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INTRODUCTION
Lymphomas are the second most common malignancy of the sinonasal tract, comprising 14% of all sinonasal malignancies. The most common subtype of sinonasal lymphoma is extranodal natural killer (NK)/T-cell lymphoma (ENKTL), nasal type. These tumors are highly aggressive and frequently result in obliteration of the nasal airway and maxillary sinuses, with subsequent bony destruction and extension into adjacent structures. Disease-specific survival (DSS) for sinonasal ENKTL remains very poor, with 5-year DSS rates of approximately 31%. Given the aggressive nature of this malignancy, identification of risk and prognostic factors is essential for optimization of management strategy.

Prior studies have identified several variables that may be valuable in prognostication of ENKTL. Investigations of the molecular basis of ENKTL tumorigenesis have reported a strong association with Epstein-Barr virus (EBV) infection, and have proposed that viral load may be a prognostic factor for ENKTL. In addition, a retrospective population-based study by Vazquez et al. suggested that lower Ann Arbor stage and treatment with radiation therapy are associated with improved OS. As with other rare diseases, no standard treatment has been established yet for ENKTL on the basis of randomized control trials, and population-level data has largely driven current practices. Regimens often entail a combination of radiation therapy and chemotherapy based on the degree of tumor burden at presentation. Radiation therapy has been previously demonstrated as a prognostic factor, but no investigation to date has utilized a population-based analysis to evaluate the effect of chemotherapy on survival.

Thus, this represents the first article to analyze the impact of chemotherapy on survival for patients with sinonasal ENKTL. The objective of this study is to assess and update the association of demographic factors, tumor characteristics, and treatment modalities—including newly available chemotherapy data—on OS and DSS in patients with ENKTL.

MATERIALS AND METHODS
A retrospective population-based cohort study was performed using the 2017 edition of the Surveillance, Epidemiology, and End Results (SEER) database. This publicly available database of cancer incidence and survival in the United States is updated annually by
the National Cancer Institute (NCI). Because SEER has removed all patient identifiers, no institutional review board approval was required to utilize the data. The 2017 registry contains data from 1973 through 2015 and includes groupings from SEER 9 (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah), SEER 13 (Los Angeles, San Jose-Monterey, Rural Georgia, and the Alaska Native Tumor Registry), and SEER 18 (Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey).

Using the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) code, 9,719 cases of ENKTL were identified. These cases were further limited by site using the equivalent ICD-O-3 anatomic codes: C30.0 (nasal cavity), C31.0 (maxillary sinus), C31.1 (ethmoid sinus), C31.2 (frontal sinus), C31.3 (sphenoid sinus), C31.8 (overlapping lesion of accessory sinuses), and C31.9 (accessory sinus, not otherwise specified). The accessory sinus codes, C31.8 and C31.9, were included in the same category for analysis. Several study parameters were collected, including gender, race, age at diagnosis, tumor site, Ann Arbor lymphoma stage, primary site, chemotherapy, radiation therapy, surgical management, and survival months.

SEER data were isolated using SEER-Stat 8.3.5 (NCI, Bethesda, MD). Overall survival and DSS were used for outcome analysis as the primary end points of the study. Survival was calculated from the date of diagnosis of malignancy to whichever of the following occurred first: date of death, date of last follow-up, or end of the study period (December 31, 2015). Any patients lost to follow-up were coded as censored observations.

SPSS version 22 (IBM Corp., Armonk, NY) was used for data analysis. Univariate Kaplan-Meier analysis was performed to evaluate the association of each of the aforementioned variables with survival. Each association was analyzed using a log-rank test. All variables were deemed statistically significant at P < .05. Any variables that were found to be significant predictors of OS or DSS were subsequently tested with a multivariable Cox proportional hazards regression analysis. Continuous variables are reported as mean ± standard deviation, and categorical variables are presented as percentage frequencies.

RESULTS

Four hundred and sixty cases of sinonasal ENKTL were analyzed (Table I). The average age of the patients was 52.2 ± 18.1 years; males comprised 60.9% of the cohort; and 71.3% of patients were Caucasian. Significant differences in age of presentation (P = .03) existed between races, with Caucasian (51.0) and African American (50.6) patients presenting at younger ages than other races, including Asian/Pacific Islander and Native American (56.2). A large majority of tumors were located within the nasal cavity (83.5%); other sites included the maxillary (4.1%) and ethmoid sinuses (2.8%). No recorded cases of ENKTL were located in the frontal or sphenoid sinus. The most common Ann Arbor stage was stage I (58.0%). With regard to treatment interventions, patients were more likely receive chemotherapy (69.8%), receive radiation therapy (65.2%), and not undergo surgery (67.4%). With regard to chemoradiation and surgical intervention, 17.8% of patients received both and 47.5% received chemoradiation alone.

OS at 2-year, 5-year, and 10-year time points was 58%, 46%, and 41%, respectively, with a median survival time of 44 ± 9.4 months. DSS was 66%, 56%, and 56%, respectively. Univariate analysis suggested that younger age (P < .001), lower Ann Arbor stage (P < .001), and administration of radiation (P < .001) were significant predictors of OS. DSS was similarly predicted by age (P = .005), Ann Arbor stage (P < .001), and administration of radiation (P < .001). Chemotherapy across the entire cohort was not significantly associated with improved survival. However, when stratified across Ann Arbor stage, chemotherapy significantly improved OS (P < .01) and DSS (P = .04) for stage I disease (Fig. 1).

The results of the Cox proportional hazards regression analysis are displayed in Table II. Multivariate analysis suggested that higher Ann Arbor stage was associated with worse OS (hazard ratio [HR] 1.46; P < .001) and DSS (HR 1.60; P < .001) as depicted in Figure 2, whereas administration of radiotherapy was associated with improved OS (HR 0.56; P < .001) and DSS (HR 0.58; P = .001) as depicted in Figure 3. In addition, higher age at diagnosis was associated with reduced OS (HR 1.01; P = .024). Surgery was not associated with improved survival.
DISCUSSION

Sinonasal ENKTL is a rare disease that most commonly presents in the upper aerodigestive tract and is responsible for substantial patient morbidity and mortality. Unlike diffuse large B-cell lymphoma (DLBCL), sinonasal ENKTL is much less studied and poorly understood. Prior population SEER studies have investigated demographic and survival differences for sinonasal ENKTL versus DLBCL and sinonasal ENKTL versus nonsinonasal ENKTL. Yet, they do not comment on age of presentation between genders, races, or significant hazard analysis for specific diagnostic and treatment factors other than radiation therapy that may impact DSS and OS. These include age, use of chemotherapy, surgical interventions, and primary site of disease. Moreover, because these studies included patients between the years 1973 through 2011 and 1973 through 2009, this study includes an additional 4 and 6 years of data, respectively. Ultimately, this study represents the first major population study using the SEER database to discuss the impact of newly added chemotherapy data on survival of sinonasal ENKTL and the significance of various other demographic and treatment interventions on DSS and OS.

Age, Gender, Race

The mean age of diagnosis in this cohort was 52.2, and the male:female ratio was 1.56, both consistent with prior studies suggesting the most common presentation is during the sixth decade of life with a male predominance. Whereas there were no significant differences in presenting age between genders, there existed a significant difference in the age of presentation between races. Asian/Pacific Islanders and Native Americans, the two races that predominantly comprise the “other” category on SEER, presented on average at a significantly older age of 56.2. This has not been previously reported in the literature. It is well established that sinonasal ENKTL is more common in Asian and Latin American than Western countries. One explanation for this is the distribution of different strains of EBV in Asian countries and the rest of the world. EBV has long been known to play a key role in the pathogenesis of ENKTL. Because EBV is present in 90% of persons worldwide, strain variations likely impact the frequency of malignant transformation. However, it is unclear why this would result in a delayed age of presentation in these populations. Patients included in the SEER database reside in the United States and may not be exposed to the same EBV strains seen in Asian countries. This suggests a geographical relationship for disease prevalence as opposed to a racial one. Ultimately, age played an independent and significant role in OS but not DSS, whereas race and gender were not significant contributors to either. This represents a novel finding and is likely explained by an overall decline in health status at older ages because it was not observed in DSS.

Ann Arbor Stage

Sinonasal ENKTL is classically staged with the Ann Arbor system. The higher the stage, the more invasive and
widespread the disease. OS and DSS of patients in this study varied significantly by Ann Arbor staging. Lower stages were associated with improved survival (Fig. 1). The proportion of patients diagnosed with stage I disease has increased in comparison to prior population studies. This may be attributed to a lower threshold for screening and advancements in detection. However, 17% of patients still presented with stage IV disease, and although patients are presenting earlier in the disease course, this remains a highly aggressive tumor.

### Primary Site

The nasal cavity (83.5%) was the most common site for sinonasal ENKTL. This agrees with prior studies; however, the proportion has slightly increased over the past few years. Several hypotheses exist for this apparent predilection for the nasal cavity. Larger tumors often pose a challenge when attempting to correctly ascertain their primary site and may spread from Waldeyer's ring. The nasal cavity is also hypothesized to house NK cell assembly during early nonspecific immunologic defense.
The increase in diagnosed cases of the nasal cavity, along with the increase in stage I disease, may be suggestive of improved early diagnostic practices in which physicians are detecting the disease before it spreads in the sinonasal tract. Although race is thought to impact the primary site of disease in DLBCL, no such association was found for sinonasal ENKTL. Primary site did not significantly impact OS and DSS.

**Treatment**

No standardized treatment regimen exists for sinonasal ENKTL. Many suggested regimens that include some form of combination chemoradiation, either concurrently or sequentially. Although this population study is limited in its database to comment on the temporal relationship of interventions, it is the first population study of sinonasal ENKTL to report the impact of chemotherapy on OS and DSS. Chemotherapy was administered in 69.8% of patients, with 65.3% receiving chemoradiation with or without surgical intervention. Unlike sinonasal DLBCL and other aggressive non-Hodgkin lymphomas, the chemotherapeutic regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone is not effective option for sinonasal ENKTL. This is due in large part to multidrug resistance patterns in ENKTL and a lack of potency of anthracycline-containing chemotherapies. Newer, novel agents such as immunotherapies have been developed in recent years to address this lack of standardization. Although SEER is unable to provide information on specific chemotherapeutic regimens, it still offers valuable patient survival data.

When assessed in the entire cohort, chemotherapy was not a significant contributor to improved OS and DSS. This is not an expected finding; however, there exist prior studies that have commented on a lack of improved survival when chemotherapy is added to radiation therapy treatment. In this case, it is likely due to the small number of stage II to IV patients. When stratified by Ann Arbor stage, use of chemotherapy significantly improved OS and DSS for stage I disease. This is a critical observation for several reasons. First, it highlights the importance of early recognition of disease and urgency for appropriate treatment. Second, it reiterates the notion that sinonasal ENKTL is a very aggressive malignancy, especially when diagnosed later in its course. Chemotherapy likely becomes less effective at higher stages due to the clinical course and rapid progression of tumor growth and metastasis. Third, it suggests that chemotherapy may be one of many treatments required for more reliable disease control.

Radiation therapy is often described as the most critical treatment modality for ENKTL, especially in early stage disease. In contrast to DLBCL, where chemotherapy followed by radiation therapy is the mainstay of treatment, the treatment regimen for ENKTL is less understood. Recent studies have recommended the opposite approach, upfront radiation therapy followed by nonanthracycline chemotherapy agents. In this study, radiation therapy was only administered in 65.2% of patients, with nearly all of these patients also receiving chemotherapy. Across all cohorts, radiation therapy significantly improved OS and DSS in univariate and multivariate analysis. Although this study was not designed to comment on the proper succession of treatment, it is clear that radiation therapy plays a critical role in the appropriate management of these patients. Previous population studies have shown a significant prolongation of survival in stage I disease with use of radiation therapy.

Surgical intervention was not significantly associated with changes in OS and DSS. Surgery was performed in 32.6% of patients and was utilized as monotherapy in only 3.7% of cases. Just as SEER is unable to differentiate between chemotherapeutic regimens, it is also limited in its ability to discern the various surgical interventions that patients may have received. Many of these procedures were likely biopsies for genetic sequencing prior to the initiation of chemotherapy. The limited cases where surgery was used as monotherapy likely represent palliative procedures for extremely aggressive disease. Surgical intervention may be beneficial in cases of severe tumor burden in which debulking may improve symptomology. Although patients are likely to present to their otolaryngologist with symptoms such nasal obstruction, epistaxis, headache, and hearing impairment, the mainstay of treatment resides with radiation and medical oncologists.

**Limitations**

As with all retrospective database-centered population studies, inherent limitations of the utilized database exist. Although EBV is classically associated with ENKTL, this study is unable to comment on its impact for the included patients because the SEER database lacks information on EBV status. Moreover, limitations exist in the level of detail with which treatments are reported. Specific chemotherapy regimens, dosage of radiation delivered, type of surgical intervention, and sequence of intervention are unavailable. Although this study has several limitations of its own, it also addresses major limitations of prior studies. The lack of available chemotherapy data has long limited SEER studies from commenting on the most pervasive treatment for lymphoma. The inclusion of chemotherapy data in this study represents a significant advancement in the ability of SEER studies to address current treatment modalities. This is vital because large population studies remain the most robust and effective study design to investigate rare and poorly understood diseases in the population.

**CONCLUSION**

Sinonasal, extranodal natural killer/T-cell lymphoma remains an exceedingly uncommon malignancy. Survival in these patients is improved by radiation therapy and lower Ann Arbor stage at diagnosis, whereas chemotherapy improves survival in patients with early stage disease. With no established treatment regimen for sinonasal ENKTL, these findings suggest that combination chemoradiation is an effective therapy for prolonged survival. Surgical intervention remains limited to assisting with diagnosis and improving morbidity and should be utilized at the discretion of the treatment team.
BIBLIOGRAPHY


