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Oropharyngeal lymphoma: A US population based analysis

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ABSTRACT

Objectives: To describe the epidemiology and analyze factors determinant of survival in patients with oropharyngeal lymphoma, using the Surveillance Epidemiology and End Results (SEER) database.
Methods: 2504 patients with oropharyngeal lymphoma were identified using the most recent SEER database entry from 1976 to 2016. Demographic information, Ann Arbor stage, tumor histopathology and location were collected. Multivariate analysis was used to analyze patient and tumor characteristics associated with survival.
Results: The mean age of the patients studied was 60.5 years, 58.4% of the subjects were male and 81% were white. Diffuse large B cell lymphoma (DLBCL) was the most common histologic subtype involving 56.9% of cases. The most common subsite of origin was the tonsil, with 71% of lymphomas originating from there. The association of survival with stage, age, tumor location, presence of B symptoms, tumor pathology, gender and race was analyzed using multivariate regression. Decreased survival was significantly associated with patient age $p < 0.0001$, Ann Arbor staging $p = 0.005$, the presence of B symptoms $p = 0.003$ and tumor histopathology (T cell tumors) $p = 0.01$. Patients with tumors originating from the soft palate were significantly more likely to die as a result of their disease $p = 0.03$.
Conclusion: Oropharyngeal lymphoma most commonly originates from the tonsil. DLBCL is the most common subtype and has a good prognosis. The presence of B symptoms, tumors originating from the soft palate and patients with T cell tumors have the worst prognosis. This information can potentially be of great utility to the head and neck surgeon discussing prognosis with patients suffering from oropharyngeal lymphoma.

Introduction

Head and neck lymphomas arise from lymph nodes as well as extranodal locations including, Waldeyer ring, the sinonasal tract, nasopharynx and salivary glands [1]. The oropharynx contains the palatine tonsils as well as the base of tongue (BOT), both of these locations are part of Waldeyer's ring and are comprised of lymphoid tissue [2]. B cells proliferate and mature at these locations, which represent the first contact point for exogenous antigens entering the aerodigestive tract [3]. Lymphomas are subdivided into Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL), with extranodal NHL being the second most common primary head and neck malignancy after squamous cell carcinoma [4]. Hodgkin's lymphoma primarily arises from lymph nodes, with only 5% arising extranodally; whereas 30% of NHL present at an extranodal location [5]. Approximately 11% of NHL patients have a primary lesion in the head and neck [6]. Waldeyer's ring is involved in approximately 5–10% of patients with NHL in the United States, with the most common subsites involved being the tonsil at 51% [7,8]. Aggressive diffuse large B cell lymphoma, most commonly arises in the paranasal sinuses, mandible, maxilla and Waldeyer's ring and Burkitt lymphoma most commonly involves the mandible and jaw [9]. DLBCL comprises approximately 30% of all NHL and is the most prevalent lymphoma subtype within the oropharynx [10].

The most common presenting symptoms of oropharyngeal lymphoma were sore throat and dysphagia, and these symptoms were most pronounced for patients with BOT malignancies. Approximately one third of patients presented with a neck mass only [8]. On imaging, extranodal lymphoma commonly appears as a well circumscribed submucosal mass with a smooth mucosal surface, aggressive lymphomas can be locally invasive making them indistinguishable from squamous cell carcinoma [1,9]. Treatment was dependent on stage and histologic subtype, with most patients receiving a combination of radiation and

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chemotherapy [2].

Most lymphomas are potentially curable, but stage at presentation significantly impacts survival as patients with disseminated disease have a poor prognosis [11,12]. Tumors in the oropharynx need to be larger than 4 cm before obvious symptoms develop, which significantly compromises early life saving diagnoses [8,13]. Information on the impact of age, gender, histologic subtype and oropharyngeal subsite on survival are scarce and conflicting, secondary to rarity of the disease. The objective of this study is to analyze a large population of patients with oropharyngeal lymphoma and determine which clinical factors impact survival.

Methods

Data source

A population based cohort was created using the most up to date November 2016 submission of the SEER database, in addition to the 18 SEER data files. This database encompasses 27.8% of the population of the United States, and has been widely used in numerous other studies on head and neck and oropharyngeal cancer. As this study used publically available information with no patient identifiers, Wayne State University IRB approval was not required.

Study population

The database was queried for patients diagnosed with lymphoma, from the years of 1973–2016 using the I*nternational Classification of Diseases for Oncology, 3rd Edition (ICDO-3)* pathologic subtypes, 9590 to 9591 (malignant lymphomas NOS), 9650–9669 (Hodgkin's lymphoma), 9670–9699 (Non Hodgkin's Lymphoma B cell subtypes), and 9700–9719 (Non Hodgkin's Lymphoma T- and Natural Killer-cell lymphomas), limited to the oropharynx, C01.9 (Base of tongue), C05.1 (Soft palate), C05.2 (Uvula), C09.1-9 (tonsil), C10.2 (lateral wall of oropharynx), C10.3 (posterior wall of oropharynx), C10.8 (overlapping lesion of oropharynx), C10.9 (Oropharynx NOS).

Statistical analysis

Demographic information, Ann Arbor stage, oropharynx subsite, presence of B symptoms, histologic subtype and survival information were obtained from the database. Surgery was not evaluated as it is not the primary treatment modality used for this disease. The association of age, gender, race, histology, oropharynx subtype, Ann Arbor stage and presence of B symptoms were analyzed with respect to the dependent variable of survival using multivariate analysis. The list of independent variables was analyzed using variance inflation factors (VIF) to assess for co-linearity. All factors had a VIF score of less than 1.5 indicating minimal co-linearity within the independent variables. A reduced model for survival was then developed using multivariate linear regression analysis. Binary nominal regression analysis was used to identify independent variables associated with death from disease. Survival curve by histologic subtype was made using the product limit Kaplan Meier for each histologic subtype. IBM SPSS statistics version 23 (IBM Corp, Chicago, Illinois) was used for the analyses and a p value threshold of < 0.05 was set for statistical significance.

Results

A total of 2504 cases were identified that met the inclusion criteria. The mean age of the patients studied was 60.5 years with a minimum of 1 year and maximum age of 85 years (Table 1). 58.4% of the subjects were male and 81% were white. The most common subsite of origin was the tonsil, with 71% of lymphomas originating from there. Diffuse large B cell lymphoma (DLBCL) was the most common histologic subtype involving 56.9% of cases.

Table 1
Summary of patient and tumor characteristics. BOT: base of tongue. Pharyn wall: pharyngeal wall. CLL: chronic lymphocytic leukemia. DLBCL: diffuse large B cell lymphoma. MALT: mucosal associated lymphoid tissue.

Factor		Values
Age (yrs)	Mean	60.5
	Min	1
	Max	85
Gender # (%)	Male	1462(58.4)
	Female	1042(41.6)
Stage # (%)	Stage I	896(35.8)
	Stage II	1006(40.2)
	Stage III	177(7.1)
	Stage IV	264(10.5)4
	Unknown	161(6.4)
Race # (%)	White	2028(81.0)
	Black	157(6.3)
	Asian	260(10.4)
Subsite # (%)	Tonsil	1800(71.9)
	BOT	523(20.9)
	Soft palate	57(2.3)
	Pharyn Wall	16(0.6)
B symptoms # (%)	Yes	312(12.5)
	No	1530(61.1)
Pathology # (%)	Hodgkin's	40(1.6)
	CLL	65(2.6)
	Mantle	196(7.8)
	DLBCL	1424(56.9)
	MALT	133(5.3)
	Follicular	312(12.5)
	Tcell	89(3.6)
	Burkitt	48(1.9)

Patients with DLBCL were most likely to present with Ann Arbor stage II disease and 72.3% of cases involved the tonsil. Hodgkin's lymphoma, had the lowest mean age at presentation at 49.6 years and the tonsil was the most common site of origin. 22.4% of patients with mantle cell histopathology presented with stage IV tumors, which was the highest proportion of all the different histopathologic subtypes. In addition, patients with Hodgkin's lymphoma had the highest rate of B symptoms at presentation at 20.0%. T cell lymphoma was more likely to present in ethnic minority patients, with African American and Asian patients comprising 15.7% and 18.0% of the patients suffering from this disease (Table 2).

The mean overall survival time was 110.5 months. The association of survival with stage, age, tumor location, presence of B symptoms, tumor pathology, gender and race was analyzed using multivariate regression. Decreased survival was significantly associated with patient age $p < 0.0001$, Ann Arbor staging $p = 0.005$, the presence of B symptoms $p = 0.003$ and tumor histopathology $p = 0.01$.

Patients with T cell lymphoma had the lowest mean overall survival time at 77.3 months (Fig. 1). Patients with MALT tumors had the highest 5 and 10 year disease specific survival rates (DSS) at 93% and 91% respectively. 5 and 10 year DSS rates were lowest for patients suffering from T cell lymphomas at 53% for both time points. Patients with tumors in the soft palate had the lowest 5 and 10 year DSS of all the subsites analyzed at, 65% and 52% respectively (Table 3).

Binary regression analysis was also performed to determine which patient and tumor characteristics were associated with death from disease. Patients with tumors originating from the soft palate and older patients were significantly more likely to die as a result of their disease, odds ratio (OR) 5.7 $p = 0.03$ and OR 1.03 $p < 0.0001$ respectively. Patients who had extranodal mucosal associated lymphomas were significantly less likely to die as a result of their malignancy OR 0.17 $p = 0.009$.