinuses	0.878 (0.752–1.025)	0.101	~	~
Nasal Cavity	0.924 (0.761–1.123)	0.427	~	~
Ann Arbor Stage				
I	1 [Reference]		1 [Reference]	
II	1.116 (0.937–1.329)	0.217	1.020 (0.750–1.387)	0.901

	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
III	1.592 (1.144–2.215)	0.006 *	0.949 (0.523–1.719)	0.862
IV	1.766 (1.463–2.132)	<0.001 *	1.912 (1.336–2.736)	<0.001 *
Surgery				
No	1 [Reference]		1 [Reference]	
Yes	0.892 (0.730–1.089)	0.261	~	~
Treatment				
MAC	1 [Reference]		1 [Reference]	
MAC + RT	0.558 (0.464–0.672)	<0.001 *	0.614 (0.467–0.807)	<0.001 *

HR: Hazard Ratio; CI: Confidence Interval; HIV: Human Immunodeficiency Virus; MAC: Multi-Agent Chemotherapy; RT: Radiotherapy

* statistically significant, $p<0.05$

Table 4:

Multivariable analysis of clinical and demographic/socioeconomic factors of sinonasal diffuse large B-cell lymphoma patients treated post-2012 who received chemotherapy.

	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age, y				
<65	1 [Reference]		1 [Reference]	
≥65	2.172 (1.425–3.313)	<0.001 *	2.686 (1.264–5.706)	0.010 *
Sex				
Male	1 [Reference]		1 [Reference]	
Female	0.841 (0.567–1.248)	0.389	~	~
Race				
White	1 [Reference]		1 [Reference]	
Black	1.000 (0.545–1.834)	0.999	~	~
Asian	1.253 (0.649–2.420)	0.502	~	~
Insurance				
Private	1 [Reference]		1 [Reference]	
Government	2.076 (1.355–3.181)	<0.001 *	1.232 (0.622–2.441)	0.549
Facility Type				
Non-Academic	1 [Reference]		1 [Reference]	
Academic	0.828 (0.561–1.222)	0.342	~	~
Charlson Comorbidity Index				
0	1 [Reference]		1 [Reference]	
1	1.223 (0.701–2.133)	0.479	1.245 (0.626–2.478)	0.532
≥2	3.144 (1.827–5.408)	<0.001 *	2.124 (0.928–4.857)	0.074
B Symptoms				
No	1 [Reference]		1 [Reference]	
Yes	2.021 (1.255–3.254)	0.004 *	1.565 (0.824–2.971)	0.171
HIV Status				
Absent	1 [Reference]		1 [Reference]	
Present	3.619 (1.726–7.588)	<0.001 *	2.353 (0.815–6.796)	0.114
Primary Site				
Nasopharynx	1 [Reference]		1 [Reference]	
Paranasal Sinuses	0.712 (0.468–1.082)	0.112	0.795 (0.414–1.524)	0.489
Nasal Cavity	0.519 (0.282–0.957)	0.036 *	0.716 (0.292–1.753)	0.464
Ann Arbor Stage				
I	1 [Reference]		1 [Reference]	
II	1.164 (0.685–1.980)	0.575	1.308 (0.617–2.772)	0.483
III	1.319 (0.590–2.949)	0.501	0.852 (0.275–2.641)	0.781

	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
IV	2.459 (1.539–3.928)	<0.001 *	2.065 (1.101–3.873)	0.024 *
Surgery				
No	1 [Reference]		1 [Reference]	
Yes	0.922 (0.505–1.684)	0.792	~	~
Immunotherapy				
No	1 [Reference]		1 [Reference]	
Yes	0.850 (0.555–1.302)	0.456	0.509 (0.284–0.915)	0.024 *
Radiotherapy				
No	1 [Reference]		1 [Reference]	
Yes	0.473 (0.308–0.727)	<0.001 *	0.354 (0.189–0.662)	0.001 *

HR: Hazard Ratio; CI: Confidence Interval; HIV: Human Immunodeficiency Virus

* statistically significant, $p<0.05$